VOLUME 37 FEBRUARY 25, 1972 NUMBER 4 JOCEAH

THE JOURNAL OF Organic Chemistry

PUBLISHED BIWEEKLY BY THE AMERICAN CHEMICAL SOCIETY

THE JOURNAL OF Organic Chemistry

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

Published biweekly by the American Chemical Society at 20th and Northampton Sts., Easton, Pa. 18042. Second-class postage paid at Washington, D. C., and at additional mailing offices.

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JOCEAH 37(4) 531–682 (1972)

THE JOURNAL OF Organic Chemistry®

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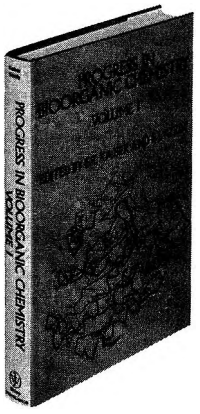

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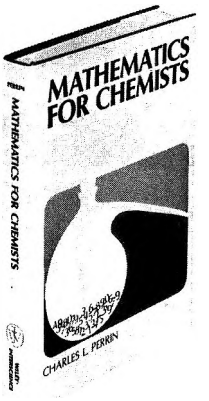

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THE JOURNAL OF Organic Chemistry®

VOLUME 37, NUMBER 4

FEBRUARY 25, 1972

Acid-Catalyzed Rearrangement of Tricyclo[4.4.0.0^{2,7}]decan-3-ols

BRUCE E. RATCLIFFE AND CLAYTON H. HEATHCOCK*

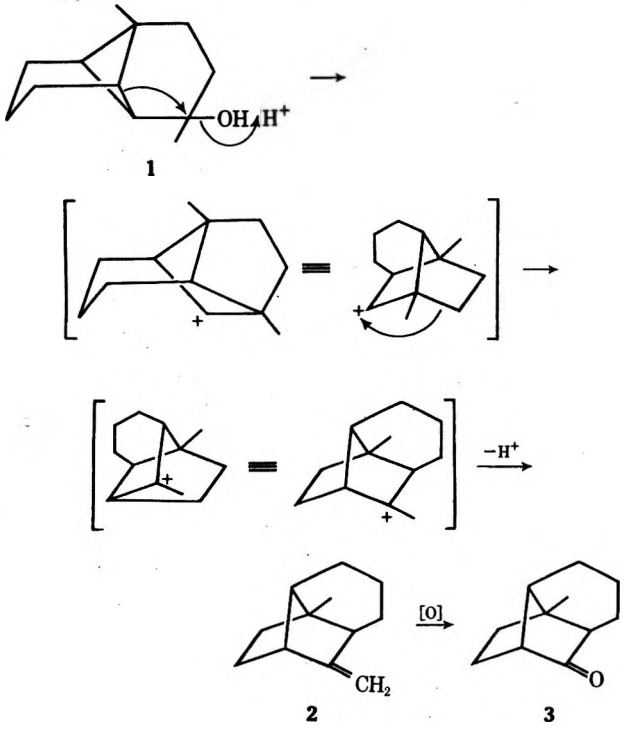
Department of Chemistry, University of California, Berkeley, California 94720

Received September 8, 1971

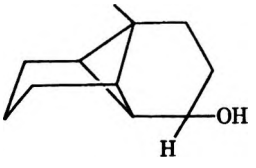
Tertiary alcohol **1** and its secondary counterpart **4** undergo acid-catalyzed rearrangement to olefin **5** and alcohol **8**, respectively. Both **5** and **8** may be oxidized to tricyclic ketone **7**, the structure of which has been rigorously defined by degradation to the known bicyclic ketone **19**. Tricyclic alcohols **34** and **35** also yield, respectively, alcohol **8** and olefin **5** when treated with acid.

We previously reported that 3,6-dimethyltricyclo-[4.4.0.0^{2,7}]decan-3-ol (**1**) undergoes acid-catalyzed rearrangement in the heterogeneous medium, ether–50% aqueous sulfuric acid, giving a single olefinic product in good yield.[1] Structure **2** was assigned to this olefin on the basis of spectral data obtained from it and the derived nor ketone (assigned structure **3**) and the reasonable mechanistic scheme outlined in Scheme I.[1]

SCHEME I



These assignments were called into question when we discovered a different tricyclic ketone with a better mechanistic claim on structure **3** in a related rearrangement.[2] In this paper we report a reexamination of the acid-catalyzed rearrangement of tertiary alcohol **1** and its secondary counterpart **4** and a rigorous identification of the products of these reactions.



4

As reported in our earlier communication,[1] alcohol **1** was found to undergo acid-catalyzed rearrangement to a single bicyclic olefin **5**, having the empirical formula $C_{12}H_{18}$. When the reaction is carried out in the heterogeneous medium, pentane–50% aqueous sulfuric acid, the olefinic product, which has a highly camphoraceous odor, is obtained in 76% yield. The presence of an exocyclic methylene group is apparent from the ir (ν_{max} 881 cm^{-1}) and pmr spectra (one-proton multiplets at δ 4.50 and 4.78) of the product. Hydrocarbon **5** reacts with osmium tetroxide to give a crystalline diol **6**, which is cleaved by periodic acid to give the tricyclic ketone **7**, $C_{11}H_{16}O$. Ketone **7** is also obtained by ozonolysis of hydrocarbon **5**. The tricyclic ketone shows typical norbornanone absorption in its ir spectrum (ν_{max} 1750 cm^{-1}),[3] possesses a bridgehead methyl group (pmr singlet at δ 1.17), and exchanges no hydrogens when passed through a deuterium exchange column.[4]

Secondary alcohol **4**, when treated under the same conditions, gives an isomeric secondary alcohol **8** in 66% yield. Oxidation of alcohol **8** affords ketone **7**,

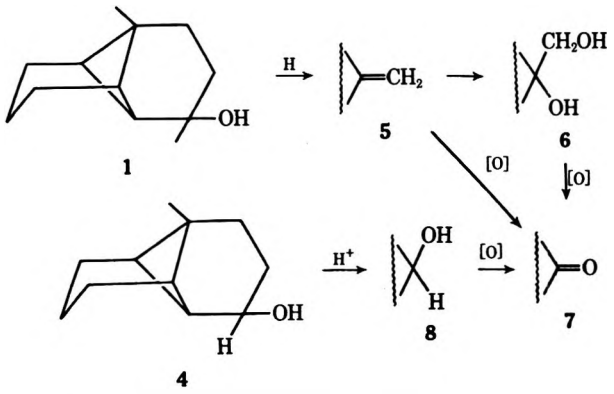
(1) C. H. Heathcock, R. A. Badger, and J. W. Patterson, Jr., *J. Amer. Chem. Soc.*, **89**, 4133 (1967).

(2) C. H. Heathcock and B. E. Ratcliffe, *J. Org. Chem.*, in press.

(3) 2-Norbornanone has ν_{max} 1751 cm^{-1}, Sadtler Standard Spectrum No. 20280.

(4) (a) M. Senn, W. J. Richter, and A. L. Burlingame, *J. Amer. Chem. Soc.*, **87**, 680 (1965). (b) G. J. Kalloe and L. B. Westover, *Tetrahedron Lett.*, 1223 (1967).

demonstrating that the two rearrangement products, hydrocarbon **5** and alcohol **8**, have the same carbon skeleton.

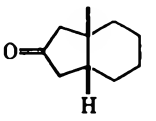


Baeyer–Villiger oxidation of tricyclic ketone **7** gives a crystalline lactone **9** in 87% yield. Saponification of **9** affords a crystalline hydroxy acid **10**, which is oxidized by chromic acid to an oily keto acid **11**. The ir spectrum of **11** contains carbonyl bands at 1755 and 1716 cm^{-1}, showing that the ketonic carbonyl is in a six-membered ring. Keto acid **11** incorporates but two deuterons per molecule when treated with sodium deuterioxide in refluxing deuterium oxide. The ir spectrum of **11** also contains a sharp band at 1422 cm^{-1}, affirming the presence of a methylene group adjacent to the cyclohexanone carbonyl.

The derived keto methyl ester **12** has corresponding spectral properties (ν_{CH_2CO} 1429 cm^{-1}). Keto ester **12** incorporates three deuterons per molecule when allowed to exchange with sodium methoxide in deuteriomethanol.[5] The evidence to this point establishes that one terminus of the carbonyl-containing bridge in tricyclic ketone **7** is a cyclohexyl position flanked by a methylene group and a quaternary carbon. The exchange data on keto ester **12** show that the other terminus (the carbon α to the new carboxyl group) bears one hydrogen.

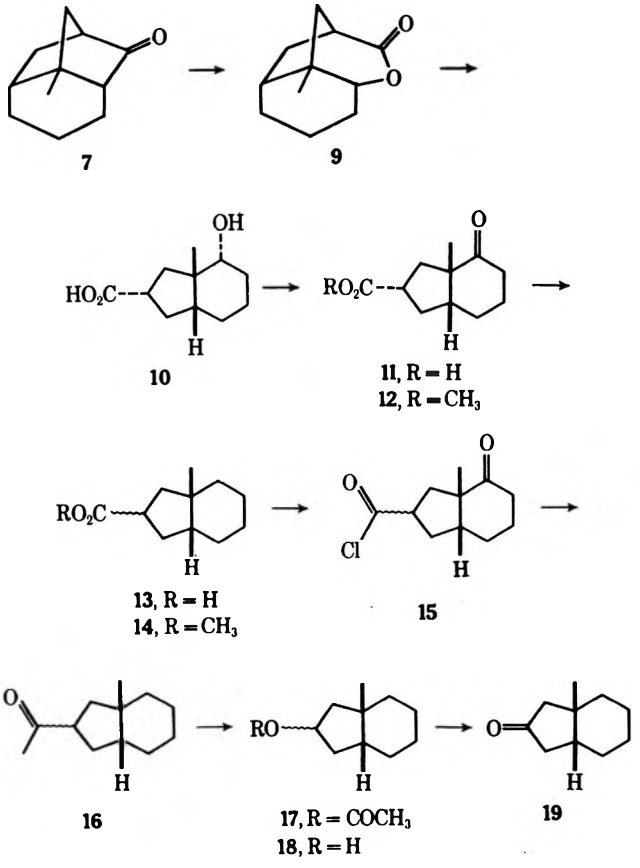
Clemmensen reduction of keto acid **11** gives a mixture of epimeric acids **13**, which react with diazomethane to give the corresponding methyl esters **14**, obtained in a ratio of 4:1 (stereochemistry undefined). The ir spectrum of this mixture ($\nu_{C=O}$ 1735 cm^{-1}) confirms the loss of the cyclohexanone carbonyl. Epimeric acids **13** are converted, by treatment of the derived acid chlorides **15** with dimethylcadmium, into methyl ketones **16**. Analysis of this mixture by glpc showed that two epimers (stereochemistry undefined) were produced in a ratio of 3:2. Baeyer–Villiger oxidation of mixture **16** gives a corresponding mixture of acetates **17**, obtained in the ratio of 7:3, which is reduced by lithium aluminum hydride to the corresponding alcohols **18**. Oxidation of this mixture by chromic acid gives a single ketone **19**, $C_{10}H_{16}O$, whose ir spectrum ($\nu_{C=O}$ 1745 cm^{-1}) reveals that the carbonyl group is in a five-membered ring. Ketone **19** also has a bridgehead methyl group (δ 1.13) and has four enolizable hydrogens adjacent to its carbonyl.

On the basis of the foregoing evidence, ketone **19** may be assigned the unambiguous structure shown below. The correctness of this assignment was confirmed

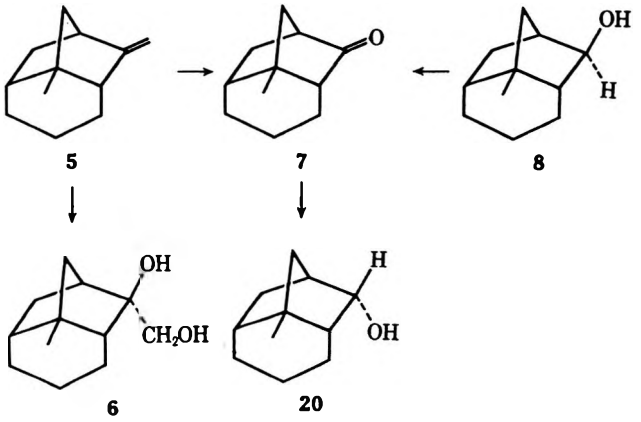


by comparison of its ir spectrum with that of an authentic sample of **19**.[6] The structure of tricyclic ketone **7**, and hence olefin **5** and alcohol **8**, is thus revealed. The complete degradative scheme is outlined in Scheme II.

SCHEME II



With the complete structure of olefin **5** and the gross structure of alcohol **8** established, it remained only to ascertain the stereochemistry of the latter substance. As reported earlier, oxidation of alcohol **8** yields tricyclic ketone **7**. Lithium aluminum hydride reduction of **7** affords a new secondary alcohol **20**, which must

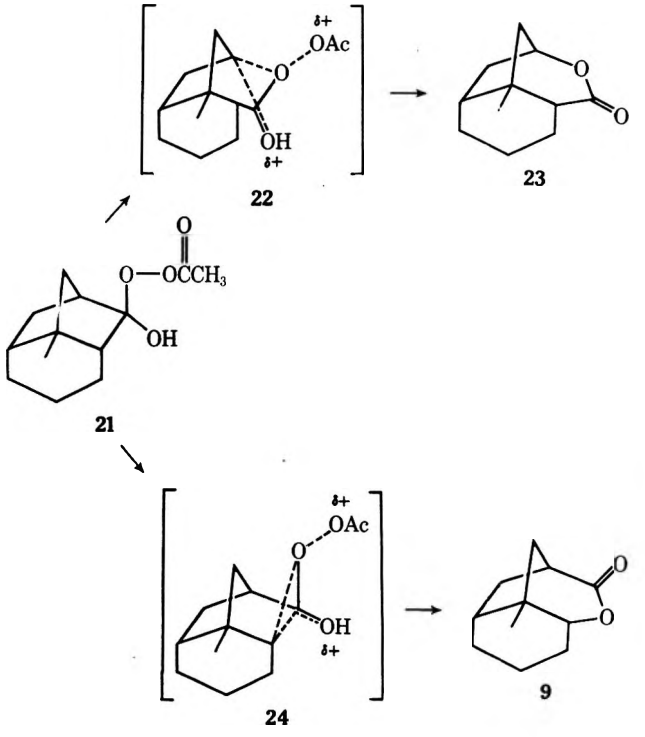


(5) We thank Professor Andrew Strietweiser, Jr., for a generous gift of CH_3OD.

(6) F. T. Bond, Ph.D. Dissertation, University of California, Berkeley, Calif., 1962. We thank Professor W. G. Dauben for providing an infrared spectrum of compound **19**.

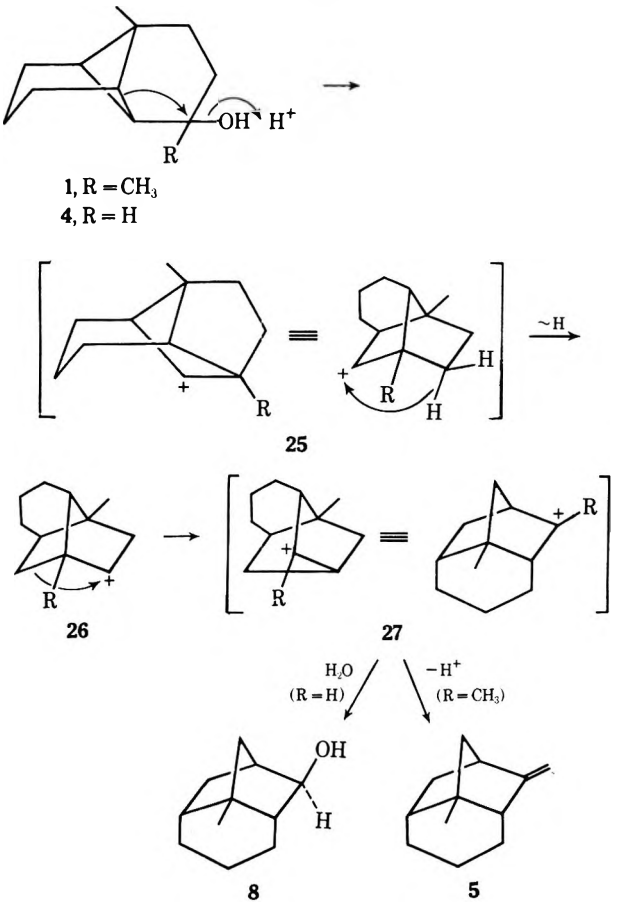
be epimeric with **8**. The well-known propensity of hindered ketones to undergo hydride reduction from the less encumbered face enables assignment of the endo configuration to the hydroxyl group in **20**, and thus the exo configuration to **8**. Confirmatory evidence for these assignments was obtained from the pmr spectra of the two alcohols. The C-2 proton of **20** (exo) should be moderately coupled to both the C-1 and C-3 protons (dihedral angles of 20 and 0°). In accord with this expectation, this resonance is found as a doublet of doublets centered at δ 4.16 with $J_{1,2} = 5$ and $J_{2,3} = 9$ Hz. The corresponding resonance in epimer **8** occurs at δ 3.58 as a broadened singlet. One expects only weak coupling in the exo alcohol (endo proton) since the dihedral angles are 85 and 120°. Diol **6**, obtained by osmium tetroxide hydroxylation of olefin **5**, may likewise be assigned the *exo*-OH configuration on steric grounds.

At this point, it is interesting to note that but one lactone is obtained in the peracid oxidation of ketone **7** (Scheme II). Assuming peracid attack from the less hindered exo face of **7**, intermediate **21** would be formed. Migration of C-1 would lead, *via* the chair-like transition state **22**, to lactone **23**. Migration of C-3 would lead, *via* the boat-like transition state **24**, to lactone **9**, the observed product. Examination of Dreiding stereomodels suggests that transition state **22** is more sterically encumbered than **24**.

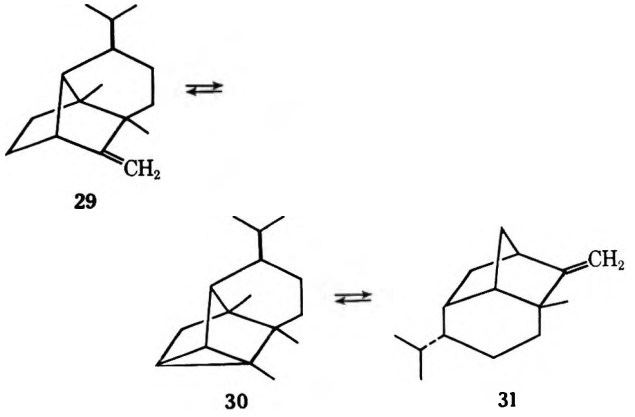


With the structures of olefin **5** and alcohol **8** rigorously defined, we may now reinterpret the rearrangement reactions. A reasonable mechanistic scheme is outlined in Scheme III. Initial expansion of the cyclobutane ring probably yields ion **25**, which suffers a 1,3-hydride shift to ion **26**, rather than a second Wagner–Meerwein shift, as we had originally proposed (Scheme I). Subsequent Wagner–Meerwein rearrangement of **26** gives the endo-bridged norbornyl cation **27**, which either ejects a proton (when R = CH_3) or becomes hydrated (when R = H).

SCHEME III



It is tempting to implicate cyclopropane **28** as an intermediate in the rearrangement of ion **25** to ion **27** (see Scheme IV). McMurry has shown that the rearrangement of (±)-sativene (**29**) to (±)-isosativene (**31**), catalyzed by cupric acetate in refluxing acetic acid, certainly involves the intermediacy of (±)-cyclosativene (**30**).[7,7a]

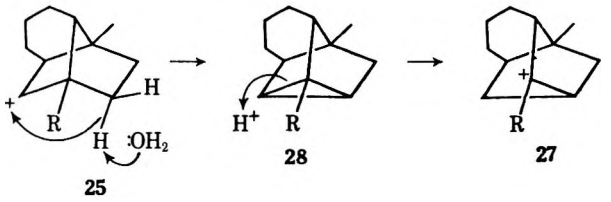


One interesting observation which we have made may be relevant to this point. Olefins **32** and **33**, obtained by dehydration of tertiary alcohol **1** with phosphoryl chloride in pyridine, *are recovered unchanged* when submitted to the pentane–50% aqueous sulfuric acid treatment. Apparently these olefins are not

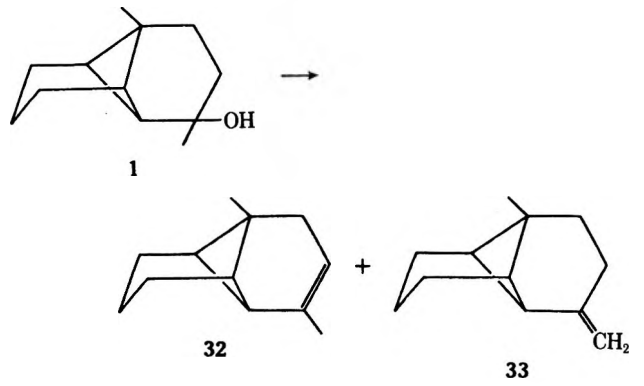
(7) J. E. McMurry, *Tetrahedron Lett.*, 55 (1969).

(7a) NOTE ADDED IN PROOF.—McMurry has now shown that hydrocarbon **30** is not an intermediate in the rearrangement of **29** to **31** when the reaction is carried out in the hexane–50% aqueous sulfuric acid system: J. E. McMurry, *J. Org. Chem.*, **36**, 2826 (1971).

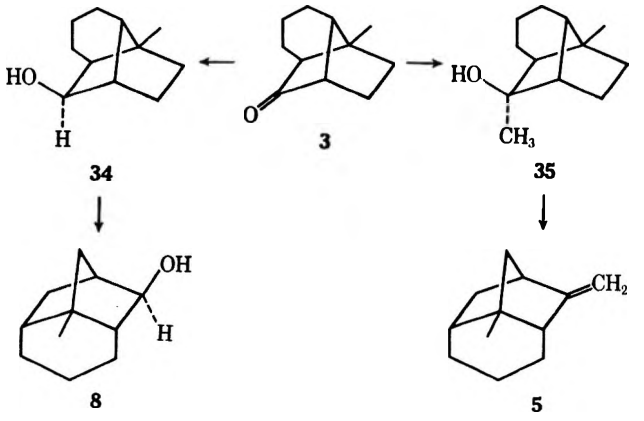
SCHEME IV



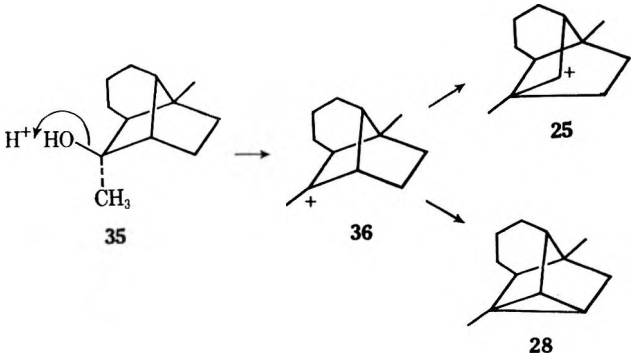
sufficiently protonated by sulfuric acid at this concentration to be drawn into the aqueous phase where rearrangement must occur.[8] Cyclopropane **28** should be even less soluble in the aqueous phase than olefins **32** and **33**. If this substance is an intermediate in the rearrangement of alcohols **1** and **4**, it must undergo protolysis before it can be extracted into the organic phase, which seems unlikely. On the basis of this argument, we favor the mechanistic scheme outlined in Scheme III. A final decision on this point must await the results of experiments with deuterium-labeled compounds.



Alcohols **34** and **35**, produced by treatment of tricyclic ketones **3**[2] with sodium borohydride or methyllithium, respectively, were also submitted to the pentane–50% aqueous sulfuric conditions. Secondary alcohol **34** gives alcohol **8** as the sole product in an isolated yield of 54%. Tertiary alcohol **35** gives olefin **5** in 75% yield.



In the case of secondary alcohol **34**, ionization of the protonated species leads to cation **25**, which can further react as in Scheme III. In the case of tertiary alcohol **35**, ionization leads to tertiary cation **36**, which must either undergo Wagner–Meerwein rearrangement to secondary cation **25** (Scheme III, R = CH_3) or suffer deprotonation to yield cyclopropane **28** (Scheme IV, R = CH_3). For the reasons advanced above, we favor the former pathway.



(8) More vigorous treatment of this mixture (pentane–70% aqueous sulfuric acid) leads to a complex mixture consisting mostly of polymeric products.

Experimental Section

Melting points (Pyrex capillary) and boiling points are uncorrected. Infared spectra (ir) were recorded on Perkin-Elmer 137 and 237 spectrophotometers. Proton magnetic resonance spectra (pmr) were recorded on Varian A-60 and T-60 spectrometers. Line positions are given in the δ scale, with internal tetramethylsilane as standard. The multiplicity, peak areas, coupling constants, and proton assignments are given in parentheses. Ultraviolet spectra (uv) were measured on a Perkin-Elmer 202 spectrophotometer. Consolidated 21-103C and Varian M-66 mass spectrometers provided the mass spectra. High-resolution molecular weight determinations were obtained on a Consolidated 21-110 spectrometer.

Gas–liquid partition chromatography (glpc) analyses were performed on Aerograph Models 204B, A90-P, and A90-P3 instruments. Silica gel G was used for thin layer chromatography (tlc) and silica gel PF_{254} for preparative tlc. Unless otherwise stated, the supports for column chromatography were Mallinckrodt 100–200 mesh SilicAR CC-7 and Woelm neutral alumina. Elemental analyses were performed by the Microanalytical Laboratory, operated by the Department of Chemistry, University of California, Berkeley, Calif.

2-Methylene-8-methyltricyclo[5.2.1.$0^{3,8}$]decane (5).—To a solution of 13.6 g of alcohol **1**[1] in 660 ml of olefin-free pentane was added 330 ml of 50% sulfuric acid. The flask was stoppered and stirred at room temperature for 18.5 hr. The pentane layer was separated, washed with water, and dried over magnesium sulfate. The solvent was removed by rotary evaporation to afford 11.43 g of a pale yellow liquid with a highly camphoraceous odor. The crude material was distilled at reduced pressure to yield 9.27 g (76%) of a water-white liquid, bp 42–43° (1.0 mm). The analytical sample was obtained by preparative glpc (5 ft × 0.25 in. Carbowax 20M at 120°, He flow = 50 cc/min): ir (CCl_4) 3067, 2933, 1664, 1460, 1372, 881 cm^{-1}; pmr (CCl_4) δ 1.08 (s, 3, angular Me), 4.50 (d, 1, J = 2.5 Hz, olefinic H), 4.78 (d, 1, J = 2.5 Hz, olefinic H).

Anal. Calcd for $C_{12}H_{18}$: C, 88.82; H, 11.28. Found: C, 88.99; H, 11.09.

***exo*-2-Hydroxy-*endo*-2-hydroxymethyl-8-methyltricyclo[5.2.-1.$0^{3,8}$]decane (6).**—To a solution of 3.0 g of osmium tetroxide in 70 ml of benzene containing 3 ml of pyridine was added 1.94 g of olefin **5**. The black solution was stirred at room temperature for 43 hr and concentrated to a viscous oil on a rotary evaporator. The oil was dissolved in 250 ml of water containing 6.0 g of potassium hydroxide and 6.0 g of mannitol. The resulting solution was stirred at room temperature for 5 hr and extracted with methylene chloride (two 100-ml portions). The extracts were washed with 50 ml of water and 200 ml of 5% hydrochloric acid and dried over anhydrous magnesium sulfate. The dried solution was evaporated to afford a dirty-white semisolid which crystallized upon addition of pentane. The crystals were filtered, washed with pentane, and air-dried. There was obtained 1.121 g of diol **6**, mp 148.5–149.5°. The analytical sample, mp 163.5–164.0°, was obtained by recrystallization from acetone–pentane: ir (KBr) 3400, 1145, 1060, 1050, 1025, 1000, 980, 960, 890 cm^{-1}; pmr ($CHCl_3$ containing 10% pyridine) δ 0.83

(s, 3, bridgehead Me), 3.82 (d, 1, J = 10 Hz), 3.45 (d, 1, J = 10 Hz).

Anal. Calcd for $C_{12}H_{20}O_2$: C, 73.43; H, 10.27. Found: C, 73.50; H, 10.17.

8-Methyltricyclo[5.2.1.0^{3,8}]decan-2-one (7). A. From Diol 6.—To a solution of 1.121 g of diol 6 in 25 ml of methanol was added a solution of 3.2 g of periodic acid in 50 ml of water. The reaction mixture was stirred for 21.5 hr at room temperature and extracted with ether (100 ml, two 50-ml portions). The ether extracts were washed with water, dried over magnesium sulfate, and evaporated at reduced pressure to yield 0.930 g (99%) of ketone 7 as a waxy solid. Sublimation of 109 mg of the crude ketone at 40° (2.0 mm) gave 100 mg of the ketone as waxy prisms, mp 151–152°. The analytical sample obtained by preparative glpc (5 ft × 0.25 in. NPGS at 180°) melts at 161.0–162.5°: ir (CCl_4) 1750, 1458, 992, 974 cm^{-1}; pmr (CCl_4) δ 1.17 (s, 3, bridgehead Me), 2.40 (broad s, 1, bridgehead H).

Anal. Calcd for $C_{11}H_{16}O$: C, 80.44; H, 9.82. Found: C, 80.24; H, 9.78.

The 2,4-dinitrophenylhydrazone melts at 165–167° after three recrystallizations from 95% ethanol.[9]

Anal. Calcd for $C_{17}H_{20}N_4O_4$: C, 59.27; H, 5.86; N, 16.28. Found: C, 59.44; H, 5.81; N, 16.40.

B. From Olefin 5.—A solution of 5.472 g of olefin 5 in 55 ml of methylene chloride containing 1.65 ml of pyridine[10] was ozonized (Welsbach Ozonator, air pressure = 8 psi, flow rate = 0.01, voltage = 82 V) for 7.5 hr at −78°. The reaction mixture was warmed to room temperature, washed with 10% hydrochloric acid (55 ml) and water (50 ml), and dried over magnesium sulfate. The solvent was removed by rotary evaporation to yield 6.229 g of viscous liquid. Glpc analysis of the crude product (6 ft × 0.25 in. 10% FFAP at 180°, He flow = 40 cc/min) showed the product to consist of a 90:10 mixture of ketone 7 and olefin 5.

C. From Alcohol 8.—To a solution 181.6 mg of tricyclic alcohol 8 in 3 ml of ether was added, dropwise over a period of 15 min, 0.8 ml of chromic acid solution.[11] The reaction mixture was stirred at room temperature for 0.5 hr and the ether layer separated. The aqueous layer was extracted with ether (two 5-ml portions). The combined ether layers were washed with saturated sodium bicarbonate and water and dried over magnesium sulfate. The ether was removed at reduced pressure to yield 156.2 mg (87%) of tricyclic ketone 7, whose spectral properties were identical with a sample prepared from olefin 5.

8-Methyltricyclo[5.2.1.0^{3,8}]decan-*exo*-2-ol (8).—To a solution of 960 mg of tricyclic alcohol 4[1] in 50 ml of olefin-free pentane was added 25 ml of 50% sulfuric acid. The flask was stoppered and stirred at room temperature for 20 hr. The pentane layer was separated, washed with water, and dried over magnesium sulfate. The solvent was removed at reduced pressure to afford 633.2 mg (66%) of crude alcohol 8 as a yellow solid. The crude alcohol was sublimed at 40° (0.2 mm) to afford 450.8 mg of a clear crystalline solid, mp 135–138°, having a camphorous odor: ir (CCl_4) 3610, 1456, 1376, 1053, 1026, 1001 cm^{-1}; pmr ($CDCl_3$) δ 1.06 (s, 3, bridgehead Me), 3.06 (s, 1, hydroxyl H, chemical shift concentration dependent), 3.58 (broad s, 1, $W_{h/2}$ = 4.5 Hz, C-2 H).

Anal. Calcd for $C_{11}H_{16}O$: C, 79.46; H, 10.91. Found: C, 79.21; H, 10.98.

4α-Hydroxy-3aβ-methyl-7aβ-octahydroinden-2α-oic Acid Lactone (9).—To a solution containing 930 mg of ketone 7, 5 ml of glacial acetic acid, and 333 mg of sodium acetate was added 1.85 ml of 40% peracetic acid.[12] The reaction mixture was stirred at room temperature for 5 days, diluted with water, and extracted with ether. The ether extracts were dried over magnesium sulfate and the solvent was removed on a rotary evaporator leaving 889 mg (87%) of lactone 9 as a white crystalline mass. The analytical sample was obtained by recrystallization from pentane as white needles: mp 135–136°; ir (CCl_4) 1745, 1724, 1370, 1239, 1050, 1022 cm^{-1}; pmr (CCl_4) δ 1.12 (s, 3, angular Me), 2.68 (broad m, 1, C-2 H).

Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C, 72.97; H, 9.10.

4α-Hydroxy-3aβ-methyl-7aβ-octahydroinden-2α-oic Acid (10).—A solution of 350 mg (8.70 mmol) of sodium hydroxide in 15 ml of water was added with stirring to 783.7 mg (4.35 mmol) of lactone 9. The stirred mixture was gently heated overnight, during which time the lactone dissolved. The reaction mixture was cooled on an ice bath and acidified until all the hydroxy acid 10 had precipitated. The mixture was extracted with ether (three 20-ml portions) and the ether extracts were dried over magnesium sulfate. The solvent was removed by rotary evaporation to yield 721.5 mg (84%) of white crystalline hydroxy acid 10. The analytical sample was obtained after recrystallization from benzene: mp 115.0–115.5°; ir (KBr) 3472, 1712, 1447, 1394, 1370, 1237, 1208, 1183, 1031, 1010, 950 cm^{-1}; pmr (CS_2) δ 1.30 (s, 3, angular Me), 2.58 (broad m, 1, C-2 H), 4.06 (m, 1, C-4 H).

Anal. Calcd for $C_{11}H_{18}O_3$: C, 66.64; H, 9.15. Found: C, 66.39; H, 9.03.

3aβ-Methyl-4-oxo-7aβ-octahydroinden-2α-oic Acid (11).—A solution of 608.5 mg of hydroxy acid 10 in 15 ml of acetone was cooled to 0° in an ice bath. Jones reagent[13] was added dropwise, with stirring, until the solution turned brown. The solution was stirred an additional 15 min, diluted to twice its volume with water, and extracted with ether (four 25-ml portions). The combined ether extracts were washed with 25 ml of water and dried over magnesium sulfate. The ether was removed by rotary evaporation to yield 560.2 mg (93%) of keto acid 11 as an oil. Crystallization was attempted in a number of solvent systems, but to no avail: ir (CCl_4) 1755, 1716, 1463, 1422, 1379, 1241, 1052, 1029 cm^{-1}; pmr (CCl_4) δ 1.18 (s, 3, angular Me), 9.44 (s, 1, acidic H).

A solution of 38.2 mg of keto acid 11, 15.7 mg of sodium metal, and 4 ml of deuterium oxide (Bio-Rad Laboratories, 99.88 mol %) was stirred overnight under gentle reflux. The solution was cooled in an ice bath and acidified to pH 3 with concentrated sulfuric acid. The solution was extracted with ether and the ether extracts were washed with water. The ether extracts were dried over magnesium sulfate and evaporated at reduced pressure to yield 29.3 mg of the deuterated keto acid. The deuterated keto acid was subjected to low-resolution mass spectral analysis for deuterium incorporation. The parent peak was measured at m/e 198 as compared to m/e 196 for the undeuterated keto acid 11, indicating the incorporation of two deuterium atoms per molecule.

Methyl 3aβ-Methyl-4-oxo-7aβ-octahydroinden-2α-oate (12).—To a cooled solution of 356.7 mg of keto acid 11 in ether was slowly added an ethereal solution of diazomethane prepared from nitrisomethylurea.[14] The diazomethane solution was added until the yellow color of diazomethane persisted for at least 15 min. The yellow solution was gently heated on a steam bath until the solution turned colorless. The ether was removed by rotary evaporation to afford 363 mg (95%) of crude keto ester 12. The analytical sample was obtained by preparative glpc (6 ft × 0.25 in. SE-30 at 190°, He flow = 40 cc/min): ir (CCl_4) 1739, 1709, 1429, 1370, 1183, 1172, 1119, 1020 cm^{-1}; pmr (CCl_4) δ 1.12 (s, 3, angular Me), 3.62 (s, 3, ester Me).

Anal. Calcd for $C_{12}H_{18}O_3$: C, 68.55; H, 8.63. Found: C, 68.82; H, 8.85.

A solution of 44.6 mg of keto ester 12, 10 mg of sodium metal, and 4 ml of deuteriomethanol (Stohler Isotope Chemicals, 99% D) was refluxed overnight with stirring. Excess deuteriomethanol was removed by rotary evaporation. The residue was dissolved in ether, washed with 10% hydrochloric acid and water, and dried over magnesium sulfate. The ether was removed by rotary evaporation to yield 36.5 mg of deuterated keto ester. The deuterated material was subjected to low-resolution mass spectral analysis for deuterium content, which showed the presence of 10.6% $C_{12}H_{17}DO$, 34.6% $C_{12}H_{16}D_2O$, and 54.8% $C_{12}H_{15}D_3O$.

3aβ-Methyl-7aβ-octahydroinden-2ξ-oic Acid (13).—A mixture of 4.0 g of mossy zinc, 0.4 g of mercuric chloride, 0.2 ml of concentrated hydrochloric acid, and 6 ml of water was stirred for 5 min. The aqueous solution was decanted and the zinc amalgam added to 950 mg of keto acid 11. The mixture was covered with 3 ml of water and 4 ml of concentrated hydrochloric acid and refluxed for 28 hr. After refluxing had proceeded for 20 hr,

(9) R. I. Shriner, R. C. Fuson, and D. Y. Curtin, "The Systematic Identification of Organic Compounds," Wiley, New York, N. Y., 1956.

(10) See J. Krepinsky, Z. Samek, and F. Sorm, *Tetrahedron, Suppl.*, **8**, 53 (1966).

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

(12) R. R. Sauers and G. P. Ahearn, *ibid.*, **83**, 2759 (1961).

(13) A. Bowers, T. G. Halsall, E. R. H. Jones, and A. J. Lemin, *J. Chem. Soc.*, 2548 (1953).

(14) F. Arndt, "Organic Syntheses," Collect. Vol. II, Wiley, New York, N. Y., 1943, p 165

an additional 2 ml of concentrated hydrochloric acid was added to the reaction mixture.[15] At the completion of the reflux period, the mixture was diluted with water and extracted with ether. The ether extracts were dried over magnesium sulfate and evaporated at reduced pressure to yield 819 mg of crude carboxylic acid **13** as an oil: ir (CCl_4) series of weak bands from 3636 to 2481, 1701, 1456, 1446, 1410, 1370, 1287, 1232, 1224 cm^{-1}; pmr (CCl_4) δ 1.01 (s, 3, angular Me), 11.00 (broad s, 1, acidic H).

Methyl 3aβ-Methyl-7aβ-octahydroinden-2ξ-oate (14).—An ethereal solution of diazomethane[14] was carefully added to a solution of 819 mg of crude carboxylic acid **13** in 25 ml of ether until the yellow color of diazomethane persisted for 15 min. The ether was removed by rotary evaporation to afford 852 mg of crude methyl ester **14** as a mixture of epimers. The two epimers could be separated by glpc (6 ft × 0.25 in. 10% FFAP at 125°, He flow = 40 cc/min) showing an 80:20 mixture. An analytical sample of the major epimer was obtained by preparative glpc: ir (CCl_4) 1735, 1456, 1429, 1373, 1353, 1200, 1170 cm^{-1}; pmr (CCl_4) δ 0.98 (s, 3, angular Me), 3.57 (s, 3, ester Me). The ir of the minor epimer was almost identical with that of the major epimer.

Anal. Calcd for $C_{12}H_{20}O_2$: mol wt, 196.1462. Found: mol wt, 196.1457 (by high-resolution mass spectroscopy).

2ξ-Acetyl-3aβ-methyl-7aβ-octahydroindene (16).—To a solution of 420 mg of 85% potassium hydroxide in 5 ml of water was added 658 mg of methyl ester **14**. The mixture was refluxed for 1 hr, cooled to room temperature, acidified with 10% hydrochloric acid, and extracted with ether (two 20-ml portions). The ether extracts were dried over magnesium sulfate and evaporated at reduced pressure to yield 565.2 mg of crude carboxylic acid **13**. Thionyl chloride (0.45 ml) was added to the crude acid in one portion. The mixture was refluxed for 2 hr and cooled to room temperature, and excess thionyl chloride was removed at reduced pressure.

A dimethylcadmium solution was prepared[16] by adding 0.6 g of anhydrous cadmium chloride to a solution containing 2.1 ml of methylmagnesium bromide (3 *M* ethereal solution) and 10 ml of ether at 0°. The solution was stirred and refluxed for 1 hr. The crude acid chloride **15**, dissolved in 20 ml of benzene, was added to the dimethylcadmium solution and the reaction mixture was refluxed for 2 hr with stirring. The reaction mixture was cooled to room temperature, acidified with excess cold dilute hydrochloric acid, and extracted with two portions of ether. The ether extracts were washed with 5% sodium bicarbonate, dried over magnesium sulfate, and evaporated at reduced pressure to afford 473.3 mg of crude ketone **16** as a dark oil. The crude ketone was chromatographed on 15 g of silica gel (20:1 petroleum ether–ether) to give 297 mg (77%) of pure ketone **16** as a clear oil. Glpc (6 ft × 0.25 in. 10% FFAP at 150°) showed the product to be a mixture of epimers in a ratio of 60:40. An analytical sample of the major epimer was obtained by preparative glpc: ir (CCl_4) 1715, 1463, 1445, 1372, 1355, 1174 cm^{-1}; pmr (CCl_4) δ 0.98 (s, 3, angular methyl), 2.03 (s, 3, acetyl Me).

Anal. Calcd for $C_{12}H_{20}O$: mol wt, 180.1513. Found: mol wt, 180.1519.

3aβ-Methyl-7aβ-octahydroinden-2ξ-ol Acetate (17).—A solution of 357 mg (1.75 mmol) of 85% *m*-chloroperbenzoic acid in 4 ml of anhydrous cloroform was added to 283.2 mg (1.57 mmol) of methyl ketone **16**. The reaction mixture was stirred in the dark at room temperature for 11 days and washed with saturated sodium bicarbonate (two 5-ml portions) and 10 ml of water. The combined aqueous washings were extracted with 20 ml of ether, and the combined organic layers were dried over magnesium sulfate. The solvents were removed by rotary evaporation to give 265.4 mg (89%) of crude acetate **17**. The pmr spectrum (CCl_4) of the crude acetate indicates it to be a 70:30 mixture of epimers.

3aβ-Methyl-7aβ-octahydroinden-2ξ-ol (18).—A solution of 265 mg of crude acetate **17** in 30 ml of anhydrous ether was added to a solution of 517 mg of lithium aluminum hydride in 20 ml of anhydrous ether. The mixture was stirred at room temperature for 22.5 hr and quenched by the dropwise addition of 3 ml of 10% potassium hydroxide. After stirring for 5 min, the solid was filtered and washed with ether. The combined ethereal solutions were dried over magnesium sulfate and evaporated at reduced pressure to yield 189.4 mg (91%) of the crude alcohol **18** as a yellowish oil. The pmr spectrum ($CDCl_3$) of the crude product indicates it to be a 70:30 mixture of epimeric alcohols.

3aβ-Methyl-7aβ-hexahydroinden-2(1*H*)-one (19).—To a solution of 180 mg of the crude alcohol **18** in 3 ml of ether was added 0.75 ml of chromic acid solution[11] over a period of 15 min. The reaction flask was fitted with a condenser and stirred at room temperature for 2.25 hr. The ether layer was separated and the aqueous layer extracted with ether (two 5-ml portions). The combined ether layers were washed with saturated sodium bicarbonate and water and dried over magnesium sulfate. Evaporation of the ether afforded 131.3 mg of crude ketone **19** as a yellowish oil. An analytical sample was obtained by preparative glpc (6 ft × 0.25 in. 10% FFAP at 150°, He flow = 40 cc/min): ir (CCl_4) 1745, 1443, 1401, 1373, 1252, 1202 cm^{-1}; pmr (CCl_4) δ 1.13 (s, 3, angular Me), 1.47 (broad s, 8, cyclohexyl methylenes). Ir (CS_2) was identical that of with a sample prepared by catalytic reduction of 7a-methyl-4,5,6,7-tetrahydroinden-2-(1*H*)-one.[6]

Anal. Calcd for $C_{10}H_{16}O$: mol wt, 152.1201. Found: mol wt, 152.1201 (by high-resolution mass spectroscopy).

The 2,4-dinitrophenylhydrazone melts at 143–144° (corrected) after two recrystallizations from methanol.

The deuterated hydrindanone was obtained by preparative glpc (6 ft × 0.25 in. 10% KOD, 20% Carbowax 20M on Chromosorb W 60–80 at 150°).[4] The procedure consisted of injecting 10 μl of ketone **19** on the column which had been equilibrated with 100 μl of deuterium oxide and collecting the effluent. The collected sample was subjected to mass spectral analysis which showed the presence of 6.1% $C_{10}H_{16}DO$, 20.4% $C_{10}H_{14}D_2O$, 40.6% $C_{10}H_{13}D_3O$, and 32.9% $C_{10}H_{12}D_4O$.

8-Methyltricyclo[5.2.1.0^{3,8}]decan-*endo*-2-ol (20).—A solution of 168.2 mg of tricyclic ketone **7** in 5 ml of anhydrous ether was added, dropwise, to a stirred refluxing suspension of 116 mg of lithium aluminum hydride in 10 ml of anhydrous ether. The reaction mixture was refluxed for 13 hr and excess lithium aluminum hydride decomposed with 10% hydrochloric acid. The ethereal solution was separated, dried over magnesium sulfate, and evaporated at reduced pressure to afford 147.1 mg (86.5%) of crude tricyclic alcohol **20** as a crystalline white solid having a highly camphorous odor. The crude alcohol was sublimed at 40° (0.4 mm) to afford 103 mg of white crystalline solid: mp 146° (sublimes); ir (CCl_4) 3665, 1456, 1376, 1140 1055 cm^{-1}; pmr (CCl_4) δ 1.00 (s, 3, bridgehead Me), 4.16 (d of d, 1, $J_{2,3}$ = 9, $J_{1,2}$ = 5 Hz, C-2 H).

Anal. Calcd for $C_{11}H_{18}O$: C, 79.46; H, 10.91. Found: C, 79.53; H, 10.89.

1-Methyltricyclo[4.4.0.0^{2,8}]decan-*exo*-7-ol (34).—A solution of 239.4 mg of tricyclic ketone **3**[2] in 10 ml of anhydrous ether was added, dropwise, to a refluxing mixture of 175 mg of lithium aluminum hydride and 20 ml of anhydrous ether. The mixture was gently refluxed for 17 hr and cooled to room temperature, and excess lithium aluminum hydride decomposed with 5% aqueous potassium hydroxide. The resulting white precipitate was filtered and washed with ether. The filtrate was dried over magnesium sulfate and evaporated at reduced pressure to yield 194.6 mg (80%) of crude alcohol **34** as a white solid. A portion of the crude product was sublimed at 40° (1.0 mm) to afford white crystals: mp 106–110° (sublimes); ir (CCl_4) 3660, 1471, 1445, 1377, 1130, 1041 cm^{-1}; pmr ($CDCl_3$) δ 1.07 (s, 3, bridgehead Me), 3.86 (d, 1, J = 6 Hz, C-7 H).

Anal. Calcd for $C_{11}H_{18}O$: C, 79.46; H, 10.91. Found: C, 79.48; H, 11.19.

1,7-Dimethyltricyclo[4.4.0.0^{2,8}]decan-*exo*-7-ol (35).—A solution of 82 mg of tricyclic ketone **3** in 5 ml of anhydrous ether was added to 20 ml of a 5.07% solution of methyllithium in ether. The reaction mixture was refluxed for 2 days under nitrogen and stirred an additional day at room temperature. The mixture was quenched with water and the ether layer separated. The aqueous layer was extracted with ether, and the combined ether layers were washed with brine and dried over magnesium sulfate. The solvent was removed by evaporation to afford 92.6 mg (100%) of methyl carbinol **35** as a crystalline solid. The analytical sample was prepared by sublimation at reduced pressure: mp 57–58°; ir (CCl_4) 3660, 1449, 1376, 1140, 1087, 1047, 924 cm^{-1}; pmr (CCl_4) δ 1.07 (s, 3, bridgehead Me), 1.23 (s, 3, C-7 Me).

Anal. Calcd for $C_{12}H_{20}O$: C, 79.94; H, 11.18. Found: C, 79.32; H, 11.25.

(15) F. E. King, *J. Chem. Soc.*, 982 (1935).

(16) J. A. Berson, A. W. MeRowe, R. G. Bergman, and D. Houston, *J. Amer. Chem. Soc.*, **89**, 2563 (1967).

Acid-Catalyzed Rearrangement of Tricyclic Alcohol 34.—To a solution of 194 mg of tricyclic alcohol **34** in 10 ml of spectroquality pentane was added 5 ml of a 50% aqueous sulfuric acid solution. The two phase system was stirred for 14 hr at room temperature. The pentane layer was separated from the aqueous layer, washed with water, and dried over magnesium sulfate. The pentane was removed by evaporation to afford 113.8 mg of tricyclic alcohol **8** as a white solid (53.6% yield). The spectral properties were identical with those of alcohol **8** prepared by rearrangement of alcohol **4**.

Acid-Catalyzed Rearrangement of Tricyclic Carbinol 35.—To a solution of 72.6 mg of tricyclic carbinol **35** in 3 ml of spectroquality pentane was added 1.5 ml of 50% aqueous sulfuric acid. The two-phase system was stirred at room temperature for 18 hr. The pentane layer was separated and washed with water. The combined aqueous layers were extracted with ether, and ether extracts were washed with water. The combined organic extracts were dried over magnesium sulfate and evaporated at reduced pressure to give 48.9 mg (75%) of a clear liquid having a camphorous odor. The spectral properties of this material were identical with those of tricyclic hydrocarbon **5** prepared from compound **1**.

3,6-Dimethyltricyclo[4.4.0.0^{2,7}]dec-3-ene (32) and 3-Methylene-6-methyltricyclo[4.4.0.0^{2,7}]decane (33).—To a solution of 180 mg of alcohol **1** in 1 ml of pyridine was added 0.25 ml of phosphorus oxychloride. The solution was slowly warmed to 90° and then allowed to cool to room temperature. The partially crystalline mixture was mixed with 25 ml of ice water and extracted with ether (three 30-ml portions). The combined ether extracts were washed with 5% HCl (50 ml), 10% K_2CO_3 (10 ml), and saturated NaCl (50 ml). After drying over $MgSO_4$, the ether was evaporated under reduced pressure to yield 135.5 mg of colorless liquid. Glpc analysis (10% NPGS, 135°) showed the product to be a mixture of **32** and **33** in a ratio of 80:20. The major product (endocyclic double bond isomer **32**) had the following spectral properties: ir (CCl_4) 3050, 3025, 2930, 2830, 1480, 1450, 1385, 1370, 1270, 1225, 1190, 1040, 982, 960, 940, 880, 860 cm^{-1}; pmr (CCl_4) δ 0.92 (s, 3, angular Me), 5.17 (m, 1, vinyl H). The minor product (exocyclic double bond isomer) had the following spectral properties: ir (CCl_4) 3030, 1680, 1500, 1480, 1470, 1465, 1400, 883 cm^{-1}; pmr (CCl_4) δ 0.87 (s, 3, angular Me), 2.60 (s, 1, C-2 H), 2.45 (broad t, 2, C-4 H's), 4.52 (q, 2, vinyl H's).

A solution of 199 mg of the olefin mixture, prepared as above, in 10 ml of pentane was layered over 5 ml of 50% aqueous sulfuric acid. After stirring vigorously for 16 hr, the pentane layer was decanted, dried, and evaporated to yield 181 mg of clear oil. Analysis by glpc and pmr showed that no reaction had occurred.

Registry No.—**5**, 32980-12-4 **6**, 32970-82-4; **7**, 32980-13-5; **7** 2,4-DNP, 32980-14-6; **8**, 32970-83-5; **9**, 32970-84-6; **10**, 32970-85-7; **11**, 32970-86-8; **12**, 32970-87-9; **13**, 32970-81-3; **13** epimer, 32970-88-0; **14**, 32970-89-1; **14** epimer, 32970-90-4; **16**, 32970-91-5; **16** epimer, 33020-76-7; **19**, 13351-29-6; **19** 2,4-DNP, 32970-93-7; **20**, 32970-94-8; **32**, 33015-39-3; **33**, 33015-40-6; **34**, 33020-77-8; **35**, 33020-78-9.

Acknowledgment.—We thank the National Science Foundation and the Alfred P. Sloan Foundation for financial support.

Synthesis and Chemistry of Some 2-Substituted Tricyclo[3.3.0.0^{3,7}]octane Derivatives[1]

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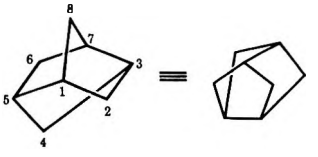
Received July 22, 1971

A survey of the chemistry of 2-substituted tricyclo[3.3.0.0^{3,7}]octyl derivatives was initiated. Experiments were conducted which produced the following reactive intermediates at the 2 position: free radicals, carbanions, and carbonium ions. It was found that those reactions which involved formation of cationic intermediates yielded rearranged products *via* a formal ring contraction of a five- to a four-membered ring. Analysis of solvolysis data of the 2-brosylate suggests that this rearrangement proceeds with a rate enhancement of the order of *ca.* 10^8.

Exploitation of the unique properties of strained molecules has provided physical organic chemists with significant insights into the mechanistic details of organic transformations. In addition, there has been a special fascination with the synthesis and behavior of molecules which possess a high degree of symmetry: *e.g.*, tetrahedrane, cubane, adamantane. These three molecules are notable in that the smallest rings in each system are all of the same size, three-, four-, and six-membered, respectively. We have for some time been interested in the most symmetrical all five-membered ring homolog: tricyclo[3.3.0.0^{3,7}]octane (**1**).[2-4] In this report we wish to detail the synthesis of several derivatives of **1** and to report the results of a survey of some of the chemistry of this system.



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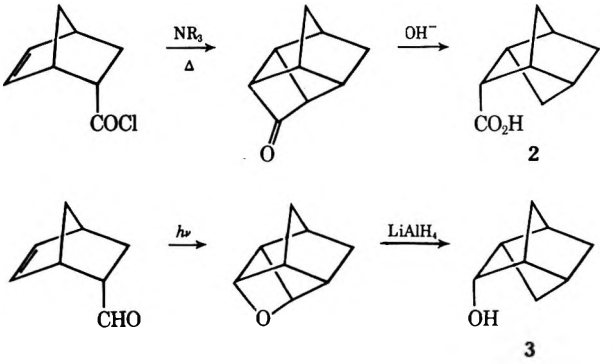
The key intermediates used in this study were the acid **2** and the alcohol **3**. The detailed procedure for



(1) Presented in part at the 158th National Meeting of the American Chemical Society, New York, N. Y., Sept 1969, Abstracts, ORGN 74; see also R. R. Sauers and B. R. Sickles, *Tetrahedron Lett.*, 1067 (1970).

(2) (a) R. R. Sauers, W. Schinski, and M. M. Mason, *ibid.*, 79 (1969); (b) R. R. Sauers and K. W. Kelly, *J. Org. Chem.*, **35**, 3286 (1970).

(3) For other syntheses of this ring system see (a) O. W. Webster and L. H. Sommer, *ibid.*, **29**, 3103 (1964); (b) P. K. Freeman, V. N. M. Rao, and G. E. Bigam, *Chem. Commun.*, 511 (1965); (c) B. R. Vogt, S. R. Suter, and J. R. E. Hoover, *Tetrahedron Lett.*, 1609 (1968).

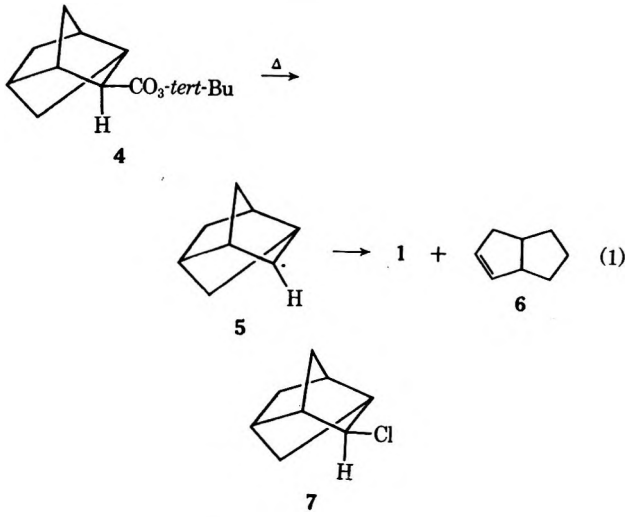
(4) This molecule may be regarded as a bis nor homo log of adamantane or twistane depending on whether the methylenes are inserted at the zero-carbon bridges or at the appropriate methylene sites, respectively. The symmetry of this molecule (D_{2d}) precludes both structural isomerism and optical activity in monosubstituted derivatives.

the preparation of 2 has been published[2b] and the details for the preparation of 3[2a] may be found in the Experimental Section.

Results and Discussion

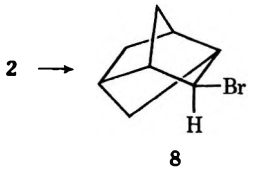
The survey of the chemistry of 1 was designed to include some representative reactions from three major categories: free radical reactions, reactions involving carbanionic intermediates, and solvolyses and other carbonium ion reactions. It was felt that the results of these studies would provide a reasonable overview of the behavior of this system.

Radical Reactions.—Our interest in exploring this area was stimulated by two previous reports dealing with the behavior of the 2-tricyclo[3.3.0.0^{3,7}]octyl radical. In our earlier study[2b] it was shown that 5 underwent cleavage in competition with chain transfer (eq 1). On the other hand, it was reported that chlorination of 1 gave chloride 7 exclusively.[5] It was of interest to



examine more fully the dependency of product distribution on reaction conditions and the nature of the termination step.

The first and simplest results were obtained on treatment of acid 2 with lead tetraacetate and lithium bromide.[6] There was obtained a 29% yield of a bromide whose spectral properties [nmr δ 4.11 (t)] and elemental analysis were compatible with those expected for 8.



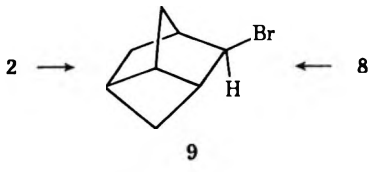
In addition, this substance could be converted to 1 by reduction (*vide infra*). The analogous reaction with lithium chloride proved to be considerably more complex in that a mixture of at least six products was obtained,[7] including a 36% yield of unrearranged chloride 7. The yield of 7 was doubled if a molar excess of lithium chloride was used.

(5) P. K. Freeman, R. B. Kinnel, and T. D. Ziebarth, *Tetrahedron Lett.*, 1059 (1970).

(6) J. K. Kochi, *J. Org. Chem.*, **30**, 3265 (1965).

(7) In addition to 7, the following components were identified: 2-acetoxytricyclo[3.2.1.0^{2,6}]octane (40%), 2-chlorotricyclo[3.2.1.0^{2,6}]octane (6%), and 2-acetoxytricyclo[3.3.0.0^{2,7}]octane (6%).

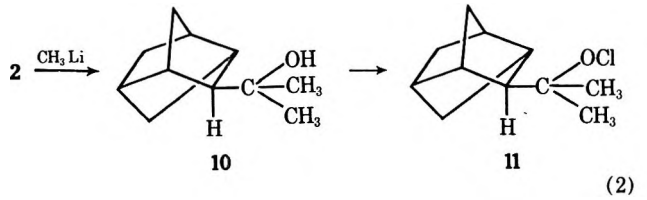
Attempts to prepare 8 by either the conventional Hunsdiecker procedure or the Cristol–Firth modification[8] led to the formation of the bromide 9. In both



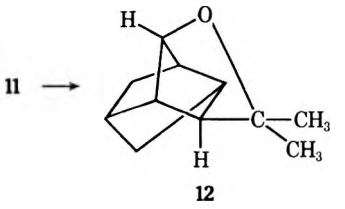
cases, it is likely that the ultimate product was formed from 8 *via* metal ion catalyzed rearrangements.

The feasibility of this sequence was demonstrated in the second case in that it was found that 8 could be transformed into 9 on treatment with mercuric oxide–mercuric bromide under the reaction conditions. Rearrangements during Hunsdiecker reactions are rare[9] and are unprecedented in Cristol–Firth reactions.

The last radical reaction studied was the decomposition of the hypochlorite 11, prepared according to eq 2.



Thermal and photochemical decompositions of hypochlorites are known to produce radicals by intramolecular hydrogen abstractions and/or by homolytic cleavages.[10] In the case at hand, both methods of decomposition gave a complex mixture of products in which only trace amounts of chloride 7 could be detected. An oxygen-containing product was isolated to which structure 12 is assigned on the basis of spectral data



[nmr δ 3.94 (d, J = 2.5 Hz)] and elemental analysis.[11] Thus the intermediate alkoxy radical undergoes preferential intramolecular hydrogen abstraction rather than homolytic cleavage. In this respect this system resembles the behavior of the analogous *endo*-norbornyl derivative (eq 3) and stands in contrast to that of the exo system (eq 4). These differences are best rationalized in terms of the distances between the δ hydrogens and the oxy radicals. It is clear from models that this distance is significantly greater in the *exo*-norbornyl system than in the other two.

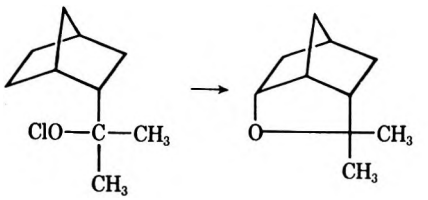
In general, it appears that the tricyclooctyl radical 4 is relatively stable and that ring cleavage is not expected except when the termination step requires significant activation energy. The fact that 4 does

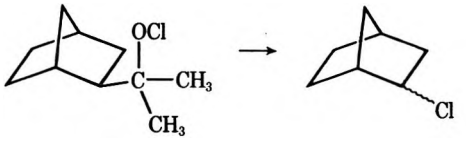
(8) S. J. Cristol and W. C. Firth, *J. Org. Chem.*, **26**, 280 (1961).

(9) W. V. E. Doering and M. Farber *J. Amer. Chem. Soc.*, **71**, 1514 (1949).

(10) F. D. Greene, M. L. Savitz, F. D. Osterholtz, N. H. Lau, W. N. Smith, and P. M. Zanet, *J. Org. Chem.*, **28**, 55 (1963).

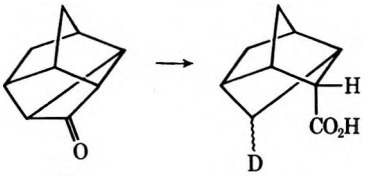
(11) The by-products formed in this reaction are believed to arise from the reaction of unreacted alcohol 10 with the HCl liberated from the cyclization step.


(3)


(4)

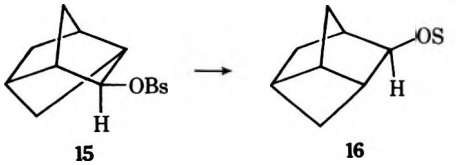
undergo ring opening under relatively mild conditions (*ca.* 125°) is evidence that strain relief provides a significant driving force in this system. The bornyl radical, for example, undergoes relatively minor ring cleavage at temperatures as high as 255°.[12]

Carbanion Reactions.—Carbanions of **1** were generated under two widely differing sets of conditions. The reduction of bromide **8** (*vide supra*) was carried out with metallic sodium in liquid ammonia and produced **1** of greater than 94% purity. The potassium *tert*-butoxide–water–ether cleavage of **13** was repeated in deuterium oxide to establish unequivocally the ultimate source of the carbon-bound hydrogen. The fact that one atom of deuterium was found in the product acid **14** confirms the presence of the postulated carban-

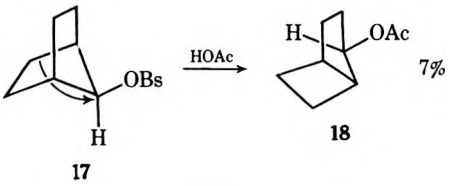

13 **14**

ion intermediate.[13] Although ring opening of carbanions in a fashion analogous to the radical cleavage (eq 1) would be expected to be exothermic, the reaction conditions in the above experiments were relatively mild.[14]

Carbonium Ion Reactions.—There are indications from the results of at least two of the reactions discussed above that rearrangements of the 2-tricyclo[3.3.0.0^{3,7}]-octyl carbonium ion are remarkably facile: the mercuric salt catalyzed rearrangement of **8** and the formation of 2-acetoxytricyclo[3.2.1.0^{3,6}]octane from **2** on treatment with lead tetraacetate.[6,15] In order to examine this rearrangement more systematically, we chose to study the behavior of brosylate **15** under solvolysis conditions. Under either acetolysis or hydrolysis con-


15 **16**

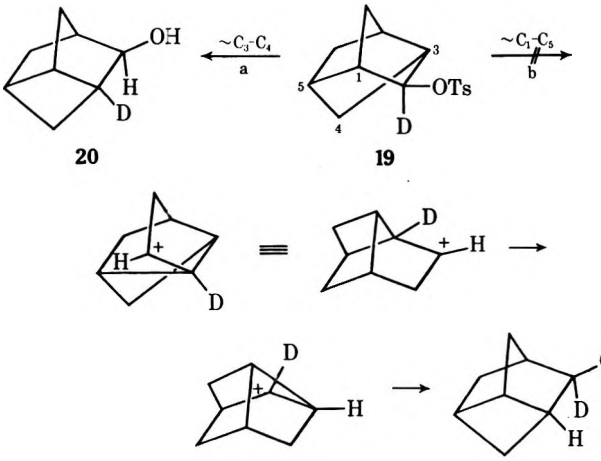
ditions the only detectable products were derivatives of the tricyclo[3.2.1.0^{3,6}]octyl system (**16**).[16] This remarkable rearrangement involves a formal ring contraction of a five- to a four-membered ring and is without precedent. In many respects (see below for details) the behavior of the 7-norbornyl system serves as a useful model for comparative analysis. In this system, kinetic and product studies led to the conclusion that the four-membered ring system **18** is *ca.* 14 kcal/mol less stable than the isomeric system **17**.[17]


7%

17 **18**

Further insight into the mechanism of the rearrangement **15** → **16** was provided by a labeling study and by measurement of the kinetics of acetolysis. The purpose of the labeling experiments was to differentiate between the direct pathway of migration (a) and a two-step sequence (b) which would lead to the same final product. As shown in Scheme I, these two paths lead

Scheme I


20 **19**

to two differently labeled deuterated isomers starting with the deuterated tosylate **19**. The finding that the alcohol isolated from the hydrolysis of **19** had essentially no deuterium at C_2 strongly supports the direct migration pathway and unequivocally eliminates the two-step mechanism.

The kinetic analysis of the acetolysis of **15** was complicated by non-first-order behavior. During the first 28% of the reaction the calculated first-order rate constants drifted downward until a constant value of 1.3×10^{-5} sec^{-1} was attained. This behavior is typical of systems which solvolyze with internal return to form a less reactive substrate, the mathematical analysis having been worked out by Young, Winstein, and Goering.[18] Our results are most consistent with the situation described by Scheme II in which direct solvolysis (**15** → **16**) and internal return (**15** → **21**) are competitive processes. Freeman and coworkers[5] arrived at the

(12) J. A. Berson, C. J. Olsen, and J. S. Walia, *J. Amer. Chem. Soc.*, **84**, 3337 (1962).

(13) P. G. Gassman and F. V. Zalar, *ibid.*, **88**, 2252 (1966); see also P. G. Gassman, J. T. Lumb, and F. V. Zalar, *ibid.*, **89**, 946 (1967).

(14) For discussions and literature analogies see E. A. Hill, R. J. Theissen, and K. Taucher, *J. Org. Chem.*, **34**, 3061 (1969), and P. K. Freeman, V. N. M. Rao, D. E. George, and G. L. Fenwick, *ibid.*, **32**, 3958 (1967).

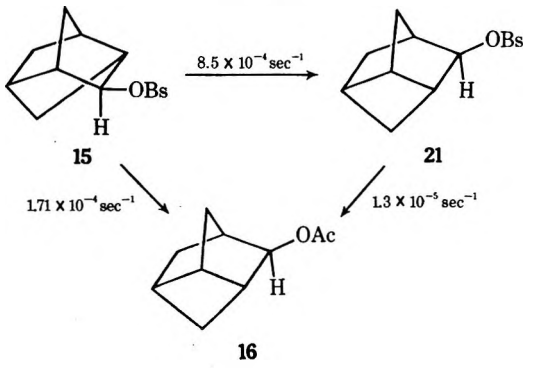
(15) Carbonium ion rearrangements have not generally been observed in these decarboxylations when lithium chloride is present owing to the rapid ligand transfer step. For example, neopentyl chloride can be prepared in high yield from β,β-dimethylbutyric acid.[6]

(16) R. R. Sauers, R. A. Parent, and S. B. Damle, *J. Amer. Chem. Soc.*, **88**, 2257 (1966).

(17) S. Winstein, F. Gadient, E. T. Stafford, and P. E. Klinedinst, Jr., *ibid.*, **80**, 5895 (1958).

(18) W. G. Young, S. Winstein, and H. L. Goering, *ibid.*, **73**, 1958 (1951).

SCHEME II

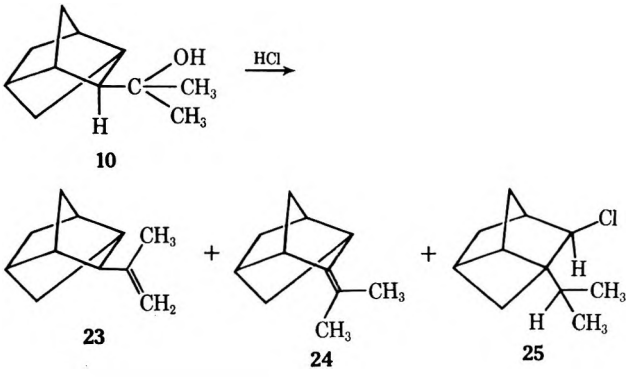


same conclusion on the basis of similar experimental results. The basis for the adoption of Scheme II rests on several additional observations. For one thing, there is good agreement between the calculated rate of disappearance of **21** and that observed: 1.4×10^{-5} sec^{-1} *vs.* 1.3×10^{-5} sec^{-1}.[16] Secondly, it was observed on monitoring the acetolysis by nmr spectroscopy that the rate of disappearance of **15** exceeded the rate of formation of **16** and that a new peak appeared in the region expected for protons bound to a secondary carbon bearing oxygen. It was shown by direct comparison that this peak had the same chemical shift as the CHO proton in **21**.

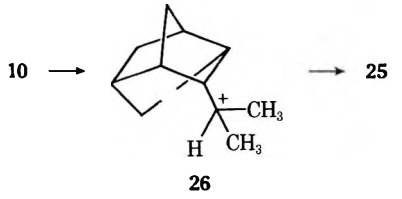
The significance of the rate data can be appreciated by comparison with model systems or by use of empirical correlations.[19] In the absence of steric complications[20] there is a good correlation between solvolysis rates and the stretching frequencies of the carbonyl derivatives located at the same sites in those cases which are believed to ionize without anchimeric assistance. On this basis it is estimated that **15** should solvolyze 10^{-7} times as fast as cyclohexyl brosylate. A rate enhancement of 10^{9} may be calculated from the actual rate ratio at 53°.[21] Alternatively, one can compare rates directly with those from model systems. As mentioned earlier, the 7-norbornyl system appears to be closely related to **15** in view of the correspondence between bond angles in the ground states and at the trigonal centers. For example, the bond angles about C_7 in norbornanes range from 92 to 97°[22] compared with the value of 93° estimated from models for the C_1–C_2–C_3 angle in **15**. The similarity in carbonyl stretching frequencies between 7-ketonorbornane (1773 cm^{-1}) and 2-ketotricyclo[3.3.0.0^{3,7}]octane (**22**) (1771 cm^{-1}) is likewise suggestive of similar geometry at the trigonal centers in these two molecules. This analysis leads to a value of 10^{7} for the rate enhancement factor.[23]

22

In view of the reservations which have arisen concerning the appropriateness of these calculations and analogies,[20,24,25] it was important to provide more compelling data to support the conclusions. It is known that alkyl groups stabilize carbonium ions to a relatively large degree. Factors as large as 10^{8} have been reported for the rate ratios of tertiary/secondary solvolyses,[25] although more typical α-CH_3/H effects are in the range 10^{4}–10^{5}.[26] Substitution of a methyl group for hydrogen in the tricyclo[3.3.0.0^{3,7}]octyl system would thus not be expected to sufficiently stabilize the resulting tertiary carbonium ion to the extent that rearrangement would be inhibited. An indication that this conclusion is indeed correct comes from the results of the reaction of alcohol **10** with hydrochloric acid. Three products were isolated from this reaction: two olefins and a chloride. The two olefins were assigned structures **23** and **24** on the basis of analysis of infrared and nmr spectral data. More importantly, the chloride formed was not the product of direct hydroxyl replacement, since the nmr spectrum displayed a low-field singlet attributable to a CHCl moiety. This finding and the fact that an isopropyl group was also present lead us to propose structure **25** for this substance. This



product could be formed by rearrangement of the tertiary ion **26**, itself the result of hydride shifts and/or



protonation of **24**. While it has not been established whether **25** is formed in a kinetically controlled reaction or not, it should be pointed out that these products were also formed as by-products during the photochemical decomposition of **11** (15 min at −10°, 30 min at 25°). For comparison, the product of kinetic control was isolated under considerably more vigorous

(19) (a) C. S. Foote, *J. Amer. Chem. Soc.*, **86**, 1853 (1964); (b) P. v. R. Schleyer, *ibid.*, **86**, 1854 (1964); (c) J. L. Fry, C. J. Lancelot, L. K. M. Lam, J. M. Harris, R. C. Bingham, D. J. Raber, R. E. Hall, and P. v. R. Schleyer, *ibid.*, **92**, 2538 (1970).

(20) H. C. Brown, W. J. Hammar, J. H. Kawakami, I. Rothberg, and D. L. Vander Jagt, *ibid.*, **89**, 6381 (1967).

(21) The value for cyclohexyl brosylate was taken from data given by H. C. Brown and G. Ham, *ibid.*, **78**, 2735 (1956).

(22) J. F. Chiang, C. F. Wilcox, Jr., and S. H. Bauer, *ibid.*, **90**, 3149 (1968).

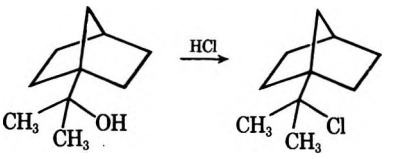
(23) The rate of acetolysis of **17** at 53° (*ca.* 10^{-11} sec^{-1}) was calculated from data given by H. Tanida, S. Ikegarni, and N. Ishitobi, *ibid.*, **89**, 2928 (1967).

(24) R. E. Davis, D. Grosse, and A. Ohno, *Tetrahedron*, **23**, 1029 (1967).

(25) J. L. Fry, J. M. Harris, R. C. Bingham, and P. v. R. Schleyer, *J. Amer. Chem. Soc.*, **92**, 2540 (1970).

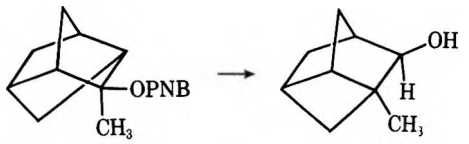
(26) K. L. Servis, S. Borčić, and D. E. Sunko, *Tetrahedron*, **24**, 1247 (1968).

conditions (30 min at 0°, 1 hr at 25°) in the case of dimethyl-1-norbornylcarbinol (eq 5).[27]



(5)

Finally, we have some preliminary results with the tertiary *p*-nitrobenzoate **27** which also undergoes rearrangement concurrent with hydrolysis.[28,29] In this case the unrearranged alcohol was shown to be stable toward the reaction conditions, and the rearranged alcohol was assigned structure **28** on the basis of its mass spectral fragmentation pattern and nmr data.



27 **28**

There can be little doubt that these cationic reactions proceed with great facility, the overall driving force being rearrangement to a more stable ring system. Although relief of nonbonded strains may be significant in promoting the rearrangements, it appears that the principal factor involves relief of bond angle strains at carbons 2 and 6. It is estimated that the C–C–C angles at these positions expand by as much as 10–12° during the course of the rearrangements. None of the other C–C–C angles appear to change by more than a few degrees during the rearrangement. In any event, these results clearly demonstrate that carbon–carbon participation in strained saturated systems can produce rather large rate enhancements. Previously, rate enhancements of the magnitude discussed here have been observed only in systems in which double bonds or cyclopropyl rings were involved. A more complete discussion of the nature of the intermediates and transition states in these solvolyses will be deferred until data is available on the substituted systems.

Summary and Conclusions

The results discussed above present an interesting spectrum of behavior. Under the conditions examined the carbanionic species proved to be stable. The free radical, given sufficient activation, rearranged *via* cleavage of one of the bonds between adjacent bridgeheads. It is interesting that the same mode of cleavage is not found in carbonium ion reactions, especially when one considers the strain relief which must accompany this process. Instead, the carbonium ion invariably suffered ring contraction with the formation of the tricyclo[3.2.1.0^{3,6}]octyl system. This latter result highlights the complexities of the chemistry of strained polycyclic ring systems and provides stimulus for further experimentation.

(27) R. R. Sauers and D. H. Ahlstrom, *J. Org. Chem.*, **32**, 2233 (1967).

(28) B. R. Sickles, M.S. Thesis, Rutgers University, 1970.

(29) Kinetic studies are in progress whose objective is to determine the magnitude of the α-CH$_3$/H effect. Complete details of the syntheses, products, and kinetics of these reactions will be presented in a subsequent communication.

Experimental Section

Elemental analyses were determined by Micro-Tech Laboratores, Skokie, Ill. Infrared spectral data was obtained from a Perkin-Elmer Model 137 spectrometer on thin films or as noted. Nuclear magnetic resonance spectra were obtained from a Varian Model A-60 spectrometer in carbon tetrachloride with tetramethylsilane as internal standard. Gas chromatograms were determined on an Aerograph A90P (analytical and preparative): (A) 15-ft 5% Carbowax 20M, (B) 12-ft 2% Carbowax 20M, (C) 12-ft 10% Apiezon L. Melting points were determined on a Mel-Temp apparatus and are uncorrected. Mass spectra were determined on an Hitachi RMU-7 mass spectrometer at 70 eV.

2-Bromotricyclo[3.2.1.0^{3,6}]octane (9).[8] **A.**—A solution of 0.54 g (3.1 mmol) of **2** and 0.54 g (3.4 mmol) of bromine in 5 ml of carbon tetrachloride was added over a 10-min period to an ice-cold suspension of 1.33 g (6.16 mmol) of red mercuric oxide in 1 ml of carbon tetrachloride. The resulting mixture was stirred at 26° for 17 hr and filtered to remove the mercury salts. Gc analysis (A, 150°) revealed a single component, which was isolated by evaporation of the solvent followed by distillation of the residue. The yield of product, bp 84° (8 mm), whose infrared and nmr spectra were identical with those of authentic[16] **9**, was 0.196 g (34%).

B.—The silver salt of **2** was prepared[30] by treatment of 1.0 g (6.58 mmol) of the acid in 10 ml of water and 0.6 ml of 28% ammonium hydroxide solution with a solution of 1.1 g of silver nitrate in 15 ml of water. The precipate was collected, washed with water and ether, and dried at 100° (0.2 mm).

A suspension of the salt in 15 ml of dry petroleum ether (bp 30–60°) was cooled to −10° and treated with a solution of 0.705 g (4.42 mmol) of bromine in 5 ml of petroleum ether. The mixture was stirred for 30 min at −10°, 30 min at 25°, and 3 hr at reflux. The solvent was evaporated after filtration and the residue was distilled at 45° (0.1 mm) to give 0.275 g (38%) of bromide **9** whose infrared and nmr spectra were identical with those of authentic material.

2-Bromotricyclo[3.3.0.0^{3,7}]octane (8).—To a solution of 1.00 g (6.58 mmol) of acid **2** and 2.92 g (6.58) mmol of lead tetraacetate in 15 ml of dry benzene was added 0.805 g (6.58 mmol) of lithium bromide dihydrate.[6] The resulting mixture was flushed with nitrogen and placed in an oil bath at 80° for 4.5 hr. The solvent was then decanted, diluted with ether, and washed with sodium bicarbonate solution. The dried solvents were evaporated to give a residue which was distilled at 60° (1 mm) to give 0.35 g (29%) of a colorless oil: nmr δ 4.11 (t, 1 H, J = 1.7 Hz) broad singlets at 2.80, 2.65, and 2.38 (5 H), and a singlet at 1.47 (5 H); ir 10.07, 10.76, 11.72, 12.42 (s), 13.10, 13.70 μ (s).

Anal. Calcd for $C_8H_{11}Br$: C, 51.37; H, 5.93; Br, 42.73. Found: C, 51.13; H, 5.68; Br, 42.36.

2-Chlorotricyclo[3.3.0.0^{3,7}]octane (7). A.—A solution prepared from lead tetraacetate (2.92 g, 6.58 mmol), 1.00 g (6.58 mmol) of acid **2**, and 0.293 g (6.92 mmol) of lithium chloride was flushed with nitrogen and heated at 80° for 4 hr. The reaction was processed as in the preceding experiment to yield 0.411 g of a complex product mixture. Gc analysis (A, 148°) revealed six compoenents in the area ratios i, 6%; ii, 2.5%; iii, 36%; iv, 40%; v, 10%; vi, 6%. Compound i had the same retention time as a sample of 2-chlorotricyclo[3.2.1.0^{3,6}]octane.[31] Compound iii was isolated by preparative gc and assigned structure **7**: nmr δ 3.95 (t, 1 H, J = 1.7 Hz), 2.8–2.10 (m, 5 H), 1.7–1.17 (m, 5 H); ir 10.05, 10.69 (s), 11.64, 12.15 μ (s).

Anal. Calcd for $C_8H_{11}Cl$: C, 67.39; H, 7.78; Cl, 24.85. Found: C, 67.49; H, 7.69; Cl, 24.62.

Compound iv was isolated and shown to be 2-acetoxytricyclo[3.2.1.0^{3,6}]octane[10] by comparitive ir and nmr spectra. Compound v had an infrared spectrum which was identical with that of 2-acetoxytricyclo[3.3.0.0^{3,7}]octane.

B.—The reaction was repeated with a twofold excess of lithium chloride. The gas chromatogram showed the following percentages of the products: i, 7.2%; ii, 1.1%; iii, 70.0%; iv, 16.1%; v, 2.6%; vi, 2.6%.

Reaction of 2 with Lead Tetraacetate.—A solution of acid **2** (0.132 g, 0.87 mmol) and 3.86 g (0.87 mmol) of lead tetraacetate in 2 ml of benzene was heated for 6 hr at 80°. The gas chromatogram showed three components in the area ratios 79:10:11.

(30) R. R. Sauers and R. J. Kiesel, *J. Amer. Chem. Soc.*, **89**, 4695 (1967).

(31) Prepared and characterized by C. Weston, Ph.D. Thesis, Rutgers University, New Brunswick, N. J., 1967.

The major component had the same retention time as compound iv above. The retention time of the next major compound was identical with that of vi in the preceding experiment.

Dimethyl-2-tricyclo[3.3.0.0^{3,7}]octylcarbinol (10).—A 1.67 *M* solution of methyllithium in ether (24 ml, 40 mmol) was added to a solution of 1.52 g (10 mmol) of 2 in 30 ml of ether. The mixture was stirred and heated at reflux for 2 hr. The reaction mixture was poured onto ice and the ethereal layer was separated and washed with sodium bicarbonate solution. Gc analysis (A, 180°) revealed two components in nearly equal quantities. The mixture was treated with a second quantity of methyllithium (18 ml) for 2 hr. After work-up, gc analysis showed one peak and evaporation of ether gave an oil which distilled at 58.5° (0.25 mm): yield 1.34 g (81%); nmr δ 2.52–2.0 (m, 5 H), 1.24–1.15 (m, 6 H), 1.18 (s), 1.12 (s), and 0.75 (m, 7 H); ir 2.83, 7.73, 8.58, 10.50, and 12.11 μ.

Anal. Calcd for $C_{11}H_{18}O$: C, 79.46; H, 10.92. Found: C, 79.68; H, 11.02.

Decomposition of 11.[10] A. Photochemical.—The hypochlorite 11 was prepared in 5.5 ml of carbon tetrachloride from 0.50 g (3.0 mmol) of 10. The solution was cooled to −10° and irradiated with a 250-W sun lamp for 15 min in a nitrogen atmosphere. The solution was allowed to stand at 25° for 30 min after which time it gave a negative starch–iodide test. Gc analysis (A, 152°) indicated the presence of six products, three of which were derived from the alcohol 10 (see below). Essentially no chloride 7 was present in the products. The major product proved to be alcohol 10. The next most significant product (12) was isolated by preparative gc: nmr δ 3.94 (d, 1 H, J = 2.5 Hz), 2.55–1.85 (m, 5 H), 1.22 (s, 3 H), 1.00 (s, 3 H), 1.62–0.90 (m, 4 H); ir 9.22 (s), 11.98, and 12.28 μ.

Anal. Calcd for $C_{11}H_{16}O$: C, 80.44; H, 9.82. Found: C, 80.20; H, 9.71.

The three minor products were isolated and shown to be **23**, **24**, and **25**. Compound **24** showed the following spectral data: nmr δ singlets at 2.61 (2 H), 2.30 (2 H), 1.55 (6 H) and a multiplet (6 H) at 1.30; no strong ir bands below 8 μ.

Anal. Calcd for $C_{11}H_{16}$: C, 89.12; H, 10.88. Found: C, 89.28; H, 11.07.

Compound **23** gave δ 4.67 (s, 1 H), 4.55 (s, 1 H), 2.27 (m, 5 H), 1.58 (s), and 1.78–0.90 (m, 9 H); ir 6.06 and 11.30 μ (s).

Anal. Found: C, 89.21; H, 10.82.

Compound **25** gave nmr identical with that found below except for a small impurity peak at δ 3.82; ir 11.55 and 13.25 μ.

Anal. Calcd for $C_{11}H_{17}Cl$: C, 71.53; H, 9.28; Cl, 19.20. Found: C, 71.71; H, 9.36; Cl, 19.30.

B. Thermal Decomposition.—On heating a carbon tetrachloride solution of 11 for 20 hr at reflux a similar product mixture was obtained.

Reduction of 8.—A solution of 0.306 g (1.64 mmol) of **8** in 1 ml of ether was added to a suspension of 0.50 g (22 mg-atom) of sodium in 15 ml of liquid ammonia. The mixture was allowed to warm to 25° over a period of 4 hr, at which time the reaction was quenched with a small amount of ethanol. Water was then added and the product was extracted into ether. The ether was evaporated carefully to a volume of 1.5 ml and then analyzed by gc (C, 168°). The major component (94%) was collected by preparative gc to yield 0.072 g (41%) of 1. The nmr spectrum showed two singlets at δ 2.24 (4 H) and 1.30 (8 H) in agreement with the literature.[3b] The retention time of the minor product was close to that of 6 but positive identification was not made.

Deuteriotricyclo[3.3.0.0^{3,7}]octane-2-carboxylic Acid (14).—The cleavage of ketone **13** was repeated[2b] except that deuterium oxide was substituted for water in the first step. An 84% yield of 14 was isolated which showed a carbon–deuterium stretching band at 4.56 μ in the infrared spectrum. The nmr spectrum displayed singlets at δ 12.13 (1 H) and 1.40 (5 H) and a multiplet at 2.70–2.25 (5 H).

Reaction of 10 with Hydrochloric Acid.—A solution of 50 mg of 10 in 0.5 ml of carbon tetrachloride was stirred for 20 hr with 50 μl of concentrated hydrochloric acid. The gas chromatogram showed three of the components which were formed from the hypochlorite photolysis in the ratios **23** (4%), **24** (19%), and **25** (77%). The nmr spectrum of **25** showed singlets (1 H) at δ 4.01 and 2.66 (2 H), doublets at 0.87 (3 H), J = 6 Hz) and 0.77 (3 H, J = 6 Hz), and a multiplet at 2.32–1.05 (8 H).

4-Oxatricyclo[4.2.1.0^{2,5}0^{3,7}]nonane.[2a]—A solution of 68 g (0.555 mol) of norbornene-5-carboxaldehyde[32] (75% endo) and 38 g of piperylene in 1 l. of ether was irradiated for 160 hr with a 450-W Hanovia immersion lamp equipped with a Vycor filter. The resulting solution was evaporated and the residue was sublimed. Crystallization of the sublimate from pentane give 28.9 g (57%) of the oxetane, mp 134–137° (lit.[2a,33] mp 136–137.5°).

Tricyclo[3.3.0.0^{3,7}]octan-2-ol (3).—A slurry of 20 g (0.19 mol) of lithium aluminum hydride in 175 ml of *N*-methylmorpholine was heated to reflux and a solution of 10 g (82 mmol) of the above oxetane in 75 ml of *N*-methylmorpholine was added over 1 hr. The reaction was heated and stirred for 5 days. The excess hydride was decomposed by dropwise addition of a solution of 70 g of sodium potassium tartrate in 70 ml of water. The resulting mixture was filtered and extracted three times with pentane and three times with ether. The combined organic extracts were washed with water, dried, and concentrated. The resulting solid was recrystallized from pentane, mp 132–135° (lit.[2a] mp 134–135°), yield 6.2 g (61.5%).[34]

The *p*-nitrobenzoate had mp 96–98°.

Anal. Calcd for $C_{15}H_{15}NO_4$: C, 65.92; H, 5.53; N, 5.12. Found: C, 66.03; H, 5.75; N, 5.33.

The brosylate ester **15** had mp 45.5–47° after crystallization from pentane at −78°.

Anal. Calcd for $C_{14}H_{15}BrO_3S$: C, 48.98; H, 4.40; S, 9.34. Found: C, 48.94; H, 4.67; S, 9.26.

The acetate ester was prepared from the alcohol by heating a solution of **3** in acetic anydride–pyridine: bp 101–103° (10 mm); ir 5.75, 8.00, 9.48, and 10.95 μ (m); nmr δ 4.5 (s, 1 H), 1.91 (s, 3 H), 2.25 (m, 4 H), and 1.4 (m, 7 H).

The *p*-toluenesulfonate ester was a viscous oil which did not crystallize. The infrared spectrum did not show OH absorptions and strong bands appeared at 6.92 and 8.51 μ.

Tricyclo[3.3.0.0^{3,7}]octan-2-one (22).—To an ice-cold solution of 4.0 g (3.2 mmol) of alcohol **2** in 25 ml of ether was added 24 ml of sodium dichromate sulfuric acid soltuion[35] and the resulting mixture was stirred at 0° for 1 hr. The layers were separated and the aqueous phase was extracted with ether. The combined ether extracts were washed with sodium carbonate solution and water and then dried. Evaporation of the ether gave 2.5 g (62%) of ketone **22**. The melting point was 106–110° after purification by gas chromatography. Nmr had three complex groups centered at δ 1.58, 2.12, and 2.50; ir (CCl_4) 5.64 μ. The carbonyl absorption was also examined more carefully on a grating spectrometer (Perkin-Elmer Model 521); two bands appeared (5.64 and 5.68 μ) whose weighted average position was 5.65 μ.

Anal. Calcd for $C_8H_{10}O$: C, 78.65; H, 8.25. Found: C, 78.51; H, 8.28.

Acetolysis of 15.—The acetolysis of **15** was followed by nmr spectroscopy by monitoring the region near δ 4.5. A solution of 0.0547 g of **15** in 0.5 ml of acetic acid (0.1 *N* in sodium acetate) was placed in the probe of the spectrometer which had been equilibrated at 56°. Within 1 min a new peak appeared (δ 4.45) adjacent to that of the H–C–O proton of **16** (δ 4.34). The area of the new peak gradually increased at the expense of the starting material. A third peak at δ 4.58 also appeared in *ca.* 2 min and increased in size at a rate *ca.* one-third that of the other. Within 18 min the starting material had completely disappeared and only the two new peaks remained with relative areas *ca.* 3:1, respectively. The peak at δ 4.45 was assigned to the H–C–O proton of **21** by direct comparison of the chemical shift with that of an authentic sample. The peak at δ 4.58 was attributed to the H–C–O proton of acetate **16**.[16] This assignment was supported by the observation that complete acetolysis (40 hr, 100°) produced a high yield of *ca.* 97% pure **16** as shown by gc and nmr comparisons.

Hydrolysis of **15** in 80% acetone–water (120°, 5 hr) likewise gave a nearly quantitative yield of pure **16** (S = H) as shown by gc and ir comparisons with authentic samples.[16]

Preparation and Hydrolsysis of 19.—A solution of 1.07 g (8.75 mmol) of ketone **22** in 10 ml of isopropyl alcohol was added dropwise to a stirred solution of 0.40 g (9.6 mmol) of sodium borodeuteride[36] in 15 ml of ice-cold isopropyl alcohol. The resulting solution was stirred at 25° for 17 hr. The reaction was

(32) O. Diels and K. Alder, *Justus Liebigs Ann. Chem.*, **460**, 117 (1928).

(33) This material was first isolated and characterized by W. Schinski, Ph.D. Thesis, Rutgers University, New Brunswick, N. J., 1968.

(34) We have since found that this reduction is more expeditiously effected by means of lithium metal in ethylenediamine: E. O'Hara, unpublished results.

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

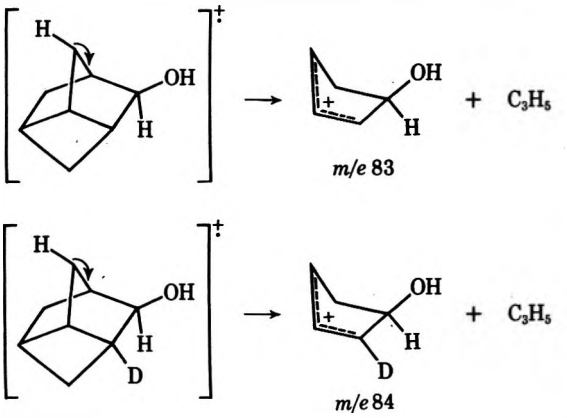
(36) Purchased from Merck, Sharp and Dohme (98% minimum deuterium content).

quenched by addition of 6 *N* hydrochloric acid and 50 ml of water. Extraction with three portions of ether gave 0.70 g of alcohol 3-*d* on evaporation of the extracts. The nmr spectrum displayed no appreciable absorption near δ 3.8. This material was converted into the corresponding *p*-toluenesulfonate ester and solvolyzed in a mixture of 12 ml of water and 18 ml of acetone (3 hr at 140°). The product displayed two peaks on gc analysis. The minor product showed the same retention time as the starting alcohol 3-*d* and is believed to have been carried over due to incomplete tosylation. The major product (>80%) was assigned structure **20**, nmr δ 3.64 (s, 1 H), 2.79–1.1 (m, 10 H). The location of the deuterium atom could not be unambiguously established, but mass spectral analysis was consistent with the assigned structure. Thus, both deuterated and undeuterated **3** showed a base peak at *m/e* 67 which corresponds to the loss of carbons C_2, C_3, and C_4. No isotopic shift was observed for this fragmentation. On the other hand the ions formed *via* related cleavage of C_4, C_5, and C_8 did show an isotopic shift from *m/e* 83 to 84, a result which is consistent with deuteration at C_3.[37]

Kinetic Experiments.—A solution of sodium acetate in acetic acid (0.1 *N*) was prepared by refluxing purified[38] reagent grade acetic acid (500 ml) with 2.65 g (0.0251 mol) of anhydrous sodium carbonate and 2.56 g (0.0251 mol) of acetic anhydride for 5 hr. Perchloric acid (0.05 *N*) was prepared from 2.1 ml of 70% perchloric acid, 2.2 ml of acetic anhydride, and enough acetic acid to bring the total volume to 500 ml. The exact normality was determined before each run by titration with standard potassium hydrogen phthalate solution in acetic acid using *p*-bromophenol as an indicator. The solvolyses were carried out in sealed ampoules into which were placed 2.5-ml samples of a *ca.* 0.1 *M* solution of brosylate **15** in the acetic acid–sodium acetate solution. At the appropriate time intervals ampoules were withdrawn from the oil bath and cooled before opening. A 2.00-ml aliquot was removed and quenched in 5 ml of purified dioxane.[39] The samples were then titrated with standardized perchloric acid. Infinity titers were obtained after warming samples to 120–130° for 2 hr and values obtained agreed to within 5% of the expected values. The first-order rate consant for production of acid drifted downward with time and remained constant for 4–5 half-lines. The values for the rate of solvolysis of the rearranged brosylate were determined at four temperatures and are recorded as follows: 47.68° (0.96×10^{-6} sec^{-1}); 53.08° (1.30×10^{-5} sec^{-1}); 61.37° (4.77×10^{-5} sec^{-1}); 83.90° (53.0×10^{-5} sec^{-1}). The rate constant for this reaction (k_3) at 25° was obtained by extrapolation: 3.79×10^{-7} sec^{-1}.

The rate constants at 53.08° for direct acetolysis (k_1) and for rearrangement (k_2) were obtained by the method of Young, Winstein, and Goering,[18] and found to be k_1, 1.71×10^{-4} sec^{-1}; k_2, 8.51×10^{-4} sec^{-1}. These rate constants were used to calculate the instantaneous brosylate ion concentrations and were found to yield values within ±4% of those determined experimentally.

(37) Schematically, these cleavages may be symbolized as follows.



(38) H. Tanida, T. Tsuji, and J. Ishitobi, *J. Amer. Chem. Soc.*, **86**, 4901 (1964).

Registry No.—**3** *p*-nitrobenzoate, 32980-15-7; **3** brosylate, 27011-51-4; **3** acetate, 32980-17-9; **7**, 26955-51-1; **8**, 32980-18-0; **10**, 32980-19-1; **12**, 32980-20-4; **22**, 32980-21-5; **23**, 32980-22-6; **24**, 32980-23-7; **25**, 32980-24-8.

Acknowledgments.—We wish to acknowledge useful discussions with P. K. Freeman. Financial aid (to K. W. K.) from Merck and Company, the donors of the Petroleum Research Fund, administered by the American Chemical Society, is gratefully acknowledged. We also wish to thank the Rutgers University Research Council for partial financial support. Funds toward the purchase of the mass spectrometer were obtained from the National Science Foundation.

(39) Commercial dioxane was passed over a column of neutral alumina.

Addition of Nitrosyl Chloride to Some Strained Bicyclic Olefins

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Received June 9, 1971

Norbornene, norbornadiene, 5-methylene-2-norbornene (**1**), and 5-ethylidene-2-norbornene (**5**) add nitrosyl chloride to give exo-cis nitrosochlorides which dimerize to azodioxy compounds. In the latter two cases, addition does not occur at the exocyclic double bond, but 1,2 addition of nitrosyl chloride to the ring double bond occurs in two directions to give, after hydrolysis, a mixture of isomeric chloro ketones. In all cases, no rearrangement products were observed. 1,2,3,4,7,7-Hexachlorobicyclo[2.2.1]hepta-2,5-diene (**13**) does not add nitrosyl chloride in solution, but 1,2,3,4,7,7-hexachloro-5-methylenebicyclo[2.2.1]hept-2-ene (**14**) reacts very slowly under pressure to give addition to the exocyclic double bond. Addition to norbornene in a two-step process involving addition of nitrosonium tetrafluoroborate followed by addition of a chloride salt leads to small yields of chloro oximes instead of an azodioxy compound.

The reaction of nitrosyl chloride with alkenes to give nitrosochlorides, which dimerize if unhindered, has been known since 1875[2a] and has been adequately reviewed.[2b,c] Addition of the chloride to the carbon which can best support a positive charge is generally observed[3] and unstrained cyclic olefins give the products of trans addition.[4,5] A mechanism involving initial attack by NO^+ to form a strong olefin–electrophile

(1) NDEA Fellow, 1965–1968; University of Alabama Fellow, 1969.

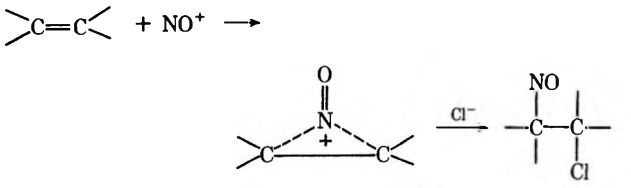
(2) (a) W. A. Tilden, *J. Chem. Soc.*, **28**, 514 (1875); (b) L. J. Beckham, W. A. Fessler, and M. A. Kise, *Chem. Rev.*, **48**, 319 (1951); (c) M. Plungian and F. E. DeVry, "Nitrosyl Chloride," An Annotated Bibliography, Hercules Technical Information Center, 1970, p 39.

(3) C. K. Ingold, "Structure and Mechanism in Organic Chemistry," Cornell University Press, Ithaca, N. Y., 1953, p 669.

(4) J. Meinwald, Y. E. Meinwald, and T. N. Baker, *J. Amer. Chem. Soc.*, **86**, 4074 (1964).

(5) B. W. Ponder, T. E. Walton, and W. J. Pollock, *J. Org. Chem.*, **33**, 3957 (1968).

complex followed by attack by Cl^- has generally been assumed.[6]



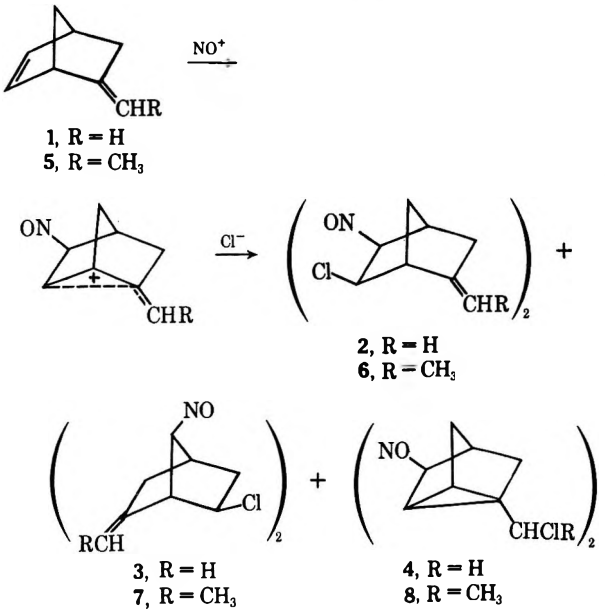
The observation that norbornene and norbornadiene react with nitrosyl chloride by cis,exo addition prompted the proposal of alternate mechanisms[4] and also initiated searches for the underlying reasons for the steric course of the reaction in these strained bicyclic systems.[7] We wish to report the results of our investigation into the generality of the cis,exo addition pathway of nitrosyl chloride with strained bicyclic olefins, and to comment upon the mechanism of this reaction.

Results

Initially, norbornene, norbornadiene, 5-methylene-2-norbornene (**1**), and 5-ethylidene-2-norbornene (**5**) were chosen for study. The addition of nitrosyl chloride to the first two, norbornene and norbornadiene, had previously been reported by Meinwald[4] and Miller,[8] but, since their reported work dealt only with the solid dimers formed, the possibility existed that any rearrangement products in the supernatant liquid might have gone undetected. Because of the plethora of literature reports on the Wagner–Meerwein type rearrangements in the [2.2.1]bicyclic system when positive charge is generated at C-2,[7] it seemed reasonable that addition of strong electrophiles such as nitrosyl chloride would lead to appreciable rearrangement. Although no examples of rearrangement during this specific reaction have been reported, Hamann and Swern[9] reported a 13% yield of a rearranged product in the mechanistically similar reaction of nitrosyl formate with norbornadiene. We therefore carried out a detailed investigation on the total reaction mixtures resulting from nitrosyl chloride addition to norbornene and norbornadiene. Fractional crystallization of the solid dimeric products and glpc analysis of the concentrated supernatant liquids revealed the presence of only nitrosochloride dimers from 1,2 addition and a small quantity of yellow oils whose infrared spectra suggested a mixture of chloro oximes.

5-Methylene-2-norbornene (**1**) was chosen as a substrate because of the possible homoallylic stabilization of an intermediate positive charge with concomitant formation of a tricyclic structure **4**, in addition to products **2** and **3**.

Nitrosyl chloride adds to 5-methylene-2-norbornene (**1**) to give a 58% yield of solid dimeric nitrosochloride adduct, mp 161–167°. The supernatant liquid from the reaction was carefully concentrated and analyzed to reveal only unreacted olefin and a small quantity of chloro oximes. The dimeric solid was subjected to fractional crystallization procedures to ensure that it



1, R = H
5, R = CH_3

2, R = H
6, R = CH_3

3, R = H
7, R = CH_3

4, R = H
8, R = CH_3

was homogeneous. The nmr proton spectrum of this solid is shown in Figure 1,[10] along with the spectrum of the starting olefin, **1**. The ring vinylic hydrogens of **1** absorb at τ 4.05, and the two exocyclic vinylic hydrogens absorb at τ 5.12 and 5.41. Inspection of the nmr spectrum of the nitrosyl chloride adduct reveals that addition takes place on the ring. This is reasonable in view of the fact that two sp^2 hybridized carbons are transformed to sp^3 carbons, which relieves a considerable amount of strain in the rigid bicyclic system. This is much more energetically favorable than the alternate path of converting only one ring sp^2 carbon to sp^3 if addition had occurred at the exocyclic double bond. It is also clear from the spectrum that one of the exocyclic vinylic hydrogens has been shifted downfield to an overlapping position with the –CHNO hydrogen. The doublet at τ 5.54 (–CHCl) is coupled by 7 Hz to the hydrogen absorbing at τ 4.84 (–CHNO). This AB pattern with J = 7 Hz is a good indication of cis,endo stereochemistry for the hydrogens at C-2 and C-3.[4] Thus, nitrosyl chloride adds to 5-methylene-2-norbornene to give only cis,exo addition, with no detectable rearrangement products **3** and **4**.

The reaction of 5-ethylidene-2-norbornene (**5**) with nitrosyl chloride, which should be mechanistically similar to **1**, proceeds rapidly in chloroform solution to yield 67% of the solid dimeric nitrosochloride, mp 135–139°. A careful analysis of the mother liquor revealed only starting olefin and a small quantity of a viscous yellow oil which was shown to be a mixture of chloro oximes. Fractional crystallization attempts on the solid dimer failed to reveal any isomeric products. The nmr spectrum of this dimer, as well as that of the starting olefin, **5**, are shown in Figure 2. The two ring vinylic hydrogens absorb at τ 4.08 and the exocyclic vinylic hydrogen absorption is centered at τ 4.7. This absorption shows the starting olefin to be a mixture of the two geometric isomers, as can be seen from the small quartet of the least abundant isomer over-

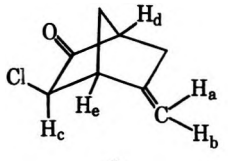
(6) L. Kaplan, H. Kwart, and P. v. R. Schleyer, *J. Amer. Chem. Soc.*, **82**, 234 (1960).
(7) T. G. Traylor, *Accounts Chem. Res.*, **2**, 152 (1969).
(8) J. B. Miller, *J. Org. Chem.*, **26**, 4904 (1961).
(9) H. C. Hamann and D. Swern, *J. Amer. Chem. Soc.*, **90**, 6481 (1968).

(10) The figures (1–5) showing the nmr spectra will appear following these pages in the microfilm edition of this volume of the journal. Single copies may be obtained from the Reprint Department, ACS Publications, 1155 Sixteenth St., N.W., Washington, D. C. 20036, by referring to author, title of article, volume, and page number. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche.

lapping the upfield side of the quartet of the major isomer. The spectrum of the nitrosyl chloride adduct (Figure 2) reveals that again addition has occurred to the endocyclic double bond, and two doublets at τ 5.21 (-CHNO) and 5.75 (-CHCl) with J = 7 Hz indicate that cis,exo addition has taken place.

Considerable difficulty was encountered during the analyses of the dimeric products resulting from nitrosyl chloride addition due to the limited solubility of most of the adducts. Several methods of modifying these dimers to make them more amenable to analysis, but without altering the original addition stereochemistry, were explored. Attempts to reduce the azodioxy linkage to the corresponding amine under a variety of conditions[11] led also to the removal of the chlorine atom from the molecule. The dimers could be converted into their corresponding chloro oximes,[12] but these were not as easily analyzed as had been hoped. These viscous oils were irreversibly absorbed on both alumina and silica gel chromatographic columns, and could not be successfully recrystallized nor distilled under vacuum.

Levulinic acid hydrolysis[13] of the methylenenorbornene adduct, (2), followed by vacuum distillation yielded a mixture of two chloro ketones, **9** and **10**, in a



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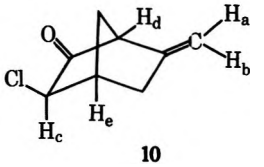

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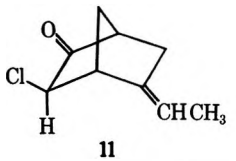
ratio of 5:1. Glpc separation and collection of these two chloro ketones gave analytical samples whose nmr spectra are shown in Figure 3. For **9**, absorptions at τ 4.79 and 5.05 are assigned to the exocyclic vinylic hydrogens, H_a and H_b. A doublet at τ 6.43 (J = 3 Hz) is assigned to H_c. A multiplet at τ 7.24 is assigned to H_d and the absorption at τ 6.90 is assigned to H_e. For **10**, absorptions at τ 4.88 and 5.02 are assigned to the exocyclic vinylic hydrogens H_a and H_b. A doublet at τ 6.28 (J = 3 Hz) is assigned to H_c and a multiplet at τ 7.12 is assigned to H_e. An absorption at τ 6.81 is assigned to the other bridgehead hydrogen, H_d. It is thus apparent that the methylenenorbornene adduct (2), which was originally thought to be homogeneous *via* recrystallization experiments, was in fact a mixture of positional isomers from cis,exo addition of nitrosyl chloride. The possibility of epimerization of the chlorine atom upon hydrolysis to give a mixture of exo and endo chloro ketones was considered, but then ruled out on the basis of infrared and nmr data.[4]

Hydrolysis of the nitrosyl chloride adduct from 5-ethylidene-2-norbornene (**5**) gave the chloro ketones **11** and **12** in a ratio of 4:1. Glpc separation and collection of the two isomers on a 15% Carbowax 20M column afforded analytical samples whose nmr spectra were very similar to those of **9** and **10**.



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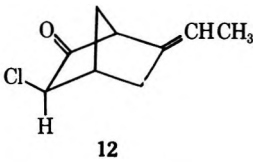

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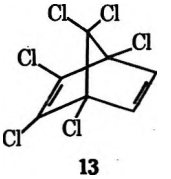
1,2,3,4,7,7-Hexachlorobicyclo[2.2.1]hepta-2,5-diene (**13**) was next chosen for study, since it should provide a convenient system for following the course of the addition of nitrosyl chloride by nmr. The spectrum of the diene consists of a singlet at τ 3.42, and the addition of NOCl should produce an AB pattern upfield from the vinyl singlet. Any rearrangement products would consequently be easily detectable. However, attempted addition to the hexachloronorbornadiene in solution produced no reaction under a variety of conditions. Traylor[7] also reports that hexachloronorbornadiene fails to undergo the oxymercuration reaction. We did observe that neat addition of nitrosyl chloride to hexachloronorbornadiene at room temperature in a pressure bottle and over a reaction time of 1 month produced a small yield of a complex mixture of products. The nmr spectrum of this mixture revealed as the most prominent feature a pair of doublets at τ 4.77 and 5.25 (J = 4 Hz) which is indicative of a trans addition of nitrosyl chloride.



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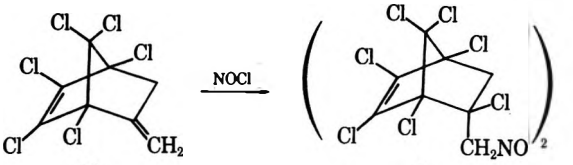


14 **15**

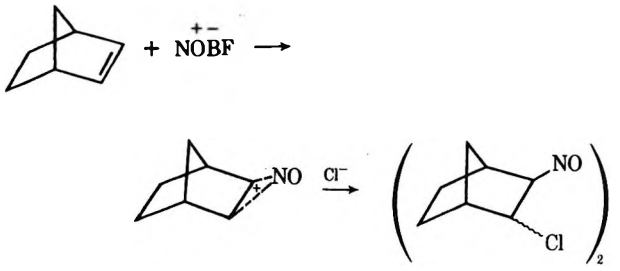
1,2,3,4,7,7-Hexachloro-5-methylene-2-norbornene (**14**) should also yield useful information upon its reaction with nitrosyl chloride. It was, first of all, of interest to determine if addition occurs at the deactivated ring double bond or at the exocyclic double bond. Addition at this latter site would give useful nmr data for comparison to the nmr data of ring double bond additions. Also, the fewer number of hydrogens in this chlorinated system should make the detection of any rearrangement products much easier by nmr. Hexachloro-5-methylene-2-norbornene (**14**) was easily prepared through the Diels–Alder condensation of hexachlorocyclopentadiene and allyl bromide,[14] followed by dehydrohalogenation.[15] The nmr spectrum of **14** is shown in Figure 4. The absorptions for the two C-6 hydrogens, which form the XY portion of an ABXY system, appear at τ 6.92 and 7.29 as a doublet of triplets (J_{XY} = 15 Hz, J_{AX} = 1.5 Hz). The exocyclic vinylic hydrogens absorb at τ 4.48 and 4.82, with the allylic coupling constant of 1.5 Hz readily apparent.

Reaction of nitrosyl chloride with **14** in solution failed to occur under a variety of conditions. The neat reaction of the diene did yield some product, **15**, however, and the nmr spectrum is shown in Figure 4. Prominent patterns of the C-6 hydrogens are located at

(11) H. Greenfield and F. Dovell, *J. Org. Chem.*, **32**, 3670 (1967).
(12) L. K. Payne, U. S. Patent 3,328,457 (1967).
(13) (a) C. H. DePuy and B. W. Ponder, *J. Amer. Chem. Soc.*, **81**, 4629 (1959); (b) B. W. Ponder and D. R. Walker, *J. Org. Chem.*, **32**, 4136 (1967).
(14) E. K. Fields, *J. Amer. Chem. Soc.*, **78**, 5821 (1956).
(15) W. Johnson and V. Mark, *J. Org. Chem.*, **26**, 4105 (1961).

τ 6.27 and 7.10 (J = 15 Hz). Lower field absorption of two doublets at τ 4.42 and 5.03 (J = 13 Hz) are assigned to the two hydrogens of the 5-nitrosomethyl group. These two hydrogens provide a striking example of nonequivalence in diasteromeric hydrogens in an nmr spectrum. Thus, from the nmr, it is readily concluded that nitrosyl chloride adds to **14** at the exocyclic double bond, with no rearrangement.

It was of interest to determine if the addition of the elements of nitrosyl chloride could be accomplished in a two-step process as shown below. Addition of nitrosyl tetrafluoroborate to norbornene could be expected to produce a nitrosonium ion which could then



undergo nucleophilic attack by chloride ion to yield the dimeric nitrosyl chloride adduct. Forcing the addition to occur in two steps should allow the maximum opportunity for rearrangement reactions to occur. The reaction was carried out in a number of solvents such as CCl_4, $CHCl_3$, DMSO, and acetone, and the appearance of a green color suggested the initial formation of a nitroso complex, but no dimeric nitrosochloride could be isolated upon addition of chloride ion. The use of iodide ion as the nucleophile resulted in its oxidation to molecular iodine by the reaction mixture. The small amount of organic product obtained was a viscous, uncharacterizable oil which had spectral properties of oximes.

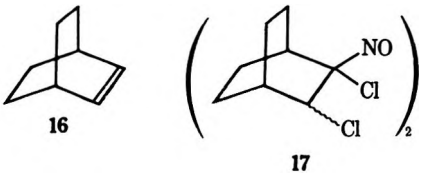
At about the same time as our work was in progress, Hamann and Swern[9] reported the addition of nitrosyl tetrafluoroborate to 2,3-dimethyl-2-butene in the presence of sodium acetate. The isolation of 2,3-dimethyl-2-acetoxy-3-nitrosobutane was attributed to the intermediate formation of a nitrosonium–olefin ion pair which then reacted with the nucleophilic acetate ion. It was of interest to determine whether norbornene would undergo a similar set of reactions, since observation of an exo,cis two-step addition of nitrosyl acetate to norbornene would establish the same point intended in the previous nitrosonium tetrafluoroborate–sodium chloride experiment. Addition of isoamyl nitrite and acetic acid to norbornene in the presence of a catalytic quantity of 70% perchloric acid yielded a white solid, which was identified as the dimeric 2-nitroso-3-nitronorbornane.[16] The addition of the elements of dinitrogen trioxide is not a new reaction, since several workers[5,17] have reported this product from nitrosyl chloride additions, and Swern[9] reported that generation of nitrosyl formate from sodium nitrite and formic acid yielded dinitrogen trioxide adducts with cyclohexene and styrene. It thus appears that the two-step addition of nitrosyl halides or acetates to norbornene is a very slow process, which allows isomerization of the nitrosonium complex to an oxime, or oxidation of the nitrosonium ion to dinitrogen trioxide, to become the predominant reaction pathway.

(16) M. L. Scheinbaum, *J. Org. Chem.*, **33**, 2586 (1968).
(17) A. Hassner and C. Heathcock, *ibid.*, **29**, 1350 (1964).

Discussion

There are several theories that have been proposed to account for the fact that cis additions of a number of electrophilic reagents occur only in rigid olefins, and these have been reviewed.[7] A combination of the twist–strain theory of Traylor[7] and the torsional effects explanation of Schleyer[18] seem particularly attractive to us.

Bicyclo[2.2.2]octene-2, (**16**) should be an excellent



16 **17**

choice to provide an evaluation of the influence of twist–strain on the addition of nitrosyl chloride to bicyclic olefins. It falls naturally between norbornene and cyclohexene in a series of decreasing strain in six-membered rings. It is also symmetrical about the double bond, so that steric hindrance should not lead to stereospecificity and torsional effects for cis or trans addition would be identical.

Nitrosyl chloride addition to bicyclo[2.2.2]octene-2 (**16**) occurs very slowly in comparison to norbornene, and the product, a white solid, has been identified as dimeric 2-nitroso-2,3-dichlorotricyclo[2.2.2]octane (**17**). The nmr of the alkene and the dichloronitroso product is shown in Figure 5. The product spectrum contains a doublet at τ 5.28 (J = 3 Hz) which is assigned to the C-3 hydrogen, and multiplets at τ 7.42 and 7.59 are assigned to the bridgehead protons. A second small doublet at τ 5.39 is due to a C-3 epimer of the main product, and the ratio of major to minor isomer is 5:1. Although products with chlorine cis and trans to the nitroso group were obtained in this experiment, this provided little information as to the stereochemistry of the initial addition reaction. One may visualize the initial nitrosochloride adduct of bicyclo[2.2.2]octene-2 to be sterically hindered from dimerizing to form the azodioxy product, which then allows tautomerization to the oxime to occur. This intermediate chlorooxime then adds a second chlorine atom at C-2 to yield the observed mixture of *cis*- and *trans*-2-nitroso-2,3-dichlorobicyclo-[2.2.2]octane.

With the evidence available in the literature on the addition of nitrosyl halides to olefins, one could legitimately consider either a molecular addition, a polar, nonconcerted addition, or a free radical addition. Preliminary experiments,[19] in which 5-ethylidene-2-norbornene adds nitrosyl chloride at the same rate whether or not a free radical inhibitor is present, seems to rule out the latter possibility in bicyclic systems. Our attempts at the trapping of any positively charged intermediate with iodide or chloride ion were frustrated due to redox reactions involving nitrosyl chloride and the halide ions. However, attempts in other laboratories to trap any such species with nucleophilic solvents

(18) P. V. R. Schleyer, *J. Amer. Chem. Soc.*, **89**, 701 (1967).
(19) P. W. Wheat, unpublished studies of this laboratory.

have also met with failure.[4] It is difficult to propose meaningful experiments whose results will give definitive answers to the question of existence or nonexistence of polar characteristics in these reactions. A study of the sensitivity of the reaction to electron-withdrawing and electron-releasing substituents should give some indication of the degree of positive charge buildup during the reaction, and these experiments are presently underway.

We feel that the exo,cis addition of nitrosyl chloride to the [2.2.1]bicyclic olefins can be best explained by a combination of factors. The torsional strain introduced in the transition state for initial endo attack and the partial blocking of the endo side of the double bond in this system would dictate an initial exo attack whether by a nitrosonium ion or molecular nitrosyl chloride. If an intermediate ion is formed in the bicyclic system similar to the intermediate formed from unstrained cases, then certain things must be true of this ion. It must have the positive charge delocalized on the nitrosonium group, since generation of positive charge at C-2 would almost certainly lead to rearrangement. Any intermediate ion must also be capable of adding the nucleophile, chloride ion, in a cis manner, since twist-strain would make trans addition implausible. A skewed ion such as that proposed by Rolston and Yates[20] in the case of bromine addition to styrene would perhaps meet this requirement. The intermediate ion would also be required to have the chloride in close association with it so that the chloride ion could add before any solvent molecule in the surrounding cage could add. As we place more and more limits on this hypothetical intermediate ion, we move closer toward a mechanism involving molecular cis addition. The real crux of the problem then is one of trying to determine if there is an intermediate or only a transition state in the addition reaction. We feel that a molecular, cis addition of nitrosyl chloride to strained bicyclic systems can be best supported with the available experimental evidence.

Experimental Section

Melting points were determined on a Fisher–Johns apparatus and are uncorrected. Infrared spectra were taken with a Perkin-Elmer Model 337 instrument, and a CEC 21-104 moderate resolution mass spectrometer system was used. Nuclear magnetic resonance spectra were taken on a Varian Associates HA-100 instrument using TMS as internal standard and either $CDCl_3$ or CF_3COOD as solvent. The general procedure used for the addition of nitrosyl chloride to olefins has been described previously.[5]

Addition of Nitrosyl Chloride to Norbornene.—A 5.8-ml (0.13 mol) sample of nitrosyl chloride was added to 12.0 g (0.13 mol) of norbornene in 150 ml of chloroform solvent by the general addition procedure at −50°. Stirring was continued for 30 min after addition was complete, and cold hexane (100 ml) was added. Suction filtration, followed by washing with cold hexane and air drying, yielded 14.8 g (75%) of *cis,exo*-3,3′-dichloro-*anti*-2,2′-azodioxynorbornane, mp 158–162° (lit.[4,8] mp 155.5–156.6°). The supernatant liquid was evaporated to a small volume and analyzed by glpc (20% SE-30 column) to reveal only chloroform, hexane, and unreacted norbornene. The yellow slurry obtained from continued evaporation of this supernatant liquid was shown by infrared analysis to have all the absorption peaks of the cis,exo nitrosyl chloride adduct, plus other peaks characteristic of oximes, particularly at 3450 (ν_{OH}) and 1635 cm^{-1} ($\nu_{C=N}$).

Addition of Nitrosyl Chloride to Norbornadiene.—A 5.8-ml (0.13 mol) sample of nitrosyl chloride was added to 11.75 g (0.13 mol) of norbornadiene in 150 ml of chloroform by the general addition method over a period of 1 hr. Work-up of the reaction as described above gave 12.3 g (63%) of *cis,exo*-6,6′-dichloro-*anti*-5,5′-azodioxy-2-norbornene as a white solid, mp 154–157° (lit.[4,8] mp 150–156°). Examination of the supernatant liquid in the manner previously described revealed the presence of only chloroform, hexane, some unreacted norbornadiene, and a small quantity of chloro oxime.

Addition of Nitrosyl Chloride to 5-Methylene-2-norbornene (1).—A 11.55-ml (0.25 mol) sample of nitrosyl chloride was added to 26.5 g (0.25 mol) of 5-methylene-2-norbornene (1) in 300 ml of chloroform at −50° by the general addition procedure. After an addition time of 50 min, 600 ml of cold hexane was added and stirring at −50° was continued for 12 hr. The yield of white solid (2), after collection by suction filtration and drying, was 30.0 g (70%), mp 157–163°. The mass spectrum of the solid showed a high mass cutoff of 171. The nmr spectrum is shown in Figure 1.

Anal. Calcd for $C_8H_{10}NOCl$: C, 56.10; H, 5.83; N, 8.18; Cl, 20.70. Found: C, 56.24; H, 5.67; N, 8.05; Cl, 20.46.

Work-up of the supernatant liquid in the manner described previously and analysis by glpc and infrared revealed a small amount of chloro oxime as the only additional product.

Addition of Nitrosyl Chloride to 5-Ethylidene-2-norbornene[21] (5).—Nitrosyl chloride (11.55 ml, 0.25 mol) was added to 30 g (0.25 mol) of 5-ethylidene-2-norbornene in 300 ml of chloroform below −50° over a period of 1 hr. After addition of 600 ml of hexane, stirring was continued for 5 hr. Work-up of the solution in the normal manner yielded 31 g (67%) of *cis,exo*-3,3′-dichloro-*anti*-2,2′-azodioxy-5-ethylidenenorbornane (6), mp 135–139°. The mass spectrum showed a high mass cutoff at 185. The nmr spectrum is shown in Figure 2.

Anal. Calcd for $C_9H_{12}NOCl$: C, 58.22; H, 6.49; N, 7.55; Cl, 19.14. Found: C, 58.45; H, 6.44; N, 7.60; Cl, 19.20.

Glpc analysis of the concentrated supernatant liquid on a 20% SE-30 column indicated only $CHCl_3$, hexane, and a trace of the starting olefin. The infrared spectrum of the final yellow residue from the evaporation of the mother liquor indicated the presence of an oxime.

Levulinic Acid Hydrolysis of the 5-Methylene-2-norbornene Nitrosochloride Dimer (2).—A 17.2-g (0.05 mol) sample of 2 in 339 ml of levulinic acid and 25 ml of 2 *N* HCl was heated with stirring at 85° for 1.5 hr. After the solution became clear, the mixture was stirred at 60° for an additional 21 hr. The mixture was diluted with 1 l. of water and extracted twice with 300-ml portions of ether. The combined ether extracts were washed with saturated sodium bicarbonate and dried over magnesium sulfate, and the ether was removed by rotary evaporation. Vacuum distillation of the remaining product gave a fraction, bp 135–138° (1 mm) whose infrared spectrum revealed it to be a mixture of two ketones, 9 and 10, in a ratio of 5:1, with an intense absorption at 1760 cm^{-1}. Glpc separation and collection of these two chloro ketones afforded analytical samples whose nmr spectra are shown in Figure 3. Satisfactory elemental analyses were obtained on each isomer.

Levulinic Acid Hydrolysis of the 5-Ethylidene-2-norbornene Nitrosochloride Dimer.—This hydrolysis was carried out in a manner identical to the preceding hydrolysis. Analysis of the product residue by glpc on a 15% Carbowax 20M column revealed two products in a ratio of 4:1. Infrared analysis of analytical samples of these two products identified them as the chloroketones 11 (ν_{max} 1760, 1665, 1660 cm^{-1}) and 12 (ν_{max} 1760, 1669 cm^{-1}) with 11 being the major isomer. Satisfactory elemental analysis were obtained on each isomer.

Addition of Nitrosyl Chloride to 1,2,3,4,7,7-Hexachloro-5-methylene-2-norbornene[14,15] (14).—This olefin failed to add nitrosyl chloride in solution under a variety of reaction conditions. However, neat addition of 0.04 mol of nitrosyl chloride to 0.02 mol of the olefin in a pressure bottle at room temperature for 1 month led to addition at the exocyclic double bond, as shown in Figure 4.

Attempted Addition of Nitrosyl Acetate to Norbornene.—Dry glacial acetic acid (200 ml) and 5 drops of 70% perchloric acid were cooled to 15° while 28.2 g (0.3 mol) of norbornene and 70.2 g (0.6 mol) of isoamyl nitrite were added over a 1-hr period.

(20) J. Rolston and K. Yates, *J. Amer. Chem. Soc.*, **91**, 1477 (1969).

(21) A generous complimentary sample of this material was supplied by Union Carbide Corp. Olefins Division, New York, N. Y.

A light green color developed and the temperature dropped to 5° during the course of the addition. Water (200 ml) was added, and the solution was extracted several times with ether. Overnight storage of the ether extract in the refrigerator led to precipitation of a white solid, which was recrystallized from chloroform to give 30 g (30%) of white needles, mp 146–148° (lit.[16] mp 135°). This was identified as 3,3′-dinitro-2,2′-azodioxynorbornane from its melting point and infrared spectrum: ir (KBr) 1540, 1355 ($-NO_2$), 1193, 1223, and 1216 cm^{-1} (azodioxy).

Anal. Calcd for $C_7H_{10}N_2O_3$: C, 49.31; H, 5.88; N, 16.47. Found: C, 49.50; H, 5.95; N, 16.34.

Addition of Nitrosyl Chloride to Bicyclo[2.2.2]octene-2[22] (16).—Nitrosyl chloride (2.3 ml, 0.05 mol) was added to 5.4 g (0.05 mol) of bicyclo[2.2.2]octene-2 in 25 ml of carbon tetrachloride by the general addition method at 10°. The color of the solution turned from red to blue in 4 hr, and a small amount (0.44 g) of white solid was isolated by filtration. Washing with acetone gave a purer material, mp 94.5–97.5°. This was identified as the dimer of a mixture of *cis*- and *trans*-2,3-dichloro-2-nitrosobicyclo[2.2.2]octane (17). The nmr spectrum is shown in Figure 5.

Anal. Calcd for $C_8H_{11}Cl_2NO$: C, 46.15; H, 5.29; Cl, 34.13; N, 6.73. Found: C, 45.96; H, 6.27; Cl, 33.87; N, 6.62.

The supernatant liquid was evaporated and the residue was shown to be a mixture of starting olefin and product 17.

(22) Chemical Samples Co., Columbus, Ohio.

Registry No.—**1**, 694-91-7; **2**, 32846-86-9; **5**, 16219-75-3; **6**, 32846-87-0; **9**, 32846-82-5; **10**, 32846-83-6; **11**, 32846-84-7; **14**, 4659-42-1; **15**, 32839-07-9; **16**, 931-64-6; **17**, 32839-08-0; nitrosyl chloride, 2696-92-6; 3,3′-dinitro-2,2′-azodioxynorbornane, 32861-60-2.

Acknowledgment.—We wish to thank Mr. William O. Brown and Mr. Russell Turner for assistance with portions of the experimental procedures.

trans,trans,cis-2,8,12-*trans*-Bicyclo[8.4.0]tetradecatriene[1,2]

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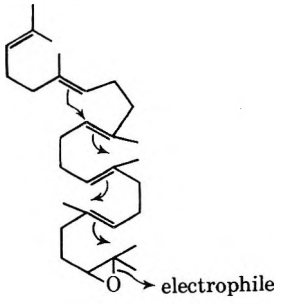
Received June 17, 1971

The synthesis is described of a *trans,trans*-1,5-cyclodecadiene **4a** which is thermally stable but not degenerate with respect to the Cope rearrangement.

One postulate for the enzymatically controlled cyclization of squalene oxide (**1**) involves epoxide cleavage with conformational holding and nucleophilic participation of remote double bonds, acting through intermediate double bonds. Attractive as such a postulate might appear, it is virtually without experimental test; and appropriate models are not easily conceived or synthesized.[3] Our experience with the *trans,trans*-2,8-*trans*-bicyclo[8.4.0]tetradecadiene system (**3a,b**)[4,5] suggested that a study of compounds like 2 should



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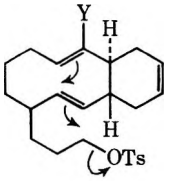
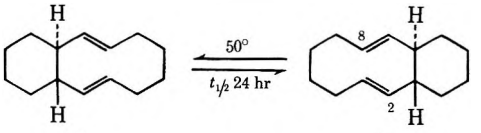
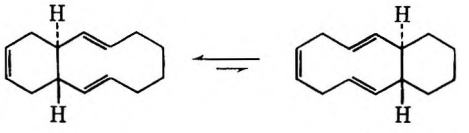


2

be informative with respect to the extent of participation of the remote bond in solvolysis of the tosylate, with Y appropriately substituted. This article details preliminary work leading to the synthesis of the corresponding unsubstituted system **4a**, *trans,trans,cis*-2,8,12-*trans*-bicyclo[8.4.0]tetradecatriene; **4a** possesses one more double bond than the system **3a,b**. This additional double bond should have the effect of heavily weighting the Cope-related equilibrium **4a,b** in favor of **4a** (**4b** is highly strained), thus avoiding the problem of constitutional isomers which arises upon substituting the **3b** system at C-4.



3a **3b**



4a **4b**

On the basis of the established synthetic route to **3a,b** (**5** → **6a** → **6c** → **3a,b** in Scheme I),[4] preparation of **4a,b** simply involved making and fragmenting the appropriately substituted *trans,syn,trans*-dodecahydroanthracene **7**. This appeared to be particularly straightforward because the synthesis of **3a,b** proceeded from **5** (formed by isomerizing the bis adduct of butadiene and benzoquinone[6]), a compound already functionalized with two identical double bonds, correctly positioned; and the simplest solution was therefore to reduce one of them. However, no conditions of catalytic hydrogenation could be found which resulted in any selectivity in the absorption of the first and second moles of hydrogen; or in any mixture which could be separated into its unreduced, partially reduced, and fully reduced components.

(1) The investigation was supported by Public Health Service Research Grant GM 16338 from the Division of General Medical Sciences, U. S. Public Health Service.

(2) The article is abstracted from the Ph.D. Thesis of G. O. S., Wesleyan University, 1971.

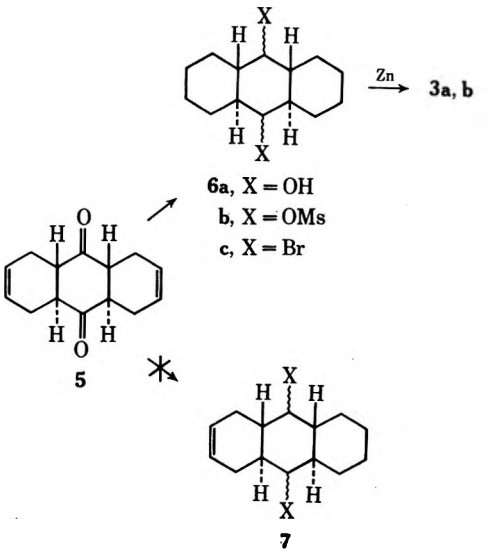
(3) For a review of polyolefin cyclizations see W. S. Johnson, *Accounts Chem. Res.*, **1**, 1 (1968). For comments, additional references, and one example of a double bond participating in an S_N2' displacement see G. D. Sargent, J. A. Hall, M. J. Harrison, W. H. Demisch, and M. D. Schwartz, *J. Amer. Chem. Soc.*, **91**, 2379 (1969).

(4) P. S. Wharton, Y. Sumi, and R. A. Kretchmer, *J. Org. Chem.*, **30**, 234 (1965).

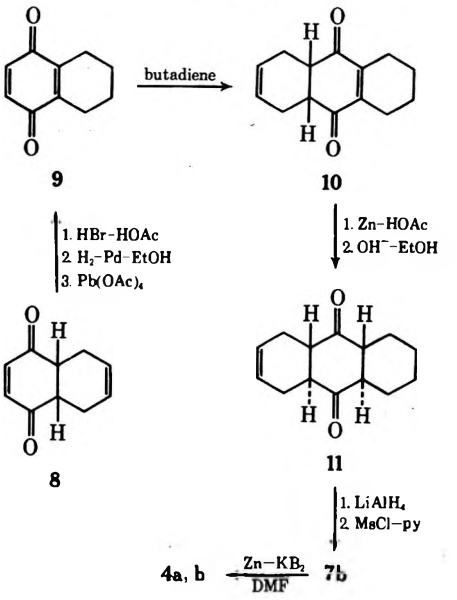
(5) P. S. Wharton and R. A. Kretchmer, *ibid.*, **33**, 4258 (1968).

(6) K. Alder and G. Stein, *Justus Liebigs Ann. Chem.*, **501**, 247 (1933).

SCHEME I



SCHEME II



A more rational route proceeding *via* quinone **9** was then pursued; see Scheme II. Quinone **9** is conveniently made in three steps from the monoadduct of butadiene and benzoquinone (**8**):[7,8] acid-catalyzed aromatization of enedione **8**, catalytic hydrogenation of the isolated double bond, and oxidation of the hydroquinone. Addition to **9** of excess butadiene in benzene solution at room temperature afforded tricyclic dione **10** in high yield (addition to the less substituted side of the quinone).[9] Reduction of the conjugated double bond of **10** was accomplished with zinc in acetic acid; the product, obtained in 87% yield, consisting of a mixture[10] of isomeric diones, mp 169–208°. This mixture was isomerized in 74% yield to white, platelike crystals, mp 225–231°, by dissolving in a small volume of hot alcohol, adding ethanolic potassium hydroxide solution while hot, and then allowing to crystallize. The crystals obtained in this way consisted principally of trans,syn,trans dione **11**, as shown by catalytic reduction and comparison of the product with authentic 9,10-diketo-*trans,syn,trans*-perhydroanthracene.[6]

Lithium aluminum hydride reduction of dione **11** gave a mixture of isomeric diols **7a** which was subjected to the fragmentation sequence successfully used in the preparation of **3a,b**: conversion of diol mixture **6a** to dibromide **6c** with phosphorus tribromide in carbon tetrachloride and then fragmentation of the dibromides with zinc.[4] However, the reported conversion of **6a** to **6c** was never very satisfactory and when it was found that attempted parallel conversion of **7a** to **7c** gave completely saturated compounds, apparently from addition of hydrogen bromide to the double bond, further attempts to effect the conversion were discontinued while alternatives were examined using the more plentiful diol mixture **6a**. A successful method was developed *via* dimesylate mixture **6b** (straightforwardly obtained, although the corresponding ditosylate could not be made) and it was eventually found that **6b** could be fragmented to **3a,b** in ~34% yield (based on diol) by treatment with zinc dust in dimethylformamide at 60–70° containing potassium bromide. Preparatively, this is simpler and also approximately five times more efficient than the former procedure.

The occurrence of an interesting set of interactions of the fragmentation reagents can be appreciated from the observations that treatment of dimesylate mixture with zinc alone induced no fragmentation and treatment with potassium bromide alone resulted mainly in elimination, not substitution, of the mesylate functions. Informative fragmentations were carried out on individual dimesylate isomers *trans*-(ee)-**6b** and *cis*-(ea)-**6b**,[11] which were made by mesylating the corresponding diols. Reactions were monitored by observation of characteristic absorptions in the nmr spectra of products obtained from aliquots periodically removed. After 70 hr trans and cis dimesylates afforded products consistent with 47 and 31% fragmentation, respectively, with much elimination apparent from the loss of mesylate hydrogen absorption and the appearance of vinyl hydrogen absorption at δ 5.0 ppm. The effect of an added equivalent amount of potassium hydroxide was striking, the extent of fragmentation of cis dimesylate decreasing only slightly from 31 to 20% and of trans dimesylate dropping sharply from 47 to 6%.

These facts are consistent with the major pathway of fragmentation consisting of (1) initial substitution to form a bromomesylate, with axial mesylate reacting faster than equatorial,[12] cis (ea) dimesylate thereby yielding trans (ee) bromomesylate preferentially and trans (ee) dimesylate giving cis (a) bromo (e) mesylate, with mesylate equatorial in both intermediate bromomesylates; (2) reaction of zinc with both equatorial and axial bromine to give carbon–zinc bonds which are

(7) O. Diels and K. Alder, *Chem. Ber.*, **62**, 2337 (1929).

(8) In principle it is simpler to reduce the isolated double bond of **8**, thereby saving several steps, but attempted catalytic reductions yielded only phenolic compounds and tars from aromatization (independent experiments of Flesch).

(9) See the following for comments on selectivity in 1,4 cycloadditions to substituted quinones: M. F. Ansell, B. W. Nash, and D. A. Wilson, *J. Chem. Soc.*, 3012 (1963).

(10) Similar zinc reductions have been found to give either cis or trans isomers or mixtures; see C. S. Barries and D. H. R. Barton, *ibid.*, 1419 (1952) and J. Scotney and E. V. Truter, *J. Chem. Soc., C*, 1079 (1969).

(11) The symbols e and a are abbreviations designating equatorial and axial stereochemistry.

(12) See the following for pertinent comments: E. L. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill, New York, N. Y., 1962, pp 224–228.

configurationally labile[13] and more stable in the less hindered equatorial position; (3) formation of trans,-trans diene **3a,b** by fragmentation of the configurationally ideal[14] trans (ee) mesyloxyzinc intermediate. Elimination is a hazard starting from either dimesylate, although only axial leaving groups are readily susceptible to E2 elimination:[12] cis dimesylate can directly afford olefin by elimination of an axial mesylate in competition with substitution; trans dimesylate can after formation of cis bromomesylate which can eliminate axial bromine in competition with reaction with zinc or further substitution. The addition of hydroxide has a relatively unfavorable action on trans dimesylate because the axial bromine of the intermediate bromomesylate is relatively more susceptible to hydroxide-induced elimination than is the axial mesylate of cis dimesylate.

Application of the dimesylate fragmentation sequence to the mixture of diols **7a** afforded in 48% yield, after chromatography, an oily triene characterized as **4a** by analytical and spectroscopic data. The oil was examined for the presence of the Cope-related isomer **4b** but none could be detected: ozonolysis, with an oxidative work-up and subsequent esterification, yielded dimethyl adipate, as expected from **4a**, but not a trace of dimethyl *trans*-1,2-cyclohexanedicarboxylate, which would be formed from any **4b** present. Based on this successful preparation of **4a**, syntheses of compounds like **2** are underway.

Experimental Section

Physical Data.—Melting points were determined in capillary tubes with a Thomas–Hoover melting point apparatus and are uncorrected. The analysis was performed by Spang Microanalytical Laboratory, Ann Arbor, Mich. Infrared spectra were obtained on Beckman IR-8 and Perkin-Elmer Model 137 Infracord spectrometers. Varian A-60 and A-60A spectrometers were used to record nmr spectra, and chemical shifts are reported in parts per million measured from an internal tetramethylsilane reference. Gas–liquid phase chromatography (glpc) was performed on Varian Aerograph A-90 and A-90-P gas chromatographs. All peak areas were measured with a Disc chart integrator.

Materials.—Activated zinc was prepared by stirring zinc dust in 1 *N* hydrochloric acid for 15 min and washing with distilled water until neutral. The zinc was then washed three times with absolute ethanol and three times with anhydrous ether, and dried at 60 or 100° overnight. Potassium bromide was recrystallized, pulverized, and dried for at least 2 hr at 110° before use. Solvents were dried and/or distilled before use with the exception of ether and alcohol. Purified pentane was prepared from distilled pentane by washing it successively with concentrated sulfuric acid, concentrated potassium permanganate in 10% sulfuric acid, and water. It was then dried and eluted through acid-washed alumina. Silica gel used in column chromatography was Grade 950, mesh size 60–200, obtained from Davison Chemical. Anhydrous magnesium sulfate was used to dry organic extracts.

***trans,trans*-2,8-*trans*-Bicyclo[8.4.0]tetradecadiene (3a,b).**—The following represents an improvement over the previously reported procedure.[4] A mixture of 100.0 g of **5**,[6] mp 235–243°, and 480 ml of absolute ethanol was hydrogenated over *ca.* 18 g of W-2 Raney nickel catalyst at 1500 psi and 150–200° for 18 hr. The resulting slurry was diluted with 5000 ml of tetrahydrofuran, heated to near boiling temperature, and filtered while hot. The liquid was cooled to 5°. Filtration and drying yielded 49.4 g (48%) of **6a** as a white powder, mp 242.5–250.5°.

To a stirred suspension of 1.12 g (5.00 mmol) of this powder in 25 ml of dry pyridine, cooled to ice-bath temperature, was added 3.75 g (32.5 mmol) of methanesulfonyl chloride. Stirring was continued for 15 min and then the mixture was allowed to stand unstirred overnight at 6°. Then after stirring for 30 min the mixture was poured into 100 ml of cold water. The white solid which formed was collected by filtration, washed with cold 5% hydrochloric acid, cold water, and ether, and then dried, yielding 1.73 g (91%) of **6b** as a white powder: mp 127.0–129.5° dec; ir (KBr) 3.47, 7.53, and 8.56 μ; nmr (acetone-d_6) δ 0.8–2.2 (complex, 20), 3.10 and 3.13 (singlets, 3.5 and 2.5, combined $-OSO_2CH_3$), and 4.20 and 4.62 ppm (complex, 1.4 and 0.6, combined methine protons at carbon bearing $-OSO_2CH_3$).

A mixture of 6.84 g (0.0180 mol) of dimesylate **6b**, similar to that obtained above, mp 124.0–127.5° dec, 8.57 g (0.0720 mol) of freshly dried potassium bromide powder, and 3.53 g (0.0540 g-atom) of activated zinc dust in 90 ml of dimethylformamide was heated to 60–70° for 47 hr. During the reaction 10 ml of dimethylformamide was added to rinse the walls of the reaction flask. The resulting mixture was filtered and the remaining zinc was washed repeatedly with pentane. The combined filtrates were diluted with additional pentane (total 500 ml) and then washed six times with 250 ml of water, dried, and concentrated under reduced pressure to give 3.35 g of a white paste (96% based on loss of both mesylate groups). This material was chromatographed on 250 g of silica gel (column length: diameter = 12.8:1), collecting 20 150-ml fractions of pentane as eluent. Fractions 2–4 yielded 0.49 g of a mixture of saturated and unsaturated compounds. Fractions 5–15 yielded 1.25 g (34% based on diol mixture **6a**) of **3a,b** as an oily, white solid whose ir and nmr spectra were identical with those of authentic diene.[4]

Fragmentation of *cis*-9,10-Dimethanesulfonyloxy-*trans,syn,-trans*-perhydroanthracene.—A sample of cis diol **6a** was obtained from catalytic hydrogenation under 2000 psi of hydrogen at 100° for 20 hr of 10.0 g (4.63 mmol) of dione **5**, mp 239.5–245.5°, in 200 ml of ethyl acetate containing 1 ml of 60% perchloric acid and 0.75 g of platinum oxide. The resulting slurry was diluted with 1000 ml of warm ethyl acetate and filtered. A precipitate formed in the filtrate. After cooling, collection and drying yielded 0.86 g (8%) of white, flocculent crystals, mp 260–263°. The mother liquor was concentrated at reduced pressure to give a second crop of 0.42 g (4%) of white powder, mp 255–262°, ir (KBr) identical with that of the first crop. Combined crops 1 and 2 were recrystallized from tetrahydrofuran, yielding 0.78 g of cis diol **6a** as fine, white needles, mp 265.5–266.5°. [Correlation of the stereochemistry of this diol with that of the known diacetates was established by acetylating a mixture of 100 mg (0.446 mmol) of diol with 1.0 ml of acetic anhydride in 5 ml of pyridine at reflux temperature for 1 hr. Work-up gave 136 mg (99%) of white powder, mp 152.0–156.5°, recrystallization of which afforded material with mp 159.0–161.0°, undepressed upon mixing with authentic cis diacetate.[4]] To a mixture of 600 mg (2.68 mmol) of diol **6a**, mp 265.5–266.5°, and 15 ml of pyridine, cooled to ice-bath temperature, was added, with stirring, 1.50 ml of distilled methanesulfonyl chloride. After 18 hr at *ca.* 6° the mixture was poured into 25 ml of cold water. The resulting precipitate was collected, washed, and dried, affording 968 mg (95%) of *cis*-**6b** as a white powder, mp 125.0–125.5° dec.

Fragmentation of 380 mg (1.00 mmol) of *cis*-**6b** was carried out in the presence of 196 mg (3.00 mg-atom) of activated zinc dust and 476 mg (4.00 mmol) of potassium bromide powder in 8 ml of dimethylformamide, heated at 60–65°, with stirring under nitrogen. Periodically, aliquots were removed to monitor the course of the reaction and, after 70 hr, the remaining reaction mixture was worked up. Analysis of the nmr spectrum of the crude product indicated a yield of **3a,b** of 30% (based on absorption at δ 4.8 ppm) with much elimination of methanesulfonic acid (based on absorption at δ 5.0 ppm).

Fragmentation of *cis*-**6b** was also carried out in the presence of base: a mixture of 300 mg (0.790 mmol) of *cis*-**6b**, 150 mg (2.37 mg-atom) of activated zinc dust, 386 mg (3.16 mmol) of potassium bromide powder, and 49 mg (1.2 mmol) of sodium hydroxide in 7 ml of dimethylformamide was heated at 60–70° and aliquots were removed periodically to monitor the course of the reaction. Work-up, after 70 hr, gave a product, the nmr spectrum of which indicated a yield of **3a,b** of 20% with much elimination of methanesulfonic acid.

Fragmentation of *trans*-9,10-Dimethanesulfonyloxy-*trans,syn,-trans*-perhydroanthracene.—A sample of trans diol **6a**, mp 284–

(13) J. Boersma and J. C. Noltes, *J. Organometal. Chem.*, **8**, 551 (1967).

(14) The stereochemistry of fragmentation reactions is discussed by C. A. Grob, *Angew. Chem., Int. Ed. Engl.*, **8**, 535 (1969), and C. A. Grob and P. W. Schiess, *ibid.*, **6**, 1 (1967).

285°, was obtained by saponification of the corresponding diacetate.[4] The remaining procedures closely followed those described for fragmentation of *cis*-6b. Mesylation of a 600-mg sample of *trans*-6a afforded 970 mg (95%) of *trans*-6b as a white powder, mp 181.0–181.5° dec.

Fragmentation of a 380 mg (1.00 mmol) sample of *trans*-6b with 196 mg (3.00 mg-atom) of activated zinc dust and 476 mg (4.00 mmol) of potassium bromide in 8 ml of dimethylformamide at 60–70° for 70 hr yielded a product containing 46% of fragmentation product 3a,b and much olefin from elimination of methanesulfonic acid. Fragmentation of a 300 mg (0.790 mmol) sample of *trans*-6b under similar conditions but with the addition of 47 mg (1.2 mmol) of sodium hydroxide afforded a product in which elimination of methanesulfonic acid had predominated, fragmentation accounting for only 6% (based on nmr absorption at δ 4.8 ppm).

9,10-Diketo-Δ^2-*trans,syn,trans*-dodecahydroanthracene (11).—A solution of 8.47 g (52.2 mmol) of quinone 9[7] in 15 ml of dry benzene solution containing 11 g (210 mmol) of butadiene was kept in the dark at room temperature for 17 days. During the reaction period an additional 2 g (38 mmol) of butadiene in benzene was added to the mixture. Finally, the reaction mixture was concentrated to dryness under reduced pressure, yielding 10.9 g (96%) of a beige powder: mp 108–111°; nmr (CCl_4) δ 1.65 (complex, 4), 2.27 (complex, 8), 3.03 (complex, 2), and 5.49 ppm (complex, 2). (Absorption at δ 7.56 ppm indicated contamination by starting material to be less than 2%.) The crude solid was crystallized from 10% ethyl acetate–hexane to yield 5.90 g (52%) of beige needles: mp 112–113.5°; ir (KBr) 6.16 μ. Concentration of the mother liquor gave a second crop of 2.60 g (23%), mp 110–112°.

Over a 15-min period, 30 g (0.46 g-atom) of activated zinc was added in portions to a solution of 10.0 g (16.0 mmol) of butadiene adduct, mp 109–112°, in 300 ml of glacial acetic acid maintained at 115°. The mixture was heated at reflux temperature under nitrogen for 85 min and then filtered while hot. Additional warm acetic acid was used to rinse the collected zinc. The combined filtrates were diluted with 1750 ml of ether and subsequently washed five times with 500 ml of water, once with 5% sodium bicarbonate solution, and again with water. Drying and concentration at reduced pressure afforded 8.82 g (87%) of a mixture of stereoisomeric diones as a white, violet-tinged solid: mp 169–208°; ir (KBr) 5.91 μ; nmr ($CDCl_3$) δ 0.7–3.7 (complex, 16), and 5.79 ppm (s, 2). The crude mixture of reduced diones (8.68 g) was dissolved with heating and stirring in 30 ml of ethanol and the solution was treated with 2 ml of a 5% ethanolic potassium hydroxide solution. A reddish-brown coloration developed and was followed by the rapid separation of white crystals. The mixture was cooled at 6° for 2 hr and the precipitate was collected, washed with cold ethanol, and dried, affording 6.41 g (74%) of white plates, mp 225–231°, ir (KBr) 5.92 μ. This substance was characterized as 11 by hydrogenation of a 250-mg sample in 80 ml of tetrahydrofuran for 100 min at room temperature under 300 psi of hydrogen and over 500 mg of 5% palladium on charcoal. The resulting mixture was heated to near reflux temperature and filtered while hot, and the filtrate was concentrated under reduced pressure to yield yellow-white prisms, mp 215–226°, no nmr (CF_3CO_2H) absorption due to vinyl hydrogen. Crystallization from ethanol yielded 180 mg (71%) of white needles, mp 249–252.5°, undepressed upon mixing with a sample of authentic 9,10-diketo-*trans,syn,trans*-perhydroanthracene,[6] ir (KBr) matched that of authentic material.

***trans,trans,cis*-2,8,12-*trans*-Bicyclo[8.4.0]tetradecatriene (4a).**—To a magnetically stirred suspension of 0.50 g (13 mmol) of lithium aluminum hydride in 75 ml of tetrahydrofuran was added 0.50 g (23 mmol) of dione 11, in portions along with 15 ml of tetrahydrofuran. Stirring under nitrogen at room temperature was continued overnight. Excess lithium aluminum hydride was destroyed by addition of ethanol and water, and 50 ml of 5% hydrochloric acid was then added. Organic solvents were removed under reduced pressure and the remaining solid was filtered and then washed successively with 10% sodium hydroxide solution, water, 5% hydrochloric acid, and ethanol, yielding, after drying, 1.29 g of yellow powder. This material was extracted with chloroform–2% hydrochloric acid, the chloroform extracts yielding 0.32 g (63%) of a mixture of diols 7a as a pale yellow powder, mp 197–227°, ir (KBr) showing no carbonyl absorption.

In a typical run, 13.8 g (120 mmol) of methanesulfonyl chloride was added to a cooled, stirred suspension of 4.08 g (18.4 mmol) of diol mixture 7a, obtained as described above, in 100 ml of dry pyridine. The mixture was stored at 5° for 2 days. Addition of 350 ml of cold water produced a white solid which was collected and washed with 5% hydrochloric acid, water, and ether. Drying yielded 6.61 g (95%) of a mixture of dimesylates 7b as a white powder, mp 129–130° dec.

A mixture of 6.39 g (16.9 mmol) of this dimesylate mixture, 8.05 g (67.6 mmol) of dried potassium bromide powder, and 3.32 g (50.7 mg-atoms) of activated zinc in 90 ml of dry dimethylformamide was stirred under nitrogen at 60–70° for 28 hr. The zinc remaining in the reaction mixture was removed by filtration and washed with pentane. Washing the combined filtrates thoroughly with water and further work-up yielded 3.00 g of a clear, slightly yellow oil: nmr (CCl_4) δ 0.6–3.0 (complex), 4.75 (complex, trans-disubstituted C=C), and 5.15 ppm (broad singlet, cis-disubstituted C=C). The integration ratio for absorbance at δ 5.15 (2 H) and 4.75 ppm (4 H) of 20:23 indicated that triene 4a formed about 58% of the mixture.

The reaction product was chromatographed on 225 g of silica gel (column length:diameter = 11:1) using eight 175-ml portions of distilled pentane followed by nine 175-ml portions of 5% ether–pentane as eluting solvents. Fractions 2 and 3 yielded 0.095 g of a white solid, probably Δ^2-*trans,syn,trans*-dodecahydroanthracene: mp 49.5–51°; nmr (CCl_4) δ 0.5–2.4 (complex, 20) and 5.60 ppm (c, 2, J = 2 Hz, disubstituted C=C). Fractions 4–7 yielded 0.458 g of a clear, colorless oil, probably a mixture of $\Delta^{2,4a(10)}$- and $\Delta^{2,10}$-*trans,cis*-decahydroanthracenes: nmr (CCl_4) δ 0.6–3.0 (complex, 17), 5.15 (complex, 11, trisubstituted C=C), and 5.68 ppm (complex, 2, disubstituted C=C). Fractions 9–14 yielded 1.530 g (48% based on starting dimesylate mixture) of *trans,trans,cis*-2,8,12-*trans*-bicyclo[8.4.0]tetradecatriene (4a) as a clear, very pale yellow oil: ir (CCl_4) 10.34 μ; nmr (CCl_4) δ 0.6–2.9 (complex, 14), 4.75 ppm (complex, 4, trans-disubstituted C=C), and 5.72 ppm (d, 2, J = 11 Hz, cis-disubstituted C=C). A portion of this material was rechromatographed over silica gel using purified pentane as eluting solvent. Evaporation of solvent from the third of five fractions afforded an analytical sample.

Anal. Calcd for $C_{14}H_{20}$: C, 89.29; H, 10.71. Found: C, 88.88; H, 10.91.

Ozonolysis of 4a.—An excess of ozone from a Welsbach ozonator, Model T-408, was bubbled into a solution of 48 mg (0.26 mmol) of triene 4a in 7 ml of dry methylene chloride at −75°. The resulting blue solution and white gelatinous precipitate were allowed to warm to room temperature and 3 ml of 40% peracetic acid (FMC Corp.) was then added. After diluting the mixture with ethyl acetate and heating it to reflux for 28 hr, 150 mg of 30% palladium on charcoal was added. The total mixture was dried, filtered, and concentrated under reduced pressure to give 70 mg of brown residue, ir ($CHCl_3$) 5.78 μ. The residue was dissolved in ether and washed with 10 ml of 10% sodium hydroxide solution. Acidification of the aqueous phase with 15 ml of 10% hydrochloric acid, followed by thorough extraction with ether, yielded, upon further work-up, 10.5 mg of yellow solid which was esterified with diazomethane. The product was subjected to glpc analysis at 150° on a 5 ft × 0.25 in. column packed with 5% Carbowax 20M on Chromasorb T; only one peak was apparent, with a retention time of 3.6 min, identical by coinjection with the retention time of an authentic sample of dimethyl adipate. The peak of an authentic sample of dimethyl *traus*-1,2-cyclohexanedicarboxylate, subjected to the above-described column conditions, appeared at 6.0 min.

Registry No.—3a,b, 17510-77-9; 4a, 32687-22-0; 6a, 3922-06-3; 6b, 32675-59-5; 7a (mixture of diols), 32675-58-4; 10, 32675-56-2; 11, 32675-57-3; Δ^2-*trans,syn,trans*-dodecahydroanthracene, 32675-60-8.

Facile Bridge Expulsion of Sulfur Heterocycles. The 7-Thiabicyclo[2.2.1]hepta-2,5-diene and 7-Thiabicyclo[4.1.0]hepta-2,4-diene Systems in Thiepin Synthesis

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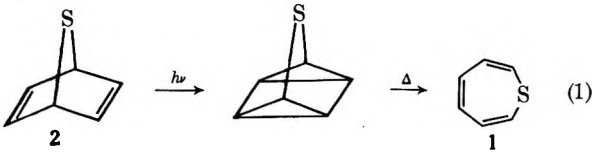
Received June 28, 1971

Dehydrohalogenation of bis-*endo*-1,5-dichloro-7-thiabicyclo[2.2.1]heptane (**3**) and 3,4-dibromo-7-thiabicyclo-[4.1.0]heptane (**9**) was attempted with a variety of rather nonnucleophilic bases. From **3** the desired 7-thianorbornadiene (**2**) was not observed but benzene was formed presumably from this intermediate. From **9** benzene was also formed and this is postulated to arise from sulfur extrusion from thiepin or thianorcaradiene.

Despite the syntheses of several substituted derivatives,[1] the parent thiepin (**1**) is yet unknown. As the parent oxepin is now known and its behavior well established,[2] it would be of considerable interest to prepare and investigate the thiepin in order to compare the properties of these two basic heterocyclic ring systems. The successful synthesis of the stable thiepin 1,1-dioxide by Mock[3] lends further impetus to this goal as does the recent report of SCF–MO calculations which indicate that **1**, if planar, would be antiaromatic.[4] We decided to attack this problem from two different directions, both of which involved elimination of two molecules of hydrogen halides from key intermediates.

The first route employed was to adapt the Prinzbach[5] method for oxepin and azepin synthesis to the synthesis of thiepin as illustrated in eq 1.



2 1 (1)

While the most obvious choice for the synthesis of 7-thiabicyclo[2.2.1]hepta-2,5-diene (**2**) would be a Diels–Alder reaction between thiophene and acetylene, the well-established lack of reactivity of thiophenes in this addition[6] makes this an unlikely route. However, the ready availability of bis-*endo*-1,5-dichloro-7-thiabicyclo[2.2.1]heptane (**3**) from the addition of sulfur dichloride to 1,4-dihydrobenzene[7] afforded a likely starting material. Unfortunately, the elimination of two molecules of hydrogen chloride from **3** proved rather frustrating in that the usual techniques afforded either no reaction or no isolable sulfur-containing products. Sodium 2-*n*-butylcyclohexoxide (BCO) had been shown to be a uniquely effective base for the elimination of hydrogen halides from endo-substituted norbornyl halides.[8] Under conditions mild enough to possibly provide an opportunity to observe thiepin, BCO proved ineffective as respectable recoveries of starting material were realized. Other bases employed for the dehydrochlorination of **3** were potassium *tert*-butoxide, 1,5-diazobicyclo[4.3.0]non-5-ene (DBN), 1,5-diazobicyclo[5.4.0]undec-5-ene (DBU), and bis-1,8-dimethylaminonaphthalene (BDMAN), the latter being a particularly good nonnucleophilic base.[9] The results of these attempted dehydrochlorinations are summarized in Table I. While BCO proved to be rather unreactive to **3**, potassium *tert*-butoxide, DBN, and BDMAN each afforded benzene in low yield. In addition, the reaction of **3** with BDMAN yielded a large amount of 1,4-dihydrobenzene. The formation of this latter product likely proceeds through cyclic episulfonium ions and is analogous to the recently reported eliminations of 4-chlorobenzenesulfenyl chloride from chloroalkyl 4-

TABLE I

Halide	Base[a]	Solvent	Temp, °C	Products identified (yield, %)[b]
3	BCO	Et_2O	0	**3** (61)
3	BCO	Et_2O–BCOH	23	**3** (75)
3	KO-*tert*-Bu (3 *N*)	*tert*-BuOH	82	Benzene (6)
3	DBN (3 *N*)	CD_3CN	50[c]	Benzene (19)
3	BDMAN	CH_3CN	65–70[c]	Benzene (10); 1,4-dihydrobenzene (57)
3	DBU	DMSO-d_6	73 ± 3	Benzene (68)
5	DBU	CD_3CN	70 ± 5	Benzene (45); 1,4-dihydrobenzene (1)
9	KO-*tert*-Bu (3 *N*)	*tert*-BuOH	30	Benzene (4)
9	DBN (3 *N*)	DMSO	23	Benzene (4)
9	BDMAN	CH_3CN	24	Benzene (36)
9	DBU (3 *N*)	Neat	25 ± 3	Benzene (38)

[a] Unless otherwise noted, 2 equiv of base were employed. [b] Benzene and 1,4-dihydrobenzene were identified by comparison and enrichment using a combination of gc and nmr spectroscopy. The gc was performed on columns of either 3% SE-30 on 100/120 Varaport 5 ft × 0.25 in. or 10% SE-30 on 60/80 Chromosorb W 10 ft × 0.25 in. Yields were calculated using the integration ratios of portions of reaction mixtures as distillates of known weights. [c] No reaction occurred at room temperature.

(1) (a) G. P. Scott, *J. Amer. Chem. Soc.*, **75**, 6332 (1953); (b) W. E. Truce and F. J. Lotspeich, *ibid.*, **78**, 848 (1956); (c) K. Dimroth and G. Lenke, *Angew. Chem.*, **68**, 519 (1956); (d) E. D. Bergmann and M. Rabinowitz, *J. Org. Chem.*, **25**, 828 (1960); (e) K. Dimroth and G. Lenke, *Chem. Ber.*, **89**, 2608 (1956); (f) R. H. Schlessinger and G. S. Ponticello, *J. Amer. Chem. Soc.*, **89**, 7138 (1967); (g) R. H. Schlessinger and G. S. Ponticello, *Tetrahedron Lett.*, 3017 (1968), 4361 (1969); (h) H. Hofmann and H. Westernacher, *Angew. Chem., Int. Ed. Engl.*, **5**, 958 (1968); (i) J. M. Hoffman, Jr., and R. H. Schlessinger, *J. Amer. Chem. Soc.*, **92**, 5263 (1970).

(2) (a) E. Vogel, R. Schubart, and W. A. Böll, *Angew. Chem., Int. Ed. Engl.*, **3**, 510 (1964); (b) E. Vogel, and W. A. Böll, and H. Gunther, *Tetrahedron Lett.*, 609 (1965); (c) E. Vogel and H. Gunther, *Angew. Chem., Int. Ed. Engl.*, **6**, 385 (1967).

(3) W. L. Mock, *J. Amer. Chem. Soc.*, **89**, 1281 (1967).

(4) M. J. S. Dewar and N. Trinajstic, *ibid.*, **92**, 1453 (1970).

(5) H. Prinzbach, M. Arguelles and E. Druckrey, *Angew. Chem., Int. Ed. Engl.*, **5**, 1039 (1966).

(6) J. F. Scully and E. V. Brown, *J. Amer. Chem. Soc.*, **75**, 6329 (1953).

(7) E. J. Corey and E. Block, *J. Org. Chem.*, **31**, 1663 (1966).

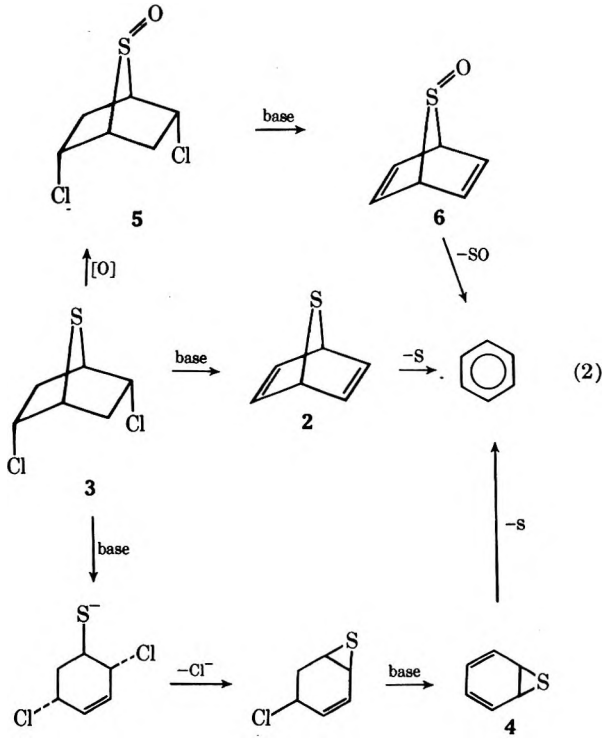
(8) (a) M. Hanack, H. Eggensperger, and R. Hähnle, *Justus Liebigs Ann. Chem.*, **652**, 96 (1962); (b) M. Hanack and R. Hähnle, *Chem. Ber.*, **95**, 191 (1962).

(9) R. W. Alder, P. S. Bowman, W. R. S. Steele, and D. R. Winterman, *Chem. Commun.*, 723 (1968).

chlorophenyl sulfides;[10] however, the reason for this singular departure is not understood at present.

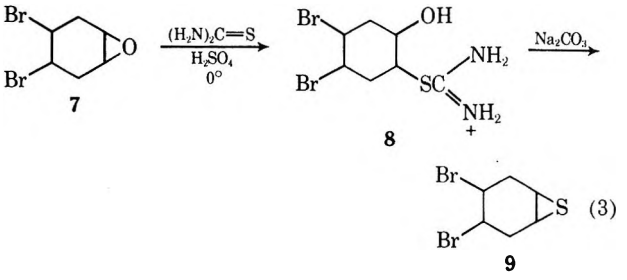
Formation of benzene from **3** may be explained as either proceeding by thermal extrusion of sulfur from **2** or initial anionic ring opening eventually leading to the thianorcaradiene **4** from which sulfur extrusion may take place. This latter pathway would be expected to lead also to thiophenol. Efforts to isolate this product were uniformly unsuccessful and if present it must be a very minor component.

If indeed benzene results from a bridge expulsion of sulfur from **2**,[11] an approach to a more stable diene could be the prior oxidation of **3** to the sulfoxide **5**. The resulting diene, **6**, would have to extrude sulfur monoxide if it were to decompose to benzene. However, reaction of **5** with DBU provides benzene as the sole isolable product in good yield (45%). This observation casts further doubt on a mechanism involving initial anionic ring opening, as the driving force of formation of the mercaptyl anion is removed in the case of **5**. Although likely and reasonable, the intermediacy of **2** cannot be said to be definite. Several of the reactions in Table I were performed in nmr tubes with continuous nmr monitoring. With the exception of BDMAN–acetonitrile system (which exhibited vinyl absorption for 1,4-dihydrobenzene), none of the nmr spectra of the reaction mixtures revealed any olefinic absorption indicative of **2** or **6**.



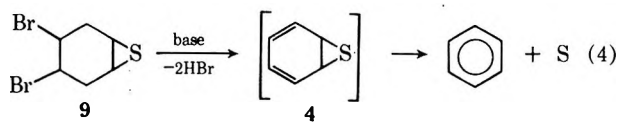
(2)

A much more straightforward route to thiepin synthesis is one similar to that used by Vogel in the synthesis of oxepin.[2] Indeed the final intermediate in Vogel's synthesis, 4,5-dibromocyclohexene oxide (**7**), can be utilized as a logical starting point for the synthesis of thiepin. Compound **7** was easily converted to the thiourium salt (**8**) in high yield by reaction with thiourea. Treatment of **8** with aqueous sodium carbonate resulted in good yields (85%) of white, crystalline 3,4-dibromo-7-thiabicyclo[4.1.0]heptane (**9**).



(3)

When **9** was treated with a variety of bases, including sodium methoxide, triethylamine, potassium *tert*-butoxide, DBN, DBU, and BDMAN in several solvents, isolation of any product even vaguely resembling thiepin could not be accomplished. Certain of these results are summarized in Table I and in each case benzene was the sole identifiable product. With the exception of the BDMAN–acetonitrile system, no olefinic products could be detected. Using BDMAN, an intermediate olefinic material(s) exhibiting complex absorptions at δ 5.5 and 4.75–4.4 was observed; it appeared to decompose to benzene. While the data do not absolutely demand the intermediacy of thianorcaradiene (**4**), it seems likely that this intermediate is formed and quickly eliminates sulfur to form benzene (eq 4). This



(4)

type of elimination is well established for substituted thiepins, although the thermal stability strongly depends upon the nature of the substituents.[1,11]

Experimental Section[12]

2,5-Bis-*endo*-dichloro-7-thiabicyclo[2.2.1]heptane (**3**) was prepared by the method of Corey and Block using sulfur dichloride and 1,4-cyclohexadiene in methylene chloride.[7] Sulfide **3** was oxidized to sulfoxide **5**, mp 170–71.5°, in 92% yield through reaction with 1 equiv of *m*-chloroperbenzoic acid in chloroform for 1 week at 0°. The ir spectrum of **5** revealed a very intense band at 1055 cm^{-1} (S=O); the nmr spectrum (CD_3CN) showed absorptions at δ 5.0 (m, 1 H), 4.48 (m, 1 H), 3.69 (m, 2 H), 2.68 (m, 1 H), and 2.37 (m, 3 H); and the molecular weight was confirmed by the mass spectrum.

Sodium 2-*n*-butylcyclohexoxide (BCO) was prepared from sodium and 2-*n*-butylcyclohexanol according to the method of Hanack.[8]

Thiouronium Salt of 7 (8).—To a stirred, ice-cooled mixture consisting of 0.51 ml of concentrated sulfuric acid, 6.0 ml of water, 50 ml of ether, and 1.30 g (17 mmol) of thiourea was added a solution of 4.35 g (17 mmol) of **7** over 1.5 hr. A thick, milky mixture soon resulted and, after stirring for an addi-

(10) G. H. Schmid and P. H. Fitzgerald, *J. Amer. Chem. Soc.*, **93**, 2547 (1971). See also ref 7 and T. Tsuji, T. Komeno, H. Itani, and H. Tanida, *J. Org. Chem.*, **36**, 1648 (1971).

(11) For reviews of the thermal extrusion of sulfur, see B. P. Stark and A. J. Duke, "Extrusion Reactions," Pergamon Press, Oxford, 1967; J. D. Louden in "Organic Sulfur Compounds," Vol. 1, N. Kharasch, Ed., Pergamon Press, Oxford, 1961, p 299; and R. Grigg, R. Hayes, and J. L. Johnson, *Chem. Commun.*, 1167 (1969).

(12) Elemental analysis was performed by Ilse Beetz, Kronach, West Germany. Infrared spectra were taken on a Perkin-Elmer Model 21 spectrophotometer. Nmr spectra were taken on a Varian Model A-60 or a Hatachi R20-B spectrophotometer using TMS as an internal standard. Mass spectra were obtained on an Atlas CH4 spectrometer. Gas chromatographic analysis was performed on either a Varian-Aerograph Hy Fi 600-C or a Varian-Aerograph 1700 using SE30 columns as indicated in the Experimental Section. Melting points are uncorrected.

tional 1 hr at 0–5°, the reaction mixture was allowed to warm to room temperature where stirring was continued for 12 hr. The white solid was then filtered, washed twice with 15 ml of absolute ethanol, and dried (5.24 g, 81%), mp 188° dec.

3,4-Dibromo-7-thiabicyclo[4.1.0]heptane (9).—A solution of sodium carbonate (0.56 g, 5.3 mmol) in 10 ml of water was added over a 30-min period to a slurry of **8** (4.00 g, 5.3 mmol) in 50 ml of water. Stirring was continued for 20 min after which the reaction temperature was raised to 50° for 15 min. After cooling, the mixture was filtered, washed three times with 25 ml of water, and dried. Recrystallization from ether–hexane afforded 2.43 g (85%) of the title compound: mp 59.5–60.5°; nmr (CCl_4) δ *ca.* 4.2 (complex m, 2 H), *ca.* 3.0 (very complex m, 6 H).

Anal. Calcd for $C_6H_8Br_2S$: C, 26.49; H, 2.96; Br, 58.76; S, 11.79. Found: C, 26.62; H, 3.08; Br, 58.60; S, 11.91.

Attempted Dehydrochlorination of 3 with BCO.—Dry nitrogen gas was bubbled through 4.40 ml (3.97 g, 25.6 mmol) of freshly distilled 2-*n*-butylcyclohexanol for *ca.* 15 min. Sodium metal (0.278 g, 12.4 mmol) was added. The magnetically stirred mixture was heated at 70° in a nitrogen atmosphere until all the sodium had reacted. Freshly distilled ethyl ether (9 ml, from $LiAlH_4$) was added to the stirred mixture followed by a solution of 1.00 g (5.5 mmol) of **3** in 4 ml of ether. After 2 days at room temperature, 5 ml of 2 *N* NaOH was added, followed by 12 ml of ether. The ether solution was extracted with 6–10-ml portions of 2 *N* NaOH. The combined alkaline extracts were acidified with HCl and extracted with three 25-ml portions of ether. After drying ($MgSO_4$), the ether was evaporated and the residue (38 mg) was analyzed by tlc (Brinkman PF_{254} and pentane). No thiophenol was observed in the many-component mixture.

The ether solution, after base extraction, was washed with water, washed with saturated NaCl solution, and dried over $MgSO_4$, and most of the ether was removed by distillation. The remaining liquid was analyzed by gc (Varian-Aerography Hy Fi 600-C) using a 5 ft × 0.125 in., 5% SE-30 on 60/80 Chromosorb W, column with a flame ionization detector. No benzene was seen. The mixture contained residual ether, 2-*n*-butylcyclohexanol, and **3**. The presence of **3** was confirmed by tlc. Dry column chromatography[13] on silica gel (pentane eluent) resulted in a 75% recovery of starting **3**.

Dehydrochlorination of 3 with Potassium *tert*-Butoxide.—To 12 ml of freshly distilled *tert*-butyl alcohol was added a mixture of 1.0 g (5.5 mmol) of **3** and 1.7 g (15 mmol) of potassium *tert*-butoxide. The magnetically stirred solution was refluxed under nitrogen for 24 hr. The *tert*-butyl alcohol was distilled in five fractions over a range of 74–82°. By gc (Varian-Aerograph 1700, 5 ft × 0.25 in. column of 30% SE-30 on 100/200 Anaport, thermal detector) and nmr it was determined that 24 mg of benzene was present in the alcohol distillate. The distillation residue was treated with aqueous KOH and then extracted with four 15-ml portions of ether. The combined ether extracts were extracted with four 15-ml portions of 2 *N* NaOH. Acidification of this aqueous solution with HCl followed by ether extraction, drying ($MgSO_4$), and evaporation afforded 13.7 mg of solid material. Analysis of this material by tlc (Brinkman PF_{254} silica gel) indicated a mixture of at least nine components. The presence of thiophenol could not be detected. The ether fraction remaining after initial base extraction was evaporated to yield 0.41 g of residue. Tlc and nmr analysis of this material indicated that it contained *ca.* 0.20 g (20% recovery) of starting **3**.

Dehydrochlorination of 3 with Bis-1,8-dimethylaminonaphthalene (BDMAN).—A mixture of 2.47 g (13.6 mmol) of **3** and 5.94 g (28.0 mmol) of BDMAN (Aldrich) was dissolved in 18 ml of acetonitrile. This solution was heated under nitrogen at 68 ± 3° for 14 days. Analysis of the reaction mixture by gc (Varian-Aerograph 1700, 10 ft × 0.25 in. column of 10% SE-30 on 60/80 Chromosorb W) and nmr indicated that benzene (10%) and 1,4-dihydrobenzene (57%) were present. Positive identification was made with both gc and nmr by enrichment of the reaction mixture with authentic materials.

Dehydrobromination of 9 with Potassium *tert*-Butoxide.—A solution containing 1.01 g (3.7 mmol) of **9** and 1.3 g (11 mmol) of potassium *tert*-butoxide in 15 ml of freshly distilled *tert*-butyl alcohol was stirred under nitrogen at 30 ± 3° for 14 days. Analysis by tlc (PF_{254}) indicated no remaining **9** in a mixture of at least four components. The alcohol was removed by distillation at 80–82° and was shown by gc and nmr to contain 4% benzene. The residue from the distillation was mixed with water and filtered to obtain 0.30 g of solid material. Chromatography on a dry column of silica gel (chloroform eluent) afforded a major fraction of 0.22 g of a very complex mixture from which no pure materials were isolated.

Dehydrobromination of 9 with DBN.—To a solution of 1.8 g (14.6 mmol) of dry DBN in 20 ml of dry DMSO was added 1.00 g (3.65 mmol) of **9** in a dry nitrogen atmosphere (glove bag). The solution was stirred for 12.5 hr at room temperature at which time it was a wine red. The stirred reaction mixture was then immersed in a water bath (20 ± 2°) and a vacuum of 0.4 Torr was applied. Three Dry Ice–acetone traps were placed in the vacuum system and the vacuum was applied for 10.5 hr. After this period the nitrogen atmosphere was restored and stirring at room temperature was continued for 2.5 days with the above vacuum treatment being applied intermittently. Benzene (4%) was found in the first two traps using gc and nmr.

Dehydrobromination of 9 with DBU.—To 88 mg (0.32 mmol) of **9** in an nmr tube was added 0.155 g (1.0 mmol) of DBU. This was performed in a dry nitrogen atmosphere at room temperature. An exothermic reaction occurred immediately which afforded a brown gum. To this was added 0.23 g of DMSO-d_6 and the nmr spectrum of this solution indicated the presence of benzene and the absence of **9**. The presence of benzne was confirmed by gc analysis and the observed yield was calculated to be 38%.

Registry No.—**3**, 6522-40-3; **5**, 32846-51-8; **9**, 32861-43-1.

(13) B. Loev and M. Goodman, *Chem. Ind. (London)*, 2026 (1967).

Specific Synthesis and Selective Alkylation and Condensation of Monoesters of Substituted Succinic Acids

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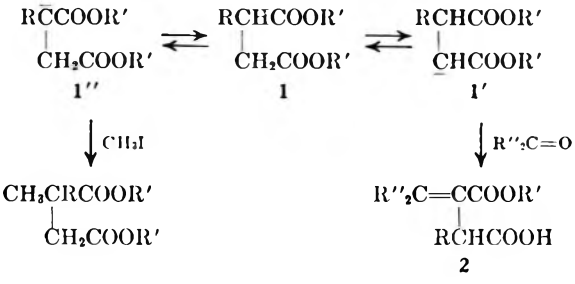
Received May 24, 1971

Monoesters of unsymmetrical alkylsuccinic acids are converted by 2 equiv of amide ion in liquid ammonia to dianions in which the proton α to the ester moiety has been ionized. The dianion reacts with alkyl halides to yield an alkylated product and with carbonyl compounds to yield a condensation product. The use of this dianion thus affords a single product of predictable structure, while alkylation of the diester or the imide yields a mixture of both possible products. The substituted monoesters are prepared by attaching an acetic acid residue to an ester chain, by attaching an acetate ester moiety to an acid chain, by hydrogenation of monoesters of itaconic acids, or by alkylation of ethyl hydrogen succinate.

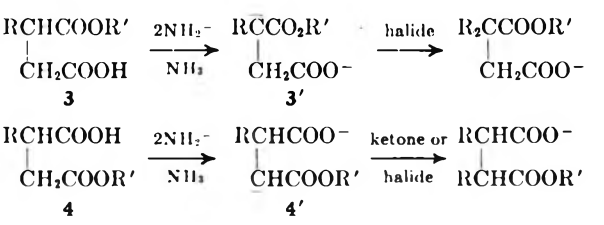
Although carbanions derived from esters of succinic acid and from succinimide have been useful synthetic intermediates in condensation and alkylation reactions,[2,3] there has been little investigation into the use of derivatives of substituted succinic acids in such reactions. Esters of alkylsuccinic acids (1, R = CH_3, $C_6H_5CH_2$, etc.) undergo the Stobbe reaction to give alkylidene products (2). This suggests ionization at the unsubstituted carbon (to give 1');[4,5] however, the Stobbe reaction involves several equilibria which are shifted toward product by formation of a carboxylate salt (of 2),[2] and the equilibrium can only be so shifted for products of ion 1' and not 1''. Esters of phenylsuccinic acid preferentially form ion 1'' (R = C_6H_5), as is demonstrated by alkylation (an irreversible reaction) of diethyl phenylsuccinate exclusively on the substituted carbon, but the product of the Stobbe reaction is derived from ion 1' (R = C_6H_5)[6] (see Scheme I).

Scheme I



The acidity of a proton α to a carboxyl function can be profoundly affected by the nature of the carboxyl derivative. Thus while ethyl 3-bromopropionate is dehydrohalogenated by potassium diphenylmethide, in the 3-bromopropionate ion the acidity of the α proton has been decreased by the negative charge of the carboxylate moiety, and reaction with potassium diphenylmethide proceeds by displacement of the bromide ion to give a salt of 4,4-diphenylbutyric acid.[7] It thus seemed reasonable that a monoester of an alkylsuccinic acid would form that dianion with a negative charge α to the ester portion regardless of the position of the substituent, and thus alkylation or condensation reactions would take place exclusively at that same position (Scheme II).

Scheme II



Alkylation and Condensation of Anions.—The dianion obtained from methyl hydrogen succinate and 2 molar equiv of lithium amide was alkylated with methyl iodide to form 2-methylsuccinic acid 1-methyl ester. As is usually the case with esters not activated by aromatic substituents, better yields were obtained by use of lithium amide in excess of the stoichiometric 2 molar equiv.[8] The structure of the alkylated esters was demonstrated by decarboxylation of the free carboxyl group by means of the Cristol modification of the Hunsdiecker reaction.[9] Thus 2-methylsuccinic acid 1-methyl ester (3, R = R' = CH_3) gave methyl 2-methyl-3-bromopropionate, while 2-methylsuccinic acid 4-methyl ester (4, R = R' = CH_3) afforded methyl 3-bromobutyrate. The linear and branched isomeric esters are readily distinguished by nmr. The isomeric monoesters (3 and 4) cannot be distinguished by nmr, since the chemical shifts of the protons are almost the same whether α to an ester or to a free carboxyl group. Thus methyl hydrogen succinate shows a singlet for the four methylene protons. However, a second useful technique for assigning structures to alkylated monoesters was provided by a comparison of the nmr spectra of the ester–acid and its potassium salt (the monomethyl esters were used to avoid overlapping of ethyl-CH_3 and alkyl resonances). Thus when potassium carbonate is added to the solution of methyl hydrogen succinate, the singlet is replaced by a complex A_2B_2 pattern. In all cases studied protons α or β (and even γ) to the carboxyl group are shifted upfield in the salt, but the shift is larger the closer the proton is to the carboxyl function. The spectra of the monoesters and their salts are summarized in Table I. Both isomers of the half-esters of 2-methylsuccinic acid, 2-isopropylsuccinic acid, and 2-phenylsuccinic acid (3 and 4, R =

(1) NDEA Fellow, 1969–1970.

(2) For a review of the Stobbe condensation, see W. H. Johnson and G. H. Daub, *Org. React.*, **6**, 1 (1951).

(3) D. R. Bryant and C. R. Hauser, *J. Amer. Chem. Soc.*, **83**, 3468 (1961).

(4) H. Stobbe and F. Gollucke, *Ber.*, **39**, 1066 (1906).

(5) A. Weizmann, *J. Org. Chem.*, **8**, 285 (1943).

(6) A. M. Islam and M. T. Zemaity, *J. Amer. Chem. Soc.*, **80**, 5806 (1958).

(7) W. G. Kofron and N. I. Gottfried, *J. Org. Chem.*, **31**, 3426 (1966).

(8) C. R. Hauser, and W. J. Chambers, *ibid.*, **21**, 1524 (1956); (b) W. R. Dunnavant and C. R. Hauser, *ibid.*, **28**, 503 (1963).

(9) S. J. Cristol and W. C. Firth, *ibid.*, **26**, 280 (1961).

TABLE I

NMR SHIFTS FOR PROTONS IN ACIDS[a]

Compd	Registry no.	Proton	$\Delta_{acid-salt}$, cps (upfield)	τ_{acid}
B A CH_3CH_2COOH	79-09-4	A	14	7.59
		B	4.5	8.90
C B A $CH_3CH_2CH_2COOH$	107-92-6	A	13	7.65
		B	5	8.35
		C	4	9.04
CH_3 A B CHCOOH CH_3	79-31-2	A	21	7.38
		B	7	8.80
A CH_2COOH CH_2COOCH_3	26248-95-3	A	9	7.30[b]
		B	5	
		C	2	6.27
B C A CH_2COOH $CH_3CHCOOCH_3$	32980-25-9	A		7.31[c]
		B	9[c]	
		C	0	8.775
C B D		D	1	6.29
B A $CH_3CHCOOH$ CH_2COOCH_3	23268-03-3	A	6	7.13
		B	4	8.78
		C	4	7.38
C D		D	0	6.28
A CH_2COOH $(CH_3)_2CCOOCH_3$	32980-26-0	A	11	7.32
		C	2	8.74
		D	0	6.26
C D				

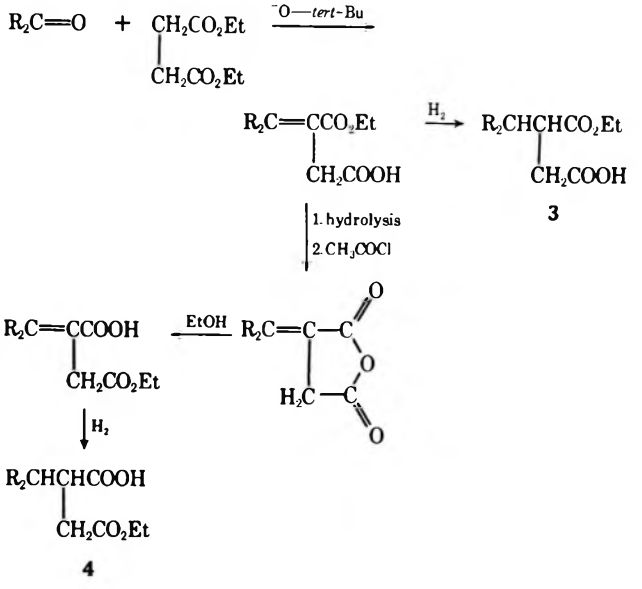
[a] Spectra were run in D_2O containing sodium dimethylsilapentanesulfonate as standard (τ 10.000) (Silanor D_2O) or in D_2O containing sodium trimethylsilylpropionate-*2,2,3,3-d*$_4$ (Silanor D_2O–TSP). The salt was prepared by addition of potassium carbonate to the sample in the nmr tube, and the spectrum was run again. Shifts were determined by measuring the midpoint of the integration trace, since multiplets were not symmetrical. [b] A singlet for both methylenes is observed in the acid. [c] Methylene and methine protons could not be completely separated, and the value is for the midpoint of the integration trace and is thus a weighted average. Both methylene and methine signals are complex multiplets.

CH_3, *i*-C_3H_7 or C_6H_5; R′ = CH_3 or C_2H_5) were studied, and in all cases, even 2-phenylsuccinic acid 4-ethyl ester, alkylation took place exclusively on the carbon atom adjacent to the ester function. In contrast, the anion obtained from diethyl 2-methylsuccinate gave on methylation a mixture of alkylated esters including the diesters of 2-methylsuccinic (starting material), 2,2-dimethylsuccinic, and 2,3-dimethylsuccinic acids. Similarly, methylation of the dianion obtained from 2-methylsuccinimide gave a mixture of 2,2- and 2,3-dimethylsuccinimide.

Condensation of the monoester dianions with ketones or benzaldehyde similarly took place at the carbon α to the ester group, but only when this methylene was not substituted (*i.e.*, **4**). Condensation products were not obtained from the isomers (**3**). During the reaction or the work-up the intermediate hydroxy acid salts cyclized to lactones. The reactions of ketones with 2-methylsuccinate and 2-phenylsuccinate diesters have already been shown to take place at the unsubstituted carbon. The alkylation and condensation reactions are summarized in Table II, p 558.

Specific Synthesis of Monoesters.—Monoesters are readily obtained by the reaction of cyclic anhydrides with 1 molar equiv of an alcohol; however, unsymmetrical (*e.g.*, monosubstituted) anhydrides might give either or both of the isomeric monoesters (**3** or **4**). Methylsuccinic anhydride, on treatment with ethanol, produced a mixture of isomers which could not be separated by distillation or gas chromatography.[10] The Stobbe condensation produces specifically a monoester, and hydrogenation of this compound affords the pure saturated monoester **3**. Also, alkylation of the dianion of monoethyl succinate affords pure **3**. The isomeric unsaturated monoester can be obtained from the itaconic anhydride,[11] and hydrogenation affords the pure saturated monoester **4** (see Scheme III).

SCHEME III



Alkylation of a carbanion with sodium chloroacetate has previously been useful to introduce a carboxymethyl group.[7] This method was applied to the synthesis of 2-phenylsuccinic acid 1-ethyl ester (**3**, R = C_6H_5; R′ = C_2H_5), by alkylation of the lithium or potassium salt of ethyl phenylacetate. Attempts to prepare analogous esters (*e.g.*, **3**, R = CH_3) were unsuccessful. Similarly, alkylation of a carboxylic acid, *via* its dianion, with ethyl bromoacetate would afford the isomeric monoester **4**. This method was successful with the dilithium derivative of phenylacetic acid but not with the dipotassium salt.

As can be seen from Table II, trialkylsuccinic acids can also readily be prepared by further alkylation of

(10) The literature on this reaction is quite confusing. The original report claimed that the product with methanol was 2-methylsuccinic acid 4-methyl ester (**4**, R = R′ = CH_3); see W. A. Bone, J. J. Sudborough, and C. H. G. Sprankling, *J. Chem. Soc.*, **85**, 534 (1904). The Beilstein listing [H **2**, 639] cites this reference for the isomer (**3**). Subsequently this reaction was used to prepare the isomer (**3**), but large amounts of **4** were also found; see J. E. H. Hancock and R. P. Linstead, *ibid.*, 3490 (1953). Authentic 2-methylsuccinic acid 4-methyl ester (**4**) was prepared by reduction of the corresponding itaconic half ester, prepared from the reaction of itaconic anhydride with 1 molar equiv of methanol.[11]

(11) B. R. Baker, R. E. Schaub, and J. H. Williams, *J. Org. Chem.*, **17**, 116 (1952). We have reexamined these reactions and agree with the latter two reports.

dialkyl compounds. In the cases where 2,3-dialkylsuccinic acids are formed, stereoisomers may be produced. Generally mixtures of threo and erythro (or *dl* and *meso*) compounds were formed and were converted to the diesters for analysis by gas chromatography.

Experimental Section

Melting points were determined on a Thomas-Hoover apparatus, using a calibrated thermometer. Infrared spectra were obtained on Nujol mulls for solids and capillary films for liquids. Nmr spectra were determined on a Varian A-60 spectrometer in D_2O containing DSS or TSP, unless otherwise specified. Microanalyses were performed by Goodyear Research Laboratories and/or Galbraith Laboratories. Gas chromatograms were obtained on an F & M Model 500 chromatograph, using a 12-ft 10% SE-30 or a 20-ft 12.5% Ucon 50 column.

Alkylation of Diethyl Succinate.—An ethereal solution of 8.7 g (0.05 mol) of diethyl succinate was added to a stirred suspension of 0.05 mol of lithium amide in 200 ml of liquid ammonia, prepared from 0.35 g (0.05 g-atom) of lithium. The mixture was stirred for 1 hr and 7.1 g (0.05 mol) of methyl iodide in a little ether was added. The mixture was stirred for 1 hr and the ammonia was evaporated. The residue was stirred with ether and ice-cold dilute hydrochloric acid, and the ethereal solution was separated, dried, and evaporated to give 6.7 g of an oil, shown by gas chromatography to be 99% diethyl succinate and 1% diethyl methylsuccinate. From the aqueous layer was obtained a mixture of succinic acid and monoethyl succinate.

The experiment was repeated using 2 molar equiv of lithium amide. Gas chromatography indicated the product (4.0 g) to contain 25% diethyl succinate, 29% diethyl methylsuccinate, 5% diethyl 2,3-dimethyl succinate, 1% diethyl 2,2-dimethylsuccinate, and several unidentified compounds.

2-Isopropylsuccinic Acid 1-Ethyl Ester.—A solution of 1.86 g (0.01 mol) of 2-isopropylidenesuccinic acid 1-ethyl ester[12] in 50 ml of methanol was hydrogenated at atmospheric pressure using 50 mg of 10% Pd/C. The solution was filtered and evaporated, and the residue was distilled at 0.1 mm to give 1.7 g (90%) of 2-isopropylsuccinic acid 1-ethyl ester, bp 102–104°; saponification with aqueous base followed by acidification gave the diacid, mp 115–116° (lit.[12] mp 115–115.5°).

Alkylation of Monoesters.—A typical procedure is given in detail. Table II indicates mole ratio of amide employed and yield obtained.

2-Isopropyl-2-methylsuccinic Acid 1-Ethyl Ester.—An ethereal solution of 2.5 g (0.013 mol) of 2-isopropylsuccinic acid 1-ethyl ester was added to 0.052 mol of lithium amide in 200 ml of liquid ammonia, and the mixture stirred for 1 hr. An ethereal solution of 1.9 g (0.013 mol) of methyl iodide was added, and the mixture was stirred for 1 hr. Ammonium chloride was added and the ammonia was evaporated. The residue was stirred with ice and dilute hydrochloric acid and ether, and the ethereal solution was dried and evaporated. The resulting oil was chromatographed over neutral alumina to give 1.1 g (43%) of 2-isopropyl-2-methylsuccinic acid 1-ethyl ester. The monoester was saponified with aqueous base to the diacid: mp and mmp 136–138°; nmr (DMSO-d_6) τ 9.16 (d, 6), 8.9 (s, 3), 7.6–8.6 (m, 3).

Anal. Calcd for $C_8H_{14}O_4$: C, 55.16; H, 8.10. Found: C, 55.26; H, 8.12.

2-Isopropylsuccinic Acid 4-Ethyl Ester.—A solution of 7.5 g (0.054 mol) of isopropylidenesuccinic anhydride[13] in 100 g of ethanol and 100 g of chloroform was refluxed for 4 hr. The solvent was evaporated and the resulting solid recrystallized from benzene–hexane to give 7.6 g (76%) of 2-isopropylidenesuccinic acid 4-ethyl ester, white needles, mp 112–114°.

Anal. Calcd for $C_9H_{14}O_4$: C, 58.06; H, 7.58. Found: C, 58.31; H, 7.33.

A solution of 1.5 g (0.008 mol) of the monoester in 50 ml of ethanol was hydrogenated for 12 hr at atmospheric pressure with 50 mg of 10% Pd/C. The solution was filtered and evaporated and the residue distilled at 0.1 mm to give 1.3 g (87%) of 2-isopropylsuccinic acid 4-ethyl ester, bp 103–105°.

Anal. Calcd for $C_9H_{16}O_4$: C, 57.44; H, 8.57. Found: C, 57.68; H, 8.49.

Saponification in aqueous base and acidification gave 2-isopropylsuccinic acid, mp and mmp 115–116°.

2-Isopropyl-3-methylsuccinic Acid.—An ethereal solution of 3.7 g (0.02 mol) of 2-isopropylsuccinic acid 4-ethyl ester was added to 0.06 mol of lithium amide in 200 ml of liquid ammonia, and the mixture was stirred for 1 hr. An ethereal solution of 5.7 g (0.04 mol) of methyl iodide was added, and the mixture was stirred for 1 hr. Ammonium chloride was added, the ammonia was evaporated, and the residue was stirred with ice and dilute hydrochloric acid and ether. The ethereal solution was dried and evaporated and the oil was chromatographed over alumina to give 2.1 g (51%) of 2-isopropyl-3-methylsuccinic acid 4-ethyl ester. Saponification afforded 2-methyl-3-isopropylsuccinic acid in 90% yield: mp 171–173° (lit.[13] 174–175°); nmr (DMSO-d_6) τ 9.06 (d, 6), 8.90 (d, 3), 7.18–8.34 (m, 3), −1.56 (s, 2).

Alkylation of 2-Methylsuccinimide.—Finely powdered 2-methylsuccinimide (5.0 g, 0.044 mol) was added to 0.088 mol of lithium amide in 250 ml of liquid ammonia. After 1 hr an ethereal solution of 7.2 g (0.044 mol) of methyl iodide was added. After 1 hr excess ammonium chloride was added and the ammonia was evaporated. The residue was stirred with ice and dilute hydrochloric acid and ether, and the ethereal solution was dried and evaporated to give 3.8 g of an oil, shown by gas chromatography to contain 2,2- and 2,3-dimethylsuccinimide (10 and 31% yields) as well as starting material and lower boiling compounds.

Condensation of Carbonyl Compounds with Monoesters.—A typical procedure is given in detail; minor variations are noted in Table II. An ethereal solution of 7.3 g (0.05 mol) of monoethyl succinate was added to a suspension of 0.15 mol of lithium amide in 200 ml of liquid ammonia, and the mixture was stirred for 1 hr. An ethereal solution of 5.6 g (0.05 mol) of cycloheptanone was added, the mixture was stirred vigorously for 3 min, and an excess of ammonium chloride was added at once. The ammonia was evaporated and the residue stirred with ice and dilute hydrochloric acid and ether. The ethereal solution was dried and concentrated to give an oil with ir bands at 1785 and 1745 cm^{-1}. Chromatography on neutral alumina gave 5.2 g (43%) of the pure paraconic ester, homogeneous by tlc.

Anal. Calcd for $C_{13}H_{20}O_4$: C, 64.98; H, 8.39. Found: C, 65.28; H, 8.55.

2-Phenylsuccinic Acid 1-Ethyl Ester.—To a stirred solution of 0.1 mol of ethyl potassiophenylacetate in 250 ml of liquid ammonia, prepared from 16.4 g (0.1 mol) of ethyl phenylacetate and 0.1 mol of potassium amide, ws added 11.6 g (0.1 mol) of sodium chloroacetate, and the resulting colorless mixture was stirred while the ammonia evaporated. The residue was stirred with water and ether, and the ethereal solution was separated, dried, and evaporated to give 2.1 g (14%) of ethyl phenylacetate. The aqueous layer was acidified with dilute hydrochloric acid and extracted with ether. The ethereal solution was separated, dried, and evaporated to give 16 g (72%) of crude monoester. Recrystallization from aqueous ethanol afforded 15.5 g (70%) of white crystals: mp 87–89°; homogeneous by tlc; ir 1720, 1745 cm^{-1}; nmr (CCl_4) τ 8.84 (t, 3), 7.16 (m, 2), 6.0 (m, 3, OCH_2 + ArCH).

Anal. Calcd for $C_{12}H_{14}O_4$: C, 64.85; H, 6.35. Found: C, 64.95; H, 6.45.

Hydrolysis afforded 2-phenylsuccinic acid, mp 166–168°, in 89% yield.

The experiment was repeated with ethyl sodiophenylacetate, and the yield of recrystallized monoester was 71%.

2-Phenylsuccinic Acid 4-Ethyl Ester.—To a solution of 0.1 mol of lithium lithiophenylacetate[14] in 250 ml of liquid ammonia was added an ethereal solution of 16.6 g (0.1 mol) of ethyl bromoacetate. The ammonia was evaporated and the residue was stirred with water and ether. Evaporation of the ether gave only a trace of ethyl bromoacetate. The aqueous layer was acidified with 10% hydrochloric acid and extracted with ether. Evaporation of the ether gave 13.8 g of residue. Recrystallization from hexane afforded 11.9 g (53%) of the monoester: mp 90–92°; ir 1720 and 1745 cm^{-1}; nmr (CCl_4) τ 8.82 (t, 3), 8.2 (m, 2), 5.96 (m, 3, OCH_2 + ArCH), −0.74 (s, 1).

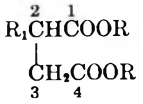
(12) C. G. Overberger and C. W. Roberts, *J. Amer. Chem. Soc.*, **71**, 3618 (1949).

(13) W. H. Bentley, W. H. Perkin, and J. F. Thorpe, *J. Chem. Soc.*, 270 (1896).

(14) P. J. Hamrick and C. R. Hauser, *J. Amer. Chem. Soc.*, **82**, 1957 (1960).

TABLE II

ALKYLATION AND CONDENSATION OF SUBSTITUTED SUCCINIC ACID DERIVATIVES



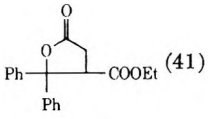
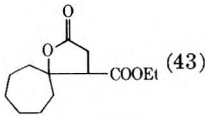
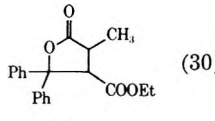
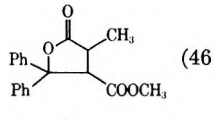
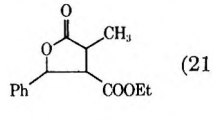
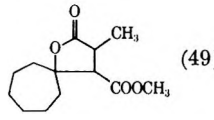
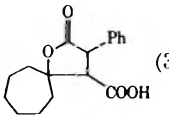
R_1	1 Function	4 Function	Amide (mol)	Reagent	Product (%)	Registry no.	Mp or bp (mm) °C	Diacid, mp (lit. mp)
H	COOEt	COOH	$LiNH_2$ (3)	CH_3I	2-CH_3 (35–46)	32980-27-1	88–89 (0.05)	108–110 (110)[a]
H	COOEt	COOH	$LiNH_2$ (4)[b]	CH_3I	2,2-$(CH_3)_2$ (21)	32980-28-2		135–137 (136–137)[a]
H	$COOCH_3$	COOH	$LiNH_2$ (3)	CH_3I	2-CH_3 (31)		92–94 (0.1)	109–110 (110)
H	COOEt	COOH	$LiNH_2$ (3)	$C_6H_5CH_2Cl$	2-$C_6H_5CH_2$ (40)	32980-29-3		162–163 (162)[c]
H	COOEt	COOH	$LiNH_2$ (3)	$(C_6H_5)_2CO$	 (41)	14596-64-6	149–150	169–170 (168–169)[d]
H	COOEt	COOH	$LiNH_2$ (3)	Cycloheptanone	 (43)	33021-07-7		187–188 (184–186)[e]
CH_3	COOEt	COOH	$LiNH_2$ (4)	CH_3I	2,2-$(CH_3)_2$ (40)			136–138 (136–137)
CH_3	$COOCH_3$	COOH	$LiNH_2$ (4)	CH_3I	2,2-$(CH_3)_2$ (31)	32980-26-0	98–99 (0.1)	135–137 (136–137)
CH_3	COOEt	COOH	$LiNH_2$ (4)	$C_6H_5CH_2Cl$	2-CH_3, 2-$C_6H_5CH_2$ (23)	32980-32-8		117–119[f]
CH_3	COOEt	COOH	$LiNH_2$ (4)	$(CH_3)_2CHI$	2-CH_3, 2-$(CH_3)_2CH$ (10)	32971-20-3		136–138[g]
CH_3	COOH	$COOCH_3$	$LiNH_2$ (3)	CH_3I	2,3-$(CH_3)_2$ (80)[h]	608-40-2	97–98 (0.07)	196–198 (198), *meso*
						608-39-9		121–123 (123), *dl*
CH_3	COOH	$COOCH_3$	$LiNH_2$ (3)	$C_6H_5CH_2Cl$	2-CH_3, 3-$C_6H_5CH_2$ (64)	32980-34-0	93–95	138–140 (138)[i]
CH_3	COOH	COOEt	$LiNH_2$ (3)	$(C_6H_5)_2CO$	 (30)	33021-08-8	144–146	*j*
CH_3	COOH	$COOCH_3$	$LiNH_2$ (3)	$(C_6H_5)_2CO$	 (46)	33021-09-9	153–154	*k*
CH_3	COOH	COOEt	$LiNH_2$ (3)	C_6H_5CHCO	 (21)	33021-10-2	135–140 (0.1)	*l*
CH_3	COOH	$COOCH_3$	$LiNH_2$ (3)	Cycloheptanone	 (49)	33980-35-1		*m*
$(CH_3)_2CH$	COOEt	COOH	$LiNH_2$ (4)	CH_3I	2-CH_3, 2-$(CH_3)_2CH$ (43)	32971-20-3		136–138
$(CH_3)_2CH$	COOH	COOEt	$LiNH_2$ (3)	CH_3I	2-$(CH_3)_2CH$, 3-CH_3 (51)	32980-36-2		171–173 (174–175)[n]
CH_3	COOEt	COOEt	$LiNH_2$ (1)	CH_3I	2-CH_3 (80)[o] 2,3-$(CH_3)_2$ (3)[o]	4676-51-1		
CH_3	COOEt	COOEt	$LiNH_2$ (2)	CH_3I	2-CH_3 (70)[o] 2,2-$(CH_3)_2$ (3)[o] 2,3-$(CH_3)_2$ (10)[o]			
C_6H_5	COOEt	COOEt	$LiNH_2$ (1)	CH_3I	2-CH_3, 2-C_6H_5 (55)	32980-38-4	110–112 (0.2)	161–163 (163–164)[p]
C_6H_5	COOEt	COOH	$LiNH_2$ (2)	CH_3I	2-CH_3, 2-C_6H_5 (86)	33021-11-3	89–91	161–163 (163–164)
C_6H_5	COOH	COOEt	$LiNH_2$ (2)	CH_3I	2-C_6H_5, 3-CH_3 (91)	32980-39-5		177–179 (170–171)[q] 190–192 (192–193)[q]

TABLE II (*Continued*)

R1	1 Function	4 Function	Amide (mol)	Reagent	Product (%)	Registry no.	Mp or bp (mm), °C	Diacid, mp (lit. mp)
C_6H_5	COOEt	COOEt	$LiNH_2$ (1)	C_6H_5CHO	2-C_6H_5, 3-benzylidene (20)	32980-40-8		187–188[r]
C_6H_5	COOH	COOEt	$LiNH_2$ (2)	$(C_6H_5)_2CO$	2-C_6H_5, 3-benzhydrylidene (45)	32980-41-9		203–205[s]
C_6H_5	COOH	COOEt	$LiNH_2$ (2)	Cycloheptanone	 (32–49)	32980-42-0		*t*
C_6H_5	COOEt	COOH	$LiNH_2$ (2)	$C_6H_5CH_2Cl$	2-C_6H_5, 2-$C_6H_5CH_2$ (74)	32980-43-1	110–112	190–192 (194)[u]
C_6H_5	COOH	COOEt	$LiNH_2$ (2)	$C_6H_5CH_2Cl$	2-C_6H_5, 3-$C_6H_5CH_2$ (64)	32980-44-2	126–130	183–185 (185)[v]
C_6H_5	COOEt	COOH	$LiNH_2$ (2)	C_4H_9Br	2-C_4H_9, 2-C_6H_5 (86)	32980-45-3	150–155 (0.01)	148–150 (152)[w]
C_6H_5	COOH	COOEt	$LiNH_2$ (2)	C_4H_9Br	2-C_6H_5, 3-C_4H_9 (58)	32980-46-4	165–170 (0.06)	183–185[z]

[a] L. Higginbotham and A. Lapworth, *J. Chem. Soc.*, 49 (1922). [b] The reaction mixture was neutralized with excess NH_4Cl 3 min after the benzophenone had been added. When the mixture was neutralized after 1 hr, starting material was recovered. Compare ref 8b. [c] J. A. McRae and L. Marion, *Can. J. Res., Sect. B*, **15**, 480 (1937). [d] H. Stobbe, *Justus Liebigs Ann. Chem.*, **308**, 89 (1899). [e] Lactone acid; J. W. Cook, R. Philip, and A. R. Sommerville, *J. Chem. Soc.*, 164 (1948). [f] Registry no. 32980-47-5. *Anal.* Calcd for $C_{12}H_{14}O_4$: C, 64.86; H, 6.31. Found: C, 64.98; H, 6.45. [g] Registry no. 5703-04-8. *Anal.* Calcd for $C_8H_{14}O_4$: C, 55.17; H, 8.05. Found: C, 55.26; H, 8.16. [h] Gas chromatography showed 90% *meso* and 10% *dl* after conversion to the diester; W. A. Bone and W. H. Perkin, *J. Chem. Soc.*, 253 (1896). [i] Gas chromatography of the diesters showed only a trace of the higher boiling isomer; C. A. Bischoff and A. von Kuhlberg, *Ber.*, **23**, 1942 (1890). [j] *Anal.* Calcd for $C_{20}H_{20}O_4$: C, 74.07; H, 6.17. Found: C, 73.88; H, 6.14. [k] *Anal.* Calcd for $C_{19}H_{18}O_4$: C, 73.55; H, 5.81. Found: C, 73.80; H, 5.69. [l] *Anal.* Calcd for $C_{14}H_{16}O_4$: C, 67.74; H, 6.45. Found: C, 67.82; H, 6.51. [m] *Anal.* Calcd for $C_{13}H_{20}O_4$: C, 65.00; H, 8.33. Found: C, 65.18; H, 8.47. [n] A trace of the ester corresponding to the acid of mp 125–126° was detected by gas chromatography after esterification; W. H. Bentley, W. H. Perkin, and J. F. Thorpe, *J. Chem. Soc.*, 270 (1896). [o] Yields were determined by gas chromatography. [p] H. LeMoal, A. Foucaud, R. Carrie, J. Hamelin, and C. Sevellec, *Bull. Soc. Chim. Fr.*, **5**, 913 (1964). [q] N. Zelinsky and L. Buchstab, *Ber.*, **24**, 1876 (1891). [r] Registry no. 32980-49-7. *Anal.* Calcd for $C_{17}H_{14}O_4$: C, 72.34; H, 4.96. Found: C, 72.18; H, 4.76. [s] Registry no. 32980-50-0. *Anal.* Calcd for $C_{23}H_{18}O_4$: C, 77.09; H, 5.02. Found: C, 77.37; H, 5.22. [t] *Anal.* Calcd for $C_{17}H_{20}O_4$: C, 70.83; H, 6.94. Found: C, 70.90; H, 6.85. [u] Anhydride, formed by distillation of monoester; F. Salmon-Legagneur and H. LeMoal, *C. R. Acad. Sci.*, **229**, 126 (1949). [v] Only a trace of higher isomer by vpc of diesters; J. Jarrouse, *ibid.*, **204**, 132 (1937). [w] G. Poulain, *Bull. Soc. Chim. Fr.*, **5**, 913 (1964). [z] Only isomer by vpc of diesters. Registry no. 32980-51-1. *Anal.* Calcd for $C_{14}H_{18}O_4$: C, 67.20; H, 7.20. Found: C, 67.50; H, 7.16.

Anal. Calcd for $C_{12}H_{14}O_4$: C, 64.85; H, 6.35. Found: C, 64.83; H, 6.54.

Registry No.—2-Isopropylidenesuccinic acid 4-ethyl ester, 32980-52-2; 2-isopropylsuccinic acid 4-ethyl ester, 32980-53-3; 2-phenylsuccinic acid 1-ethyl ester, 32971-21-4; 2-phenylsuccinic acid, 635-51-8; 2-phenylsuccinic acid 4-ethyl ester, 32980-55-5;

Acknowledgment.—This research was supported in part by a grant from the Petroleum Research Fund of the American Chemical Society.

Cycloreversions of Anions from Tetrahydrofurans. A Convenient Synthesis of Lithium Enolates of Aldehydes[1]

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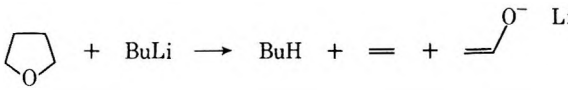
Received July 23, 1971

Tetrahydrofuran (THF), 3,4-dialkyltetrahydrofurans, and 3,3,4,4-tetraalkyltetrahydrofurans are cleaved smoothly by *n*-butyllithium in hexane yielding alkenes and lithium enolates of aldehydes. The reactions appear to proceed by abstraction of an α hydrogen followed by $-[{}_{\pi}4_s + {}_{\pi}2_s]$ cycloreversion. In the case of THF itself, evidence was obtained for an 8% buildup of the α-metalated THF intermediate.

During lithiations with *n*-butyllithium in tetrahydrofuran (THF) at room temperature, we noted that, in cases in which the substrate metalates slowly, butyllithium cleaves THF smoothly to give butane, ethylene, and the lithium enolate of acetaldehyde. This type of



reaction has been reported previously[2] but not extensively studied. Because of the possibility that this reaction would provide the most convenient route to certain enolates (aldol condensation and polymerization can complicate the reaction of an aldehyde with base, but, in this cleavage route, *aldehyde is never present*), we decided to look further at the scope and mechanism of this reaction.

Experimental Section

Nmr spectra were recorded on Varian A-60 and HA-100 spectrometers; coupling constants are reported in hertz. Mass spectra were measured with a Hitachi Perkin-Elmer RMU-6E double-focusing spectrometer. Melting points are uncorrected.

3,4-Dimethyltetrahydrofuran.—A 2.3-g (0.016 mol) sample of 2,3-dimethylsuccinic acid (Aldrich Chemical Co.) was placed in a Soxhlet cup and the Soxhlet extractor was mounted above a three-necked flask containing 0.9 g (0.023 mol) of $LiAlH_4$ and 100 ml of ether. The ether was refluxed until all of the diacid had dissolved. The reaction flask was cooled to 0° and H_2O (6 ml) was added slowly with stirring. The ether solution was decanted and then used to extract the solid residue for 24 hr in a Soxhlet apparatus. The solvent was removed by distillation at atmospheric pressure, and 85% H_3PO_4 (0.2 ml) was added. After the mixture was refluxed for 2 hr, the material boiling below 100° was distilled out and dried by running a pentane solution of it through a short alumina column (basic, activity I). Removal of the bulk of the pentane by distillation gave 3,4-dimethyltetrahydrofuran[3] (0.5 g, 30%).

2,2,3,3-Tetramethylbutane-1,4-diol.—A solution of 0.49 g (0.0031 mol) of tetramethylsuccinic anhydride[4] in 3 ml of THF was added to a stirred solution of 1 g of lithium aluminum hydride in 100 ml of THF. After 16 hr at reflux, 1 ml of water, 1 ml of 15% NaOH, and 3 ml of water were added dropwise. The liquid was decanted and the solids were rinsed with ether. Evaporation gave crude diol, which on recrystallization from 60–90° petroleum ether gave 0.21 g (47%) of 2,2,3,3-tetramethylbutane-1,4-diol: mp 210–212° (sealed capillary; reported[5] 224°); nmr ($DCCl_3$) τ 4.7 (broad s, 2), 6.7 (s, 4), and 9.1 (s, 12).

3,3,4,4-Tetramethyltetrahydrofuran.—In a sublimation apparatus, a solution of 0.22 g of the above diol in 1.3 ml of redistilled dimethyl sulfoxide was heated for 16 hr at 160°.[6] The sublimate was resublimed at 100° to give 0.082 g (42%) of 3,3,4,4-tetramethyltetrahydrofuran: mp 106–107°; nmr ($DCCl_3$) τ 6.4 (s, 4), 9.1 (s, 12); mass spectrum 56 (base) and 128 (parent).

Reaction of Tetrahydrofurans with *n*-Butyllithium.—The tetrahydrofurans were dried over 4A molecular sieves activated by heating at 210° for 8 hr. A 0.012-mol sample was placed in an nmr tube. After cooling in a Dry Ice–isopropyl alcohol bath, *n*-butyllithium (Foote Mineral Co., 0.5 ml, 0.0008 mol) in hexane was added and the tube was sealed. The reactants were mixed thoroughly by shaking, and the tube was placed in an nmr probe at 35° for analysis at various time intervals. Sources of the tetrahydrofurans, their half-lives, and the products found are listed in Table I.

The various products were identified most conveniently by their nmr properties, especially ethylene, τ 4.7 (s, 4); propyl-

TABLE I

HALF-LIVES FOR CLEAVAGES AT 35°

Ether	Registry no.	$t_{1/2}$ for α cleavage, min	$t_{1/2}$ for β cleavage, min
Tetrahydrofuran[a]	109-99-9	10	
3-Methyltetrahydrofuran[b]	13423-15-9	50[f]	
3,4-Dimethyltetrahydrofuran[c]	32970-37-9	70	
3,3,4,4-Tetramethyltetrahydrofuran[c]	32970-38-0	15 (at 80°)	
2-Methyltetrahydrofuran[d]	96-47-9	130[g]	70[h]
2,2-Dimethyltetrahydrofuran[e]	1003-17-4	>3000	700[h]
2,5-Dimethyltetrahydrofuran[b]	1003-38-9	>3000	700[h]
 [b]	279-49-2	10	
Oxepane[c]	592-90-5		350

[a] Mallinckrodt Chemical Works. [b] Aldrich Chemical Co. [c] See Experimental Section. [d] Eastman Organic Chemicals. [e] Chemical Samples Co. [f] Nearly equal amounts of the two sets of α-cleavage products (propylene, the enolate of acetaldehyde; ethylene, the enolate of propionaldehyde) were observed. [g] The only observed α-cleavage products were the enolate of acetaldehyde and propylene. [h] β cleavage involves only β protons *external* to the ring (*i.e.*, in the methyl groups) in these cases.

(1) Taken in part from the Ph.D. thesis of D. E. P., 1969, and the M.S. thesis of L. M. K., 1970.

(2) (a) R. L. Letsinger and D. F. Pollart, *J. Amer. Chem. Soc.*, **78**, 6079 (1956), cleaved 2-phenyltetrahydrofuran with propylsodium and after workup obtained (among other products) propane, ethylene, and acetophenone. (b) A. Rembaum, S. P. Siao, and N. Indictor, *J. Polym. Sci.*, **56**, 517 (1962), reported that ethyllithium decomposed in THF at 25° to give, among other products, ethylene and the lithium enolate of acetaldehyde. (c) Gilman and coworkers [H. Gilman and G. L. Schwebke, *J. Organometal. Chem.*, **4**, 483 (1965), and references cited therein] have measured the rates of decomposition of many organolithium compounds, including *n*-butyllithium, in THF, but do not report the products in the cases of present interest. (d) S. C. Honeycutt, *ibid.*, **29**, 1 (1971), has recently reported a kinetic study of the cleavage of THF by *n*-butyllithium.

(3) This material, like the starting acid, must be a mixture of *dl* and *meso* forms. For earlier preparations of mixtures of these stereoisomers by different methods, see Yu. K. Yur'ev and G. Ya. Kondrat'eva, *Zh. Obshch. Khim.*, **24**, 1645 (1954), and G. A. Razuvaev and L. S. Boguslavskaya, *ibid.*, **32**, 2320 (1962).

(4) A. F. Bickel and W. A. Waters, *Recl. Trav. Chim. Pays-Bas*, **69**, 312 (1950).

(5) M. F. Ansell, W. J. Hickenbottom, and P. G. Holton, *J. Chem. Soc.*, 349 (1955).

(6) B. T. Gillis and P. E. Beck, *J. Org. Chem.*, **28**, 1388 (1963).

ene, vinyl pattern at τ 4.4, 5.1, and 5.2; the enolate of acetaldehyde τ 3.08 (1, q, H_2), 6.85 (1, q, H_{3c}), 6.4 (1, q, H_{3t}), J_{23c} = 5.4, J_{23t} = 13.4, J_{3c3t} = 2.0 Hz; the enolate of propionaldehyde, τ 3.30 (1, d, H_2), 6.3 (1, m, H_{3t}), J_{23} = 11.5; the enolate of isobutyraldehyde, τ 3.44 (1, s, H_2), 8.44 (3, s, CH_3), 8.51 (3, s, CH_3). Ethylene was also characterized by its ir and mass spectra. Further evidence for the presence of the enolate of acetaldehyde was obtained by adding its THF solution dropwise to an aqueous solution with vigorous stirring at 0°; distillation gave acetaldehyde (ir, nmr).

Reaction of Oxepane with *n*-Butyllithium.—Oxepane was β cleaved smoothly under the above conditions to give the lithium salt of 5-hexen-1-ol, characterized by nmr absorption for the vinyl group at ~4.18 (1, m), 4.98 (1, d, J = 16 Hz), and 5.12 (1, d, J = 10 Hz), and for the methylene next to oxygen at 5.48 (2, m).

Reaction of 2,5-Dihydrofuran with *n*-Butyllithium.—2,5-Dihydrofuran (Aldrich Chemical Co.) cleaved rapidly under the above conditions to give the sickle isomer I of the enolate of crotonaldehyde: nmr τ 3.26 (1, m, H_4), 3.30 (1, d, H_2), 5.42 (1, q, H_3), 5.48 (1, q, H_{5t}), 5.75 (1, q, H_{5c}), J_{23} = 6, J_{34} = 10.5, J_{45t} = 17, J_{45c} = 10.5, J_{5c5t} = 2 Hz.[7] After heating to 150° in a sealed tube, the nmr was unchanged.

Evidence for α-Lithiotetrahydrofuran.—A kinetic study of the THF cleavage was carried out in an nmr tube in the nmr probe at 35°. The decrease in butyllithium absorption at τ 11 and the increase in lithium enolate absorption at τ 3.1 were observed at 20 intervals over a period of 1 hr. The curves obtained were matched as well as possible using an analog computer and the assumption of the system

$$A \xrightarrow{k_1} B \xrightarrow{k_2} C$$

(A = butyllithium, C = enolate). The resulting rate constants were $k_1 = 1 \times 10^{-3}$ sec^{-1} and $k_2 = 6 \times 10^{-3}$ sec^{-1}; the curves suggest an intermediate substance B which builds to a maximum concentration of 10% after 4 min.

A similar reaction was quenched with D_2O after 4 min. The extra height of the mass spectral peak at m/e 73 as compared to a standard from quenching with H_2O suggested that lithiotetrahydrofuran had been present in 8% yield.

Lithium Enolate of Acetaldehyde·$^3/_2$Tetrahydrofuran.—A mixture of THF (1.0 ml, 0.012 mol) and *n*-butyllithium (4.0 ml, 0.0064 mol) in hexane was allowed to stand at room temperature for 6 days. The liquid was decanted, and the crystals were washed several times with hexane and then dissolved in THF-d_8; integration of the nmr spectrum showed THF and enolate in a 1.5 molar ratio.[8] The crystals decomposed when exposed to the atmosphere for a few seconds.

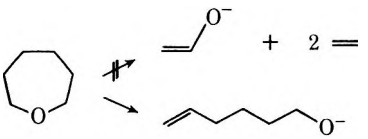
Discussion

Scope.—As indicated by the first four entries in Table I, it appears that "α cleavage" to an olefin and the enolate of an aldehyde goes smoothly and quantitatively on tetrahydrofurans bearing no α substituents. After the cleavage of THF, the resulting lithium enolate solution is stable for at least 6 months. If desired, the ethylene (and butane) can be removed without affecting the lithium enolate by heating at 40° for several hours while passing nitrogen over the solution. The unsymmetrical example, 3-methyltetrahydrofuran, cleaved about equally in each direction, suggesting that only with symmetrical tetrahydrofurans will useful enolate syntheses be observed. The slowing effect of alkyl groups observed in this series is presumably due largely to the decreasing polarity of the solvent; the THF is present in large excess and serves as the principal solvent as well as a reactant.

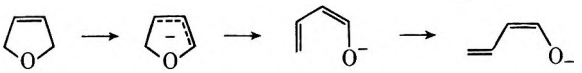
The next three entries in Table I show that, with an α-methyl substituent, "β cleavage," involving abstraction of a β proton from a methyl group, becomes the predominant reaction. α cleavage is appreciably slowed; it was observed only in the case of 2-methyltetrahydrofuran, whose α cleavage to the enolate of acetaldehyde and propylene rather than the enolate of propionaldehyde and ethylene can be rationalized on the basis that the more stable carbanion intermediate was involved.

The α cleavage observed for 7-oxabicyclo[2.2.1]heptane is probably fast for the same reason that bridgehead protons in bicyclic sulfides have been found to be more readily exchanged in base than the corresponding protons in acyclic sulfides.[9]

In none of the tetrahydrofurans was β cleavage involving abstraction of a ring hydrogen observed. This is probably because the geometry is so unfavorable for an E2 reaction in these five-membered ring compounds. Tetrahydropyran and oxepane were also reacted under these conditions; the products from the former are unknown, but the latter β cleaved smoothly with abstraction of a β hydrogen *in the ring*. With a ring as large as seven membered, the geometry required for an E2 reaction of this sort is apparently accessible.



Under these conditions, 2,5-dihydrofuran reacts vigorously to give an electrocyclic ring-opening product, the sickle-shaped dienolate ion I. This reaction has been reported by Kloosterziel and van Drunen[7] to occur with potassium amide in liquid ammonia. By heating in a sealed tube at 150° we were unable to convert I to the W-shaped ion,[7] indicating a barrier to rotation about the 2,3 bond of at least 23 kcal/mol.



I

Mechanism.—Letsinger and Pollart[2a] noted that 2-phenyltetrahydrofuran cleaves much faster than THF itself and deduced that the first step was α-proton abstraction to give an anion, as shown below. In an effort to detect such an intermediate from THF, we ran a cleavage in an nmr tube at 35°. Although no signals were detected due to an intermediate, a plot of decreasing butyllithium concentration and increasing enolate concentration *vs.* time showed that at least one intermediate was involved and that it achieved its maximum concentration of about 10% after 4 min. When the reaction was quenched with D_2O after 4 min, the resulting THF was shown by mass spectral analysis to contain monodeuteriotetrahydrofuran in the amount expected if an 8% yield (based on BuLi) of THF anion had been present. This result contrasts with the failure to gain evidence for an intermediate in the related cleavages of dioxolanes and 1,3-dithiolanes;[10] in those cases, cleavage is probably faster because negative

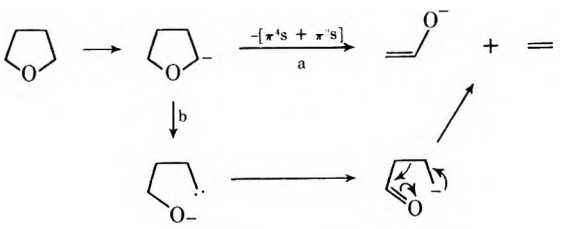
(7) H. Kloosterziel, J. A. A. van Drunen, and P. Galama, *Chem. Commun.* 885 (1969), report similar values for the potassium salt in NH_3 at −60°.

(8) We are indebted to Dr. S. Brenner for this result.

(9) S. Oae, W. Tagaki, and A. Ohno, *J. Amer. Chem. Soc.*, **83**, 5036 (1961).

(10) D. Seebach, *Angew. Chem., Int. Ed. Engl.*, **8**, 639 (1969), and references cited therein.

charge develops in the transition state on *two* electronegative atoms rather than one.



In certain reactions of epoxides with strong bases, α-proton abstraction is apparently followed by carbon–oxygen bond cleavage to a carbene, which gives rise to several products.[11] A carbene path in the current cleavages (path b above) is ruled out, at least in the 2-methyl- and 2-phenyltetrahydrofuran[2a] cases, by the cleavage products obtained; *e.g.*, the former gives propylene and the enolate of acetaldehyde rather than ethylene and the enolate of acetone. Relief of ring strain in the epoxide cases presumably aids considerably in the formation of the high-energy carbene intermediates.

(11) J. K. Crandall and L. H. C. Lin, *J. Amer. Chem. Soc.*, **89**, 4526 (1967), and references cited therein.

The exclusion of path b leaves the much simpler, symmetry-allowed[12] $-[{}_{\pi}4_{s} + {}_{\pi}2_{s}]$ cycloreversion path a as most likely for these reactions. Honeycutt's finding[2d] that the rate of disappearance of butyllithium in THF is first order in butyllithium and *2.5* order in THF is understandable in terms of this mechanism, assuming 1.5 mol of THF on the average are necessary to solvate the lithium ions in the first step. In this connection, by increasing the butyllithium–THF ratio in a THF cleavage, we obtained a highly crystalline air-sensitive substance which appears to be lithium enolate of acetaldehyde·$^{3}/_{2}$ tetrahydrofuran.[8]

Registry No.—2,2,3,3-Tetramethylbutane-1,4-diol, 10519-69-4; lithium enolate of acetaldehyde, 2180-63-4; lithium enolate of propionaldehyde, 33020-96-1; lithium enolate of isobutyraldehyde, 32970-42-6; lithium enolate of crotonaldehyde, 32970-43-7.

Acknowledgment.—We are grateful to the Petroleum Research Fund, Ethyl Corporation, and National Science Foundation for financial support.

(12) R. B. Woodward and R. Hoffmann, *Angew. Chem., Int. Ed. Engl.*, **8**, 781 (1969).

The Crystal and Molecular Structure of 5′-Demethoxy-β-peltatin A Methyl Ether[1]

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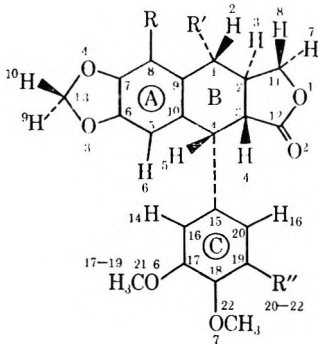
Received July 14, 1971

The constitution and relative configurations proposed for this natural antitumor agent by Bianchi, Sheth, and Cole were confirmed by an X-ray study on the polymorph with mp 142–143°, and the conformation was revealed for the first time. The C ring is rotated so that a methoxyl group lies above the A ring. The carbons in the methoxyls on the C ring lie in the plane of the C ring, as far from one another as possible. The carbon in the methoxyl attached to ring A is nearly as far from the plane of the A ring as possible, on the same side as the C ring. An attempt to confirm the absolute configuration using anomalous scattering by oxygen gave inconclusive results but seemed to favor the configuration opposite to that proposed earlier. The structure was solved by symbolic addition and refined to an R of 0.039.

Although the antitumor activity of podophyllotoxin (I) and several related lignans has long been known,[2] no X-ray or other study showing their preferred conformation has been reported. 5′-Demethoxy-β-peltatin A methyl ether (II), one of the most active of these lignans, was recently isolated from a Mexican plant, *Bursera fagaroides*, and characterized by spectral comparisons with β-peltatin A methyl ether (III).[3] As a check on the proposed constitution and configurations, and to learn the conformational preferences of a lignan of this series, we undertook an X-ray study on this substance.



	R	R′	R″
I	H	OH	OCH_3
II	OCH_3	H	H
III	OCH_3	H	OCH_3

(1) This paper is based in part on the Ph.D. thesis of J. B. W., University of Arizona, 1971; some of the results were presented at the 161st National Meeting of the American Chemical Society, Los Angeles, Calif., March 1971, ORGN 71.

(2) M. Belkin, *Proc. Soc. Exp. Biol. Med.*, **6**, 308 (1947); J. L. Hartwell and M. J. Shear, *Cancer Res.*, **7**, 716 (1947); M. G. Kelly and J. L. Hartwell, *J. Nat. Cancer Inst.*, **14**, 967 (1954).

Experimental Section

Collection and Reduction of the Data.—A clear needle of dimensions 0.2 × 0.2 × 0.7 mm of 5′-demethoxy-β-peltatin A methyl ether (II), mp 142–143°, was mounted for rotation about the needle axis (c). Oscillation and Weissenberg photographs indicated space group $P2_12_12_1$ or $P2_12_12$; the former was later established by the full intensity data. The crystal was mounted on a Picker FACS-1 four-circle automated diffractometer set for graphite-monochromatized Cu Kα radiation, λ = 1.54051 Å. Unit cell dimensions, determined by least-squares refinement of the angular settings of seven reflections, were a = 9.174 (3), b = 27.628 (7), and c = 7.620 (1) Å.

For data collection, the 2θ scan technique using a basic 2° scan width modified for radiation dispersion was employed. After scanning at 2°/min, 10-sec background counts were taken at both ends of the scan. Three standard reflections were

(3) E. Bianchi, K. Sheth, and J. R. Cole, *Tetrahedron Lett.*, 2759 (1969).

Table I

Absolute Configuration Results from Pair Measurements

h	k	l	D[a]	I_{hkl}	$I_{\overline{hkl}}$	F_c+	F_c-	Configuration indication[b]
1	6	6	4.9	128.6	124.8	46.1155	48.0222	−
4	5	1	2.8	44.1	40.2	11.4796	12.0651	−
2	8	2	1.2	144.2	145.1	29.4003	29.8750	+
4	6	1	1.1	46.3	45.3	17.0872	16.7117	+
5	10	1	1.1	12.7	14.7	14.1211	13.6527	−
6	4	1	1.0	166.6	160.9	45.3743	44.6065	+
6	1	3	0.9	30.0	27.4	19.6333	20.1580	−
3	14	1	0.9	142.5	147.2	38.8724	39.4858	+
1	9	3	0.8	424.5	426.7	52.2592	53.1525	+
4	4	2	0.8	189.0	192.2	38.3309	38.8640	+

[a] $D = [|F_c(hkl)| - |F_c(\overline{hkl})|]^2/\sigma^2|F_o(hkl)| \times 10^2$. [b] Plus means result agrees with literature absolute configuration.

measured 23 times during the data collection; there was no evidence for crystal decomposition. Of 1901 unique reflections measured up to $2\theta = 125°$, 1762 were judged to be statistically significant on the basis of $I \geq 2\sigma$.

Solution and Refinement.—The structure was solved by symbolic addition[4] using the MULTAN programs.[5] Given the top 207 E's, the program selected 1 6 0, 7 7 0, 0 16 5, and 0 5 7 as the origin- and enantiomorph-fixing reflections. From an E map using the set of phases having the highest figure of merit (1.03), and bond angles and distances between the top 51 peaks in this E map, all nonhydrogen atoms were found. After four cycles of isotropic refinement,[6] $R = \Sigma ||F_o| - |F_c||/\Sigma|F_o| = 0.16$ with C14 in a wrong position. A difference map showed the correct position of C14 and, after another refinement cycle, $R = 0.11$. After three anisotropic cycles, R was 0.076. All 22 hydrogens were found on the difference map used to find C14; three anisotropic cycles including hydrogens (which were given the same anisotropic temperature factors as the carbon to which they were attached) dropped R to its final value, 0.0394. No correction was made for extinction or absorption (μ 8.5 cm^{-1}).

An earlier partial solution had been obtained using the MAGIA programs with the starting set 1 7 0, 5 0 4, 0 24 5, and 2 15 0. An E map clearly showed a benzene ring with three substituents attached. Starting with these nine atoms, six F maps yielded positions for all the nonhydrogen atoms, but this solution would not refine below $R = 0.35$. At this time, the MULTAN programs gave the true solution, and it was discovered that the x and y coordinates for each atom in the partial solution were very close, but the z coordinates were displaced by about 0.8 Å. As partially correct structures of this type often result from direct methods, it seemed worth considering how the true structure might have been derived from the partial solution in this case. Accordingly, R's were calculated separately for the zero level data on the a, b, and c axes. The values obtained were 0.42, 0.52, and 0.22, respectively, providing strong evidence that the problem was with the z coordinates. By calculating R's for molecules shifted at regular intervals along the c axis, the true positions would presumably have been obtained.

Absolute Configuration.—R was 0.039529 when a value of +0.04 was used for $\Delta f_o''$ for oxygen and 0.039439 when a value of −0.04 was used. The R-factor ratio was thus 1.00228, and, according to Hamilton's test,[7] the absolute configuration with the higher R (the literature configuration, shown in the formula for II) can be rejected with 99.5% certainty.

To gain further evidence regarding the absolute configuration, the intensities of each of the ten reflections with the highest D values[8] and their negatives were each remeasured ten times, averaged, and corrected for background. The results are given in Table I.

Table II

Fractional Coordinates and Estimated Standard Deviations

Atom	x/a	y/b	z/c
O1	0.2199 (3)	0.3694 (1)	−0.0713 (4)
O2	0.2147 (3)	0.3929 (1)	0.2101 (4)
O3	−0.5946 (3)	0.4989 (1)	0.1019 (3)
O4	−0.6192 (3)	0.4862 (1)	−0.1977 (3)
O5	−0.3976 (3)	0.4384 (1)	−0.4150 (3)
O6	−0.4102 (3)	0.2591 (1)	0.1592 (3)
O7	−0.2640 (3)	0.2279 (1)	0.4263 (3)
C1	−0.1412 (4)	0.4039 (1)	−0.2589 (5)
C2	−0.0268 (4)	0.3794 (1)	−0.1480 (5)
C3	0.0083 (4)	0.4104 (1)	0.0140 (5)
C4	−0.1214 (4)	0.4124 (1)	0.1391 (4)
C5	−0.3566 (4)	0.4577 (1)	0.1298 (5)
C6	−0.4743 (4)	0.4742 (1)	0.0405 (5)
C7	−0.4895 (4)	0.4671 (1)	−0.1407 (5)
C8	−0.3847 (4)	0.4439 (1)	−0.2331 (4)
C9	−0.2603 (4)	0.4271 (1)	−0.1485 (4)
C10	−0.2475 (4)	0.4336 (1)	0.0361 (4)
C11	0.1250 (5)	0.3723 (2)	−0.2245 (6)
C12	0.1549 (4)	0.3909 (1)	0.0704 (6)
C13	−0.6824 (5)	0.5095 (1)	−0.0479 (6)
C14	−0.4891 (6)	0.3992 (2)	−0.4637 (7)
C15	−0.1592 (4)	0.3628 (1)	0.2159 (4)
C16	−0.2724 (4)	0.3345 (1)	0.1501 (4)
C17	−0.3030 (4)	0.2897 (1)	0.2189 (4)
C18	−0.2228 (4)	0.2723 (1)	0.3629 (4)
C19	−0.1107 (4)	0.2997 (1)	0.4275 (5)
C20	−0.0793 (4)	0.3447 (1)	0.3545 (5)
C21	−0.4900 (6)	0.2732 (2)	0.0075 (7)
C22	−0.1925 (6)	0.2112 (2)	0.5809 (8)
H1	−0.197 (4)	0.379 (1)	−0.340 (5)
H2	−0.099 (4)	0.430 (1)	−0.334 (5)
H3	−0.062 (4)	0.340 (1)	−0.103 (4)
H4	0.034 (4)	0.448 (1)	−0.017 (5)
H5	−0.092 (4)	0.437 (1)	0.239 (4)
H6	−0.333 (4)	0.467 (1)	0.248 (4)
H7	0.131 (4)	0.334 (1)	−0.275 (5)
H8	0.162 (4)	0.401 (1)	−0.302 (5)
H9	−0.791 (4)	0.503 (1)	−0.024 (5)
H10	−0.682 (4)	0.549 (1)	−0.062 (5)
H11	−0.430 (4)	0.365 (2)	−0.411 (5)
H12	−0.580 (5)	0.400 (2)	−0.421 (6)
H13	−0.506 (5)	0.392 (1)	−0.587 (6)
H14	−0.339 (4)	0.348 (1)	0.071 (4)
H15	−0.047 (4)	0.288 (1)	0.517 (4)
H16	−0.003 (4)	0.363 (1)	0.395 (4)
H17	−0.555 (5)	0.237 (2)	−0.016 (6)
H18	−0.418 (5)	0.274 (2)	−0.086 (6)
H19	−0.547 (5)	0.309 (2)	0.028 (6)
H20	−0.234 (5)	0.177 (1)	0.591 (6)
H21	−0.082 (5)	0.207 (1)	0.556 (6)
H22	−0.213 (5)	0.235 (1)	0.676 (6)

(4) J. Karle and I. L. Karle, *Acta Crystallogr.*, **21**, 849 (1966).

(5) G. Germain, P. Main, and M. M. Woolfson, *Acta Crystallogr., Sect. B*, **26**, 274 (1970).

(6) Refinements were by full-matrix least squares with the ORFLS program of W. R. Busing, K. O. Martin, and H. A. Levy, ORNL-TM-305, Oak Ridge National Laboratory, 1962. Unit weights were used. Form factors were obtained by graphical interpolation of those in the International Tables for X-ray Crystallography, Vol. III, Table 3.3.1A, except for hydrogen, for which the form factors of R. F. Stewart, E. R. Davidson, and W. T. Simpson, *J. Chem. Phys.*, **42**, 3175 (1965), were used.

(7) W. C. Hamilton, *Acta Crystallogr.*, **18**, 502 (1965).

(8) H. Hope and U. de la Camp, *Nature (London)*, **221**, 54 (1969).

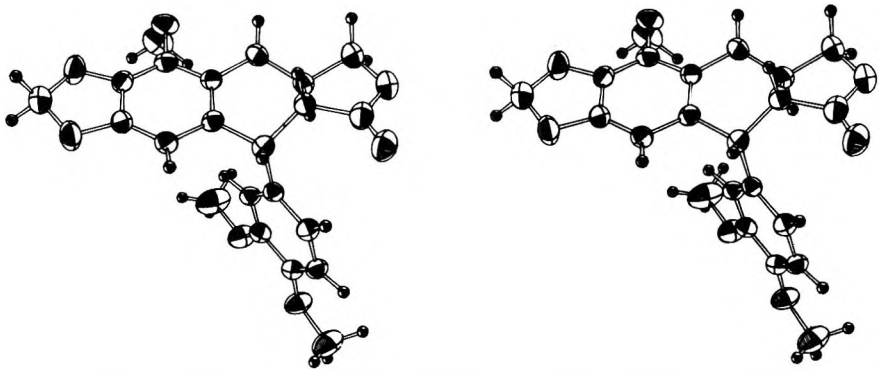


Figure 1.—Stereoscopic view of 5′-demethoxy-β-peltatin A methyl ether (II). Thermal ellipsoids enclose 50% probability.

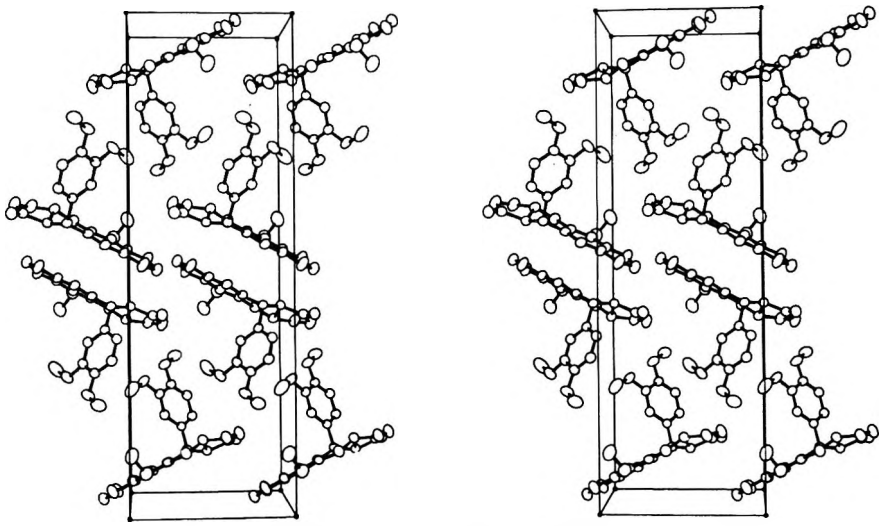


Figure 2.—Stereoscopic view of the unit cell, c-axis projection.

Results and Discussion

The final positional parameters are given in Table II. Temperature factors, bond angles, and distances were normal.[9] The average benzene bond lengths were 1.387 (5) Å for ring A and 1.385 (5) Å for ring C. The C–H distances ranged from 0.90 (4) to 1.19 (5) Å.

As can be seen from the ORTEP drawing in Figure 1, this study confirms the constitution and relative configurations proposed by Bianchi, Sheth, and Cole.[3] However, our attempts to verify the absolute configuration, while certainly not definitive, seem to provide weak evidence against the literature configuration. The significance test[7] on the R factor calculated for each enantiomer suggests a 99.5% probability that the literature configuration is wrong; however, as the general reflection data were not corrected for absorption or extinction, errors due to these may have been dominant in causing the difference in R's. D values[8] were calculated for all of the reflections, and the reflections with the top ten D values and their negatives in 2θ were carefully measured; this technique minimizes absorption and extinction errors. As seen from Table I, six of ten values favor the literature configuration; however, the top two do not, and, as these two are much more sensitive than the others and should be weighted more heavily, the overall result seems to be "weakly against" the literature configuration. Anomalous scattering by oxygen was successfully used by Hope and de la Camp[8] on tartaric acid, which is 64% oxygen as compared to 28% in the current case. The absolute configurations of the lignans of this class rest on a 20-step sequence of chemical interconversions and rotation comparisons completed by Schrecker and Hartwell;[10] the current study casts a small measure of doubt on the result, and an independent check would seem worthwhile.

The C ring occupies a pseudoaxial position and is nearly at right angles (88.8°) to the A ring. It is rotated in such a way that C21 lies over the aromatic ring and H16 is only 2.58 (3) Å from O2.

C21 and C22 in methoxyl groups are only −0.15 and 0.17 Å out of the plane of ring C (the dihedral angles between C21–O6–C17 and ring C, and C22–O7–C18 and ring C are 4.3 and 5.8°, respectively), whereas C14 is almost as far as possible from the plane of the adjacent benzene ring (the angle between C14–O5–C8 and ring A is 80.2°). The coplanarity of the first two methoxyls permits overlap of a p orbital on oxygen with the p orbital on the adjacent ring carbon and gives relatively short bonds [both 1.373 (4) Å]. Nonbonded steric interactions with the adjacent ortho substituents presumably outweigh this resonance ef-

(9) Tables of temperature factors, bond distances, bond angles, least-squares plane deviations, and structure factors will appear following these pages in the microfilm edition of this volume of the journal. Single copies may be obtained from the Business Operations Office, Books and Journals Division, American Chemical Society, 1155 Sixteenth St., N.W., Washington, D. C. 20036, by referring to author, title of article, volume, and page number. Remit check or money order for $5.00 for photocopy or $2.00 for microfiche.

(10) J. L. Hartwell and A. W. Schrecker, *Fortschr. Chem. Org. Naturst.*, **15**, 115 (1958).

fect in the case of the third methoxyl group, and the C8–O5 bond is accordingly long [1.399 (4) Å]. All three methoxyl groups adopt staggered conformations about the methyl–oxygen bond.

A projection down the *c* axis (Figure 2; the *a* axis is horizontal and the *b* axis vertical) shows the molecular packing. The shortest intermolecular distance is 2.21 (5) Å, between H4 and H9. The shortest intermolecular distance between nonhydrogen atoms (O7 and C11) is 3.325 (5) Å.

Registry No.—5′-Demethoxy-β-peltatin A methyl ether, 32970-80-2.

Acknowledgments.—We thank Drs. E. Bianchi and J. R. Cole of our Pharmacy Department for providing crystals, Drs. L. L. Reed and Paul Johnson for helpful advice, the Computer Center of the University of Arizona for computer time, and the National Cancer Institute (CA-10944) and Sloan Foundation (fellowship to R. B. B.) for financial aid.

Reduction of α,β-Oxido Ketones with Chromous Acetate. Synthesis of 3β,5β,17β,19-Tetrahydroxy-5β-androstane, a Degradation Product of Strophanthidin[1,2]

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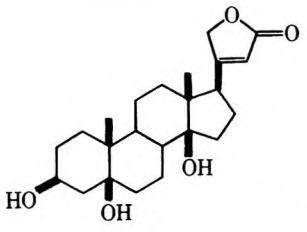
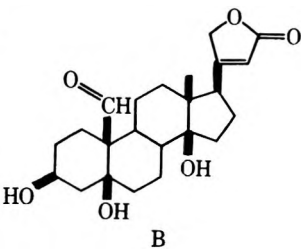
Received July 22, 1971

The reaction of steroidal α,β-oxido ketones with chromous acetate has been studied, using a variety of solvents, as a potential route to the A/B ring system of some cardiac-active steroids. These reductions generate β-hydroxy ketones with retention of configuration at the β-carbon atom, along with the corresponding α,β-unsaturated ketones. The β-hydroxy ketone formed in the reaction is stable to the reaction conditions. Steroidal 4β,5β-oxido-3 and 4α,5α-oxido-3 ketones give respectively 5β-hydroxy- and 5α-hydroxy-3-oxo steroids on reduction with chromous acetate, while 6α,7α-oxido-4-cholesten-3-one generates the biosynthetically interesting 7α-hydroxy-4-cholesten-3-one. Yields of β-hydroxy ketone are approximately 50% in the cases studied. The reaction has been used to prepare 3β,5β,17β,19-tetrahydroxy-5β-androstane, a degradation product of strophanthidin.

In a search for new ways to generate the 3β,5β-dihydroxy system found in cardiac-active steroids such as periplogenin (A) and strophanthidin (B), we con-

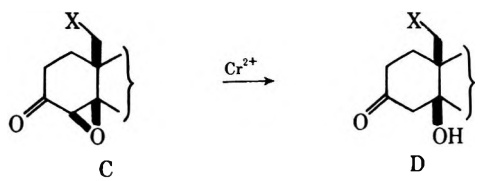


A



B

sidered the possibility of reduction of an α,β-oxido ketone (as C) with chromous ion. Cleavage of the C–O bond α to the ketone should occur, giving the required stereochemistry for the resulting tertiary hydroxyl group at the β carbon. Furthermore, α,β-oxido ketones are readily available by the action of alkaline hydrogen peroxide on the corresponding α,β-unsaturated ketones. If X were hydrogen or an oxygenated function, subsequent reduction of the carbonyl group in D to an axial alcohol would provide the re-



C D

quired A/B ring system found in such compounds as periplogenin and strophanthidin.

(1) Abstract 158, 23rd International Congress of Pure and Applied Chemistry, Boston, Mass., July 1971.

(2) This work was supported, in part, by U. S. Public Health Service Grants HE-08913, AM-07422, and GM 16492.

Numerous examples of the reaction of α,β-oxido ketones with chromous chloride can be found in the literature.[3,4] These reactions, however, invariably generate the α,β-unsaturated ketone in high yield, as illustrated[3a] by the conversion of 4,5β-oxidocholestan-3-one to 4-cholesten-3-one with chromous chloride. The conversions[5] of steroidal 16α,17α-oxido-20 ketones to the corresponding 16α-hydroxy-20 ketones using chromous acetate in acetic acid represent the only reported examples of β-hydroxy ketone formation from α,β-oxido ketone with chromous ion. These observations, coupled with the fact that the reported chromous chloride reactions all involve strongly acid solutions (which might convert any β-hydroxy ketone to the conjugated ketone), encouraged us to study reduction of the model compound 4β,5β-oxidocholestan-3-one (1) (Chart I) with chromous acetate.

Studies were carried out with a variety of solvents (dimethylformamide, *N*-methylpyrrolidinone, tetrahydrofuran, diglyme, ethanol, aqueous acetone, acetic acid–sodium acetate) at room temperature, under an atmosphere of carbon dioxide, using up to a tenfold excess of chromous acetate. Conversion of the oxido ketone 1 to the 5β-hydroxy ketone 2 was best effected (*ca.* 50% yield of isolated pure product) by use of a large excess (5–10 molar equiv) of freshly prepared chromous acetate in absolute ethanol or, better,

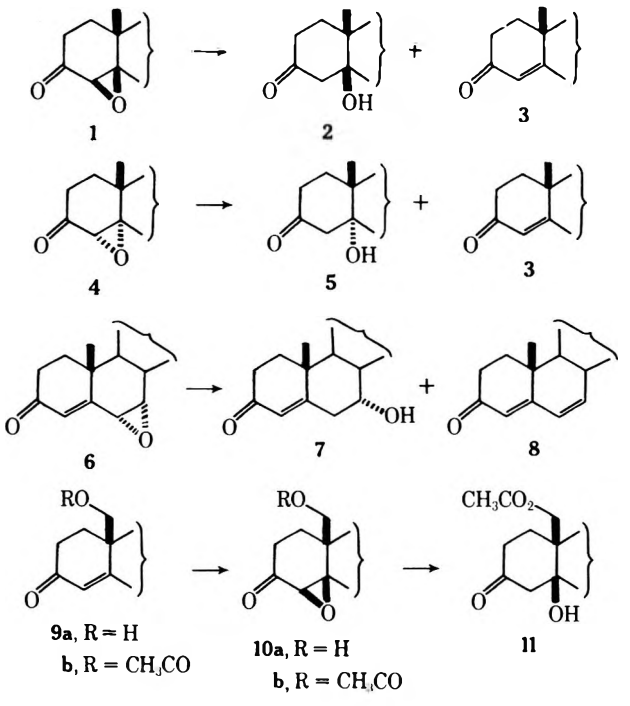
(3) *Cf.* (a) W. Cole and P. L. Julian, *J. Org. Chem.*, **19**, 131 (1954); (b) D. Arigoni, D. H. R. Barton, E. J. Corey, and O. Jeger, *Experientia*, **16**, 41 (1960); (c) A. Akisanya, C. W. L. Bevan, T. G. Halsall, J. W. Powell, and D. A. H. Taylor, *J. Chem. Soc.*, 3705 (1961).

(4) For a recent review of reductions of organic compounds with chromous salts, see J. R. Hanson and E. Premuzic, *Angew. Chem., Int. Ed. Engl.*, **7**, 247 (1968).

(5) V. Schwarz, *Collect. Czech. Chem. Commun.*, **26**, 1207 (1961). See also R. Neher, P. Desaulles, E. Vischer, P. Wieland, and A. Wettstein, *Helv. Chim. Acta*, **41**, 1667 (1958), as well as ref 3 and 4.

in aqueous acetone. In the latter case, buffering with sodium acetate–acetic acid had a beneficial effect[6] because work-up was easier. The balance of the reaction product was invariably the α,β-unsaturated ketone **3**. Lowering the reaction temperature to $-60°$ had essentially no effect on the ratio of products **2** and **3**. Because compound **3** can be reconverted to oxido ketone **1** in yields of better than 90%, the reduction of **1** to 5β-hydroxy ketone **2** can be accomplished efficiently if recycling of **3** is undertaken.

CHART I
CHOLESTANE SERIES



We had supposed originally that the conjugated ketone **3** arose by dehydration of β-hydroxy ketone **2**. However, the formation of **3** in closely similar proportions in both ethanol and the buffered aqueous acetone system seems to contradict this notion. Furthermore, when β-hydroxy ketone **2** was subjected to the chromous acetate–ethanol reaction conditions, it was recovered unchanged. Thus, **2** and **3** appear to be formed from the oxido ketone **1** by different pathways. Such paths might include delivery of electrons from chromous ion directly into the C-3 carbonyl, with eventual formation of a 5β-hydroxy-Δ^3-enol, or attack by chromous ion at C-4 with oxide opening to produce a C-4 organochromium intermediate.

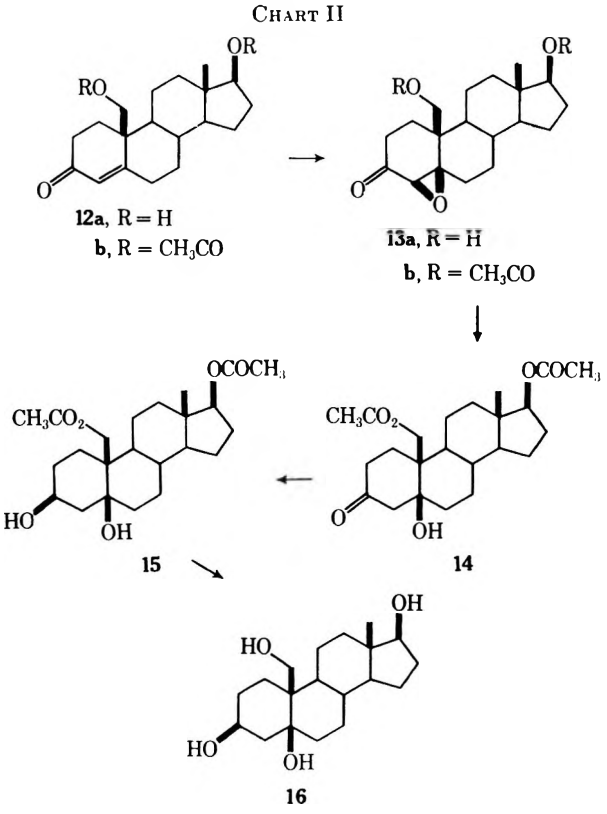
Two other steroidal oxido ketones were then studied. When the 4α,5α-oxido-3 ketone[7] **4** was reduced with chromous acetate in ethanol, the 5α-hydroxy-3 ketone **5** was obtained pure in 46% yield, along with the conjugated ketone **3**.

The γ,δ-oxido-α,β-unsaturated ketone[8] **6** gave, on reduction with chromous acetate in aqueous acetone, 7α-hydroxy-4-cholesten-3-one[9] (**7**) in 50% yield, as well as the dienone[10] **8**. The 7α-hydroxy compound **7** has been of considerable interest in connection with bile acid biosynthesis, and its synthesis[9,11] has hitherto been difficult. The present method offers a simple route from readily available starting material.

In the above cases, as well as in the reported[5] reductions of the 16α,17α-oxido-20-oxo steroid system to 16α-hydroxy-20 ketone with chromous acetate, stereochemical integrity is retained at the carbon bearing the new hydroxyl group.

We now turned to C-19-oxygenated steroids, and converted 19-hydroxytestosterone[12] (**12a**) (Chart II)

CHART II



to the 4β,5β-oxido compound **13a** and thence to the corresponding 17β,19-diacetate **13b**. The analytical and spectroscopic data were consistent with the structures and stereochemistry shown, and the β orientation of the oxido group was further confirmed by CD measurements.[13,14] Reduction of compounds **13a** and **13b** with chromous acetate in aqueous acetone gave interesting and unexpected results. In contrast to our earlier observations with C-10 methyl steroids, the 4β,5β-oxido diol **13a** gave a quantitative yield of 19-hydroxytestosterone, with *none* of the expected 5β-hydroxy ketone. On the other hand, the 4β,5β-oxido diacetate **13b** behaved as expected, and gave 5β,17β,19-trihydroxyandrostan-3-one 17β,19-diacetate (**14**) in

(6) We thank Dr. K. H. Overton (Glasgow University) for kindly providing unpublished details of chromous acetate reductions in buffered aqueous acetone in the triterpene series.

(7) E. P. Oliveto, C. Gerold, and E. B. Hershberg, *J. Amer. Chem. Soc.*, **79**, 3596 (1957).

(8) A. Nickon and J. F. Bagli, *ibid.*, **83**, 1498 (1961).

(9) H. Danielsson, *Acta Chem. Scand.*, **15**, 242 (1961).

(10) L. Mandell, *J. Amer. Chem. Soc.*, **78**, 3199 (1956).

(11) I. Björkhem, H. Danielsson, C. Issidorides, and A. Kallner, *Acta Chem. Scand.*, **19**, 2151 (1965).

(12) M. Ehrenstein and K. Otto, *J. Org. Chem.*, **24**, 2006 (1959).

(13) *Cf.* K. Kuriyama, H. Tada, Y. K. Sawa, S. Ito, and I. Itoh, *Tetrahedron Lett.*, 2539 (1968).

(14) We thank Dr. G. Snatzke (Bonn) for the circular dichroism data reported in this paper.

over 60% yield, under exactly the same conditions. The structure and stereochemistry of **14** followed from the analytical and spectroscopic data, including CD. In addition, 19-hydroxytestosterone diacetate (**12b**) was isolated from the chromous acetate reduction of **13b**.

Exactly analogous observations were made in the cholestane series. Thus, whereas the 19-hydroxy-4β,5β-oxido-3 ketone **10a** gave 19-hydroxy-4-cholesten-3-one (**9a**) quantitatively on reduction with chromous acetate, the corresponding 19-acetoxy-4β,5β-oxido compound **10b** gave the 5β-hydroxy-3 ketone **11** under the same conditions. This difference between 10-methyl- and 19-acetoxy-4β,5β-oxido-3 ketones on the one hand and the corresponding 19-hydroxy compounds on the other is interesting. If, as suggested by our earlier experiments, conjugated ketone formation occurs by a different path than does β-hydroxy ketone formation, the presence of a 19-hydroxyl apparently assists the former process. The C-19 hydroxyl group may act as a ligand to chromium, and may then facilitate intramolecular electron delivery.

Returning now to the 5β-hydroxyandrostane derivative **14**, it remained only to reduce the C-3 carbonyl to an axial hydroxyl group, in order to secure the 3β,5β,19-triol system. Model experiments carried out with 5β-hydroxycholestan-3-one showed that, of a variety of reducing agents (sodium borohydride–methanol, lithium aluminum tri-*tert*-butoxyhydride, lithium aluminum hydride–methanol–tetrahydrofuran, trimethylamine–borane in diglyme, W-2 Raney nickel in ethanol) only W-2 Raney nickel in refluxing ethanol favored reduction to axial alcohol at C-3, giving predominantly cholestane-3β,5β-diol. The 5β-hydroxyandrostane derivative **14** was then reduced at C-3 with W-2 Raney nickel in refluxing ethanol to give, in 70% yield, the desired 3β,5β,17β,19-tetrahydroxyandrostane 17β,19-diacetate (**15**). This product (**15**) could be oxidized back to the starting ketone **14** with chromium trioxide–acetone–sulfuric acid, and the nmr spectrum of **15** attested to the axial nature of the newly introduced C-3 hydroxyl group. Finally, basic hydrolysis of compound **15** yielded 3β,5β,17β,19-tetrahydroxyandrostane (**16**) which proved to be identical with an authentic sample obtained[15] by degradation of strophanthidin. The sequence of reactions outlined above seems to have promise as a route to 3β,5β-dihydroxy steroids, with or without C-19 oxygenation. More generally, the chromous acetate method appears to be useful for reduction of α,β- and vinylogous α,β-oxido ketones to the often difficultly accessible β- and vinylogous β-hydroxy ketones.

Experimental Section[16]

5β-Hydroxycholestan-3-one (2) by Chromous Acetate Reduction of 4,5β-Oxidocholestan-3-one (1). A.—To a stirred solution of 4,5β-oxidocholestan-3-one (**1**, 509 mg) in ethanol (50 ml) at room temperature, under an atmosphere of carbon dioxide, was added freshly prepared chromous acetate[17] (1.9 g) and after 1 hr the mixture was evaporated *in vacuo* at 30°. Water was added, the mixture was extracted with ethyl acetate, and the organic extract was filtered through Celite. The filtered ethyl acetate solution was washed with water, dried (Na_2SO_4), and evaporated *in vacuo*. Preparative tlc of the residue (chloroform–ethyl acetate, 92.5:7.5) gave (a) 264 mg of 4-cholesten-3-one (**3**) identical with an authentic specimen as judged by melting point, mixture melting point, tlc, and infrared comparison and (b) 232 mg of 5β-hydroxycholestan-3-one[18] (**2**), identical with an authentic sample by melting point, mixture melting point, tlc, and infrared comparison.

B.—To a stirred solution of 4,5β-oxidocholestan-3-one (**1**, 15.4 mg) in acetone (3.1 ml) and water (0.5 ml) under an atmosphere of carbon dioxide was added freshly prepared chromous acetate (32 mg). After 10 min a further portion (26 mg) of chromous acetate was added, and stirring was continued for another 15 min. The reaction mixture was evaporated under a jet of nitrogen, and the residue was triturated with water and extracted with chloroform. The chloroform extract was washed with water, dried (Na_2SO_4), and evaporated *in vacuo*. Preparative tlc (solvent system as in A above) gave 4-cholesten-3-one (**3**, 7 mg) and 5β-hydroxycholestan-3-one (**2**, 7 mg), each compound being identified by melting point, mixture melting point, tlc, and infrared comparison with authentic samples.

5α-Hydroxycholestan-3-one (5) by Chromous Acetate Reduction of 4,5α-Oxidocholestan-3-one (4).—4,5α-Oxidocholestan-3-one (**4**, 140 mg) in ethanol (15 ml) was allowed to react with freshly prepared chromous acetate (560 mg) for 30 min, exactly as for the preparation of compound **2** above, except that the product was extracted with benzene. Preparative tlc (chloroform–ethyl acetate, 9:1) gave (a) 4-cholesten-3-one (**3**, 37 mg) identical with an authentic sample as judged by melting point, mixture melting point, tlc, and infrared comparison; (b) 5α-hydroxycholestan-3-one[19] (**5**, 65 mg), identity with an authentic specimen proved by melting point, mixture melting point, tlc, and infrared comparison.

Reduction of 5α,7α-Oxido-4-cholesten-3-one (6) with Chromous Acetate to Give 7α-Hydroxy-4-cholesten-3-one (7).—To a stirred solution of the oxido ketone **6** (160 mg) in acetone (36 ml) was added a solution of sodium acetate trihydrate (1.47 g) in water (4.0 ml) and acetic acid (1.0 ml) followed by chromous acetate (500 mg) in one portion. After 25 min the reaction mixture was evaporated *in vacuo* at 25°, and the residue was triturated with water and extracted with ethyl acetate. The organic extracts were washed with water, dried (Na_2SO_4), and evaporated *in vacuo* at 25°, and the crude product was chromatographed on silica gel (9.5 g). Elution with benzene–chloroform (3:7) gave 4,6-cholestadien-3-one[10] (**8**, 54 mg) identical with authentic material[20] as judged by melting point, mixture melting point, infrared spectra, and tlc comparison.

Elution with benzene–chloroform (1:1) gave crude 7α-hydroxy-4-cholesten-3-one (**7**, 80 mg) which was freed from minor impurities by preparative tlc (chloroform–ethyl acetate, 49:1), giving pure 7α-hydroxy-4-cholesten-3-one[11] (**7**, 60 mg), mp 179–182° (undepressed on admixture with authentic material[21] of mp 180–182°), identical with authentic material by infrared and tlc comparison.

Although the above experiment was carried out using sodium acetate buffer, a subsequent experiment using acetone–water (9:1) alone as the reaction medium gave closely comparable results.

(15) M. Ehrenstein and M. Dünnenberger, *J. Org. Chem.*, **21**, 774 (1956).

(16) Melting points were measured on the Kofler block. Optical rotations were measured in chloroform solution and circular dichroism measurements were made with the Roussel–Jouan dichrograph using dioxane solutions (0.5–0.6 mg/g) at 20°. Nmr chemical shifts are given in parts per million on the δ scale (TMS = 0), and infrared spectra were recorded using chloroform solutions unless otherwise specified. For tlc, silica gel GF254 was used in 0.25-mm layers for analytical purposes and in 2-mm layers for preparative work.

(17) Chromous acetate was obtained by reaction of air-free sodium acetate solution with aqueous chromous chloride, under an atmosphere of carbon dioxide, essentially as described by J. H. Balthis and J. C. Bailar, *Inorg. Syn.*, **1**, 122 (1939). The precipitated chromous acetate was filtered off and washed successively with deoxygenated water, absolute ethanol, and ether, all operations being carried out under an atmosphere of carbon dioxide. The brick red precipitate was dried by suction on the filter, still in the absence of air, and was then used immediately. Prolonged drying in a vacuum desiccator often resulted in decomposition of the chromous acetate, and such drying was therefore avoided.

(18) P. A. Plattner, H. Heusser, and A. B. Kulkarni, *Helv. Chim. Acta*, **31**, 1822 (1948).

(19) P. A. Plattner, A. Fürst, F. Koller, and W. Lang, *ibid.*, **31**, 1455 (1948).

(20) We thank Dr. A. Nickon, Johns Hopkins University, for kindly supplying an authentic specimen of 4,6-cholestadien-3-one.

(21) We thank Dr. H. Danielsson, Karolinska Institute, for kindly supplying an authentic sample of 7α-hydroxy-4-cholesten-3-one.

4β,5β-Oxido-19-hydroxycholestan-3-one (10a).—Ice-cold 30% aqueous hydrogen peroxide (8.5 ml) was added dropwise to a stirred ice-cooled solution of 19-hydroxy-4-cholesten-3-one[22] (**9a**, 1.67 g) in dioxane (100 ml) and aqueous sodium hydroxide (5 *N*, 8.5 ml). The reaction mixture was allowed to warm to 25°, and stirring was continued for 20 hr at 25°. Acetic acid (2 ml) was then added, followed by water, and the mixture was extracted three times with methylene chloride. The organic extract was washed successively with aqueous ferrous sulfate solution and water, dried (Na_2SO_4), and evaporated *in vacuo*, giving the crude product (1.73 g). Crystallization from ethyl acetate–petroleum ether (bp 30–60°) gave pure oxido ketone **10a** (1.14 g): mp 160–162°; $[\alpha]D$ +123°; ν_{max} 3660, 3510, 1715 cm^{-1}; nmr ($CDCl_3$) δ 0.73 (s, 3, C-18 CH_3), 2.91 (s, 1, C-4 H), 3.98 (2 d, 2, J = 11 Hz, C-19 CH_2OH); mass spectrum m/e 416 (M^+), 400, 398, 386, 385, 370.

Anal. Calcd for $C_{27}H_{44}O_3$: C, 77.83; H, 10.65. Found: C, 77.79; H, 10.65.

4β,5β-Oxido-19-hydroxycholestan-3-one 19-Acetate (10b).—The oxido compound **10a** (100 mg) was acetylated in pyridine and acetic anhydride at room temperature for 16 hr in the usual manner. The crude product was an uncrystallizable glass: ν_{max} 1739, 1718, 1242 cm^{-1}; nmr ($CDCl_3$) δ 0.68 (s, 3, C-18 CH_3), 2.1 (s, 3, acetate CH_3), 2.87 (s, 1, C-4 H), 4.45 (2 d, 2, J = 11 Hz, C-19 CH_2OAc); mass spectrum m/e 458 (M^+), 442, 416, 400, 398, 370.

Reduction of 4β,5β-Oxido-19-hydroxycholestan-3-one 19-Acetate (10b) with Chromous Acetate.—The 19-acetate **10b** (115 mg) in ethanol (40 ml) was allowed to react with chromous acetate (768 mg) for 10 min exactly as in the preparation of compound **2** above. Preparative tlc (petroleum ether–ethyl acetate, 4:1) gave pure 19-acetoxy-4-cholesten-3-one (**9b**, 38 mg), identified by comparison (melting point, mixture melting point, tlc, infrared) with authentic material prepared by acetylation of 19-hydroxy-4-cholesten-3-one (**9a**). In addition, 70 mg of 5β, 19-dihydroxycholestan-3-one 19-acetate (**11**) was obtained, contaminated with the Δ^4-3 ketone **9b**. This material was again subjected to preparative tlc [chloroform–ethyl acetate (9:1)] and gave 5β-hydroxy compound **11** as an uncrystallizable glass, ν_{max} 3630, 1730 (broad), 1242 cm^{-1}. This glass, when treated with a saturated solution of sodium hydrogen carbonate in 95% ethanol under reflux for 0.5 hr, was converted quantitatively to 19-hydroxy-4-cholesten-3-one (**9a**), identical with authentic material by melting point, mixture melting point, tlc, and infrared comparison.

4β,5β-Oxido-17β,19-dihydroxyandrostan-3-one (13a).—A stirred solution of 19-hydroxytestosterone (**12a**, 584 mg) in 95% ethanol (60 ml) was cooled in ice, and ice-cold sodium hydroxide solution (5 *N*, 2.4 ml) was added quickly, followed by dropwise addition of ice-cold hydrogen peroxide (30%, 2.4 ml). Stirring was continued, and the solution was maintained at 0–5° for 3.5 hr. The reaction mixture was worked up exactly as for compound **10a** above. The crude product was chromatographed on silica gel (60 g), and elution with chloroform–ethanol (97:3) gave the 4β,5β-oxido ketone **13a** (412 mg) as a colorless glass: ν_{max} 3650, 3510, 1720 cm^{-1}; nmr ($CDCl_3$) δ 0.77 (s, 3, C-18 CH_3), 2.92 (s, 1, C-4 H), 4.0 (2 d, 2, J = 11 Hz, C-19 CH_2OH); mass spectrum m/e 320 (M^+), 304, 302, 290, 289, 274, 273.

4β,5β-Oxido-17β,19-dihydroxyandrostan-3-one 17β,19-Diacetate (13b).—The foregoing dihydroxy oxido ketone **13a** (219 mg) was acetylated with pyridine–acetic anhydride at room temperature for 16 hr, giving pure diacetate **13b** (185 mg): mp 133–135° (from aqueous methanol); CD λ_{max} 335 nm ($\Delta\epsilon$ + 1.50), 321 (+3.78), 310 (+4.42), and 300 nm (+3.86); ν_{max} 1745–1739 (broad), 1250 cm^{-1}; nmr ($CDCl_3$) δ 0.82 (s, 3, C-18 CH_3), 2.03 and 2.13 (s, each 3, C-17 and C-19 acetate CH_3), 2.90 (s, 1, C-4 H), 4.43 (2 d, 2, J = 12 Hz, C-19 CH_2); mass spectrum m/e 404 (M^+), 388, 376, 375, 362, 361, 347, 344, 316.

(22) H. Dannenberg, H. G. Neumann, and D. D. v. Dressler, *Justus Liebigs Ann. Chem.*, **674**, 152 (1964).

Anal. Calcd for $C_{23}H_{32}O_6$: C, 68.29; H, 7.97. Found: C, 68.49; H, 8.04.

Reduction of 4β,5β-Oxido-17β,19-dihydroxyandrostan-3-one 17β,19-Diacetate (13b) with Chromous Acetate.—The oxido ketone **13b** (370 mg) in acetone (83 ml) containing sodium acetate trihydrate (3.38 g), water (9.2 ml), and acetic acid (2.3 ml) was reduced for 25 min with freshly prepared chromous acetate (1.18 g) exactly as in the preparation of compound **6** above. The residue (323 mg) was chromatographed on silica gel (384 g) using chloroform–ethyl acetate (1:1) as eluent and taking 10-ml fractions with an automatic fraction collector. The early fractions contained 17β,19-diacetoxy-4-androsten-3-one (**12b**, 85 mg), which was crystallized from ether–petroleum ether to give pure **12b** (35 mg), mp 124–126°, identical with authentic material[23] as judged by melting point, mixture melting point, and infrared comparison. Later fractions contained 5β,17β,19-trihydroxyandrostan-3-one 17β,19-diacetate (**14**, 242 mg) which was crystallized from ether–petroleum ether to give the analytical sample of **14**: mp 151–153°; CD λ_{max} 307 nm ($\Delta\epsilon$ −0.27), 299 (−0.41), 289 (−0.46); ν_{max} 3580, 1712, 1240 cm^{-1}; nmr ($CDCl_3$) δ 0.82 (s, 3, C-18 CH_3), 2.05 and 2.08 (s, each 3, C-17 and C-19 acetate CH_3), 4.48 (s, 2, C-19 CH_2); mass spectrum m/e 388 ($M - H_2O$), 346, 328, 316.

Anal. Calcd for $C_{23}H_{34}O_6$: C, 67.95; H, 8.43. Found: C, 68.15; H, 8.20.

Oxidation of 3β,5β,17β,19-Tetrahydroxyandrostane 17β,19-Diacetate (15) Back to 5β,17β,19-Trihydroxyandrostan-3-one 17β,19-Diacetate (14) with Jones Reagent.—The tetrol diacetate **15** (5 mg) in acetone (1.0 ml) was oxidized with Jones reagent, giving the crude 3 ketone **14** (4.5 mg), identical with authentic material by melting point, mixture melting point, infrared, and tlc comparison.

3β,5β,17β,19-Tetrahydroxyandrostane 17β,19-Diacetate (15).—5β,17β,19-Trihydroxyandrostan-3-one 17β,19-diacetate (**14**, 170 mg) was reduced with W-2 Raney nickel in refluxing ethanol (1 hr). Preparative tlc (chloroform–ethyl acetate, 3:2) gave pure tetrol diacetate **15** (140 mg) as a colorless glass: ν_{max} 1740, 1245 cm^{-1}; nmr ($CDCl_3$) δ 0.78 (s, 3, C-18 CH_3), 2.03 and 2.07 (s, each 3, C-17 and C-19 acetate CH_3), 3.33 (s, 2, OH), 4.13 (s, $W_{1/2}$ = 8 Hz, 1, C-3 H), 4.38 (s, 2, C-19 CH_2); mass spectrum m/e 408 (M^+), 390, 372, 348, 336, 330.

3β,5β,17β,19-Tetrahydroxyandrostane (16).—The tetrol diacetate **15** was hydrolyzed in 1% methanolic potassium hydroxide solution (18 hr reflux), giving pure tetrol **16**: mp 204–207° (from acetone–hexane), undepressed on admixture with an authentic sample[24] of **16** of mp 205–208°; $[\alpha]D$ +44° (chloroform–ethanol, 9:1) [lit 38° (solvent "chloroform (2 ml) containing 1 drop of ethanol")];[16] mass spectrum m/e 306 ($M - 18$), 288, 276, 270, 258, 252, indistinguishable from the mass spectrum of the authentic sample.

Registry No.—**10a**, 33066-33-0; **10b**, 33065-66-6; **11**, 33065-67-7; **13a**, 23463-01-6; **13b**, 30517-97-6; **14**, 33065-70-2; **15**, 33065-71-3; **16**, 33065-72-4; chromous acetate, 628-52-4.

Acknowledgments.—We thank Sharon Cylus for excellent technical assistance. Our best thanks are also due to Dr. A. Nickon and Syntex Corporation for generous gifts of steroids. We also thank Drs. D. P. Hollis and C. C. Fenselau for 100-MHz nmr spectra and mass spectra, respectively.

(23) *Cf.* M. Ehrenstein and K. Otto, *J. Org. Chem.*, **24**, 2006 (1959). The authentic sample was prepared by acetylation of 19-hydroxytestosterone with pyridine–acetic anhydride at room temperature.

(24) The authentic sample of **16** was provided by the late Dr. M. Ehrenstein, University of Pennsylvania.

Steroids and Related Natural Products. 69. Synthesis of 20(22)-Dihydro-23-deoxodigitoxigenin[1,2]

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Received June 28, 1971

A synthetic route from digitoxigenin to 20(22)-dihydro-23-deoxodigitoxigenin (**10a**) has been developed. Digitoxigenin was acetylated, dehydrated, and selectively hydrogenated to give 3β-acetoxy-5β,20ξ-card-14-enolide (**4**). Reduction with lithium aluminum hydride gave diol **5** which was cyclized to yield 3β-hydroxy-23-deoxo-5β,20ξ-card-14-enolide (**6**). Introduction of the 14β-hydroxyl (**10a**) group was achieved by successive formation of the 14β-hydroxy-15α-bromo (**7**) and β-epoxide (**8**) derivatives followed by a reduction step.

The relationship of structure to cardiac activity in naturally occurring cardenolides has been receiving increased attention.[3] For example, the effect on activity with respect to type and number of glycoside units and location of certain oxygen functional groups on the steroid nucleus has been studied by Chen.[3] Less attention has been given to the lactone ring, but it is known[4] that a 20-fold decrease in cardiac activity results when the lactone ring of digitoxigenin is modified by hydrogenation. Thus, we undertook synthesis of 20(22)-dihydro-23-deoxodigitoxigenin (**10a**) to provide a model lacking the entire lactone π-bond system.

Digitoxin (**1a**) served as starting material and was hydrolyzed[5] in high yield to digitoxigenin (**1b**). Preparation of 3β-acetoxy-5β-carda-14,20(22)-dienolide (**2b**) was achieved as described by Engel.[6] Application of 5% palladium on calcium carbonate catalyst was successful in selective reduction of olefin **2b** to 3β-acetoxy-5β,20ξ-card-14-enolide (**4**, 86% overall yield from digitoxigenin). A second pathway to Δ^{14} olefin **4** which involved hydrogenation of the C-20(22) double bond in digitoxigenin (**1b**) to give dihydrodigitoxigenin (**3a**) followed by the preceding acetylation–dehydration sequence led to a 72% overall yield from digitoxigenin (**1b**).

Next, 3β,21-dihydroxy-20ξ-(β-hydroxyethyl)-5β-pregna-14-ene (**5**) was obtained (35% yield) by reduction of lactone **5** with lithium aluminum hydride. An attempt at reducing lactone **2b** directly to triol **5** with lithium aluminum hydride produced a complex mixture and was discontinued. Once alcohol **5** was in hand, cyclization to 3β-hydroxy-23-deoxo-5β,20ξ-card-14-enolide (**6**) was explored. Gillis and Beck[7] reported high yields for diol → tetrahydrofuran cyclization using hot dimethyl sulfoxide. Another method frequently employed utilizes *p*-toluenesulfonyl chloride in pyridine.[8] The dimethyl sulfoxide method was evaluated first. In a series of accessory experiments redistilled dimethyl sulfoxide (from calcium hydride) was found acidic enough to cleave tetrahydropyranyl ethers. Later it was determined that neutral dimethyl sulfoxide was best obtained by passing through a column of basic alumina. When diol **5** was heated in neutral dimethyl sulfoxide at 150° for 5 hr, 3β-hydroxy-23-deoxo-5β,20ξ-card-14-enolide (**6**) resulted in 45% yield. The same cyclization to tetrahydrofuran **6** was also realized in 34% yield by heating diol **5** in pyridine with *p*-toluenesulfonyl chloride.

The final sequence involved reintroduction of the 14β-hydroxyl group. Formation of the 14β-hydroxyl derivative of a Δ^{14} steroid usually involves preparation of the corresponding 14β,15β epoxide. Reduction of such 14,15 epoxides with lithium aluminum hydride readily gives the 14β alcohol.[9] Several methods for obtaining 14β,15β epoxides exist. Addition of hypobromous acid to the Δ^{14} position leads to 14β-hydroxy-15α-bromo derivatives which can be converted to β epoxides by base treatment.[9c,10] Another method involves oxidation of the Δ^{14} olefin with a peracid to give a 14α,15α epoxide followed by acid cleavage to a 14β,15α diol and treatment with a sulfonyl chloride to effect ring closure.[11] On one occasion[12] involving 14-dehydrobufalin, *m*-chloroperbenzoic acid was shown to give resibufogenin, the 14β,15β epoxide, rather than the 14α,15α epoxide expected from peracid treatment. However, in later experiments[2] with different specimens of *m*-chloroperbenzoic acid only the expected 14α,15α epoxide was obtained. Thus, treatment of 3β-hydroxy-23-deoxo-5β,20ξ-card-14-enolide (**6**) with *m*-chloroperbenzoic acid afforded a 14,15 epoxide which showed a proton magnetic resonance chemical shift of 3 Hz upfield for the C-18 methyl resonance. Furthermore, lithium aluminum hydride reduction of this epoxide gave a C-14 alcohol which also showed an upfield shift of 7 Hz for the C-18 methyl group. Previously, studies of Δ^{14} steroids have shown that the C-18 methyl group is shifted up-

(1) This investigation was supported by Public Health Service Research Grants CA-10612-03 and CA-10612-04 from the National Cancer Institute and was abstracted in part from the Ph.D. dissertation of F. W. V., Arizona State University, April 1971.

(2) For part 68 of this series, see G. R. Pettit, Y. Kamano, F. Bruschweiler, and P. Brown, *J. Org. Chem.*, **36**, 3736 (1971).

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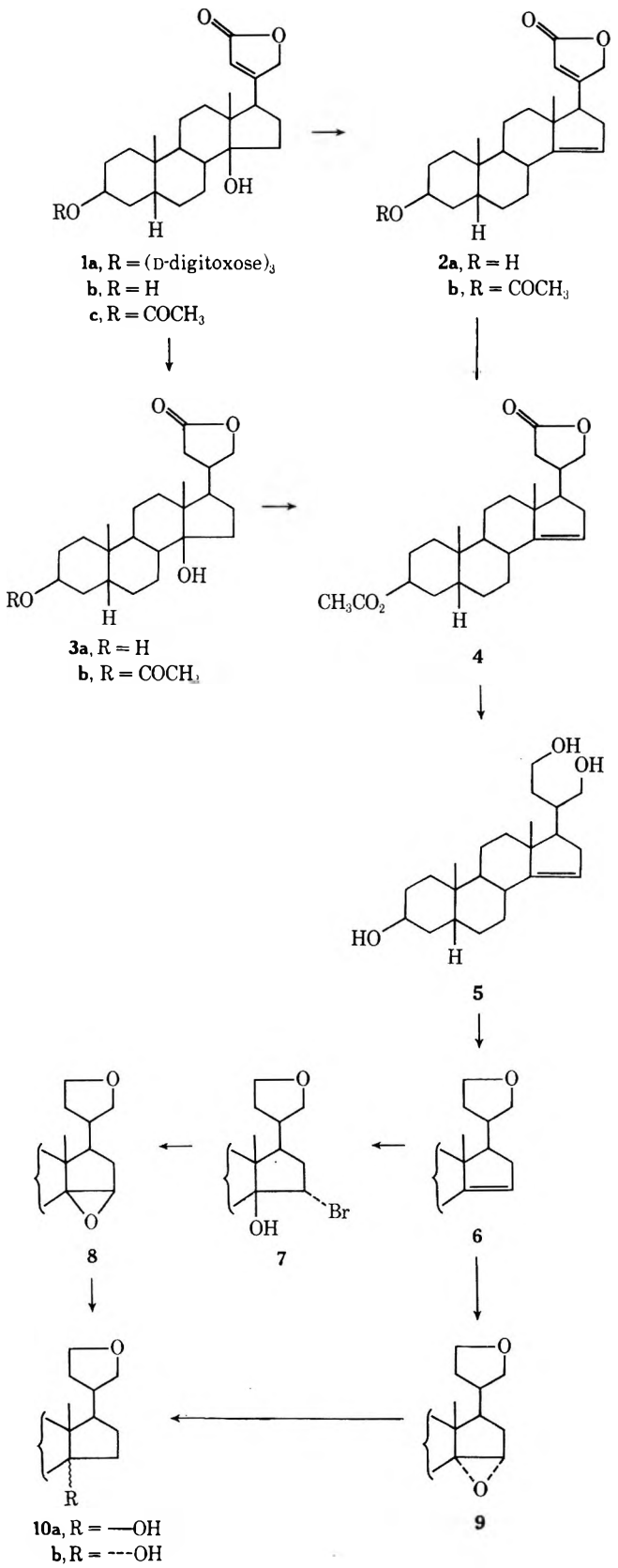

field for an α-epoxide[13] and a 14α-hydroxyl group[14] and downfield for β substitution. Therefore, the upfield shifts serve to confirm that both substances were substituted on the D ring α side and were thus formulated as α epoxide **9** and 14α alcohol **10b**. The same result was obtained when 3β-acetoxy-14-dehydrodigitoxigenin (**2b**) was epoxidized by means of *m*-chloroperbenzoic acid. Support for this conclusion came from a shift in the C-18 methyl resonance of 2 Hz upfield and comparison of physical data with that reported by Meyer[10] for both the 14α,15α and 14β,15β epoxides of digitoxigenin.

Attention was next directed to a halohydrin approach to the 14β alcohol. Reaction of olefin **6** with *N*-bromoacetamide and perchloric acid in dioxane afforded the 14β-hydroxy-15α-bromo derivative **7**. Crude bromohydrin **7** was cyclized to β epoxide **8** employing methanolic potassium acetate. The β-epoxide configuration was confirmed by shift of the C-18 methyl resonance downfield 9 Hz. Reduction of epoxide **8** by means of lithium hydride gave 20(22)-dehydro-23-deoxodigitoxigenin (**10a**). The 14β-hydroxyl configuration was substantiated by a 5-Hz downfield shift of the 18-methyl group signal.

Experimental Section

All common reagents and solvents used were "Baker Analyzed," Mallinckrodt AR, or Matheson Coleman and Bell AR. Ligroin refers to Skellysolve B, bp 65–70°. Tetrahydrofuran, ether, benzene, *p*-dioxane, and pyridine were purified and redisdilled. Dimethyl sulfoxide was purified by passing through a column of basic alumina. *N*-bromoacetamide was recrystallized and employed immediately. *m*-Chloroperbenzoic acid (from Aztec Chemical Co.) was purified by the method of Schwartz and Blumbergs.[15] The following materials were used as obtained from the sources indicated: 5% palladium on calcium carbonate, Englehard Industries; digitoxin, Centerchem, Inc.; lithium aluminum hydride, Ventron Corp.

Silica gel HF_{254} (E. Merck, Darmstadt, Germany) spread on microscope slides was used for thin layer chromatograms (tlc). The same silica gel on plates measuring 20 × 20 × 0.2 cm was used for preparative layer chromatograms (plc). Development of tlc plates was performed by charring with 2% ceric sulfate in 2 *N* sulfuric acid. Plc development was conducted under ultraviolet light and/or by spraying a thin strip down the side of the plate with 2% ceric sulfate in 2 *N* sulfuric acid and charring with a hot glass rod. Silica gel (E. Merck) for column chromatography was 0.05–0.20 mm in diameter (70–325 mesh). Chromatography columns were prepared using a slurry of silica gel in a solvent system of lesser polarity than that to be used for initial elution. If the mixture to be chromatographed was not soluble in this solvent system it was dissolved in chloroform, and silica gel (10% of the weight used for the column) was added. Removal of the chloroform *in vacuo* gave a silica gel powder coated with the mixture. Addition of the powder to the column gave a uniform band of adsorbed material.

Solvent extracts of aqueous solutions were dried over anhydrous magnesium sulfate. Solvents were concentrated *in vacuo*. Melting points were determined on a Kofler melting point apparatus and are uncorrected. All analytical samples were colorless. Elemental microanalysis were performed in the laboratory of Dr. A. Bernhardt, 5251 Elbach uber Engelskirchen, West Germany. Mass spectra were determined using an Atlas CH-4B mass spectrometer by Messrs. R. Scott or E. Bebee. Proton magnetic resonance spectra (pmr) were recorded by Miss K. Reimer using a Varian A-60 spectrometer (deuteriochloroform solution with tetramethylsilane as an internal standard unless stated otherwise). Infrared spectra (in potassium bromide) were determined (K. Reimer) with a Beckman IR-12 instrument.

3β-Acetoxy-5β,20ξ-card-14-enolide (4). Method A.—A solution of digitoxigenin **5** (**1b**, 3.6 g) in tetrahydrofuran (80 ml) containing suspended 5% palladium on calcium carbonate (0.40 g) was stirred under a hydrogen atmosphere (1 atm pressure) for 48 hr. The solution was filtered and solvent was removed *in vacuo*. A solution of the oily residue in ethyl acetate was passed through a short column of silica gel to yield 2.9 g (80%) of **3β,14-dihydroxy-5β,14β,20ξ-cardanolide (3a)**: mp 174–182°

(13) See, for instance, N. S. Bhacca and D. H. Williams, "Applications of NMR Spectroscopy in Organic Chemistry," Holden-Day, San Francisco, Calif., 1964, pp 13–32.

(14) See also Zürcher, ref 3.

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(lit.[16] 222–224°); ir 3420 (–OH), 1770 cm^{-1} (C=O); pmr δ 0.95 (s, 6 H, 18 and 19 methyl), 2.43 (br, 2 H, $-CH_2C=O$), 4.05 (br, 1 H, H-3), 4.38 (br, 2 H, $-CH_2O-$); mass spectrum *m/e* (rel intensity) 376 (M^+, 80), 358 (100), 341 (46), 246 (62), 203 (75), 182 (98).

A solution of crude alcohol **3a** (2.9 g, 7.7 mmol) in pyridine (25 ml)–acetic anhydride (13 ml) was allowed to stand at room temperature for 11 hr and poured onto crushed ice. The precipitate was collected, washed well with water, and dried to yield 3.2 g of crude acetate (**3b**). To a cold (ice bath) solution of the crude acetate in pyridine (25 ml) was added dropwise with stirring a solution of thionyl chloride (4 ml) in pyridine (8 ml). The reaction mixture was stirred for an additional 1 hr, stoppered, stored at −2° for 5 hr, and poured onto crushed ice. After 12 hr standing at room temperature the semicrystalline solid was collected and dissolved in chloroform (200 ml). The resulting solution was washed with water, 1 *N* hydrochloric acid, saturated sodium bicarbonate solution, and water and dried, and the solvent removed *in vacuo*. The resultant solid was chromatographed (powder loading technique) on silica gel (70 g). Elution with ethyl acetate–ligroin ether (3:17) yielded 3.0 g (72% from **1b**) of **3β-acetoxy-5β,20ξ-card-14-enolide** (**4**). A small portion was recrystallized four times from ethanol–water to afford an analytical sample: mp 201–204°; ir 1770 (lactone C=O), 1730 (acetate C=O), 1640 cm^{-1} (C=C); pmr δ 0.92 (s, 18 methyl), 0.98 (s, 19 methyl), 2.03 (s, acetate), 3.90 and 4.40 (two broad multiplets each integrating for 1 H, $-CH_2O-$, chemically nonequivalent), 5.03 (br, 1 H, H-15), 5.13 (br, 1 H, H-3); mass spectrum *m/e* (rel intensity) 400 (M^+, 41), 340 (100), 325 (59), 315 (50), 314 (38), 255 (70).

Anal. Calcd for $C_{25}H_{36}O_4$ (400.5): C, 74.96; H, 9.06. Found: C, 75.05; H, 8.76.

Method B.—A solution of 3β-acetoxy-5β-carda-14,20(22)-dienolide[7] (**2b**, 3.8 g) in tetrahydrofuran (100 ml) containing suspended 5% palladium on calcium carbonate (0.38 g) was stirred under a hydrogen atmosphere (1 atm pressure) for 45 hr. The solution was filtered and solvent was removed *in vacuo* to yield 3.9 g (98%) of crude **3β-acetoxy-5β,20ξ-card-14-enolide** (**4**). A small amount was crystallized from ethanol–water, mp 192–198°, identical[17] with that obtained by method A.

3β,21-Dihydroxy-20ξ-(β-hydroxyethyl)-5β-pregna-14-ene (**5**).—To a stirred, ice-cold suspension of lithium aluminum hydride (1.0 g) in dry ether (200 ml) was added dropwise (under nitrogen) a solution of 3β-acetoxy-5β,20ξ-card-14-enolide (**4**, 2.5 g) in dry ether (100 ml). The mixture was stirred for an additional 1 hr, ethyl acetate (10 ml) was added, and the ice bath was removed. The resulting suspension was separated and the filtrate was evaporated to yield a very small amount of product. A solution of the product in ethyl acetate was used to extract the solid, recovered by filtration, in a Soxhlet extractor for 3.5 hr. Allowing the solution to stand overnight at room temperature produced 0.33 g of colorless crystals, mp 197–204°. Evaporation of the mother liquor *in vacuo* gave 1.70 g of residue which was chromatographed (powder leading technique) on silica gel (50 g) and eluted with ethyl acetate–ligroin (1:1) to yield 0.38 g of diol **5**. Another 0.09 g was obtained by an additional 20-hr extraction of the solid products. The total yield of **3β,21-dihydroxy-20ξ-(β-hydroxyethyl)-5β-pregna-14-ene** (**5**) was thus 0.80 g (35%). A small portion recrystallized twice from ethanol–water afforded an analytical sample as plates: mp 226–234°; ir 3360 (–OH), 1635 cm^{-1} (C=C); pmr (DMSO-d_6, external TMS) δ 0.97 (s, 18 methyl), 1.00 (s, 19 methyl), 3.80 (m, 2 H, $-CH_2O-$), 4.13 (m, 2 H, $-CH_2O-$), 4.27 (br, 1 H, H-3), 5.02 (br, 1 H, H-15); mass spectrum *m/e* (rel intensity) 362 (M^+, 3), 344 (21), 329 (8), 314 (7), 311 (7), 275 (21), 274 (84), 273 (82), 272 (100), 256 (30), 255 (82).

Anal. Calcd for $C_{23}H_{38}O_3$ (362.5): C, 76.20; H, 10.56. Found: C, 75.69; H, 10.60.

3β-Hydroxy-23-deoxy-5β,20ξ-card-14-enolide (**6**). **Method A.**—A mixture of 3β,21-dihydroxy-20ξ-(β-hydroxyethyl)-5β-pregna-14-ene (**5**, 0.38 g) and dimethyl sulfoxide (4 ml) was placed in an oil bath at 90°. After 5 hr no reaction was evident by tlc and the temperature was increased to 150°. Five hours later the reaction mixture was poured into saturated sodium chloride solution (60 ml) and extracted with chloroform. The combined extract was washed with water and dried and the solvent was removed *in vacuo* to yield 0.38 g of red oil which solidified on standing (overnight). The solid was combined with 0.22 g of red oil from another experiment, chromatographed (powder loading technique) on silica gel (20 g), and eluted with ligroin–ethyl acetate (9:1) to afford 0.26 g of **3β-hydroxy-23-deoxy-5β,20ξ-card-14-enolide** (**6**). Two recrystallizations from ethanol–water gave an analytical sample as microneedles: mp 162–165°; ir 3380 (–OH), 1645 (C=C), 1040 cm^{-1} (COC); pmr δ 0.95 (s, 18 methyl), 0.98 (s, 19 methyl), 3.00–3.92 (complex region, 4 H, $-CH_2OCH_2-$), 4.00 (br, 1 H, H-3), 5.05 (br, 1 H, H-15); mass spectrum *m/e* (rel intensity) 344 (M^+, 69), 329 (20), 326 (11), 311 (16), 275 (75), 274 (100), 273 (54), 272 (80), 259 (25), 257 (22), 256 (25), 255 (62), 241 (45).

Anal. Calcd for $C_{23}H_{36}O_2$ (344.5); C, 80.18; H, 10.53. Found: C, 79.92; H, 10.17.

Method B.—A solution of 3β,21-dihydroxy-20ξ-(β-hydroxyethyl)-5β-pregna-14-ene (**5**, 0.64 g) and *p*-toluenesulfonyl chloride (1.0 g) in pyridine (20 ml) was heated (steam bath) in a stoppered flask for 1.5 hr. Pyridine was removed by azeotroping with benzene. The residual oil in chloroform was washed with cold 2 *N* hydrochloric acid, saturated sodium bicarbonate solution, and water and dried, and the solvent was removed *in vacuo* to yield 0.85 g of brown oil. The oil was chromatographed (powder loading technique) on silica gel (50 g) and product was eluted with ligroin–ethyl acetate (9:1) to yield 0.21 g (34%) of **3β-hydroxy-23-deoxo-5β,20ξ-card-14-enolide** (**6**). Crystallization from ethanol–water afforded microneedles, mp 165–170°, identical[17] with the product from method A.

3β,14-Dihydroxy-23-deoxo-5β,14α,20ξ-cardanolide (**10b**).—To a solution of 3β-hydroxy-23-deoxy-5β,20ξ-card-14-enolide (**6**, 200 mg) in chloroform (15 ml) was added (small portions) *m*-chloroperbenzoic acid (0.17 g). After 0.5 hr the reaction mixture was washed with 5% sodium hydroxide solution and water and dried, and the solvent was removed *in vacuo* to yield 0.20 g of foamy solid. Chromatography (powder loading technique) on silica gel (5 g) and elution with ligroin–ethyl acetate (4:1) yielded 0.10 g of 3β-hydroxy-14,15α-epoxy-23-deoxo-5β,14α,20ξ-cardanolide (**9**). A portion recrystallized twice from ethyl acetate–hexane led to pure needles of 14α,15α epoxide **9**: mp 164–166°; ir 3380 (–OH), 3025 (epoxide CH), 1040 cm^{-1} (COC); pmr δ 0.88 (s, 18 methyl), 0.98 (s, 19 methyl), 3.35 (d, $J < 1$ Hz, H-15), 2.96–3.98 (complex, $-CH_2OCH_2-$), 4.07 (br, H-3); mass spectrum *m/e* (rel intensity) 360 (M^+, 61), 345 (87), 343 (23), 327 (24), 316 (80), 301 (23), 290 (57), 289 (95), 275 (28), 271 (23), 250 (45), 215 (47), 149 (100).

To a stirred suspension of lithium aluminum hydride (0.9 g) in refluxing dry ether (70 ml) was added (dropwise under nitrogen) a solution of α epoxide **9** (68 mg) in dry ether (50 ml). The solution was heated (reflux) for 24 hr and diluted with water (cautiously at first). The phases were separated, the organic layer was washed with 1 *N* hydrochloric acid, saturated sodium bicarbonate solution, and water and dried, and the solvent was removed *in vacuo* to yield 60 mg of clear oil. Following combination with 25 mg of crude product from a previous experiment and purification by plc (1:1 ligroin–ethyl acetate mobile phase), 52 mg of **3β,14-dihydroxy-23-deoxo-5β,14α,20ξ-cardanolide** (**10b**) was obtained as a pale yellow solid. Two recrystallizations from acetone–hexane gave an analytical sample as needles: mp 188–192°; ir 3490 (–OH), 1035 cm^{-1} (COC); pmr δ 0.82 (s, 3 H, 18 methyl), 0.98 (s, 3 H, 19 methyl), 3.05–3.98 (complex, 4 H, $-CH_2OCH_2-$), 4.08 (br, 1 H, H-3); mass spectrum *m/e* (rel intensity) 362 (M^+, 13), 344 (56), 329 (52), 326 (52), 311 (34), 275 (43), 274 (74), 273 (43), 272 (55), 255 (45), 250 (67), 241 (31), 215 (30), 203 (55), 183 (30), 177 (65), 168 (50), 164 (100).

Anal. Calcd for $C_{23}H_{38}O_3$ (362.5): C, 76.20; H, 10.56. Found: C, 75.55; H, 10.75.

3β,14-Dihydroxy-23-deoxo-5β,14β,20ξ-cardanolide (**10a**).—To a cold (ice bath) solution of 3β-hydroxy-23-deoxo-5β,20ξ-card-14-enolide (**6**, 150 mg) in *p*-dioxane (15 ml)–water (2 ml) was added with stirring 5 drops of 0.39 *M* perchloric acid. The slushlike mixture was elevated from the ice bath until it was just slightly cloudy, 120 mg of *N*-bromoacetamide was added, and the flask was reimmersed in the ice bath. After 40 min, ice–water (50 ml) was added and the resultant mixture was extracted with ethyl acetate. The combined extract was washed with 5% sodium bicarbonate solution and water and dried, and the solvent was removed *in vacuo* (minimum heat) to yield 0.23 g of crude bromohydrin **7** as an orange oil. The oil

(16) B. T. Brown and S. E. Wright, *J. Pharm. Pharmacol.*, **13**, 262 (1961).

(17) The samples gave identical infrared, nuclear magnetic resonance, and mass spectra and exhibited identical R_f values on thin layer chromatograms.

was dissolved in 5% potassium acetate in methanol (25 ml) and heated (reflux) with stirring for 11 hr. The solution was poured into saturated aqueous sodium chloride (100 ml) and extracted with chloroform. The combined extract was dried and solvent was removed *in vacuo* to yield 161 mg of yellow solid. Purification by plc (4:1 benzene–acetone mobile phase) provided 100 mg of pale yellow oil which solidified on standing. A second plc purification (2:1 benzene–acetone mobile phase) afforded 51 mg of β epoxide **8**: pmr δ 1.00 (s, 19 methyl), 1.10 (s, 18 methyl), 3.37 (d, $J < 0.5$ Hz, 1 H, H-15), 2.95–3.97 (complex, $-CH_2-OCH_2-$), 4.08 (br, 1 H, H-3).

To a stirred suspension of lithium aluminum hydride (400 mg) in refluxing tetrahydrofuran (40 ml) was added (dropwise) a solution of the β epoxide **8** in tetrahydrofuran (10 ml, under nitrogen). After 3 hr the solution was cooled (ice bath), a few drops of water were added, and then the solution was filtered at room temperature. Solvent was removed and the residue was dissolved in chloroform. The solid products were extracted with chloroform and the extract was washed with water, dried, and evaporated to yield 44 mg of crude product. The solid was combined with 20 mg of crude product from a previous experiment and purified by plc (2:1 benzene–acetone mobile phase) to give 44 mg of clear oil. A second plc purification (3:2 benzene–acetone mobile phase) gave 25 mg of **3β,14-dihydroxy-23-deoxo-5β,14β,20ξ-cardanolide (10a)** as a colorless solid. Several recrystallizations from ethanol–water afforded an analytical specimen as needles: mp 163–173°; ir 3420 (–OH), 1040 cm^{-1} (COC); pmr δ 0.95 (s, 19 methyl), 1.02 (s, 18 methyl), 3.10–3.95 (complex, $-CH_2OCH_2-$), 4.08 (br, 1 H, H-3); mass spectrum *m/e* (rel intensity) 362 (M^+, 9), 344 (65), 329 (34), 326 (24), 311 (23), 275 (26), 274 (100), 273 (34), 272 (61), 259 (17), 258 (18), 257 (31), 256 (23), 255 (35), 250 (11), 241 (16).

Anal. Calcd for $C_{23}H_{38}O_3$ (362.5): C, 76.20; H, 10.56. Found: C, 76.41; H, 11.22.

Registry No.—**3a**, 32970-98-2; **4**, 32970-99-3; **5**, 32971-00-9; **6**, 32971-01-0; **8**, 33020-99-4; **9**, 32971-02-1; **10a**, 32971-04-3; **10b**, 32971-04-3.

Photochemical Addition of Acetone to D-Glucal Triacetate and Subsequent Oxetane Ring Cleavage[1]

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Received June 10, 1971

3,7-Anhydro-1-deoxy-2-*C*-methyl-2-*O*-methyl-D-*glycero*-D-*ido*-octitol (**3**) and 3,7-anhydro-1,2-dideoxy-2-methylene-D-*glycero*-D-*ido*-octitol (**4**) are obtained from acid-catalyzed methanolysis of 5,6,8-tri-*O*-acetyl-2,4:3,7-dianhydro-1-deoxy-2-*C*-methyl-D-*glycero*-D-*ido*-octitol (**1**), obtained from ultraviolet irradiation of 3,4,6-tri-*O*-acetyl-D-glucal in acetone. Oxetane ring opening in benzene affords **4**. Ethanolysis of **1** yields the 2-*O*-ethyl derivative **5** in addition to **4**. Saturation of the methylene group in **4** followed by acetylation yields crystalline 4,5,6,8-tetra-*O*-acetyl-3,7-anhydro-1,2-dideoxy-2-*C*-methyl-D-*glycero*-D-*ido*-octitol (**10**). Benzylidenation of deacetylated **1** gives the 2,4:6,8-di-*O*-benzylidene derivative **6**.

Cycloaddition of carbonyl compounds to olefins leading to oxetane ring formation in the presence of ultraviolet irradiation has been extensively examined in aliphatic and aromatic compounds.[2-4] We have examined the photoaddition of acetone to 3,4,6-tri-*O*-acetyl-D-glucal and also have characterized the products obtained from opening of the produced oxetane ring.

Ultraviolet irradiation of 3,4,6-tri-*O*-acetyl-D-glucal in acetone at 10–15° for 5 hr gives 5,6,8-tri-*O*-acetyl-2,4:3,7-dianhydro-1-deoxy-2-*C*-methyl-D-*glycero*-D-*ido*-octitol (**1**) as the major product in 33% yield. The oxetane ring is thought to be formed through a stable biradical intermediate.[2] It is expected that carbon–oxygen bond formation at C-2 of the glucal predominates over its formation at C-1, because a carbon radical at C-1 has higher stability than a radical at C-2 of the sugar. Attachment at C-2 would be expected to position the oxygen trans to the acetoxy group at C-3. The dimethyl radical group presumably joins with the radical at C-1 to develop a ring of minimum strain resulting in the formation of the D-*glycero*-D-*ido*-octitol derivative. The gross structure of **1** may be assigned with the aid of nmr spectroscopy.[4] The signal of H-4 in the oxetane ring gives a quartet at τ 5.42 with $J_{4,5} = 3.5$ Hz and $J_{3,4} = 5.5$ Hz. Irradiation of the H-4 proton signal collapses the quartet ($J_{4,5} = 3.5$; $J_{5,6} = 9$ Hz) at τ 4.87 into a doublet with 9-Hz coupling constant. A triplet at τ 5.22 is due to H-6 and the signal of H-3 is superimposed in the τ 5.60–6.15 region which integrates for four protons.

Acid-catalyzed ring opening of oxetane rings has been reported.[2] However, deacetylation of **1** with 0.1 *N* sodium methoxide followed by deionization with excess Amberlite IR-120H at 25° for 16 hr affords a mixture of **3** and **4**, separated by column chromatography, in 45 and 10% yield, respectively. The oxetane ring of **2** is acid labile and is opened on a silica gel column eluted with chloroform–methanol, giving a mixture containing **3** and **4** in 10% yield. Compounds **3** and **4** can also be obtained by refluxing **1** in methanol in the presence of IR-120H; the yields of **3** and **4** are 41 and 14%, respectively. Treatment of **1** with IR-120H resin in benzene gives a 33% yield of the methylene derivative **4**. Ethanolysis of **2** at 25° in the presence of IR-120H resin for 16 hr provides a 34% yield of the methylene derivative **4** and a 21% yield of **5**. When direct ethanolysis is performed on **1** under reflux, the main product is the unsaturated octitol **4** (40%), while the *O*-ethyl derivative **5** is isolated in only 9% yield. Reaction of **2** with benzaldehyde and zinc chloride gives the 2,4:6,8-di-*O*-benzylidene compound **6** which is further characterized as its acetate **7**.

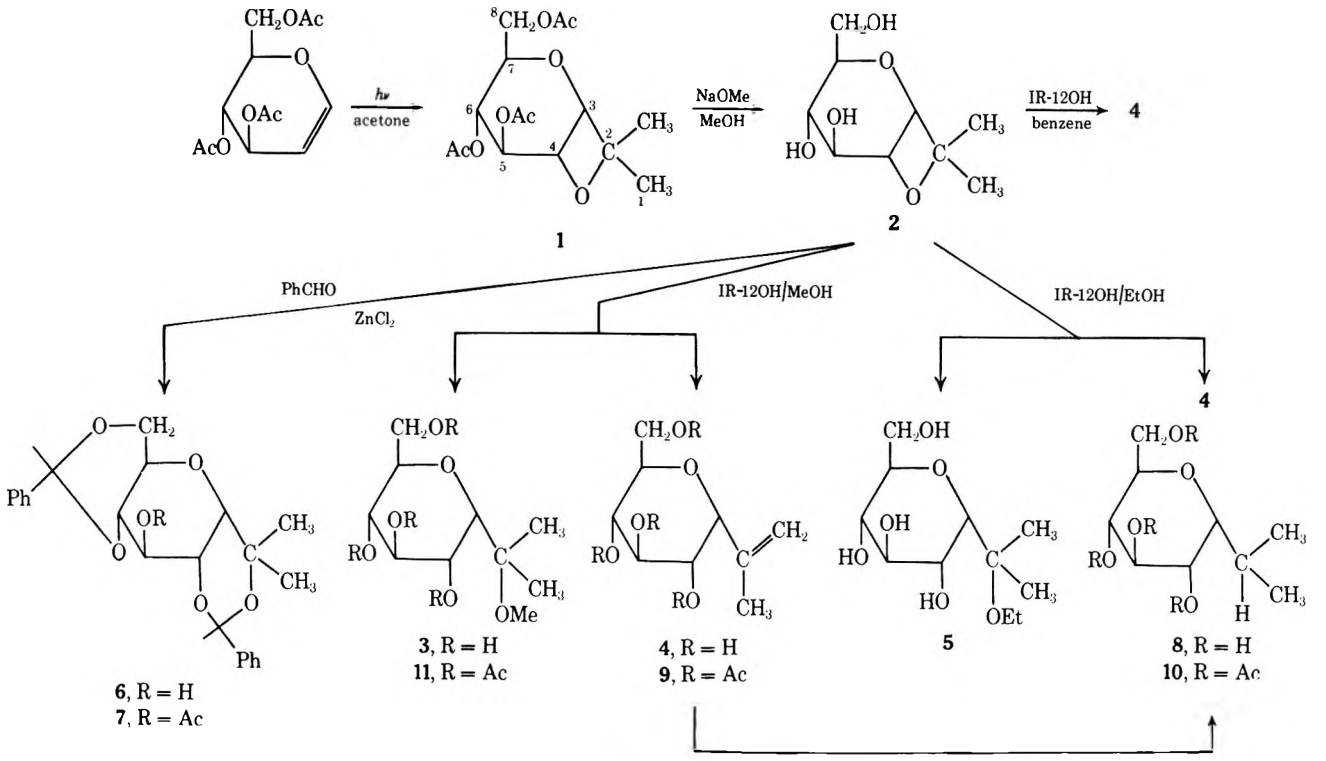
The nmr spectra of **4** and **8** permit assignment of structures. The methylene signals of **4** appear at τ 4.75, while these signals disappear in the reduction product **8**. In the nmr spectrum of **8**, resonance for the methine proton (H-2) appears as a multiplet around τ 8.20. The nmr spectrum of **3** demonstrates

(1) Journal Paper No. 4458 of the Purdue Agricultural Experiment Station.

(2) G. Büchi, C. G. Inman, and E. S. Lipinsky, *J. Amer. Chem. Soc.*, **76**, 4327 (1954).

(3) D. R. Arnold, *Advan. Photochem.*, **6**, 31 (1968).

(4) N. C. Yang and W. Eisenhardt, *J. Amer. Chem. Soc.*, **93**, 1277 (1971).



signals with seven-proton intensity in the τ 5.95–6.60 region and a methoxy peak at τ 6.78. Because of overlapping of the signals in these spectra, they cannot be used to deduce the configuration at C-4 or at C-3. Evidence indicating that the substituent at C-4 is trans to that of C-5 may be deduced from the nmr spectrum of 4,5,6,8-tetra-*O*-acetyl-3,7-anhydro-1,2-dideoxy-2-methylene-D-*glycero*-D-*ido*-octitol (**9**). Here the proton at C-3 appears as a multiplet at τ 6.20, and the methylene protons give signals at τ 4.75. There is a quartet at τ 4.95, with spin–spin couplings of 9 and 5 Hz. Irradiation of the multiplet at τ 6.20 results in collapse of the quartet at τ 4.95 to a doublet ($J_{4,5}$ = 9 Hz) and irradiation of the quartet at τ 4.95 decreases the multiplicity at τ 6.20. Thus, the quartet at τ 4.95 is attributable to H-4. Since H-4 is trans diaxial to either H-3 or H-5 and is axial–equatorial to the other and since H-5 is axial, H-3 must be equatorial. Additional evidence for the axial orientations of these two protons is provided by nmr analysis of **11**. Signals for H-3, H-6, and H-5 appear respectively at τ 6.18 (doublet), 5.10 (triplet), and 4.40 (triplet). A quartet at τ 4.82 has the coupling constants 4.5 and 8 Hz. Irradiation of the doublet at τ 6.18 (H-3, $J_{3,4}$ = 4.5 Hz) collapses the quartet at τ 4.82 into a doublet with an 8-Hz splitting. Therefore, the quartet at τ 4.82 is assigned to H-4 and the larger J value must arise from the coupling of H-4 and H-5, configurational findings in **9**, and the configuration of **1** is hence D-glycero-D-ido.

Hydrogenation of the unsaturated acetate **9** using palladium on charcoal gives crystalline 4,5,6,8-tetra-*O*-acetyl-3,7-anhydro-1,2-dideoxy-2-*C*-methyl-D-*glycero*-D-*ido*-octitol (**10**), identical with the product obtained from the acetylation of **8** in pyridine with acetic anhydride. It is interesting to note that this is the first time a crystalline product has been obtained by C-alkylation of carbon C-1 of a sugar. C-1 alkylation of acetohalo sugars employing Grignard reagents, such as butyl and isopropyl,[5] fails to give crystalline products possible because a mixture of isomers is produced in each instance.

Experimental Section

Irradiations were made with a 450-W Hanovia 679A-36 mercury lamp in a quartz immersion well without filter under oxygen-free nitrogen. The progress of reactions and purity of products were checked by thin layer chromatography (tlc) on silica gel G[6] coated glass plates (5 × 13 cm) irrigated with (A) benzene–ethyl acetate (4:1 v/v) or (B) chloroform–methanol (9:1 v/v). Melting points were determined on a Fisher-Johns apparatus and were corrected. Infrared spectra were recorded in Nujol with a Perkin-Elmer Model 337 spectrometer, and nmr spectra were determined in deuteriochloroform (TMS as internal standard) and deuterium oxide (DSS as internal standard), unless otherwise mentioned, using Varian Associates A-60 or A-60A spectrometers. Optical rotations were measured at 25° in a Perkin-Elmer automatic polarimeter Model 141

5,6,8-Tri-*O*-acetyl-2,4:3,7-dianhydro-1-deoxy-2-*C*-methyl-D-*glycero*-D-*ido*-octitol (1).—A solution of 3,4,6-tri-*o*-acetyl-D-glucal[7] (10 g) in 180 ml of acetone was irradiated for 5 hr at 10–15°, after which the solution was concentrated to a syrup. The syrup was applied to a silica gel[8] column (450 g) and eluted with benzene–ethyl acetate (95:5 v/v). Progress was checked by tlc using solvent A and the fractions containing the starting material, D-glucal triacetate (4.65 g), and **1** (2.05 g), were separately collected. The yield of **1**, based on the amount of starting material consumed, was 33%: $[\alpha]^{25}D$ + 54.1° (*c* 1.0, $CHCl_3$); nmr (CCl_4) τ 4.87 (q, 1, $J_{4,5}$ = 3.5, $J_{5,6}$ = 9 Hz, H-5), 5.22 (t, 1, $J_{5,6} = J_{6,7}$ = 9 Hz, H-6), 5.42 (q, 1, $J_{4,5}$ = 3.5, $J_{3,4}$ = 5.5 Hz, H-4), 7.98–8.02 (three s, OAc), 8.60 and 8.64 (two s, CCH_3).

Anal. Calcd for $C_{15}H_{22}O_8$: C, 54.55; H, 6.71. Found: C, 54.30; H, 7.00.

3,7-Anhydro-1-deoxy-2-*C*-methyl-2-*O*-methyl-D-*glycero*-D-*ido*-octitol (3) and 3,7-Anhydro-1,2-dideoxy-2-methylene-D-*glycero*-D-*ido*-octitol (4). A. From Methanolysis of Deacetylated 1.—Compound **1** (1.62 g) was deacetylated in absolute methanol (50 ml) with 0.1 *N* sodium methoxide (10 ml) at 0°. Deacetylation was completed overnight at 25°. The reaction mix-

(5) C. D. Hurd and W. A. Bonner, *J. Amer. Chem. Soc.*, **67**, 1972 (1945).

(6) E. Merck, Darmstadt, Germany. Distributors: Brinkmann Instruments Inc., Westbury, N. Y. 11590.

(7) Pfanstiehl Laboratories, Inc., Waukegan, Ill.

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

ture was then deionized with Amberlite IR-120H (methanol-washed and air-dried) until neutral and then an additional 6 ml of the resin was added and stirred at 25° for 16 hr. After filtration, the resin was washed thoroughly with methanol and the combined filtrate was evaporated to a syrup which was applied to a silical gel column (30 g) and eluted with chloroform–methanol (95:5 v/v) to give 0.52 g of **3**, crystallized from ethyl acetate–hexane: mp 141–142°; $[\alpha]^{25}D$ +39.9° (*c* 1.0, CH_3OH); yield 45%; nmr (D_2O) τ 5.95–6.60 (m, 7, H-3, H-4, H-5, H-6, H-7, and H-8,) 6.78 (s, 3, OMe), 8.70 (s, 6, CCH_3).

Anal. Calcd for $C_{10}H_{20}O_6$: C, 50.83; H, 8.53. Found: C, 50.67; H, 8.55.

Further elution of the column gave 0.101 g of **4**, crystallized from ethyl acetate: mp 150–152°; $[\alpha]^{25}D$ +35.9° (*c* 1.0, CH_3OH); yield 10%; ν_{max} 1640 cm^{-1} (methylene); nmr (D_2O) τ 4.75 (m, 2, methylene), 5.60 (m, 1, H-3), 6.0–7.80 (m, 6, H-5, H-6, H-7, and H-8), 8.25 (s, 3, CCH_3).

Anal. Calcd for $C_9H_{16}O_5$: C, 52.93; H, 7.89. Found: C, 52.76; H, 7.84.

B. From Methanolysis of 1.—A mixture of compound **1** (1.0 g) and 8 ml of Amberlite IR-120H in 30 ml of methanol was refluxed with stirring for 16 hr. The syrup (0.711 g), obtained after filtration and concentration of the reaction mixture, was applied to a silica gel column (25 g) and eluted with chloroform–methanol (99:1 v/v) and the fractions containing **3** (0.293 g, yield 41%) and **4** (0.084 g, yield 14%) were separated and crystallized as previously described.

Oxetane Ring Cleavage of 1 in Benzene.—A mixture of compound **1** (1.6 g) and 10 ml of Amberlite IR-120H (benzene-washed and air-dried) in 35 ml of benzene was refluxed with stirring for 45 hr. After cooling and filtration, the filtrate was evaporated to a syrup which was deacetylated with sodium methoxide (0.1 *N*, 25 ml) at 25° for 3 hr. The solution was deionized with IR-120H and evaporated to a residue. The residue was crystallized from 50 ml of boiling ethyl acetate to give 0.318 g of **4**, yield 33%.

3,7-Anhydro-1-deoxy-2-*O*-ethyl-2-*C*-methyl-D-*glycero*-D-*ido*-octitol (5). A. From Ethanolysis of Deacetylated 1.—Compound **1** (0.76 g) was deacetylated in absolute methanol (25 ml) with 0.1 *N* sodium methoxide (6 ml) at 0° for 16 hr. The reaction mixture gave 0.496 g of syrup **2**, after deionization with Amberlite IR-120H (ethanol-washed and air-dried) followed by filtration and concentration. Compound **2** was then stirred with 4 ml of the resin for 16 hr at 25°. After filtration, the resin was washed with 10 ml of ethanol and the combined filtrate was evaporated to a syrup which was applied to a silica gel column (20 g) and eluted with chloroform–methanol (95:5 v/v) to give 0.123 g of **5**, crystallized from ethyl acetate–hexane: mp 133–135°; $[\alpha]^{25}D$ +26.2° (*c* 0.30, CH_3OH); yield 21%; nmr (D_2O) τ 5.80–6.30 (m, 7, H-3, H-4, H-5, H-6, H-7, and H-8), 6.42 (q, 2, CH_2 of OEt) 8.70 (s, 6, CCH_3), 8.85 (t, 3, CH_3 of OEt).

Anal. Calcd for $C_{11}H_{22}O_6 \cdot {}^1/_4H_2O$: C, 51.82; H, 8.91. Found: C, 51.99; H, 8.79.

Further elution of the column gave 0.16 g of **4** (34%).

B. From Ethanolysis of 1.—A mixture of compound **1** (1.0 g) and 8 ml of Amberlite IR-120H in 25 ml of ethanol was refluxed with stirring for 20 hr. The syrup obtained after filtration and concentration of the reaction mixture was applied to a silica gel column (40 g) and eluted with chloroform–methanol (99:1 v/v) to give 0.277 g of **4** (40%) and 0.766 g of **5** (9%).

4,5,6,8-Tetra-*O*-acetyl-3,7-anhydro-1,2-dideoxy-2-methylene-D-*glycero*-D-*ido*-octitol (9).—Compound **4** (0.20 g) was acetylated in pyridine (10 ml) with acetic anhydride (0.50 ml) at 25° for 15 hr. The reaction mixture was then poured into ice–water (200 ml) and stirred vigorously. The crystalline product was filtered, washed thoroughly with ice–water, air dried, and recrystallized from ethyl acetate–hexane: mp 105–106°; $[\alpha]^{25}D$ +27.6° (*c* 0.60, $CHCl_3$); yield 0.247 g; ν_{max} 1650 cm^{-1} (methylene); nmr ($CDCl_3$) τ 4.40 (t, 1, $J_{4,5} = J_{5,6}$ = 9 Hz, H-5), 4.60 (t, 1, $J_{5,6} = J_{6,7}$ = 9 Hz, H-6), 4.75 (m, 1, H-7), 4.82 (m, 2, H-8), 6.20 (m, 1, H-3), 7.90, 7.96 (12, OAc), 8.22 (s, 3, CCH_3).

Anal. Calcd for $C_{17}H_{24}O_7$: C, 54.83; H, 6.49. Found: C, 54.63; H, 6.79.

4,5,6,8-Tetra-*O*-acetyl-3,7-anhydro-1,2-dideoxy-2-*C*-methyl-D-*glycero*-D-*ido*-octitol (10). A. From Acetylation of 8.—Methylene derivative **4** (0.12 g) was hydrogenated in 20 ml of ethanol with 0.050 g of palladium over charcoal. The completion of the reaction was followed by tlc, irrigated with solvent B, and the disappearance of the unsaturated compound **4** was checked by using aqueous potassium permanganate as spraying agent. The residue which was obtained after filtration and concentration was recrystallized from ethyl acetate–hexane: mp 127–128°; $[\alpha]^{25}D$ +58.2° (*c* 0.50, CH_3OH); yield 0.093 g; nmr (D_2O) τ 6.10–6.82 (m, 7, H-3, H-4, H-5, H-6, H-7, and H-8), 8.20 (m, 1, methine), 8.98 (d, 3, CCH_3), 9.08 (d, 3, CCH_3). Compound **8** (0.10 g) was acetylated in pyridine (5 ml) with acetic anhydride (0.3 ml) at 25° for 16 hr. The reaction mixture was then poured into ice–water (80 ml), the aqueous solution was extracted with chloroform (two 25-ml portions) and washed with sodium bicarbonate solution and water, and the chloroform extract was dried (Na_2SO_4) and evaporated to a syrup. The syrup was dissolved in 8 ml of hot hexane and crystallized at 0° to yield 0.135 g of **10**: mp 54–56°; $[\alpha]^{25}D$ +32.3° (*c* 1.0, $CHCl_3$); nmr ($CDCl_3$) τ 4.76–5.30 (m, 3, H-4, H-5, and H-6), 5.50–6.20 (m, 3, H-7 and H-8), 6.42 (q, 1, H-3), 7.92–8.20 (13, overlapping OAc and methine), 9.06 (t, 6, CCH_3).

B. From Catalytic Hydrogenation of 9.—Compound **9** (0.20 g) was hydrogenated in 10 ml of ethanol using 0.10 g of palladium over charcoal. The completion of the reaction was checked by tlc (irrigated with solvent A and visualized with potassium permanganate spray). After filtration, the filtrate was evaporated to a syrup which was dissolved in 15 ml of hot hexane and crystallized at 0°, yield 0.178 g. The product was identical with **10**.

Anal. Calcd for $C_{17}H_{26}O_9$: C, 54.54; H, 7.00. Found: C, 54.40; H, 7.13.

4,5,6,8-Tetra-*O*-acetyl-3,7-anhydro-1-deoxy-2-*C*-methyl-2-*O*-methyl-D-*glycero*-D-*ido*-octitol (11).—Compound **3** (0.10 g) was acetylated in pyridine (6 ml) with acetic anhydride (0.2 ml) and the product was worked up in the usual way to give 0.121 g of **11**, crystallized from 10 ml of hexane at 0°: mp 79–80°; $[\alpha]^{25}D$ +45.3° (*c* 0.40, $CHCl_3$); nmr ($CDCl_3$) τ 4.40 (t, 1, $J_{4,5}$ = $J_{5,6}$ = 8 Hz, H-5), 4.82 (q, 1, $J_{3,4}$ = 4.5, $J_{4,5}$ = 8 Hz, H-4), 5.10 (t, 1, $J_{5,6} = J_{6,7}$ = 8 Hz, H-6), 5.50–6.05 (m, 3, H-7 and H-8), 6.18 (d, 1, $J_{3,4}$ = 4.5 Hz, H-3), 6.72 (s, 3, methoxy), 7.96–8.0 (12, Ac), 8.75 (s, 6, CCH_3).

Anal. Calcd for $C_{18}H_{28}O_{10}$: C, 53.43; H, 6.98. Found: C, 53.63; H, 7.02.

3,7-Anhydro-2,4:6,8-di-*O*-benzylidene-1-deoxy-2-*C*-methyl-D-*glycero*-D-*ido*-octitol (6).—Compound **2** (0.75 g) was treated with benzaldehyde in the presence of zinc chloride (1.0 g) at 25° for 16 hr. The reaction mixture was poured into ice–water (300 ml) and stirred vigorously after 100 ml of hexane was added. The solid was filtered, washed with ice–water (100 ml), and air dried to give 0.67 g of **6**, recrystallized from ethyl acetate–hexane: mp 221–222°; $[\alpha]^{25}D$ +75.4° (*c* 0.50, $CHCl_3$).

Anal. Calcd for $C_{23}H_{26}O_6$: C, 69.32; H, 6.58. Found: C, 69.07; H, 6.50.

5-*O*-Acetyl-3,7-anhydro-2,4:6,8-di-*O*-benzylidene-1-deoxy-2-*C*-methyl-D-*glycero*-D-*ido*-octitol (7).—Compound **6** (0.71 g) was acetylated in pyridine (8 ml) with acetic anhydride (0.3 ml) at 25°. The reaction mixture was poured into ice–water (200 ml) and the crystalline solid was collected and air dried, yield 0.178 g, and then recrystallized from ethyl acetate–hexane: mp 180–181°; $[\alpha]^{25}D$ +62.3° (*c* 0.70, $CHCl_3$).

Anal. Calcd for $C_{25}H_{28}O_7$: C, 68.18; H, 6.41. Found: C, 67.91; H, 6.49.

Registry No.—**1**, 32970-01-7; **3**, 32970-02-8; **4**, 32970-03-9; **5**, 32970-04-0; **6**, 32970-05-1; **7**, 32970-06-2; **9**, 32970-07-3; **10**, 32970-08-4; **11**, 32970-09-5; acetone, 67-64-1; D-glucal triacetate, 2873-29-2.

The Photochemistry of Benzophenone Azine[1]

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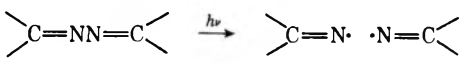
Received July 22, 1971

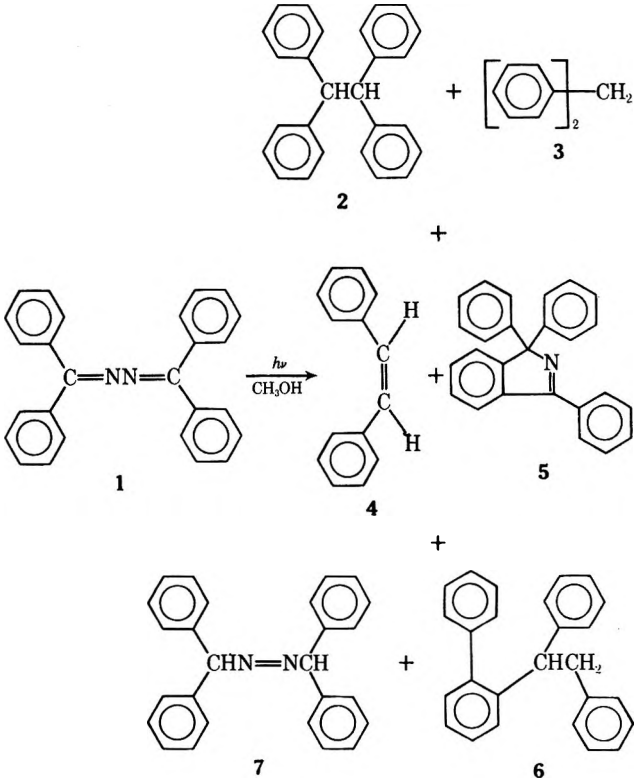
Benzophenone azine (1) has been found to be the beginning point for two different types of photochemical reaction. The first of these is a molecular rearrangement leading to 1,3,3-triphenylisoindole (5) while the second is a photoreduction resulting in the formation of 1,1,1′,1′-tetraphenylazomethane (7). 1,1,1′,1′-Tetraphenylazomethane (7) has also been found to be photochemically unstable yielding 1,1,2,2-tetraphenylethane (2) and diphenylmethane (3). 1,1,2,2-Tetraphenylethane (2) has been previously shown to decompose upon photolysis to give *cis*-stilbene (4), 1-(2-biphenylyl)-1,2-diphenylethane (6), and biphenyl (8). All of these compounds (2–8) are isolated from the photolysis of benzophenone azine (1).

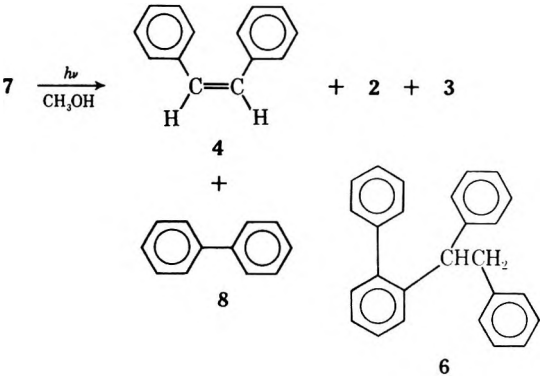
Benzophenone azine (1) has been found to be photochemically unique among azine systems. It does not participate in nitrogen–nitrogen bond homolysis, the major light-initiated reaction experienced by other acyclic azines.[3] It does, however, undergo two reactions, a photoreduction and a molecular rearrangement. At this time we would like to describe our findings related to these two photochemical reactions of benzophenone azine (1).



Results

Vycor-filtered irradiation of 3.00 mmol of benzophenone azine (1) in 1200 ml of methanol under nitrogen for 24 hr with a 450-W Hanovia mercury-vapor lamp produced, after solvent removal, a dark yellow oil containing some solid material. Chromatography on Florisil separated the reaction mixture into seven fractions, one of which was unreacted starting material. Three of the remaining six photoproducts were easily identified as 1,1,2,2-tetraphenylethane (2, 10%), diphenylmethane (3, 8%), and *cis*-stilbene (4, 2%) by comparison of their ir and nmr spectral data (and melting point for 2) with those of commercial materials. Spectral data (nmr, ir, and uv) indicated the 1,3,3-triphenylisoindole (5), 1-(2-biphenylyl)-1,2-diphenylethane (6), and the 1,1,1′,1′-tetraphenylazomethane (7) structures for the remaining three photoproducts. Independent syntheses of these compounds and their comparison with the isolated photoproducts confirmed the assignment of structures 5, 6, and 7 to these three products (isolated in 43, 4, and 2% yields, respectively).





Benzophenone azine (1) was not photochemically reactive under all conditions. Replacing the Vycor filter (transparent above 210 nm) by a Pyrex filter (transparent above 280 nm) completely stopped its photochemical reaction. Also, conducting the reaction in benzene caused reaction to cease.[4] Photolysis in cyclohexane or 2-propanol, however, gave the same reaction observed in methanol.

The photolysis of 1,1,1′,1′-tetraphenylazomethane (7) under the same conditions as benzophenone azine (1) led to a much more rapid and less complex reaction (3 mmol completely reacted in 45 min). The following five photoproducts were formed: 1,1,2,2-tetraphenylethane (2, 58%), 1-(2-biphenylyl)-1,2-diphenylethane (6, 18%), diphenylmethane (3, 10%), *cis*-stilbene (4, 5%), and biphenyl (8, 2%).[5]

(1) Paper VIII in a series on the photochemistry of unsaturated nitrogen-containing compounds. For paper VII see R. W. Binkley, *J. Org. Chem.*, **35**, 2796 (1970).

(2) Author to whom inquires should be addressed.

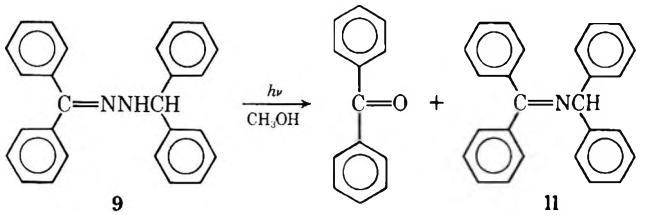
(3) (a) J. F. Ogilvie, *Chem. Commun.*, 359 (1965); (b) R. K. Brinton, *J. Amer. Chem. Soc.*, **77**, 842 (1955); (c) R. W. Binkley, *J. Org. Chem.*, **33**, 2311 (1968).

(4) The lack of reactivity of benzene may be because it is a poor hydrogen donor or because it absorbs higher energy light or for both of these reasons.

(5) It is likely that biphenyl was present in the reaction mixture from benzophenone azine (1) photolysis; however, its amount was too small to be detected.

It has been previously shown[6] that 1-(2-biphenylyl)-1,2-diphenylethane (**6**), *cis*-stilbene (**4**), and biphenyl (**8**) arise from the photolysis of 1,1,2,2-tetraphenylethane (**2**).

Vycor-filtered irradiation of benzophenone benzhydrylhydrazone (**9**) under the same conditions as the benzophenone azine (**1**) irradiation resulted in the formation of the following five photoproducts: benzophenone[7] (**10**, 58%), diphenylmethane (**3**, 11%), 1,1,2,2-tetraphenylethane (**2**, 11%), 1-(2-biphenylyl)-1,2-diphenylethane (**6**, 4%), and benzhydrylidenebenzhydrylamine (**11**, 7%). Of these five photoproducts,



9 **10** **11**

+

2 + **3** + **6**

three (**2**, **3**, and **6**) had been obtained and identified in the irradiation of benzophenone azine (**1**). The remaining two (**10** and **11**) were assigned structures after comparison with independently obtained samples.

Discussion

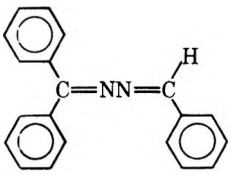
The photochemical reaction of benzophenone azine (**1**) has several unique aspects which merit discussion. Benzophenone azine (**1**) occupies a place by itself in azine photochemistry because it (a) gives no evidence of participation in the nitrogen–nitrogen bond cleavage process, the major reaction process in other azine systems; (b) undergoes a photoreduction to produce an azo system [1,1,1′,1′-tetraphenylazomethane (**7**)]; (c) experiences a complex molecular rearrangement leading to an isoindole [1,3,3-triphenylisoindole (**5**)].

The lack of formation during photolysis of **1** of any products such as benzophenone imine or benzophenone which would have arisen from a simple N–N fragmentation is one of the initially surprising aspects of its photochemistry. There appear to be two possible explanations for this lack of reactivity. First, the π system of benzophenone azine (**1**) is a considerably extended one when compared to other azines studied.[3] This factor may result in the formation of an excited state which is quite different in reactivity from those encountered in other azine systems. This type of change in reactivity is known in ketone photochemistry, where extending the π system changes the lowest excited state from an $n \rightarrow \pi^*$ to a $\pi \rightarrow \pi^*$ state. A second possible explanation for the lack of formation of simple nitrogen–nitrogen bond cleavage products is that N–N bond homolysis and hydrogen migration may be a concerted process. In this case the absence of a hydrogen atom directly attached to the azine system would prevent reaction.

(6) J. A. Ross, W. A. Schumann, D. B. Vashi, and R. W. Binkley, *J. Org. Chem.*, in press. The mechanism for formation of various products from photolysis of 1,1,2,2-tetraphenylethane (**2**) is discussed in this paper.

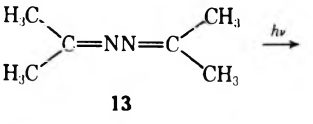
(7) Benzophenone imine hydrolyses to benzophenone under the conditions of this experiment (see ref 1).

The former of these two possibilities is in best agreement with experimental observation. The first fact relating to this question is that in the photolysis of benzhydrylidene benzylidene azine (**12**), where a



12

hydrogen bound to the azine system does exist, no products from an N–N bond cleavage are formed. Such a result argues against azine homolysis being dependent upon the presence of a transferable hydrogen atom. A second piece of information, arising from the recently reported photolysis of acetone azine[8] (**13**), also speaks against the presence of an azine bound hydrogen being necessary for N–N bond homolysis. Acetone azine (**13**) cleaves photochemically to produce imino radicals (experimentally observed) which react further to form the methylimine of acetone and acetonitrile. Clearly, **13** undergoes a cleavage of the nitrogen–



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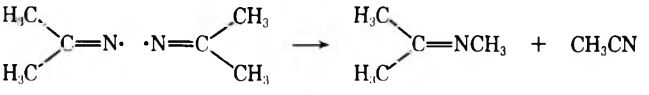


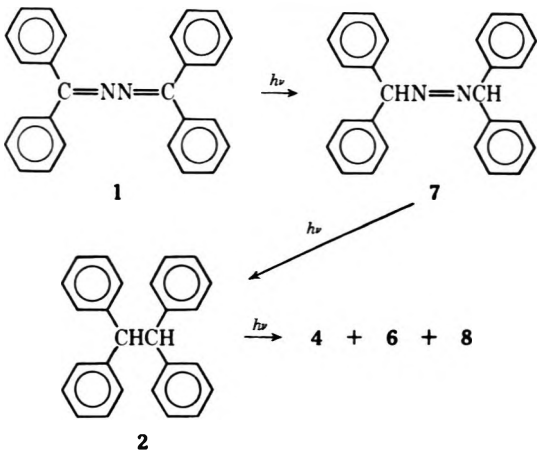
nitrogen bond independent of a hydrogen atom transfer process.

As mentioned above, the photoreduction of benzophenone azine (**1**) to 1,1,1′,1′-tetraphenylazomethane (**7**) is one of the unique aspects of its photochemistry. In this reaction, as in most photoreduction processes, the usual source of hydrogen atoms is the reaction solvent. Also in the case of benzophenone azine (**1**) assigning this role to the reaction solvent is supported by the fact that no reaction of **1** takes place in the poor hydrogen donor benzene.[4] Perhaps the most interesting facet of this reduction process is that it makes possible the series of photochemical transformations leading from benzophenone azine (**1**) to the various hydrocarbon rearrangement and fragmentation products (**2**, **3**, **4**, **6**, and **8**) (Scheme I). The products from individual photolyses of 1,1,1′,1′-tetraphenylazomethane (**7**) and 1,1,2,2-tetraphenylethane[6] (**2**) provide convincing evidence that these two are intermediates in this reaction series.

In contrast to the series of reactions just described where intermediates have been isolated and themselves irradiated, the intermediate stages of the conversion of benzophenone azine (**1**) into 1,3,3-triphenylisoindole (**5**) are not well understood. The studies which have been made relating to the mechanism of this reaction serve primarily to eliminate a variety of possible intermediates; however, they are able to provide an indirect indication of the course which this reaction is following.

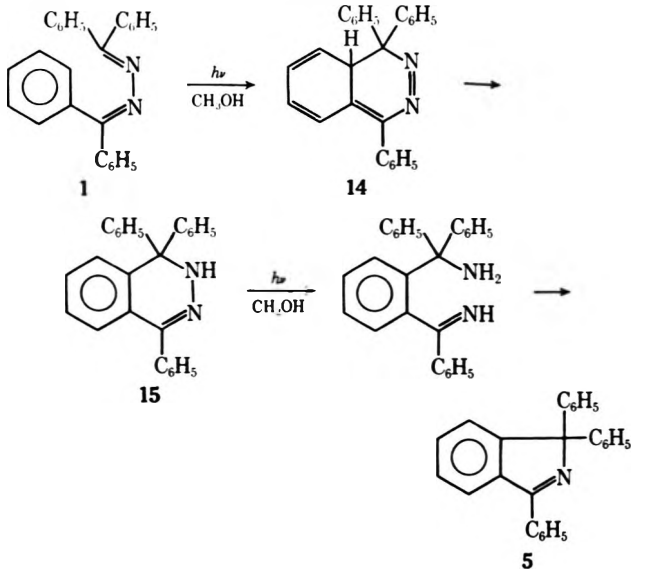
(8) (a) D. G. Horne and R. G. W. Norrish, *Proc. Roy. Soc., Ser. A.*, **315**, 301 (1970); (b) R. K. Brinton and S. Chang, *Ber. Bunsenges. Phys. Chem.*, **72**, 217 (1968).

SCHEME I

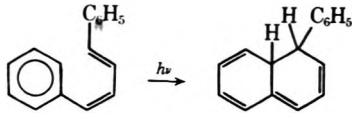


We would like to propose the mechanism shown in Scheme II as being, at present, the best explanation for

SCHEME II

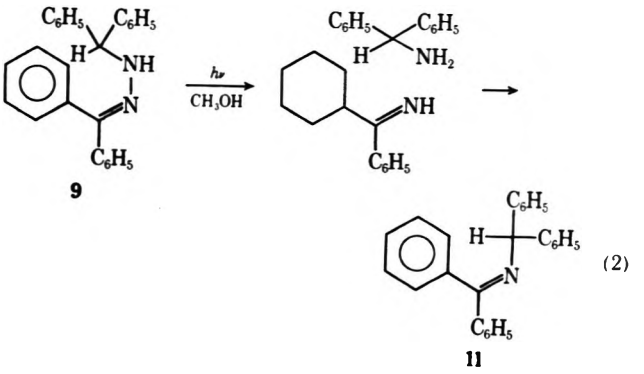


the formation of 1,3,3-triphenylisoindole (**5**) from the photolysis of benzophenone azine (**1**). This mechanism proposes the photochemical cyclization of **1** to produce the dihydrophthalazine intermediate **14**. This reaction is analogous to the known photochemical closure of 1,4-diphenylbutadienes to phenyl-substituted dihydronaphthalenes[9] (eq 1). The dihydronaphthalene system



(1)

is, of course, easily aromatized by oxidation to a substituted naphthalene. The dihydrophthalazine **14**, which cannot undergo a similar oxidation, is proposed to rearomatize *via* a hydrogen migration to an aromatic dihydrophthalazine (**15**). This mechanism further suggests that upon photolysis, **15** rearranges to give 1,3,3-triphenylisoindole (**5**) in a manner analogous to the observed rearrangement of benzophenone benzhydrylhydrazone (**9**) to give benzhydrylidenebenzhydrylamine (**11**)[10] (eq 2).



(2)

The results from the photolysis of benzophenone azine (**1**) may be summarized by saying that it participates in two photochemical processes. The first of these is a photoreduction to give 1,1,1′,1′-tetraphenylazomethane (**7**), a compound which reacts photochemically to give 1,1,2,2-tetraphenylethane (**2**) and diphenylmethane (**3**). The second is a rearrangement, probably passing through dihydrophthalazine intermediates, to give 1,3,3-triphenylisoindole (**5**).

Experimental Section

Vycor-Filtered Irradiation of Benzophenone Azine (1) in Methanol.—Benzophenone azine[11] (1.08 g, 3.00 mmol) in 1200 ml of methanol was irradiated for 24 hr with a 450-W Hanovia high-pressure quartz mercury-vapor lamp which had been lowered into a water-cooled quartz immersion well. Prepurified nitrogen was passed through the solution for 1 hr prior to irradiation and a slow stream of nitrogen was continued during photolysis. A Vycor filter was placed between the reaction mixture and the light source.

After 24 hr, the solvent was removed by distillation *in vacuo* below 30°, leaving a dark yellow mixture of solid and liquid. The residual solid was chromatographed on an 85 × 2.5 cm Florisil column slurry packed in 1:9 ether–hexane; 60-ml fractions were collected. The column was eluted as follows: 0.5 l. of hexane, 0.5 l. of 1:49 ether–hexane, 0.5 l. of 1:24 ether–hexane, 0.5 l. of 1:12 ether–hexane, 0.5 l. of 1:6 ether–hexane, 0.5 l. of 1:3 ether–hexane, 0.5 l. of 1:1 ether–hexane, and 0.5 l. of ether.

Fractions 7 and 8 afforded 13.5 mg (0.08 mmol) of diphenylmethane, identified by ir and nmr spectral comparison with a known sample.[12] Fraction 9 gave 4 mg (0.02 mmol) of *cis*-stilbene, also identified by comparison with a known sample.[12] Fractions 14–19 produced 21 mg of a clear oil which crystallized on standing and was recrystallized from hexane to give 13.5 mg (0.04 mmol) of 1-(2-biphenylyl)-1,2-diphenylethane, mp 80° (lit.[6] mp 79–81°), identified by nmr and mixture melting point comparison with an authentic sample.[6] Fractions 20–25 yielded 33 mg of 1,1,2,2-tetraphenylethane, mp 205–210° (lit.[13] mp 209–211°), also identified by nmr and mixture melting point comparison with an authentic sample.[12] Fractions 27–31 gave 24 mg of a crystalline solid which was recrystallized from ethanol to give 7 mg (0.02 mmol) of 1,1,1′,1′-tetraphenylazomethane, mp 110–114° (lit.[14] mp 115°), identified by nmr and mixture melting point comparison with an authentic sample.[14] Fractions 34–40 afforded 726 mg (2.00 mmol) of unreacted benzophenone azine. Fractions 43–48 produced 173 mg of a yellow oil which crystallized on standing and was recrystallized from ethanol to

(9) (a) G. J. Fonken, *Chem. Ind.* (London), 1327 (1962); (b) C. C. Leznoff and R. J. Haywark, *Can. J. Chem.*, **48**, 1842 (1970).

(10) E. S. Huyser, R. H. S. Wang, and W. T. Short, *J. Org. Chem.*, **33**, 4323 (1968).

(11) D. H. R. Barton, R. E. O Brien, and S. Sternhell, *J. Chem. Soc.*, 470 (1962).

(12) Aldrich Chemical Co., Inc., 940 W. St. Paul Ave., Milwaukee, Wis. 53233.

(13) H. Blitz, *Justus Liebigs Ann. Chem.*, **296**, 220 (1897).

(14) S. G. Cohen and C. H. Wang, *J. Amer. Chem. Soc.*, **77**, 2457 (1955).

give 148 mg (0.43 mmol) of 1,3,3-triphenylisoindole, mp 145° (lit.[15] mp 145.5°), identified by comparison with a known sample.[16]

Pyrex-Filtered Irradiation of Benzophenone Azine (1) in Methanol.—The reaction procedure was the same as that described for the Vycor-filtered irradiation of 1 except that a Pyrex filter was used and the reaction time was extended to 72 hr. At the end of this time no reaction had taken place.

Vycor-Filtered Irradiation of Benzophenone Azine (1) in Benzene.—The procedure was again the same as the irradiation procedure for 1 in methanol except that the solvent was changed to benzene. The irradiation time was 72 hr. No reaction was observed.

Vycor-Filtered Irradiation of 1,1,1′,1′,-Tetraphenylazomethane (7) in Methanol.—The irradiation and isolation procedures were the same as those used in the Vycor-filtered irradiation of 1 except that 1.09 g (3.00 mmol) of 1,1,1′,1′-tetraphenylazomethane was irradiated and the irradiation time was 45 min.

Fractions 7 and 8 afforded 61 mg of a mixture of biphenyl and diphenylmethane. Rechromatography separated this pair into 9 mg (0.06 mmol) of biphenyl and 51 mg (0.30 mmol) of diphenylmethane, both identified by ir and nmr spectroscopy. Fraction 9 yielded 27 mg (0.15 mmol) of *cis*-stilbene, also identified by ir and nmr spectroscopy. Fractions 14–19 gave 180 mg of 1-(2-biphenylyl)-1,2-diphenylethane, mp 75–78°. Fractions 20–25 produced 511 mg (0.54 mmol) of 1,1,2,2-tetraphenylethane, mp 206°. Fractions 27–31 gave 22 mg of unreacted 1,1,1′,1′-tetraphenylazomethane.

(15) W. Theilacker, H.-J. Bluhm, W. Heitmann, H. Kalenda, and H. J. Meyer, *Justus Liebigs Ann. Chem.*, **673**, 96 (1964).

Vycor-Filtered Irradiation of Benzophenone Benzhydrylhydrazone (9) in Methanol.—The isolation and irradiation procedures were the same as those used in the Vycor-filtered irradiation of 1 except that the material irradiated was benzophenone benzhydrylhydrazone (9) and the irradiation time was 4.5 hr.

Fractions 7 and 8 gave 33 mg (0.20 mmol) of diphenylmethane, identified by ir spectroscopy. Fractions 14–19 gave 24 mg (0.07 mmol) of 1-(2-biphenylyl)-1,2-diphenylethane, mp 65–69°. Fractions 20–24 afforded 66 mg of 1,1,2,2-tetraphenylethane, mp 205–207°. Fractions 25–27 yielded 53 mg of a white solid, recrystallized from ethanol to give 38 mg (0.13 mmol) of benzhydrylidenebenzhydrylamine, mp 150° (lit.[10] mp 152°), identified by comparison with an authentic sample. Fractions 34–39 produced 189 mg (1.04 mmol) of benzophenone, identified by ir spectroscopy. Fractions 50–55 afforded 448 mg (1.21 mmol) of unreacted starting material.

Vycor-Filtered Photolysis of Benzhydrylidene Benzylidene Azine (12) in Methanol.—The photolysis and isolation procedures were the same as those described for the Vycor-filtered irradiation of 1 except that 3.00 mmol of benzhydrylidene benzylidene azine[16] (14) were irradiated. No single product could be isolated in sufficient quantity for identification; in particular, no benzonitrile, benzophenone, or benzaldehyde were isolated.

Registry No.—1, 983-79-9.

Acknowledgment.—The authors gratefully acknowledge the support of the National Science Foundation (GP 16664) for this research.

(16) S. S. Hirsch, *J. Org. Chem.*, **32**, 2433 (1967).

Studies on the Acylation of Some 6-Aminouracil Derivatives

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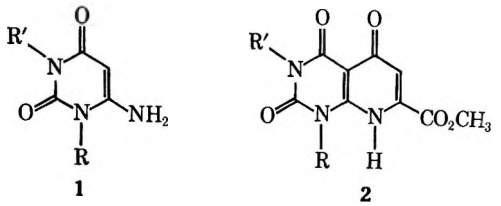
Received July 26, 1971

Attempts to prepare pyrido[2,3-*d*]pyrimidine derivatives by the reaction of various alkyl 6-aminouracils with dimethyl acetylenedicarboxylate have led instead to the synthesis of 6-amino-5-(3-carbomethoxy-2-propynoyl)-uracils (**3**). It was found, using acetylation as a model reaction, that acylation occurs at C-5 if an alkyl group is present on N-1 of 6-aminouracil; in the absence of such a substituent the 6-acetamido derivative is formed. Reduction of **3** leads to cis olefin formation. The pmr spectra and some mechanistic considerations are discussed.

Antitumor activity against Walker muscular tumor in rats has recently been demonstrated for 4-oxopyrido-[2,3-*d*]pyrimidine (NSC 112518) and 2,4-dioxopyrido-[2,3-*d*]pyrimidine (NSC 112519). Attempts to develop new approaches to the synthesis of this ring system and to make hitherto inaccessible derivatives have led to the preparation of an unexpected and interesting series of compounds, the synthesis and characterization of which form the basis of this report.

The reagent selected for the conversion of a series of 6-aminouracil derivatives (**1a–d**) to the corresponding pyrido[2,3-*d*]pyrimidine derivatives (**2a–d**) was dimethyl acetylenedicarboxylate. This compound has been widely used in the synthesis of a variety of heterocyclic compounds.[2] Attack usually occurs at the triple bond in a Michael-type reaction followed by cyclization either through the other carbon of the acetylene or through the β-carbomethoxy group, depending on whether nucleophilic or electrophilic attack is appropriate. The only reported use of an acetylenic compound in the synthesis of pyrido[2,3-*d*]pyrimidines appeared in a 1958 German patent[3] and involved the use of 3-phenylprop-1-yn-3-one with 6-aminouracil to give 2,4-dioxo-7-phenylpyrido[2,3-*d*]-pyrimidine. This product would require attack upon the triple bond by carbon 5 of the pyrimidine. Such attack is reasonable based upon the elegant studies of Taylor and coworkers on the total synthesis of the antibiotic fervenulin and its derivatives,[4] in which a 6-aminouracil reacted with diethyl azodicarboxylate yielding the product of attack by the pyrimidine carbon 5 on the nitrogen of the reagent.



1 **2**

a, R = R′ = CH_3
b, R = CH_3; R′ = H
c, R = R′ = $CH_2C_6H_5$
d, R = R′ = H

(1) (a) This research was supported by Research Grant T491 from the American Cancer Society; (b) to whom correspondence should be addressed.

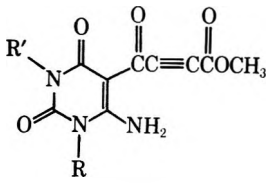
(2) J. B. Hendrickson, R. Rees, and J. F. Templeton, *J. Amer. Chem. Soc.*, **86**, 107 (1964).

(3) H. Pasedach and M. Seefelder, German Patent 1,040,040 (1958); *Chem. Abstr.*, **55**, 6507e (1961).

(4) E. C. Taylor and F. Sowinski, *J. Amer. Chem. Soc.*, **90**, 1374 (1968); **91**, 2143 (1969).

Results and Discussion

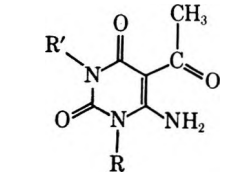
Treatment of 1,3-dimethyl-6-aminouracil with dimethyl acetylenedicarboxylate in DMF led, however, not to **2a**, but to a compound having nearly the correct elemental analysis for **2a** but spectral properties incompatible with it. The observed pmr spectrum for new compound **3a** had, as expected, one *O*-methyl and two *N*-methyl groups, but there was no peak corresponding to the expected "aromatic" proton and there were two downfield peaks (δ 9.97 and 9.37) corresponding to two protons and readily exchangeable upon addition of D_2O to DMSO-d_6 solution. These data strongly suggest the structure designated as **3a**. The downfield position of the amino group relative to that in the starting 1,3-dimethyl-6-aminouracil is readily accounted for on the basis of the deshielding effect of the anisotropy of the carbonyl and the acetylene moiety, which are coplanar with the amino group and in close proximity to it.



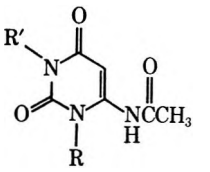
3a, R = R′ = CH_3
b, R = CH_3; R′ = H
c, R = R′ = $CH_2C_6H_5$
d, R = R′ = H

The same reaction was carried out with compounds **1b–d**. Treatment of **1b** and **1c** with dimethyl acetylenedicarboxylate in DMF gave good yields of the corresponding 5-acyl derivatives **3b** and **3c**. 6-Aminouracil itself (**1d**), however, gave only a complex mixture of products from which none of the 5-acyl derivative could be isolated. It thus appeared that substitution at position 1 might be essential for the success of this reaction. In an attempt to resolve this apparent anomaly, the reaction of 6-aminouracil derivatives with acetic anhydride was evaluated.

Examination of the literature revealed a study by Pfleiderer[5] in which treatment of 1,3-dimethyl-6-aminouracil (**1a**) with acetic anhydride at reflux gave as the only isolated product the 5-acetyl derivative **4a**. Repetition of this experiment did indeed give **4a**. The specific reaction conditions of Pfleiderer were not applicable to the other compounds in this series, however, because of solubility difficulties. It was found that solubility problems could be overcome by the use of acetic anhydride–acetic acid mixtures, however, and the reaction was run on 6-aminouracil[6] (**1d**) and its 1-methyl[7] (**1b**), 3-methyl[8] (**5**), and 1,3-dimethyl[9] (**1a**) derivatives. In the two cases in which the 1 position was substituted by methyl, only the 5-acetyl product was obtained; identical treatment of compounds **1d** and **5**, each of which has a proton at N-1, gave as the only compound isolated the *N*-6-acetyl derivative (**6a,b**).



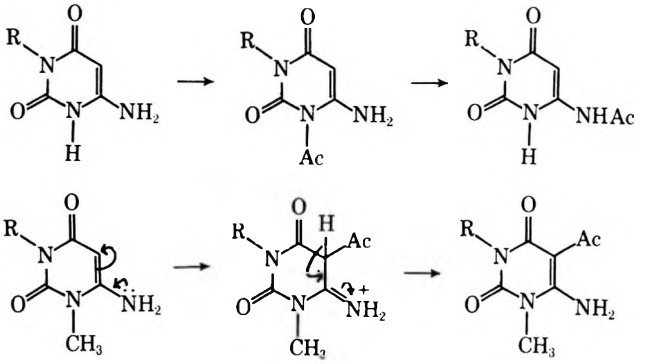
4a, R = R′ = CH_3
b, R = CH_3; R′ = H



6a, R = R′ = H
b, R = H; R′ = CH_3

It is felt that the reason for this difference in position of acylation may lie in the finding that uracil and thymine may be acylated at position 1, and that these 1-acyl derivatives are very unstable and are powerful acylating agents.[10] It is suggested that the initial attack in the N-1 unsubstituted derivatives occurs at N-1, and that this is followed by intramolecular rearrangement to the exocyclic acetamido derivatives. This mechanism is precluded in those compounds which are substituted at N-1; in these cases, acylation at C-5 is preferred over the unassisted acylation of the exocyclic amino group (Scheme I). This argument, then, supports the finding that only in the case of 1-substituted compounds can acylation at position 5 of the pyrimidines studied occur with dimethyl acetylenedicarboxylate.

Scheme I



7

R = CH_3, H

Examination of the pmr data on these compounds strongly supports the structure assignments. Comparison of the C-5 protons of the two 6-acetamidouracils (**6a,b**) with those of the corresponding starting materials (**1d**, **5**) shows a downfield shift in the former of δ 0.87 in each case as a result of acylation. This shift is expected based both on the electron-withdrawing effect and the anisotropic effect of the acetyl group. Acylation at the 5 position causes even larger shifts

(5) W. Pfleiderer and G. Strauss, *Justus Liebigs Ann. Chem.*, **612**, 173 (1958).

(6) Commercially available from Aldrich Chemical Co.

(7) (a) T. Takeda, Japanese Patent 7026 (1954); *Chem. Abstr.*, **50**, 4240*d* (1956). (b) T. Ukai, Y. Yamamoto, and S. Kanetomo *J. Pharm. Soc. Jap.*, **74**, 674 (1954); *Chem. Abstr.*, **48**, 10743*f* (1954).

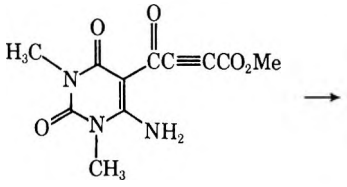
(8) W. Pfleiderer, *Chem. Ber.*, **90**, 2272 (1957).

(9) Commercially available from Heterocyclic Chemical Corp.

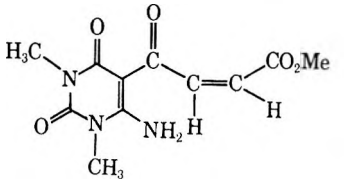
(10) (a) D. J. Brown, "The Pyrimidines," 1st ed, Wiley, New York, N. Y., 1962, pp 25, 252; (b) L. B. Spector and E. B. Keller, *J. Biol. Chem.*, **232**, 185 (1958).

in the resonance of the amino protons. This is readily accounted for on the basis of the anisotropic and electron-withdrawing effects cited above. In addition to these effects, however, in this series of compounds, which may be regarded as vinylogous amides, restricted rotation around the N−C bond would be expected.[11] This accounts for the high degree of nonequivalence of the amino protons, since such restricted rotation would result in continuous exposure of one amino proton to the anisotropic deshielding field of the carbonyl.

Catalytic hydrogenation of 1,3-dimethyl-6-amino-5-(3-carbomethoxy-2-propynoyl)uracil (**3a**) gave the cis olefin **8**. It is interesting to note that olefin **8** is extremely resistant to further reduction. Numerous attempts to reduce **8** to the succinoyl derivative using a variety of catalysts gave no reaction.

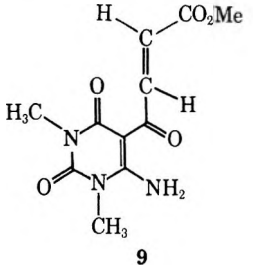


3a



8

The trans isomer **9** was synthesized by an alternate route. Treatment of 1,3-dimethyl-6-aminouracil (**1a**) with methyl 3-chloroformyl-*trans*-acrylate[12] gave, as expected, the product of acylation at C-5 (**9**). Com-



9

pounds **8** and **9** were readily characterized by pmr spectroscopy. Each had the expected peaks corresponding to two *N*-methyl groups, one *O*-methyl, two low-field nonequivalent protons of the amino group, and two doublets corresponding to olefinic protons. For the cis isomer the coupling constant J was found to be 9 Hz, while for the trans compound J was 16 Hz. The chemical shifts of the olefinic protons of **9** (δ 8, 37, 6.47) were downfield from the corresponding protons of **8** (δ 6.77, 5.80) as would be predicted from the anisotropic deshielding effect of a carbonyl group on an adjacent cis proton.[13]

Alternative procedures have led to the formation of the initially sought pyrido[2,3-*d*]pyrimidines. A report of this work will be forthcoming shortly.

(11) H. E. A. Kramer and R. Gompper, *Z. Phys. Chem.*, **43**, 292 (1964).

(12) R. M. Acheson, R. S. Feinberg, and A. R. Hands, *J. Chem. Soc.*, 526 (1963).

(13) L. M. Jackman and S. Sternhell, "Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press, Oxford, 1969, p 185.

Experimental Section

Materials and Methods.—Pmr spectra were run on a Jeolco C60H spectrometer using DMSO-d_6 as solvent and TMS or DSS as an internal reference. Uv spectra were run on a Cary 15 spectrophotometer. Melting points were taken on a Thomas-Hoover melting point apparatus and are uncorrected.

Acetylation of 6-Aminouracil Derivatives. General Procedure.—Compounds **1a**, **1b**, **1d**, and **5** (100 mg each) were refluxed (unless otherwise specified) in a solution of acetic acid (15 ml) and acetic anhydride (5 ml). Each of the reaction mixtures formed a clear solution. Reflux times, yields, and melting points of the products are shown in the following table.

Starting material	Reflux time, min	Yield, %	Mp, °C
1,3-Dimethyl-6-aminouracil	120 (80°)	83	202–205
1-Methyl-6-aminouracil	50	99	308–310
3-Methyl-6-aminouracil	50	50	280–281
6-Aminouracil	70	76	>350

1,3-Dimethyl-5-acetyl-6-aminouracil (**4a**).—After reflux (by the above general procedure), the reaction mixture was evaporated to dryness and the residue was recystallized from ethyl acetate yielding 107 mg (83%) of product: uv (pH 1) 276 nm (ϵ 15,600), 247.5 (10, 240), (pH 7) 276 (15,450), 247.5 (10,190), (pH 11) 276 (15,600), 247.5 (10, 310); nmr (DMSO-d_6) δ 11.1, 8.13 (2 s, 2, NH_2), 3.25, 3.08 (2 s, 6, NCH_3), 2.42 (s, 3, CH_3CO).

Anal. Calcd for $C_8H_{11}N_3O_3$: C, 48.73; H, 5.58; N, 21.32. Found: C, 48.69; H, 5.50; N, 21.41.

1-Methyl-5-acetyl-6-aminouracil (**4b**).—After reflux (general procedure) the reaction mixture was cooled and filtered, the filtrate was evaporated to dryness, and the residue was recrystallized from a MeOH–H_2O (1:1) mixture yielding 129 mg of pure product (99%): uv (pH 1) 275 nm (ϵ 13,800), 244 (10,630), (pH 7) 275 (13,200), 244 (10,250), (pH 11) 279 (13,200), 245 (8700), 229 (9040); nmr (DMSO-d_6) δ 11.20, 8.20 (2 s, 2, NH_2), 10.77 (s, 1, CONHCO), 3.18 (s, 3, NCH_3), 2.40 (s, 3, CH_3CO).

Anal. Calcd for $C_7H_9N_3O_3$: C, 45.90; H, 4.92; N, 22.95. Found: C, 45.67; H, 5.01; N, 22.62.

3-Methyl-6-acetamidouracil (**6b**).—Reaction conditions were identical with those for the preparation of **4b**, yielding 62 mg (50%): uv (pH 1) 278 nm (ϵ 11,200), (pH 7) 280 (8970), (pH 11) 288 (6430); nmr (DMSO-d_6) δ 10.52 (broad s, 2, 2 NH), 5.35 (s, 1, CH), 3.03 (s, 3, NCH_3), 2.07 (s, 3, CH_3CO).

Anal. Calcd for $C_7H_9N_3O_3 \cdot {}^1/_2H_2O$: C, 43.75; H, 5.21; N, 21.88. Found: C, 43.89; H, 5.14; N, 22.73.

6-Acetamidouracil (**6a**).—After reflux, the reaction mixture was cooled to room temperature, and a white solid precipitated. Filtration gave 101 mg of pure product (76%): uv (pH 1) 278 nm (ϵ 17,600), (pH 7) 280 (14,400), (pH 11) 288 (10,300); nmr (DMSO-d_6) δ 10.90 (s, 1, OCHNCO), 10.48 (s, 2, 2 NH), 5.22 (s, 1, CH), 2.07 (s, 3, CH_3CO).

Anal. Calcd for $C_6H_7N_3O_3$: C, 42.60; H, 4.14; N, 24.85. Found: C, 42.58; H, 4.24; N, 24.57.

1,3-Dimethyl-6-amino-5-(3-carbomethoxy-2-propynoyl)uracil (**3a**).—To the suspension of 1,3-dimethyl-6-aminouracil (1.55 g, 10 mmol) in 20 ml of DMF, the dimethyl acetylenedicarboxylate (1.56 g, 11 mmol) was added, and the mixture was heated at 110° for 2 hr. A clear, red solution resulted. After cooling to room temperature, 25 ml of ether was added to give an orange precipitate which was filtered and washed with 10 ml of ether, yielding 1.6 g (60%). To a filtered solution of 1.0 g of the product in warm DMF was added H_2O (10 ml). The solution was cooled and the product was filtered, yielding 0.7 g of pure product: mp 300–301° dec (285° getting dark); uv (pH 1) 436 nm (ϵ 4370), 338 (6900), 268 (16,700), (pH 7) 327 (19,900), 273 (7420), (pH 11) 327 (19,900), 273 (7420); nmr (DMSO-d_6) δ 9.97, 9.37 (2 s, 2, NH_2), 3.77 (s, 3, OCH_3), 3.17, 3.13 (2 s, 6, NCH_3).

Anal. Calcd for $C_{11}H_{11}N_3O_5$: C, 49.81; H, 4.18; N, 15.84. Found: C, 49.73; H, 4.23; N, 15.78.

1-Methyl-6-amino-5-(3-carbomethoxy-2-propynoyl)uracil (**3b**).—1-Methyl-6-aminouracil (1.41 g, 10 mmol) was suspended in 20 ml of DMF, and dimethyl acetylenedicarboxylate (1.56 g, 11 mmol) was added to it. This mixture was heated at 110° for 5 hr and cooled to 5° and the product was filtered to yield 0.7 g of a yellow-orange compound (28%), mp 326–329°.

Recrystallization of a 0.5-g sample from DMF–H_2O gave 0.35 g: mp 332° dec; uv (pH 1) 437 nm (ε 5780), 336 (7300), 268 (15,600), (pH 7) 328 (22,800), 268 (8900), (pH 11) 328 (22,900), 268 (9670); nmr (DMSO-d_6) δ 10.80 (s, 1, OCHNCO), 9.64, 9.37 (2 s, 2, NH_2), 3.70 (s, 3, OCH_3), 3.07 (s, 3, NCH_3).

Anal. Calcd for $C_{10}H_9N_3O_5 \cdot {}^1/_2H_2O$: C, 46.15; H, 3.85; N, 16.15. Found: C, 46.21; H, 3.64; N, 16.23.

1,3-Dibenzyl-6-amino-5-(3-carbomethoxy-2-propynoyl)uracil (3c).—To a suspension of 1,3-dibenzyl-6-aminouracil (3.07 g, 10 mmol) in 20 ml of DMF was added dimethyl acetylenedicarboxylate (1.56 g, 11 mmol) and the mixture was heated at 110° for 2 hr. To the dark red solution was added 150 ml of ether. The resulting precipitate was filtered and washed with 40 ml of ether to yield 1.62 g (39%), mp 235°. Recrystallization of a 1.1-g sample from DMF–H_2O gave 0.9 g: mp 239–240° uv (pH 1) 438 nm (ε 5500), 336 (6850), 270 (15,830), (pH 7) 330 (22,400), 273 (7930), (pH 11) 330 (22,100), 273 (7930); nmr (DMSO-d_6) δ 9.93, 9.63 (2 s, 2, NH_2), 7.20 (s, 10, 2 C_6H_5), 4.97 (s, 2, CH_2), 4.87 (s, 2, CH_2), 3.68 (s, 3, OCH_3).

Anal. Calcd for $C_{23}H_{19}N_3O_5$: C, 66.18; H, 4.59; N, 10.07. Found: C, 66.32; H, 4.55; N, 10.12.

1,3-Dimethyl-6-amino-5-(*cis*-3-carbomethoxypropenoyl)uracil (8).—1,3-Dimethyl-6-amino-5-(3-carbomethoxy-2-propynoyl)-uracil (3a) (500 mg, 1.9 mmol) was dissolved in a dimethoxyethane–water (1:1) mixture with warming and hydrogenated at 46 psi using PtO_2 (200 mg) as catalyst overnight.

The reaction mixture was filtered through Celite and washed thoroughly with hot dimethoxyethane. The filtrate was evaporated to dryness, and the residue was triturated with MeOH and filtered to give 340 mg (68%): mp 310° dec; uv (pH 1) 346 nm (ε 18,400), 276 (18,330), 230 (9950), (pH 7) 347 (18,850), 277 (18, 450), 230 (9950), (pH 11) 345 (18,700), 277 (18,800), 231 (9350); nmr (DMSO-d_6) δ 8,48, 7.87 (2 s, 2, NH_2), 6.77, 5.80 (2 d, 2, CH, J = 9 Hz), 3.58 (s, 3, OCH_3), 3.05, 2.97 (2 s, 6, NCH_3).

Anal. Calcd for $C_{11}H_{13}N_3O_5$: C, 49.44; H, 4.87; N, 15.73. Found: C, 49.63; H, 4.88; N, 15.61.

1,3-Dimethyl-6-amino-5-(*trans*-3-carbomethoxypropenoyl)-uracil (9).—1,3-Dimethyl-6-aminouracil (0.8 g, 5 mmol) and methyl 3-chloroformyl-*trans*-acrylate (1 g) were stirred in 30 ml of DMF at room temperature overnight. The reaction mixture was filtered, the filtrate was evaporated, and the oily residue was allowed to stand overnight at room temperature. The product was filtered and recrystallized from methanol, giving 300 mg of pure product (22%): mp 220–223°; uv (pH 1) 314 nm (ε 9100), 223 (20,800), (pH 7) 314 (8280), 223 (21,600), (pH 11) 307 (6360), 245 (sh), 229 (25,600); nmr (DMSO-d_6) δ 11.07 (s, 1, NH), 8.60 (s, 1, NH overlaps with CH), 8.37, 6.47 (2 d, 2, CH, J = 16 Hz), 3.77 (s, 3, OCH_3), 3.35, 3.17 (2 s, 6, NCH_3).

Anal. Calcd for $C_{11}H_{13}N_3O_5$: C, 49.44; H, 4.87; N, 15.73. Found: C, 49.59; H, 5.10; N, 15.79.

Registry No.—**3a**, 32970-29-9; **3b**, 32970-30-2; **3c**, 32970-31-3; **4a**, 32970-32-4; **4b**, 32970-33-5; **6a**, 32970-34-6; **6b**, 32970-35-7; **8**, 33016-10-3; **9**, 33016-11-4.

The Synthesis of 2-Methyl-7-ketoundecanolide, 8-Ketoundecanolide, and 2,4,6-Trimethyl-7-ketodecanolide[1]

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Received June 24, 1971

The Michael addition of acrylate esters to cyclic enamines has been extended to synthesize 2,4,6-trimethyl-7-ketodecanolide and 2-(3′-hydroxypropyl)cyclooctanone. The latter is converted to 8-ketoundecanolide by previously described procedures. The pyrrolidine enamines of 2-methylcycloheptanone (3) or *cis,trans*-2,*cis*-4,6-trimethylcycloheptanone (4) failed to give C-alkylation with 4-bromobutyl acetate (12). Attempted alkylation of the anions of the corresponding cyclohexylamine or aniline imines gave complex product mixtures. The 7-carbethoxy derivatives of 3 or 4 were alkylated with either 12 or 4-bromobut-1-ene to give intermediates which were converted to the desired 7-(4′-hydroxybutyl)cycloheptanones. These hydroxy ketones were cyclized, with difficulty, to give isomeric mixtures of the corresponding "7-7" enol ethers which could be oxidized with *m*-chloroperbenzoic acid (MCPBA) to 2-methyl-7-ketoundecanolide but not to 2,4,6-trimethyl-7-ketoundecanolide. A new synthesis of 7-carbethoxy-*cis,cis*-2,4,6-trimethylcycloheptanone from *cis,cis*-2,4,6-trimethylcyclohexanone is described. Extensions of aromatic solvent-induced nmr shifts to some of the intermediates are discussed.

We have previously reported the synthesis of bicyclic enol ethers *via* (a) the lithium–amine reduction of chromans[3] and (b) the acid-catalyzed closure of 2-(ω-hydroxyalkyl)cycloalkanones derived from enamine alkylations.[4] The enol ethers have been oxidized by a variety of reagents[3-6] to 10–12-membered ring ketolactones, including 7-ketoundecanolide, which represents the structural system of the methymycin group of macrolide antibiotics.

We now report extensions of these synthetic methods as well as new approaches involving β-keto esters which lead to 2,4,6-trimethyl-7-ketodecanolide and undecanolides. The substituents are located at some of the positions where methyl groups are found in methymycin.

We had originally planned on extending the synthesis of 2-(ω-hydroxyalkyl)cycloalkanones to methyl-substituted 7-ketoundecanolides *via* the alkylation of the pyrrolidine enamines 1 and 2 of 2-methylcycloheptanone (3) and 2,4,6-trimethylcycloheptanone (4) with 4-bromobutyl acetate (12). The cycloheptanones 3 and 4 were prepared by the diazoethane ring expansion of cyclohexanone (5) and 3,5-dimethylcyclohexanone (6) in 46 and 52% yields, respectively.[7] Commercial

(1) This investigation was supported by Public Health Service Research Grants AI 06303 and 07455 from the National Institute of Allergy and Infectious Diseases and by the Eli Lilly Co. This is part VII of the series, Medium Ring Compounds.

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(3) (a) I. J. Borowitz, G. Gonis, R. Kelsey, R. Rapp, and G. J. Williams, *J. Org. Chem.*, **31**, 3032 (1966); (b) I. J. Borowitz and G. Gonis, *Tetrahedron Lett.*, 1151 (1964).

(4) I. J. Borowitz, G. J. Williams, L. Gross, and R. Rapp, *J. Org. Chem.*, **33**, 2013 (1968).

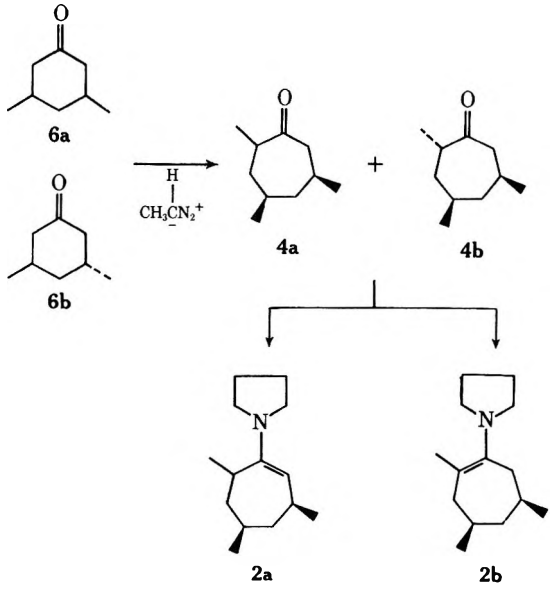
(5) I. J. Borowitz and R. Rapp, *ibid.*, **34**, 1370 (1969).

(6) I. J. Borowitz and R. Rapp, *Chem. Commun.*, 1202 (1969).

(7) (a) By a modification of the procedure of D. W. Adamson and J. Kenner, *J. Chem. Soc.*, 181 (1939), suggested by Dr. Adnan Sayigh. (b) For related cycloheptanone syntheses *via* a higher yield procedure and for stereochemical relationships see J. Marshall and J. J. Partridge, *J. Org. Chem.*, **33**, 4090 (1968).

6 (*ca.* 85% cis and 15% trans) was utilized. It was deemed unnecessary, at least in this initial phase of the work, to utilize pure *cis*-6 [available by the hydrogenation of 3,5-dimethylphenol[8] or from 3,5-dimethylcyclohexenone (7)]. This was because we found that diazoethane reacted much more rapidly with *cis*-6 than with *trans*-6. Indeed, most of the *trans*-6 of the original 85:15 mixture could be recovered unreacted. This observation is reasonable considering the generally slow addition of nucleophiles to cyclohexanones with axial substituents at C_3 (as in *trans*-6). Thus *cis*-6 is reduced 25 times faster than is *trans*-6 with sodium borohydride.[8] The ring expansion of 6 led to a 58:42 mixture of what is most likely *cis,cis*-2,4,6-trimethylcycloheptanone (4a) and the trans,cis isomer 4b (Scheme I).[7b] Equilibration of 4a and 4b gave a

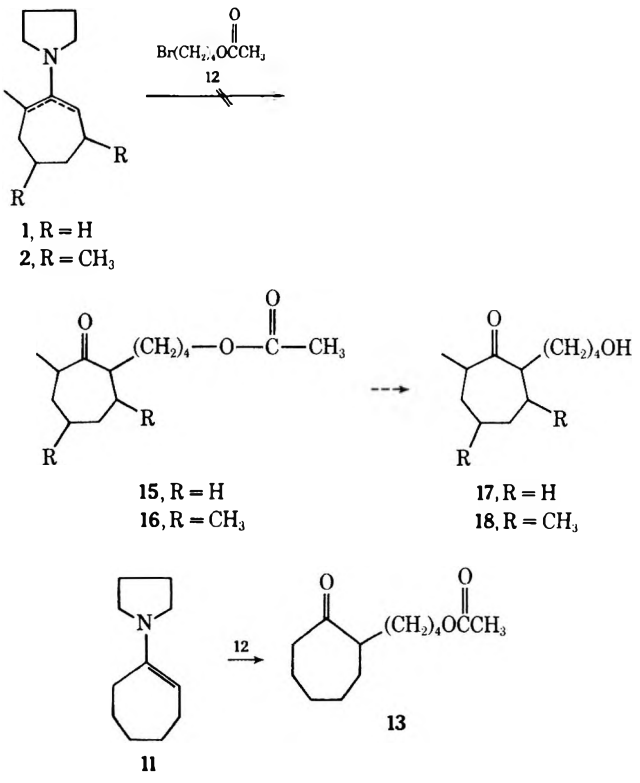
SCHEME I



change in composition to 88:12. The major isomer might be 4b if 2,4,6-trisubstituted cycloheptanones have energy profiles related to those of 2,5-disubstituted cycloheptanones.[7b]

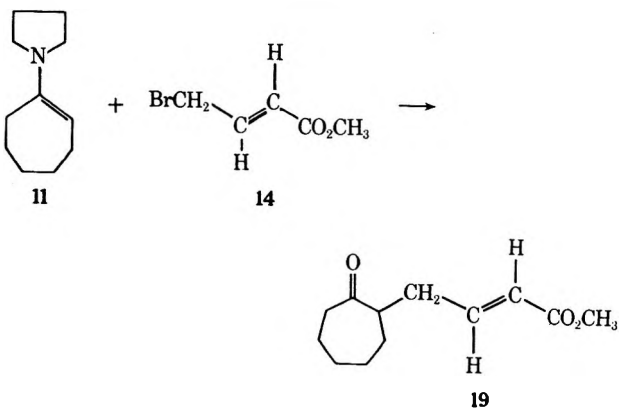
The pyrrolidine and morpholine enamines (1, 8) of 3 and the morpholine enamine (9) of 4 could not be consistently prepared by the usual azeotropic method. The pyrrolidine enamine (2) of 4 could not be made at all this way. The best method for the synthesis of 1, 2, and other pyrrolidine enamines of ketones which react sluggishly with pyrrolidine involves the use of trispyrrolidinylboron–pyrrolidine mixtures.[9] Enamines 1 and 2 were thus reproducibly prepared (52 and 89%, respectively). Other enamine syntheses involving trispyrrolidinylarsine[10] and the conversion of immonium perchlorates[11] are mentioned in the Experimental Section. The enamines 1 and 2 were found to consist of mixtures of the less substituted (1a, 2a) and the more substituted (1b, 2b) isomers in 68:32 and 46:54 ratios, respectively, by their nmr spectra. How this ground-state isomer distribution would influence the site of reaction of 1 and 2 was of concern since we wanted alkylation to occur on the less substituted side.[12] Both 1 and 2 gave no alkylation with 12.[13] These results are in contrast to our previously described reaction of pyrrolidinocycloheptene (11) with 12 to give 2-(4′-acetoxybutyl)cycloheptanone (13) in 48% yield (Scheme II).[4]

SCHEME II



It had been hoped that allylic halides such as methyl 4-bromocrotonate (14) would show reasonable reactivity with cycloheptanone enamines. The alkylation of 11 with 14 to give the desired 19 occurred in only 13% yield, however. This rather cumbersome pathway for the synthesis of 2-(4′-hydroxybutyl)cycloheptanones was therefore abandoned since it was anticipated that the alkylation of 1 or 2 with 14 would give even lower yields (Scheme III).

SCHEME III



(8) B. Rickborn and M. T. Wuesterhoff, *J. Amer. Chem. Soc.*, **92**, 6894 (1970).

(9) P. Nelson and A. Pelter, *J. Chem. Soc.*, 5142 (1965).

(10) H. V. Hirsch, *Chem. Ber.*, **100**, 1289 (1967).

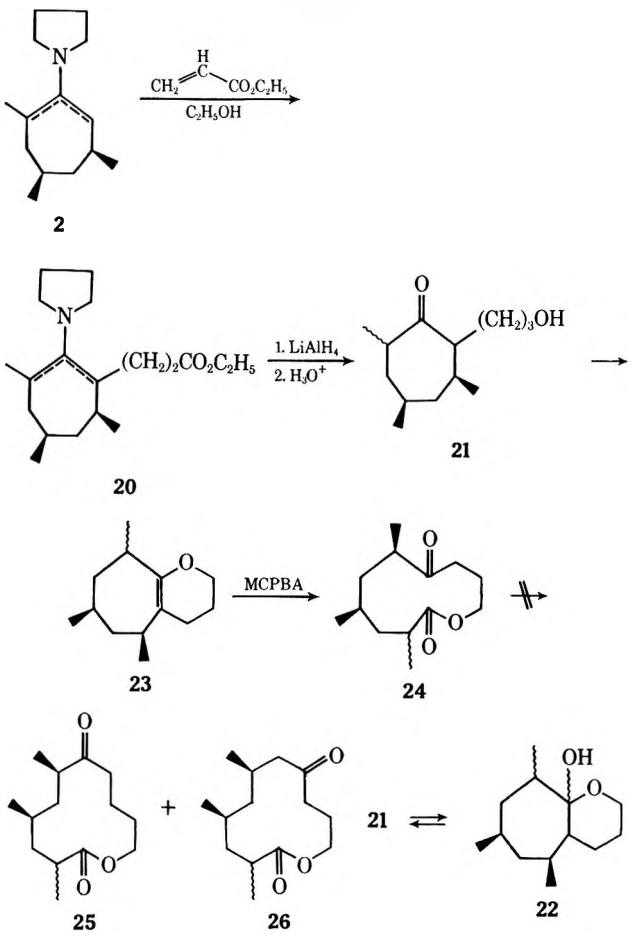
(11) S. Etheredge, Ph.D. Thesis, Columbia University, 1965; *Diss. Abstr.*, **26**, 4232 (1966).

(12) (a) W. D. Gurowitz and M. A. Joseph, *Tetrahedron Lett.*, 4433 (1965); (b) W. D. Gurowitz and M. A. Joseph, *J. Org. Chem.*, **32**, 3289 (1967); (c) F. Johnson, *Chem. Rev.*, **68**, 375 (1968).

(13) Cycloheptyl enamines are known to give 1:1 C to N alkylation: G. Opitz and H. Mildenberger, *Justus Liebigs Ann. Chem.*, **649**, 47 (1961).

Enamine 2 was allowed to react with ethyl acrylate to give the enamine ester 20 (80%) which was reduced with lithium aluminum hydride and acid hydrolyzed by described procedures[4] to give 7-(3′-hydroxypropyl)-2,4,6-trimethylcycloheptanone (21, Scheme IV). In

SCHEME IV



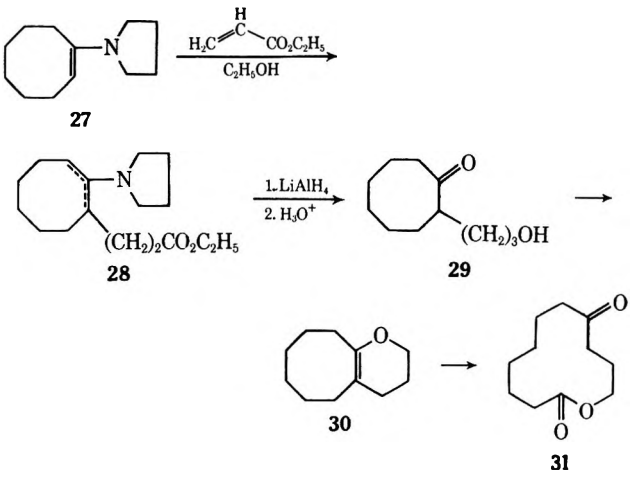
comparing the lack of alkylation of 1 or 2 with 12 to the facile Michael addition of 2, several points can be made. The extent to which 1 or 2 are N-alkylated by 12 is not known but it is presumably not exclusive since some 12 is recovered.[13] Both N and C alkylation of enamines with alkyl halides are irreversible while Michael addition on nitrogen, if it occurs, is reversible.[14] The C-alkylated Michael adduct is thus thermodynamically favored. The hydroxy ketone 21 exists mainly in the hydroxy ether form 22, a harbinger of its facile conversion to the enol ether 23, which was done with acid catalysis. The overall yield of 23 from 2 was 48%. The stereochemistry of the indicated methyl group in 23 remains undefined.

As previously found for other bicyclic enol ethers, only the endocyclic isomer (23) was formed. Oxidation of 23 with *m*-chloroperbenzoic acid (MCPBA) gave 2,4,6-trimethyl-7-ketodecanolide (24, 66%) as essentially one stereoisomer.

Keto lactone 24 is a possible precursor of 2,4,6-trimethyl-7-ketoundecanolide (25) which has three of the five alkyl substituents present in methymycin. An attempt at the ring expansion of 24 with diazomethane–aluminum chloride to give 25 and/or 26 was unsuccessful.[15,16]

2-(3′-Hydroxypropyl)cycloalkanones close fairly readily to the corresponding bicyclic hydroxy ethers when the cycloalkanones are six or seven membered.[4] We now demonstrate this closure for the eight-membered ring case as well. Pyrrolidinocyclooctene (27) was converted to 2-(3′-hydroxypropyl)cyclooctanone (29) *via* the enamine ester 28 (Scheme V). Dehydra-

SCHEME V



tive closure of 29 to the "8-6" enol ether 30 and MCPBA oxidation gave 8-ketoundecanolide (31). The overall yield of 31 from 27 was only 4%, considerably lower than those obtained in our previously described cases.[4]

Our second pathway toward the synthesis of 2-(4′-hydroxybutyl)cycloheptanones involved the Stork alkylation of Schiff base anions.[17] Unfortunately, the magnesium anion of the cyclohexylimine of cyclohexanone (32) reacted with both the acetate and bromo groups of 12 so that this readily obtained[4] precursor of the hydroxybutyl moiety could not be used directly. Preliminary reactions of the magnesium anion of the anil of 2-methylcycloheptanone (33) with 1-bromo-4-trimethylsilyloxybutane or 1-chloro-4-pyranyloxybutane gave little of the desired products. We then turned to the use of 4-bromobut-1-ene (34) which is convertible to ω-hydroxybutyl at a later stage. Alkylation of the anion of 32 with 34 gave 36 (63%). Similar reaction of the cyclohexylimine of cycloheptanone (35) with 34 gave a complex mixture. Compounds 36 and 37 (the latter obtained in 72% yield from 44) were converted to their respective ketals 38 and 39 and hydroborated to give the desired hydroxybutyl ketones 40 and 41 (Scheme VI).

Our third and best route for the synthesis of 2-(4′-hydroxybutyl)cycloheptanones involved the alkylation of β-keto esters. 2-Methylcycloheptanone (3) readily gave the 7-carbethoxy derivative 45, upon reaction with diethyl carbonate.[18] The formation of 45, whose structure was established by nmr, is related to the α′

(14) (a) G. Stork, A. Brizzolara, H. Landesman, and J. Szmuszkovicz, *J. Amer. Chem. Soc.*, **85**, 207 (1963); (b) M. E. Kuehne in "Enamines", A. G. Cook, Ed., Marcel Dekker, New York, N. Y., 1969, Chapter 8.

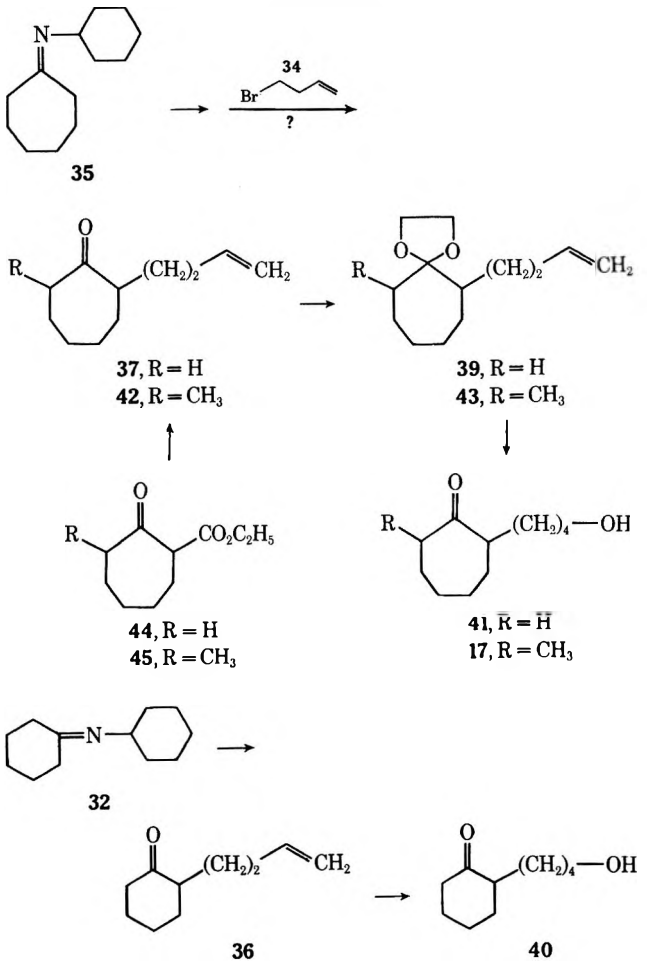
(15) Cycloundecanones have been ring expanded in 15% yield: E. Mueller and M. Bauer, *Justus Liebigs Ann. Chem.*, **654**, 92 (1962).

(16) R. Mayer, *Chem. Ber.*, **96**, 3096 (1963).

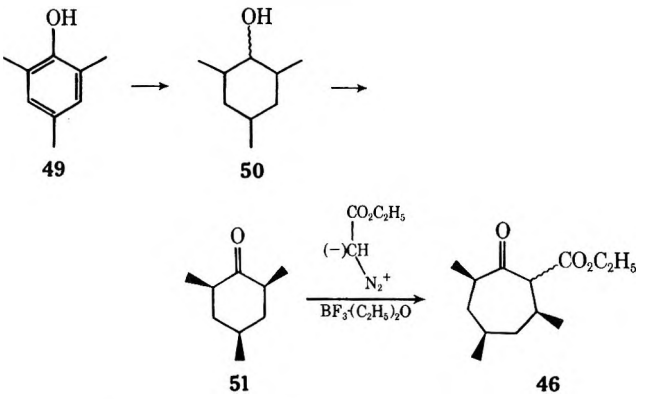
(17) G. Stork and S. R. Dowd, *J. Amer. Chem. Soc.*, **85**, 2178 (1963).

(18) S. J. Rhoads, J. C. Gilbert, A. W. Decora, T. R. Garland, R. J. Spangler, and M. J. Urbigkit, *Tetrahedron*, **19**, 1625 (1963).

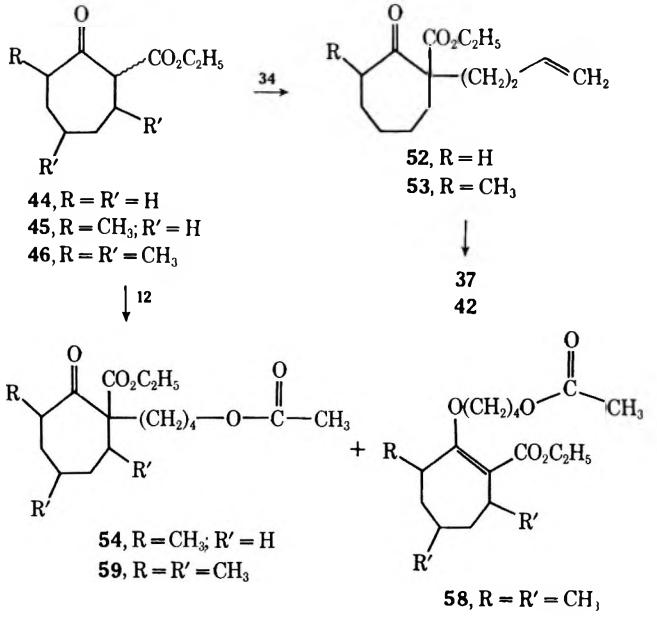
SCHEME VI



SCHEME VII



SCHEME VIII



carbethoxylation of 2-methylcyclopentanone[19a] or 2-methylcyclohexanone.[19b] Attempts to carbethoxylate **4** gave low yields of 2,4,6-trimethyl-7-carbethoxycycloheptanone (**46**) and led to ring opening to give diethyl 2,4,6-trimethylsuberate (**47**). Attempts at the base-catalyzed reclosure of **47** to **46** failed. In view of this result and because of the known nonstereohomogeneity of **4**, a stereospecific route of reasonable yield for **46** was sought. It was developed *via* a higher temperature (35°) modification of the boron trifluoride etherate catalyzed ring expansion of *cis,cis*-2,4,6-trimethylcyclohexanone (**51**) with ethyl diazoacetate.[20] Ketone **51** was synthesized by the hydrogenation of 2,4,6-trimethylphenol (**49**) to give a mixture of stereoisomeric alcohols **50** and ketone **51** which was oxidized with chromic acid.[21] Ketone **51** was shown to be mainly one isomer, *i.e.*, the all-equatorial cis,cis configuration, by nmr and vpc examination. Furthermore the β-keto ester **46** also appeared to be essentially one isomer upon examination of its nmr spectrum (Scheme VII, Table I).

While **44** was readily converted to its enolate with sodium ethoxide and then gave **52** (72%, Scheme VIII), **45** reacted much more slowly and gave only 24% of **53** upon alkylation with **34**. The stronger base, potassium triphenylmethide, afforded the conversion of **45** to **53** in 76% yield. Decarboxylation of **52** or **53** gave **37** or **42** (Scheme VI). Alkylation of **45** with **12** using sodium hydride–glyme gave **54** in 56% yield without the complication of reaction of the acetate group noted for Schiff base anions.

Hydrolysis of **54** with alcoholic potassium hydroxide gave 2-methyl-7-(4′-hydroxybutyl)cycloheptanone (**17**). The acid-catalyzed cyclization and dehydration of **17** to **56** (Scheme IX) proved to be much more difficult than were similar conversions on **21**, **41**, or other ω-hydroxyalkylcycloalkanones. The azeotropic removal of water with acid in toluene failed. In the various possible transition states leading to ring closure, the carbonyl group must become tetrahedral, thereby going through an eclipsing interaction with the adjacent methyl group. This interaction is presumably the cause for the unfavorable closure encountered. The effect of an α′ methyl group is evidently more pronounced in the formation of a seven-membered ether ring than for the corresponding six-membered ring. Thus **21** closed to **22** normally (Scheme IV) but 2-methyl-7-(4′-hydroxybutyl)cyclohexanone closed to its hydroxy ether with much more difficulty than did 2-(4′-hydroxybutyl)cyclohexanone (**40**).

The conversion of **17** to a mixture of the "7-7" enol ethers **56a** and **56b** was accomplished by utilizing *p*-

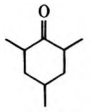
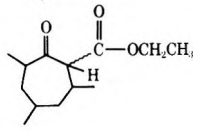
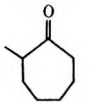
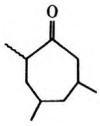
(19) (a) K. Sisido, K. Utimoto, and T. Isida, *J. Org. Chem.*, **29**, 2781 (1964); (b) E. J. Corey, T. H. Topie, and W. A. Wozniak, *J. Amer. Chem. Soc.*, **77**, 5415 (1955).

(20) W. T. Tai and E. W. Warnhoff, *Can. J. Chem.*, **42**, 1333 (1964).

(21) A previous synthesis of **51** from **49** gave no physical constants: J. Seibl and T. Gäumann, *Helv. Chim. Acta*, **46**, 2857 (1963).

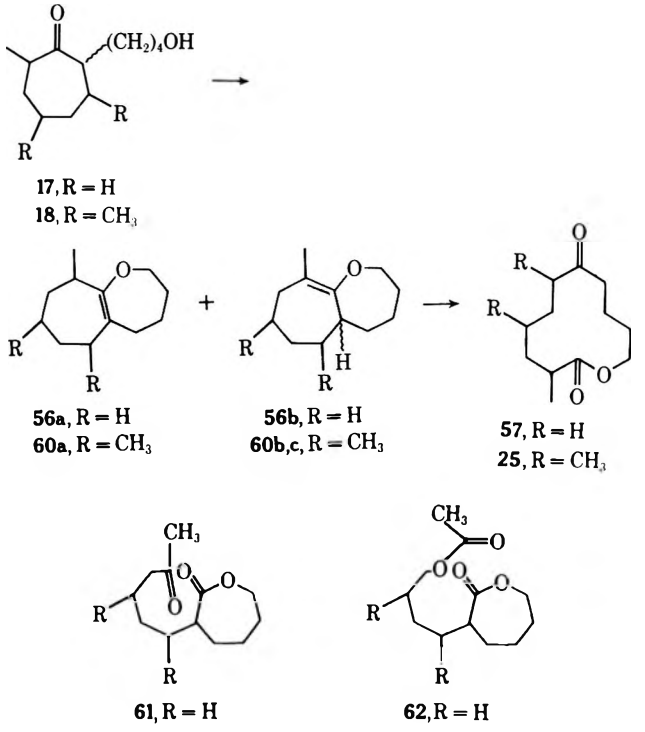
TABLE I

AROMATIC SOLVENT-INDUCED SHIFTS FOR VARIOUS KETONES

Compd	No.	Group	$\Delta = \delta_{CCl_4} - \delta_{C_6H_6}$, Hz	$\Delta = \delta_{CCl_4} - \delta_{1\text{-methylnaphthalene}}$, Hz
	65	C_2 Methyl[a]	−1.3[c]	+4.8
	66	$C_{2,6}$ Dimethyl[b]	−1.5[c]	+2.7
	51	$C_{2,6}$ Dimethyl[a]	−2.4	+3.6
		C_4 Methyl[d]	+15.6	+33
		C_2 Methyl[e]	+5.1	+14.7
		C_4 Methyl[f]	+13.2	+31
	46	C_8 Methyl[g]	+12.6	+13
		C_7 H[h]	−13.2	
		OCH_2[i]	+13.8	
		OCH_2CH_3[j]		
	3	C_2 Methyl[k]	+1.5	+6.5
	4a,b (3:1)	C_2 Methyl[l] (minor)	−2.6	+1.8
		(major)	+0.3	+6.4
		C_4 Methyl[m]	+11.5	+26
		C_6 Methyl[n]	+11.8	+23.8

[a] d, J = 5.7 in all solvents. [b] J = 5.9 (CCl_4), 5.8 (C_6H_6), 5.6 Hz (1-methylnaphthalene). [c] Reference 23. [d] J = 5.4 (C_6H_6), 5.2 Hz (1-methylnaphthalene). [e] J = 6.8, 6.1, 6.4 Hz. [f] J = 5.4, 5.3, 4.8 Hz. [g] J = 6.4, 5.2, 6.8 Hz. [h] J = 10.2 (CCl_4), 10.5 Hz (C_6H_6). [i] q, J = 7.2 (CCl_4), 7.0 Hz (C_6H_6). [j] t, J = 7.2, 6.5, 5.9 Hz. [k] d, J = 7 Hz (all solvents). [l] C_2 methyl resolved into two doublets on 100-Hz full scale; J = 6.6, 5.7 Hz (CCl_4). [m] d, J = 6.7 (CCl_4), 6.0 Hz (1-methylnaphthalene). [n] d, J = 5.8, 6.0 Hz.

SCHEME IX



toluenesulfonic acid catalysis and the solvent system toluene–dimethylformamide.[22]

Oxidation of **56** with excess MCPBA gave 2-methyl-7-ketoundecanolide (**57**, 27%). None of the anticipated **61** or **62** was isolated, although these products may have been formed (see Experimental Section).

The alkylation of **46** with **12** utilizing sodium hydride in glyme or toluene gave poor yields of **59** (*ca.* 9%, Scheme VIII). Reaction of **46** with **12** using potassium triphenylmethide in glyme was also poor. The use of sodium hydride in toluene–dimethylformamide (in ratios varying from 4:1 to 2:1) gave a mixture of O- and C-alkylated products (**58**, **59**) in total yield of *ca.* 40% in each case. The mixture of **58** and **59** was hydrolyzed with base and then with dilute aqueous acid to remove **58** and to give the desired hydroxy ketone **18**. The closure and dehydration of **18** occurred to a minor extent to give a mixture of three enol ethers, **60a**, **60b**, and **60c** (Scheme IX). Attempts to improve the conversion of **18** to **60** failed. Oxidation of a mixture of **60** and some **18** gave a mixture of products which may have contained **25** (see Experimental Section). The difficulties encountered in the closure of **18** made necessary the finding of another route to **60** and yet more substituted "7-7" enol ethers. Research toward this goal is in progress.

ASIS Measurements.—The assignment of cis,cis stereochemistry to 2,4,6-trimethylcyclohexanone (**51**) is based partially upon nmr solvent shift data (Table I). The magnitude of ASIS (aromatic solvent induced shifts)[23] for the C_2 and C_6 methyl groups when compared to the model compounds 2-methylcyclohexanone (**65**) and *cis*-2,6-dimethylcyclohexanone (**66**) suggests that **51** is the all-equatorial isomer as shown (Scheme VII). The C_4 methyl group becomes relatively more

(22) This solvent system may enhance the proton transfers needed for the dehydrative cyclizations. See C. D. Hurd and W. H. Saunders, *J. Amer. Chem. Soc.*, **74**, 5324 (1952), for similar effects in acetal formation.

(23) M. Fétizon, J. Goré, P. Laszlo, and B. Waegell, *J. Org. Chem.*, **31**, 4047 (1966).

shielded in benzene (as compared to carbon tetrachloride) while the C_2 and C_6 methyls become deshielded. This is in agreement with previous measurements on substituted cyclohexanones, which indicate that groups furthest away from the carbonyl oxygen become most shielded in benzene.[23] The larger shifts obtained with 1-methylnaphthalene suggest that it may prove to be more useful than is benzene. In the case of **46**, the largest ASIS is again found for the C_4 methyl. The doublet for this methyl is broadened, as compared to the other methyls, in all solvents because of "virtual coupling" with the C_3 and C_5 methylene groups.[24] The observed coupling of the $C_{6,7}$ protons (10.2 Hz) is equally compatible with dihedral angles of 0 or 140°. The former suggests a cis $C_{6,7}$ stereochemistry, while the latter is compatible with a trans stereochemistry.[25] Inspection of Drieding models indicates that both are reasonable; so a choice between them is not yet possible. Our limited data suggests that cycloheptanone ASIS may be quite different from those found for cyclohexanones, although larger shifts can be expected for methyl groups further away from the carbonyl in both ring systems.

Experimental Section[26]

Ring Expansion of Cyclohexanones.—2-Methylcycloheptanone (**3**) was synthesized in 46–49% yield (1 peak by vpc on 20% SE-30 at 120°) by the reaction of cyclohexanone with diazoethane generated *in situ* from the reaction of *N*-nitroso-*N*-ethylcarbamate with potassium carbonate and methanol.[27] Similar reaction of 82:18 *cis*/*trans*-3,5-dimethylcyclohexanone (**6a**, **6b**)[28a] (62 g, 0.5 mol) gave (1) material with a boiling point up to 105°, discarded; (2) 24.5 g, bp 105–200° (mostly 175–185°) [vpc[28b] unknown peak (6%), **6a** (30%), **6b** (47%), unknown peak (17%)]; and (3) 38 g, bp 200–210°, pure 2,4,6-trimethylcycloheptanone (**4**).

This represents a yield of 52% of **4** and a recovery of *ca.* 11.5 g of **6b**. Since the original **6** contained *ca.* 11 g of **6b**, only **6a** was ring expanded; *i.e.*, **4** is composed of *cis*-4,6-dimethyl isomers. Redistillation of fraction 3 gave **4**: bp 96° (16 mm); ir (CCl_4) 1704 cm^{-1}; nmr (CCl_4) τ 7.4–7.8 (m, 3, $C_{2,7}H$), 8.4 (m, 6), 8.96 (d, 3, C_2CH_3), 9.00 (d, 3, C_6CH_3), 9.05 (broad d, virtually coupled,[24] 3, C_4CH_3); (CCl_4, after treatment with Na–CH_3OD) τ 8.4 (m, 6), 8.98 (s, 3, C_2CH_3), 9.00 (d, 3, C_6CH_3), 9.05 (broad d, 3, C_4CH_3); vpc (20% SE-30 at 129–163° or 20% XF-1150 at 115–135°) one peak but two peaks (58:42) on 20% DEGS at 117°; 88:12 after treatment with $NaOCH_3$–CH_3OH or CH_3OD; 2,4-DNP of original mixture of isomers had mp 88–90° (C_2H_5OH). *Anal.* Calcd for $C_{10}H_{18}O$: C, 77.86; H, 11.76. Found: C, 77.97; H, 11.92.

Attempted separation of 38:62 **6a**:**6b** by the anticipated faster reaction of **6a** with sodium bisulfite failed to change the isomeric ratio. The mixture (5.1:1) of **6a**:**6b** was converted to the semicarbazone, mp 194–197°. Four recrystallizations from C_2H_5OH–H_2O gave mp 200–200.5° (lit.[29] mp semicarbazone of **6a** 200.5–201.5°, mp semicarbazone of **6b** 178.4–179.3°). Acid hydrolysis gave 7:1 **6a**:**6b** (vpc on 5% FFAP at 113°). Reduction of 3,5-dimethylcyclohexenone (**7**) in C_2H_5OH with Pd/C, H_2, and 3 *N* HCl gave 8:1 **6a**:**6b**.[29] Similar reduction under neutral or basic conditions gave 4:1 **6a**:**6b** (vpc, 15% Carbowax at 110°).

Formation of Enamines. A. Acid-Catalyzed Treatment with Pyrrolidine or Morpholine.—Treatment of **3** with pyrrolidine (2 equiv) under azeotropic conditions in benzene gave the enamine **1** (71%), bp 136–137° (15 mm), ir (film) 1630 cm^{-1}. Later repetition or reaction in toluene gave poorer yields. Similar treatment of **4** gave no enamine. Treatment of **3** or **4** with morpholine in benzene gave the enamines **8** (72%), bp 137–139° (15 mm), ir (film) 1640 cm^{-1}, and **9** (27%), bp 143–145° (9 mm), ir (film) 1637 cm^{-1}.

B. Trispyrrolidinylboron (67) Method. Trispyrrolidinylboron (67).—To a solution of pyrrolidine (42.7 g, 0.600 mol) in *n*-hexane (100 ml) in an ice–salt bath was added boron trichloride (11.7 g, 0.100 mol) with stirring. A two-phase system resulted and stirring was continued as the reaction mixture was brought to room temperature. Upon slight warming an exothermic reaction began so that cooling was again needed. During this reaction the lower layer solidified. After the reaction subsided, stirring was briefly continued, the hexane layer was combined with benzene washings of the solid layer, and the combined organic solution was distilled to give **67** (10.68 g, 0.0483 mol, 48%), bp 130–140° (0.15 mm), low-melting solid. Exposure to the atmosphere during work-up should be kept to a minimum, since **67** is readily hydrolyzed.[9] Reaction of **3** (12.4 g, 0.056 mol) with **67** (1 equiv), pyrrolidine (2 equiv), and *p*-toluenesulfonic acid (0.2 g) in benzene (60 ml) at reflux for 6.5 hr gave **1** (5.1 g, 0.029 mol, 52%), bp 119–120° (6 mm), ir (CH_2Cl_2) 1630 cm^{-1}, and recovered **3** (0.9 g, 0.0079 mol, 14%). Similar reaction of **4** for 6 days gave **2** in 89% yield: bp 92–94° (0.05 mm); ir (CH_2Cl_2) 1630 cm^{-1}; nmr (CCl_4) τ 6.0 (m, 0.46, vinyl H), 7.1–7.45 (m, 4, CH_2N), 8.2 (m, 12.54), 8.85 (d, 3, CH_3), 9.0 (d, 3, CH_3), 9.12 (d, 3, CH_3).

C. Conversion of Immonium Perchlorates.[11]—Treatment of **3** with pyrrolidinium perchlorate (1 equiv) and triethylamine (1 drop) in benzene gave the immonium perchlorate **68** (83%). Treatment of **68** with potassium *tert*-butoxide (2 equiv) in benzene gave **2** (40%), bp 112–116° (6 mm), and recovered **3** (29%), bp 69–70° (6 mm).

D. Trispyrrolidinylarsine Method.—A solution of trispyrrolidinylarsine[10] (**69**, 75.9 g, 0.263 mol) and cycloheptanone (**10**, 45.1 g, 0.403 mol) was stirred at room temperature. After 7 min a white precipitate of As_2O_3 formed. The mixture was stirred for a total of 1 hr and diethyl ether (100 ml) was added. The filtrate, after removal of As_2O_3, was combined with one from **69** (12.5 g, 0.043 mol) and **10** (7.4 g, 0.066 mol), dried, and distilled to give a forerun (3.3 g, mostly **10**) and **11** (62.6 g, 0.38 mol, 81%), bp 115–117° (2.3 mm), ir identical with that of genuine **11**. Treatment of **69** with **3** (1.5 equiv) gave no reaction at room temperature after 1 hr. Pyrrolidine (7 drops, *ca.* 0.5 ml) was added and the mixture was heated for 15 hr at 150–160°. Work-up as above gave recovered **3** and examine **1** (*ca.* 1:1 by ir). Similar treatment of **69** with **4** gave very slow formation of a white precipitate and little conversion to the enamine.

Attempted C Alkylation of Enamines.—Treatment of 4-bromobutyl acetate (**12**) with **1** in xylene at reflux for 24 hr or with **2** in toluene (40 hr) or in acetonitrile (60 hr) gave no C alkylation and partial recovery of starting compounds. Reaction of pyrrolidinocycloheptene (**11**, 13.2 g, 0.080 mol) and methyl ω-bromocrotonate (**14**, 18 g, 0.10 mol) in dry methanol (125 ml) at reflux (24 hr) gave **19** (2.2 g, 0.010 mol, 13%): bp 113° (0.1 mm); ir (film) 1730, 1710 cm^{-1}; nmr (CCl_4) τ 7.2–9.0 (m, 13), 4.3 (d, 1, vinyl H), 3.2 (m, 1, vinyl H), and 6.35 (s, 3, OCH_3). Reaction of pyrrolidinocyclohexene with **14** gave 35% of C-alkylated ketone instead of the reported[30] 54% yield.

Synthesis of 2,4,6-Trimethyl-7-ketodecanolide (24).—Reaction of **2** with ethyl acrylate (2 equiv) in ethanol[4,11] gave the pyrrolidine enamine of 7-(2′-carbethoxyethyl)-2,4,6-trimethylcycloheptanone (**20**, 80%), bp 144–146° (0.2 mm), ir (film) 1740, 1640 cm^{-1}. Reduction of **20** with lithium aluminum hydride gave **7-(3′-hydroxypropyl)-2,4,6-trimethylcycloheptanone (21)**, which existed mostly as the hydroxy ether tautomer, ir (CH_2Cl_2) 3600 (sharp), 3400 (broad), 1680 cm^{-1} (w). Crude **21** was treated with *p*-TSA in benzene under azeotropic conditions for 90 hr to give enol ether **23** (60% from **20**): bp 70–71.5° (0.35 mm); ir (CH_2Cl_2) 1665 cm^{-1}; nmr (neat) τ 6.25 (t, 2, CH_2O), 7.52 (d of t, 2, allylic methine H), 8.0–8.8 (m, 9), 9.02 (d, 6, allylic CH_3, J =

(24) E. D. Becker, "High Resolution Nuclear Magnetic Resonance," Academic Press, New York, N. Y., 1969, pp 163–166.

(25) (a) Reference 24, pp 103–105; (b) M. Karplus, *J. Chem. Phys.*, **30**, 11 (1959); (c) M. Karplus, *J. Amer. Chem. Soc.*, **85**, 2870 (1963).

(26) Instrumental techniques have been described elsewhere: I. J. Borowitz, K. C. Kirby, Jr., P. E. Rusek, and E. W. R. Casper, *J. Org. Chem.*, **36**, 88 (1971). Mass spectra were done on Hitachi RMU-6 mass spectrometers at Einstein Medical School, N. Y., and Columbia University, unless otherwise noted. Solvents used were dried by distillation from phosphorus pentoxide, calcium hydride, or lithium aluminum hydride. Reactions involving carbanions were conducted under an atmosphere of prepurified nitrogen. All vpc columns employed Chromosorb W and were 5 ft × 1/4 in. unless otherwise noted.

(27) D. W. Anderson and J. Kenner, *J. Chem. Soc.*, 181 (1939).

(28) (a) A commercial sample from Aldrich Chemical Co. was used; (b) a 20% XF-1150 column at 140° was used.

(29) R. L. Augustine and A. D. Broom, *J. Org. Chem.*, **25**, 802 (1960).

(30) A. Chatterjee, *Tetrahedron Lett.*, 959 (1965).

7.5 Hz), and 9.16 (d, 3, CH_3, J = 7.5 Hz). Addition of **23** (4.0 g, 0.021 mol) to MCPBA (85% purity, 12.2 g, 0.060 mol) in CH_2Cl_2 (80 ml) over 15 min was followed by a reflux period of 20 min. After 1 hr at 25° work-up gave **24** (3.1 g, 0.0136 mol, 65%): mp 68.5–69.5° [recrystallized from petroleum ether (bp 30–60°)]; ir (CCl_4) 1740, 1720 cm^{-1}; nmr (CCl_4) τ 5.90 (m, 2, CH_2O), 7.4–8.8 (m, 11), 8.93 (d, 3, CH_3), 8.95 (d, 3, CH_3), 9.00 (br d, 3, C_4 CH_3); mass spectrum (70 eV) m/e 226 ($M^{\cdot+}$), 211, 198, 183, 155, 140, 125, 111, 98, 87, 82, 69, 55. *Anal.* Calcd for $C_{13}H_{22}O_3$: C, 68.99; H, 9.80. Found: C, 68.81; H, 9.80.

Treatment of **24** with diazomethane and aluminum chloride in diethyl ether[16] gave only **24** and no **25**.

8-Ketoundecanolide (31).—Treatment of pyrrolidinocyclooctene with ethyl acrylate (1.5 equiv) in C_2H_5OH for 22 hr at reflux gave **1-pyrrolidino-2-(2′-carbethoxyethyl)cyclooctene (28,** 35%): bp 124–136° (0.1 mm); ir (film) 1730, 1630 cm^{-1}; nmr (CCl_4) τ 5.47 (t, 0.67, vinyl H), 5.98 (q, 2, CH_2CH_3), 7.28 (m, 4, CH_2N), 8.16 (m, 19.3), 8.80 (t, 3, CH_3CH_2). Reduction of **28** with $LiAlH_4$ gave **2-(3′-hydroxypropyl)cyclooctanone (29),** ir (film) 3380, 1705 cm^{-1}. The 2,4-DNP of **29** had mp 136–137° (C_2H_5OH–H_2O). *Anal.* Calcd for $C_{17}H_{24}N_4O_5$: C, 56.03; H, 6.64; N, 15.38. Found: C, 56.23; H, 6.51; N, 15.50.

Crude **29** gave **2-oxabicyclo[4.6.0]dodec-1(6)-ene (30)** in 38% yield upon reflux in benzene, p-TSA with azeotropic removal of water (40 hr): bp 106–108° (14 mm); ir (film) 1685 cm^{-1}; nmr (CCl_4) τ 6.20 (2 t, 2, CH_2O), 7.95, 8.15, 8.5 (m, 16). Addition of **30** to MCPBA (3 equiv) in CH_2Cl_2 at a slow rate (to allow solution to gently reflux), followed by 30 min at room temperature, gave, after work-up,[4] **8-ketoundecanolide (31,** 51%): mp 35–37°; ir (CH_2Cl_2) 1730, 1710 cm^{-1}; nmr (CCl_4) τ 5.99 (t, 2, CH_2O), 7.4–8.0, 8.0–8.8 (m, 16). *Anal.* Calcd for $C_{11}H_{18}O_3$: C, 66.64; H, 9.15. Found: C, 66.52; H, 9.07.

Conversion of Schiff Base Anions to 2-Alkylated Ketones. A. Schiff Bases.—*N*-Cycloheptylidenecyclohexylamine (**35,** 61% from cycloheptanone and cyclohexylamine) gave bp 91–95° (0.10 mm) [lit.[17] bp 83–88° (0.05 mm)]; ir (film) 1645 cm^{-1}. 2-Methylcycloheptanone gave the cyclohexylimine in 90% yield, bp 107° (1.6 mm), ir (CH_2Cl_2) 1645 cm^{-1}, and the anil **33** (90%), bp 107–112° (1.2 mm), ir (film) 1645 cm^{-1}. 2,4,6-Trimethylcycloheptanone gave no cyclohexylimine but gave the anil (70%), bp 114–116° (0.65 mm), ir (film) 1650 cm^{-1}. *Anal.* Calcd for $C_{16}H_{23}N$: C, 83.76; H, 10.10. Found: C, 83.53; H, 10.31.

B. Alkylations.—*N*-Cyclohexylidenecylohexylamine (**32,** 35.8 g, 0.20 mol)[17] was added to butylmagnesium chloride (66 ml of a 3 *N* solution, 0.2 mol) in THF (400 ml), and the mixture was heated at reflux for 2 hr and cooled. 4-Bromobut-1-ene (**34,** 27 g, 0.20 mol) was added slowly, and the resultant mixture was heated at reflux for 15 hr and cooled. After hydrolysis with aqueous hydrochloric acid (10%, 100 ml) at reflux for 20 hr, the mixture was extracted with ether. The organic layer was washed with 5% $NaHCO_3$ (five 150-ml portions) and H_2O (100 ml), dried, and distilled to give **2(3′-butenyl)cyclohexanone (36,** 19.1 g, 0.126 mol, 63%): bp 82–86° (2.5 mm); ir (film) 1730, 1640 cm^{-1}; nmr (CCl_4) τ 4.17 (m, 1, $CH{=}CH_2$), 5.01 (m, 2, $CH{=}CH_2$), 6.43 (m, 1, $CHC{=}O$) and 7.51-8.85 (m, 12).

Similar treatment of **35** with butylmagnesium chloride gave little product. Formation of the Schiff base anion of **35** with methylmagnesium bromide in dibutyl ether followed by alkylation with **34** gave a mixture (many peaks by vpc on 20% SE-30).

Attempted alkylations of the anion of **32,** formed with butylmagnesium chloride or ethylmagnesium bromide, with 4-bromobutyl acetate (**12**) or 3-bromopropyl acetate (reflux *ca.* 18 hr) gave complex mixtures (by tlc and vpc on 20% SE-30).

C. Formation of 2-(3′-Butenyl)cycloalkanone Ketals.—The dioxolane **38** (75% from **36** and ethylene glycol, p-TSA, benzene azeotrope, 12 hr) had bp 60–66° (0.05 mm); ir (film) 1640 cm^{-1}; nmr (neat) τ 4.21, 5.12 (vinyl H), 6.16 (s, 4, $-OCH_2CH_2O-$), and 7.82–8.92 (m, 13). The dioxolane **39** (78% from **37**) had bp 91–93° (0.5 mm); ir film) 1640 cm^{-1}; nmr (neat) τ 4.22, 5.02, 6.21 (assigned as for **38**), and 8.33 (m, 15). 2-Methyl-7-(3′-butenyl)cycloheptanone (**42**) slowly gave the dioxolane **43** (19%) after treatment with ethylene glycol in toluene azeotrope for 5 days: bp 148–149° (14 mm); nmr (neat) τ 3.9–4.55, 4.98, 5.22 (vinyl H), 6.12, 6.14 ($-OCH_2CH_2O-$), 7.8–8.8 (m, 14), 9.12 (d, 3, CH_3, J = 7 Hz).

D. Hydroboration of Butenyl Ketals.—Hydroboration[31] of **38** gave the dioxolane of 2-(4′-hydroxybutyl)cyclohexanone, ir (film) 3320 cm^{-1}. The ketal was hydrolyzed with concentrated HCl (5 ml) in C_2H_5OH (50 ml) to give 2-(4′-hydroxybutyl)-cyclohexanone (**40**),[4] which was treated with p-TSA in benzene under azeotropic conditions as previously reported[4] to give 2-oxabicyclo[5.4.0]undec-1(7)-ene (3.76 g, 0.024 mol, 28% from the butenyl ketal **38**), bp 68–72° (2.0 mm), spectral data identical with that of a genuine sample.[4]

Similar hydroboration of **42** gave 2-methyl-7-(4′-hydroxybutyl)cycloheptanone (**17**) in 42% yield; spectral data are as given below.

2,4,6-Trimethylcyclohexanone (51). A. Reduction of 2,4,6-Trimethylphenol.—A mixture of 2,4,6-trimethylphenol (**49,** 27.2 g, 0.20 mol) and 5% Rh–Al_2O_3 (2.5 g) in absolute C_2H_5OH (150 ml) and HOAc (5 ml) was hydrogenated at 25–50 psig and 25° in a Parr shaker until 48 lb of hydrogen (*ca.* 0.6 mol) was consumed. Filtration and evaporation *in vacuo* gave a residue which was dissolved in ether (250 ml), washed with $NaHCO_3$ (two 100-ml portions) and NaCl (100 ml), dried, and evaporated to give a mixture of **50** and **51** (22.18 g, 0.157 mol if pure **50**, 78%), ir (film) 3610, 1710 cm^{-1}. To crude **50, 51** (63.0 g, *ca.* 0.44 mol) in acetone (360 ml) in an ice bath was added CrO_3 (30 g, 0.30 mol) in water (84 ml) and H_2SO_4 (23.2 ml) at a rate sufficient to maintain a reaction temperature of 10–15° (2 hr). The mixture was stirred at 22° for 1 hr, and $NaHSO_3$ (18.2 g) was added with ice bath cooling (exothermic reaction) until the mixture became green. The organic layer, combined with ether and acetone washings of the inorganic layer, gave **51** (50.3 g, 0.36 mol, 81%): bp 72–79° (15 mm); ir (film) 1710 cm^{-1}; nmr (CCl_4) τ 7.3–8.3 (m, 7), 9.05 (d, 3, C_4CH_3, J = 5.6 Hz), 9.07 (d, 6, $C_{2,6}$ CH_3, J = 6.0 Hz); (C_6H_6) 9.03 (d, 6), 9.31 (d, 3); vpc (15% Carbowax 20M) one peak at 120°. *Anal.* Calcd for $C_9H_{16}O$: C, 77.09; H, 11.50. Found: C, 76.90; H, 11.67.

2,4,6-Trimethyl-7-carbethoxycycloheptanone (46).—Ethyl diazoacetate (18.7 g, 0.15 mol) in ether (20 ml) was added dropwise with stirring over 3 hr to a solution of BF_3·C_2H_5O (44.7 g, 0.31 mol, freshly distilled from CaH_2) and **51** (44.0 g, 0.31 mol) in ether (40 ml) under nitrogen. The reaction temperature did not exceed 35°. Lower yields of **46** were obtained at 0–5° or >35°. After 15 hr at 22°, the reaction mixture was poured over ice (110 g) and extracted with ether (five 120-ml portions) to give **46** (21.4 g, 0.095 mol, 60% based on 1 equiv of **51**): bp 100–105° (0.1 mm); ir (film) 1740, 1710 cm^{-1}; vpc one peak (5% SE-30, 145°); nmr (CCl_4) τ 5.89 (q, 2, CH_2CH_3), 7.5–8.5 (m, 7), 8.76 (t, 3, CH_2CH_3, J = 7.2 Hz), 9.01 (d, 3, C_2CH_3), 9.03 (d, 3, C_6CH_3), 9.11 (d, 3, C_4CH_3), 7.09 (d, 1, C_7 H, J = 10.2 Hz). The data (Table I) are consistent with the presence of one isomer of **46**. Reaction of **51** with 1 equiv of ethyl diazoacetate gave 18% of **46**. *Ancl.* Calcd for $C_{13}H_{22}O_3$: C, 68.99; H, 9.80. Found: C, 68.70; H, 9.84.

Formation and Alkylation of β-Keto Esters.—2-Carbethoxycycloheptanone (**44,** 92%) had bp 118–124° (14 mm). Similar reaction of 2-methylcycloheptanone with diethyl carbonate and NaH gave **2-methyl-7-carbethoxycycloheptanone (45,** 89%): bp 113–136° (14 mm) [lit.[32] bp 113–116° (6 mm)]; ir (film) 3400 (w, enolic OH), 1745 (s, ester), 1710 (s, ketone), 1640, 1610 cm^{-1}; nmr (neat) τ 5.88 (q, 2, CH_2CH_3), 6.2–6.65 (m, 0.76 H ketonic isomer $CH(C{=}O)O$), 7.3, 8.4 (m, 9.3), 8.81 (t, 3, CH_2CH_3), 8.90 (d, 3, CH_3CH). The presence of **45** and not 2-methyl-2-carbethoxycycloheptanone is confirmed by the partial presence of the enolic form and a doublet at τ 8.90. Similar reaction of **4** gave **46** (19–25%), ir and nmr identical with those of **46** from ring expansion of **51**, and diester **47** (26%): bp 150–159° (14 mm); ir (film) 1730 cm^{-1}; nmr (CCl_4) τ 5.87 (q, 4, CH_2CH_3), 7.9 (br s, 2, α H), 8.6–9.15 (complex m, 22, CH, CH_2, CH_3). Reaction of **4** with ethyl chloroformate and potassium triphenylmethide in glyme gave only starting ketone. Hydrolysis of **46** with ethanolic KOH (reflux for 18 hr) gave 85:15 **4a**:**4b**.[33] Attempted closure of **47** with potassium *tert*-butoxide in ether gave no reaction.

Alkylation of the sodium enolate of **45** (from **45** and NaH in toluene at reflux for 3 hr) with **12** (10 equiv, at reflux overnight in toluene) gave **2-methyl-7-carbethoxy-7-(4′-acetoxybutyl)cycloheptanone (54,** 56%): bp 118–156° (0.3 mm); ir (film) 1735, 1705 cm^{-1}; nmr (CCl_4) τ 5.85 (q, 2, CH_2CH_3), 6.0 (t, 2, CH_2O),

(31) H. C. Brown, "Hydroboration," W. A Benjamin, New York, N. Y., 1962.

(32) J. R. Mahajan and P. C. Dutta, *J. Chem. Soc.*, 62 (1960).

(33) This mixture of **4a,b** is probably formed from one initially formed isomer during the prolonged exposure to base.

7.3 (m, 1, C_7 H), 8.05 (s, 3, $CH_3(C{=}O)O$), 8.2–8.8 (m, 14), 8.74 (t, 3, CH_2CH_3), 8.97 (d, 3, CH_3CH, J = 7 Hz).

2-Carbethoxy-2-(3′-butenyl)cycloheptanone (52), from the sodium enolate of carbethoxycycloheptanone (from **44** and Na-OC_2H_5 in C_2H_5OH at reflux for 15 hr) with **34** (1.1 equiv, at reflux for 15 hr), 72%, had bp 103–109° (0.25 mm); ir (film) 1730, 1700, 1640 cm^{-1}; nmr (neat) τ 4.25 (m, 1, $CH{=}CH_2$), 5.01 (m, 2, $CH{=}CH_2$), 5.87 (q, 2, CH_2CH_3), 6.49 (m, 2, allylic H), 7.50–8.48 (m, 12), 8.80 (t, 3, CH_2CH_3).

2-Methyl-7-carbethoxy-7-(3′-butenyl)cycloheptanone (53), from the potassium enolate of **45** (from **45** and potassium triphenylmethide) with **34** (at reflux in DME for 15 hr), 85%, had bp 136–138° (0.75 mm); ir (neat) 1740, 1720, 908 cm^{-1} ($CH{=}CH_2$); nmr (neat) τ 3.85–4.55, 4.98, 5.2 (as above, vinyl H), 5.82 (q, 2, CH_2CH_3), 7.2, 8.0, 8.3 (m, 13), 8.74 (t, 3, CH_2CH_3), 8.91 (d, 3, C_7 CH_3); mass spectrum (70 eV) m/e (rel intensity) 252 ($M\cdot^+$, 4), 244 (8), 207 (12), 198 (100), 166 (26), 155 (75), 151 (50), 148 (70), 136 (28), 123 (32), 108 (92), 94 (35), 80 (48). The use of $NaOC_2H_5$–C_2H_5OH for enolate formation gave **53** in 24% yield. *Anal.* Calcd for $C_{15}H_{24}O_3$: C, 71.39; H, 9.59. Found: C, 71.51; H, 9.73.

2,4,6-Trimethyl-7-carbethoxy-7-(4′-acetoxybutyl)cycloheptanone (59).—Addition of **46** (26.0 g, 0.116 mol) to NaH (hexane washed, 5.7 g, 0.118 mol) in toluene (110 ml)–DMF (30 ml) gave a clear solution after a 30-min reflux period. Alkylation with 12 (23.0 g, 0.118 mol) at reflux for 18 hr (pH then *ca.* 7) gave NaBr (12 g, 0.116 mol) and a mixture of **59** and O-alkylated diester **58** (15.6 g, 0.046 mol, 40%): bp 150–155° (0.15 mm); (film) 1700 sh, 1730 cm^{-1}; nmr (CCl_4) τ 5.8–6.1 (m, OCH_2), 8.05 (s, 3, $OCOCH_3$), 8.15–8.55 (m, CH, CH_2), 8.58–8.92, 9.0–9.1 (m, 12, CH_3); vpc (10% SE-30 at 200°) three peaks in ratio of 23 (**58**): 25:52 (**59** isomers). The assignment of **58** is based on its disappearance (and appearance of **46**) after treatment of **58** and **59** with dilute aqueous HCl, *i.e.*, **58** was hydrolyzed to **46**. *Anal.* Calcd for $C_{19}H_{32}O_5$: C, 67.03; H, 9.47. Found: C, 66.82; H, 9.43.

Decarboxylation of β-Keto Esters.—Basic hydrolysis (10% NaOH in 3:1 C_2H_5OH–H_2O) of **52** gave 2-(3′-butenyl)cycloheptanone (**37**, 31%): bp 105–134° (0.6 mm); ir (film) 1670, 1695 cm^{-1}; nmr (neat) τ 4.27, 5.00 (vinyl H), 7.25–8.84 (m, 15). *Anal.* Calcd for $C_{11}H_{18}O$: C, 79.46; H, 10.91. Found: C, 79.64; H, 11.00. Similar hydrolysis of **53** gave **2-methyl-7-(3′-butenyl)cycloheptanone (42)**, 84%: bp 93–97° (3.5 mm); ir (film) 1705, 905 cm^{-1}; nmr (neat), τ 3.9–4.5, 4.99, 5.22 (as above, vinyl H), 7.5, 7.9, 8.8 (m, 14), 9.02 (d, 3, CH_3, J = 7 Hz); vpc one peak; mass spectrum (70 eV) m/e (rel intensity) 180 ($M\cdot^+$, 15), 168 ($M - H_2O$, 14), 126 (72), 111 (23), 84 (100), 52 (52), 41 (95). *Anal.* Calcd for $C_{12}H_{20}O$: C, 79.94; H, 11.18. Found: C, 79.78; H, 11.25. Hydrolysis of **54** with KOH, C_2H_5OH–H_2O (8:1) at reflux for 20 hr gave **2-methyl-7-(4′-hydroxybutyl)cycloheptanone (17**, 47%): bp 113–117° (0.05 mm); ir (film) 3580, 1705 cm^{-1}; nmr (CCl_4) τ 6.1 (s, 1, OH), 6.48 (t, 2, CH_2O), 8.1–8.85 (m, 16), 9.02 (d, 3, CH_3). Hydrolysis of the mixture of **58** and **59** with aqueous alcoholic NaOH for 48 hr at reflux, followed by treatment with 1 *N* HCl at room temperature for 24 hr, gave **2,4,6-trimethyl-7-(4′-hydroxybutyl)-cycloheptanone (18**, 43%): bp 140° (0.1 mm); ir (film) 3500, 1700 cm^{-1}; nmr (CCl_4) τ 5.95 (s, 1, OH), 6.45 (t, 3, CH_2O), 7.2 (m, 1, α H), 8.4 (m, 13), 8.98 (d, 3, C_2 CH_3), 9.05 (d 3, C_6 CH_3), 9.10 (d, 3, C_4 CH_3); vpc (5% SE-30 at 190°) one peak; mass spectrum (70 eV) m/e (rel intensity) 226 ($M\cdot^+$, 4), 208 ($M - H_2O$, 4), 154 (21), 139 (42), 112 (100), 109 (38), 95 (65), 83 (68), 70 (32). *Anal.* Calcd for $C_{14}H_{26}O_2$: C, 74.29; H, 11.58. Found: C, 74.07; H, 11.58.

Hydrolysis of **58** and **59** with aqueous alcoholic KOH at 22° for 8 hr gave crude **2,4,6-trimethyl-7-carbethoxy-7-(4′-hydroxybutyl)cycloheptanone (64)** which was decarboxylated with anhydrous LiI, collidine[34] at reflux for 48 hr to **18** (20–55% in several runs).

Cyclization of 4′-Hydroxybutyl Ketones to Bicyclic Enol Ethers.—No reaction occurred when **17** was treated with *p*-TSA in benzene under azeotropic conditions. Little conversion to the "7-7" enol ethers **56a,b** was observed upon distillation of **17** from *p*-TSA (at 0.1 or 14 mm), potassium pyrosulfate, or acid-washed alumina (at 260°). A solution of **17** (5.99 g, 0.030 mol) and *p*-TSA (10 mg) in toluene (125 ml)–DMF (25 ml) was heated at reflux through a Soxhlet extractor filled with CaH_2 for 7 days. Pyridine (3 ml) was added to the cooled mixture, which was distilled to give 12-methyl-2-oxabicyclo[5.5.0]-dodec-1(7)ene (**56a**) and an isomer **56b**, 22%: bp 105–125° (14 mm); ir (film) 1665 cm^{-1}; nmr (CCl_4) τ 6.25, 6.45 (m, 2, CH_2O), 7.7–8.8 (m, CH_2, vinyl CH_3 of **56b**), 8.95 (d, 1.7, CH_3-CH, 57% of **56a**); vpc–mass spectrum[35] (70 eV) m/e (rel intensity) component A 180 ($M\cdot^+$, 57), 165 (22), 151 (30), 137 (56), 126 (48), 121 (25), 109 (37), 95 (56), 81 (61), 67 (74), 55 (83), 41 (100); component B differing intensities for above peaks; M + 1 = 13.0, M + 2 = 1.12; calcd for $C_{12}H_{20}O$, M + 1 = 13.3, M + 2 = 1.02.

Similar treatment of **18** (or azeotropic removal of H_2O for up to 8 days) gave **8,10,12-trimethyl-2-oxabicyclo[5.5.0]dodec-1(7)-ene (60a)** and isomers **60b** and **60c** (three peaks by vpc on 10% SE-30 at 180°): ir (film) 1680 cm^{-1}; vpc–mass spectrum[36] (70 eV) m/e (rel intensity) peak A 208 (86), 193 (100), 179 (17), 166 (100), 165 (100), 151 (32), 139 (37), 137 (32), 126 (53), 123 (38), 112 (45), 111 (73), 109 (38), 97 (43), 95 (68), 81 (63), 67 (53), 55 (100); vpc peaks B and C gave very similar fragmentation; M + 1 = 16.2; calcd for $C_{14}H_{24}O$, M + 1 = 15.6. The isomers **60a–c** were generally formed in minor yield along with much starting material (**18**). Attempts to separate reasonable amounts of **60a–c** were not successful. Similar results were obtained upon treatment of **18** in toluene–DMF with methanesulfonic acid. Other attempted dehydrative cyclization of **18** with *p*-TSA in benzene, HMPA–toluene, etc., gave no reaction.

Oxidation of Bicyclic Enol Ethers to Keto Lactones.—Addition of **56a** and **56b** to MCPBA (3 equiv) in CH_2Cl_2 at a slow rate to maintain reflux (20 min), followed by 2 hr at room temperature, and work-up,[4] gave **2-methyl-7-ketoundecanolide (57**, 27%): mp 70–71.5°; ir (KBr) 1717, 1695 cm^{-1}; nmr (CCl_4) τ 5.9 (m, 2, CH_2O), 7.55 (m, 5, $C_{2,6,8}$ H), 8.4 (m, 10), and 8.90 (d, 3, CH_3, J = 7 Hz); vpc (10% SE-30 at 180°); one peak; mass spectrum[37] (70 eV) m/e (rel intensity) 212.1440 (M^+, 16), 156 (5), 139 (37), 126 (47), 112 (42), 111 (28), 101 (33), 98 (100), 84 (47), 69 (67), 68 (70), 56 (40), 55 (92); calcd for $C_{12}H_{20}O_3$, 212.1412. *Anal.* Calcd for $C_{12}H_{20}O_3$: C, 67.89; H, 9.50. Found C, 67.90; H, 9.56.

The crude oxidation mixture had an nmr peak at τ 7.8, suggestive of a methyl ketone such as **61** which would form from the endocyclic olefin **56b**.

Similar oxidation of the crude mixture of **60a–c** and **18** resultant from the attempted dehydrative closure of **18** gave oils: one main and several minor isomers by vpc (5% SE-30 at 160°); ir (film) 1728, 1700 cm^{-1}; nmr (CCl_4) τ 5.95 (t, CH_2O), 8.05, 8.1–8.8, 8.75, 8.9–9.1 (CH_3); mass spectrum (70 eV) m/e 254, 240 (weak); calcd for $C_{14}H_{24}O_3$, 240.

Registry No.—**1a**, 33015-68-8; **1b**, 33015-99-5; **2a**, 32971-08-7; **2b**, 33016-00-1; **3**, 932-56-9; **4a**, 32971-09-8; **4a** 2,4-DNP, 32971-10-1; **4b**, 32971-11-2; **4b** 2,4-DNP, 33021-04-4; **8**, 33068-10-9; **9**, 33015-70-2; **11**, 14092-11-6; **17**, 33015-72-4; **18**, 33015-73-5; **19**, 32971-12-3; **21**, 32971-13-4; **23**, 32971-14-5; **24**, 32971-15-6; **25**, 32971-19-0; **28**, 33015-74-6; **29**, 33015-75-7; **29** 2,4-DNP, 33016-01-2; **30**, 33015-76-8; **31**, 33015-77-9; **33**, 33015-78-0; **35**, 6114-69-8; **36**, 16178-83-9; **37**, 33015-80-4; **38**, 33015-81-5; **39**, 33068-12-1; **42**, 33015-82-6; **43**, 33015-83-7; **45**, 2206-76-0; **46**, 32971-16-7; **47**, 33015-85-9; **51**, 32971-17-8; **52**, 33015-86-0; **53**, 33068-13-2; **54**, 33015-87-1; **56a**, 33015-88-2; **56b**, 33015-89-3; **57**, 33015-90-6; **58**, 33015-91-7; **59**, 33015-92-8; **60a**, 33015-93-9; **60b**, 33015-94-0; **65**, 583-60-8; **66**, 766-42-7; **67**, 4426-24-8; 2-methylcycloheptylcyclohexylimine, 33015-97-3; 2,4,6-trimethylcycloheptanone anil, 33015-98-4.

Acknowledgment.—We are indebted to Dr. Edward W. R. Casper for some of the ASIS measurements.

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(35) Performed on an LKB vpc-inlet mass spectrometer at the University of Pittsburgh by Dr. Gary Koppel.

(36) Performed on a Varian Atlas CH-5 vpc-inlet mass spectrometer by Mr. Jack Landis, City University of New York.

(37) High resolution mass spectral data were obtained on an MS-9 mass spectrometer by Dr. Rodger Foltz at the Battelle High Resolution Mass Spectrometry Center supported by the National Institutes of Health, Division of Research Resources, Contract No. NIH-69-2226.

A New Route to Phenazine 5,10-Dioxides and Related Compounds[1]

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Received July 19, 1971

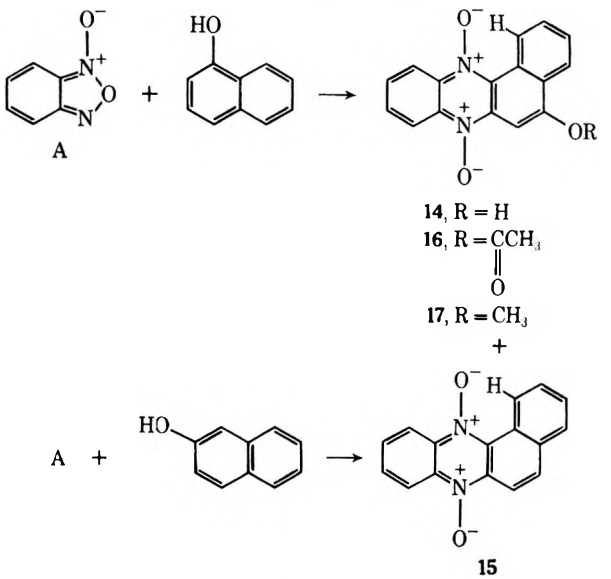
A new one-step synthetic route is described for the preparation of phenazine 5,10-dioxide derivatives and related compounds from benzofurazan 1-oxide and phenolic compounds. Mechanistic possibilities are presented.

Certain phenazine 5,10-dioxides are known to have antibacterial activity. Two of these, iodinin[2] and myxin,[3,4] are microbial metabolites. Previously, compounds of this class were prepared in low yields by a multistep synthetic route.[5] We now report a facile one-step synthesis of substituted phenazine 5,10-dioxides and some related compounds. This versatile synthesis has afforded novel compounds hitherto inaccessible by classical synthetic methods.[5]

Enamines[6] and β diketones[7] react with benzofurazan 1-oxide to yield substituted quinoxaline 1,4-dioxides. It has now been found that phenolate anions react in the same sense with benzofurazan 1-oxides to afford phenazine 5,10-dioxide derivatives. Some of the successful reactions are listed in Table I. Surprisingly, the reaction of phenol with benzofurazan 1-oxide does not give the expected compound, phenazine 5,10-dioxide, but resulted in the formation of 2-phenazinol 5,10-dioxide in 5–10% yield. The same product, **1**, is obtained in better yield from the reaction of benzofurazan 1-oxide (A) with *p*-hydroquinone or *m*-methoxyphenol. In the latter case no 1-methoxyphenazine 5,10-dioxide was detected.

The presence of electron-withdrawing substituents on monohydroxybenzenes impedes the reaction, possibly due to the decreased nucleophilicity of the phenolate anions. The presence of electron-withdrawing groups on dihydroxybenzenes, however, does not affect the course of the reaction, as is shown by the reaction of carbomethoxy-*p*-hydroquinone with benzofurazan 1-oxide to furnish **13**.

The synthesis of benzo[*a*]phenazine 7,12-dioxide derivatives was achieved by allowing benzofurazan 1-oxide to react with α- and β-naphthols in the presence of base. Two compounds were obtained from α-naphthol: **14**, resulting from an initial para coupling, and **15**,[8] resulting from an initial ortho coupling. From β-naphthol, **15** was the sole product. Acetylation (acetic anhydride) and methylation (diazomethane) of **14** gave the corresponding acetoxy **16** and methoxy **17** derivative respectively. The structures were assigned



to the benzo[*a*]phenazine class on the basis of the large chemical shift of the hydrogens at C_1 in the nmr spectra due to the proximity of the 12-oxide. The C_1 hydrogen appears as a multiplet at δ 10.0 in **14** and at 10.65 in **15**.

The reactivities of some heterocyclic analogs of phenols toward benzofurazan 1-oxides have been examined and, in most cases, a reaction occurred affording novel heterocyclic compounds, as shown in Scheme I. Monohydroxypyridines are not nucleophilic enough to react with benzofurazan 1-oxide, but 2,3-dihydroxypyridine did react to yield the pyrido[2,3-*b*]quinoxaline **18**. 8-Hydroxyquinoline coupled with benzofurazan 1-oxide to yield the pyrido[2,3-*a*]phenazinol **19**.

In the nmr spectrum of **19**, the C_1 hydrogen appears at δ 11.6 owing to the proximity effect of the 12-oxide. The quinolino[2,3-*a*]phenazine **20** was obtained from 1-phenazinol and benzofurazan 1-oxide. Furthermore, indole reacted with benzofurazan 1-oxide to give the indoloquinoxaline **21**; the structure of **21** was confirmed by the synthesis of this product, in poor yield, from benzofurazan 1-oxide and indoxyl acetate in alcoholic base. Reduction of **21** with sodium dithionite gave the product **22**, which was identical with an authentic sample synthesized from *o*-phenylenediamine and isatin.

Possible mechanisms for the formation of phenazine 5,10-dioxides from benzofurazan 1-oxides and phenolate anions are outlined in Scheme II. Depending on the substitution pattern on the phenolate anion, the reaction may follow one of three different pathways. If the para position of the phenolate anion is unsubstituted, the attack on the benzofurazan 1-oxide pro-

(1) Presented in part at (a) IUPAC Meeting in London, July 1968, Abstract H4, 437; (b) 156th National Meeting of the American Chemical Society, Atlantic City, N. J., Sept 1968, Medicinal Chemistry Abstract 15. Related work has been published by K. Ley, F. Seng, V. Eholzer, R. Nast, and R. Schubart, *Angew. Chem., Int. Ed. Engl.*, **8**, 596 (1969).

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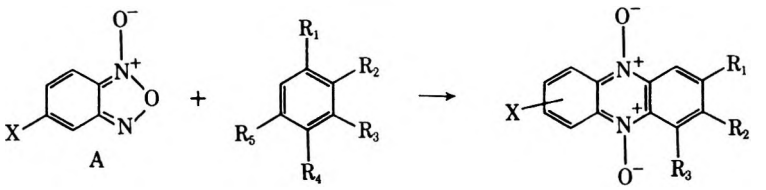
Table I



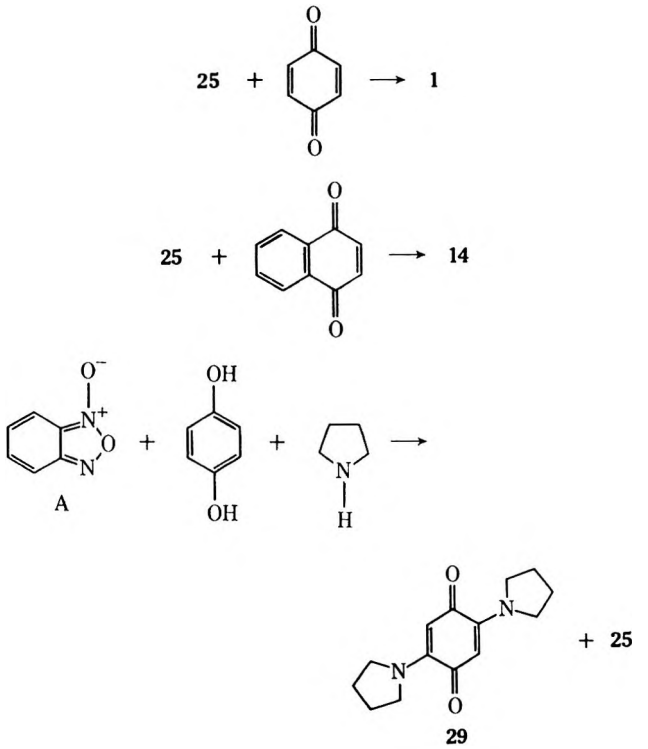
Phenazine	X	R_1	R_2	R_3	R_4	R_5	Yield, %	Method	Mp, °C	Recrystn solvent	Formula[e]
1[a]	H	OH	H	H	H	H	5–10	C	230	CF_3CO_2H–MeOH	$C_{12}H_8N_2O_3$
1	H	OH	H	H	OH	H	30	C	230	CF_3CO_2H–MeOH	$C_{12}H_8N_2O_3$
1	H	OH	H	H	H	OCH_3	15	C	230	CF_3CO_2H–MeOH	$C_{12}H_8N_2O_3$
2[b]	Cl	OH	H	H	OH	H	60	B	208	CF_3CO_2H–MeOH	$C_{12}H_7ClN_2O_3$
3[b]	OCH_3	OH	H	H	OH	H	22	B	196	CH_3CO_3H–MeOH	$C_{13}H_{10}N_2O_4$
4	H	NH_2	H	H	OH	H	56	C	215	CF_3CO_2H	$C_{12}H_9N_3O_2$
5	H	OH	OH	H	H	H	66	A + C	250	CF_3CO_2H–AcOH	$C_{12}H_8N_2O_4$
6	H	$-OCH_2O-$		H	OH	H	35	C	207–208	CF_3CO_2H–MeOH	$C_{13}H_8N_2O_4$
7[b]	Cl	$-OCH_2O-$		H	OH	H	25	C	207–208	$CHCl_3$–MeOH	$C_{13}H_7ClN_2O_4$
8[c]	H	OH	OCH_3	H	H	H	80	A + C	212–214	CF_3CO_2H–MeOH	$C_{13}H_{10}N_2O_4$
9	H	OH	CO_2H	H	OH	H	70	A	>300	CF_3CO_2H–MeOH	$C_{13}H_8N_2O_5$
10	H	OCH_3	H	H	OH	H	37	B	184	MeOH	$C_{13}H_{10}N_2O_3$
11[d]	H	OH	H	OH	H	OH	34	B	220	CF_3CO_2H–MeOH	$C_{12}H_8N_2O_4$
12	H	OH	OH	CH_3	H	H	82	A	235	CF_3CO_2H–MeOH	$C_{13}H_{10}N_2O_4$
13	H	OH	CO_2CH_3	H	OH	H	20	A	204–205	MeOH–Et_2O	$C_{14}H_{10}N_2O_5$

[a] D. L. Vivian, *J. Amer. Chem. Soc.*, **71**, 1139 (1949). [b] Position of X in the products is either at 7 or 8. [c] Product characterized as the dimethoxy derivative. [d] Product characterized as the diacetoxy derivative. [e] All compounds were analyzed for C, H, N, and Cl. The analyses were within ±0.4% of the theoretical values: Ed.

ceeds exclusively *via* pathways a or c, followed by cyclization through a Michael-type addition to the quinoidal intermediates. In pathway a, the dihydro intermediate cannot be isolated even if the reaction is conducted under an atmosphere of nitrogen; oxidation of the dihydro intermediate may be effected by benzofurazan 1-oxide, as evidenced by the isolation of benzofurazan **23** from the reaction mixture. In pathway c, elimination of an alcohol (ROH) produces the fully aromatic product. In pathway b, a substituent at the para position forces the phenolate anion to couple at the ortho position followed by cyclization and elimination of water to yield the product.

The oxidizing capacity of benzofurazan 1-oxide is illustrated in Scheme III. Thiophenol and β-thionaphthol are oxidized to the disulfides **24** and **26** respectively, while benzofurazan 1-oxide is reduced to *o*-quinonedioxime (**25**). Hydroquinones may be oxidized to quinones by benzofurazan 1-oxide as illustrated by the oxidation of 2,5-di-*tert*-butylhydroquinone to the quinone **27**. Oxidation of *o*-aminophenol with benzofurazan 1-oxide, in the presence of base, gave as one of the products the phenoxazone **28**. Other oxidizing agents, such as benzoquinone, are known to effect the same transformation.[9]

The ability of benzofurazan 1-oxide to oxidize hydroquinones to quinones may suggest alternate mechanistic possibilities for the formation of 2-phenazinol 5,10-dioxide based on an initial one- or two-electron oxidation. A radical coupling could then occur after a one-electron transfer, or, for a two-electron transfer, the resulting bisoxime **25** could then condense with the quinone. Such a condensation was observed to occur with *p*-quinone to yield **1** and with 1,4-naphthoquinone to afford **14**. Furthermore, when the reaction between benzofurazan-1-oxide and *p*-hydroquinone was catalyzed by pyrrolidine, the product was



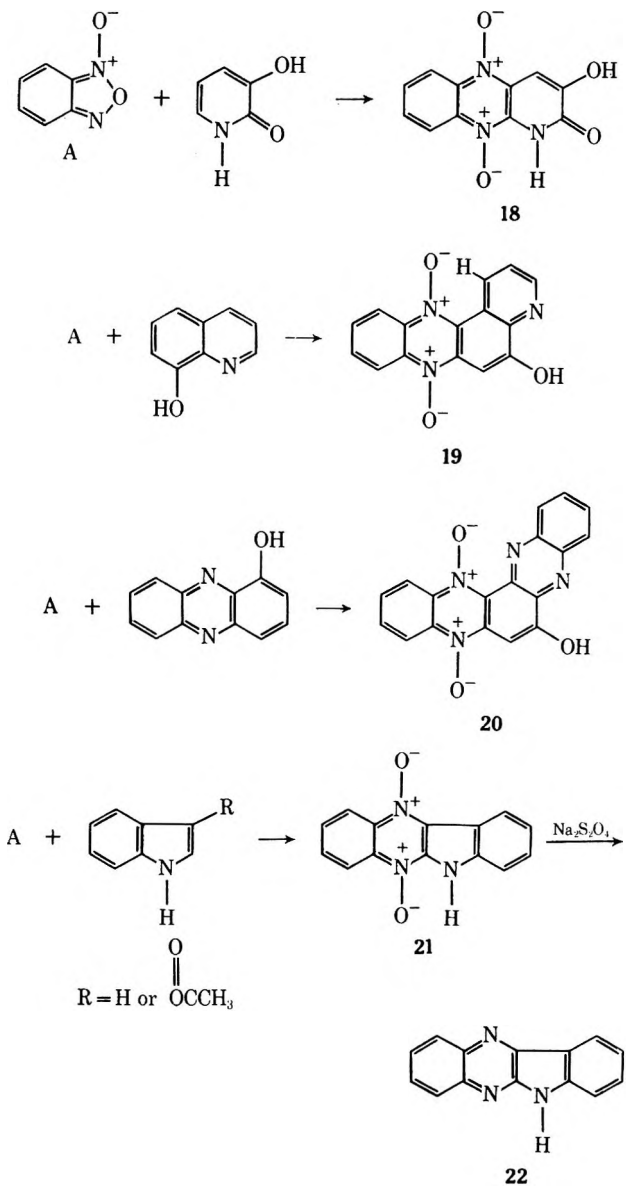
not the expected 2-phenazinol 5,10-dioxide (**1**), but the dipyrrolidinoquinone **29**. This could be the result of a reaction between pyrrolidine and either a phenolate radical anion or *p*-quinone followed by oxidations with benzofurazan 1-oxide. At present, it is not possible to choose among the mechanistic possibilities discussed above.

Experimental Section

All melting points are uncorrected and were obtained with the Buchi apparatus. The analyses were performed by the Analytical Department of Pfizer Inc., and by F. Pascher, Bonn, Germany. The phenazine 5,10-dioxides were mainly prepared

(9) A. Korczynski and S. Obarski, *Bull. Soc. Chim. Fr.*, **33**, 1823 (1923).

SCHEME I



by one of the three general methods illustrated below and the ir, uv, and nmr spectra of the reported compounds were in agreement with the assigned structures.

Method A. Methyl 3-Hydroxy-2-phenazinecarboxylate 5,10-Dioxide (13).—A solution of 5.0 g (0.029 mol) of methyl 2,5-dihydroxybenzoate and 4.0 g (0.029 mol) of benzofurazan 1-oxide in 100 ml of THF was saturated with NH_3 and the reaction mixture was stirred overnight at room temperature in a tightly stoppered flask. The following day the solution was evaporated and, after trituration with 1 *N* HCl, the residue was recrystallized from MeOH–Et_2O to give 1.5 g of a purple solid. Another recrystallization gave a dark yellow sample of **13**.

Method B. 2-Methoxyphenazine 5,10-Dioxide (10).—A solution of 6.2 g (0.048 mol) of *p*-methoxyphenol and 6.5 g (0.048 mol) of benzofurazan 1-oxide in 100 ml of 5% KOH in MeOH was allowed to stand for 3 days at room temperature and then the reaction mixture was heated to reflux overnight. The resulting slurry was filtered to give 4.5 g of a dark brown solid which decomposed at 174–184°. Recrystallization from MeOH gave a red solid, mp 184° dec (lit. 174–175°).

Method C. 2-Phenazinol 5,10-Dioxide (1).—To a solution of 12.4 g (0.1 mol) of *m*-methoxyphenol, 5.4 g (0.1 mol) of NaOMe, and 100 ml of MeOH was added a solution of 13.6 g (0.1 mol) of benzofurazan 1-oxide in 100 ml of MeOH. The reaction mixture was heated to reflux for 2 hr to yield 1.0 g of a dark purple solid (Na), mp >300°. Acidification of the filtrate yielded 2.7 g of a red solid, mp 230° dec. Recrystallization from trifluoroacetic acid–MeOH gave a red sample of **1**.

Methylation of 8.—Treatment of a slurry of 0.1 g of 2-hydroxy-3-methoxyphenazine 5,10-dioxide (**8**) in MeOH with ethereal diazomethane gave 2,3-dimethoxyphenazine 5,10-dioxide, which was recrystallized from $CHCl_3$–EtOH to give orange needles (80 mg) that melted at 222–223° with decomposition. This compound was identical with that obtained by the treatment of 2,3-dihydroxyphenazine 5,10-dioxide (**5**) with diazomethane.

Anal. Calcd for $C_{14}H_{12}N_2O_4$: C, 61.76; H, 4.44; N, 10.29. Found: C, 61.62; H, 4.34; N, 10.14.

Acetylation of 11.—A solution of 0.9 g of 1,3-dihydroxyphenazine 5,10-dioxide (**11**) in Ac_2O–pyridine was allowed to stand at room temperature for 12 hr, and poured onto ice–water. The precipitated solid was filtered and washed with H_2O to give 0.9 g of 1,3-diacetoxyphenazine 5,10-dioxide, which was recrystallized from MeOH to give an orange solid that melted at 135°.

Anal. Calcd for $C_{16}H_{12}N_2O_6$: C, 58.54; H, 3.68; N, 8.53. Found: C, 58.70; H, 3.83; N, 8.64.

Benzo[*a*]-phenazine 7,12-Dioxide (15) and 5-Hydroxybenzo-[*a*]phenazinol 7,12-Dioxide (14).—To a solution of 14.4 g (0.1 mol) of α-naphthol, 5.4 g (0.1 mol) of NaOMe, and 150 ml of MeOH was added a solution of 13.6 g (0.1 mol) of benzofurazan 1-oxide in 100 ml of MeOH. After stirring overnight, the resulting slurry was filtered to yield 5.2 g of **15**, mp 169–170°. Recrystallization from $CHCl_3$–MeOH gave 4.0 g of a yellowish orange solid, mp 178–178.5°.

Anal. Calcd for $C_{16}H_{10}N_2O_2$: C, 73.27; H, 3.84; N, 10.68. Found: C, 73.29; H, 3.95; N, 10.69.

The mother liquor from the reaction mixture was acidified with AcOH to yield 7.4 g of **14**, mp 230–231°. Recrystallization from trifluoroacetic acid–AcOH gave 4.65 g, mp 250–253° dec.

Anal. Calcd for $C_{16}H_{10}N_2O_3$: C, 69.06; H, 3.62; N, 10.07. Found: C, 69.20; H, 3.56; N, 10.11.

Benzo[*a*]phenazine 7,12-Dioxide (15).—To a solution of 14.4 g (0.1 mol) of β-naphthol, 5.4 g (0.1 mol) of NaOMe, and 150 ml of MeOH was added a solution of 13.6 g (0.1 mol) of benzofurazan 1-oxide in 100 ml of MeOH. A few minutes later, the slurry was filtered to give 7.6 g of a yellowish-orange solid, mp 179–180°. The mother liquor was heated to reflux for 30 min to yield an additional 5.25 g of product, mp 177–179°.

5-Acetoxybenzo[*a*]phenazine 7,12-Dioxide (16).—5-Hydroxybenzo[*a*]phenazine 7,12-dioxide (**14**, 0.15 g) was dissolved with warming in 4 ml of pyridine and 6 ml of Ac_2O and after being stirred at room temperature for 16 hr the reaction mixture was poured onto ice–water. The resulting yellow-orange solid was collected and washed with H_2O and MeOH. Recrystallization from benzene (20 ml) gave thin orange-yellow needles that melted at 204° dec.

Anal. Calcd for $C_{18}H_{12}N_2O_4$: C, 67.50; H, 3.78; N, 8.75. Found: C, 67.61; H, 3.61; N, 8.65.

5-Methoxybenzo[*a*]phenazine 7,12-Dioxide (17).—A slurry of 0.5 g of 5-hydroxybenzo[*a*]phenazine 7,12-dioxide (**14**) in MeOH was treated with etherial diazomethane and after evaporation of the solution the residue was recrystallized from $CHCl_3$–MeOH to give orange needles (300 mg) that melted at 197–198° dec.

Anal. Calcd for $C_{17}H_{12}N_2O_3$: C, 69.85; H, 4.14; N, 9.59. Found: C, 69.75; H, 4.04; N, 9.43.

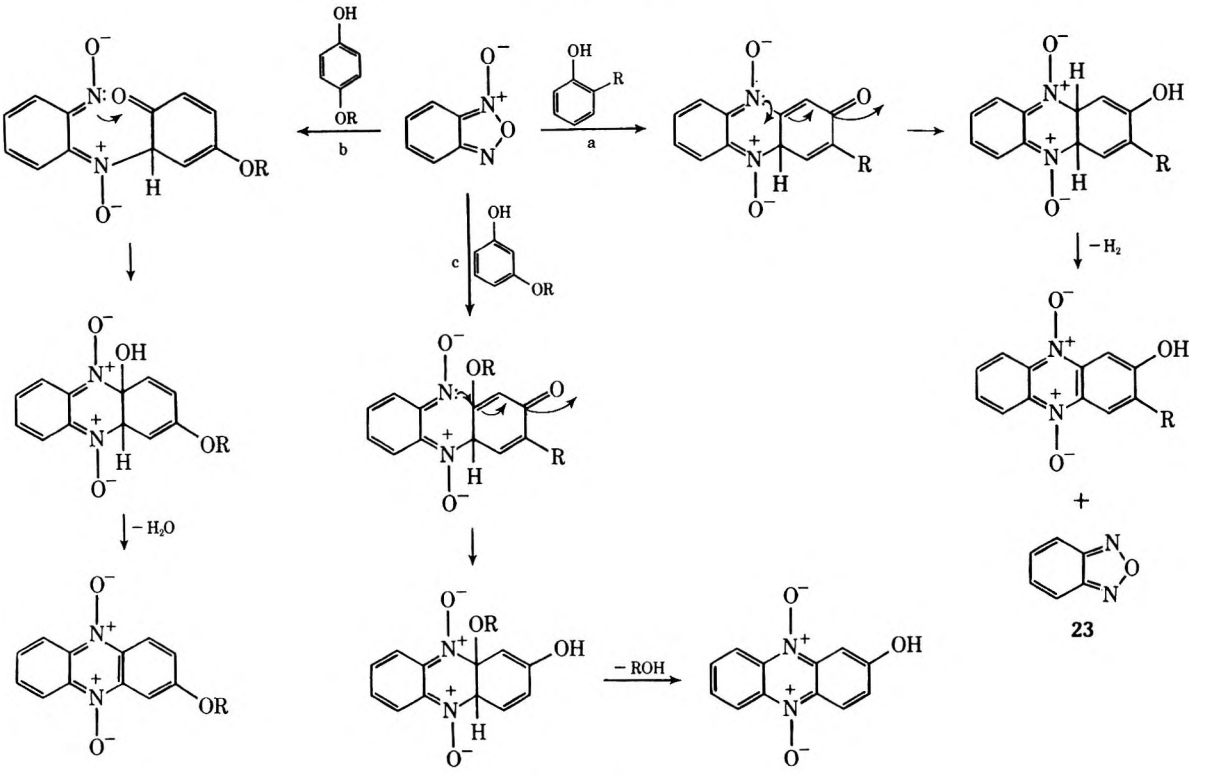
Pyrido[2,3-*b*]quinoxaline-2,3-diol 5,10-Dioxide (18).—A solution of 5.0 g (0.046 mol) of 2,3-dihydroxypyridine and 6.2 g (0.046 mol) of benzofurazan 1-oxide in 100 ml of THF was saturated with NH_3 and the flask was tightly sealed. After sitting overnight at room temperature, the reaction mixture was filtered to give 5.0 g (22%) of a brown solid which did not melt below 300°. An analytical sample was prepared by recrystallization from AcOH.

Anal. Calcd for $C_{11}H_7N_3O_4$: C, 53.88; H, 2.88; N, 17.14. Found: C, 53.84; H, 3.25; N, 16.41.

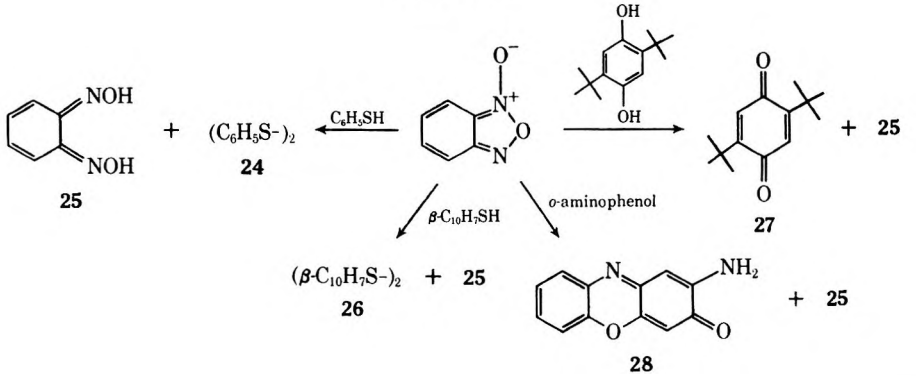
5-Pyrido[3,2-*a*]phenazinol 7,12-Dioxide (19).—To a hot solution of 14.5 g (0.1 mol) of 8-hydroxyquinoline, 5.4 g (0.1 mol) of NaOMe, and 100 ml of MeOH was added a hot solution of 13.6 g (0.1 mol) of benzofurazan 1-oxide in 150 ml of MeOH. The reaction was heated to reflux for 2.5 hr, and after cooling, filtration gave 11.4 g of a purple solid, mp >300° (sodium salt). Acidification of the filtrate with excess AcOH gave 2.1 g of an orange solid as the free phenol, mp 240–242° dec, which was recrystallized from trifluoroacetic acid–AcOH, mp 242° dec. The sodium salt may be converted to **19** by dissolving it in H_2O and acidifying the purple solution with 6 *N* HCl.

Anal. Calcd for $C_{15}H_9N_3O_3$: C, 64.51; H, 3.25; N, 15.05. Found: C, 64.48; H, 3.29; N, 14.93.

SCHEME II



SCHEME III



6-Hydroxyquinoxalino[2,3-*a*]phenazine 8,13-Dioxide (20).—To a solution of 5.0 g (0.025 mol) of 1-hydroxyphenazine and 1.35 g (0.025 mol) of NaOMe in 100 ml of MeOH was added 3.4 g (0.025 mol) of benzofurazan 1-oxide. After stirring at room temperature overnight 1.5 g (0.025 mol) of AcOH was added and the resulting slurry was filtered to give 5.0 g (60%) of a brown solid, mp >300°. Trituration of the brown solid with AcOH gave a red solid and an analytical sample was obtained by recrystallization from trifluoroacetic acid–Et_2O.

Anal. Calcd for $C_{18}H_{10}N_4O_3$: C, 65.50; H, 3.25; N, 16.98. Found: C, 65.43; H, 2.98; N, 16.78.

6*H*-Indolo[2,3-*b*]quinoxaline 5,11-Dioxide (21).—A solution of benzofurazan 1-oxide (1.4 g) and indole (1.2 g) in 5% methanolic KOH (10 ml) was heated to reflux for 2 min and allowed to stand at room temperature for 3 hr. Dilution with H_2O and acidification with dilute HCl afforded a yellow solid which was filtered and washed with H_2O and MeOH. The dried product **21** weighed 0.6 g (37% yield) and recrystallization from AcOH gave bright yellow rosettes, mp 284° dec.

6*H*-Indolo[2,3-*b*]quinoxaline (22).—To a warm solution of 6*H*-indolo[2,3-*b*]quinoxaline 5,11-dioxide (**21**, 0.1 g) in AcOH (20 ml) was added in portions a solution of $Na_2S_2O_4$ (0.5 g) in 5 ml of hot H_2O and the solution was heated to reflux for 5 min. The solution was then diluted with H_2O and the resulting yellowish solid was collected and washed with H_2O and MeOH. Recrystallization of the product from C_6H_6–MeOH gave yellow needles (100 mg), mp 296–298° (lit. 294–295°). 6*H*-Indolo[2,3-*b*]quinoxaline (**22**) prepared by the above method was identical (ir and mixture melting point) with an authentic sample synthesized from *o*-phenylenediamine and isatin.

The Reaction of Pyrocatechol and Benzofurazan 1-Oxide.—A solution of pyrocatechol (2.2 g) and benzofurazan 1-oxide (2.8 g) in 15% ethanolic potassium hydroxide (10 ml) was steam distilled to give 1.3 g of benzofurazan (**23**). Acidification of the red solution in the reaction flask with dilute HCl gave 1.6 g of 2,3-dihydroxyphenazine 5,10-dioxide (**5**).

The Reaction of Thiophenol and Benzofurazan 1-Oxide.—To a solution of 5.0 g (0.0457 mol) of thiophenol and 6.2 g (0.0457 mol) of benzofurazan 1-oxide in 50 ml of THF was added, dropwise, a solution of 2.5 g (0.0457 mol) of NaOMe in 25 ml of MeOH. After 2 hr, the solution was evaporated and H_2O was added to give a precipitate, mp 57–60° [diphenyl disulfide (**24**), mp 59–60°]. The filtrate was then acidified and concentrated to give 3.0 g (98%) of *o*-quinonedioxime (**25**) which was identified by a mixture melting point test.

The Reaction of β-Thionaphthol and Benzofurazan 1-Oxide.—To a slurry of 5.0 g (0.031 mol) of β-thionaphthol and 1.7 g (0.031 mol) of NaOMe in 50 ml of MeOH was added 4.2 g (0.031 mol) of benzofurazan 1-oxide. The slurry was stirred overnight and then filtered to give 4.5 g (90%) of a colorless solid, mp 137–139° [lit. mp 139° for 2,2′-dinaphthyl disulfide (**26**)].

The Reaction of 2,5-Di-*tert*-butylhydroquinone and Benzofurazan 1-Oxide.—A solution of 3.0 g (0.022 mol) of benzofurazan 1-oxide and 5.0 g (0.022 mol) of 2,5-di-*tert*-butylhydroqui-

none in 50 ml of THF was saturated with NH_3 and stirred overnight at room temperature. The yield of the resulting red precipitate **27**, which turned yellow on drying, was 4.5 g (98%), mp 152–153° [2,5-di-*tert*-butylquinone (**27**) mp 152.5°]. The only other product in this reaction was *o*-quinonedioxime (**25**) which was identified by tlc.

The Reaction of *o*-Aminophenol and Benzofurazan 1-Oxide.—To a solution of 5.0 g (0.045 mol) of *o*-aminophenol and 2.4 g (0.045 mol) of NaOMe in 5.0 ml of MeOH was added 6.1 g (0.045 mol) of benzofurazan 1-oxide. After stirring at room temperature for 2.5 hr, 2.7 g (0.045 mol) of AcOH was added and the resulting slurry was filtered to give 3.0 g (62%) of 2-amino-3*H*-phenoxazin-3-one (**28**) which melted after recrystallization at 254–255°.

Anal. Calcd for $C_{12}H_8N_2O_2$: C, 67.9; H, 3.78; N, 13.2. Found: C, 67.79; H, 3.85; N, 13.45.

The addition of H_2O to the filtrate resulted in the isolation of 5.0 g (82%) of *o*-quinonedioxime (**25**) which was identified by tlc and a mixture melting point test.

2-Phenozinol 5,10-Dioxide (**1**).—A solution of 0.9 g (0.0065 mol) of *o*-quinonedioxime (**25**) and 0.7 g (0.0065 mol) of *p*-quinone in 10 ml of THF after standing overnight at room temperature was filtered to give 0.5 g (34%) of a red solid which was identical in every respect with an authentic sample of 2-phenazinol 5,10-dioxide (**1**).

5-Hydroxybenzo[*a*]phenazinol 7,12-Dioxide (**14**).—A solution of 1.0 g (0.0063 mol) of 1,4-naphthoquinone and 0.88 g (0.0063 mol) of *o*-quinonedioxime (**25**) in 20 ml of THF was allowed to stand at room temperature for 1 day. Filtration gave 0.050 g (3%) of a red solid, mp 230–235°. The filtrate was allowed to sit for 2 more days and filtered again to give 0.45 g (25.6%), mp 233–235°. Finally the filtrate was allowed to stand 7 more days the solution was filtered again to give 0.7 g (40%) of a brown solid, mp 236–238°.

The three solids were combined and recrystallized from AcOH–trifluoroacetic acid to give 1.0 g of **14** (57%) which melted at 242° dec. This compound was identical in every respect with an authentic sample.

Registry No.—**1**, 303-80-0; **2**, 32839-15-9; **3**, 32839-16-0; **4**, 26390-70-5; **5**, 24890-65-1; **6**, 25629-71-4; **7**, 32845-85-8; **8**, 26390-41-0; **8** dimethoxy derivative, 32866-02-7; **9**, 25629-68-9; **10**, 303-78-6; **11**, 25629-70-3; **11** diacetate, 32861-63-5; **12**, 25629-67-8; **13**, 25629-69-0; **14**, 26390-71-6; **15**, 18636-88-9; **16**, 32861-68-0; **17**, 32861-69-1; **18**, 32861-70-4; **19**, 25629-73-6; **20**, 32861-72-6; **21**, 32861-73-7; **22**, 243-59-4; **24**, 882-33-7; **27**, 2460-77-7; **28**, 1916-59-2.

Acknowledgments.—We thank Mr. D. A. Johnson and Mrs. P. Greenleaf for their technical assistance.

Phenylfurazan Oxide. Chemistry

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Received August 24, 1971

The facile stepwise transformation of 4-phenylfurazan 2-oxide (**1**) under a variety of conditions into α-hydroxyimino-*anti*-phenylacetonitrile oxide (**2a**), α-hydroxyiminophenylacethydroxamic acid (**3**), and 3-phenyl-1,2,4-oxadiazol-5-one (**7**), as proposed in the early literature, has been confirmed. Comparison samples of compounds **3** and **7** were synthesized by independent routes. The same α-hydroxyiminophenylacethydroximoyl chloride (**6**) was obtained by the addition of hydrogen chloride to the nitrile oxide **2a**, by chlorination of *anti*-phenyl-*amphi*-glyoxime (**5**), and by reaction of α-ketophenylacethydroximoyl chloride (**9**) with hydroxylamine hydrochloride; dehydrohalogenation of this yielded the nitrile oxide isomer opposite to **2a**. 4-Phenylfurazan 2-oxide could not be methylated by methyl iodide nor by dimethyl sulfate. No reaction occurred when 4-phenylfurazan 2-oxide was irradiated with uv light. A 1:1 adduct of 4-phenylfurazan 2-oxide (or of α-hydroxyimino-*anti*-phenylacetonitrile oxide) with mesityl oxide was isolated.

4-Phenylfurazan 2-oxide (**1**) is a compound with a long history and most investigations of it preceded the arrival of instrumental techniques. In our investigation of this area of chemistry, we have shown that three isomers of phenylglyoxime, *anti*-phenyl-*amphi*-glyoxime, phenyl-*anti*-glyoxime, and phenyl-*syn*-glyoxime are present in the conventional synthesis of this precursor to phenylfurazan oxide.[1] Further, oxidation of each isomer by dinitrogen tetroxide yielded only 4-phenylfurazan 2-oxide (**1**).[2] These results contrasted with the conclusions of previous investigators who described the oxidations of only two isomers into two different phenylfurazan oxides, 3-phenylfurazan 2-oxide and 4-phenylfurazan 2-oxide.[3] In view of these discrepancies between our results and those of former researchers and considering the interesting rearrangements described for phenylfurazan oxide,[4] a reexamination of 4-phenylfurazan 2-oxide chemistry, using modern instrumentation, appeared justified.

It had been reported that phenylfurazan oxide will rearrange into α-hydroxyiminophenylacetonitrile oxide (**2**) completely in base or to the extent of 2–5% in solvents such as benzene or ether.[4,5] We have found that most handlings of 4-phenylfurazan 2-oxide result in significant or complete rearrangement into α-hydroxyimino-*anti*-phenylacetonitrile oxide (**2a**). Thus dissolution of **1** in some solvents, *e.g.*, acetone, alcohol–water, contact with alumina or treatment with a basic buffer, or heating with activated charcoal have all caused this rearrangement. This transformation was not observed when 4-phenylfurazan 2-oxide was dissolved in chloroform, *m*-xylene, or in solvents acidified with hydrogen chloride. The conversion was readily monitored by infrared spectral measurement, by observing the appearance of the strong nitrile oxide absorbance at 2288 cm^{-1} and the disappearance of the strong double bond absorbance associated with the furazan oxide ring at 1610 cm^{-1}. In the very early literature, the product from the rearrangement of phenylfurazan oxide in base was incorrectly described

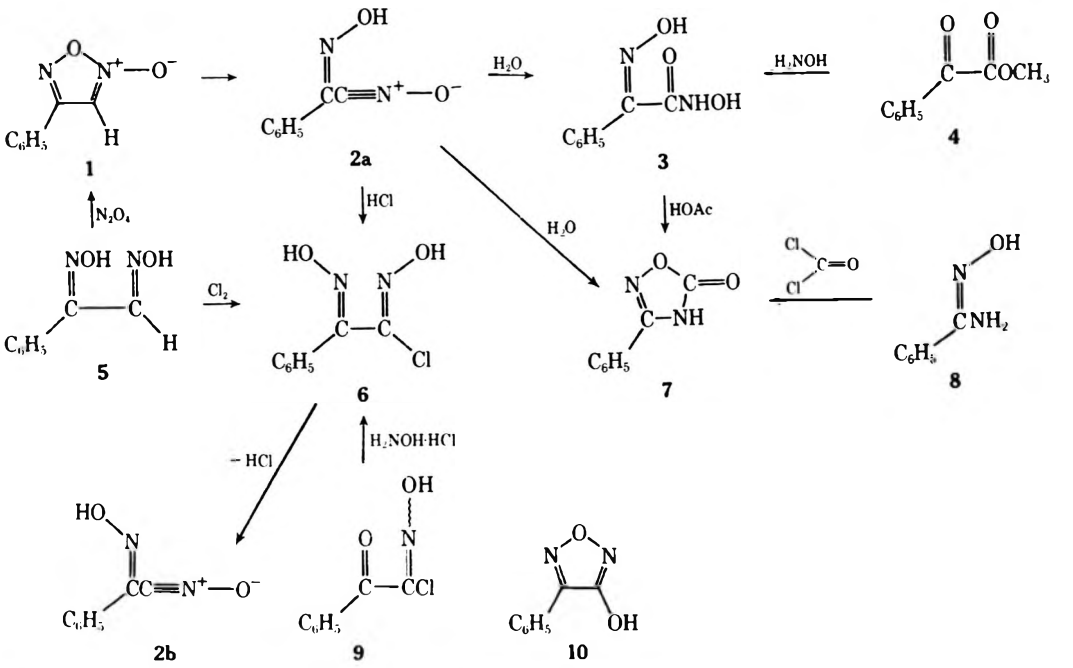
(1) J. V. Burakevich, A. M. Lore, and G. P. Volpp, *J. Org. Chem.*, **36**, 1 (1971).

(2) J. V. Burakevich, A. M. Lore, and G. P. Volpp, *ibid.*, **36**, 5 (1971).

(3) For a discussion and references, see the publications cited in footnotes 1 and 2.

(4) For reviews, see J. H. Boyer in "Heterocyclic Compounds," Vol. 7, R. C. Elderfield, Ed., John Wiley & Sons, New York, N. Y., 1961, pp 499–503; L. C. Behr 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, pp 287, 298.

(5) (a) G. Ponzio, *Gazz. Chim. Ital.*, **66**, 127 (1936); (b) G. Ponzio, *ibid.*, **66**, 119 (1936).



as 3-hydroxy-4-phenylfurazan (**10**);[4] infrared spectral measurement leaves no doubt as to the correctness of the nitrile oxide structure. Solid α-hydroxyimino-*anti*-phenylacetonitrile oxide (2a) was unstable at room temperature and decomposed into a complex mixture on standing. It could be stored at low temperature.

Solutions of **2a** in the presence of moisture yielded mixtures of α-hydroxyiminophenylacethydroxamic acid (**3**) and 3-phenyl-1,2,4-oxadiazol-5-one (**7**) as proposed;[4,5b] acetic acid catalyzes the reaction. Both structures were confirmed by comparison of physical constants with samples obtained by independent syntheses. Compound **3** was synthesized from methyl phenylglyoxylate (**4**) and hydroxylamine in base[6] and compound **7** was synthesized from benzamidoxime (**8**) and phosgene. Product **7** can arise from **3** by a Lossen rearrangement with internal cyclization and this conversion has been effected by acetic acid, alone or in the presence of acetic anhydride to aid in dehydration. Since the oxadiazolone **7** is isomeric with the nitrile oxide **2a**, only a trace of water is required for the transformation of **2a** into **7** through the hydroxamic acid **3**; thus, it is often encountered in various handlings and on storage of the furazan oxide **1**. The characteristic ir band at 1764 cm^{-1} signals its presence. Alternatively, the heterocycle **7** can be formed directly from **2a** by rearrangement of the nitrile oxide function into an isocyanate followed by cyclization.[7]

Configuration **2a** was assigned to the isomer resulting from the rearrangement of 4-phenylfurazan 2-oxide on the basis of the following experiments. The same α-hydroxyiminophenylacethydroximoyl chloride (**6**) was obtained by the addition of hydrogen chloride to the nitrile oxide **2a**,[5a] by chlorination of *anti*-phenyl-*amphi*-glyoxime (**5**) and by reaction of α-ketophenylacethydroximoyl chloride (**9**) with hydroxylamine hydrochloride. The hydrogen chloride introduced or produced during these reactions caused isomerization to the *anti*-glyoxime structure as indicated by the formation of a red nickelous complex.[1,8] Dehydrohalogenation of **6** under basic, neutral, or acidic conditions did not yield the original nitrile oxide **2a** but an isomer which dimerized spontaneously when the isolation of a solid product was attempted, in contrast to the easily obtainable solid **2a**. Since sterically unhindered nitrile oxides readily dimerize to furazan oxides and sterically hindered nitrile oxides can be isolated as solids with indefinite stability,[7] the solid nitrile oxide rearrangement product of 4-phenylfurazan 2-oxide must have configuration **2a**.

Unchanged 4-phenylfurazan 2-oxide was isolated from methylation attempts by refluxing it in neat methyl iodide and from neat dimethyl sulfate treatment at 100°. No reactions were observed when a solution of 4-phenylfurazan 2-oxide in ether was treated with hydrogen chloride or when irradiated with ultraviolet light.

After long standing, a solution of 4-phenylfurazan 2-oxide in mesityl oxide yielded a 1:1 adduct between solvent and solute. Presumably this product arises from slow decomposition of the 4-phenylfurazan 2-oxide into the nitrile oxide **2a** which then adds to the double bond in a 1,3-dipolar addition reaction characteristic of nitrile oxides.[7]

Experimental Section[9]

4-Phenylfurazan 2-Oxide (1).—This compound was obtained by oxidation of phenylglyoxime with dinitrogen tetroxide as previously described.[2] 4-Phenylfurazan 2-oxide has the fol-

(6) "Beilstein's Handbuch der Organischen Chemie," 4th ed, Vol. X, 2nd suppl, F. Richter, Ed., Springer Verlag, Berlin, 1949, pp 458–460.

(7) C. Grundmann, *Fortschr. Chem. Forsch.*, **7**, 62 (1966); C. Grundmann in "Methoden der Organischen Chemie (Houben-Weyl)," Vol X/3, E. Müller, Ed., Georg Thieme Verlag, Stuttgart, pp 841–870; C. Grundmann and P. Kochs, *Angew. Chem., Int. Ed. Engl.*, **9**, 635 (1970); C. Grundmann and S. K. Datta, *J. Org. Chem.*, **34**, 2016 (1969); A. Quilico, *Experientia*, **25**, 1169 (1970).

(8) L. L. Meritt, Jr., *Anal. Chem.*, **25**, 718 (1953); L. E. Godycki and R. E. Rundle, *Acta Crystallogr.*, **6**, 487 (1953); R. C. Voter, C. V. Banks, V. A. Fassel, and P. W. Kehres, *Anal. Chem.*, **23**, 1730 (1951).

(9) The melting points were determined with a Mettler FP1 melting point apparatus equipped with a Bausch and Lomb VOM 5 recorder except where noted. Infrared spectra were recorded on a Perkin-Elmer Model 137 spectrophotometer. A Varian A-60 spectrometer was used to obtain the nmr spectra and tetramethylsilane was used as the internal standard. The mass spectra were determined on a Consolidated Electrodynamics Corporation Model 21-103C spectrometer.

lowing physical properties: mp 108–110°; ir ($CHCl_3$) 3165 (w), 1610 (s), 1603 (m), 1471 (w), 1451 (m), 1399 (m), 1182 (w), 1000 (w), 985 (w), and 935 cm^{-1} (w); nmr ($CDCl_3$) δ 7.26 (s, 1, –CH=N) and 7.60 ppm (m, 5, phenyl); mass spectrum (70 eV) *m/e* (rel intensity) 162 (15), 146 (6), 145 (2), 132 (14), 103 (44), 102 (100).

Anal. Calcd for $C_8H_6N_2O_2$: C, 59.26; H, 3.73; N, 17.28. Found: C, 59.41; H, 4.01; N, 17.02.

α-Hydroxyimino-*anti*-phenylacetonitrile Oxide (2a).—A solution of 300 mg of 4-phenylfurazan 2-oxide (1) in 50 ml of chloroform was stirred at room temperature for 17 hr with 50 ml of a pH 8.0 buffer solution (Fisher Catalog No. SO-B-112, monobasic potassium phosphate–sodium hydroxide). The chloroform layer was removed and was washed twice with distilled water. The chloroform solution was dried azeotropically by first passing it through phase-separating paper (Whatman 1 PS) followed by removal of the solvent on a rotary evaporator. The crystalline residue was washed with a small amount of benzene. Recrystallization was accomplished by adding petroleum ether (bp 30–60°) to a chloroform solution of the nitrile oxide at room temperature to about the cloud point followed by slow cooling to below 0°. The crystals were collected by filtration and were washed with chloroform–petroleum ether (bp 30–60°): yield 63 mg; mp 101–102° dec (lit.[5a] mp 112–113° dec); ir ($CHCl_3$) 3584 (oxime –OH) and 2288 cm^{-1} ($C{\equiv}N^+{-}O^-$); nmr ($CDCl_3$) δ 8.56 (s, 1, –OH) and 7.22–8.00 ppm (m, 5, phenyl); mass spectrum (70 eV) *m/e* (rel intensity) 162 (42), 132 (38), 115 (12), 103 (38), 102 (100), 77 (28). The nitrile oxide can be stored for three months at −25° with practically no decomposition. During the same period at room temperature, a sample showed massive decomposition (11 spots on tlc) with a prominent carbonyl absorption at 1739 cm^{-1}.

Anal. Calcd for $C_8H_6N_2O_2$: C, 59.26; H, 3.73; N, 17.28. Found: C, 59.26; H, 3.96; N, 17.15.

Comparison of the furazan oxide absorption at 1610 cm^{-1} *vs.* the nitrile oxide absorption at 2288 cm^{-1} was used to observe the conversion of the furazan oxide **1** into the nitrile oxide **2a** in many varied handlings of 4-phenylfurazan 2-oxide. In the present work, this conversion has been observed upon simple dissolution of the heterocycle **1** in acetone or ethanol–water, and by treatment with activated carbon, alumina, or silica gel G.[4,5] Concentration can make a difference; for example, the transformation of **1** into **2a** proceeds rapidly in dilute solutions in acetone but not in concentrated solutions. The furazan oxide can be recovered unchanged from solutions in chloroform, *m*-xylene, ethanol, and organic solvents acidified with hydrogen chloride gas. Infrared monitoring must be employed during any experimentation with 4-phenylfurazan 2-oxide.

α-Hydroxyiminophenylacethydroxamic Acid (3) and 3-Phenyl-1,2,4-oxadiazol-5-one (7) from α-Hydroxyimino-*anti*-phenylacetonitrile Oxide (2a).—A 10-g sample of α-hydroxyimino-*anti*-phenylacetonitrile oxide (2a) (synthesized by dissolution of 4-phenylfurazan 2-oxide in acetone followed by evaporation of the solvent) was refluxed for 1 hr in 200 ml of acetic acid. The addition of 600 ml of water caused a precipitate to form which was discarded after filtration. The evaporation of the filtrate to dryness yielded a mixture of **3** and **7**. Since the hydroxamic acid **3** is chloroform insoluble, chloroform was used to extract the oxadiazolone **7** from the mixture.

The solid residue left after the chloroform extraction (1.2 g) required several recrystallizations before an analytically pure sample was obtained even though the infrared spectrum of the crude product was virtually superimposable upon that of the pure sample. Water, ethyl acetate–petroleum ether (bp 30–60°), and ethyl acetate–chloroform were used as the recrystallization solvents. The analytically pure α-hydroxyiminophenylacethydroxamic acid (**3**) melted at 173.5–175.5° (lit.[5] mp 187–188°) and its ir spectrum was superimposable upon that of a sample synthesized from methyl phenylglyoxylate (see below): ir (KBr) 3311 (s), 1650 (s), 1616 (m), 1513 (w), 1418 (s), 1305 (w), 1008 (s), 858 (m), 716 (m), and 689 cm^{-1} (m).

Anal. Calcd for $C_8H_8N_2O_3$: C, 53.33; H, 4.48; N, 15.55. Found: C, 53.17; H, 4.64; N, 15.21.

The chloroform was evaporated from the extraction solution leaving a residue (3.0 g) whose ir spectrum showed it to be mainly the oxadiazolone **7**. Several recrystallizations from water were required to obtain an analytically pure sample of 3-phenyl-1,2,4-oxadiazol-5-one (**7**) whose ir spectrum was superimposable upon that of a sample of the compound obtained from benzamidoxime and phosgene (see below). The analytically pure sample (1.3 g) melted at 203–205° (lit.[5] mp 202–203°) and no depression in melting point was observed in a 1:1 mixture of the product and that from benzamidoxime and phosgene: ir ($CHCl_3$) 3125 (w), 1764 (s), 1616 (w), 1567 (w), 1464 (w), 997 (w), 953 (m), and 893 cm^{-1} (w).

Anal. Calcd for $C_8H_6N_2O_2$: C, 59.26; H, 3.73; N, 17.28. Found: C, 59.47; H, 4.02; N, 17.15.

3-Phenyl-1,2,4-oxadiazol-5-one (7) from α-Hydroxyiminophenylacethydroxamic Acid (3).—A mixture of 200 mg of α-hydroxyiminophenylacethydroxamic acid, 113 mg of acetic anhydride, and 10 ml of acetic acid was refluxed for 1 hr. The solvent was then removed under reduced pressure and the infrared spectrum of the residue showed a strong carbamate band at 1773 cm^{-1} and the disappearance of the bands associated with the hydroxamic acid. Several recrystallizations, first from water and then from chloroform–petroleum ether (bp 30–60°), were required to raise the melting point to 202–203.5° (capillary, oil bath). The product gave the same ir spectrum as that described above for this compound.

α-Hydroxyiminophenylacethydroxamic Acid (3) from Methyl Phenylglyoxylate (4).[6]—A solution of 10.2 g of potassium hydroxide in 25 ml of methanol at 40° was added to a solution of 8.5 g of hydroxylamine hydrochloride in 44 ml of methanol also at 40°. The resulting mixture was cooled to 0° and 5 g of methyl phenylglyoxylate was added and the mixture was filtered immediately. The filtrate was allowed to stand for four days whereupon it was acidified by a solution of 2 ml of acetic acid in 16 ml of water. The mixture was heated until a clear solution resulted. The product was extracted with ether and the ether was evaporated to give a residue which yielded 1.4 g of crystals upon trituration with chloroform. Recrystallization from water yielded analytically pure α-hydroxyiminophenylacethydroxamic acid: mp 173.5–175.5°; ir, same as described above for this compound; nmr (DMSO-d_6) δ 7.15–7.80 (m, 5, phenyl), 9.12 (s, 1, –NH), 11.04 (s, 1, –OH), and 11.80 ppm (s, 1, –OH).

Anal. Calcd for $C_8H_8N_2O_3$: C, 53.33; H, 4.48. Found: C, 53.41; H, 4.65.

3-Phenyl-1,2,4-oxadiazol-5-one (7) from Benzamidoxime (8) and Phosgene.—A solution of 2 g of benzamidoxime[10] and 4 g of triethylamine in 180 ml of benzene was cooled to 5° while phosgene was passed in until about 20 ml was collected. The mixture was allowed to stand in an unstoppered flask for 40 hr and was then washed with 100 ml of water. The water wash was then extracted with benzene. The combined benzene solutions were dried over magnesium sulfate. Evaporation of the solvent left a residue (1.2 g) whose ir spectrum was virtually the same as that of the pure compound but for a small amount of a nitrile impurity. Several recrystallizations from water and chloroform–petroleum ether (bp 30–60°) yielded analytically pure material: mp 203.5–205.5°; ir the same as that described for the compound above.

Anal. Calcd for $C_8H_6N_2O_2$: C, 59.26; H, 3.73; N, 17.28. Found: C, 59.09; H, 4.00; N, 17.02.

α-Hydroxyiminophenylacethydroximoyl Chloride (6) from α-Hydroxyimino-*anti*-phenylacetonitrile Oxide (2a).[5a]—A solution of 150 mg of the nitrile oxide **2a** (prepared by the buffer treatment of 4-phenylfurazan 2-oxide) in 50 ml of absolute ethanol was cooled in ice while it was being saturated with hydrogen chloride gas. The mixture was stirred at room temperature for 2 hr. The solvent was removed on a rotary evaporator and the crystalline residue was triturated with chloroform and was collected by filtration: yield 80 mg; mp 186–188° dec (lit.[5a] 199–200° dec); ir (KBr) 3322, 1399, 1143, 982, 867, 767, 714, and 690 cm^{-1}.

Anal. Calcd for $C_8H_7ClN_2O_2$: C, 48.38; H, 3.55; N, 14.11. Found: C, 48.13; H, 3.68; N, 13.97.

α-Hydroxyiminophenylacethydroximoyl Chloride (6) from *anti*-Phenyl-*amphi*-glyoxime (5).[11]—A solution of 10 g of *anti*-phenyl-*amphi*-glyoxime[1] in 185 ml of glacial acetic acid was cooled to about the freezing point while chlorine gas was passed in for 0.5 hr, and then the mixture was allowed to come to room temperature while chlorination was continued. The solvent was removed on a rotary evaporator under high vacuum. The residue

(10) "Beilstein's Handbuch der Organischen Chemie," 4th ed, Vol. IX, B. Prager, P. Jacobson, P. Schmidt, and D. Stern, Ed., Springer Verlag, Berlin, 1926, pp 304–306.

(11) J. Armand, P. Souchay, and F. Valentini, *Bull. Soc. Chim. Fr.*, 4585 (1968), and references therein.

was extracted with petroleum ether (bp 30–60°) and the crude product was removed by filtration. Recrystallization was accomplished from ethyl acetate–petroleum ether (bp 30–60°): yield 2.2 g; mp 187–188.5°; ir the same as that described for the compound above; molecular weight by mass spectrometry, 198 (calcd 198); nmr (DMSO-d_6) δ 7.37 (s, 5, phenyl), 12.12 (s, 1, –OH) and 12.54 ppm (s, 1, –OH). The product gave a red complex with nickelous acetate, indicating an *anti*-glyoxime structure.[8]

Anal. Calcd for $C_8H_7ClN_2O_2$: C, 48.38; H, 3.55; N, 14.11. Found: C, 48.12; H, 3.43; N, 13.82.

α-Hydroxyiminophenylacethydroximoyl Chloride (6) from α-Ketophenylacethydroximoyl Chloride (9).[11]—The procedure appearing in the literature[11] for reacting α-ketophenylacethydroximoyl chloride (9) and hydroxylamine hydrochloride without base yielded α-hydroxyiminophenylacethydroximoyl chloride melting at 187–189° dec and having an ir spectrum superimposable upon that of the sample obtained by hydrogen chloride addition to the nitrile oxide 2a.

Dehydrohalogenation of α-Hydroxyiminophenylacethydroximoyl Chloride (6).[5a]—When a suspension of α-hydroxyiminophenylacethydroximoyl chloride in chloroform was shaken with neutral or pH 4.0 buffered solutions, or sodium bicarbonate solutions, dehydrohalogenation was effected smoothly.[5a] The chloroform solutions were then dried azeotropically by first passage through phase-separating paper (Whatman 1 PS) followed by concentration under vacuum. The prominent band in the ir spectrum of these solutions is the nitrile oxide. Removal of the remaining solvent caused spontaneous dimerization of the nitrile oxide to a furazan oxide[5a] as shown by the disappearance of the nitrile oxide band (2288 cm^{-1}) in the ir and the appearance of strong double bond absorption associated with the furazan oxide ring (1600 cm^{-1}).[7,12] The dimer structure was also confirmed by mass spectrometry which showed a molecular ion at m/e 324. When the nitrile oxide was generated by simply shaking the hydroximoyl chloride 6 in chloroform–water,[13] the chloroform solution, after drying and concentration as above, showed a strong nitrile oxide absorption in its ir spectrum, but again dimerization occurred when all of the solvent was removed.

Attempted Methylations of 4-Phenylfurazan 2-Oxide.—Samples of 4-phenylfurazan 2-oxide were recovered unchanged after dissolution and refluxing in methyl iodide for 1 hr, or after dissolution in dimethyl sulfate with heating at 100° for 1 hr. Evaporation of the reactants under high vacuum and comparison of the ir spectra and melting points after recrystallization of the residues established that no reaction had occurred.

Irradiation of 4-Phenylfurazan 2-Oxide.—A 1% ethereal solution of 4-phenylfurazan 2-oxide in a quartz flask was subjected to 7 hr irradiation at 253 nm from 16 75-watt low pressure mercury vapor lamps at 35–40°. Ir analyses showed no decomposition of the starting material when the experiment was performed either under a nitrogen atmosphere or with air bubbling through the solution.

1:1 Adduct between 4-Phenylfurazan 2-Oxide (or α-Hydroxyimino-*anti*-phenylacetonitrile Oxide) and Mesityl Oxide.—A solution of 1 g of 4-phenylfurazan 2-oxide in 10 ml of mesityl oxide was allowed to stand for 20 days. Evaporation of the solvent left 1.7 g of a solid residue which was recrystallized from chloroform–petroleum ether (bp 30–60°). The melting point was erratic between 150 and 166°, perhaps indicating a mixture of the two possible isomers although the compound was homogeneous on tlc; ir ($CHCl_3$) 3571, 1709, 1370, and 1353 cm^{-1}; mass spectral molecular weight 260 (calcd 260).

Anal. Calcd for $C_{14}H_{16}N_2O_3$: C, 64.60; H, 6.20; N, 10.76. Found: C, 64.41; H, 6.13; N, 10.39.

Registry No.—**1**, 7707-64-4; **2a**, 32971-22-5; **3**, 32971-23-6; **6**, 33021-14-6; **7**, 1456-22-0; 1:1 adduct of **1** and mesityl oxide, 33015-59-7.

(12) J. H. Boyer, D. I. McCane, W. J. McCarville, and A. T. Tweedie, *J. Amer. Chem. Soc.*, **75**, 5298 (1953); N. E. Boyer, G. M. Czerniak, H. S. Gutowski, and H. R. Snyder, *ibid.*, **77**, 4238 (1955).

(13) In solution there is the following equilibrium: RC(=NOH)C(=NOH)Cl ⇄ RC(=NOH)C≡N⁺—O⁻ + HCl.[11] Since the hydroximoyl chloride is insoluble in chloroform in contrast to the nitrile oxide which is soluble, simply shaking the hydroximoyl chloride with chloroform–water yields a chloroform solution of the nitrile oxide.

Synthesis of 1-Aza-2-silacyclopentane Compounds

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Received May 19, 1970

Ethoxy derivatives of the 1-aza-2-silacyclopentane[1a] ring system were prepared and their reactions investigated. Cyclotri(2-ethoxy-1-aza-2-silacyclopentane) reacted with ethanol to form 3-aminopropyltriethoxysilane and with ethyllithium and phenyllithium to form cyclotri[2-ethyl- (or phenyl-) 1-aza-2-silacyclopentane].

In our previous note,[1b] we have reported the synthesis of 1-(trimethylsilyl)-2,2-diethoxy-1-aza-2-silacyclopentane. The ring structure in this compound showed remarkable stability toward cleavage either on standing (which resulted in cleavage of its oxygen analogs)[2-5] or in Grignard reactions in which the two side ethoxy groups were replaced. Since the 1-aza-2-silacyclopentane ring system has received little attention, we extended our study to the synthesis of additional derivatives of this rather stable silazane structure.

Hexaphenyldisilazane and 3-aminopropyltriethoxysilane were allowed to react as indicated in eq 1. Fifty

$$(C_2H_5O)_3SiC_3H_6NH_2 + (C_6H_5)_3SiNHSi(C_6H_5)_3 \xrightarrow[\Delta]{NH_4^+\ salt} (C_2H_5O)_2\underbrace{SiC_3H_6NSi(C_6H_5)_3}_{A} + (C_6H_5)_3SiOC_2H_5 \quad (1)$$

per cent of the theoretical amount of ammonia was evolved after heating the reaction mixture for 4 days and a small amount of 1-(triphenylsilyl)-2,2-diethoxy-1-aza-2-silacyclopentane (A) was obtained upon work-up. The silazane was found to have been primarily converted into ethoxytriphenylsilane. Since steric effect[6-8] from bulky substituents on nitrogen atoms has been claimed as a main factor in preventing amine

(1) (a) In order to conform to the IUPAC nomenclature system, the name of the ring system, -1-sila-2-azacyclopentane used in our previous report,[1b] was changed to 1-aza-2-silacyclopentane. (b) T. T. Tsai and C. J. Marshall, Jr., *J. Org. Chem.*, **34**, 3676 (1969).

(2) J. L. Speier, M. P. David, and B. A. Eynon, *J. Org. Chem.*, **25**, 1637 (1960).

(3) V. C. Rossney and G. Koerner, *Makromol. Chem.*, **73**, 85 (1964).

(4) W. H. Knoth, Jr., and R. V. Lindsey, Jr., *J. Amer. Chem. Soc.*, **80**, 4106 (1958).

(5) K. A. Andrianov, V. I. Pakhonlov, and H. E. Lapteva, *Dokl. Akad. Nauk SSSR*, **151**, 849 (1963).

(6) L. W. Breed and R. L. Elliott, *Inorg. Chem.*, **3**, 1624 (1964).

(7) C. H. Yoder and J. J. Zuckerman, *ibid.*, **4**, 116 (1965).

(8) S. H. Langer, S. Connel, and I. Wender, *J. Org. Chem.*, **23**, 50 (1958).

exchange reactions between silazane and amines, it seems quite likely that the three bulky phenyl groups on a silicon atom exerted a similar effect in this reaction. In addition to the isolation of compound A, ethoxytriphenylsilane, and ammonia, there was evidence from mass spectrometric analysis of the formation of two other products with molecular weights of 387 [possibly corresponding to cyclotri(2-ethoxy-1-aza-2-silacyclopentane), trimer D] and 516 [possibly corresponding to cyclotetra(2-ethoxy-1-aza-2-silacyclopentane), tetramer E], respectively.

An attempt to synthesize compound A by the reaction of 1-ethoxydimethylsilyl-2,2-diethoxy-1-aza-2-silacyclopentane with ethoxytriphenylsilane, as illustrated in eq 2, was unsuccessful.

$$(C_2H_5O)_2SiC_3H_6NSi(CH_3)_2(OC_2H_5) + (C_6H_5)_3SiOC_2H_5 \xrightarrow[\text{or } NH_4Br]{Li_3N} (C_2H_5O)_2SiC_3H_6NSi(C_6H_5)_3 + (CH_3)_2Si(OC_2H_5)_2 \quad (2)$$

A

The reaction of hexamethylcyclotrisilazane and 3-aminopropyltriethoxysilane in the presence of a catalytic amount of ammonium bromide yielded 1-(ethoxydimethylsilyl)-2,2-diethoxy-1-aza-2-silacyclopentane (B) (eq 4 and 5) as the main product. In this reaction, it was noted that (a) ammonia evolution was rapid and stoichiometric; (b) the yield of B was 49% and only a small amount of diethoxydimethylsilane was formed; and (c) the formation of high molecular weight substances containing ethoxydimethylsilyl end groups (see Table I) occurred.

Based on the above observations and a reported reaction (1) as shown by eq 3, we suggest the following mechanism.

$$(C_2H_5O)_3SiC_3H_6N[Si(CH_3)_3]_2 \longrightarrow (C_2H_5O)_2SiC_3H_6NSi(CH_3)_3 + (CH_3)_3Si(OC_2H_5) \quad (3)$$

(1) Transamination

$$(C_2H_5O)_3SiC_3H_6NH_2 + [(CH_3)_2SiNH]_3 \longrightarrow (C_2H_5O)_3SiC_3H_6N\langle \text{Si}(CH_3)_2\text{-NC}_3\text{H}_6\text{Si}(C_2H_5O)_3 \rangle + NH_3 \quad (4)$$

(2) Condensation

$$(C_2H_5O)_3SiC_3H_6N\langle \text{Si}(CH_3)_2\text{-NC}_3\text{H}_6\text{Si}(C_2H_5O)_3 \rangle \longrightarrow 2(C_2H_5O)_2SiC_3H_6NSi(CH_3)_3(OC_2H_5) \quad (5)$$

B

$$\text{C}_3\text{H}_6\text{Si}(C_2H_5O)_3 \longrightarrow (C_2H_5O)_2SiC_3H_6NSiNC_3H_6Si(C_2H_5O)_2 + (C_2H_5O)_2Si(CH_3)_2 \quad (6)$$

C

It was surprising to find that C, which would be expected to form (eq 6), was not isolated. A liquid, isolated by preparative glpc, had a molecular weight and elementary analysis corresponding to that calculated for C. However, its nmr spectrum indicated the presence of three different ethoxy groups suggesting a possible structure M as indicated below.

TABLE I

m/e	Possible structures
350	$(C_2H_5O)_2SiC_3H_6NMe_2SiNHMe_2SiOC_2H_5$ or $(C_2H_5O)_2SiC_3H_6N(C_2H_5O)_2SiC_3H_6NH_2$
351[a]	$(C_2H_5O)_2SiC_3H_6NMe_2SiOMe_2SiOC_2H_5$
387[a]	$[-SiC_3H_6N(OC_2H_5)-]_3$ (trimer D)
406[a]	$(C_2H_5O)_2SiC_3H_6NSi(OC_2H_5)C_3H_6NMe_2SiOC_2H_5$
516	$[-SiC_3H_6N(OC_2H_5)-]_4$ (tetramer E)
535	$(C_2H_5O)_2SiC_3H_6NSi(OC_2H_5)C_3H_6NSi(OC_3H_6)C_3H_6NSi(Me_2)OC_2H_5$

[a] Isolated and had molecular weight and elementary analysis.

$$(C_2H_5O)_2SiC_2H_6NSi(OC_2H_5)C_2H_6NSi(CH_3)_2(OC_2H_5)$$

M

In a separate experiment, the residue obtained after removal of B was analyzed by mass spectrometric techniques. Among numerous *m/e* peaks observed in the spectrum there were six peaks (Table I) to which structures could be assigned.

In spite of the fact that 3-aminopropyltriethoxysilane reacted with hexamethylcyclotrisilazane in one case and with hexaphenyldisilazane in the other, both reactions produced trimer D and tetramer E, along with other products. The formation of these oligomers appeared to have resulted from some secondary condensations reactions. For example, B may have decomposed in the presence of a trace of lithium nitride, in accordance with eq 7, to yield such oligomers.

$$(C_2H_5O)_2SiC_3H_6NSi(CH_3)_2(OC_2H_5) \longrightarrow \text{B} \rightarrow [-SiC_3H_6N(OC_2H_5)-]_{n \geq 3} + (C_2H_5O)_2Si(CH_3)_3 \quad (7)$$

Trimer D was prepared in 26% yield by refluxing 3-aminopropyltriethoxysilane and hexamethylcyclotrisilazane under nitrogen with a trace of lithium nitride until no more ammonia generated over (eq 8).

$$(C_2H_5O)_3SiC_3H_6NH_2 + [(CH_3)_2SiNH]_3 \longrightarrow [-SiC_3H_6N(OC_2H_5)-]_{n \geq 3} + (C_2H_5O)_2Si(CH_3)_2 + NH_3 \quad (8)$$

Because of the slow evolution of ammonia and the low yield of A as well as high yield of ethoxytriphenylsilane obtained, it is believed that trimer D and tetramer E formed from the reaction of hexaphenyldisilazane and 3-aminopropyltriethoxysilane were not formed by

condensation of A, but by a series of displacement and condensation reactions as shown in eq 9 and 10.

$$(C_2H_5O)_3SiC_3H_6NH_2 + 2(C_6H_5)_3SiNHSi(C_6H_5)_3 \longrightarrow [(C_6H_5)_3SiNH)_2(C_2H_5O)SiC_3H_6NH_2 + 2(C_6H_5)_3SiOC_2H_5 \quad (9)$$

$$[(C_6H_5)_3SiNH]_2(C_2H_5O)SiC_3H_6NH_2 \longrightarrow \left[\begin{array}{c} OC_2H_5 \\ | \\ -SiC_3H_6N- \end{array}\right]_{n \geq 3} + (C_6H_5)_3SiNHSi(C_6H_5)_3 + NH_3 \quad (10)$$

An attempt to separate trimer D from the reaction mixture containing ethoxytriphenylsilane was unsuccessful. In view of the fact that Wannagat, *et al.*,[9] had converted silicon–oxygen compounds into silazanes by treating alkoxysilanes with alkali metal derivatives of amines, we used lithium nitride instead of the hexaphenyldisilazane in the reaction with 3-aminopropyltriethoxysilane and obtained trimer D in 30% yield. An attempt to isolate the tetramer E was unsuccessful.

Although evidence from elemental analysis and molecular weight determinations [obtained from mass spectrometry (387) and from vapor osmometry (384.28, 380.32)] are in agreement with the proposed structure

$$\left[\begin{array}{c} OC_2H_5 \\ | \\ -SiC_3H_6N- \end{array}\right]_3$$

D

for trimer D, the nmr spectrum of the compound is not as well defined as those of monocyclic compounds. The peaks arising from the ethoxy groups consist of two sets of triplets centered at δ 1.03 and 1.06, and two sets of quartets centered at δ 3.53 and 3.58, respectively. The anomalous observation is believed to result from the presence of asymmetric silicon atoms.

Further evidence for the proposed structure of the trimer D has been obtained from the following chemical reactions: (1) alcoholysis of trimer D; (2) alkylation and arylation of trimer D.

(1) Trimer D was found to react slightly with anhydrous ethanol. However, it gave a 79% yield of 3-aminopropyltriethoxysilane when allowed to react with ethanol in the presence of a catalytic amount of lithium ethoxide.

(2) Trimer D reacted readily with ethyllithium or phenyllithium (prepared from bromoethane or bromobenzene and lithium) to apparently form cyclotri(2-ethyl-1-aza-2-silacyclopentane) in 45% yield and cyclotri(2-phenyl-1-aza-2-silacyclopentane) in 64% yield.

Because of the unusual cyclic structures, the nmr spectra of the presumed cyclotri(2-ethyl-1-aza-2-silacyclopentane) and cyclotri(2-phenyl-1-aza-2-silacyclopentane) were found to be very complex. Attempts to analyze the spectra in detail were thus unsuccessful. Evidence for the proposed structures was based on elemental analyses, molecular weight determinations, and alcoholysis, the reaction of cyclotri(2-ethyl-1-aza-2-silacyclopentane) with ethanol in which 3-aminopropyldiethoxyethylsilane was the only isolable product. We believe that the corresponding product, 3-aminopropyldiethoxyphenylsilane, was also formed in the reaction of cyclotri(2-phenyl-1-aza-2-silacyclopentane) with ethanol. Evidence for its identity was obtained from a comparison of its ir and nmr spectra with that of its ethyl analog. A quantitative identification was not made owing to the following reasons. (1) The compound was not so stable as its ethyl analog. It could not be obtained pure even after several purifications by glpc. (2) When the sample was introduced into the mass spectrometer through a heated inlet system (240°), the highest peak in the mass spectrum occurred at *m/e* 207. A small molecular ion peak at *m/e* 253, in addition to the peak at *m/e* 207, was observed only when a special injection was made directly into the ion source chamber. It is unknown at the present time if the *m/e* peak corresponding to 207 is due to F (mol wt 207). If this is the case, the compound must be formed from decomposition in the mass spectrometer, because its presence is not indicated by its ir and nmr spectra.

$$C_2H_5O(C_6H_5)SiCH_2CH_2CH_2NH$$

F

Experimental Section

Reagent grade 3-aminopropyltriethoxysilane was purchased from Union Carbide Corp., New York, N. Y., hexamethylcyclotrisilazane from Peninsular ChemResearch Inc., Gainesville, Fla., and lithium nitride from Foote Mineral Co., Exton, Pa. All reagents were used without further purification. Hexaphenyldisilazane (mp 174–175°) was prepared by refluxing chlorotriphenylsilane and lithium nitride in THF solution for 48 hr and recrystallizing the product from absolute ethanol.

Analytical glpc's were run on a F & M Model 500 chromatograph using a 0.25 in. × 6 ft stainless steel column packed with 10% SE-30 on 60–80 Chromosorb W.

Elemental, mass (obtained on a CEC 21-110B mass spectrometer), and nmr spectral analyses (Varian A-56/60A spectrometer, operating at 60 Mc) were performed by the Analytical Branch, Air Force Materials Laboratory. Boiling points of all compounds reported are uncorrected.

1-(Triphenylsilyl)-2,2-diethoxy-1-aza-2-silacyclopentane.—A mixture of 3-aminopropyltriethoxysilane (9.4 g, 0.043 mol), hexaphenyldisilazane (17.0 g, 0.032 mol), and ammonium chloride (trace) was heated under nitrogen for 4 days. The gas generated from the reaction was periodically neutralized by standard HCl solution (2.17 *N*) to the methyl red end point and a total of 0.016 mol of ammonia was collected. After the reaction mixture was allowed to cool to room temperature, hexane (30 ml) was added. The insoluble hexaphenyldisilazane (3.0 g) was removed by filtration and identified by its ir spectrum and melting point. The filtrate was concentrated and vacuum distilled. The first fraction (15.6 g), bp 110–165° (0.06 mm), was identified by its ir spectrum as ethoxytriphenylsilane. One crystallization from hexane gave a white solid, mp 58–63° (lit.[10] mp 65°). The second fraction, bp 168–222° (0.06 mm), was a yellow liquid which was taken up in hexane and which afforded 0.61 g of 1-(triphenylsilyl)-2,2-diethoxy-1-aza-2-silacyclopentane upon cooling. Upon recrystallization from hexane the solid product gave white crystals, mp 99–101°.

Anal. Calcd for $C_{25}H_{31}NO_2Si_2$: C, 69.28; H, 7.16, N, 3.20; Si, 12.92; mol wt, 433. Found: C, 68.82, 69.16; H, 7.21, 7.02; N, 3.31, 3.15; Si, 12.82, 12.67; mol wt, 449, 452 (osmometry), 433 (mass spectrometry).

The residue from vacuum distillation was analyzed by mass spectrometry and found to contain compounds with *m/e* peaks of 304 [$(C_6H_5)_3SiOC_2H_5$], 433 (A), 387 (trimer D), and 516 (tetramer E) as well as other peaks for which assignment could not be made.

Attempted Synthesis of 1-(Triphenylsilyl)-2,2-diethoxy-1-aza-2-silacyclopentane.—A mixture of 1-(ethoxydimethylsilyl)-2,2-diethoxy-1-aza-2-silacyclopentane (11.1 g, 0.04 mol), ethoxytriphenylsilane (12.2 g, 0.04 mol), and ammonium bromide (trace) was heated to reflux for 24 hr. No apparent reaction was observed. The mixture, after cooling, was heated again to

(9) U. Wannagat, P. Geymeyer, and G. Sehreiner, *Angew. Chem., Int. Ed. Engl.*, **3** (2), 135 (1964).

(10) C. Eaborn, "Organosilicon Compounds," Butterworths, London, 1960, p 311.

reflux with a trace amount of lithium nitride. The distillate was periodically removed by means of a Claisen head take-off adapter. The reaction mixture was allowed to reflux for an additional 16 hr, after which time a total of 4.7 g (80%) of diethoxydimethylsilane was collected. From the residue in the flask, only ethoxytriphenylsilane and hexaphenyldisiloxane were isolated.

1-(Ethoxydimethylsilyl)-2,2-diethoxy-1-aza-2-silacyclopentane.—A mixture of 3-aminopropyltriethoxysilane (96.5 g, 0.44 mol), hexamethylcyclotrisilazane (32.0 g, 0.15 mol), and ammonium bromide (0.062 g) was heated to reflux for 3 days. The ammonia generated from the reaction was neutralized periodically with standard hydrochloric acid solution (2.02 *N*). In the first 4 hr. 0.40 mol of ammonia was collected and a total of 0.43 mol (100%) was obtained at the end of the reaction. The reaction mixture was first distilled at atmospheric pressure to yield 10.0 g of diethoxydimethylsilane, bp 110° (lit.[10] bp 113–114°), and further identified by its ir spectrum. Vacuum distillation of the remaining substance gave the expected compound (60.0 g, 49%), bp 70–73° (5 mm). Glpc indicated only one component: nmr (neat) δ 0.00 (s, $SiCH_3$), 0.41 (t, $SiCH_2$), 1.04 (t, chain OCH_2CH_3), 1.07 (t, ring OCH_2CH_3), 1.66 (quintet, CH_2CH_2N), 2.85 (t, NCH_2), 3.56 (quartet, chain OCH_2), 3.64 (quartet ring OCH_2)

Anal. Calcd for $C_{11}H_{27}NO_3Si_2$: C, 47.65; H, 9.74; N, 5.05; Si, 20.22; mol wt, 277. Found: C, 48.01, 47.96; H, 9.89, 9.86; N, 4.92, 4.76; Si, 19.59, 19.97; mol wt, 277 (mass spectrometry).

A second fraction was obtained as a viscous liquid (21 g), bp 96–130° (5 mm). Glpc indicated that it was a mixture of a number of compounds. The major component isolated by preparative glpc was identified as 1-(ethoxydimethylsilyl)-2-ethoxy-2-(2′-diethoxy-1′-aza-2′-silacyclopentane)-1-aza-2-silacyclopentane (M): nmr (neat) δ 0.00 (s 6, $SiCH_3$), 0.22–0.57 (m, 4, $SiCH_2$), 0.90–1.18 (t of t, 12-OCH_2CH_3), 1.32–1.75 (m, 4, -CH_2CH_2N), 2.63–2.92 (m, 4 NCH_2), 3.30–3.80 (t of q, 8, OCH_2).

Anal. Calcd for $C_{16}H_{38}N_2O_4Si_3$: C, 47.29; H, 9.36; N, 6.90; Si, 20.68; mol wt, 406. Found: C, 46.92; H, 8.80; N, 6.83; Si, 20.30; mol wt, 406 (mass spectrometry)

In another similar experiment, one component from the mixture, isolated by glpc, was identified as 1-(ethyoxydimethylsiloxydimethylsilyl)-2,2-diethoxy-1-aza-2-silacyclopentane, $(C_2H_5O)_2SiC_3H_6NSi(CH_3)_2OSi(CH_3)_2(OC_2H_5)$.

Anal. Calcd for $C_{13}H_{33}NO_4Si_3$: C, 44.44; H, 9.68; N, 3.98; Si 23.93; mol wt, 351. Found: C, 44.33, 44.49; H, 9.51, 9.56; N, 4.77, 4.77; Si, 23.51, 23.28; mol wt, 351 (mass spectrometry).

The higher boiling residue from these reactions was vacuum distilled and analyzed by mass spectrometry, giving the *m/e* peak shown in Table I.

Cyclotri(2-ethoxy-1-aza-2-silacyclopentane). A. From the Reaction of 3-Aminopropyltriethoxysilane and Hexamethylcyclotrisilazane.—A mixture of 3-aminopropyltriethoxysilane (93.0 g, 0.42 mol), hexamethylcyclotrisilazane (31.0 g, 0.14 mol), and lithium nitride (0.53 g, 0.015 mol) was heated under nitrogen to initiate reaction. The ammonia generated from the reaction was periodically neutralized by standard HCl solution to the methyl red end point. In 5 days, 0.43 mol of ammonia was collected. At the end of ammonia generation, the reaction mixture was distilled under nitrogen to remove the diethoxydimethylsilane (58 g, 93.5%), bp 110–115° (lit.[11] bp 113–114°). The residue, upon vacuum distillation, gave 14.0 g (26%) of the expected compound, bp 120–140° (0.05 mm). A sample for analysis was purified by preparative glpc: nmr (neat) δ 0.3–0.7 (t, 2, $SiCH_2$–), 0.8–1.3 (d of t, 3, $-CH_3$), 1.4–2.1 (m, 2, $-CH_2$–), 2.5–3.2 (m, 2, $-CH_2N$), 3.3–4.0 (d of quartet, 2, $-OCH_2$–).

Anal. Calcd for $C_{15}H_{33}N_3O_3Si_3$: C, 46.51; H, 8.53; N, 10.85; Si, 21.71; mol wt, 387. Found: C, 46.41, 46.04; H, 9.19, 8.81; N, 10.59, 10.56; Si, 21.55, 21.47; mol wt, 387 (mass spectrometry), 384.28, 380.32 (osmometry).

B. From the Reaction of 3-Aminopropyltriethoxysilane and Lithium Nitride.—Into 3-aminopropyltriethoxysilane (151.0 g, 0.68 mol) warmed to about 50° in a three-necked flask equipped with mechanical stirrer, condenser, and nitrogen inlet and outlet tubes, was added slowly 14.3 g (0.41 mol) of lithium nitride. Reaction took place with generation of heat and ammonia (not collected). From time to time the external heat source had to be removed to ensure a smooth reaction. After complete addition, the reaction mixture was heated to reflux for 2 hr, then cooled to room temperature. The lithium ethoxide was precipitated by addition of 250 ml of xylene and removed by filtration under nitrogen. The filtrate was distilled at atmospheric pressure to remove the solvent. Vacuum distillation gave 28.0 g of the desired compound, bp 115–138° (0.05 mm). Redistillation under vacuum gave 24.0 g (30%) of pure sample. The molecular weight [387 (mass spectrometry)], ir spectrum, and glpc retention time were identical with those of the sample obtained from reaction A.

Condensation Reaction of 1-(Ethoxydimethylsilyl)-2,2-diethoxy-1-aza-2-silacyclopentane and Lithium Nitride.—1-(Ethoxydimethylsilyl)-2,2-diethoxy-1-aza-2-silacyclopentane (29 g) and lithium nitride (0.0050 g) were heated together under nitrogen overnight. The reaction mixture, after cooling to room temperature, was vacuum distilled. There was obtained 14.2 g of starting material and a small amount of trimer D, identified by its glpc retention time, which was identical with that of an authentic sample.

Alcoholysis of Trimer D.—A mixture of anhydrous ethanol (50 ml) and a few drops of benzene was distilled under nitrogen until the distillation temperature reached 78°. After the alcohol was cooled to room temperature, trimer D (11.0 g) was added and the reaction mixture was heated to reflux for 10 hr. Upon vacuum distillation of the mixture 4.8 g (25%) of 3-aminopropyltriethoxysilane was obtained.

In another similar experiment, a small piece of lithium was added to the alcohol before the addition of 12.5 g of trimer D. Upon refluxing the mixture of 1 hr and vacuum distillation there was obtained 17.0 g (79%) of pure 3-aminopropyltriethoxysilane whose identity was confirmed by its ir spectrum and glpc retention time.

Arylation of Trimer D.—Into a mixture of trimer D (20.6 g, 0.05 mol), 250 ml of anhydrous diethyl ether, and shredded lithium (2.24 g, 0.32 g-atom) was added slowly an excess of bromobenzene (35.0 g). The reaction took place with generation of heat and proceeded smoothly during the addition (3 hr). Lithium salts were precipitated by addition of 200 ml of benzene and removed by filtration under nitrogen. After removal of the benzene, the filtrate was taken up in 100 ml of petroleum ether (bp 30–60°) and cooled. There was obtained 13.7 g of cyclotri(2-phenyl-1-aza-2-silacyclopentane), mp 129–131°. Concentration of the mother liquid gave an additional 1.8 g of the compound for a total yield of 64%. Upon recrystallization from hexane an analytical sample, mp 133°, was obtained: nmr ($CDCl_3$) δ 0.5–1.3 (m, 2, $SiCH_2$–), 1.4–2.2 (m, 2, $SiCH_2CH_2$–), 2.4–3.6 (m, 2, NCH_2), 6.9–8 (m, 5, SiC_6H_5).

Anal. Calcd for $C_{27}H_{33}N_3Si_3$: C, 67.08; H, 6.83; N, 8.70; Si, 17.39; mol wt, 483. Found: C, 67.20, 67.03; H, 6.76, 6.86; N, 8.88, 8.90; Si, 17.31, 17.29; mol wt, 483 (mass spectrometry).

Alcoholysis of Cyclotri(2-phenyl-1-aza-2-silacyclopentane).—Cyclotri(2-phenyl-1-aza-2-silacyclopentane) (5.09 g) was refluxed in excess anhydrous ethanol under nitrogen for 24 hr. After removal of excess alcohol by distillation the residue was vacuum distilled. A fraction (5.7 g) which distilled over at 110° (2 mm) was found by glpc to exhibit three peaks: a small one for a low-boiling substance, a broad shoulder, and a large major peak, the latter two overlapping. Repeated glpc did not provide any improvement in the resolution: nmr (neat) δ 0.6–1.8 (m, 9.4, $SiCH_2CH_2$–, $-NH_2$, and $-CH_3$), 2.62 (t, 2, $-CH_2N$), 3.87 [q, 2.7 (theoretical, 4, $-OCH_2$–), 7–7.9 (m, 5, C_6H_5).

Anal. Calcd for $C_{13}H_{23}NO_2Si$: C, 61.66; H, 9.09; N, 5.53; Si, 11.06; mol wt, 253. Found: C, 61.43, 61.52; H, 8.70, 8.96; N, 5.53, 5.53; Si, 12.12, 11.96; mol wt, 265.4, 268.5 (osmometry); *m/e* 253 (weak), 207 (strong).

The liquid product was hydrolyzed in a mixed solvent (benzene, ethyl alcohol, and ammonium hydroxide). After removal of the solvent by distillation, a transparent gluelike substance was obtained.

The nmr spectrum of the substance had four broad peaks [phenyl H(5) and three methylene H(2:2:2)] and a sharp peak for amino-H which corresponded to the structure of 3-aminopropylphenylpolysiloxane, $[NH_2C_3H_6(C_6H_5)SiO]_n$.

Anal. Calcd for $(C_9H_{13}NOSi)_n$: C, 60.34; H, 7.26; N, 7.82; Si, 15.64. Found: C, 59.36, 59.43; H, 7.11, 6.93; N, 8.02, 8.13; Si, 15.42, 15.53.

Alkylation of Trimer D.—1-Bromoethane instead of bromobenzene was used in the above reaction (trimer D, 14 g, 0.036 mol). After the removal of lithium salts, the filtrate was concentrated and vacuum distilled. A fraction, 5.5 g (45%), dis-

tilled at 136–156° (0.1 mm) and was shown by glpc to be a pure sample of the desired compound: nmr (neat) δ 0.3–1.2 (m, 7, C_2H_5–$SiCH_2$–), 1.4–2.1 (m, 2, –CH_2–), 2.6–3.2 (m, 2, NCH_2–).

Anal. Calcd for $C_{15}H_{33}N_3Si_3$: C, 53.10; H, 9.73; N, 12.39; Si, 24.77; mol wt, 399. Found: C, 52.97; H, 10.15; N, 11.86; Si, 25.13; mol wt, 339 (mass spectrometry).

Alcoholysis of Cyclotri(2-ethyl-1-aza-2-silacyclopentane).—Cyclotri(2-ethyl-1-aza-2-silacyclopentane) (0.81 g) was refluxed with excess anhydrous ethanol overnight. A fraction, 0.82 g (56%), distilled at 54° (0.1 mm) and was shown by glpc to be pure 3-aminopropyldiethoxylethylsilane: nmr (neat) δ 0.1–1.6 (m, 10.4, $SiCH_2CH_2$–, $SiCH_2CH_3$, and $-NH_2$), 0.95, (t, 6, OCH_2CH_3), 2.37 (t, 2, NCH_2–), 3.49 (q, 4, OCH_2).

Anal. Calcd for $C_9H_{23}NO_2Si$: C, 52.68; H, 11.22; N, 6.83; mol wt, 205. Found: C, 53.08, 53.14; H, 11.54, 11.69; N, 6.91, 6.88; mol wt, 205 (mass spectrometry).

Registry No.—1-(Triphenylsilyl)-2,2-diethoxy-1-aza-2-silacyclopentane, 32284-27-8; 1-(ethoxydimethylsilyl)-2,2-diethoxy-1-aza-2-silacyclopentane, 32284-28-9; trimer D, 32974-82-6; $(C_2H_5O)_2SiC_3H_6NSi(CH_3)_2OSi(CH_3)_2(OC_2H_5)$, 32974-83-7; cyclotri(2-ethoxy-1-aza-2-silacyclopentane, 32974-84-8; cyclotri(2-phenyl-1-aza-2-silacyclopentane, 32974-85-9; 3-aminopropyldiethoxyphenylsilane, 32974-86-0; $[NH_2C_3H_6(C_6H_5)SiO]_n$, 33029-43-5; cyclotri(2-ethyl-1-aza-2-silacyclopentane), 32974-87-1; 3-aminopropyldiethoxylethylsilane, 20723-29-9.

Acknowledgment.—We wish to thank Dr. Daniel S. Dyer, Mr. Lee D. Smithson, and Miss M. T. Ryan, Analytical Branch, Materials Physics Division, Air Force Materials Laboratory, for the nmr and mass spectral measurements, and Dr. Harold Rosenberg of this laboratory for assisting in the revisions of this manuscript.

The Preparation and Reactions of Some 2-Keto-2*H*-pyrido[1,2-*a*]pyrimidines

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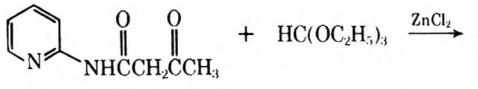
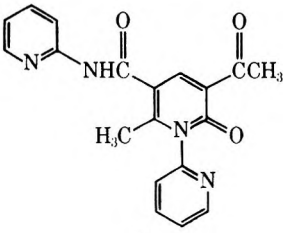
Received August 31, 1971

The title compounds are obtained by the reaction of 2-acetoacetylaminopyridines with dimethylformamide dimethyl acetal yielding *N*-(2-pyridyl)-2-acetyl-3-dimethylaminoacrylamides, followed by ring closure with acetic anhydride. The title compounds revert to the starting acrylamides on reaction with dimethylamine; other amines also react with ring opening. The zinc chloride catalyzed reaction with acetoacetamides and the base-catalyzed reaction with acetoacetic esters yield substituted 2-pyridones.

Recently[1] we found that the reaction of 2-acetoacetylaminopyridines (*e.g.*, **1**) with triethyl orthoformate and zinc chloride yields substituted 2-pyridones such as **2**. To explain this result we proposed a mechanism

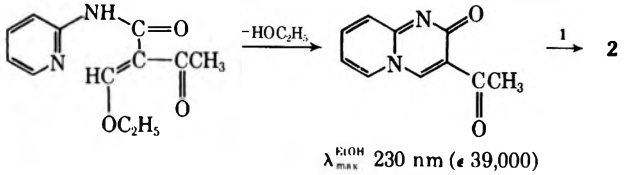


1



2

which involved the formation of a 2-keto-2*H*-pyrido[1,2-*a*]pyrimidine (**3**) as an intermediate. If **3** really



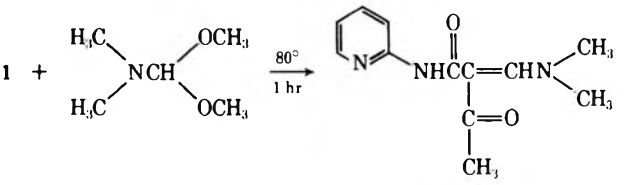
λ_{max}^{EtOH} 230 nm (ε 39,000)
355 (4500)

3

is an intermediate in the formation of products such as **2**, it should be quite reactive and form **2** on reaction with **1**. The present work was undertaken to prove this point by isolating **3**.

(1) M. C. Seidel, G. C. Van Tuyle, and W. D. Weir, *J. Org. Chem.*, **35**, 1475 (1970).

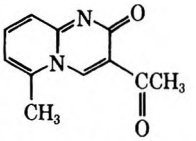
Since the reaction of **1** with triethyl orthoformate does not yield the expected ethoxymethylene derivative, the reaction of **1** with dimethylformamided imethyl acetal was used to obtain **4** in 59% yield. Similar



4

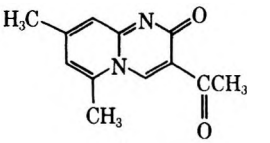
results were obtained with other acetoacetylaminopyridines and a carbethoxyacetylaminopyridine (see Table I).

Brief boiling of **4** in acetic anhydride gave an 89% yield of **3** which crystallized out of the hot reaction mixture. A total of five (see Table II) 2-keto-2*H*-pyrido[1,2-*a*]pyrimidines were prepared. Of these, **5** and **6** are of special interest, since they are the product

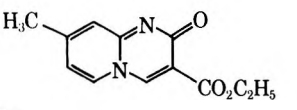


λ_{max}^{EtOH} 226 nm (ε 29,000), 363 (3800)

5



6

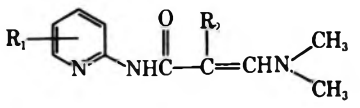


λ_{max}^{EtOH} 231 nm (ε 55,000), 341 (5100)

7

TABLE I[a]

N-(2-PYRIDYL)-3-DIMETHYLAMINOACRYLAMIDES

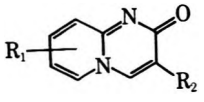


Compd	R_1	R_2	Yield, %	Mp, °C
4	H	$-C(=O)-CH_3$	59	172–174
12	4-CH_3	$-CO_2C_2H_5$	70	84–86
22	6-CH_3	$-C(=O)-CH_3$	47	148–148.5
23	5-Cl	$-C(=O)-CH_3$	54	172.5–173.5
24	4,6-$(CH_3)_2$	$-C(=O)-CH_3$	68	159–161

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

TABLE II[a]

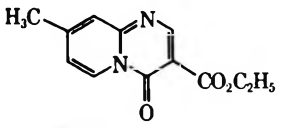
2-KETO-2*H*-PYRIDO[1,2-*a*]PYRIMIDINES



Compd	R_1	R_2	Yield, %	Mp, °C
3	H	$-C(=O)-CH_3$	89	221–222 dec
5	6-CH_3	$-C(=O)-CH_3$	49	194–196 dec
6	6,8-$(CH_3)_2$	$-C(=O)-CH_3$	32	188–189 dec
7	8-CH_3	$-CO_2C_2H_5$	66	220–223 dec
25	7-Cl	$-C(=O)-CH_3$	60	231–232 dec

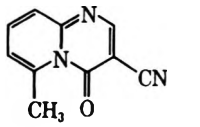
[a] Satisfactory analytical data (±0.3% for C, H, N) were reported for all compounds in this table. Ed.

of a ring closure onto a pyridine ring nitrogen in the presence of a 6 substituent (for some of the few other examples see ref 2–4). A compound with structure **7** has already been described in the literature[3] as having a melting point (164°) different from that of our sample (220–223° dec). The present assignment, however, is supported by the fact that **7** was converted back to the starting acrylamide (*i.e.*, 4-CH_3 **4**) by mild treatment with dimethylamine. Antaki's compound most probably was the isomeric 4-keto compound **8**, mp 172°.[5] Comparison of uv spectra lends support to this view. The spectra of **8** (prepared according to Lappin[5]) and **9** (reported by Antaki[3]) are similar in shape and relative height of the peaks. The spectra



λ_{max}^{EtOH} 216 nm (ε 30,000)
364 (31,000)

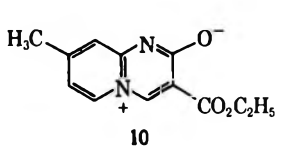
8



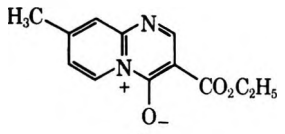
λ_{max}^{EtOH} 220 nm (ε 12,000)
365 (20,000)

9

of the 2-keto compounds **3**, **5**, and **7** are different in that the absorption at 341–365 nm is much weaker. This band can be considered evidence[6] for the contribution of the zwitterionic structures **10** and **11** corresponding



10

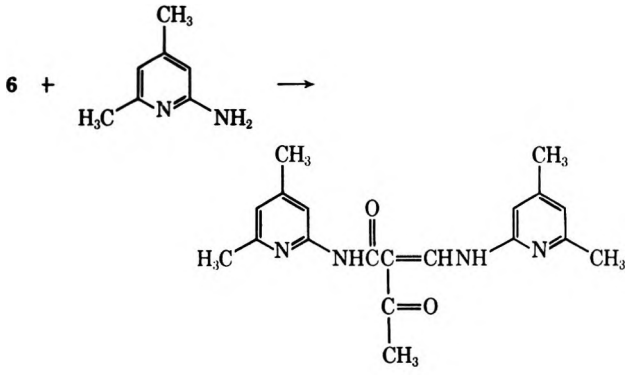


11

to **7** and **8**. The contribution of **10** to the ground state of **7** can be assumed to be less than that of **11** to the ground state of **8** since the charge separation energy should be greater for **10**. Thus, the band at 341–365 nm should be weaker in the spectra of the 2-keto compounds, which was found to be the case.

The 2-keto-2*H*-pyrido[1,2-*a*]pyrimidines (such as **3**) react with amines with ring opening. Dimethylamine yields the starting acrylamides (such as **4**) in yields of 85–96%.

The reaction of 2-amino-4,6-dimethylpyridine with **6** yielded **13**. As pointed out above, the 2-keto-2*H*-



13

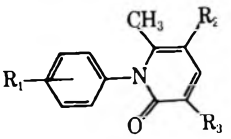
pyrido[1,2-*a*]pyrimidines were thought to be intermediates in the reaction of 2-acetoacetylaminopyridines with triethyl orthoformate and $ZnCl_2$.[1] In order to test this postulate, the 2-keto-2*H*-pyrido[1,2-*a*]pyrimidines were allowed to react with 2-acetoacetylaminopyridines in ethanol with $ZnCl_2$ as catalyst.

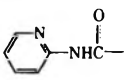
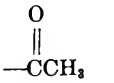
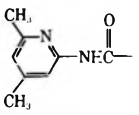
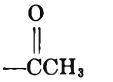
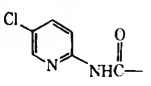
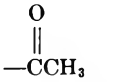
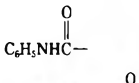
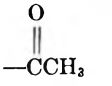
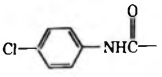
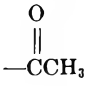
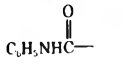
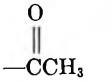
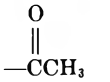
This reaction yielded the same condensed products (type **2**, **15**, and **16**; see Table III) as in our previous work[1] except in better yields, with shorter reaction times (1 hr *vs.* 3 hr), and in higher purity. By comparison, the reaction of **14** with triethyl orthoformate and $ZnCl_2$ had given a mixture of **13** and **15** in poor yields.[1]

(2) M. Shur and S. S. Israelstam, *J. Org. Chem.*, **33**, 3015 (1968).
(3) H. Antaki, *J. Amer. Chem. Soc.*, **80**, 3066 (1958).
(4) G. R. Lappin, *J. Org. Chem.*, **26**, 2350 (1961).
(5) G. R. Lappin, *J. Amer. Chem. Soc.*, **70**, 3348 (1948).
(6) R. Adams and I. J. Pachter, *ibid.*, **74**, 5491 (1952).

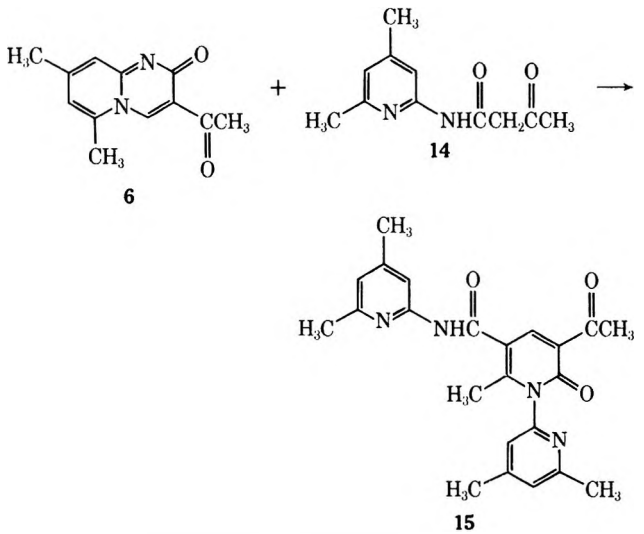
TABLE III[a]

1-PYRIDYL-2-PYRIDONES



Compd	R_1	R_2	R_3	Yield, %	Mp, °C
2	H			100	228–230
15	4,6-$(CH_3)_2$			89	248–252
16	H			90	232–234
17	H			80	233.9
18	6-CH_3			86	229.5–231.5
19	4-CH_3		$C_2H_5O_2C$–	72	260–261
20	H	*tert*-$C_4H_9O_2C$–		95	172–173.5
21	H	$C_2H_5O_2C$–		87	152.7

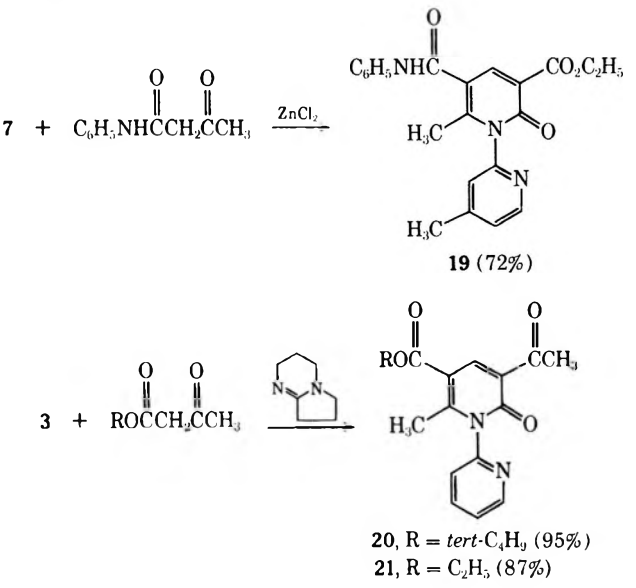
[a] Satisfactory analytical data (±0.3% for C, H, N) were reported for all compounds in the table except **2**, **15**, **17**, and **18**: Ed. The latter were shown by mixture melting point determination and comparison of the ir spectra to be identical with compounds of the same structure referred to in ref 1.



6 **14** **15**

Mixed condensed products were obtained in equally high yields in the reaction of 2-keto-2*H*-pyrido[1,2-*a*]-pyrimidines with acetoacetanilides (see also compounds **17** and **18** in Table III). Similarly high yields were obtained in base-catalyzed reactions with acetoacetic esters.

Compound **20** was used to independently synthesize **17**. Acid hydrolysis of **20** yielded the corresponding carboxylic acid, which without isolation was transformed into the mixed anhydride with triethylamine and ethyl chloroformate. Reaction of the crude mixed anhydride with aniline gave **17** in 43% overall yield.



19 (72%)

20, R = *tert*-C_4H_9 (95%)
21, R = C_2H_5 (87%)

Experimental Section

All melting points are uncorrected; those given as a single value were taken on a Mettler FPI apparatus. The microanalyses were carried out by Mr. C. W. Nash and his associates. For the preparation of the acetoacetylaminopyridines see ref 1.

2-Carbethoxyacetylamino-4-methylpyridine (26).—To an ice-cooled solution of 39 g (0.36 mol) of 2-amino-4-methylpyridine and 36 g (0.36 mol) of triethylamine in 250 ml of toluene was added 54 g (0.36 mol) of carbethoxyacetyl chloride, slowly and with stirring. After standing overnight, the reaction mixture was washed with water and the organic layer was dried and evaporated. The residue was recrystallized from methylcyclohexane to yield 42 g (52%) of **26**, mp 89.5°.

Anal. Calcd for $C_{11}H_{14}N_2O_3$: C, 59.46; H, 6.35; N, 12.61. Found: C, 59.17; H, 6.54; N, 12.70.

***N*-(4-Methyl-2-pyridyl)-2-carbethoxy-3-dimethylaminoacrylamide (12).**—See also Table I; the other compounds in this table were prepared in analogous fashion.

A solution of 40 g (0.172 mol) of **26** and 36 g (0.3 mol) of dimethylformamide dimethyl acetal in 200 ml of 1,2-dimethoxyethane was refluxed for 1.5 hr. The solvent was then removed on a rotatory evaporator and the residue was recrystallized from methylcyclohexane, yield of **12** 33 g.

2-Keto-3-acetyl-2*H*-pyrido[1,2-*a*]pyrimidine (3).—See also Table II; the other compounds in Table II were prepared similarly.

A slurry of 10 g (0.045 mol) of **4** in 70 ml of acetic anhydride was quickly heated to a boil and kept gently boiling for 10 min, during which time the starting material dissolved and, later, the product precipitated. After cooling, the product was separated, washed with 2-propanol, and dried, yield 7.5 g of **3**. All the compounds in Table II were appreciably soluble in water.

1-(2-Pyridyl)-3-acetyl-6-methyl-2-pyridone-5-(5-chloro-2-pyridyl)carboxamide (16).—See also Table III; compounds **2**, **15**, **17**, **18**, and **19** in this table were prepared in analogous fashion.

A mixture of 4.7 g (0.025 mol) of **3**, 10.6 g (0.05 mol) of 2-acetoacetylamino-5-chloropyridine,[1] and 200 mg of $ZnCl_2$ in 150 ml of ethanol was refluxed for 1 hr. The starting materials soon dissolved and the product began to crystallize. The mixture was cooled, and the product was filtered and recrystallized from methylcellosolve, yield 8.6 g of **16**.

***N*-(4,6-Dimethyl-2-pyridyl)-2-acetyl-3-(4,6-dimethyl-2-pyridyl)-aminoacrylamide (13).**—A solution of 3 g (0.014 mol) of **6** and 2.4 g (0.02 mol) of 2-amino-4,6-dimethylpyridine in 100 ml of ethanol was refluxed for 1 hr. The mixture was then cooled, and the product was filtered off and dried, yield 3.5 g (74%) of **13**, mp 226–227°. By mixture melting point and ir spectra, this material was identical with compound **7** of ref 1.

1-(2-Pyridyl)-3-acetyl-5-carbo-*tert*-butoxy-6-methyl-2-pyridone (20).—See also Table III; compound **21** in this table was prepared in the same way.

A slurry of 9.4 g (0.05 mol) of **3**, 16 g (0.1 mol) of *tert*-butyl acetoacetate, and 0.5 g of 1,5-diazabicyclo[4.3.0]-5-nonene in 200 ml of dimethylformamide was stirred at room temperature for 30 min. The starting material had dissolved to form a red solution. The solution was poured into excess water, and the product was filtered off, washed with water, and dried, yield 15.5 g of **20**. Recrystallization from 2-propanol did not raise the melting point.

1-(2-Pyridyl)-3-acetyl-6-methyl-2-pyridone-5-carboxylic Acid Anilide (17). Independent Synthesis.—A solution of 8.0 g (0.024 mol) of **20** in 50 ml of 6 *N* HCl was heated on a steam bath for 15 min and then left standing at room temperature for 1 hr. The solvent was then removed in a rotatory evaporator and the product was dried, yielding 5.5 g (0.02 mol) of the HCl salt of the carboxylic acid corresponding to **20**. This material was slurried in 100 ml of benzene, and 6 g (0.06 mol) of triethylamine was added. Most of the solid dissolved. Then, while applying ice cooling, 2.2 g (0.02 mol) of ethyl chloroformate was added. After 30 min at room temperature, 1.86 g (0.02 mol) of aniline was added and the mixture was refluxed for 30 min. Then water was added, and the benzene layer was separated, dried, and evaporated. The residue was recrystallized from ethanol, yield 3 g (43%), mp 235.1°; on admixture of **17**, the material melted at 235.2°. The ir spectra were identical.

Registry No.—**2**, 23600-24-0; **3**, 33068-07-4; **4**, 33015-41-7; **5**, 33015-42-8; **6**, 33015-43-9; **7**, 33015-44-0; **12**, 33068-08-5; **15**, 23600-27-3; **16**, 33015-46-2; **17**, 23600-41-1; **18**, 23646-60-8; **19**, 33015-49-5; **20**, 33015-50-8; **21**, 33015-51-9; **22**, 33015-52-0; **23**, 33068-09-6; **24**, 33015-53-1; **25**, 33015-54-2; **26**, 33015-56-4.

Acknowledgment.—I should like to gratefully acknowledge the encouragement of this work by Dr. C. L. Levesque, Rohm and Haas Company.

Relative Rates of N-Methylation of Ortho-Substituted Pyridines. Steric and Electronic Effects

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Received June 29, 1971

Relative rates of N-methylation of eleven 2-substituted and two 2,6-disubstituted pyridines by methyl iodide in DMSO at 23° were obtained by nmr methods. Rate constants relative to pyridine for the monosubstituted compounds are NH_2, 1.23; CH_3, 0.38; C_2H_5, 0.17; $C_6H_5CH_2$, 0.081; CO_2CH_3, 0.0084; CH_3CONH, 0.0082; Cl, 0.0039; Br, 0.0039; 2-C_5H_4N, 0.0026; and CN, 0.0022. Results for the disubstituted pyridines are CH_3,NH_2, 0.050; and $(CH_3)_2$, 0.023. Kinetic results are only poorly correlated with pK_a values. It is suggested that steric effects are superimposed on electronic effects in the N-methylation reactions and that steric effects can be surprisingly constant.

Our understanding of the effects of ortho substituents on chemical equilibria and reactivity has undergone a recent and profound change. It was long held that steric effects could and often did influence reactions at ortho positions in a nonadditive way. However, in the absence of steric and hydrogen-bonding factors, electronic effects of ortho groups were expected to be proportional to those of para substituents.[2,3]

Charton has challenged this view. He has employed a multiparameter equation to correlate all the known sets of ortho substituent constants.[4] Except for some very bulky groups and those capable of intramolecular hydrogen bonding, previously defined ortho substituent constants have been expressed in terms of inductive and resonance components which often are not related to those for para or even meta groups. Steric effects were said to be absent or constant.[4]

Of the series of compounds statistically examined by Charton, all are monosubstituted and nearly all have the geometry given by I where G is the ortho substituent and Y is a reactive center such as CO_2R, CN, OH, and NH_3^+.

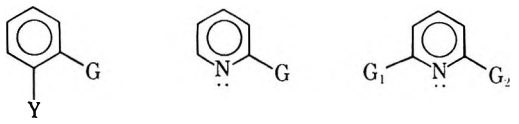
(1) On leave from LaTrobe University, Melbourne, Australia.

(2) L. P. Hammett, "Physical Organic Chemistry," McGraw-Hill, New York, N. Y., 1940, pp 204–207.

(3) R. W. Taft, Jr., in "Steric Effects in Organic Chemistry," M. S. Newman, Ed., Wiley, New York, N. Y., 1956, Chapter 13.

(4) For a list of references, see M. Charton, *J. Org. Chem.*, **36**, 882 (1971); *Prog. Phys. Org. Chem.*, **8**, 235 (1971).

We felt it desirable to examine structures where the substituent and reactive center have a different geometrical relationship. The relative rates of N-methylation of a series of 2-substituted (II) and 2,6-disubstituted pyridines (III) by methyl iodide in dimethyl sulfoxide (DMSO) were obtained. Our results provide the most extensive set of rate data yet reported for ortho-substituted pyridines.



I II III

The use of II and III as nucleophiles is extensive but G almost always is an alkyl group. It has been said that these nucleophiles exhibit steric effects in their reactions with electrophiles, including hydrogen,[5,6] saturated[3,7-12] and carbonyl carbon,[13] and phosphorus.[14] However, the dissociation constants, K_a, of a wide variety of ortho-substituted pyridines, including many with alkyl groups, are said to be free of the influence of steric effects.[4,7,15] Our purpose was to determine the relative importance of steric and electronic effects on the rates of reaction of II and III with methyl iodide.

Results

Relative rates of N-methylation of 2-substituted and 2,6-disubstituted pyridines as well as a few quinolines were obtained by competition methods. Pairs of heterocycles were allowed to compete for methyl iodide in dimethyl sulfoxide (DMSO) at 23°. Relative rate constants were obtained from the product ratios, as determined by nmr analysis of the *N*-methyl product peaks. Three different methods of analysis were employed.

In the first a deficiency of methyl iodide was utilized and the product ratio was determined when all of this reactant had been consumed.[16] This method was not employed with the less reactive pyridines, owing to side reactions.

When the substrates were about 100 times less reactive than pyridine, a significant amount of the methyl iodide reacted with the DMSO.[17] Two variations of the competition method then were followed. The second method involved determining the product ratio after small amounts of the heterocycles had reacted. The rate constant ratio was calculated from a knowledge of the initial concentration ratio of the heterocyclic reactants, $[\text{Het}]_0$, and the product ratio (eq 1). This essentially is the initial rate method. Whereas

$$\frac{k_1}{k_2} \cdot \frac{[\text{Het}_1]_0}{[\text{Het}_2]_0} \approx \frac{[\text{CH}_3\text{Het}_1]}{[\text{CH}_3\text{Het}_2]} \quad (1)$$

in the initial rate method often only 1–2% of a product is allowed to form before a product analysis is made, larger amounts of product were allowed to form in our experiments in order to provide strong nmr signals. In the results reported here, the error introduced by conversions as large as 25% is only on the order of the error in the nmr measurements, ~4%.

A third variation involved determining the product concentration as a function of time. Rate constant ratios then were calculated using a standard, integrated rate expression (eq 2). This method was

$$\frac{k_1}{k_2} = \frac{\log ([\text{Het}_1]/[\text{Het}_2]_0)}{\log ([\text{Het}_2]/[\text{Het}_2]_0)} \quad (2)$$

employed in a competition involving 2-chloro- and 2-carboxymethylpyridine where >50% product was formed. The rate constant ratio determined at various stages of the reaction agreed to ±10% and this average value agreed with that given by the product ratio early in the reaction to ±10%. Note that for the latter two methods, unlike the first, a knowledge of the methyl iodide concentration is not necessary. Equation 2 is an exact solution and applies generally.

Rate constant ratios for 13 pyridines and 2 quinolines are given in Table I. These values are based on the several competition standards indicated. Using these data and eliminating the comparison heterocycle, rate constant ratios, k^G/k^H, with pyridine as the standard are obtained. The uncertainty in k^G/k^H is estimated to be about 6–10%. No results were obtained for 2-methoxypyridine, owing to product instability.[18]

A control experiment showed that only a negligible amount of hydrolysis of N-methylated 2-bromopyridine to *N*-methylpyridone took place under the conditions of the competition experiment. A small amount of water added to a reaction mixture following N-methylation was without effect over 24 hr. The ring protons of *N*-methylpyridone served as a sensitive test for this material. Thus, residual water in the DMSO has no influence on the competition constant.

Since oxotrimethylsulfonium iodide (methylated DMSO, τ 6.0) is present in some of the reactions, a check was made to determine whether this material would compete with methyl iodide as an N-methylating agent. The methylated DMSO failed to give a significant amount of N-methylated methyl 2-pyridinecarboxylate. It seems likely that other pyridines are not N-methylated by this reagent in the presence of the more reactive methyl iodide.

Our k^{Br}/k^H value of 0.0039 for 2-bromopyridine is similar to the value of 0.0031 (25°, nitrobenzene) derived from other studies[7,12] where rate constants rather than rate constant ratios were obtained. However, our results indicate that 2-chloro- and 2-bromopyridine have about the same reactivity and the earlier report indicated that the chloro is about twice as reactive as the bromo compound.[12] However, the chloro to ester rate constant ratio we obtained indirectly using 3-

(5) F. Covitz and F. H. Westheimer, *J. Amer. Chem. Soc.*, **85**, 1773 (1963).
(6) E. S. Lewis and L. H. Funderburk, *ibid.*, **89**, 2322 (1967).
(7) For a summary of extensive work and a list of references, see H. C. Brown, *J. Chem. Soc.*, 1248 (1956); *J. Chem. Educ.*, **36**, 424 (1959).
(8) R. F. Hudson and R. J. Withey, *J. Chem. Soc.*, **41**, 3513 (1964).
(9) N. Tokura and Y. Kondo, *Bull. Chem. Soc. Jap.*, **37**, 133 (1964).
(10) J. Packer, J. Vaughan, and E. Wang, *J. Amer. Chem. Soc.*, **80**, 905 (1958).
(11) K. Clarke and K. Rothwell, *J. Chem. Soc.*, 1885 (1960).
(12) G. Coppens, F. Declereck, C. Gillet, and J. Nasielski, *Bull. Soc. Chim. Belg.*, **72**, 25 (1963).
(13) A. R. Butler and V. Gold, *ibid.*, 4362 (1961).
(14) H. J. Brass, J. O. Edwards, and M. J. Biallas, *J. Amer. Chem. Soc.*, **92**, 4675 (1970).
(15) M. Charton, *ibid.*, **86**, 2033 (1964).
(16) L. W. Deady and J. A. Zoltewicz, *ibid.*, **93**, 5475 (1971).
(17) T. Durst, *Advan. Org. Chem.*, **6**, 285 (1969); R. Kuhn, *Angew. Chem., Int. Ed. Engl.*, **69**, 570 (1957).
(18) For examples of possible reactions, see T. Severin, D. Batz, and H. Lerche, *Chem. Ber.*, **103**, 1 (1970).

Table I

Relative Rate Constants for Reactions of Substituted Pyridines with Methyl Iodide in DMSO at 23° [a]

Substituent(s)	Registry no.	Pyridine [b]	Competition std: 2-Cyanopyridine	2-Carboxymethylpyridine	3-Bromoquinoline	1,10-Phenanthroline
H	110-86-1	(1.0)			(0.016[c,d])	(0.047[d,f])
2-NH_2	504-29-0	1.23 (1.23)				
2-CH_3	109-06-8	0.38 (0.38)				
2-C_2H_5	100-71-0	(0.17[e])				
2-$NHCOCH_3$	5231-96-9	(0.0082)		0.97		
2-CO_2CH_3	2459-07-6	(0.0084)			0.52	
2-Cl	109-09-1	(0.0039)	1.8	0.50	0.24	
2-Br	109-04-6	(0.0039)	1.8			
2-$CH_2C_6H_5$	101-82-6	(0.081)				1.7[f]
2-CN	100-70-9	(0.0022)				
2-(2-Pyridyl)	366-18-7	(0.0029[f])	1.2[f]		0.21[f]	
2,6-$(CH_3)_2$	108-48-5	(0.023)			1.4	
2-CH_3-6-NH_2	1824-81-3	(0.050)				1.05[f]
2-CH_3Q[g]	91-63-4	(0.0062)		0.74		

[a] Comparison of substituted pyridine to standard compound. [b] Values in parentheses are relative rate constants using pyridine as a standard; see text. [c] Reference 16. [d] Reference 20. [e] 2-Ethylpyridine–pyridazine = 0.667 and pyridine–pyridazine = 4.0. [f] Statistically corrected for reaction of two equivalent nitrogen atoms. [g] 2-Methylquinoline.

bromoquinoline and the ratio obtained directly agreed to ±4%.

Our relative rate constants for quinoline and 2-methyl-, 2-ethyl-, and 2,6-dimethylpyridines are very similar to those reported.[10] Our relative rate constant for 2-methylquinoline is about one-half that reported; nitrobenzene was the solvent.[10] Some small variation in this ratio with solvent change is to be expected.

2-Methyl-6-aminopyridine underwent methylation at both the annular and amino nitrogen atoms; 1,2-dimethyl-6-aminopyridinium and 2-methyl-6-trimethylammoniopyridine iodides were isolated from a reaction mixture. The rate constant ratio given in Table I reflects reaction at just the annular nitrogen atom and results from the use of eq 1. Although the *N*-methyl peaks of both of the isolated products overlapped in DMSO-d_6, the addition of KOD to a mixture resulted in signal separation. The *N*-methyl peak of the aminopyridinium salt shifted upfield by about 25 Hz.

A Brønsted plot of log k^G/k^H *vs.* pK_a for pyridines and quinolines is given in Figure 1. The k^G/k^H values cover a range of $\sim 5 \times 10^2$ while the K_a[19] values range over a factor of $\sim 5 \times 10^7$. Thus, the nucleophilicity of the heterocycles toward methyl iodide is only moderately dependent on basicity. Results for quinoline are taken from ref 20. The pK_a and log k^G/k^H values for the pyridyl group in 2,2′-bipyridyl are statistically corrected by −0.30.

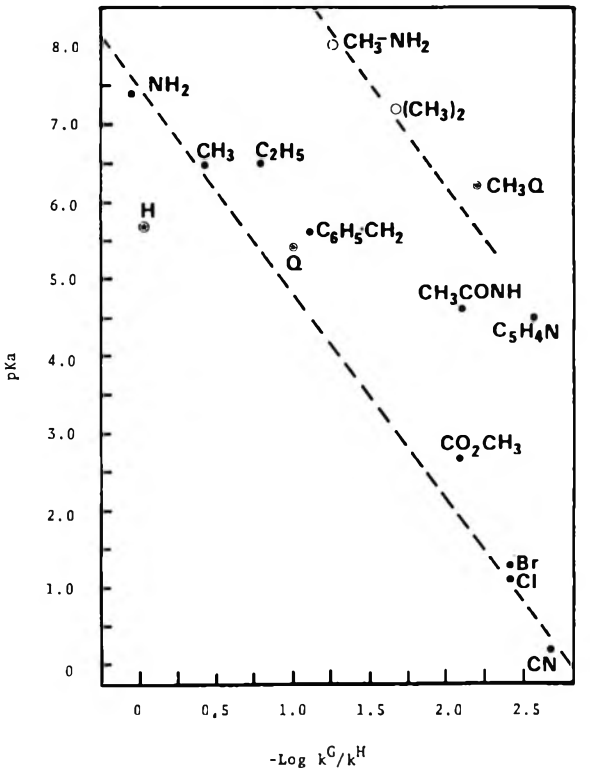


Figure 1.—Brønsted plot of the relative rates of N-methylation of 2-substituted (filled circles) and 2,6-disubstituted pyridines (open circles) and quinoline (Q) and 2-methylquinoline (CH_3Q) *vs.* the dissociation constants of the heterocyclic conjugate acids in water. Rate studies employ DMSO solvent at 23°. Pyridine (H) is the rate standard.

Discussion

The kinetic results found for the N-methylation of II and III differ substantially from those for N-alkylation of meta- and para-substituted pyridines.[11,16,20,21] For example, while the *o*-amino group is just slightly activating, the *p*-amino group activates strongly. *o*-Alkyl groups deactivate while *m*- and *p*-alkyl groups activate. In general, meta- and para-substituted pyridines give a good Brønsted plot with both groups lying on the same line.

That the results for ortho and para N-methylation are not simply related is to be anticipated from a knowledge of the effects of substituents on pK_a values. The pK_a values of II show a good correlation with meta σ values and not with para σ values.[15] Inductive effects are relatively more important in the ortho series.

In an attempt to correct for the special nature of the electronic effects of ortho substituents, we have compared the relative rates of N-methylation with experi-

(19) K. Schofield, "Hetero-Aromatic Nitrogen Compounds," Plenum Press, New York, N. Y., 1967, pp 146–149; D. D. Perrin, "Dissociation Constants of Organic Bases in Aqueous Solution," Butterworths, London, 1965.

(20) J. A. Zoltewicz and L. W. Deady, unpublished results.

(21) A. Fischer, W. J. Galloway, and J. Vaughan, *J. Chem. Soc.*, 3596 (1964).

mental K_a values for the same bases. It is clear from Figure 1 that there is considerable scatter in this Brønsted plot. All of the kinetic data cannot be incorporated into a single, satisfactory correlation. Some of the scatter is larger than the 25% commonly found in linear free-energy relationships.[22] For example, the effect of a methyl group is not additive. 2-Methyl- is 2.6 times and 2,6-dimethylpyridine is 43 times less reactive than pyridine. 2-Ethyl- is about 2 times less reactive than 2-methylpyridine. 2-Acetylamino- negatively deviates by a factor of about 10 and 2-(2-pyridyl)pyridine by about 25 from the Brønsted line drawn for monosubstituted compounds.

The results in Figure 1 suggest that separate correlation lines are required for 2-substituted and 2,6-disubstituted pyridines, not including pyridine, the parent compound. The line for the monosubstituted compounds is drawn so as to favor the smaller groups. Both lines are drawn with the same slope. Even with two lines, there is scatter. That the results for the 2,6-disubstituted compounds show a Brønsted correlation is only a suggestion because of our limited study. It is interesting that the quinoline and 2-methylquinoline results fit the Brønsted lines for mono- and disubstituted pyridines, respectively, about as well as any pyridine. The effect of the fused benzene ring appears to be much like that of an ortho substituent. By comparison, isoquinoline lies on a Brønsted line which includes pyridine and meta- and para-substituted pyridines.[20,21] The slope of the line we have drawn for ortho-substituted pyridines is 0.4, the same as that found for meta-substituted pyridines reacting with methyl iodide in DMSO.[20]

Proton transfer reactions involving II and III are expected to be good models for the alkylation reaction. These proton transfer reactions reflect the electronic effects of the substituents on the rates of attack of the pyridines on water molecules. This follows because (1) $pK_w = pK_a + pK_b$ where K_b is the equilibrium constant for the reaction $B + H_2O \rightleftarrows BH^+ + OH^-$ and (2) the rate constant for the reaction of BH^+ and OH^- is expected to be that for a diffusion-controlled reaction.[23] That is, changes in K_b with pyridine structure reflect changes in the rate of reaction of pyridine B with H_2O. Steric factors are not important because of the small size of the proton which is being transferred. Thus, the results in Figure 1 indicate that ortho substituents do not influence the rates of reaction of pyridine nucleophiles with methyl iodide and with water in exactly the same way.

Consider now the question of the cause of the scatter in the Brønsted plot. It may be suggested that the scatter is a consequence of the use of different solvents. The rate data were derived using DMSO but the pK_a values result from studies using aqueous solutions. While this suggestion can not be ruled out rigorously, it does not seem likely that this is the primary cause of the scatter. (1) No such scatter results in the case of N-methylation of meta-substituted pyridines; again data are derived using DMSO and water solvents.[20,24] (2) The same reactivity order, H > 2-CH_3 > 2-C_2H_5, is consistently reported for a variety of alkylating agents in a variety of solvents, including water.[7-9,11]

We can think of two possible reasons for the poor fit of the data in Figure 1. (1) The K_a values do not correctly express the nature of the electronic effects in the alkylation reactions and/or (2) steric factors are important.

It is to be expected that our data could be better fit by a multiparameter equation,[25] but the following conclusion is still expected to hold. Steric effects influence the rates of N-methylation of II and III.

The term steric effects is used in a broad sense and includes the common notion of steric compressions as well as steric hindrance to solvation, resonance, and motion (a conformational factor).[15,26]

Since steric effects are expected to be more important for the reactions of III, the central question raised by our results is whether steric effects influence the rates of N-methylation of less bulky II. That steric effects do operate throughout the monosubstituted pyridine series is indicated by the positive deviation of the hydrogen "substituent" from the Brønsted correlation line.[27]

Superimposed on the electronic effect of an ortho substituent is a steric effect which is nearly constant for those substituents lying close about the Brønsted line for monosubstituted pyridines. It is surprising how insensitive the rates of N-methylation are to small changes in substituent size. However, for groups such as 2′-pyridyl, steric effects dominate reactivity.

The N-alkylation reaction is especially suited to probing subtle changes in steric requirements at the reaction site. It would be of interest to determine how the size of other alkylating agents would influence the scatter in Brønsted plots for ortho-substituted pyridines.

Experimental Section

Materials.—All compounds were obtained from Aldrich Chemical Co. except 2-acetylaminopyridine, mp 68–69° (lit.[28] mp 71°), which was prepared from the amine. All but one of the methiodides reported in this study have been prepared.[7,10,12,28,29]

From the reaction of 2-amino-6-methylpyridine and methyl iodide in DMSO, two products were isolated. Addition of ethyl acetate to a reaction mixture resulted in the formation of an oily precipitate. This material on fractional crystallization from ethanol gave two iodides: 1,6-dimethyl-2-aminopyridinium iodide, mp 191–193° (*Anal.* Calcd for $C_7H_{11}IN_2$: C, 33.6; H, 4.4; N, 11.2. Found: C, 33.6; H, 4.5; N, 11.1.); 2-methyl-6-trimethylammoniopyridine iodide, mp 182.5–183.5° dec (*Anal.* Calcd for $C_9H_{15}IN_2$: C, 38.8; H, 5.4; N, 10.1. Found: C, 38.6; H, 5.3; N, 9.9).

DMSO was dried over molecular sieves. DMSO-d_6 was obtained from Stohler Isotope Chemicals.

Relative Rates of Methylation with Methyl Iodide in DMSO.—Three methods were employed but the preparations of reaction mixtures were essentially the same and have been reported.[16] Various compounds served as internal standards; they are listed in Table I. Analyses were made using nmr at 60 MHz.

(22) C. D. Ritchie and W. F. Sager, *Progr. Phys. Org. Chem.*, **2**, 323 (1964).

(23) M. Eigen, *Angew. Chem., Int. Ed. Engl.*, **3**, 1 (1964); E. E. Grunwald and E. K. Ralph, *Accounts Chem. Res.*, **4**, 107 (1971).

(24) The data in ref 16 may be employed to give such a Brønsted plot.

(25) P. R. Wells, "Linear Free Energy Relationships," Academic Press, New York, N. Y., 1968, p 7.

(26) J. Hine, "Physical Organic Chemistry," 2nd ed, McGraw-Hill, New York, N. Y., 1962, Chapter 4.

(27) It has been noted that the value for a hydrogen "substituent" often deviates from correlation lines established by other substituents.[15,22]

(28) "Dictionary of Organic Compounds," 4th ed, Oxford University Press, New York, N. Y., 1965.

(29) E. Koenigs, K. Köhler, and K. Blindow, *Chem. Ber.*, **58**, 933 (1925); A. E. Tschitschibabin, R. A. Konowalowa, and A. A. Konowalowa, *ibid.*, **54**, 814 (1921); O. Magidson and G. Menschikow, *ibid.*, **59**, 1209 (1926); F. H. Westheimer and O. T. Benfey, *J. Amer. Chem. Soc.*, **78**, 5309 (1956).

TABLE II

CHEMICAL SHIFTS OF THE *N*-METHYL GROUPS OF 2-SUBSTITUTED AND 2,6-DISUBSTITUTED *N*-METHYLPYRIDINIUM IODIDES IN DMSO[a,b]

Substituent	τ	Substituent	τ
H	5.51	Cl	5.55
CH_3	5.63	Br	5.50
C_2H_5	5.58	CN	5.33
NH_2	6.13	2′-C_5H_4N	5.63
$NHCOCH_3$	5.70	$C_6H_5CH_2$	5.55
CO_2CH_3	5.35	2,6-diCH_3	5.88
		2-CH_3-6-NH_2	6.31

[a] The DMSO satellite peak at τ 6.23 served as a reference standard. [b] Value for 2-methylquinoline is τ 5.50.

Results for pyridine, 2-aminopyridine, and all alkylated compounds except 2-methylquinoline were obtained by a method reported earlier.[16] This method is based upon a determination of the relative amounts of N-methylated products after all the methyl iodide limiting reagent had been consumed.

Rate constant ratios for all other compounds were calculated from product ratios using eq 1 or from product concentrations using eq 2. In order to determine product concentrations, mesitylene (ring signals) was employed as an internal standard. Chemical shifts for the *N*-methyl peaks are listed in Table II.

Registry No.—Methyl iodide, 74-88-4; 1,6-dimethyl-2-aminopyridinium iodide, 32654-50-5; 2-methyl-6-trimethylammoniopyridine iodide, 34314-77-7.

Acknowledgment.—This work was supported in part by the the National Science Foundation (GP 25500).

Formation of Triazabenzacephenanthrylium Salts. Their Solvolysis and Borohydride Reduction

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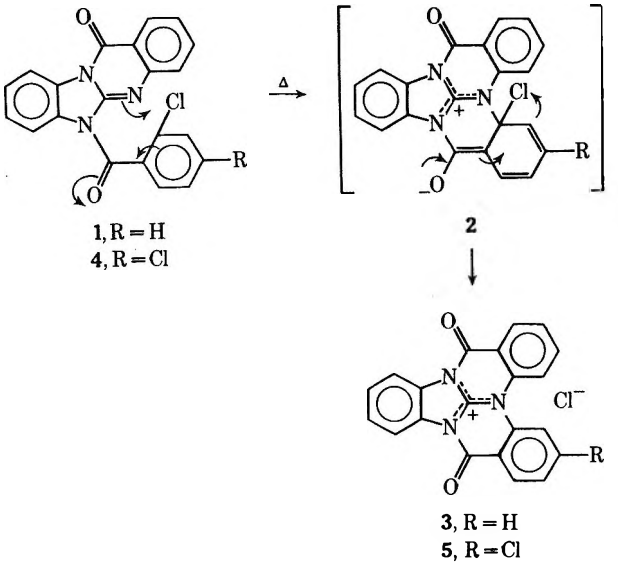
Received January 12, 1971

The preparation[1] of a series of benzimidazo[2,1-*b*]quinazolin-12-ones possessing potent immunosuppressive activity[2] has been described. A novel rearrangement of 6-(2-chlorobenzoyl)benzimidazo[2,1-*b*]quinazolin-12-ones is now discussed, together with the solvolytic cleavage of the resulting ionic pentacyclic salts. Borohydride reduction of this type of salt leads to unusual products containing the CH(N<)$_3$ unit.

The chlorobenzoyl compound **1** undergoes pyrolytic rearrangement which, we suggest, involves intermediate **2**. The initial rearrangement product **3** was not identified directly but by means of the derivatives described later. Similarly, the corresponding 2,4-dichlorobenzoyl derivative **4** gives the ionic chloride **5**.



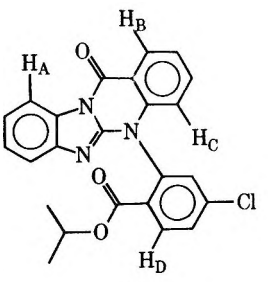
1, R = H
4, R = Cl

2

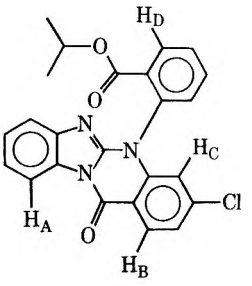
3, R = H
5, R = Cl

The solvolysis of **5** on refluxing with isopropyl alcohol will be discussed first since this is the only case in which *both* of the two possible isomeric products were actually isolated in the pure state.

These isomers analyzed as $C_{24}H_{18}N_3O_3Cl$; and this, together with the infrared and nmr spectra, is consistent for the isopropyl esters **6** and **7**.



6



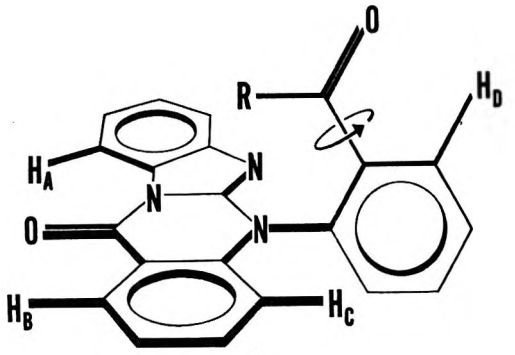
7

Inspection of Dreiding models of structures of type **8** (Figure 1) reveals that the likely conformation is as shown. The plane of the aroyl benzene ring is approximately at right angles to the plane of the tetracyclic system, while the position of the aroyl carbonyl group is, as will be seen later, dependent on the nature of R.

The nmr spectra of **6** and **7** each exhibit signals integrating for three protons between 8.9 and 8.4 ppm. These are due to H_A, H_B,[3] and presumably H_D in the deshielding zones of the two carbonyl groups, with the aroyl carbonyl function in the position shown in the diagram. Also, both spectra contain a single proton signal, in the vicinity of 7 ppm; this arises from H_C which is shielded by the aroyl benzene ring. In the case of **6** this signal is in the form of a broad doublet (J = 7.5 cps) centered at 6.99 ppm; each of the peaks was widened by m and p coupling. In the spectrum of **7**, however, a narrowly spaced doublet (J = 1.7 cps) is evident (very small p coupling accounts for the sharpness of the doublet).

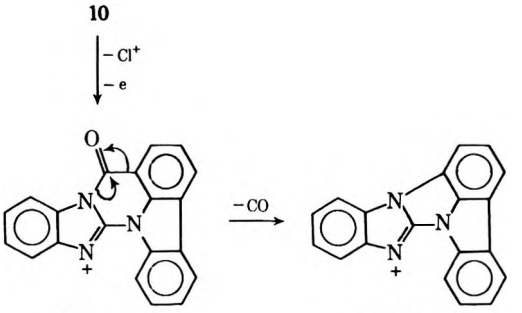
It was hoped that mass spectroscopy might confirm these assignments, but the mass spectra of **6** and **7**

(1) W. H. W. Lunn and R. W. Harper, *J. Heterocycl. Chem.*, **8**, 141 (1971).
(2) W. H. W. Lunn and R. W. Harper, *J. Med. Chem.*, **14**, 1069 (1971).
(3) W. H. W. Lunn and R. W. Harper, *Tetrahedron*, **27**, 2079 (1971).



8

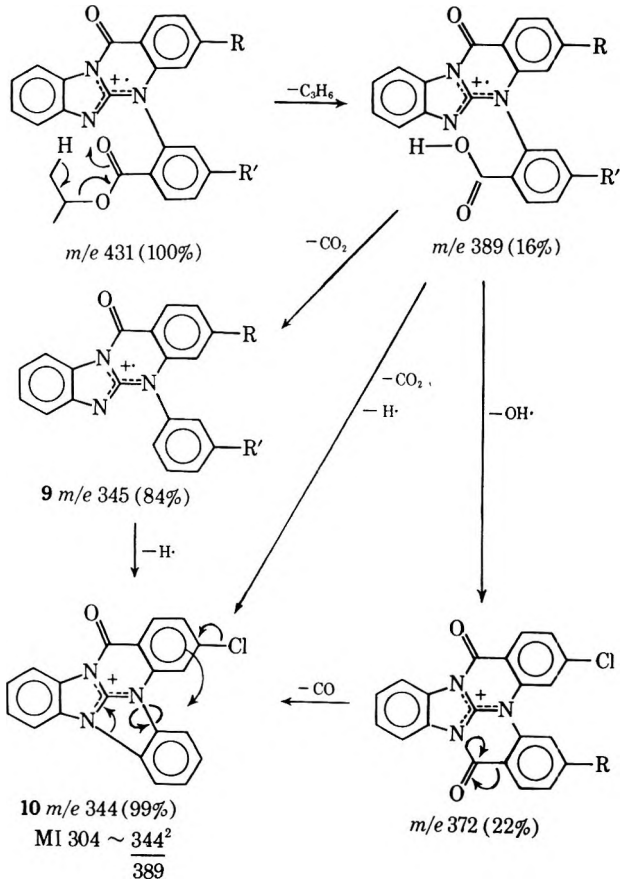
Figure 1.



MI = metastable ion

proved to be extremely similar. This situation is quite reasonable if we presume that the first cleavage to occur with each compound is, predominantly, the well-established loss of alkoxide from esters.[4] This is probably the case since anchimeric assistance from the tetracyclic nucleus would give rise to the relatively stable common ion, namely, the cation of **5**, which would then result in similar spectra for both esters.

Apart from the parent peaks, the most intense peaks in the mass spectra of these two compounds lie at *m/e* 345 and 344 which, we suggest, are due to ions **9** and **10**. These would be expected to be rather stable but would give rise to **11**, *m/e* 280, as shown.



It is significant that the peaks corresponding to those cleavages leading to ions **5**, **9**, **10**, and **11** are important in the mass spectra of **12**–**17** inclusively.

On heating in methanol, **3** gave methyl ester **12**, while **13** was isolated from **5**. When refluxed in water, **3** and **5** provided carboxylic acids **14** and **15**, respectively, the latter being a member of the series isomeric with **13**. Similarly, heating **3** and **5** in dimethylformamide led to the formation of **16** and **17**, respectively.

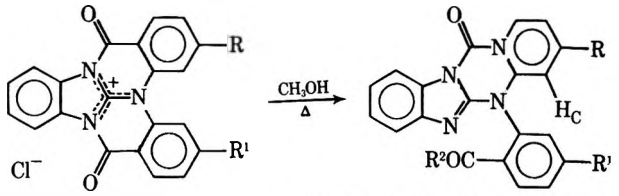
There is an interesting conformational difference between the dimethyl amides **16** and **17** and the rest of the rearrangement products. The nmr spectra of the four esters and the carboxylic acids all exhibit signals for three protons between 8.9 and 8.4 ppm, these arising from the protons H_A, H_B, and H_D with the conformation shown in **8**. However, there are signals for only two protons in this region in the nmr spectra of the two amides. Since H_A and H_B are fixed in relation to the quinazolone carbonyl function, we must assume that in the amides the aroyl carbonyl group is not directed toward H_D as it is in the other compounds. The reason for this different conformation is probably largely steric hindrance.

Reduction of the benzimidazo[2,1-*b*]azaquinolinium-12-one nucleus was then investigated. Treatment of **18**[1] with sodium borohydride in methanol gave a compound with an analysis indicating the addition of a hydrogen atom and loss of chloride; and the mass 277 of the parent ion, in its mass spectrum, confirmed this.

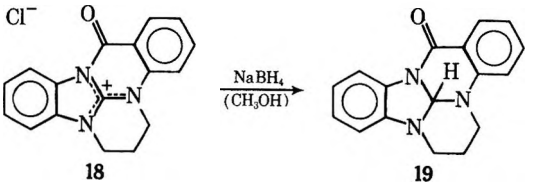
The outstanding features of the nmr spectrum ($CDCl_3$) of the reduction product are two single-proton quartets centered at 8.05 and 7.88 ppm and a sharp single-proton signal at 5.59 ppm. Two low-field quartets are found in the nmr spectra of benzimidazo[2,1-*b*]-azaquinolizin-12-ones,[3] albeit at somewhat lower field, about 8.6 and 8.5 ppm, and have been shown to arise from H-1 and H-10 (see structure **21**), which are in the deshielding zone of the carbonyl group. Thus, it would seem that the pentacyclic nucleus has been retained on reduction, but the completely planar character of the system may have been lost. These various data conform to structure **19**, the sharp uniproton signal being due to the new NNCHN unit.

Details of the mass spectrum of **19** further support this structure. The most intense peak lies at *m/e* 276, with other strong peaks at *m/e* values of 277, 248,

(4) H. Budzikiewicz, C. Djerassi, and D. H. Williams, "Interpretation of Mass Spectra of Organic Compounds," Holden-Day, San Francisco, Calif., 1964, pp 11–14.

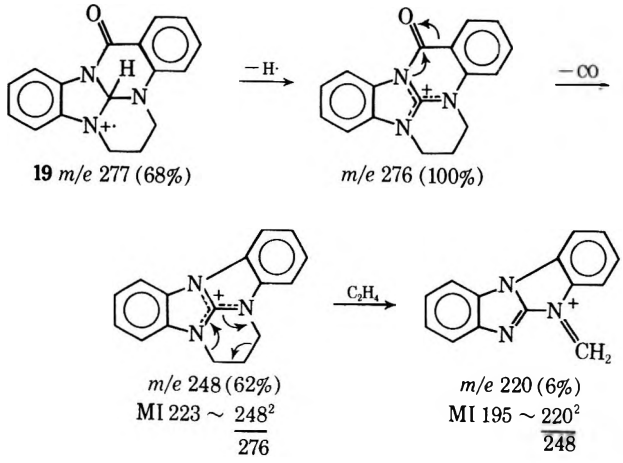


		nmr H_C
3, R = R^1 = H	**12**, R = R^1 = H; R^2 = OCH_3	6.93 ppm (J = 8.1 cps)
5, R = H; R^1 = Cl	**13**, R = H; R^1 = Cl; R^2 = OCH_3	6.98 ppm (J = 8.2 cps)
3, R = R^1 = H	**14**, R = R^1 = H; R^2 = OH	6.95 ppm (J = 8.1 cps)
5, R = H; R^1 = Cl	**15**, R = Cl; R^1 = H; R^2 = OH	6.94 ppm (J = 1.9 cps)
3, R = R^1 = H	**16**, R = R^1 = H; R^2 = $N(CH_3)_2$	7.09 ppm (J = 8.3 cps)
5, R = H; R^1 = Cl	**17**, R = Cl; R^1 = H; R^2 = $N(CH_3)_2$	7.10 ppm (J = 1.8 cps)



18 **19**

and 220. These could be accounted for very well by the following processes.

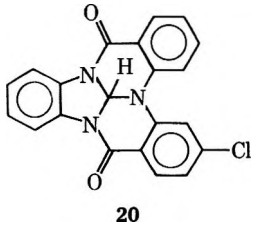


19 *m/e* 277 (68%) *m/e* 276 (100%)

m/e 248 (62%) *m/e* 220 (6%)

MI 223 ~ $\frac{248^2}{276}$ MI 195 ~ $\frac{220^2}{248}$

In a similar fashion the ionic chloride **5** was reduced with sodium borohydride to **20**.

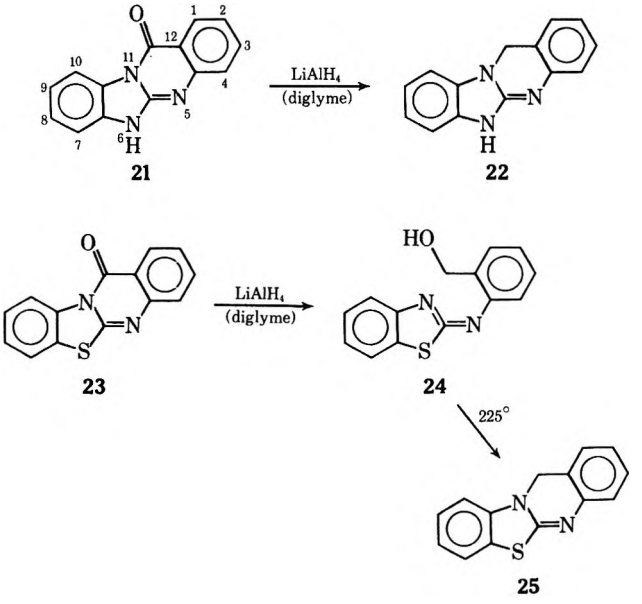


20

The NNCHN proton of **20** gives rise to a sharp nmr signal at 7.01 ppm, and the principal peaks in the mass spectrum of **20** can be assigned to the anticipated cleavages: *m/e* 372 (M − H), 344 (M − H − CO), 337 (M − H − Cl), and 309 (M − H − CO − Cl).

At this point we will describe some reductions of the related but nonionic tetracyclic compounds **21** and **23**.

Compound **21** was reduced by lithium aluminum hydride to the deoxy compound **22**, whereas **23** afforded the hydroxy compound **24** under the same conditions. Pyrolysis of **24** produced the deoxy compound **25**. The position of the C=N double bond shown in **22** is presumed because of the similarity of the ultraviolet spectra of **22** and **25**.



21 **22**

23 **24** **25**

The action of zinc on **23** in refluxing acetic acid resulted in cleavage and rearrangement to give 2-(2-aminophenyl)benzothiazole (**26**), identified as its *N*-acetyl derivative. It is suggested that intermediate **27**, formed first, is cleaved to **28**, which is reduced to **29**. Hydrolysis of **29** would lead to loss of the NCH_2N methylene group as formaldehyde and dehydration of the resulting product would afford **26**.

The corresponding benzimidazo compound **21** proved resistant to this treatment and was recovered unchanged.

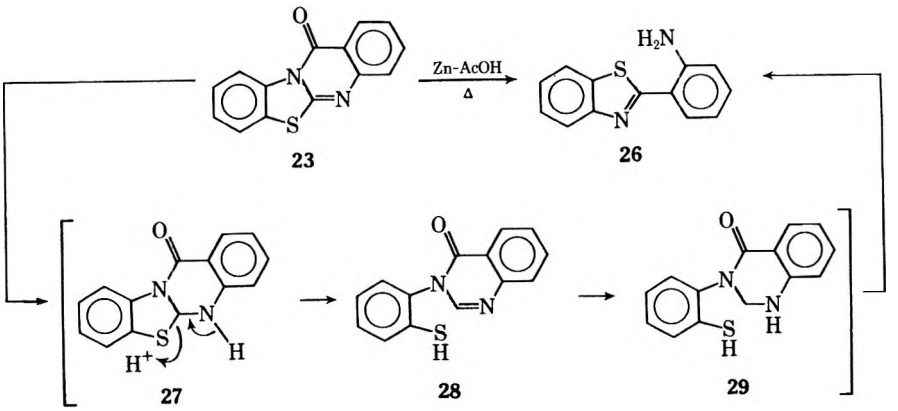
Experimental Section

Unless otherwise stated, all the nmr spectra were run in a solution in trifluoroacetic acid-d_1.

Pyrolysis of 6-(2-Chlorobenzoyl)benzimidazo[2,1-*b*]quinazolin-12-one (1) and the 6-(2,4-Dichloro) Analog (4).—Chlorobenzoyl compound 1[1] (5.5 g) was heated at 245° for 50 min. It slowly melted; then, after about 20 min, it commenced to resolidify. Solidification was complete after 40 min. The material, crude **3**, was collected and ground in a mortar and pestle in preparation for further reactions.

Dichlorobenzoyl compound 4[1] was treated as described above to yield crude **5**.

Treatment of 6-Chloro-9,14-dioxo-9*H*,14*H*-4b,9a,13b-triazabenz[*a*,*e*]acephenanthrylium Chloride (5) with Isopropyl Alcohol.—Crude **5** (1.0 g) was refluxed with stirring in dry *i*-PrOH (20 ml) for 14 hr; the mixture was allowed to cool and then was evapo-



rated to dryness under reduced pressure. The residue was slurried in CH_2Cl_2 (10 ml) and filtered. Evaporation to dryness under reduced pressure and fractional recrystallization of the residue from $CHCl_3$–*i*-PrOH gave two crops of **7** (265 and 37 mg), mp 278–279° and 277–279°, respectively.

Anal. Calcd for $C_{24}H_{18}N_3O_3Cl$: C, 66.74; H, 4.20; N, 9.73; Cl, 8.21. Found: C, 66.88; H, 4.12; N, 9.98; Cl, 8.41.

The mother liquors afforded two crops of **6** (293 and 69 mg), mp 188–190° and 186–188°, respectively.

Anal. Calcd for $C_{24}H_{18}N_3O_3Cl$: C, 66.74; H, 4.20; N, 9.73; Cl, 8.21. Found: C, 66.93; H, 4.48; N, 9.87; Cl, 8.09.

5-(2-Carbomethoxyphenyl)benzimidazo[2,1-*b*]quinazolin-12(5*H*)-one (12).—Crude **3** (1.0 g) was refluxed with stirring in dry CH_3OH (20 ml) for 14 hr and then treated as **5** above. Recrystallization from the same solvent mixture gave **12** (278 mg), mp 232–234°.

Anal. Calcd for $C_{22}H_{15}N_3O_3$: C, 71.53; H, 4.09; N, 11.38. Found: C, 71.63; H, 4.08; N, 11.05.

5-(5-Chloro-2-carbomethoxyphenyl)benzimidazo[2,1-*b*]quinazolin-12(5*H*)-one (13).—Crude **5** (1.0 g) was refluxed in dry CH_3OH (20 ml) for 14 hr, allowed to cool, and evaporated to dryness under reduced pressure. The residue was slurried in $(CH_3)_2CO$ (10 ml) and filtered. Evaporation of the filtrate under reduced pressure yielded a solid which, after three recrystallizations from CH_3OH–*i*-PrOH, gave **13** (273 mg), mp 208–210°.

Anal. Calcd for $C_{22}H_{14}N_3O_3Cl$: C, 65.43; H, 3.49; N, 10.41; Cl, 8.78. Found: C, 65.27; H, 3.74; N, 10.14; Cl, 8.99.

5-(2-Carboxyphenyl)benzimidazo[2,1-*b*]quinazolin-12(5*H*)-one (14).—Crude **3** (1.0 g) was refluxed in diglyme (5 ml) containing H_2O (1 ml) for 4 hr; the mixture was allowed to cool and then was evaporated to dryness under reduced pressure. The residue was slurried in DMF (6 ml) and filtered. Concentration of the filtrate and addition of CH_3OH provided crystals from which pure **14** (149 mg), mp 287–289°, was obtained by one recrystallization from DMF–CH_3OH.

Anal. Calcd for $C_{21}H_{13}N_3O_3$: C, 70.99; H, 3.69; N, 11.82. Found: C, 70.70; H, 3.64; N, 11.62.

3-Chloro-5-(2-carboxyphenyl)benzimidazo[2,1-*b*]quinazolin-12(5*H*)-one (15).—Crude **5** (1.0 g) was refluxed in diglyme (5 ml) containing H_2O (1 ml) for 4 hr. The mixture was allowed to cool and was evaporated to dryness under reduced pressure. Pure **15** (374 mg), mp 302–304°, was obtained after recrystallization of the residue from DMF.

Anal. Calcd for $C_{21}H_{12}N_3O_3Cl$: C, 64.71; H, 3.10; N, 10.78; Cl, 9.10. Found: 63.26; H, 3.29; N, 10.38; Cl, 8.80.

5-(2-Dimethylcarbamoylphenyl)benzimidazo[2,1-*b*]quinazolin-12(5*H*)-one (16).—Crude **3** (1.0 g) was refluxed in dry DMF (7 ml) for 2 hr. The resulting solution was concentrated to about 3 ml and allowed to cool. Crude **16** crystallized and was collected by filtration. The filtrate was concentrated to about 1.5 ml and, after cooling, diluted with C_6H_6 (10 ml). This led to the deposition of colorless plates of dimethylamine hydrochloride, which were removed by filtration. The mother liquors from the amine hydrochloride were evaporated to dryness under reduced pressure, and the residue, bulked with the above crystals of **16** and recrystallized from $CHCl_3$–*i*-PrOH, afforded pure **16** (216 mg), mp 255–256°.

Anal. Calcd for $C_{23}H_{18}N_4O_2$: C, 72.23; H, 4.74; N, 14.65. Found: C, 71.93; H, 4.49; N, 14.66.

3-Chloro-5-(dimethylcarbamoylphenyl)benzimidazo[2,1-*b*]quinazolin-12(5*H*)-one (17).—Crude **5** (1.0 g) was treated as described in the preparation of **16**. Recrystallization of crude **17** from DMF–*i*-PrOH provided pure material (470 mg), mp 216–218°.

Anal. Calcd for $C_{23}H_{17}N_4O_2Cl$: C, 66.26; H, 4.11; N, 13.44; Cl, 8.50. Found: C, 66.39; H, 4.11; N, 13.29; Cl 8.74.

2,3-Dihydro-1*H*,8*H*-3a,7b,12b-triazobenz[*c*]acephenanthrylen-8-one (19).—Salt **18** (5.0 g) was stirred in aqueous CH_3OH (250 ml, 80%) and $NaBH_4$ (0.83 g) was added portionwise, the temperature being maintained at 20–25° by intermittent cooling. The mixture effervesced, and a yellow material precipitated during the borohydride addition. The mixture was stirred at room temperature for 0.5 hr, cooled in an ice bath, and acidified to pH 1.5 with 10% HCl; then a solution of Na_2CO_3 (3 g) in H_2O (300 ml) was added. The resulting suspension was filtered to give crude product **19** (4.1 g), mp 139–143°.

Anal. Calcd for $C_{17}H_{15}N_3O$: C, 73.63; H, 5.45; N, 15.15; O, 5.77. Found: C, 74.03; H, 5.53; N, 15.15; O, 6.10.

6-Chloro-9*H*,14*H*-4b,9a,13b-triazadibenz[*a*,3]acephenanthrylene-9,14-dione (20).—Finely divided ionic chloride **5** (1.0 g) was stirred in CH_3OH (5 ml) while $NaBH_4$ (1.2 g) was added slowly in small portions; 0.5 hr after the addition, the mixture was processed as in the above borohydride reduction. Compound **20** (0.27 g), mp 205–207°, was obtained on recrystallization of the crude product from DMF.

Anal. Calcd for $C_{21}H_{12}N_3O_2Cl$: C, 67.47; H, 3.24; N, 11.24; Cl, 9.49. Found: C, 67.23; H, 2.98; N, 11.46; Cl, 9.69.

Reduction of Benzimidazo[2,1-*b*]quinazolin-12(6*H*)-one (21) with $LiAlH_4$.—The parent nitrogen tetracyclic **21** (7.05 g) was stirred, in an ice bath, in dry diglyme (250 ml); $LiAlH_4$ (2.28 g) was added in portions. The mixture was stirred at room temperature for 24 hr and then was cooled in an ice–water bath while H_2O (4.6 ml) and then aqueous NaOH (4.0 ml, 10%), was added dropwise. $CHCl_3$ (200 ml) was added to make the inorganic precipitate more granular; after stirring for 2 hr at room temperature, the mixture was filtered; the solid on the filter was washed with diglyme (50 ml). The filtrate was evaporated to dryness at reduced pressure, and the residue was recrystallized twice from $CHCl_3$ to give **22** (2.03 g): mp 363–366° dec; λ_{max}^{EtOH} 212 mμ (ε 29,000), 265 (10,800), 295 (20,400), and 304 (19,300).

Anal. Calcd for $C_{14}H_{11}N_3$: C, 75.99; H, 5.01; N, 18.99. Found: C, 75.83; H, 5.35; N, 19.20.

Reduction of Benzothiazo[2,3-*b*]quinazolin-12-one (23) with $LiAlH_4$.—Quinazolinone **23** (7.56 g) was treated with $LiAlH_4$ (1.70 g) in diglyme (150 ml) and processed in the manner described above. Recrystallization from $CHCl_3$ provided **24** (0.83 g), mp 155–157°.

Anal. Calcd for $C_{14}H_{12}N_2OS$: C, 66.13; H, 3.96; N, 11.02; S, 12.61. Found: C, 65.82; H, 4.19; N, 11.06; S, 12.59.

Benzothiazo[2,3-*b*]quinazoline (25).—Benzimidazole **8** (1.50 g) was heated in a nitrogen atmosphere at 265° for 15 min. The resulting glass was twice recrystallized from $(CH_3)_2CO$ at the temperature of a $(CH_3)_2CO$–solid CO_2 bath to give pure **25** (0.28 g): mp 155–157°; λ_{max}^{EtOH} 219 mμ (ε 27,000), 231 (25,300), 322 (19,300), 334 (20,700), and 350 (11,700).

Anal. Calcd for $C_{14}H_{10}N_2S$: C, 70.58; H, 4.23; N, 11.76; S, 13.43. Found: C, 70.32; H, 4.50; N, 11.63; S, 13.19.

Reduction of Benzothiazo[2,3-*b*]quinazolin-12-one (23) with Zinc in AcOH.—The tetracyclic benzothiazoquinazolone (5.04

g) was refluxed vigorously with zinc dust (12 g) in glacial AcOH (70 ml) for 3.5 hr. After cooling to room temperature, the mixture was filtered, and the filtrate was evaporated under reduced pressure until the AcOH was removed. The residue, a thick oil containing some solids, was stirred with $(CH_3)_2CO$ (150 ml) and filtered to remove the last traces of zinc acetate. The resulting solution was evaporated to dryness, leaving a thick oil (3.37 g).

A portion (1.0 g) of this oil was dissolved with Ac_2O (2 ml) in dry pyridine (7 ml). After 16 hr the mixture was poured into ice–water, and the resulting mixture was extracted with ether. The ether extract was dried over anhydrous $MgSO_4$, filtered, and evaporated under reduced pressure to give an oil which slowly crystallized on standing. Recrystallization from CH_3OH gave the product (0.53 g), mp 115–118°. Another recrystallization from CH_3OH provided an analytical sample, mp 120–121°, of 2-(2-acetylaminophenyl)benzothiazole.

Anal. Calcd for $C_{15}H_{12}N_2OS$: C, 67.14; H, 4.51; N 10.44; S, 11.95. Found: C, 67.05; H, 4.29; N, 10.22; S, 11.89.

Registry No.—**3**, 32612-56-9; **5**, 32612-57-0; **6**, 32827-40-0; **7**, 32675-27-7; **12**, 32722-78-4; **13**, 32675-28-8; **14**, 32722-79-5; **15**, 32675-29-9; **16**, 32675-30-2; **17**, 32675-31-3; **19**, 32675-32-4; **20**, 32675-33-5; **22**, 32675-34-6; **24**, 32675-35-7; **25**, 243-95-8; 2-(2-acetylaminophenyl)benzothiazole, 32675-37-9.

Acknowledgments.—We wish to thank Dr. P. V. Demarco for valuable discussions concerning the nmr spectra and Mr. J. Occolowitz for assistance in interpreting the mass spectra, and to express our appreciation to our colleagues in physical chemistry and microanalysis.

Synthesis of 2-Methoxyallyl Chloride, Bromide, and Iodide by Two Independent Routes. The Reaction of *N*-Halosuccinimides with 2-Methoxypropene and the Pyrolysis of 1-Halo-2,2-dimethoxypropanes

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Received July 22, 1971

2-Methoxyallyl chloride (**3a**), the corresponding bromide **3b**, and iodide **3c** have been synthesized by two independent routes, and like the series of previously unknown 1-halo-2-methoxypropenes **4a–c** are now readily available for the first time. Our first route is the reaction of 2-methoxypropene (**1**) with the *N*-halosuccinimides (**2a–c**), especially *N*-chlorosuccinimide (**2a**) and *N*-bromosuccinimide (**2b**), to give a series of five products, namely, in the case of **2b**, the desired 2-methoxyallyl bromide (**3b**), 1-bromo-2-methoxypropene (**4b**), 1-bromo-2-methoxy-2-succinimidopropane (**7b**), as well as minor amounts of 1-bromo-2,2-dimethoxypropane (**5b**) and bromoacetone (**6b**). The reaction of *N*-bromosuccinimide (**2b**) and **1** is completely ionic, being insensitive to free-radical donors and inhibitors, and represents the first thoroughly studied example of the reaction of *N*-bromosuccinimide with an enol ether. A second entry into the 2-methoxyallyl system has been provided by the pyrolysis of 1-chloro-2,2-dimethoxypropane (**5a**) above 180° in the presence of Lewis acids. As in the reaction of 2-methoxypropene (**1**) with *N*-chlorosuccinimide (**2a**), not only 2-methoxyallyl chloride (**3a**) is formed in this pyrolysis but also the isomeric 1-chloro-2-methoxypropene (**4a**). Interestingly, even the ratio of **3a**:**4a** is similar to that obtained in the first route. Thermolysis of 1-bromo-2,2-dimethoxypropane (**5b**) proceeds in milder conditions and again produces **3b** as well as **4b**. 2-Methoxyallyl iodide (**3c**) is most readily available from the corresponding bromide **3b** by treatment with NaI in acetone.

2-Alkoxyallyl halides represent a simple class of bifunctional compounds which aside from having intrinsic interest deserve attention in synthesis. For example, we have used **3b** as a precursor in 4 + 3 → 7 cycloadditions,[1,2] and one may easily envisage further applications, for example, in the realm of organometallic chemistry. Curiously, apart from a claim in a dated patent[3] which we have reinvestigated, there is to our knowledge nowhere in the chemical literature any mention of these simple compounds, be it as the parent, *i.e.*, **3a–c**, or more highly substituted, say as part of a ring. As enol ethers[4] and alkyl halides the desired compounds are expected to be electron rich and electron deficient at the same time. Naturally, the confrontation of two such sites within one molecule will not only present problems in synthesis but also new properties, and it seemed to us from the very beginning that neither strongly acidic nor strongly basic conditions could be part of any satisfactory approach and that also some care would be required in working up any potentially interesting reaction mixture.

We now wish to record the synthesis of 2-methoxyallyl chloride (**3a**), bromide **3b**, and iodide **3c** by two efficient routes.

Results

A. Product Analysis and Structural Assignments.—Generally, *N*-halosuccinimides (**2a–c**) have been found to react with 2-methoxypropene (**1**) to give succinimide and five other products as exemplified in Scheme I for the reaction with *N*-bromosuccinimide (**2b**).

(1) (a) H. M. R. Hoffmann, D. R. Joy, and A. K. Suter, *J. Chem. Soc. B*, 57 (1968); (b) H. M. R. Hoffmann and D. R. Joy, *ibid.*, 1182 (1968); (c) H. M. R. Hoffmann and N. F. Janes, *J. Chem. Soc. C*, 1456 (1969); (d) H. M. R. Hoffmann, G. F. P. Kernaghan, and G. Greenwood, *J. Chem. Soc. B*, 2257 (1971); (e) H. M. R. Hoffmann, K. E. Clemens, and R. H. Smithers, *J. Amer. Chem. Soc.*, in press; (f) G. Greenwood, A. E. Hill, and H. M. R. Hoffmann, unpublished work.

(2) Cycloadditions classified according to the ring-size criterion; see R. Huisgen, *Angew. Chem., Int. Ed. Engl.*, **7**, 321 (1968). For 4 + 3 → 7 cycloadditions involving oxyallyl, see N. J. Turro, S. S. Edelson, J. R. Williams, T. R. Darling, and W. B. Hammond, *J. Amer. Chem. Soc.*, **91**, 2283 (1969); R. C. Cookson, M. J. Nye, and G. Subrahmanyam, *J. Chem. Soc. C*, 473 (1967), 2009 (1965); A. W. Fort, *J. Amer. Chem. Soc.*, **84**, 2620, 2625, 4979 (1962).

(3) K. Westphal and H. Klös, German Patent 614,462 [*Chem. Abstr.*, **29**, 5994[4] (1935)]; U. S. Patent 2,119,802 (1938).

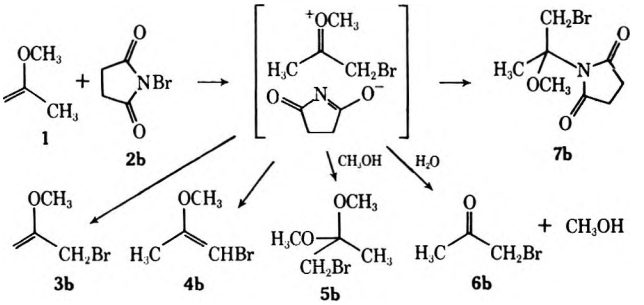
(4) For reviews of enol ethers, see (a) H. Meerwein, "Methoden der Organischen Chemie," Houben–Weyl–Müller, Ed., Vol. 6/3, Thieme, Stuttgart, 1965, p 97; (b) F. Effenberger, *Angew. Chem., Int. Ed. Engl.*, **8**, 295 (1969); (c) M. F. Shostakovskii, A. V. Bogdanova, and G. I. Plotnikova, *Russ. Chem. Rev.*, **33**, 66 (1964); see also M. F. Shostakovskii, B. A. Trofimov, A. S. Atavin, and V. I. Lavrov, *ibid.*, **37**, 907 (1968).

Of the products obtained, compounds **3**, **4**, **5**, and **6** are volatile, lachrymatory liquids, while the adducts **7a–c** proved to be solids. The identification of these products rests on combined glc–nmr, mass spectroscopy, and chemical transformations. Specifically, the peak areas of the volatile products **3**, **4**, **5**, and **6** in gas–liquid chromatograms (*cf.* Table V for retention times) were matched by corresponding intensities of nmr peaks, and preparative glc allowed us to isolate individual compounds whenever desirable. The enol ethers **3a** and **4a**, as well as **3b** and **4b**, were further identified by their reactions with various alcohols. For example, 2-methoxyallyl bromide (**3b**), as well as its isomer **4b**, reacts very smoothly with methanol to give quantitatively the bromo ketal **5b**; not unreasonably, **3b** reacts somewhat faster than **4b**.

A priori, the enol ethers **4a**, **4b**, and **4c** could be present as a mixture of cis/trans isomers. That only one respective isomer had been formed could be shown as follows. (1) **4a**, **4b**, and **4c** gave perfectly symmetrical peaks on glc. Specifically, **4a** was examined on five different columns and proved to be a single compound. (2) A cis/trans mixture if present should also be discernible in the nmr spectrum. No additional peaks beyond those ascribable to one isomer were observed. (3) Expansion of the peak at τ 4.88 in **4a** and at τ 4.91 in **4b** revealed a broad quartet (coupling to CCH_3), while the methyl protons appeared on expansion as a doublet with $J_{H,CH_3} \sim 0.7$ Hz, coupling being confirmed by double irradiation. Whether the halogen atoms in the enol ethers **4a**, **4b**, and **4c** are actually cis or trans to the methoxy grouping can at present not be decided from the magnitude of allylic coupling, since examples are known where $|J_{cis}| > |J_{trans}|$ and vice versa.[5] However, some work in related systems discussed below suggests the formation of cis isomers.[6]

Of the three adducts **7a**, **7b**, and **7c**, 1-bromo-2-methoxy-2-succinimidopropane (**7b**) has been investigated in detail. It is a stable crystalline solid, mp 32–34°, which shows a molecular ion *m/e* 249 for $C_8H_{12}NO_3{}^{79}Br$, provided that the vapor pressure of the sample is sufficiently high, and prominent fragmentation peaks $m - CH_3$ and $m - OCH_3$ in excellent accord with the assigned structure. The nmr spectrum is

SCHEME I



interesting in that it displays the expected AB quartet for the diastereotopic CH_2Br protons, which are, however, separated rather widely ($\Delta\nu_{AB}$ = 116 Hz), presumably because the neighboring asymmetric carbon is attached to three widely dissimilar groups. Integration shows that the peak at τ 8.15 has the same area as the sharp methoxy singlet at τ 6.83; on expansion the downfield half of the quartet appears as two broad quartets, *i.e.*, H^c is coupled further to the CCH_3 protons with J_{H^c,CH_3} = 1 Hz. From the "W" rule[5] and also the work of Davis and Roberts[7] it can be concluded with confidence that it is the proton anti to the methyl group which shows long-range coupling. Presumably the conformation of **7b**, in which the succinimidyl grouping is anti to the bromine atom, is preferred.

Adduct **7b** can be heated in chlorobenzene up to 120° and does not suffer any detectable decomposition; only the nmr spectrum changes slightly, with $\Delta\nu_{AB}$ = 104 Hz at 120°. On the other hand, in nitrobenzene solution at room temperature both $\Delta\nu_{AB}$ and $J_{CH_3,H}$ are smaller, being 88 and 0.6 Hz, respectively.

B. Synthesis of the 2-Methoxyallyl Halides (3a–c). (1) Reaction of 2-Methoxypropene (1) with *N*-Halosuccinimides (2a–c).—The reaction of 2-methoxypropene (**1**) and *N*-bromosuccinimide (**2b**) gives an array of products and has been investigated in depth (Table I) with the aim of optimizing the formation of 2-methoxyallyl bromide (**3b**), which not unexpectedly is a sensitive compound and is best handled in solution. In the course of our work the conditions detailed in run 9, Table I, have emerged as optimum for the preparation of **3b**. After careful work-up of the reaction mixture a 50% solution in CCl_4 of 2-methoxyallyl bromide (**3b**) (68–70%), **4b** (28–30%), and **5b** + **6b** + **7b** (0–4%) is obtained which can be stored over Na_2CO_3 in the dark at room temperature. Although neat 2-methoxyallyl bromide (**3b**) and 1-bromo-2-methoxypropene (**4b**) decompose at room temperature, both compounds can be isolated in pure form by preparative glc.

Not unexpectedly, the reaction of *N*-chlorosuccinimide (**2a**) and 2-methoxypropene (**1**) requires slightly more vigorous conditions, *i.e.*, refluxing CCl_4 in any case. The product mixture can be worked up as described for the bromo derivatives and it is clear that this reaction provides a simple and satisfactory route to the previously unknown 2-methoxyallyl chloride (**3a**) as well as 1-chloro-2-methoxypropene (**4a**).

In contrast *N*-iodosuccinimide (**2c**) and the enol ether **1** react only incompletely in refluxing CCl_4,

(5) (a) S. Sternhell, *Quart. Rev., Chem. Soc.*, **23**, 236 (1969); (b) L. M. Jackman and S. Sternhell, "Applications of Nmr Spectroscopy in Organic Chemistry," 2nd ed, Pergamon Press, Elmsford, N. Y., 1969; (c) M. Barfield and B. Chakrabarti, *Chem. Rev.*, **69**, 757 (1969).

(6) *A priori*, the isomer is either pure *cis*-**4a** (*cis*-**4b**) or pure *trans*-**4a** (*trans*-**4b**). While it would be desirable to obtain the series of both *cis*-**4a–c** and *trans*-**4a–c** in order to reach a firm structural assignment, there are a number of indications which suggest the formation of *cis*-**4a–c**. For example, on pyrolysis over $K_2S_2O_7$ at 140° 1-chloro-2,2-diethoxyethane has been reported to lose ethanol with formation of mainly cis isomer: J. F. Arens, J. Vegter, and C. de Boer, *Recl. Trav. Chim. Pays-Bas*, **77**, 753 (1958); see also J. F. Arens, *Advan. Org. Chem.*, **2**, 117, 123, 124 (1960), and references cited therein. Similarly, pyrolysis of 1-chloro-2,2-dimethoxyethane over activated carbon at 270° affords 70% *cis*- and 30% *trans*-β-chlorovinyl ether: E. Kobayashi S. Hattori, and K. Tada, Japanese Patent 158 (1958) [see *Chem. Abstr.*, **52**, 19953*g* (1958)]. Elimination of HCl from 1,2-dichloroethyl ethers with tertiary amine has been reported to yield cis isomers in excess (75–90%) over trans isomers (10–25%): M. Farina, M. Peraldo, and G. Bressan, *Rend. Ist. Lomb. Sci. Lett., A, Cl.* **94**, 600 (1960) [*Chem. Abstr.*, **56**, 7115*e* (1962)].

Generally, the formation of cis isomer follows the cis rule of Viehe [H. G. Viehe, *Chem. Ber.*, **93**, 1697 (1960)], who proposed that, in the case of cis/trans isomers the substituents of which constitute an electron donor–electron acceptor pair, the cis isomer is more stable unless the substituents have particularly large steric requirements. However, that one stereoisomeric β-halovinyl ether can be formed *to the exclusion* of the other, as in our case, is of considerable interest and apparently without precedent.

(7) D. R. Davis and J. D. Roberts, *J. Amer. Chem. Soc.*, **84**, 2252 (1962).

Table I

Products[a] from the Reaction of 2-Methoxypropene (1) and *N*-Bromosuccinimide (2b) in CCl_4[b]

Run	Reagents, mol/l. 1	Reagents, mol/l. 2b	Temp, °C	Reaction time, min	Product compn, % 3b	4b	5b	6b	7b
1[b]	1.8, *ca.* 3	1.8	25	5	30	10	30	5	25
2[b]	1.6	*ca.* 2 (excess)	25	90	33	13	7	7	40
3[b]	1.85	1.87	0	120	36	14	7	7	36
4	1.43	1.12	25	5	50	17	1	8	24
5[c]	1.43	1.12	25	5	50	17	1	8	24
6[d]	1.85	1.5	25	5–75	50	17	1	8	24
7[e]	1.85	1.87[f]	25	120	46	17	2	8	27
8	1.43	1.12	55–65	10	48	20	1	7	24
9[g]	1.85	1.87	55–65	50	54	18	6	3	19
10	1.85	1.87	60–70	30	42	16	1	5	36
11[i]	1.98	1.6	Reflux–80[h]	10	29	14	1	8	48
12[j]	1.85	1.5	Reflux–80[h]	10–15	29	13	1	2	54
13	1.85	1.87	Reflux–80[h]	20	44	17	9	6	24

[a] Product distribution determined by glc (**3b**, **4b**, **5b**, and **6b**) and nmr which gave per cent **7b** relative to **3b** and **4b**. The error for measuring peak areas is *ca.* 2.5–4% in general but obviously greater for compounds present in less than 10%. [b] Except for runs 1–3, CCl_4 (analytical grade) was dried (P_4O_{10}) before use. 2-Methoxypropene was dried ($CaCl_2$) and redistilled except for runs 1–3 and always added to the suspension of **2b** in CCl_4 with shaking. *N*-Bromosuccinimide was usually finely ground but otherwise not treated any further (*cf.*, however, run 7). [c] Reaction solution contained 0.01 g of galvinoxyl. In two more runs under the conditions of run 4, but, in the presence of 1 mol % of benzoyl peroxide and 1 mol % of iodine, the composition of product remained unchanged. [d] Product ratios stay constant throughout reaction time. [e] Variation of solvent: CH_2Cl_2 (homogeneous) no change, except perhaps more adduct **7b**. In chlorobenzene (semihomogeneous) more **7b** was formed. [f] *N*-Bromosuccinimide dried (P_4O_{10}, desiccator). [g] Reaction mixture was stirred. [h] Refluxing causes a slightly yellow coloration of the reaction products. [i] 2,6-Lutidine (*ca.* 0.2 *M*) present. [j] Solid Na_2CO_3 (0.5 g) present.

Table II

Products from the Pyrolysis of 1-Chloro-2,2-dimethoxypropane (5a)

Run	Catalyst[a]	Column[b]	Temp, °C Metal bath	Temp, °C Head	Products,[c] % 3a	4a	5a	6a
1	$K_2S_2O_7$	2 Vigreux	180–210	108	26.5	43	19	11.5
2	$K_2S_2O_7$	Vigreux	180–200	110–112	25	27	31.5	16
3	QP	2 air condensers	180–230	106–110	35.9	32.5	22.3	9.3
4	QP, Q[d]	2 air condensers	210–250	108–112	37	34.5	19	9.5
5	QP	2 Vigreux	*ca.* 200	120	25.5	17	41	16.5
6	QP	Air condenser	200–210	<124	24	13.4	50	12.6
7	QOTs	2 air condensers	225–235	103–105	38.2	43.6	13.4	4.7
8	Ac_2O, AcOH quinaldine	Vigreux	150–185	102–107	32	56	10	2

[a] QP = quinaldine phosphate; QOTs = quinaldine tosylate. [b] Vigreux column (24 × 1.5 cm) and air condenser (45 × 2 cm) used. [c] Some chloroacetone is present as an impurity in **5a** and could also be formed during the pyrolysis. [d] Quinaldine (1.2%) and phosphoric acid (0.5%) used as catalyst.

iodine being liberated. However, we have found that 2-methoxyallyl iodide (**3c**) can be prepared conveniently from **3b** and NaI in acetone.

(2) Thermolysis of 1-Chloro-2,2-dimethoxypropane (5a) and 1-Bromo-2,2-dimethoxypropane (5b).—Having uncovered a simple reaction for preparing the 2-methoxyallyl halides we became aware of a patent according to which the dimethyl ketal of chloroacetone is to break up at 200–270° in the presence of catalytic amounts of quinoline phosphate into **3a** and methanol.[3] Of course, the synthesis of enol ethers from acetals and ketals *via* elimination of alcohols is a well-established reaction,[4] but we noted with more than casual concern that formation of any isomeric enol ether such as **4a** had not been mentioned, although the pyrolysis of **5a** like the reaction of 2-methoxypropene (**1**) with *N*-chlorosuccinimide (**2a**) seemed likely to proceed *via* an ionic mechanism involving similar intermediates. In any event we decided to reinvestigate the patented procedure from the vantage point of modern analytical techniques and our earlier experience with this class of compounds. Accordingly, 1-chloro-2,2-dimethoxypropane (**5a**) which is readily available from chloroacetone was pyrolyzed in the presence of various Lewis acids above 180° (Table II). It became clear immediately that under all conditions, including those cited in the patent,[3] not only methanol and 2-methoxyallyl chloride (**3a**) but also an isomeric enol ether were produced which proved to be a single isomer and identical with 1-chloro-2-methoxypropene (**4a**) characterized previously.

In contrast to **5a** the corresponding bromo ketal **5b** was found to break up more readily, elimination occurring during the preparation of **5b** on distillation and giving rise to 2-methoxyallyl bromide (**3b**) and its isomer **4b** in a ratio of 3:1. Conceivably, HBr was liberated during the distillation and catalyzed the breakup of the ketal. Distillation of chloro ketal **5a** under reduced pressure in the presence of catalytic amounts of H_2SO_4 afforded mainly unchanged starting material and only a small quantity of **3a** and **4a**, but the ratio **3a**:**4a** was again rather high, being 3:2.

Discussion

Turning to the reaction of the enol ether **1** and *N*-bromosuccinimide (**2b**) first, it is striking that dibenzoyl peroxide which is an efficient free-radical initiator and inhibitors such as molecular iodine and galvinoxyl have no effect on the reaction (Table I,

run 5). Clearly, an ionic reaction is indicated and it suffices to invoke an intermediate oxonium succinimidate ion pair (Scheme I), which should be formed on the surface of the *N*-bromosuccinimide before breaking down to the three major products **3b**, **4b**, and **7b**. It should be mentioned explicitly that all products are stable during the reaction (Table I, run 6); *i.e.*, adduct **7b** is not a precursor of either **3b** or **4b**, nor can these two isomeric enol ethers equilibrate under our conditions.

As regards the proportion of the desired 2-methoxyallyl halides **3a–c**, it is of interest that **3b** predominates over **4b** and, even more so, **3c** over **4c** (Table III).

TABLE III

TYPICAL PRODUCT DISTRIBUTION IN THE REACTION OF *N*-HALOSUCCINIMIDES WITH 2-METHOXYPROPENE IN BOILING CCl_4

3a (27%)	**4a** (31%)	**5a** (9%)	**6a** (3%)	**7a** (29%)
3b (54%)	**4b** (18%)	**5b** (6%)	**6b** (3%)	**7b** (19%)
3c (36%)	**4c** (3%)	**5c** (15%)	**6c** (6%)	**7c** (40%)

Apparently, the ratio **3**:**4** is at least partly controlled by the acidity of the CH_2Hal protons, increasing with decreasing acidity (*cf.* nmr of **5a**, **5b**, and **5c** in Table IV).

How are bromoacetone (**6b**) and the corresponding ketal **5b** formed? Although the isomeric enol ethers **3b** and **4b** react readily with solvent methanol and with any traces of moisture, it seems more likely that water and methanol would have to intervene at the earlier ion-pair stage to be effective. A further possible route to bromoacetone (**6b**) is the transfer of the methyl group to succinimidyl anion with release of **6b**. While *N*-methylsuccinimide has not been detected, it cannot be ruled out that this compound if formed would have been precipitated together with succinimide and so escaped detection. Any contaminants such as methanol or water are most likely to be introduced through 2-methoxypropene (**1**), which is difficult to obtain absolutely pure; in any case, drying of *N*-bromosuccinimide did not make any discernible difference to the product composition (run 7).

It is noteworthy that simply by adding solid Na_2CO_3 or 2,6-lutidine to the heterogeneous reaction mixture the proportion of adduct **7b** can be increased to 48% and more (Table I, runs 11 and 12). Although the formation of 1:1 adducts in the reaction of *N*-bromosuccinimide with olefins is not unknown,[8] it seems clear that there have been cases in the past where the formation of adduct has gone undetected, especially when reaction mixtures were analyzed by glc only. Compared with 5–30% adduct in the case of simple olefins,[8b] the proportion of adduct **7b** in the presence of base is, perhaps not surprisingly, large. It should be mentioned that the reaction of *N*-bromosuccinimide with an enol ether, namely dihydropyran, has been studied some time ago by Shelton and his coworkers,[9] who not only reported the formation of an analogous adduct but, in contrast to the results in our system, the formation of a vicinal dibromide and also some effect of free-radical initiators. Altogether, the literature on reactions of *N*-bromosuccinimides seems still in some disarray and need for repair. While it has been recognized that an ionic and a free-radical path may compete,[10] the reaction described herein presents to our knowledge the first clear example of a completely ionic reaction of *N*-bromosuccinimide with an olefin.

In considering the results of the second route to 2-methoxyallyl chloride (**3a**) one should bear in mind that the starting material, *i.e.*, 1-chloro-2,2-dimethoxypropane (**5a**), boils at 132–134°,[3] while the products will be more volatile; furthermore, an estimate based on glc retention indices suggests that the desired 2-methoxyallyl chloride (**3a**) boils about 14° higher than its isomer **4a**. [The same difference in boiling points has been estimated for the isomeric bromides **3b** and **4b** (*cf.* Table V, footnote *c*).] Hence, if a reasonably low proportion of chloro ketal **5a** in the distillate be ensured, it is advisable to maintain the temperature at the column head below 120°. Consistently, the higher the temperature at the column head, the more favorable the ratio **3a**:**4a**, but also the greater the percentage of starting material **5a** (Table II, runs 3–6). A compromise such as the conditions of run 3 and 4 seems optimum for preparing 2-methoxyallyl chloride (**3a**); in point of fact a temperature of 110–112° has been quoted in the patent[3] and it is again evident that the erstwhile product must have contained isomer **4a**.

It is especially interesting that both the first and the second route to 2-methoxyallyl chloride (**3a**) yield this isomer **4a**. Similarly, the first and the second route to 2-methoxyallyl bromide (**3b**) afford **4b** which is isomeric with **3b**.[6] Since the ratio of **3a**:**4a** (**3b**:**4b**) is also comparable for both routes, the ionic path proposed for the two sets of reactions gains additional credence.

Conclusions

The 2-methoxyallyl system is now readily available by the way of two different reactions. While the first route to **3a** and **3b** is more simple as a laboratory procedure in that the reaction starts from nonlachrymatory materials and involves high conversions, there can be little doubt that the pyrolysis of the halo ketals **5a** and **5b** is adaptable to large-scale preparations and technically attractive.

Experimental Section

Preparation of Starting Materials.—2-Methoxypropene (**1**) was obtained by the published procedure[11] in at least 95% purity, some methyl acetate and 2,2-dimethoxypropane generally being present as well. The *N*-halosuccinimides (**2a–c**) were commercial materials.

1-Chloro-2,2-dimethoxypropane (**5a**)[12] was obtained from chloroacetone (**6a**) (0.9 mol), a redistilled commercial sample being used, and trimethyl orthoformate (1 mol) in methanol

(8) (a) K. Ziegler, A. Späth, E. Schaaf, W. Schumann, and E. Winkelmann, *Justus Liebigs Ann. Chem.*, **551**, 80 (1942); for a reinvestigation, see G. Peiffer, J.-C. Traynard, and A. Guillemonat, *Bull. Soc. Chim. Fr.*, 1910 (1966); (b) A. Guillemonat, G. Peiffer, J.-C. Traynard, and A. Leger, *ibid.*, 1192 (1964); (c) I. Horman, S. S. Friedrich, R. M. Keefer, and L. J. Andrews, *J. Org. Chem.*, **34**, 905 (1969); (d) see also J. M. Landesberg and M. Siegel, *ibid.*, **35**, 1674 (1970); L. H. Zalkow and C. D. Kennedy, *ibid.*, **29**, 1290 (1964).

(9) J. R. Shelton and C. Cialdella, *ibid.*, **23**, 1128 (1958); J. R. Shelton and T. Kasuga, *ibid.*, **28**, 2841 (1963); see also R. Paul and S. Tchelitcheff, *C. R. Acad. Sci.*, **236**, 1968 (1953).

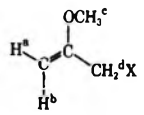
(10) J. H. Incremona and J. C. Martin, *J. Amer. Chem. Soc.*, **92**, 627 (1970); C. W. Jefford and W. Wojnarowski, *Helv. Chim. Acta*, **53**, 1194 (1970); D. I. Davies and L. T. Parfitt, *Tetrahedron Lett.*, 293 (1969); N. A. LeBel, J. E. Huber, and L. H. Zalkow, *J. Amer. Chem. Soc.*, **84**, 2226 (1962); S. D. Ross, M. Finkelstein, and R. C. Petersen, *ibid.*, **80**, 4327 (1958); J. D. Roberts, E. R. Trumbull, W. Bennett, and R. Armstrong, *ibid.*, **72**, 3116 (1950).

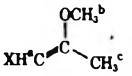
(11) G. Saucy and R. Marbet, *Helv. Chim. Acta*, **50**, 1158 (1967).

(12) Reference 4a, p 199.

Table IV

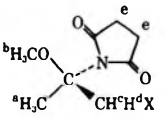
Nmr Spectra of Products from Reaction of 2-Methoxypropene (1) and *N*-Halosuccimimides (2a–c) in CCl_4[a]





$CH_3^aC(OCH_3^b)_2CH_2^cX$

$CH_3^aCOCH_2^bX$



X = Cl

3a	4a	5a	6a	7a
a + b 5.79 (d), 5.98 (d, $J_{Ha,Hb}$ = 2.5 Hz), c 6.43 (s), d 6.14 (s)	a 4.88 (broad q), b 6.50 (s), c 8.11 (d, $J_{CH_3,H}$ = 0.7 Hz)	a 8.7 (s), b 6.85 (s), c 6.6 (s)	a 7.75 (s), b 5.7 (s)	a 8.15 (d), b 6.79 (s), c 5.28 (broad q) + 5.47 (broad q, $J_{Hc,Hd}$ = 18 Hz), d 6.48 + 6.66, e 7.4 (s)

X = Br

3b	4b	5b	6b	7b
a + b 5.78 (d), 5.98 (d, $J_{Ha,Hb}$ = 2.5 Hz), c 6.42 (s), d 6.24 (s)	a 4.91 (broad q), b 6.45 (s), c 8.06 (d, $J_{CH_3,H}$ = 0.7 Hz)	a 8.66 (s), b 6.87 (s), c 6.74 (s)	a 7.72 (s), b 6.06 (s)	a 8.15 (d, $J_{CH_3,Hc}$ = 1 Hz), b 6.83 (s), c 5.46 (broad q) + 5.56 (broad q, $J_{CH_3,Hc}$ = 1 Hz), d 6.62 + 6.72 ($J_{Hc,Hd}$ = 10 Hz), e 7.52 (s)

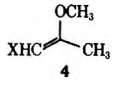
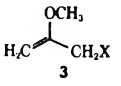
X = I

3c	4c	5c	6c	7c
a + b 5.74 (d), 5.98 (d, $J_{Ha,Hb}$ = 2.5 Hz), c 6.42 (s), d 6.20 (s)	a 5.2 (broad), b 6.46 (s), c obscured	a 8.64 (s), b 6.84 (s), c 6.76 (s)	a 7.86 (s), b 6.18 (s)	a 8.12 (d), b 6.79 (s), c 5.48 (broad q) + 5.67 (broad q), d obscured, e 7.41 (s)

[a] All spectra were recorded at 60 MHz in *ca.* 10% CCl_4 solution except for adduct **7b**, which was studied in detail at 100 MHz. Chemical shifts are quoted on the τ scale. The positions of the CH_2X resonances in **3a–c**, **5a–c**, **6a–c**, and **7a–c** are solvent and concentration dependent. For example, the signals for the CH_2Cl protons of neat **3a** and of a 50% solution in acetone are separated by 0.07 ppm; CH_2Br of **6b** resonates at τ 6.08 in a *ca.* 50% solution in CCl_4 and at τ 6.18 in 20% solution.

Table V

Glc Retention Times of 3–6 Relative to CCl_4[a]

	X = Cl	X = Br	X = I[b]
 4	1.6 (941)[c]	2.4 (1025)[c]	
 3	2.2 (1009)[c]	3.6 (1095)[c]	6.2
$CH_3C(OCH_3)_2CH_2X$ 5	2.8	4.6	
CH_3COCH_2X 6	3.4	5.7	

[a] Griffin F.I.D. gas chromatograph, 13-ft Carbowax 20M column at 80°. [b] The reaction mixtures of *N*-iodosuccinimide and 2-methoxypropene were analyzed mainly by their nmr spectra. [c] The values in parentheses are retention indices $I_{80°}^{C20M}$ as introduced by E. Kováts, *Helv. Chim. Acta*, **41**, 1915 (1958); *Z. Anal. Chem.*, **181**, 351 (1960). On a nonpolar stationary phase the difference d*I* of retention indices of isomeric compounds can be calculated from the difference d*t* of boiling points and vice versa; since d*I* ~ 5 d*t*, compound **3a** should boil *ca.* 14° higher than **4a**. Similarly, **3b** should boil *ca.* 14° higher than **4b**.

(0.75 mol) in the presence of catalytic amounts (2.5 ml) of concentrated H_2SO_4. After the mixture had been refluxed for 2 hr, it was cooled, washed with aqueous Na_2CO_3, and taken up in isopentane. Distillation under reduced pressure [38–40° (*ca.* 15 mm)] gave 1-chloro-2,2-dimethoxypropane (**5a**) (*ca.* 55%) in 85–90% purity, the accompanying compound being chloroacetone which can be removed by shaking with dilute aqueous KOH.

1-Bromo-2,2-dimethoxypropane (**5b**) was prepared analogously starting from bromoacetone[13] (**6b**).

Quinaldine Phosphate.—Quinaldine was mixed with 85% phosphoric acid in methanol as described for the reaction of related amines with phosphoric acid.[14] A white crystalline solid was precipitated, which melted at least above 216° and gave a satisfactory analysis for $C_{10}H_{12}NO_4P$. Addition of an excess of quinaldine to this compound did not appear to make any difference to the catalytic activity (Table II, run 4).

Quinaldine Tosylate.[15]—Quinaldine was added with stirring to a concentrated solution of *p*-toluenesulfonic acid in methanol until in excess which was recognizable by the persistence of the dark orange color of the amine. On slow addition of the resulting solution to ether a white solid precipitated which was collected, redissolved in methanol, and reprecipitated until all impurities had been removed. The solid was washed with ether, acetone, and isopentane and then dried giving quinaldine tosylate, mp 148–150°.

Reaction of *N*-Bromosuccinimide (2b) and 2-Methoxypropene (1). 2-Methoxyallyl Bromide (3b) and 1-Bromo-2-methoxypropene (4b).—2-Methoxypropene (1) and *N*-bromosuccinimide (**2b**) were allowed to react under the general conditions for allylic bromination[16] (*cf.* Table I, footnote *b*). The following conditions were found optimum for the preparation and isolation of **3b** (*cf.* Table I, run 9).

(a) The suspension of *N*-bromosuccinimide (50 g) in CCl_4 (150 ml) is preheated to *ca.* 55° (temperature measured inside reaction flask) on a water bath. Heating is then stopped, since the heat of the reaction sustains a temperature between 55 and 65°.

(b) An equimolar amount of 2-methoxypropene (20 ml), the purity of which is crucial for reducing the amount of undesirable by-products, is stirred into the reaction flask over a period of 30 min. Slow addition and vigorous stirring ensure a high conversion of enol ether.

(c) The reaction mixture is cooled to *ca.* 10–20° by immersion of the flask into ice for 15 min. Very little *N*-bromosuccinimide remains and any dissolved succinimide is precipitated.

(13) J. R. Catch, D. F. Elliott, D. H. Hey, and E. R. H. Jones, *J. Chem. Soc.*, 272 (1948).

(14) K. H. Engel, U. S. Patent 2,408,975 (1946) [*Chem. Abstr.*, **41**, 999*b* (1947)].

(15) A. F. Thomas, *J. Amer. Chem. Soc.*, **91**, 3282 (1969).

(16) L. Horner and E. H. Winkelmann, "Newer Methods of Preparative Organic Chemistry," Vol. 3, W. Foerst, Ed., Academic Press, New York, N. Y. 1964, p 151; C. Djerassi, *Chem. Rev.*, **43**, 271 (1948).

(d) The suspension is filtered quickly. Rapid removal of any remaining *N*-bromosuccinimide and the following step (e) prevent any undesirable consecutive reactions of the products.

(e) The filtered solution is concentrated at the water pump for *ca.* 15 min by immersion of the flask into warm water. This step removes any excess of 2-methoxypropene, methanol (which can be formed through adventitious water), any methyl acetate, and 2,2-dimethoxypropane (present as impurities in 2-methoxypropene) as well as some of the solvent CCl_4.

(f) The remaining solution is washed with dilute aqueous KOH (two 300-ml portions) and then with ice-cold water (two 100-ml portions). Shaking with dilute alkali destroys the adduct **7b**, any bromoacetone (**6b**), and any harmful traces of acid. Alkaline conditions also discourage the hydrolysis of any bromo ketal **5b** to bromoacetone and methanol and suppress the addition of water to enol ethers. Washing with ice-cold water neutralizes the solution and removes any methanol which in any event is unlikely to be present (also any acetone and 2,2-dimethoxypropane).

(g) The organic layer is dried immediately over $CaCl_2$ (enol ethers react with water!) and stored over anhydrous Na_2CO_3 in the dark as a *ca.* 50% solution of product in CCl_4 [neat 2-methoxyallyl bromide (**3b**) and 1-bromo-2-methoxypropene (**4b**) decompose at room temperature]. The solution so prepared contains **3b** (68–70%), **4b** (28–30%), and **5b** + **6b** + **7b** (0–4%). Pure **3b** as well as pure **4b** was isolated by preparative glc (Hewlett-Packard 776 preparative gas chromatograph, 20 ft × 0.75 in. Carbowax 20M column at 100°). 2-Methoxyallyl bromide (**3b**): *m/e* 152 ($C_4H_7O^{81}Br$), 150 ($C_4H_7O^{79}Br$); nmr (Table IV); glc retention time and retention index (Table V); and chemical transformations (see below). 1-Bromo-2-methoxypropane (**4b**): *m/e* 152 ($C_4H_7O^{81}Br$), 150 ($C_4H_7O^{79}Br$); nmr (Table IV); glc retention time and retention index (Table V); and its reaction with methanol (see below).

1-Bromo-2-methoxy-2-succinimidopropane (7b).—On removal of the bulk of the volatile products from the reaction mixture of **1** and **2b**, a dark brown residue remained which was kept for several days in a refrigerator. The impurity was absorbed on filter paper, and on standing for 2–3 weeks one obtained 1-bromo-2-methoxy-2-succinimidopropane (**7b**) as white, needle-like crystals: mp 32–34°; very soluble in acetone, benzene, CCl_4, $CHCl_3$, ethanol, furan, and glyme; slightly soluble in CH_2Cl_2, 1-pentene, chlorobenzene, and nitrobenzene; insoluble in isopentane, hexane, and petroleum ether (bp 40°); mass spectrum at 70 eV *m/e* 249 (at high pressure), 233.9775 (*m* − CH_3) (calcd for $C_7H_9NO_3{}^{79}Br$ 233.9776), 217.9818 (*m* − OCH_3) (calcd for $C_7H_9NO_2{}^{79}Br$ 217.9817), 170 (*m* − ^{79}Br), 156 (base peak) (*m* − $CH_2{}^{79}Br$), 151 (*m* − $C_4H_4NO_2$), 150 (*m* − $C_4H_5NO_2$).

The nmr spectrum (*cf.* Table IV) was recorded in chlorobenzene solution from 27 to 120°. While the succinimido and the methoxy resonances showed no change, those of the CH^cH^dBr and CCH_3 protons were temperature dependent. Specifically, the peaks at τ 5.38 and 5.48 (broad quartets) shifted upfield by 10 Hz, the peaks at τ 6.58 and 6.68 downfield by 2.2 Hz, and that at τ 8.13 upfield by 3.5 Hz. Also, the two broad quartets showed a small decrease in coupling, although the main part of this coupling was still present at 120°. All spectral changes were reversible over this temperature range. Nmr (100-MHz) in nitrobenzene solution (*ca.* 10%) at 27° was c 5.34 (broad quartet) + 5.44 (broad quartet, $J_{CH_3,H^c} \sim 0.6$ Hz), d 6.22 + 6.32 ($J_{H^c,H^d} = 10$ Hz), b 6.66 (s), e 7.22 (s), a 7.96 (d, $J_{CH_3,H^c} \sim 0.6$ Hz).

Reaction of *N*-Chlorosuccinimide (2a) and 2-Methoxypropene (1). 2-Methoxyallyl Chloride (3a) and 1-Chloro-2-methoxypropene (4a).—The reaction of 2-methoxypropene with *N*-chlorosuccinimide was very clean and carried out as that with *N*-bromosuccinimide, the only difference being that refluxing was required. The product mixture was analyzed (*cf.* Table III for a typical product distribution) and worked up as before yielding **3a** and **4a**. 2-Methoxyallyl chloride (**3a**): *m/e* 108 ($C_4H_7O^{37}Cl$), 106 ($C_4H_7O^{35}Cl$); nmr (*cf.* Table IV); glc retention times and retention indices (Table V); and chemical transformations (see below). 1-Chloro-2-methoxy propene (**4a**): *m/e* 108 ($C_4H_7O^{37}Cl$), 106 ($C_4H_7O^{35}Cl$); nmr (Table IV); glc retention times and retention indices (Table V); and its reaction with methanol (*cf.* below).

N-Iodosuccinimide (**2c**) and 2-methoxypropene (**1**) were refluxed in dry CCl_4 for 10 min, giving rise to a pink violet solution and a low conversion to products (*cf.* Table III), which included 2-methoxyallyl iodide (**3c**) and 1-iodo-2-methoxypropene (**4c**). **3c** can be prepared more conveniently from **3b** and NaI in acetone solution (*cf.* below).

Reaction of 2-Methoxyallyl Bromide (3b) and 1-Bromo-2-methoxypropene (4b) with Alcohols.—A 50% solution of **3b** and the isomeric enol ether **4b** in CCl_4 was mixed with methanol at room temperature and the ensuing reaction followed by nmr. After about 20 min the formation of 1-bromo-2,2-dimethoxypropane (**5b**) was complete, **3b** reacting somewhat faster than **4b**. The reaction time of the enol ethers toward ethanol was about the same (*ca.* 20 min) and *ca.* 40 min toward isopropyl alcohol, mixed ketals being formed. With *tert*-butyl alcohol 50% reaction occurred after 30 min at room temperature.

2-Methoxyallyl Chloride (3a) and 1-Chloro-2-methoxypropene (4a) by Pyrolysis of 1-Chloro-2,2-dimethoxypropane (5a).—The pyrolysis of 1-chloro-2,2-dimethoxypropane (**5a**) under the conditions of run 3 (Table II) may serve to illustrate our general procedure. **5a** (20 ml) and quinaldine phosphate (0.5 g) in a 50-ml flask attached to an air condenser (90 × 2 cm) were heated on a metal bath (180–250°), the temperature at the column head being kept below 111°.[17] The distillate was collected in a flask containing a stirred solution of aqueous Na_2CO_3. Methanol came over first and the fraction collected (106–110°) was found to contain unchanged starting material as well as *two* products rather than one[3] which were recognized and separated as described above and shown to be identical with authentic 2-methoxyallyl chloride (**3a**) and **4a** obtained by the reaction of *N*-chlorosuccinimide and 2-methoxypropene.

Except for the case of the acetic anhydride–acetic acid–quinaldine combination (Table II, run 8), elimination of methanol was found to require temperatures above 170°. Obviously, even then and in the presence of catalysts, loss of methanol was not instantaneous but a slow process. It commenced at about 180° with $K_2S_2O_7$ and at around 200° with quinaldine phosphate, while quinaldine tosylate seemed to have intermediate activity. Although $K_2S_2O_7$ and the conditions of run 8 produced the highest conversions of starting material at comparatively low temperature, the less acidic quinaldine phosphate appeared to give a higher proportion of 2-methoxyallyl chloride (**3a**). Addition of free quinaldine to the catalyst (run 4) made no discernible difference. Distillation of 1-chloro-2,2-dimethoxypropane (**5a**) under reduced pressure (bath temperature below 150°) in the presence of catalytic amounts of H_2SO_4 gave, aside from unchanged starting material **5a** (67%) and chloroacetone (**6a**) (16%), the desired 2-methoxyallyl chloride (**3a**) (10%) and **4a** (7%) (*cf.* also Table II, footnotes).

As regards the possible condenser types it would appear that a simple air condenser is more effective for pyrolysis than a Vigreux column, possibly because mixing of the components in the open tube will be minimized and recombination of methanol with the enol ether becomes less likely.

2-Methoxyallyl Bromide (3b) and 1-Bromo-2-methoxypropene (4b) by Thermolysis of 1-Bromo-2,2-dimethoxypropane (5b).—1-Bromo-2,2-dimethoxypropane (**5b**) was distilled for 2 hr under reduced pressure (bath temperature below 150°) and found to lose methanol readily, giving apart from starting material **5b** (53%), bromoacetone (**6b**) (12%), an unknown compound (6.3%), and the desired 2-methoxyallyl bromide (22%) and **4b** (7%).

Interconversion of 2-Methoxyallyl Halides *via* Halide Ion Displacement in Acetone.—2-Methoxyallyl chloride (**3a**) was dissolved in an excess of a saturated solution of LiBr in acetone and refluxed for *ca.* 6 hr. A 15% conversion into 2-methoxyallyl bromide (**3b**) occurred.

2-Methoxyallyl Iodide (3c).—A 50% solution (25 ml) of 2-methoxyallyl bromide (**3b**) and **4b** in CCl_4 was added dropwise at room temperature to an excess of a stirred saturated solution of NaI (40g) in acetone (400 ml). After 1 hr the mixture was washed with water (two 400-ml portions) and the lower dark brown layer separated and dried ($CaCl_2$). Swift distillation from mercury at reduced pressure gave a forerun of solvent and then a light yellow liquid [bp 18–20° (0.5–1 mm)] which proved to be pure 2-methoxyallyl iodide (**3c**) (2.5 ml, *ca.* 20% yield), mp −18 to −20°. **3c** is highly lachrymatory and decomposes

(17) Recently, Mr. C. Gatford has shown that **5a** can be pyrolyzed by dropwise addition to a mixture of catalyst in high-boiling solvent, *e.g.*, decalin (bp 189–196°). This method provides a convenient control of the pyrolysis and is more easily adaptable to a large-scale preparation.

rapidly at room temperature to give a thick black tar and was therefore stored at −80° in the dark.

Registry No.—**1**, 116-11-0; **2**, 128-08-5; **3a**, 32730-64-6; **3b**, 26562-24-3; **3c**, 32730-66-8; **4a**, 32730-67-9; **4b**, 26562-25-4; **4c**, 32730-69-1; **5a**, 32730-70-4; **5b**, 126-38-5; **5c**, 32730-72-6; **6a**, 78-95-5; **6b**, 598-31-2; **6c**, 3019-04-3; **7a**, 32827-44-4; **7b**, 32730-75-9; **7c**, 32730-76-0.

Acknowledgment.—We thank the Science Research Council (London) for a research studentship to G. G.

Alkaline Hydrolysis of Phosphoramidothioate Esters[1]

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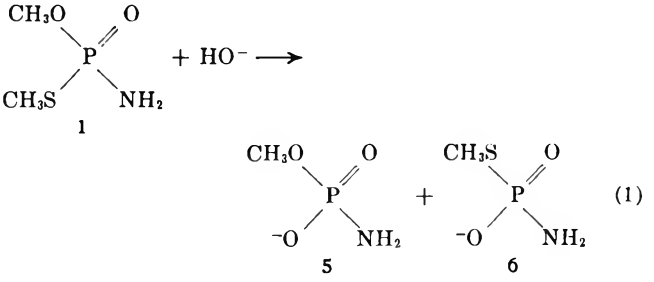
Received April 29, 1971

Products from the alkaline hydrolysis of *O*-methyl *S*-methyl phosphoramidothioate and its *N*-methyl and *N,N*-dimethyl derivatives were determined by analysis of pmr spectra and by glc. In aqueous potassium hydroxide *O*-methyl *S*-methyl phosphoramidothioate is hydrolyzed by P–O bond cleavage to give potassium *S*-methyl phosphoramidothioate as the major product while in the less polar solvents, methanol and acetone, P–S bond cleavage occurred to give mainly potassium *O*-methyl phosphoramidate. In ethanolic or propanolic potassium hydroxide the main products were potassium *O*-ethyl and *O*-propyl phosphoramidate, respectively, and dimethyl sulfide. Kinetic analysis showed that in water the second-order rate constants for P–O and P–S bond cleavage of *O*-methyl *S*-methyl phosphoramidothioate are 8.4 and 0.6 M^{-1} min^{-1}, respectively. Both rate constants and the relative rates of P–O/P–S bond cleavage decreased markedly with sequential substitution of the amido protons with methyl groups, and the *N,N*-dimethyl derivative hydrolyzed virtually exclusively by P–S bond cleavage but at a rate some 10^3 times slower than P–S cleavage in unsubstituted phosphoramidothioate. Exclusive P–S bond cleavage in the *N,N*-dimethylphosphoramidothioate evidently occurs by a normal concerted S_N2 reaction in which the best leaving group departs. In phosphoramidothioates containing at least one amido proton the results are rationalized in terms of two competing processes, an addition–elimination reaction on phosphorus leading to P–O bond cleavage and an elimination reaction involving the amido proton to give P–S bond cleavage.

O-Methyl *S*-methyl phosphoramidothioate[2,3] (Monitor, Chevron Chemical Co.) is a relatively simple organophosphorus ester which is currently under development as a potential insecticide. Monitor or **1** is highly toxic to a variety of insects,[4] producing typical cholinergic symptoms of intoxication. In an earlier investigation[4] on the mode of action of **1** and related esters it was suggested that the alkylthiolate moiety was released when the cholinesterase enzyme was inhibited by the phosphoramidothioate ester. Subsequently, however, examination of the reaction between **1** and hydroxide ion has shown that methylthiolate ion is not always the major product but methoxide also is liberated, the relative amounts depending on the conditions of the reaction. Because of the possible connection between alkaline hydrolysis rates and anticholinesterase activity, an examination of the alkaline hydrolysis of **1** and its *N*-methyl (**2**) and *N,N*-dimethyl (**3**) analogs was initiated. Product and kinetic analyses were undertaken to sort out the various individual reactions and to assess quantitatively their relative importance in the overall hydrolysis reaction. Particular attention was given to the effect of sequential substitution of methyl groups on the nitrogen atom and of solvent on the specific rates of P–O and P–S bond cleavage.

Results

Products of Alkaline Hydrolysis.—Pmr spectra of the products obtained from the hydrolysis of *O*-methyl *S*-methyl phosphoramidothioate (**1**) with equimolar amounts of potassium hydroxide in water and in 50% aqueous acetone showed that two monoanionic products were obtained, one by P–S cleavage giving *O*-methyl phosphoramidate anion (**5**) and the other by P–O cleavage giving *S*-methyl phosphoramidothioate anion (**6**). In water the major product obtained was **6**, since analysis of the pmr integrals for P–OCH_3 protons



(1)

(doublet centered at δ 3.7, J = 11 Hz) and P–SCH_3 protons (doublet centered at δ 2.2, J = 12 Hz) showed a ratio of **5**:**6** of 1:4.5. In 50% aqueous acetone, however, **5** was the major product, and the ratio of **5**:**6** in this case was 5.1:1. Support for the ratio of products obtained by integration of pmr spectra was provided by glc analysis after remethylation of the mixture of **5** and **6** with diazomethane. Remethylation of **5** and **6** gave dimethyl phosphoramidate (**4**), retention time 1.75 min, and **1**, retention time 3.50 min, respectively, and the ratio of these products was virtually identical with the ratio of **5**:**6** obtained by proton integration. Confirmation of product ratios by glc, therefore, allowed the use of pmr as the major means of product analysis.

Data for product analysis by pmr after alkaline hydrolysis of **1** in a variety of solvent systems are given in Table I. The results indicate that the solvent strongly influences the relative percentages of **5** and

(1) This investigation was supported in part by the U. S. Public Health Service Research Grant No. EP 00806 from the Environmental Protection Agency; The Rockefeller Foundation; and Cotton Incorporated.

(2) Chevron Research Corp., Netherlands Patent Application 6,602,588 (Jan 2, 1967); *Chem. Abstr.*, **67**, 10691y (1967).

(3) W. Lorenz, G. Schrader, G. Unterstenkoefer, and I. Hammermann, A. G. Belgian Patent 666,143 (Dec 30, 1965); *Chem. Abstr.*, **65**, 16864 (1966).

(4) G. B. Quistad, T. R. Fukuto, and R. L. Metcalf, *J. Agr. Food Chem.*, **18**, 189 (1970).

TABLE I
SALT DISTRIBUTION IN ALKALINE HYDROLYSIS OF O-METHYL S-METHYL PHOSPHORAMIDOTHIOATE IN VARIOUS ORGANIC–WATER SOLVENT MIXTURES AT 23°

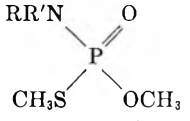
% Organic solvent in aqueous mixture (v/v)	% Salt containing— P-OCH_3	P-SCH_3
Methanol 100	93	7
95	86	14
90	79	21
85	76	24
80	67	33
75	63	37
65	50	50
50	40	60
0	18	82
Acetone 50	83	17
Mesityl oxide 10, ethanol 30	33	67
Propionaldehyde 50, ethanol 25	80	20
Formaldehyde[a] 30	100	
Acetophenone 20, ethanol 60	25	75
Acetonitrile 50	23	77
2-Butanone 45, ethanol 10	60	40
Ethanol 100	7.5	12.5
	80[b]	
Propanol 100	10	22.5
	67.5[c]	
Benzaldehyde 25, ethanol 20	83	17

[a] Extensive polymerization occurred. [b] P-OC_2H_5. [c] P-OC_3H_7.

6 produced and, in the case of the methanol–water system, an increasingly larger amount of P–O bond cleavage was obtained with increasing amounts of water; *e.g.*, 5:6 in absolute methanol was 93:7 compared to 18:82 in water.

When **1** was treated with an equimolar amount of potassium hydroxide in absolute ethanol or propanol, the major product was neither **5** nor **6** but the potassium salt of *O*-ethyl and *O*-propyl phosphoramidic acid, respectively. Further, distillation of the reaction mixture containing 1-propanol or ethanol as a solvent gave a low-boiling fraction (37–40°) which was identified by glc and pmr as dimethyl sulfide. Dimethyl sulfide also was isolated by the same procedure in varying quantities after the treatment of **1**, *O*-methyl *S*-methyl *N*-methylphosphoramidothioate (**2**), and *O*-methyl *S*-methyl *N*,*N*-dimethylphosphoramidothioate (**3**) with potassium hydroxide in water (Table II). Dimethyl sulfide apparently is formed

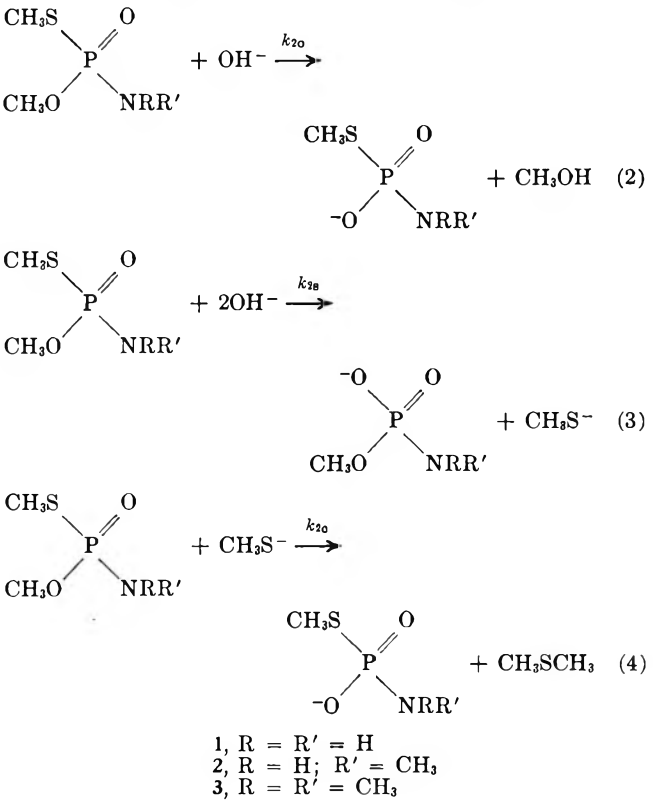
TABLE II
PRODUCT DISTRIBUTION AFTER HYDROLYSIS OF PHOSPHORAMIDOTHIOATES BY AQUEOUS POTASSIUM HYDROXIDE IN A SEALED AMPOULE



R	R′	Reac- tion Temp, °C	tion time, hr	% Salt containing— P-OCH_3	P-SCH_3	% MeOH	% CH_3SCH_3
H	H	23	4	18	82	75	10
H	CH_3	23	16	52	48	30	19
CH_3	CH_3	23	96	50	50	13–15[a]	*b*
CH_3	CH_3	96	14	42	58	24	32

[a] Reaction mixture was distilled to obtain methanol in high concentration for glc. [b] Reaction at atmospheric pressure; dimethyl sulfide was not determined.

from the reaction between methylthiolate anion, produced by P–S bond cleavage, and the starting ester. O-Demethylation by thiolate anions has been demonstrated by others.[5] Therefore, the reactions involved in the decomposition of **1** and related esters by hydroxide ion may be depicted as follows (eq 2–4). Here



1, R = R′ = H
2, R = H; R′ = CH_3
3, R = R′ = CH_3

k_{2o}, k_{2s}, and k_{2c} are the specific second-order rate constants for P–O, P–S, and C–O bond cleavage, respectively.

Evidently, *S*-methyl phosphoramidothioate anion (**6**) may be produced in two ways, from replacement by hydroxide ion according to eq 2 or from O-demethylation by methylthiolate ion according to eq 4. The extent of **6** (or its *N*-methyl and *N*,*N*-dimethyl equivalent) formed by replacement of methoxide by hydroxide ion was determined by glc analysis for methanol in the reaction mixture. Quantitative data showing the relative amounts of the various products produced after treatment of **1**, **2**, and **3** by equimolar aqueous potassium hydroxide are presented in Table II. The results indicate that the O-demethylation reaction to produce **6** or its *N*-alkyl derivatives becomes increasingly important with sequential methylation of nitrogen.

Finally, in order to determine whether potassium hydroxide treatment of **1** produced methanol by P–O or C–O bond cleavage, the reaction was carried out in water enriched with $H_2{}^{18}O$. The liberated methanol was examined by mass spectrometry and no significant ^{18}O incorporation was found, indicating that hydrolysis occurred by P–O bond cleavage.

Kinetic Analysis.—Equations 2–4 provide an example in which the second-order reactions are both parallel and in series.[6] By restricting the conditions of the reactions it was possible to evaluate the various rate constants with reasonable confidence.

Hydrolysis of *O*-Methyl *S*-Methyl Phosphoramidothioate (1).—Under conditions of high concentrations

(5) B. Miller, *Proc. Chem. Soc.*, 303 (1962).
(6) A. A. Frost and R. G. Pearson, "Kinetics and Mechanism," Wiley, New York, N. Y., 1961, p 178.

of 1 compared to hydroxide, the values for the overall pseudo-first-order rate constant k_1 were obtained by following hydroxide ion consumption from estimation of the change in pH. Under these conditions eq 4 may be omitted in the kinetic analysis of 1 since hydroxide ion is not involved in this equation. Figure 1 shows the plot of pH *vs.* time based on the relation $pH = -k_1t/2.303 + pH_0$ where pH_0 is the initial pH and k_1 is the overall pseudo-first-order constant at constant phosphoramidothioate concentration. Also, $k_1 = k_{1o} + ak_{1s}$ where k_{1o} and k_{1s} are the pseudo-first-order constants for P–O and P–S cleavage, respectively. The value of the coefficient a depends on the pH of the solution; *i.e.*, a is 2 at pH substantially greater than the pK_a of methanethiol (10.7) and a is 1 at pH lower than 10.7. From the slope of the line, the values for the overall pseudo-first-order constant k_1 and overall second-order constant k_2 at 27° was calculated to be 0.96 min^{-1} and 9.6 M^{-1} min^{-1} (1 was 0.1 M), respectively.

The value of k_{2o}, the second-order constant for P–O bond cleavage, was determined directly by following methanol production under second-order conditions of 1 and hydroxide ion as shown in Figure 2. The plot was reasonably linear up to about 65% reaction and k_{2o} was calculated to be 8.4 M^{-1} min^{-1} at 27°. From the relationship $k_2 = k_{2o} + 2k_{2s} = 9.6$ M^{-1} min^{-1}, k_{2s} was calculated to be 0.6 M^{-1} min^{-1}. Values for k_{2o} and k_{2s} are given in Table III.

TABLE III
SECOND-ORDER RATE CONSTANTS FOR P–O (k_{2o}) AND P–S (k_{2s}) CLEAVAGE OF PHOSPHORAMIDOTHIOATES IN AQUEOUS POTASSIUM HYDROXIDE AT 27°

	k_{2o}, M^{-1} min^{-1}	k_{2s}, M^{-1} min^{-1}
$(CH_3O)(CH_3S)P(O)NH_2$	8.4	0.6
$(CH_3O)(CH_3S)P(O)NHCH_3$	1.0×10^{-3}	4.4×10^{-2}
$(CH_3O)(CH_3S)P(O)N(CH_3)_2$		1.5×10^{-4}

Effect of Acetone on Hydrolysis of 1.—The effect of acetone on the values of the pseudo-first-order constants k'_{1o} and k'_{1s} under conditions of constant pH for P–O and P–S cleavage is shown in Table IV. Because of

TABLE IV
PSEUDO-FIRST-ORDER RATE CONSTANTS IN AQUEOUS ACETONE FOR THE ALKALINE HYDROLYSIS OF *O*-METHYL *S*-METHYL PHOSPHORAMIDOTHIOATE AT pH 10, μ = 0.2 M

% Acetone (v/v)	$k'_{1s} \times 10^3$, min^{-1}	$k'_{1o} \times 10^2$, min^{-1}	Calcd from CH_3SH release ($t_{1/2}$)	Calcd from HO^- consumption
0				3.0
10	1.6	5.0	6.9	
20	3.1	5.5	8.6	
30	4.2	5.9	10.6	10.1
40	6.2	6.0	12.5	12.2

interference by acetone in the glc analysis of methanol, it was not possible to determine k'_{1o} directly in solvents containing acetone. Therefore, k'_{1o} was calculated from the values of k'_1 (overall pseudo-first-order constant at constant pH) and k'_{1s} was determined at pH 10.0 in aqueous solvents containing 0–40% acetone and sodium carbonate as the buffer. k'_{1s} was calculated from the relationship below (eq 5) by following

$$\frac{[CH_3SH]}{[A_0]} = \frac{k'_{1s}}{k'_1}(1 - e^{-k'_1t}) \qquad (5)$$

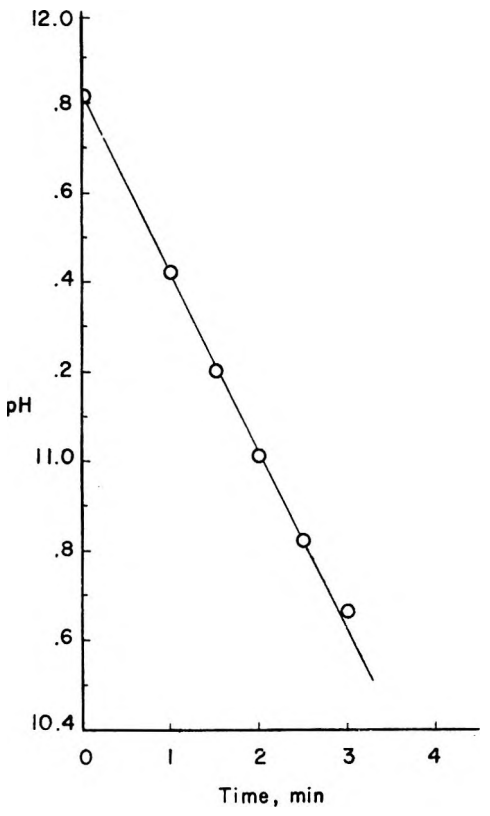


Figure 1.—Plot showing rate of hydroxide ion decrease at 27°; *O*-methyl *S*-methyl phosphoramidothioate (1) is 0.1 M.

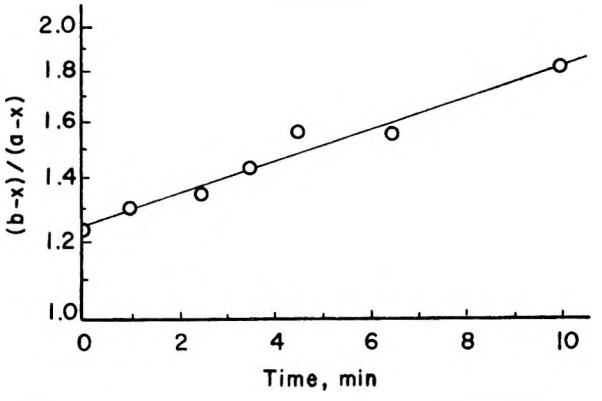


Figure 2.—Second-order plot showing rate of P–O bond cleavage from estimation of methanol formation at 27°; a = 2.0 × 10^{-2} M *O*-methyl *S*-methyl phosphoramidothioate (1), $b = HO^- = 2.4 \times 10^{-2}$ M, x = methanol concentration.

methanethiol formation where $[A_0]$ is the initial concentration of 1. A plot of $[CH_3SH]/[A_0]$ *vs.* $(1 - e^{-k'_1t})$ gave the linear relationship shown in Figure 3 and k'_{1s} was calculated from the slope. The value of k'_1 was determined from the amount of base needed to maintain a pH of 10.0 using a micrometer-driven syringe containing standardized aqueous potassium hydroxide. k'_1 also was calculated from the relationship $t_{1/2} = \ln 2/k'_1$ which follows from eq 5 where $t_{1/2}$ is the time required to liberate one-half of the total amount of methanethiol released. The data in Table IV show good agreement between the values of k'_1 obtained by estimation of potassium hydroxide consumption and that calculated from the $t_{1/2}$ value for methanethiol release.

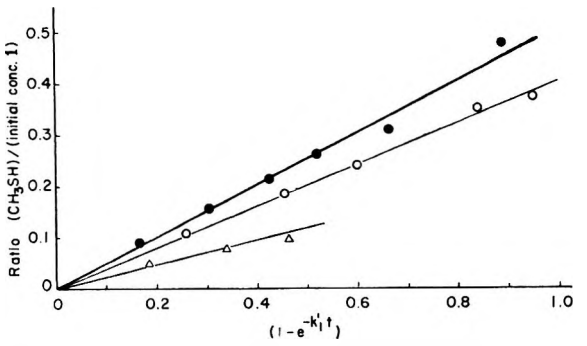


Figure 3.—Plots showing the rate of P–S bond cleavage of *O*-methyl *S*-methyl phosphoramidothioate (1) according to eq 5 in aqueous acetone at 27°: initial concentration of 1 = 8×10^{-3} *M*; ●, 40% acetone; ○, 30% acetone; △, 10% acetone.

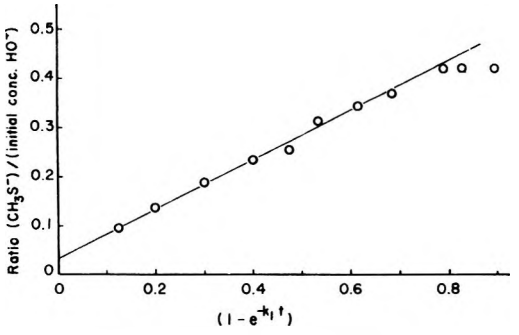


Figure 4.—A plot showing the rate of P–S bond cleavage of *O*-methyl *S*-methyl *N*-methylphosphoramidothioate (2) according to eq 13 at 27°: 2 = 0.5 *M*, HO^- = 2.48×10^{-2} *M*.

Hydrolysis of *O*-Methyl *S*-Methyl *N*-Methylphosphoramidothioate (2).—The overall rate of reaction between *O*-methyl *S*-methyl *N*-methylphosphoramidothioate (2) and hydroxide ion determined by estimating change in pH was approximately 110-fold slower than **1**, with a pseudo-first-order rate (excess of 2) constant k_1 of 4.45×10^{-2} min^{-1} and a second-order rate constant k_2 of 8.9×10^{-2} M^{-1} min^{-1}. Because of the slow rate of reaction between 2 and hydroxide ion, loss of 2 by dealkylation (eq 3) was significant and it was possible to determine k_{1c} (the pseudo-first-order rate constant for C–O cleavage) as well as k_{1o} and k_{1s}. Kinetic analysis was accomplished by imposing again, as in the case of **1**, pseudo-first-order conditions, *i.e.*, high concentrations of 2 relative to hydroxide ion. Under these conditions, eq 2, 3, and 4 may be designated as follows

$$A + B \xrightarrow{k_{1o}} C \quad (6)$$

$$A + B \xrightarrow{k_{1s}} D \quad (7)$$

$$A + D \xrightarrow{k_{1c}} G \quad (8)$$

where A = 2, B = hydroxide ion, C = methanol, D = methylthiolate ion, and G = dimethyl sulfide. From eq 6, 7, and 8, and since A is constant, eq 9 and 10 may be obtained.

$$\frac{-d[B]}{dt} = k_1[B] = k_{1o}[B] + 2k_{1s}[B] \quad (9)$$

$$\frac{d[D]}{dt} = k_{1s}[B] - k_{1c}[D] \quad (10)$$

Since $[B] = [B_0]e^{-k_1 t}$, where $[B_0]$ is the initial hydroxide ion concentration, eq 10 becomes eq 11.

$$\frac{d[D]}{dt} = k_{1s}[B_0]e^{-k_1 t} - k_{1c}[D] \quad (11)$$

This first-order differential equation has the following solution.

$$[D] = \frac{k_{1s}[B_0]}{k_{1c} - k_1}(e^{-k_1 t} - e^{-k_{1c} t}) \quad (12)$$

When k_{1c} is small compared to k_{1s}, integration of eq 11 results in eq 13.

$$\frac{[D]}{[B_0]} = \frac{k_{1s}}{k_1}(1 - e^{-k_1 t}) \quad (13)$$

This equation is similar to eq 5 where $[B_0]$ (initial hydroxide ion concentration) is substituted for $[A_0]$ (phosphoramidothioate concentration).

Figure 4 gives the plot of $[CH_3S^-]/[OH_0^-]$ *vs.* $(1 - e^{-k_1 t})$. Expected linearity was obtained over the major portion of the reaction from which k_{1s} at 27° was calculated as 2.20×10^{-2} min^{-1}. From the relation $k_1 = k_{1o} + 2k_{1s} = 4.45 \times 10^{-2}$ min^{-1} the value of k_{1o} was calculated as 5×10^{-4} min^{-1}. The corresponding second-order rate constants k_{2o} and k_{2s} given in Table III were obtained by dividing the values of k_{1o} and k_{1s} by 0.5 *M* (initial concentration of 2). It should be noted that the line in Figure 4 does not pass through the origin. This was interpreted as being attributable to localized hydrolysis when the potassium hydroxide solution was mixed with the compound. This corresponds to about 7% reaction.

The value of k_{1c} was calculated by using eq 12 with the aid of a computer. By setting the value of k_1 to 4.45×10^{-2} min^{-1}, estimated values of k_{1s} and k_{1c} were substituted in eq 12 until the calculated values of methylthiolate ion concentration at different time intervals coincided with the experimental values. Best fit of the data was obtained when k_{1s} was 2.2×10^{-2} min^{-1} and k_{1c} was 3.6×10^{-3} min^{-1}. Figure 5 shows the relationship between the curve calculated from eq 12 and the observed curve after correction for localized hydrolysis.

Hydrolysis of *O*-Methyl *S*-Methyl *N*,*N*-Dimethylphosphoramidothioate (3).—The rate of hydrolysis of **3** was much slower than that of 2 under identical first-order conditions of excess phosphoramidothioate over base with a pseudo-first-order constant k_1 for the disappearance of hydroxide ion of 1.4×10^{-4} min^{-1}. No methanethiol was detectable at any time during the course of the reaction, indicating that the rate of reaction between methanethiolate ion and **3** to form dimethyl sulfide was considerably faster than the initial reaction between hydroxide ion and **3**. k_{1c}, the pseudo-first-order rate constant for methyl–oxygen bond cleavage for 2 and **3** under the same condition, should be similar, and based on the value of $k_{1c} = 3.6 \times 10^{-3}$ min^{-1} obtained for 2, the dealkylation reaction for **3** should be approximately 25-fold faster than the initial reaction.

Analysis of products after reaction between **3** and potassium hydroxide showed that P–O cleavage was much slower than P–S cleavage (23°) and this coupled with the above information gives the order $k_{1c} > k_{1s} \gg k_{1o}$. By making the assumption that k_{1o} is negligibly small compared to k_{1s}, the kinetics of the reac-

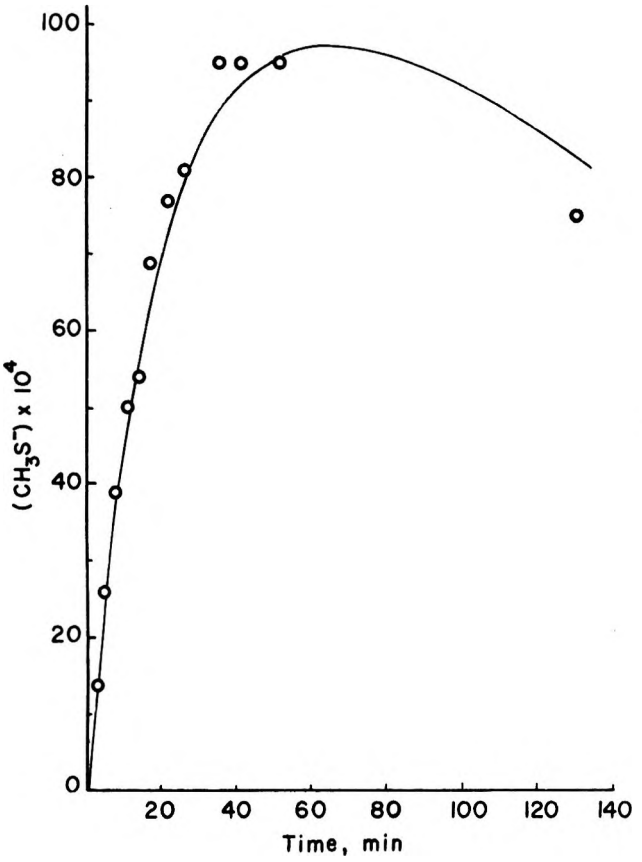
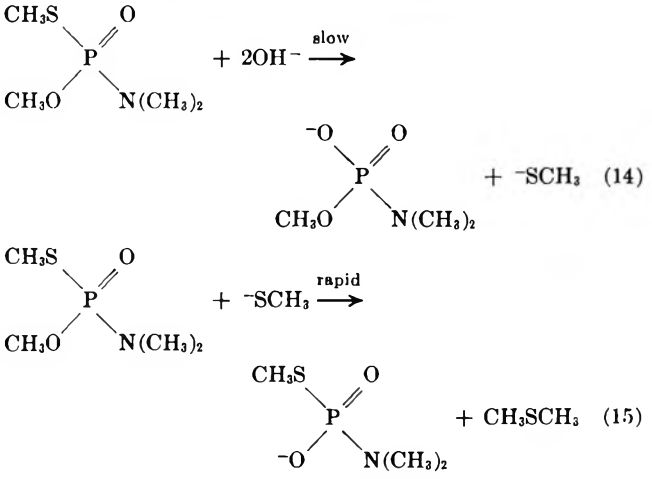


Figure 5.—A curve showing the relationship between the amount of methylthiolate calculated from eq 12 (solid line) and the experimental values (O) during the reaction between *O*-methyl *S*-methyl *N*-methylphosphoramidothioate and hydroxide ion.

tion may be approximated to a second-order situation with the provision that 2 mol of **3** are consumed (1 mol by P–S cleavage in the rate-determining step and 1 mol by a rapid dealkylation reaction) with 2 mol of hydroxide ion (1 mol for P–S cleavage and 1 mol for rapid neutralization of the resulting phosphoramidic acid) according to the following equations.



By using equimolar amounts of **3** and hydroxide ion the value for the second-order rate constant k_{2s} for P–S cleavage may be determined from eq 16 where

$$1/[OH^-] = 1/[OH^-_0] + 2k_{2s}t \quad (16)$$

$[OH^-]$ and $[OH_0^-]$ are the concentrations of hydroxide ion at time t and time zero, respectively. Figure 6

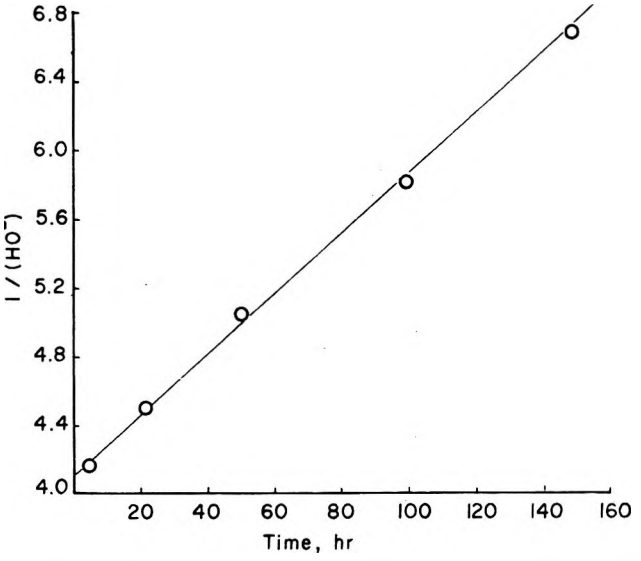


Figure 6.—A second-order plot of the reaction between *O*-methyl *S*-methyl *N*,*N*-dimethylphosphoramidothioate (**3**) and hydroxide ion.

gives the relation obtained when $1/[OH^-]$ is plotted against time from data obtained in a separate experiment using equimolar concentrations of **3** and hydroxide ion. The excellent straight line obtained over a 45% reaction range provides support for the assumptions made in the kinetic approach; *i.e.*, the overall reaction is second-order. From the plot, k_{2s} was found to be $1.5 \times 10^{-4}\ M^{-1}\ \text{min}^{-1}$ (27°).

The value of k_1 ($1.4 \times 10^{-4}\ \text{min}^{-1}$) obtained under the pseudo-first-order condition of excess phosphoramidothioate (**3** was 0.5 M) also is equal to $2k_{1s}$ since k_{1o} is negligible. From this relationship also k_{2s} may be calculated as $1.4 \times 10^{-4}\ M^{-1}\ \text{min}^{-1}$, in good agreement with the value obtained under second-order conditions.

Hydrolysis of *S*,*S*-Dimethyl Phosphoramidodithioate (7).—*S*,*S*-Dimethyl phosphoramidodithioate (**7**) was examined, since under alkaline conditions it can hydrolyze only by P–S bond cleavage without other competing reactions. The second-order rate constant k_2 for the reaction between **7** and aqueous potassium hydroxide (0.1 M) was 0.65 $M^{-1}\ \text{min}^{-1}$ at 25°. When the solvent was changed to 10% acetone–water (by volume), k_2 increased to 9.0 $M^{-1}\ \text{min}^{-1}$ and in 20% acetone–water k_2 was 19 $M^{-1}\ \text{min}^{-1}$. Thus, the addition of acetone caused an increase in k_2 similar to the effect of acetone on k'_{1s} observed with **1**.

Hydrolysis of *O*,*O*-Dimethyl Phosphoramidothioate (8).—Compared to simple trialkyl phosphorothionates, the rate of reaction between hydroxide ion and *O*,*O*-dimethyl phosphoramidothioate was relatively fast with a second-order constant for P–O cleavage of 1.1 $M^{-1}\ \text{min}^{-1}$ at 37°, a value which is about fivefold smaller than that obtained for dimethyl phosphoramidate ($5.0\ M^{-1}\ \text{min}^{-1}$) at the same temperature.[7]

Discussion

Effect of Solvent.—Because of the greater lability of the P–S bond,[8,9] the hydrolysis of **1** in aqueous potas-

(7) I. Öney and M. Caplow, *J. Amer. Chem. Soc.*, **89**, 6972 (1967).
(8) E. M. Thain, *J. Chem. Soc.*, 4694 (1957).
(9) D. C. Dittmer and O. B. Ramsay, *J. Org. Chem.*, **28**, 1268 (1963).

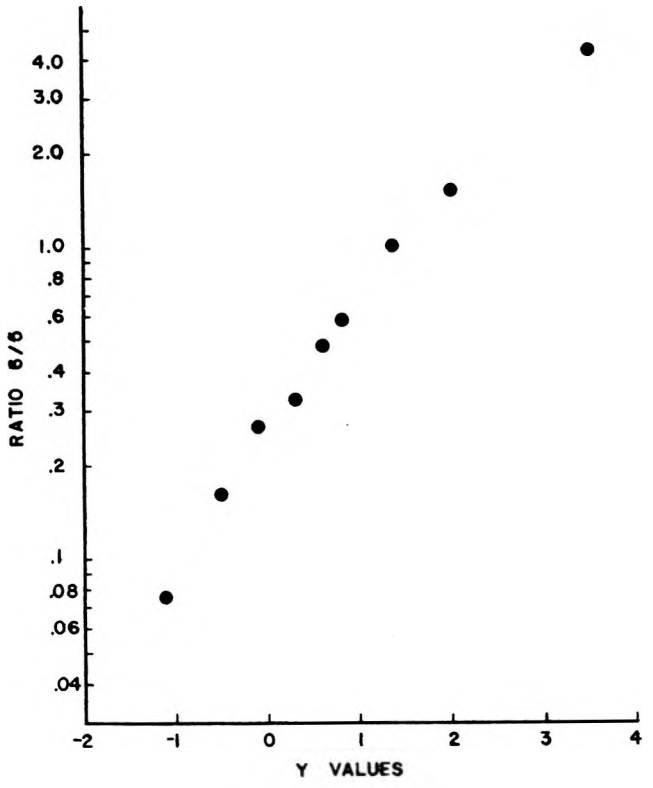


Figure 7.—Relation between Grunwald–Winstein Y values and the logarithm of the ratio of potassium S-methyl phosphoramidothioate (6) to O-methyl phosphoramidate (5).

sium hydroxide by predominantly P–O bond rather than P–S bond cleavage was unexpected. The ionizing capacity of the solvent evidently plays a dominant role in establishing the direction in which **1** is hydrolyzed by potassium hydroxide. The influence of solvent on the reaction is illustrated in Figure 7 which shows the relation between Grunwald–Winstein Y values for water–methanol[10,11] and the logarithm of the ratio of **6** to **5**. Although the product ratio in two parallel second-order reactions at any time is equal to the ratio of rate constants,[12] the value of **6**/**5** may only be considered as an approximation of the relative rate constants for P–O and P–S cleavage, since the same salt is obtained by O-demethylation and P–O cleavage. Figure 7 shows, however, that alkaline hydrolysis of **1** by P–O bond cleavage is favored in solvents of greater ionizing capacity. In less polar solvents P–S bond cleavage predominates, suggesting that the two competing reactions (P–O and P–S cleavage) occur by different mechanisms.

Table IV shows the effect of increasing amounts of acetone on the pseudo-first-order rate constants for P–O (k'_{1o}) and P–S (k'_{1s}) cleavage of **1** at pH 10.0. Figure 8 gives the relation between these constants and Grunwald–Winstein Y values for the relevant acetone–water mixtures. Although the relationship is clearly not linear, it does focus on the far greater dependency of k'_{1s} on solvent polarity; *e.g.*, k'_{1s} increases almost fourfold from 10% to 40% acetone while k'_{1o} remains virtually constant. Thus, in increasing apolar solvent P–S cleavage becomes increasingly important,

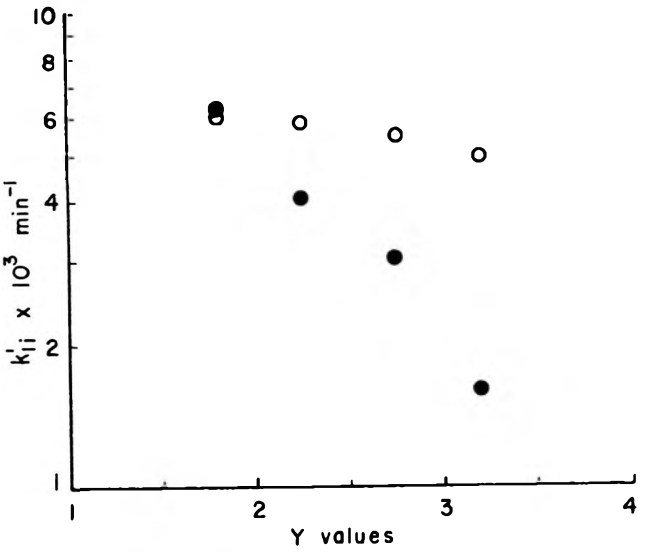


Figure 8.—Relationship between k_{1s} (●) and k_{1o} (○) and Grunwald–Winstein Y values for the alkaline hydrolysis of O-methyl S-methyl phosphoramidothioate in aqueous acetone.

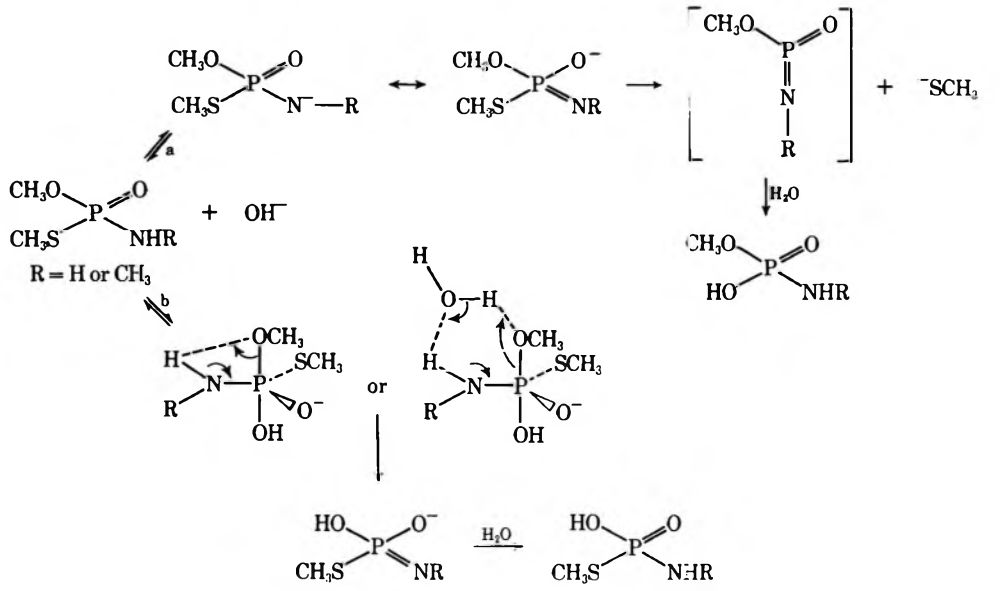
resulting eventually in a changeover in ratio of products.

The effect of acetone on the rate of P–S cleavage was even more pronounced in the alkaline hydrolysis of S,S-dimethyl phosphoramidodithioate (**7**). In water the second-order rate constant for the alkaline hydrolysis of **7** after correction for two methylthiolate leaving groups is 0.65 M^{-1} min^{-1} at 25°, virtually identical with the k_{2s} value of 0.6 M^{-1} min^{-1} for **1** at 27°. In alkaline solutions containing 10% and 20% acetone, the rate constant for **7** increased approximately 15- and 30-fold, respectively.

Effect of Methyl Substitution.—The values for the specific second-order rate constants for P–O (k_{2o}) and P–S (k_{2s}) bond cleavage for **1**, **2**, and **3** in aqueous potassium hydroxide at 27° in Table III show that there is a marked decrease in both k_{2o} and k_{2s} with sequential substitution of amido protons by methyl. In addition, the relative rates for P–O and P–S cleavage also decreased; *e.g.*, k_{2o}/k_{2s} was 14 for **1**, 0.023 for **2**, and presumably much smaller for **3**. Thus, **1** was hydrolyzed predominantly by P–O cleavage while P–S cleavage predominated with **2** and **3**.

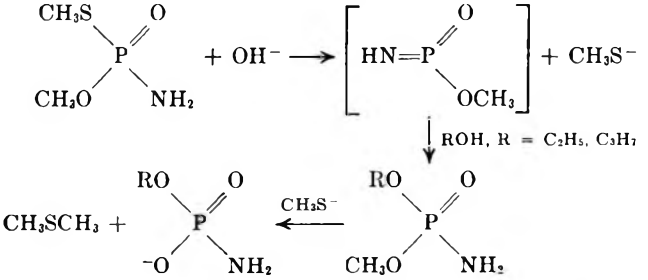
The value for k_2 of 5.0 M^{-1} min^{-1} (37°) previously reported for hydroxide ion catalyzed hydrolysis of dimethyl phosphoramidate[7] (**4**) is close to that for **1** at 27° and suggests that P–O cleavage in **1** and **4** occurs by a similar mechanism. Since compound **4** undergoes alkaline hydrolysis 10^4-fold faster than its N,N-dimethyl analog, a mechanism involving a metaphosphorimidate intermediate formed after removal of one of the nitrogen protons was suggested. In addition, a similar mechanism involving a phosphorimidate intermediate has been proposed by others[13,14] to account for the rapid hydrolysis of certain phosphoramidic chlorides. Our results, however, are difficult to rationalize in terms of a single process of this type alone. A plausible mechanism in which two different processes are taking place simultaneously may be suggested from the data: process a, which involves hy-

(10) E. Grunwald and S. Winstein, *J. Amer. Chem. Soc.*, **70**, 846 (1948).
(11) E. Alexander, "Principles of Ionic Organic Reactions," Wiley, New York, N. Y., 1961, p 91.
(12) Reference 6, p 165.
(13) P. S. Traylor and F. H. Westheimer, *J. Amer. Chem. Soc.*, **87**, 553 (1965).
(14) A. F. Gerrard and N. K. Hamer, *J. Chem. Soc. B*, 539 (1968).



droxide ion attack on the amido proton, leading to the phosphoramidothioate anion which decomposes in a rate-determining step to give P–S cleavage, and process b, which involves attack of hydroxide ion on the phosphorus atom, eventually resulting in P–O cleavage.

Process a, leading to P–S cleavage and phosphorimidate formation, is analogous to the mechanism proposed for base-catalyzed hydrolysis of phosphoramidic chlorides.[13,14] Direct support for this mechanism is found in results obtained from the analysis of products after base-catalyzed hydrolysis of **1** in absolute ethanol and propanol. The observation that **1** reacts with potassium hydroxide in absolute ethanol or propanol to give as major products dimethyl sulfide and the potassium salt of ethyl and propyl phosphoramidic acid, respectively, strongly indicates that this reaction proceeds through a metaphosphorimidate. In ethanol or propanol the intermediate is solvolyzed to give ethyl or propyl methyl phosphoramidate, which is in turn demethylated by methylthiolate anion to produce the respective products as shown below.



The finding that P–O cleavage predominates in highly polar solvents suggests that this reaction proceeds by a process involving hydroxide ion attack on the phosphorus atom, either by a concerted S_N2 (P) or by an addition–elimination reaction. Although a concerted S_N2 reaction may lead to P–O cleavage, it does not account for the preponderance of P–O over P–S cleavage, particularly since methylthiolate ion is a superior leaving group compared to methoxide ion. Thus, process b, leading to P–O cleavage, probably involves, at least in the case of **1** and **2**, the addition of the hydroxide ion to the phosphoramidothioate followed by a rapid elimination of the alkoxy group rather than a concerted S_N2 type reaction. The addition step is expected to lead to a trigonal bipyramidal intermediate and from preference rules[15] the methoxy and hydroxy groups should occupy apical positions. With the methoxy group in an apical position, its departure may be assisted by the nitrogen proton either directly or indirectly by the intervention of a water molecule as indicated in the mechanism given above. The addition–elimination mechanism explains why P–O cleavage takes place with **1** and **2** but does not occur with **3** where the nitrogen atom is fully substituted with methyl groups. The exclusive cleavage of the P–S bond in **3** probably occurs by a concerted S_N2 mechanism in which the best leaving group, *i.e.*, methylthiolate, is displaced by hydroxide ion.[8,9] This is the usual type of substitution reaction with most triesters of phosphoric acid.[16] The fact that the hydrolysis of **3** by P–S cleavage is approximately 3×10^3 times slower than that of **1** suggests different mechanisms for the hydrolysis of **1** and **3**.

Other evidence which is consistent with a mechanism postulating initial hydroxide attack on phosphorus to explain P–O bond cleavage is that *O,O*-dimethyl phosphoramidothioate (**8**) hydrolyzes approximately fivefold slower than the corresponding P=O analog in aqueous alkali, resulting exclusively in P–O cleavage. The difference in rates is consistent with the known deactivating effect of thiono sulfur[16] in reactions involving attack of a nucleophile on phosphorus. Further, the approximately threefold greater rate of P–O cleavage of **1** by hydroxide ion compared to dimethyl phosphoramidate (**4**) also is consistent with this mechanism owing to less d_π–p_π overlap between sulfur and phosphorus in **1**. In contrast, *O*-methyl *N*-cyclohexylphosphoramidothioic chloride has been reported[17] to hydrolyze substantially faster than its P=O derivative with elimination of chloride ion. These results have been rationalized on the basis of a mechanism involving hydroxide ion attack on amido proton with subsequent elimination of chloride, a good leaving group, and to the relative ease of formation

(15) F. H. Westheimer, *Accounts Chem. Res.*, **1**, 70 (1968).
(16) J. R. Cox and O. B. Ramsay, *Chem. Rev.*, **64**, 317 (1964).
(17) A. F. Gerard and N. K. Hamer, *J. Chem. Soc. B*, 369 (1969).

of P=S phosphorimidate compared to P=O phosphorimidate. It is unlikely, however, that P–O cleavage occurs by this type of mechanism because of the poor leaving ability of the methoxide moiety.[18]

The rate of P–O cleavage in the reaction between **1** and aqueous potassium hydroxide is more than tenfold greater than the rate at which **7** undergoes P–S cleavage under similar conditions. This may be attributed to the catalytic effect provided by the amido proton through hydrogen bonding with the leaving methoxyl moiety in the transition state. Catalytic effects of this type where a nucleophile attacks the reactive center and a proton assists the leaving group are known.[19] The substantial drop in rate of P–O cleavage of **2** compared to **1** may be attributed to steric interference by the methyl group combined with the decrease in the tendency of the amido proton to dissociate, hence decreasing proton assistance in the transition state.

The nature of the products obtained after alkaline hydrolysis of **1** or **2** depends on the relative rates of the two competing reactions a and b in the mechanistic scheme. The competition between these two reactions in different solvent systems bears a striking resemblance to the well-established competition between nucleophilic substitution and elimination reactions in the alkaline hydrolysis of alkyl halides, *e.g.*, 2-bromopropane.[20]

Finally, the discrepancy observed between the ratio of rate constants k_{2o}/k_{2s} and the ratio of products obtained experimentally from product analysis[1] for **2** and **3** deserves comment. Considering **2** first, product analysis after using equimolar amounts of **2** and potassium hydroxide in water gave a ratio of P–O to P–S cleavage of about 1:2. In contrast, the ratio k_{2o}/k_{2s} determined by using 50-fold more **2** than hydroxide ion was in the order of 1:44. Because of the high nucleophilicity of hydroxide ion toward phosphorus, it is possible that at the higher concentration of hydroxide the bimolecular mechanism leading to P–O cleavage benefits more than the elimination reaction leading to P–S cleavage. However, it was not possible to provide support for this statement owing to the complex nature of the kinetic analysis under second-order conditions.

In the case of **3** where the kinetic analysis precluded P–O cleavage, *i.e.*, the assumption was made that k_{2o} is negligibly small compared to k_{2s}, product analysis using equimolar amounts of **3** and potassium hydroxide showed that a significant amount of methanol was liberated, indicating P–O cleavage. The results here, however, are not directly comparable since product analysis for methanol was made after distillation of the reaction mixture to avoid the masking effect of dimethyl sulfide in the glc determination and to obtain methanol in high concentration. According to eq 14 and 15, half of the original amount of **3** should be in the form of the anion of methyl *N*,*N*-dimethylphosphoramidic acid after consumption of potassium hydroxide, and it is likely that during distillation of the reaction mixture C–O bond fission occurred by attack of water on the methyl carbon to produce methanol. Support for this possibility is found in the facile C–O bond cleavage of methyl and dimethylphosphoric acid in water at high temperature under neutral conditions.[21]

Experimental Section

The phosphoramidothioate esters used in this study have been described previously.[4] The pmr spectrum of *O*-methyl *S*-methyl phosphoramidothioate (**1**) showed a doublet centered at δ 3.6 (J = 13 Hz) for $POCH_3$ protons and a doublet centered at δ 2.2 (J = 15 Hz) for $PSCH_3$ protons; *O*-methyl *S*-methyl *N*-methylphosphoramidothioate (**2**) showed a multiplet centered at δ 5.3 for the NH proton, a doublet centered at δ 3.7 for the $POCH_3$ protons (J = 13 Hz), a quartet centered at δ 2.5 for $PNCH_3$ protons, and a doublet centered at δ 2.2 for $PSCH_3$ protons (J = 15 Hz); *O*-methyl *S*-methyl *N*,*N*-dimethylphosphoramidothioate (**3**) showed a doublet centered at δ 3.6 for $POCH_3$ protons (J = 12 Hz), a doublet centered at δ 2.7 for $PN(CH_3)_2$ protons (J = 11 Hz), and a doublet centered at δ 2.2 for $PSCH_3$ protons (J = 14 Hz). Pmr spectra were obtained on a Varian T-60 spectrometer using deuteriochloroform or deuterium oxide as the solvent. Tetramethylsilane was used as the internal standard.

S,*S*-Dimethyl phosphoramidodithioate (**7**) was prepared as follows. Ammonia was passed into a solution of 10 g of *S*,*S*-dimethyl phosphorochloridodithioate,[22] bp 68–70° (0.05 mm), $n^{24}D$ 1.5734, in 150 ml of anhydrous toluene until cessation of precipitate formation. The mixture was warmed to 50° for 30 min and cooled, and the toluene-insoluble product and ammonium chloride were collected by filtration. The crude product was taken up in 30 ml of warm methanol and filtered to remove ammonium chloride, and toluene was added to the filtrate until crystallization occurred. Recrystallization from a methanol–toluene mixture gave 7.1 g of product (80%), mp 105–106°.

Anal. Calcd for $C_2H_8NOPS_2$: C, 15.29; H, 5.10. Found: C, 15.66; H, 5.49.

Alkaline Hydrolysis.—All solvents used in this study were redistilled under nitrogen before use. In a typical hydrolysis reaction to determine products 1.41 g (0.01 mol) of **1** was dissolved in 10.0 ml of water (or appropriate solvent) to which was added 0.6 g of reagent grade potassium hydroxide in 10 ml of water and the mixture was allowed to stand in a 23° thermostated water bath for 4 hr. Removal of the solvent under reduced pressure produced a solid salt residue which was washed three times each with 5 ml of acetonitrile and dried at 0.02 mm pressure at 90° for 30 min. Analysis of the pmr spectra showed that the coupling of CH_3O (J = 11 Hz) and CH_3S (J = 12 Hz) protons with phosphorus in the two salts (**5** and **6**) was distinctly different from the coupling of CH_3O (J = 13 Hz) and CH_3S (J = 15 Hz) in the starting material (**1**).

Reaction in absolute ethanol or propanol (dried and distilled over magnesium) was carried out similarly by dissolving equimolar amounts of **1** and potassium hydroxide in solvent and allowing the mixture to stand for 4 hr. The reaction flask was attached to a 15-cm Vigreux column connected to a distillation head through which chilled water was passed and the mixture was heated to distil dimethyl sulfide, which was collected at 37–40°. Dimethyl sulfide was identified by pmr (singlet at δ 2.0) and by gas–liquid chromatography. The residual salts obtained after removal of ethanol or propanol were identified by pmr. Potassium ethyl phosphoramidate in deuterium oxide showed a multiplet at δ 4.0 for methylene protons and a triplet or a multiplet (depending on resolution) at δ 1.4 for methyl protons. Potassium propyl phosphoramidate showed a multiplet at δ 3.9 for OCH_2 protons, a multiplet at δ 1.7 for methylene protons, and a triplet at δ 1.0 for methyl protons.

Alkaline hydrolysis of **1** in ^{18}O-enriched water was carried out as described above using 1.5% ^{18}O water obtained from Bio Rad Laboratories, Richmond, Calif. After standing for 4 hr at 50°, the reaction mixture was heated to collect a water–methanol azeotropic mixture, which was examined in a Hitachi Perkin-

(18) R. F. Hudson, "Structure and Mechanism in Organophosphorus Chemistry," Academic Press, New York, N. Y., 1965, p 280.

(19) J. Epstein, D. H. Rosenblatt, and M. M. Demek, *J. Amer. Chem. Soc.*, **78**, 341 (1956).

(20) K. A. Cooper, M. L. Dhar, E. D. Hughes, C. K. Ingold, B. J. MacNulty, and L. I. Wolf, *J. Chem. Soc.*, 2043 (1948).

(21) W. C. Barnard, C. A. Bunton, D. R. Llewellyn, C. A. Vernon, and V. A. Welch, *J. Chem. Soc.*, 2670 (1961).

(22) T. W. Mastin, G. R. Norman, and E. A. Wellmuenster, *J. Amer. Chem. Soc.*, **67**, 1662 (1945).

Elmer Model RMO-693 double focus mass spectrometer. Analysis of the mass spectral data showed no significant incorporation of ^{18}O in methanol, *i.e.*, the $(M^+ + 2)$ peak for methanol had a relative abundance of only 0.28%.

Methanol and dimethyl sulfide were determined quantitatively by glc using an F & M Model 402 gas chromatograph equipped with hydrogen flame detector and a 6-ft 5% Carbowax Gas-Chrom Q column at 78°. For dimethyl sulfide determinations after hydrolysis of the phosphoramidothioate esters, the reactions were carried out in sealed ampoules and cooled in ice–water prior to glc analysis. Estimations of methanol and dimethyl sulfide were made by comparing peak areas obtained from standard solutions of methanol in water or dimethyl sulfide in a dimethyl sulfoxide–water mixture.

Methylation of **5** and **6** for glc analysis was carried out with diazomethane.[23] The sample to be esterified was dissolved in 1:9 methanol–ether, acidified with methanolic HCl, and treated with excess diazomethane at room temperature for 1 hr. The solution was concentrated and an aliquot was analyzed by glc using a hydrogen flame detector modified for thermionic detection of phosphorus by mounting a KCl pellet in the hydrogen jets. A 6-ft column containing 3.5% diethylene glycol succinate on SupelCoport (mesh size 80/100) at a temperature of 210° was used. Nitrogen, hydrogen, and air flow rates were 51, 41, and 40 ml/min, respectively.

Kinetic Methods. A. *O*-Methyl *S*-Methyl Phosphoramidothioate (1).—The overall rate of reactions between **1** and hydroxide ion (combined P–S and P–O cleavage) was determined under pseudo-first-order conditions (excess **1**) by following the drop in pH of the reaction mixture using a Corning Model 12 research pH meter equipped with an expanded scale accurate to ±0.005 pH unit. Reactions were carried out under nitrogen in a double-wall thermostated glass cell maintained at 27.0° and provided with a magnetic stirrer and glass electodes. Typically, to 19.6 ml of an aqueous solution containing 282 mg of **1** (2 mmol) was added 0.4 ml of 0.495 *M* aqueous sodium hydroxide and the rate was monitored by measuring the drop in pH.

5,5′-Dithiobis(2-nitrobenzoic) acid[24,25] (DTNB) was used to follow the rate of methanethiol release (P–S bond cleavage). Rates of P–S bond cleavage were determined under pseudo-first-order conditions in carbonate buffer at pH 10.0, ionic strength 0.2 *M*. Sealed ampoules initially containing 8×10^{-3} *M* **1** in carbonate buffer were removed at intervals from a constant-temperature bath and chilled in ice, and an aliquot was added to a solution consisting of 0.2 ml of 0.01 *M* DTNB in pH 7.0 phosphate buffer to make a final volume of 5.0 ml. The magnitude of the yellow color produced was estimated at 412 mμ in a Bausch and Lomb Spectronic-20 spectrophotometer. Amounts of methanethiol present in solution were determined from a standard curve.

Combined rates of P–S and P–O cleavage also were determined at constant pH. As hydrolysis of **1** occurred the amount of standard sodium hydroxide necessary to maintain the pH at the initial setting of 10.0 ± 0.1 was estimated by means of a manually operated micrometer-driven microsyringe. In experiments involving the effect of added acetone on pseudo-first-order hydrolysis rates, the pH of the initial alkaine solutions containing variable amounts of acetone (10, 20, 30, and 40% v/v) was standardized to equal the pH of a sodium carbonate buffer (pH 10.0 in water) containing the same amount of acetone. In these experiments the ionic strength was maintained constant at 0.2 *M* by the use of sodium chloride.

Rates of methanol release (P–O bond cleavage) were estimated by glc as previously described. For the hydrolysis of **1**, a 1-ml aliquot of a reaction mixture consisting of 2×10^{-2} *M* **1** and 2.4×10^{-2} *M* potassium hydroxide was withdrawn at different time intervals and acidified with 0.1 ml of 1 *N* hydrochloric acid, and a sample was analyzed by glc.

B. *O*-Methyl *S*-Methyl *N*-Methylphosphoramidothioate (2).—The overall pseudo-first-order rate of reaction between **2** and hydroxide ion was followed by the pH-drop method described above for **1**. Because of the slower rate of reaction of **2**, the initial concentration of this material was set at 0.5 *M*. P–S bond cleavage was estimated by DTNB reagent under the same pseudo-first-order conditions of excess **2** over potassium hydroxide used to determine overall rate except that the reactions were carried out in sealed ampoules as described for **1**. Ionic strength was maintained at 0.2 *M* with sodium chloride.

C. *O*-Methyl *S*-Methyl *N*,*N*-Dimethylphosphoramidothioate (3).—Because of its greater stability compared to **1** and **2**, estimation of the rate of hydrolysis of **3** was possible by titration with standardized hydrochloric acid of the amount of hydroxide ion remaining after different time intervals. Rate measurements were made under pseudo-first-order conditions identical with that described for **2** and also under second-order conditions of equimolar amounts (approximately 0.25 *M*) of potassium hydroxide and **3**.

D. *S*,*S*-Dimethyl Phosphoramidodithioate (7).—The rate of the reaction of **7** with hydroxide ion was followed by use of the DTNB reagent according to the method described for **1** and **2**. Hydroxide ion concentration was 0.1 *M* and **7** was 1×10^{-3} *M*.

E. *O*,*O*-Dimethyl Phosphoramidothioate (8).—The rate of hydrolysis of **8** was determined in equimolar concentrations of **8** and hydroxide ion (0.055 *M*) by titration with standardized hydrochloric acid. The reaction was carried out in a 20% ethanol–water mixture.

Registry No.—**1**, 10265-92-6; **2**, 28167-49-9; **3**, 25218-42-2; **5**, 32979-53-6; **6**, 32979-54-9; **7**, 32979-55-8; **8**, 17321-47-0; potassium hydroxide, 1310-58-3.

Acknowledgments.—We gratefully acknowledge valuable discussions with Dr. Lyle K. Gaston. We are indebted also to the granting agencies for financial support of this work.

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Ether Cleavage by Triphenyldibromophosphorane[1,2]

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Received June 14, 1971

Triphenyldibromophosphorane has been found to effect the cleavage of dialkyl and phenyl ethyl ethers under essentially neutral conditions. Primary and secondary alkyl groups gave good yields of alkyl bromides with benzonitrile or chlorobenzene as the solvent. Cleavage of alkyl *tert*-butyl ethers in DMF solvent converted the *tert*-butyl group primarily to isobutene. No rearrangements were observed. The phenyl group was first obtained as part of a phosphonium bromide salt which was converted to bromobenzene at higher (>230°) temperatures. Vinyl and β-chloroalkyl ethers were much less reactive. Two epoxides, a ketal, and three thioethers were treated with inconsistent results.

The common methods for the cleavage of nonactivated ethers have employed strong acids. Milder conditions using boron trihalides (or diborane or sodium borohydride plus iodine) have been extended recently[3] and found to give cleavage at room temperature or below in most cases. However, only with BI_3 are both carbon–oxygen ether bonds cleaved and BF_3 gives alkenes with other than methyl and ethyl ethers (which form stable adducts). Less commonly, ethers have been cleaved by strong bases (*e.g.*, alkyl- and aryllithium reagents,[4] alkali metals[5]).

The finding that alkylhalotriphenoxyphosphoranes[6] and triphenyldihalophosphoranes[7,8] would effect the conversion of alcohols to alkyl halides led us to consider tertiary phosphine dihalides for the cleavage of ethers[9] as a method to avoid the presence of strong acids and bases. Ethers would be expected to react with the tertiary phosphine dihalides[10] to form an oxonium intermediate (eq 1). This conjugate–Lewis acid of the ether could then react in the usual manner

$$\mathrm{ROR} + \mathrm{Ph_3PX_2} \rightleftharpoons \mathrm{R{-}\overset{\overset{\mathrm{Ph_3PX}}{|}}{\overset{+}{O}}{-}RX^-} \longrightarrow \mathrm{Ph_3\overset{+}{P}ORX^-} + \mathrm{RX} \quad (1)$$

to give alkyl halide and a quasiphosphonium ion[11] intermediate corresponding to that proposed for phenols and alcohols,[7,8,9b,12,13] which, for dialkyl ethers, could afford a second molecule of RX (eq 2). The present

$$\mathrm{Ph_3\overset{+}{P}ORX^-} \longrightarrow \mathrm{Ph_3PO} + \mathrm{RX} \quad (2)$$

study was directed toward and limited to the finding of conditions with triphenyldibromophosphorane which would effect cleavage yet appreciably reduce the side reactions caused by strong acids and bases. No effort was made to find optimum conditions; therefore yields higher than those obtained should be possible with some ethers. Tertiary phosphine dihalides are known to react with a number of functional groups (*e.g.*, acidic hydrogen, reactive carbonyl, alkoxide, hydrazine, and peroxide) and these would interfere if present.

Acetonitrile, benzonitrile, dimethylformamide (DMF), 1-methyl-2-pyrrolidone, chlorobenzene, and the less polar *p*-xylene were all used as the solvent with varying degrees of success and particular advantages and disadvantages. Acetonitrile and also carbon tetrachloride could be used for preforming the reagent if isolation of the latter was desired, but their low boiling points precluded general use in cleavage reactions. The reagent could be formed (with cooling) in DMF but not in 1-methyl-2-pyrrolidone (decomposition occurred). For other than short ether cleavage reaction times these solvents (especially the pyrrolidone) formed gases and dark, nonvolatile by-products. *p*-Xylene as the reaction solvent led to high boiling products. Long reaction times gave some darkening with all solvents but least with benzonitrile and chlorobenzene. With DMF and acetonitrile, work-up was facilitated by adding water and extracting the alkyl halide. Yields of alkyl halide for short reaction times (often corresponding to incomplete reaction) were comparable for the various solvents except for certain bromide products (*e.g.*, *tert*-butyl bromide) which reacted with DMF.[14] Cleavage reactions were run under an

(1) Supported in part by a grant from the Petroleum Research Fund of the American Chemical Society. From the Ph.D. thesis of F. J. F.

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TABLE I

CLEAVAGE OF PRIMARY AND SECONDARY SYMMETRICAL ETHERS

Ether	Solvent	Temp, °C	Time, hr	RBr product[a]	Bp (mm), °C[b]	Yield of RBr, %[c]	Total RBr, %[d]
n-Pentyl	C_6H_5CN	122–130	4	*n*-Pentyl	128–129.5	77.8	98.9
n-Butyl	C_6H_5CN	122	4	*n*-Butyl	100–101	71.9	76
Allyl	C_6H_5CN	121	1	Allyl	69–70	63.4	68.6
Isopropyl	C_6H_5CN	122–127	9	Isopropyl	59–60	59.2	66.7
						(62.7)[e]	(70.7)[e]
Tetrahydrofuran	C_6H_5Cl	126	0.67	1,4-Dibromobutane	94–95 (14)		75.1

[a] Shown by vpc to be identical with an authentic sample. [b] Boiling range of pure product fraction. [c] Yield of pure isolated product. [d] Total recovered yield of halide; the yield of pure product plus the percentage in other distillation fractions as determined by vpc. [e] Based on recovered ether.

TABLE II

CLEAVAGE OF ALKYL *tert*-BUTYL ETHERS

Alkyl *tert*-butyl ether	Solvent	Temp, °C	Time, hr, >90% reaction	Total time, hr	Yield of RBr, %[a]	Total RBr, %[b]	*tert*-BuBr, %	Isobutene, %
n-Butyl	DMF	60–110	1	2	69.6	89.5	1.5	(Small)[c]
sec-Butyl	DMF	70–80	2	4.5	37.5	66.9	1	51.3[d]
Isobutyl	DMF	80	3.5	3.5	18.4	53.5	4.4	11.5[d]
tert-Butyl	DMF	*ca.* 25	0.1	1	(Small)[c]	(Small)[c]		(Small)[c]
Neopentyl	DMF	77–91	4	4		33.9 (41.8)[e]	(Small)	37.4[d]

[a] Yield of pure isolated product. [b] Total recovered yield (see Table I). [c] Identified but not measured. [d] Isolated as the dibromide. [e] Based on recovered ether.

inert atmosphere and were monitored by the vpc analysis of aliquots.

Several series of ethers of different types were studied. The first, symmetrical ethers having primary or secondary alkyl groups, were cleaved in benzonitrile or chlorobenzene and the results are summarized in Table I. Allyl ether and tetrahydrofuran were cleaved most and isopropyl ether, probably due to steric factors, least readily. The lower yields for the more volatile bromide products are thought to be due, at least in part, to loss by volatilization. Bromine addition to the allyl unsaturation did not appear to have occurred.

Another series studied was of alkyl *tert*-butyl ethers (Table II). The selection of DMF as the solvent provided the desired simplification in work-up mentioned above and also conditions corresponding to those reported[9b] for the reaction with alcohols. However, it was found that little *tert*-butyl bromide was obtained. The rapid conversion of the bromide to isobutene under the reaction conditions, and more rapidly than in DMF alone, was shown to occur. Thus hydrogen bromide was being formed as the reaction progressed, and some ether cleavage *via* proton-acid catalysis was probably also occurring. That the latter was not the primary mode of reaction was indicated by the fact that, with the exception of di-*tert*-butyl ether for which the reaction rate was too rapid to follow by the procedure used, the rate of disappearance of starting ether did not accelerate as the amount of hydrogen bromide increased. In addition, starting ether was recovered in two cases after extended reaction time. Benzonitrile is therefore suggested instead of DMF to avoid the formation of stronger acids and for the isolation of *tert*-alkyl bromides. The reason for the somewhat lower yields of alkyl halide from the *sec*-butyl and neopentyl groups was not apparent in that no alkenes or isomeric alkyl bromides were observed.[15]

(15) Other than isobutene, no by-products were found for the reactions of the other ethers, though dimethylammonium bromide could be obtained from the water-soluble portion when DMF was the solvent.

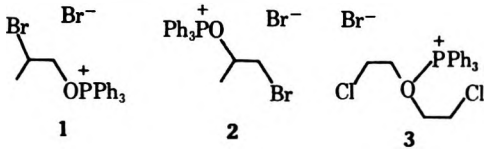
Ethers containing an α-vinyl or -aryl group, one having a β-chloro group, and furan were tested. The bond linking these groups to the ether oxygen was quite resistant to cleavage. The reaction of phenetole, for example, produced ethyl bromide (40%) under the conditions used for the dialkyl ethers but the solid product containing the aromatic moiety required heating above 230° to form bromobenzene (24%). The solid product was found to correspond to that formed by the reaction of phenol with the reagent and therefore was most probably the known $(PhOPPh_3)^+Br^-$ species.[7,12] Dihydropyran in DMF at room temperature or with no solvent at 220° gave essentially no volatile products or recovered ether. Di-2-chloroethyl ether in benzonitrile at 125° appeared to give halogen exchange as the main reaction with less than one-fourth of the ether cleaved after 12 hr. A reasonable path for the halogen exchange would be abstraction of the chlorine by Ph_3P^+Br assisted by back-side participation of ether oxygen electrons (analogous to the formation of sulfur and nitrogen mustard gases) followed by halogen substitution with bromide or chloride. The tendency for this reaction to occur may account, in part, for the slowness of the cleavage process. Other possible factors are steric shielding and inductive effects by the halogens.

It is reasonable to consider that the cleavage of the second carbon–oxygen bond to form the halide is the same as that found in the conversion of alcohols to halides by this type of reagent, *i.e.*, nucleophilic reaction of halide ion with an alkoxyphosphonium intermediate. The probable finding of the corresponding intermediate in the cleavage of phenetole supports this. With regard to the cleavage of the first ether carbon–oxygen bond, a likely course would be equilibrium formation of an oxonium salt and subsequent elimination of the alkyl bromide as depicted above (eq 1). A side reaction would be the formation of an alkene and hydrogen bromide from alkyl groups other than methyl. It would appear that there is little tendency for car-

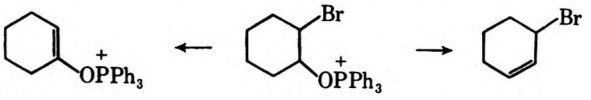
bonium ion formation as no rearranged bromides were found. When a *tert*-butyl group was present, the small yields of *tert*-butyl bromide indicate some SN1 reaction. The isobutene could have been formed *via* β elimination on the oxonium salt or on *tert*-butyl bromide under the conditions employed.

Three epoxides and a ketal were also examined as special ether-like compounds. The reaction with 1,2-epoxypropane in DMF gave a good yield of 1,2-dibromopropane but 1,2-epoxycyclohexane gave several unidentified products including an unsaturated bromo compound in rather low yield but no dibromocyclohexane. 1-Chloro-2,3-epoxypropane gave a mixture from which none of the corresponding dibromo derivative was obtained. From 2,2-dimethoxypropane were obtained methyl bromide and two other products tentatively identified as 2-bromopropene and 2,2-dibromopropane.

The result with 1,2-epoxypropane is of interest in comparison with the inertness of di-2-chloroethyl ether since a reasonable intermediate in the formation of 1,2-dibromopropane would be **1** and/or **2** having a β-halo group and thus analogous to the intermediate (**3**) expected from the chloro ether. This suggests that the low reactivity of the chloro ether is due to nonformation of **3**. The results with epoxycyclohexane are



consistent with the probable intermediate (**4**) undergoing primarily elimination (rather than substitution by bromide) to form a nonvolatile phosphonium salt plus some cyclohexenyl bromide.



Treatment of alkyl sulfides under conditions which were effective with ethers showed the sulfides to be very resistant to cleavage. *n*-Butyl sulfide and triphenylphosphine dibromide in DMF at 155° or in benzonitrile at 207° gave only a trace of *n*-butyl bromide. This was formed at the start of the reaction and appeared to be due to the presence of a small amount of hydrogen bromide as there was no further change on extended heating. 3-(Ethyl propanoate) sulfide in DMF at 155° was also inert. Benzyl sulfide, in contrast, reacted fairly rapidly and benzyl bromide and triphenylphosphine sulfide was identified as products.

Experimental Section

General.—Melting points were taken on a Fischer apparatus and are uncorrected. A 580 × 10 mm glass helices packed column fitted with a heated jacket and total reflux, partial take-off head was used for fractional distillations unless otherwise noted. Nmr spectra were obtained on a Varian Model A-60 analytical spectrometer with tetramethylsilane as an internal standard. Vpc analyses were made with an Aerograph Model A-90-C using a 0.25 in. × 5 ft silicone Dow 710 on Chromosorb W column. Peak identities were determined by comparisons (retention times and mixed chromatography) with authentic samples.

Triphenylphosphine was generously provided by M & T Chemicals, Inc., and was not further purified. Baker Analyzed Reagent bromine was used as obtained. DMF (Aldrich Chemical Co., Inc.) was distilled, bp 43–44° (12 mm), from sodium sulfate or dried over Linde 4 Å molecular sieves. Ethers for which no preparation is given were stock samples which were dried and redistilled.

The nmr spectra of the ethers used and the alkyl halides isolated were in agreement with their molecular structures.

Neopentyl Chloride.—The method was that of Whitmore and Fleming[16] who reported no details. In that explosions or fires occurred unless specific precautions were taken, a detailed procedure is given here. 2,2-Dimethylpropane (Phillips Petroleum Co.) (88 g, 1.22 mol) was condensed into a tared, oven-dried apparatus swept with dry, O_2-free nitrogen and consisting of a 500-ml, three-necked, round-bottom flask equipped with a sealed (ground glass) stirrer, a solid CO_2 cooled condenser, a drying tube ($CaSO_4$), and a gas inlet. Cl_2 gas was then admitted very slowly over the hydrocarbon until a light yellow color was apparent in the liquid and the condensate. Cl_2 admission was then stopped and reaction was initiated by short bursts of light from a 100-W bulb directed at the gas inlet joint. When condensation was observed on the inside of this joint, a slow flow of Cl_2 was resumed. The addition rate was increased slowly until a steady production of HCl and a slow, steady drip from the condenser occurred. When a weight increase of 43 g had occurred (equivalent to 88.5 g, 1.25 mol of Cl_2), addition was stopped and the mixture, after attaining room temperature, was removed and distilled to give 54.3 g (42%) of pure [bp 83.5–84.5° (lit.[16] 84.4°)] neopentyl chloride.

Di-*tert*-butyl Ether.—The method of Erickson and Ashton[17] was used with the modification of a dry, O_2-free nitrogen atmosphere. Vpc analysis of the reaction mixture after 24 hr showed 44.9% ditertiary butyl ether, 27.8% 2-methyl-2-propanol, and 27.4% 2-chloro-2-methylpropane (exclusive of diethyl ether and isobutene) and after 48 hr 59, 39.4, and 1.7%, respectively, of these compounds. Filtration, washing with water, drying, and distillation gave 2.099 g [bp 105–106° (lit.[17] 106.5–107°)] consisting of 97.1% ditertiary butyl ether and 2.9% 2-methyl-2-propanol and a residue (1.947 g) of pure ether, total yield 35.6%.

***tert*-Butyl *n*-Butyl Ether.**—The method of S.-O. Lawesson and N. C. Yang[18] was modified in the work-up to include, for a 0.5-mol reaction, washing with four 100-ml portions of 5% $FeSO_4$ following the 2 *N* NaOH washes. The product (31.3 g, 47.5%) obtained [bp 123.5–124.5° (lit.[19] 124°)] was shown by vpc to be 95.1% *tert*-butyl *n*-butyl ether, 3.49% 2-methyl-2-propanol, 0.44% 1-chlorobutane, and 1.05% unknown compound.

***tert*-Butyl *sec*-Butyl Ether.**—The method for *tert*-butyl *n*-butyl ether was used and gave 36.3 g (56.9%) of product, bp 24–25 (10 mm) and 114.5–115.5° (760 mm) (lit.[20] 114–115°).

***tert*-Butyl Neopentyl Ether.**—The method for *tert*-butyl *n*-butyl ether was used and gave 59.3 g (82.3%) of product, bp 122–123°.

Anal. Calcd for $C_9H_{20}O$: C, 75.00; H, 13.89. Found: C, 75.11; H, 13.87.

***tert*-Butyl Isobutyl Ether.**—The method for *tert*-butyl *n*-butyl ether was used and gave 55.01 g of material [bp 112.5–114° (lit.[20] 114°)] shown by vpc to consist of 97.5% (82.5% yield) of product.

Triphenyldibromophosphorane.—The following procedure is representative of those used with the various solvents (benzonitrile, DMF, CCl_4, acetonitrile, and chlorobenzene).

The method of Schaefer and Higgins[21] was followed using a 200-ml flask, oven-dried glassware, a positive pressure O_2-free N_2 atmosphere, 20.2 g (0.077 mol) of triphenylphosphine, 12.3 g (0.077 mol) of Br_2, and 100 ml of dry benzonitrile. Colorless crystalline phosphorane precipitated when the addition of Br_2 was *ca.* one-half complete.

If solvent-free product was desired, acetonitrile or CCl_4 was used as the solvent, the flask was then cooled to −68° or until the solvent solidified and connected to an aspirator through a

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solid CO_2 cooled trap, and the pressure was reduced to *ca.* 12 mm. The solvent, especially the last portion, was removed slowly as the mixture was allowed to come slowly to room temperature (too high temperatures or vacuum cause sublimation of the phosphorane and leave a yellow-orange tinged product). The dry product was carefully protected from moisture. The addition of 1-methyl-2-pyrrolidone at this point afforded solutions in this solvent.

Procedure for Reaction of Ethers and Sulfides with Triphenyldibromophosphorane.—The phosphorane reagent was prepared immediately prior to use. For benzonitrile and chlorobenzene solvents, the ether was added in one portion to the preheated reagent mixture (unless specified otherwise) and this temperature was maintained until vpc analysis showed the presence of little or no starting ether. The cooled mixture was transferred with the aid of ethyl ether or CCl_4 to a boiling flask and distilled (vacuum if needed) through the column described in the General section. Further work-up was as given for a particular ether.

A. Di-*n*-pentyl Ether.—The reagent (0.052 mol), benzonitrile (50 ml), and the ether (6.6 g, 0.0416 mol) were heated at 122–130° for 4 hr and then distilled. The material having a boiling point up to 72° (12 mm) was washed with aqueous Na_2CO_3, dried ($MgSO_4$), and distilled. The fraction (2.02 g) of bp 120–128° contained 60.7% 1-bromopentane, the fraction (9.83 g, 78%) of bp 128–129.5° was pure 1-bromopentane, and the residue (12.9 g) contained 11% 1-bromopentane, total yield 12.47 g (99%).

B. Di-*n*-butyl Ether.—The distillate (12 mm) from 0.077 mol of the reagent in benzonitrile (100 ml) and 10 g (0.077 mol) of the ether mixed at room temperature and heated at 122° for 4 hr was collected in solid CO_2 cooled traps, washed with aqueous Na_2CO_3, dried ($MgSO_4$), and distilled. The fraction (15.17 g, 71.9%) of bp 100–101° was pure 1-bromobutane. A forerun (1.66 g, bp 35.5–100°) contained 50% 1-bromobutane, total yield 16 g (76%).

C. Diallyl Ether.—The distillate (12 mm) from 0.052 mol of the reagent in benzonitrile (50 ml) and 4.9 g (0.05 mol) of the ether heated at 121° for *ca.* 1 hr was collected. The fraction (7.67 g, 63.4%) of bp 69–70° was pure allyl bromide and a forerun (1.24 g, bp 35–69°) contained 50% allyl bromide, total yield 8.29 g (68.5%).

D. Diisopropyl Ether.—The reagent (0.53 mol), benzonitrile (50 ml), and the ether (5.1 g, 0.05 mol) were heated at 122° for 6 hr and then at 127° for 3 hr, and the mixture was distilled (12 mm) using a solid CO_2 cooled receiver and trap. The combined contents of the receiver and trap were washed with aqueous Na_2CO_3, dried ($MgSO_4$), and distilled. The fraction (7.28 g, 59.2%) of bp 59–60.1° was >99% 2-bromopropane, the forerun (0.505 g, bp 35–59°) contained 44.2% 2-bromopropane, and the residue (4.743 g) contained 14.5% 2-bromopropane and 6% diisopropyl ether, total yield 8.19 g (66.7%, 70.7% net).

E. Tetrahydrofuran.—The reagent (0.052 mol), 50 ml of chlorobenzene, and the ether (3.6 g, 0.05 mol) were heated at 126° for 1 hr. Diphenylmethane (75 ml) was added prior to distillation. The fraction (13.194 g) collected at 94–95° (*ca.* 14 mm) contained 61.5% 1,4-dibromobutane, yield 75.1%.

F. *tert*-Butyl *n*-Butyl Ether.—The ether (29.3 g, 0.225 mol) was added to the reagent (0.25 mol) in *ca.* 175 ml of DMF at room temperature. After 12 min vpc analysis showed a small amount of 2-bromo-2-methylpropane and a larger proportion of isobutene in addition to the ether. There was no further change after 42 min at room temperature or after 1 hr at *ca.* 60°. The mixture was heated to 110° over a 1-hr period during which time (at 85°) darkening and gas evolution began and increased as the temperature rose. Analysis showed 1-bromobutane, 2-bromo-2-methylpropane, isobutene, and a small amount of the ether. Distillation (12 mm) of the mixture after an additional hour at 115° and addition of the distillate (*ca.* 170 ml) to 450 ml of ice water caused separation of an oil. Extraction with three 75-ml portions of ethyl ether left a dark, tarry residue which contained no starting ether or bromoalkanes and was discarded. Distillation of the dried ($MgSO_4$) ether extract gave 21.715 g (bp 99.5–102°) of liquid containing 98.8% 1-bromobutane. The forerun (3.53 g, 85–99.5°) contained 13.5% 2-bromo-2-methylpropane and 75.4% 1-bromobutane, and the residue (6.492 g) contained 53.3% 1-bromobutane. The total yield of 1-bromobutane was 89.5%, and of 2-bromo-2-methylpropane 1.55%.

G. *tert*-Butyl *sec*-Butyl Ether.—A solid CO_2 cooled trap was placed in the N_2 exit line of the apparatus. The ether (30 g, 0.231 mol) was added to 0.25 mol of the reagent and 200 ml of DMF and the temperature of the mixture was raised to 70° in 20 min. Analysis showed the presence of a very small amount of 2-bromobutane, a larger amount of isobutene, and starting ether. After 2 hr (80°) gas evolution had become pronounced and this temperature was maintained for 2.5 hr. Analysis during this period showed little change in composition. The distillate (*ca.* 12 mm) from the mixture was added to ice water and extracted with ethyl ether. The dried ($MgSO_4$) extracts were distilled. Forerun fractions (3.206 g, bp 62–87°, and 1.35 g, bp 87–88°) contained 9.9 and 1.2% 2-bromo-2-methylpropane and 64.6 and 95.3% 2-bromobutane, respectively. The volatile portion (5.95 g) of the residue was pure 2-bromobutane. The total yield of 2-bromobutane was 66.9% and the yield of 2-bromo-2-methylpropane was 1.05%.

Bromine was added to the contents of the cold trap until the red-brown color persisted. The mixture was allowed to stand overnight at room temperature and yielded 25.7 g (51.3%) of 1,2-dibromo-2-methylpropane.

H. *tert*-Butyl Isobutyl Ether.—The ether (30 g, 0.231 mol) was added to 0.25 mol of the reagent in 220 ml of DMF and the mixture was maintained at room temperature for 2 hr. Analysis showed small amounts of 1-bromo-2-methylpropane and isobutene. The mixture was then heated such that it reached 80° after 1 hr and was held at this temperature for 3 hr. During this period there was a steady decrease in ether content and a slow increase in the alkyl bromide, except in the last minutes when the latter began to decrease. The mixture was distilled (*ca.* 12 mm) with a maximum pot temperature of 105°. A tarry residue remained. The distillate was added to 400 ml of cold water, the mixture was extracted (ethyl ether) and the dried ($MgSO_4$) extracts were distilled. The fraction (6.184 g) of bp 88.3–91.2° contained 94% (5.81 g) 1-bromo-2-methylpropane, 3.98% 2-bromo-2-methylpropane, 1.88% isobutene, and 0.179% *tert*-butyl iso-butyl ether. During the collection of this material isobutene was continuously evolved from the mixture, hence the observed boiling range.

The volatile portion (11.5 g) of the pot residue consisted of 94.2% (10.83 g) 1-bromo-2-methylpropane, 1.79% unchanged ether, 3.46% 2-bromo-2-methylpropane, and 0.47% isobutene. An additional 0.26 g of 1-bromo-2-methylpropane was found in the forerun (bp 60–88.3°) for a total of 16.9 g (53.5%). The yield of 2-bromo-2-methylpropane was 4.43% and of isobutene (including the dibromide from reaction of the contents of the cold trap with bromine) was 19%.

I. Di-*tert*-butyl Ether.—The ether (5.13 g, 39.6 mmol) was added to 40 mmol of the reagent and 50 ml of DMF. The mixture became warm and darkened and the undissolved reagent disappeared in *ca.* 5 min. Some gas was evolved. The flask was covered with Al foil and allowed to stand for 2 days. Analysis showed the presence of 2-bromo-2-methylpropane and isobutene (*ca.* 1:2) but no ether. Distillation (*ca.* 12 mm) was accompanied by gas evolution and gave less than 0.1 g of the alkyl bromide.

In a separate run on a test tube scale no starting ether remained after 5 min.

J. *tert*-Butyl Neopentyl Ether.—The ether (34.6 g, 0.24 mol) was added to 0.25 mol of the reagent and 225 ml of DMF. No reaction had occurred after 2 hr. The mixture was then heated such that it reached 77° in 45 min and 91° 4 hr later. At *ca.* 80° the mixture darkened and evolved gas and the latter continued until *ca.* 85°. After an additional day at room temperature, the mixture was distilled (12 mm). The majority of distillate was collected up to 43°, after which time the rate decreased and, finally, a viscous colorless material (bp 87–88°) crystallized and plugged the receiver. The distillate (containing some of the high boiling solid) was added to 300 ml of cold water and extracted with ethyl ether. The dried ($MgSO_4$) extract was distilled. The fraction of bp 96–101° (1.471 g) contained 65.5% neopentyl bromide, 19.6% unchanged ether, 3.16% 2-bromo-2-methylpropane, 2.81% isobutene, and 6.39% ethyl ether. The fraction of bp 101–104.5° (6.547 g) contained 75% neopentyl bromide, 0.5% isobutene, and 23.5% of unchanged ether. A third fraction of bp 104.5–105° (7.917 g) contained 65.4% neopentyl bromide and 33.9% unchanged ether. The volatile portion (3.3 g) of the residue contained 37.55% neopentyl bromide and 60.8% unchanged ether. The total recovered unchanged ether was 6.52 g and the total yield of neopentyl bromide was 11.81 g (32.8%, 40.5% net) and of isobutene (including the dibromide from the contents of the cold trap) 37.4%. The nonvolatile portion of the residue contained

2.39 g of colorless hygroscopic, crystalline solid, mp 128–134°, which was not characterized further.

An *n*-propyl alcohol solution of the material which plugged the receiver in the vacuum distillation was heated at 80° for 10 min. Analysis showed the presence of 1-bromopropane. On standing, colorless crystals of triphenylphosphine oxide [mp 153–154° (lit.[22] 156°)] separated. The crystalline material of bp 87–88° (12 mm) was probably triphenyldibromophosphorane as this is known to react with alcohols to form alkyl bromides and triphenylphosphine oxide.[7,9b]

The residue from the vacuum distillation was dissolved in water plus benzene–ether. After concentration, the black water solution yielded crystalline dimethylammonium chloride, and a total of 63.6 g (93%) of triphenylphosphine oxide was obtained from the organic solution.

K. Ethyl Phenyl Ether. In Benzonitrile.—To 0.104 mol of the reagent in 100 ml of benzonitrile at 110° was added 12.2 g (0.1 mol) of the ether and the mixture was heated to 124° over a 45-min period and maintained at that temperature for 7 hr during which time analysis showed a continual decrease in ether and an increase in bromoethane.[23] From the distillate [bp up to 79° at (12 mm)] and the contents of two solid CO_2 cooled traps was obtained a total of 4.35 g (40%) of bromoethane (bp 38.5–40°).

The distillation residue, from which small aggregates of colorless crystals had separated after 1 day, was dissolved in dichloromethane and CCl_4 was added slowly until colorless crystals began to separate. After 2 days the mixture was chilled and the collected hygroscopic tan and white solid was washed with a little cold solvent mixture. Dissolution of a sample in wet acetone formed phenol (vpc and mp 38–41°). Reaction with H_2O gave an acidic solution and an oil from which, after dissolution in ether and chromatography over alumina, was obtained triphenylphosphine oxide (mp 154–155°). The properties of the solid corresponded to those of the product obtained from the reaction of phenol with the reagent and thus the solid was probably triphenylbromophenoxyphosphine but a satisfactory elemental analysis could not be obtained.

Neat.—The reagent (0.52 mol) was prepared in 60 ml of acetonitrile and the solvent was removed. The ether (6.1 g, 0.05 mol) was added and the mixture was heated on a sand bath. Above 140° bromoethane was given off and removed by distillation. Near 180° the mixture became black. The bath temperature was kept at 230–245°. After 45 min a small sample of the mixture was dissolved in wet acetone and vpc analysis of the solution showed phenol and bromobenzene (2:1) but almost no ether. After an additional 1.5 hr at 230°, the black glass which formed on cooling was dissolved in dichloromethane. Water (200 ml) was added and the mixture distilled. The initial distillate was made slightly acidic and extracted with ethyl ether and the dried ($MgSO_4$) extracts were concentrated. A small amount of phenol was removed by washing with aqueous NaOH and then removal of the solvent gave 1.91 g (24%) of bromobenzene. A small amount (0.09 g) of phenol (mp 38–41°) was obtained from the distillation residue.

L. 1,2-Epoxypropane.—The epoxide (5.8 g, 0.1 mol) was added to 0.107 mol of the reagent and 100 ml of DMF and the mixture was cooled (water bath) until the exothermic reaction had subsided and the reagent had disappeared (*ca.* 5 min). Analysis showed the absence of epoxide and a small amount of a volatile product. The mixture was then heated at 127° for *ca.* 45 min. Vacuum distillation afforded a colorless distillate and a dark gray crystalline residue. The latter was impure triphenylphosphine oxide, mp 149–153°. The addition of one-half of the distillate (half was lost) to 150 ml of cold water formed an oil layer and extraction (ether) and concentration of the dried ($MgSO_4$) extracts gave 9.87 g of light yellow oil which was shown by vpc analysis to contain 8.17 g (corresponding to 81% yield) of 1,2-dibromopropane.

M. 2,2-Dimethoxypropane.—The solvent was removed (vacuum distillation) from 0.107 mol of the reagent prepared in 100 ml of acetonitrile and the ketal (5.2 g, 0.05 mol) was added. After 3 hr at room temperature, the now dark mixture was heated. At *ca.* 100° bromomethane and at *ca.* 230° HBr were evolved. After 45 min at 230° the mixture was cooled and the black glossy material dissolved in 80 ml of DMF and then distilled. The distillate was added to 300 ml of H_2O and the whole mixture was extracted with ethyl ether. Removal of solvent from the dried ($MgSO_4$) extracts left 9.32 g of oil. Vpc analysis showed 41.2% of material (bp *ca.* 120°) which gave an nmr spectrum consistent with the structure of 2,2-dibromopropane (37.6% yield) and 13.9% of low boiling (*ca.* 50°) material which rapidly decolorized bromine and slowly reacted with alcoholic silver nitrate. This product was thought to be 2-bromopropene (21.5% yield).

N. Dibenzyl Sulfide.—The sulfide (10.7 g, 0.05 mol) was added to 0.052 mol of the reagent in 100 ml of DMF. After standing at room temperature overnight (the reagent had dissolved), the mixture was heated rapidly to 150°, then at 120° for 1 hr, at 140° for 2 hr, and at 150° for 2.5 hr during which time vpc analysis showed three products with increasing amounts of the two highest boiling products (the lower boiling of which was benzyl bromide) and decreasing amounts of the lowest boiling product. The highest and lowest boiling products were not starting sulfide or benzyl alcohol, respectively, and were not identified. The cold distillate [bp up to 59° (12 mm)] from the red-brown mixture was added to 300 ml of water and ice. Ether extraction and removal of the solvent from the dried ($MgSO_4$) extracts left a residue which contained *ca.* 2.4 g (14%) of benzyl bromide and *ca.* 4.9 g of DMF. Addition of 40 ml of ether to a solution of the pot residue in 30 ml of acetonitrile gave two layers and enough additional acetonitrile was added to form a homogeneous solution. Concentration under a N_2 stream to one-half volume and then cooling caused separation of crystalline triphenylphosphine sulfide which was collected, rinsed with cold acetonitrile, and dried at 0.01 mm for 12 hr, 7.57 g (51.5%), mp 156.5–158° (lit.[24] 157–158°).

Registry No.—Triphenyldibromophosphorane, 1034-39-5; *n*-pentyl ether, 693-65-2; *n*-butyl ether, 142-96-1; allyl ether, 557-40-4; isopropyl ether, 108-20-3; tetrahydrofuran, 109-99-9; *n*-pentyl bromide, 110-53-2; *n*-butyl bromide, 109-65-9; allyl bromide, 106-95-6; isopropyl bromide, 75-26-3; 1,4-dibromobutane, 110-52-1; *n*-butyl *tert*-butyl ether, 1000-63-1; *sec*-butyl *tert*-butyl ether, 32970-45-9; isobutyl *tert*-butyl ether, 33021-02-2; *tert*-butyl *tert*-butyl ether, 6163-66-2; neopentyl *tert*-butyl ether, 32970-46-0; dibenzyl sulfide, 538-74-9; ethyl phenyl ether, 103-73-1.

(22) R. Sauvage, *C. R. Acad. Sci.*, **139**, 674 (1904).

(23) Some bromoethane was lost *via* the N_2 exit line.

(24) L Maier, *Helv. Chim. Acta*, **47**, 27 (1964).

Pentacovalent Phosphorus. I. Reactions of Dimethylketene Dimers with Tertiary Phosphites[1]

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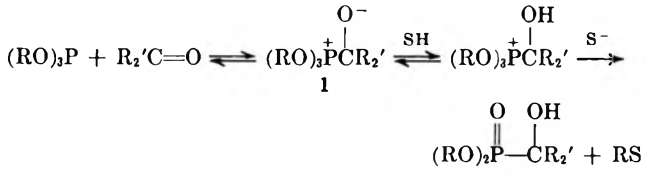
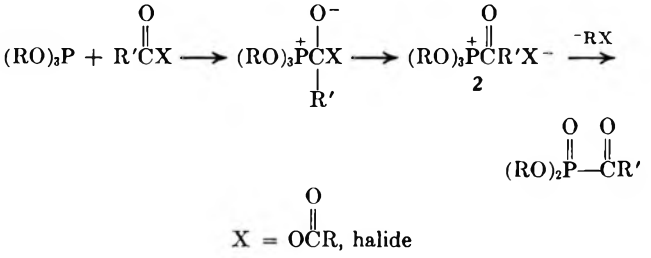
Received July 12, 1971

Studies of the reactions of the dione **3** and lactone **4** dimers of dimethylketene with a series of trialkyl phosphites and with dimethyl methylphosphonite have been carried out. The reactions of **4** give generally a carboalkoxy enol phosphite **9**, whereas the dione **3** reactions yield either **9** or a carboalkoxyl oxophosphonite **8** depending on the phosphite used. Tri-*n*-butylphosphine effects the isomerization of **3** to **4**. These results are explained in terms of a suggested series of reactions which includes formation of a five-membered ring pentacovalent phosphorus intermediate in an unusual ring expansion involving the postulated initial product of phosphorus attack on carbonyl carbon of **3** or **4**.

Simple unsubstituted dialkyl and diaryl ketones are generally unreactive[3] toward tertiary phosphites except at temperatures above 170°[4] unless the initial adduct **1** can be trapped by protonation.[5] Alternatively,

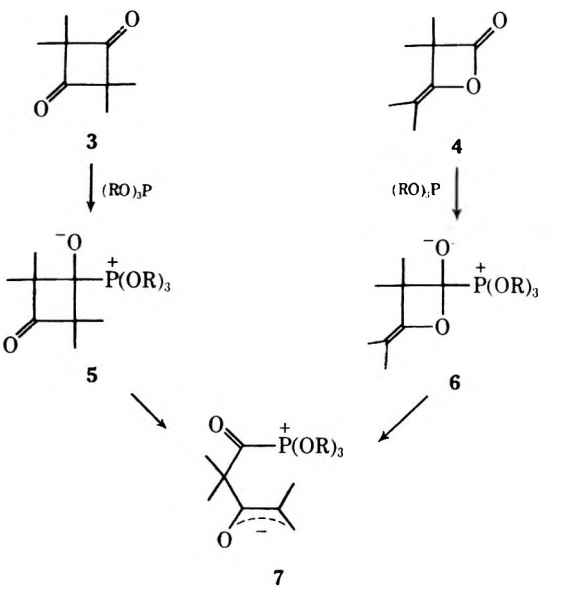


the intermediate **1** can be trapped and lead to ultimate product if one of the groups attached to carbonyl carbon is an easily displaced substituent (X in **2**).



Thus acyl halides[6] and acid anhydrides[7] are reactive in this manner.

The departure of the group X might also be expected to be facilitated by ring strain in the reactant carbonyl compound. It therefore seemed probable that the dimers of dimethylketene, 2,2,4,4-tetramethyl-1,3-cyclobutanedione (**3**) and 3-hydroxy-2,2,4-trimethyl-3-pentenoic acid β-lactone (**4**), would be reactive toward trivalent phosphorus. These dimers had been found to react readily to give a common ring-opened product with other nucleophiles such as amines, mercaptans, and alcohols.[8] Potentially, phosphites would be expected to give the same one of several conceivable products from either dimer *via* the common intermediate **7** resulting from ring opening of the initial dimer–phosphite adduct **5** or **6**.[9] Surprisingly, distinctly different products were realized from the two dimers in proportions dependent on the nature of the alkoxy groups on phosphorus. We believe the results we report here to be best explained in terms of a novel reaction series in which the incipient phosphonium enolate **7** is trapped *via* ring expansion to a five-membered ring pentacovalent phosphorus intermediate. Although formation of a pentacovalent intermediate from a phosphonium salt is not an uncommon process, its formation *via* a ring expansion is unusual. The ultimate product is postulated as arising from a novel alkoxy migration from phosphorus to carbonyl carbon.



Results

Dione Reactions—Two types of products result from the reaction of phosphites with dione and have the

(1) Part of this work has been published in preliminary form: W. G. Bentrude and E. R. Witt, *J. Amer. Chem. Soc.*, **85**, 2522 (1963). This work was supported by Public Health Service Grant No. CA-11045 from the National Cancer Institute.

(2) (a) Address correspondence to this author, University of Utah. (b) Taken in part from the Ph.D. Thesis of the W. Delmar Johnson, University of Utah, June 1969. National Institutes of Health Predoctoral Fellow, 1966–1969. (c) University of Utah. (d) Celanese Research Laboratories.

(3) A. J. Kirby and S. G. Warren, "The Organic Chemistry of Phosphorus," Elsevier, New York, N. Y., 1967, p 60.

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(5) P. A. Chopard, V. M. Clark, R. F. Hudson, and A. J. Kirby, *Tetrahedron*, **21**, 1961 (1965).

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(7) M. S. Kabachnik and P. A. Rossiiskaya, *Izv. Akad. Nauk SSSR*, 364 (1945).

(8) (a) R. H. Hasek, E. U. Elam, J. C. Martin, and R. G. Nations, *J. Org. Chem.*, **26**, 700 (1961); (b) R. H. Hasek, E. U. Elam, and J. C. Martin, *ibid.*, **26**, 4340 (1961); (c) G. R. Hansen and R. A. DeMarco, *J. Heterocycl. Chem.*, **6**, 291 (1969).

(9) Although the ring opening in the reactions of amines with **3** apparently involves hydrolysis of the four-membered ring Schiff base,[8c] the potential for reaction *via* **7** is evident.

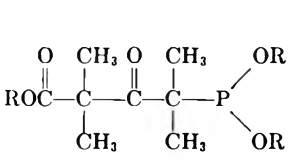
TABLE I

REACTIONS OF DIONE 3 WITH PHOSPHITES AND PHOSPHONITE

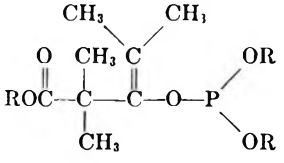
PXYZ			Mol of PXYZ/ mol of 3	Time, hr	T, °C	% convn	% yield of 8	% yield of 9	% yield of 4	% yield of other products
X	Y	Z								
OMe	OMe	OMe	2.0	218	120	100[a]	75[a] (33)[b]	15[a] (10)[b]	Trace	
OEt	OEt	OEt	2.0	541	120	80[a]	47[a] (20)	44[a] (20)	Trace	
O-*n*-Pr	O-*n*-Pr	O-*n*-Pr	2.0	704	120	75[a]	0	70[a] (26)	Trace	
O-*n*-Bu	O-*n*-Bu	O-*n*-Bu	2.0	704	120	80[a]	0	75[a] (40)	Trace	
O-*i*-Pr	O-*i*-Pr	O-*i*-Pr	2.0	301	120	80[c]	85[c] (63)	4[c]	10	
O-*sec*-Bu	O-*sec*-Bu	O-*sec*-Bu	2.0	928	120	80[c]	85[c] (59)	3[c]	12	
OMe	OMe	OC_6H_5	2.0	672	120	20	65[b,d]	0	0	10[e] 10[f]
OMe	$-OCH_2CH_2O-$		1.4	4[g]	110	60[c]	0	100[c,d] (45)	Trace	
Me	OMe	OMe	1.0	16	80	100	100[h]	0	0	

[a] Yield calculated by vpc method A (isolated yield in parenthesis). Based on reacted dione. [b] Observed products were a result of thermal Arbuzov rearrangements of precursors. [c] Vpc method B. [d] Methyl carboxylate, 10 hr. [e] Methyl 2,2,4-trimethyl-3-oxovalerate. [f] Phenyl 2,2,4-trimethyl-3-oxovalerate. [g] Months. [h] From weight of crude product shown by nmr to be nearly pure.

general structures **8** and **9**. The relative amounts of these adducts were found to be dependent on the group R as shown in Table I.



8

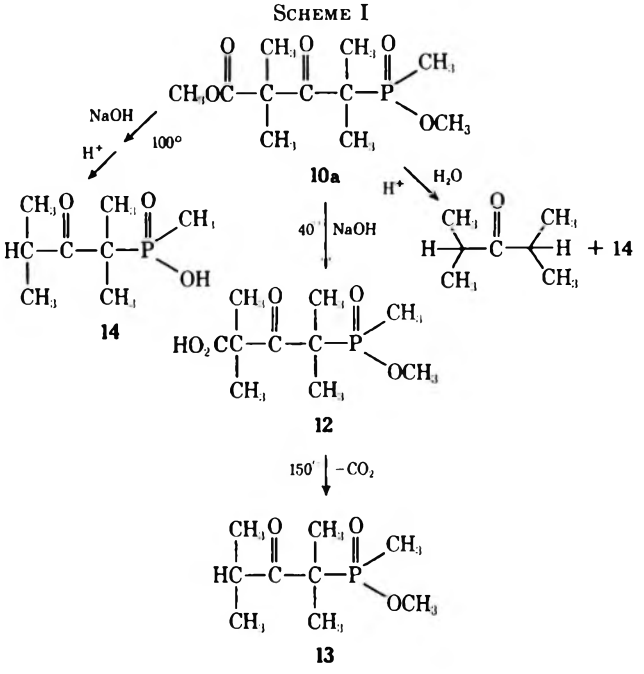


9

The structure of **8a**, R = CH_3, was proved rigorously by chemical as well as spectroscopic means. Products **8** from other phosphites were identified by spectral comparisons and quantitative elemental analysis. All were shown (Table II) to exhibit pmr resonances (singlet) of appropriate area assignable to the isolated *gem*-methyls (CH_{3A}) in the range δ 1.29–1.49, and a 6 H doublet (J_{HP} = 11 Hz) at δ 1.17–1.49 resulting from the *gem*-methyl grouping adjacent to phosphorus (CH_{3B}). Ready conversion with methyl iodide at room temperature to the corresponding methylphosphinate **10** or on warming with elemental sulfur to the thiophosphonate **11** showed products **8** to be trivalent. Apparently a combination of hindered rotation and/or the asymmetry of phosphorus[10] in the methylphosphinate rendered the methyls of each geminal pair nonequivalent. The isolated pair (CH_{3A}) now appears as two singlets at δ 1.38–1.50 and the CH_{3B} protons as two doublets at δ 1.42–1.58. The only exception is **10h** with a single peak at δ 1.49 for the isolated *gem*-methyl pair and pair of *gem*-methyls on the carbon α to phosphorus with coincidentally identical chemical shifts (δ 1.62). Their nonequivalence is shown by the fact that they have different J_{HP} values as do those of the other compounds (**10**). It is interesting that the effect is often greater on the more remote A protons than on the adjacent B protons in a given molecule. The unusually high chemical shifts for the A and B methyl protons of **10h** probably result from shielding by the aromatic ring.

Chemical degradation provides convincing evidence for the structure of **10a**. In Scheme I are given the

SCHEME I



reactions employed along with the products formed. (See Experimental Section for complete spectral, physical, and analytical data on **12**–**14**.) Mild treatment with aqueous NaOH led largely to saponification of the carboxy ester group to give **12** as noted chiefly by loss of the methoxy singlet in the pmr and introduction of unmistakeable CO_2H ir absorption. [The low-frequency carbonyl absorption in all these compounds is assigned to the highly hindered ketone grouping which is situated in a position similar to that of the carbonyl in di-*tert*-butyl ketone[11] (1687 cm^{-1}).] Vigorous saponification conditions (100°) cleaved both the carboxylate and phosphinate esters to give the phosphinic acid **14**. This compound clearly shows the presence of an isopropyl group in the pmr and loss of the methoxyl doublet ($POCH_3$). The doublet as-

(10) Long-range effects of asymmetric phosphorus centers are well established: L. Frankel, J. Cargioli, H. Klapper, and R. Danielson, *Can. J. Chem.*, **47**, 3167 (1969); R. V. Jardine, A. H. Gray, and J. B. Reesor, *ibid.*, **47**, 35 (1969); L. S. Frankel, H. Klapper, and J. Cargoli, *J. Phys. Chem.*, **73**, 91 (1969); D. G. Rowsell, *J. Mol. Spectrosc.*, **23**, 32 (1967); R. Keat, W. Sim, and D. S. Payne, *Chem. Commun.*, 191 (1968); W. McFarlane, *ibid.*, 229 (1968); A. P. Lane, D. A. Morton-Blake, and D. S. Payne, *J. Chem. Soc. A*, 1492 (1967); T. H. Sidall, III, *J. Phys. Chem.*, **70**, 2249 (1966); T. H. Sidall, III, and C. A. Prohaska, *Inorg. Chem.*, **4**, 783 (1965); *J. Amer. Chem. Soc.*, **84**, 2502, 3467 (1962).

(11) J. Lascombe, P. Grange, and M. Josien, *Bull. Soc. Chim. Fr.*, 773 (1957).

signed to the *gem*-methyl grouping adjacent to phosphorus and the PCH_3 doublet, which are seen in the spectra of **8a**, **10a**, **12**, and **13**, persist. A single carbonyl absorption is now present (1696 cm^{-1}). Loss of one carbonyl absorption and the introduction of an isopropyl group (pmr) also accompanies the decarboxylation of **12** at 150° to **13**. The pmr spectrum of **13** is identical with that of **14** except for the presence of the $POCH_3$ doublet in the **13** spectrum and small chemical shift differences. The single sharp peak in the ir at 1225 cm^{-1} is clearly that of the phosphinate phosphoryl bond.[12] The mass spectrum of **13** also confirmed its structure. Elemental analyses were obtained for **12** and **14**.

Acid hydrolysis of **10a** gives both decarboxylation and carbon–phosphorus cleavage. The latter finds precedent in other hydrolyses of compounds which have a phosphoryl group β to a ketone carbonyl.[13] The isopropyl ketone formed firmly established the carbon skeleton of **10a**.

With tri-*n*-propyl, tri-*n*-butyl, and methyl ethylene phosphites, no products of type **8** or **10** were detected. The proportions of **8** and **9** from the trimethyl and triethyl phosphite reactions were dependent on the extent of reaction. This is shown clearly for the triethyl phosphite reaction in Table III. The ratio **9**/**8** increased with time. Table IV presents evidence using triethyl phosphite that **8** is actually formed reversibly. That is, a mixture of **8b** and **9b** containing no phosphite or dione when allowed to stand at room temperature or heated to 120–150° is observed to give dione, phosphite, and a trace of lactone **4** along with a slow decrease in **8b** and proportionate increase in **9b**. **9b** heated alone does not give **3**, **4**, or **8b**.

In every reaction of phosphite with dione a small amount of lactone (<5%) was formed and persisted throughout the reaction with the exception of the reaction of dimethyl phenyl phosphite, which also gives no lactone product **9**. A relatively large amount of lactone **4** built up during reaction of the secondary alkyl phosphites.

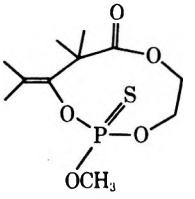
Dimethyl methylphosphonite proved to be very reactive with dione, the reaction being complete at 80° in 18 hr. The product **8i** underwent isomerization to the dimethyl phosphinate at room temperature in a few days. At 120° isomerization was complete in a maximum of 3 hr. No evidence was found for formation of either the starting phosphonite, dione, lactone, or **9i** under isomerization conditions.

When the dione **3** was heated with tri-*n*-butylphosphine at 120° for 18 hr, it was completely consumed and converted to the lactone and its polymer **22**. The polymer is identical with that formed from reaction of **4** with traces of sodium methoxide.[14]

Lactone Reactions.—When **4** was heated with the above phosphites and dimethyl methylphosphonite, products of the general type **9** were formed exclusively. No **8** has ever been observed in any reaction of these or any other trivalent phosphorus derivatives with **4**. The products and yields are listed in Table V. Physical and spectral data for **9** and sulfur derivatives (**15**) or methyl iodide Arbuzov products **16** appear in Table VI. Characteristic of the ir spectra in each case, **9**, **15**, and **16**, was an intense band at 1730 cm^{-1} (C=O) and a weak absorption near 1670 cm^{-1} (C=C). The nmr spectra peaks assignable to the vinyl methyls are at δ 1.47–1.55 (J_{PH} = 3.0–5.0) and 1.67–1.73 (J_{HP} = 1.5–3.5). **16h** and **16h'** fall somewhat outside the chemical shift range as a result of the shielding effects of the phenoxy groups. Griffin and Gordon have assigned the larger couplings in $H_3CC{=}CCP$ systems to the methyl group trans to phosphorus.[15] Products **9**, **15**, and **16** ($CDCl_3$) showed a single peak for the *gem*-methyls at δ 1.30–1.34 for the phosphites **9** and 1.41–1.43 for **15** and **16** with the exception of **16h** and **16h'**, again affected by the phenyl. The asymmetric center at phosphorus in **16h** and **16h'** apparently does not affect the CH_{3C} pair which appears as a singlet.

Chemical evidence for the structure **9a**, the adduct of **4** with trimethyl phosphite, arises from the facile acid- or base-catalyzed methanolysis of **9a** to trimethyl phosphite and methyl 2,2,4-trimethyl-3-oxovalerate and its acid-catalyzed hydrolysis to the same valerate. **9d** and **9g** were similarly converted to the corresponding ester and phosphite.

Several of the reactions with lactone deserve special mention. Methyl ethylene phosphite gives two products, one from migration of methoxy to carbonyl to give methyl carboxylate **9g** (isolated as **15g**). The structure of **9g** was further shown by its methanolysis products. A minor product of the reaction appeared to come from migration of ring oxygen to give a nine-membered ring product isolated as the thiophosphate **17-S**. Spectral and elemental analysis data (Experimental Section) were entirely consistent with structure **17-S**.



17-S

With dimethyl phenyl phosphite, lactone **4** gave both methyl and phenyl carboxylates isolated as the methylphosphonates, **16h** and **16h'**. In contrast this phosphite gave only methyl carboxylate with dione **3**. Because of extended reaction times the latter product had been isomerized to the methylphosphonate, **10h**.

Triisopropyl and tri-*sec*-butyl phosphites reacted with the lactone in an unusual manner. Both reactions proceeded very slowly compared to those of the *n*-alkyl counterparts, tri-*n*-propyl and tri-*n*-butyl. Further, very little 1:1 adduct **9** was formed (Table V). Only a small amount of somewhat impure **9e** and **9f** could be isolated, but these were readily characterized by their ir and nmr spectra. The sulfur derivatives **15e** and **15f** decomposed on attempted vpc purification. The major product in each instance consisted of polyenol ester material containing 2–3 lactone units for every

(12) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," 2nd ed, Wiley, New York, N. Y., 1958, p 312.

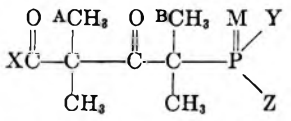
(13) N. Kreutzkamp and H. Kayser, *Chem. Ber.*, **89**, 1614 (1956); A. N. Pudovik and B. A. Arbuzov, *Dokl. Akad. Nauk SSSR*, **73**, 327 (1950); L. D. Freedman and G. O. Doak, *Chem. Rev.*, **57**, 479 (1957).

(14) R. H. Hasek, R. D. Clark, E. U. Elan, and J. C. Martin, *J. Org. Chem.*, **27**, 60 (1962).

(15) D. J. Martin, M. Gordon, and C. E. Griffin, *Tetrahedron*, **23**, 1831 (1967).

TABLE II

PHYSICAL, SPECTRAL, AND ANALYTICAL DATA FOR[a]



Compd[b]	X	Y	Z	M	Chemical shifts[c] (J_{HP} or J_{HH})[d] CH_{3A}	CH_{3B}	X[e]	Y[e]	Z	Solvent	Ir bands, cm^{-1}	Bp or mp, °C
10a	CH_3O	CH_3O	CH_3	O	1.39 (s) 1.48 (s)	1.39 (d, 15.0) 1.41 (d, 15.5)	3.29 (s)	3.32 (d, 10.5)	1.36 (d, 14.0)	Benzene	2990, 2953, 1743, 1720 (w), 1687, 1465, 1395, 1372, 1305, 1265, 1230, 1195, 1145, 1050, 1035, 1005, 987, 892, 797, 745 (film)	95 (0.1 Torr)
8a	CH_3O	CH_3O	CH_3O		1.29 (s)	1.17 (d, 11)	3.67 (s)	3.58 (d, 10.5)	3.58 (d, 10.5)	CCl_4	2987, 2940, 2837, 1750, 1732 (w), 1687, 1472, 1394, 1372, 1270, 1200, 1065, 1042, 1008, 994, 907, 747 (film)	76–77 (0.03 Torr)
8b	C_2H_5O	C_2H_5O	C_2H_5O		1.30 (s)	1.23 (d, 11)	1.22, OCH_2CH_3 (t, 7) 3.9,[f] OCH_2CH_3 (m)	1.30, OCH_2CH_3 (t, 7) 3.9, OCH_2CH_3 (m)		CCl_4	2980, 1740, 1680, 1462, 1388, 1267, 1148, 1103, 1063, 1040, 1000, 920, 740 (film)	106 (0.2 Torr)
10b	C_2H_5O	C_2H_5O	CH_3	O	1.38 (s) 1.42 (s)	1.43 (d, 15) 1.43 (d, 16)	0.91, OCH_2CH_3 (t, 7) 3.8,[f] OCH_2CH_3 (m)	0.98, OCH_2CH_3 (t, 7) 3.8,[f] OCH_2CH_3 (m)	1.37, PCH_3 (d, 14)	Benzene	2980, 1745, 1695, 1473, 1390, 1370, 1300, 1255, 1220, 1162, 1142, 1030, 957, 884, 787 (film)	
8e	*i*-C_3H_7O	*i*-C_3H_7O	*i*-C_3H_7O		1.33 (s)	1.27 (d, 11.5)	1.19, $HC(CH_3)_2$ (d, 6) 5.0, $OCH(CH_3)_2$ (m)	1.23, $HC(CH_3)_2$ (d, 6) 4.2, $OCH(CH_3)_2$ (m)	1.25, $HC(CH_3)_2$ (d, 6)	$CDCl_3$	2980, 1730, 1670, 1465, 1385, 1258, 1148, 1108, 1030, 980, 952, 899, 862, 754, 742 (film)	62–72 (0.025 Torr)
11e	*i*-C_3H_7O	*i*-C_3H_7O	*i*-C_3H_7O	S	1.49 (s)	1.62 (d, 19.5)	1.06, $HC(CH_3)_2$ (d, 7) 4.8,[f] $HC(CH_3)_2$ (broad m)	1.18, $HC(CH_3)_2$ (d, 7) 4.8, $HC(CH_3)_2$ (broad m)	1.27, $HC(CH_3)_2$ (d, 7) 4.8, $HC(CH_3)_2$ (broad m)	Benzene	2980, 1735, 1720 (w), 1690, 1465, 1385, 1255, 1165, 1146, 1106, 900, 888, 784 (film)	
10e	*i*-C_3H_7O	*i*-C_3H_7O	CH_3	O	1.43 (s) 1.50 (s)	1.50 (d, 15) 1.52 (d, 15.5)	1.03, $HC(CH_3)_2$ (d, 7) 4.5,[f] $HC(CH_3)_2$ (m)	1.03, $HC(CH_3)_2$ (d, 7) 4.5, $HC(CH_3)_2$ (m)	1.43 (d, 14)	Benzene	2980, 1730, 1715 (w), 1680, 1465, 1383, 1255, 1220, 1166, 1148, 1108, 983, 897, 775 (film)	
8f	*sec*-C_4H_9O	*sec*-C_4H_9O	*sec*-C_4H_9O		1.49 (s)	1.47 (d, 11)	1.07, $OCH(CH_3)C_2H_5$ (d, 7) 4.8, $OCH(CH_3)C_2H_5$ (m)	1.10, 1.13 $OCH(CH_3)C_2H_5$ (d, 7) 3.8, $OCH(CH_3)C_2H_5$ (m) 0.86,[f] $OCH(CH_3)CH_2CH_3$ (broad overlapping t, ~7) 1.5,[f] $OCH(CH_3)CH_2CH_3$ (broad m)		Benzene	2980, 2950, 1735, 1680, 1465, 1385, 1258, 1150, 1125, 1115, 1098, 1029, 995, 926, 838, 793, 730 (film)	116–117 (0.25 Torr)

10f	*sec*-C_4H_9O	CH_3	O	1.40 (s)	1.48 (d, 14.0)	0.79, 0.86	$OCH(CH_3)CH_2CH_3$ (broad, t)	1.38 (13.5)	Benzene	2980, 1730, 1720 (w), 1685, 1465, 1385,
				1.43 (s)	1.52 (d, 14.5)	1.10[f]	$OCH(CH_3)CH_2CH_3$ (d, 7)			1297, 1250, 1222, 1162, 1150, 1112,
						1.5[f]	$OCH(CH_3)CH_2CH_3$ (broad m)			1092, 1030, 992, 955, 874 (film)
						4.3, 4.8	$OCH(CH_3)CH_2CH_3$ (multiplets)			
10h	CH_3O	C_6H_5O	CH_3	O	1.49 (s)	1.62 (d, 15) 1.62 (d, 16)	3.78 (s)	7.3 (m)	1.69 (d, 14)	$CDCl_3$	2950, 1730, 1690, 1590, 1495, 1385, 1365, 1250, 1200, 1150, 1070, 1030, 1000, 813, 793, 685, 638 ($CHCl_3$)
10i	OCH_3	CH_3	CH_3	O	1.36 (s)	1.30 (d, 14.0)	3.24 (s)	1.21 (d, 12.0)	1.21 (d, 12.0)	Benzene	2980, 1750, 1730 (w), 1695, 1480, 1397, 1387, 1320, 1305, 1275, 1165, 1050, 1013, 1000, 949, 830, 880, 673 ($CHCl_3$)

[a] All compounds are colorless liquids or oils, unless otherwise noted. [b] Satisfactory C, H, and P analyses (±0.4%) were obtained for each of these compounds with the following exceptions. **10b**, an Arbuzov reaction product, was analyzed as the parent compound **8b**. **8e** was analyzed as its sulfur derivative **11e**. The Arbuzov product **10e** was not analyzed. **8f** was analyzed as its Arbuzov product **10f**. [c] In ppm downfield from internal TMS. [d] Multiplicity and coupling constant (J_{HP} or J_{HH}) in parenthesis below chemical shift value. [e] In some instances it was not possible to make a clear choice of assignment of chemical shifts when the same type of group was attached to both carbonyl and to phosphorus. Arbitrary assignments are made. [f] Resolution would not allow distinction between phosphorus and carbon attachment of the group.

TABLE III

EFFECT OF TIME AND SOLVENT ON 9/8 RATIO FROM REACTION OF DIONE 3 WITH TRIETHYL PHOSPHITE, 150°

Solvent	Time, hr[a]	% unreacted 3[b]	9/8[c]
None	68	39	1.2
None	143	33	2.7
None	398	21	9.0
CH_3CN	144	49	2.7
CH_3CN	305	42	3.2
CH_3CN	660	34	7.4
n-C_7H_{16}	144	55	0.67
n-C_7H_{16}	305	60	0.72
n-C_7H_{16}	660	48	2.1

[a] Trace (<5%) of **4** noted at all times after start of reaction. [b] Determined from vpc by reference to internal standard decane. [c] Ratio of peak areas by vpc.

TABLE IV

CONVERSION OF 8b TO 9b

T, °C	Time, hr	Amount of product[a] $(C_2H_5O)_3P$	3[b]	8b	9b	9b/8b[c]
25	0					0.50
25	168					0.65
25	336					0.65
120	27					1.1
120	160					2.0
150	0	0.63[d]	<0.1	2.6	1.7	0.65
150	24	1.9	0.85	0.40	1.8	4.5
150	87	1.5	0.80	0.17	2.1	13
150	111	1.6	0.52	0.18	2.5	14

[a] Figures reported are peak areas by vpc relative to that of internal standard decane. Total area 4.2 ± 0.5. Trace (relative area <0.07) of **4** noted in all samples except at $t = 0$. [b] Based on soluble **3** only. Considerable amounts crystallized out of reaction mixture before analysis. [c] Ratio peak areas by vpc. [d] A sample which originally contained **9b**/**8b** ratio of 0.5 and no dione or phosphite which had been kept 1 week at room temperature.

phosphite unit. This was supported by the fact that several times as much **4** was consumed as was phosphite.

Attempted reactions of a four-membered ring monoketone, 2,2,4,4-tetramethylcyclobutanone, with trimethyl phosphite and with trisdimethylaminophosphine failed to show any vpc evidence of reaction in 3 weeks at 115°. However, the phosphine and 3-dicyanomethylene-2,2,4,4-tetramethylcyclobutanone were both consumed at 60° in 3 weeks as were the above cyano ketone and trimethyl phosphite after 15 days at 120°. No vpc evidence for formation of tractable product was found.

Discussion

Most aspects of our results can be explained reasonably in terms of Scheme II by consideration of the effects of structure on the relative rates of various steps and stabilities of the proposed intermediates and products. The most remarkable aspect of these reactions is the failure in many instances to observe the same reaction pattern as was noted with other nucleophiles,[8] *i.e.*, formation of the same ring-opened product from either **3** or **4**. *E.g.*, alcohols give alkyl 2,2,4-trimethyl methyl-3-oxobutyrate on reaction with either **3** or **4**. We interpret the phosphite results to mean that the likely formed initial adducts **5** and **6** do not in such cases undergo transformation to a common intermediate such as **7**. Plausible reactions which would account for failure to form common products are

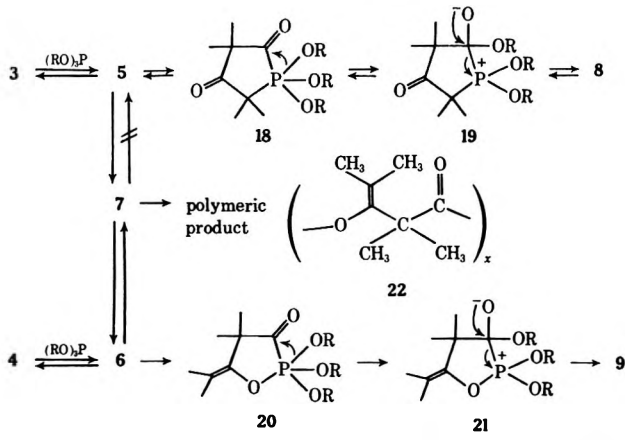
TABLE V

REACTIONS OF LACTONE 4 WITH PHOSPHITES AND PHOSPHONITE

PXYZ			Mol of PXYZ/					% yield of
X	Y	Z	mol of 4	Time, hr	T, °C	% convn[a]	% yield of 9[a]	other products
OMe	OMe	OMe	2.0	41	120	100	100[b] (74)	
OEt	OEt	OEt	2.0	81	120	95	100[b] (66)	
O-*n*-Pr	O-*n*-Pr	O-*n*-Pr	2.0	109	120	95	90[b] (48)	
O-*n*-Bu	O-*n*-Bu	O-*n*-Bu	2.0	109	120	95	95[b] (50)	
O-*i*-Pr	O-*i*-Pr	O-*i*-Pr	2.0	943	120	84	(15)[a]	high[a,c]
						22[d]	(28)[d]	
O-*sec*-Bu	O-*sec*-Bu	O-*sec*-Bu	2.0	928	120	45	(11)[a]	high[a,c]
						7[d]	(32)[d]	
OMe	OMe	OC_6H_5	2.0	408	120	80	40[e,f]	2[g]
							35[e,h] (35)[i]	15[j]
OMe	$-OCH_2CH_2O-$		2.0	369	110	65	15[e,k]	
							80[e,f] (61)[e,i]	

[a] Based on reacted lactone. [b] Yield calculated by vpc method A, isolated yields in parentheses. [c] Viscous cloud residue. [d] Based on reacted phosphite. [e] Vpc method B. [f] Methyl carboxylate. [g] Methyl 2,2,4-trimethyl-3-oxovalerate. [h] Phenyl carboxylate, Arbuzov rearranged. [i] Yield of mixture of products obtained by distillation. [j] Phenyl 2,2,4-trimethyl-3-oxovalerate. [k] Product is nine-membered ring containing a trialkyl phosphite and a carboxylic ester 17.

SCHEME II



shown in Scheme II. In reaction **5** → **18** and **6** → **20** the incipient phosphonium enolate is trapped *via* a ring expansion to give a pentacovalent species, **18** or **20**. In this way the basic structure of **3** or **4** is preserved in the products **8** and **9**. Such a ring expansion is not unlike that noted in certain carbonium ion rearrangements.[16] Migration to a positive phosphorus center, however, is not a common reaction. This amounts to formation of a pentacovalent intermediate *via* intramolecular nucleophilic attack. The lack of reaction of 2,2,4,4-tetramethylcyclobutanone and the high reactivity of 3-dicyanomethylene-2,2,4,4-tetramethylcyclobutanone is indicative of negative charge development at carbon during the ring opening. We also believe the steps **18** → **19** and **20** → **21** as postulated to be novel. This reaction system is further unusual in that the ordinary Arbuzov-like reactions generally noted[6,7] for trialkyl phosphites and reactive carbonyl compounds are not observed.

Formation of **8** is depicted in Scheme II as being reversible in keeping with the interconversion of **8b** to **9b** (Table IV). Since the production of **3** and the phosphite accompanies **8b** → **9b**, the process **3** → **5** also is written as a reversible reaction.

The small steady state concentration of **4** formed during the reaction **8** → **9** and in all reactions of **3** which give some **9** is accommodated in Scheme II by ring opening to **7** followed by closure and reversal of the reaction converting **4** to **6**. In most cases the reaction of **4** is fast so that **4** does not build up to any extent. However, with the triisopropyl and tri-*sec*-butyl phosphites, **4** reacts only slowly thus allowing **4** to build up to account for 10–12% of dione consumed. The slow reaction of **4** with the branched alkyl phosphites may result, for reasons proposed below, from a greater degree of reversibility of **4** → **6** step. The sequence **3** → **5** → **7** → **6** → **4** also accounts nicely for the conversion of **3** to **4** by tributylphosphine. Since product formation cannot proceed through alkyl migration through intermediates **19** or **21**, **4** is formed. This interconversion may also be catalyzed by $AlCl_3$.[14] Apparently **4** is the thermodynamically more stable dimer of dimethylketene. The step **5** → **7** seems to be nonreversible as in no instance have we noted either production of dione or formation of **8** from reaction of lactone with any of 15–20 trivalent phosphorus nucleophiles.

Scheme II also accounts for the formation of both products **8** and **9** from reactions with **3**. Several influences likely will be important in determining the partition of products of reaction with **3** between products **8** and **9**. One is the relative rates of the reaction **5** → **18** and **5** → **7**. These will in turn be affected by the relative stabilities of **18** and **7**. **7** will be favored by substituents on phosphorus which stabilize a positive charge. Conversely, **18** will be stabilized by electron-withdrawing substituents.[17,18] Bulky substituents on phosphorus in **18** will probably destabilize **18**, since the trigonal bipyramidal structures of related pentacovalent species show considerable crowding about phosphorus.[19] To the extent that the process **5** → **18** is rapidly reversible, then the ease of the migration (step **18** → **19**) also will influence the distribution between **8** and **9**. The crossover between the routes to give **8** and **9** *via* **7** may indeed involve **18** and **20** rather than **5** and **6** in which case the ease of migration becomes an obvious factor in the choice between **8** and **9** formation from **3**. A

(16) For examples in deamination reactions, see P. A. S. Smith, *Org. React.*, **11**, 1157 (1960).

(17) D. B. Denny and D. H. Jones, *J. Amer. Chem. Soc.*, **91**, 5821 (1969);

(18) F. Ramirez, C. P. Smith, J. F. Pilot, and A. S. Gulati, *J. Org. Chem.*, **33**, 3787 (1968); F. Ramirez, J. F. Pilot, O. P. Madan, and C. P. Smith, *J. Amer. Chem. Soc.*, **90**, 1275 (1968).

(19) W. C. Hamilton, S. J. LaPlaca, F. Ramirez, and C. P. Smith, *ibid.*, **89**, 2268 (1967); R. D. Spratley, W. C. Hamilton, and J. Ladell, *ibid.*, **89**, 2272 (1967).

second important consideration, where the question of relative amounts of **8** and **9** is concerned, is the previously discussed conversion of **8** to **9**. This phenomenon readily explains the observed (Table III) time dependence of **8**/**9** ratio for both the trimethyl and triethyl phosphite reactions. It may be important in cases where no **8** is formed. Thirdly, we would suggest that the ease of subsequent irreversible thermal Arbuzov rearrangement of **8** to **10** also can be an important factor in the **8**/**9** ratio, since the conversion of **8** → **9** can be thereby prevented. *E.g.*, we have found that **8a** undergoes considerable rearrangement to **10a** at 150°. This is not true of **8b**. In a reaction at 150° of dione and trimethyl phosphite in heptane, 40% of the dione was consumed in 200 hr at which time the ratio of (**8a** + **10a**)/**9a** was 85/15, and the **10a**/**8a** ratio was about 5/95. After about 500 hr the **8a**/**9a** ratio was only reduced to 50/50. In the meantime the **10a**/**8a** ratio was increased to 67/33. By contrast, as noted in Table III, at about 45% reaction at 150° of **3** and $(C_2H_5O)_3P$, the **8b**/**9b** ratio is 68/42. After another several hundred hours the ratio is reduced to 33/67. In another experiment in a neat reaction of **3** with triethyl phosphite, after extensive heating only 5% of **8b** remained. The reaction with triethyl phosphite allows more of the **8b** to be converted to **9b** since **8b** is not isomerized to **10b**. At 120° less **8a** than **10a** occurs, but the **8a**/**9a** ratio at 25 and 50% conversions of **3** only changed from 97/3 to 83/13. Thus, the propensity toward reversal of **8a** formation also is reduced at the lower temperature.

We suggest that the failure to observe formation of **8** in the reactions of the longer chain phosphites, tri-*n*-propyl and tri-*n*-butyl, may result from the following. In these cases product **8**, if formed, probably would not undergo the **8** → **10** isomerization, and any **8** formed initially may be rapidly isomerized to **9**. Alternately, since no **8** is ever detected at any stage in these reactions, the increased alkyl chain lengths in the alkoxy groups attached to phosphorus may have induced steric strain in the phosphorane **18**. Consequently, the rate of formation of **18** may be significantly decreased leading to predominant conversion of **5** to **7**.

In the reaction of phenyl dimethyl phosphite with dione, no product **9** is seen, and not even traces of lactone **4** are noted. The rate of reaction of this phosphite with both **3** and **4** is reduced by the phenoxy substituent, and it seems likely that phosphorus in **8** would also be of reduced nucleophilicity which precludes the conversion of **8** to **9** in this instance. Another factor could be reduced stability of **7** resulting from replacement of CH_3O by C_6H_5O.

Reaction of **3** with methyl ethylene phosphite gives no **8**. Such a result is not unreasonable, since the presence of two five-membered rings might be expected to force the methoxy into predominantly the equatorial position where it would be less reactive.[20] The rate of the step **18** → **19** would then be reduced for the adduct **18** from methyl ethylene phosphite allowing an increased proportion of reaction to proceed through **7**.

(20) The influences of ring size and electronegativity on axial and equatorial preferences of substituents on pentacovalent phosphorus as well as the relative reactivities of axial and equatorial positions have been summarized recently: E. L. Muetterties, *Accounts Chem. Res.*, **3**, 266 (1970); F. H. Westheimer, *ibid.*, **1**, 70 (1968); K. Mislow, *ibid.*, **3**, 321 (1970); F. Ramirez, *ibid.*, **1**, 168 (1968).

Apparently the expected increased stability of **18** from the presence of a second five-membered ring is not able to direct the reaction in favor of **8**. This again suggests that the migration step may be of controlling importance. It may be noted that the product of methoxyl migration is still observed. This suggests that placement of an alkoxy group in a five-membered ring lowers its migration potential in spite of the preferred axial position of the ring oxygen.

The **8** → **9** product distribution from reaction of **3** with dimethyl methylphosphonite is not strictly comparable to the others since the reaction temperature is low. Formation of **8i** at 80° is not reversible; and at higher temperatures **8i** is readily converted to **10i** which may preclude formation of **9i**.

We find the results of the dione reactions with triisopropyl and tri-*sec*-butyl phosphite difficult to rationalize. Factors which would destabilize **18** in the tri-*n*-propyl and tri-*n*-butyl cases would be expected to be operative here as well. For some unknown reason, alkoxy migration may be rapid and may, in fact, relieve strain in **18**. Alternatively; the branched alkyl cases may simply undergo reversal of **8** formation very slowly compared to the *n*-alkyl cases because of steric hindrance.

The lactone reactions seem fairly straightforward with the exception of triisopropyl and tri-*sec*-butyl phosphites. The low reactivity of **3** and the building up of **4** in the analogous reactions of **3** with these nucleophiles suggests that the **4**–**6** conversion is highly reversible. Steric strain in the intermediate **6** may be an important factor. The predominance of product containing several lactone molecules for every phosphite suggests that **7** is favored kinetically or thermodynamically over **20** or its subsequent products. **7** apparently adds more molecules of lactone before the ultimate product is formed.

When only alkyl substituents are attached to phosphorus, as in tri-*n*-butylphosphine, **7** adds to several molecules of **4** before the phosphine is removed giving the polymer **22**.

Finally, the greater ease of methoxy over phenoxy migration in the dione reaction and their nearly equal migrational abilities in the lactone reaction are of considerable interest but are not readily explainable. Migrational aptitudes could depend on several kinetic factors: product stability; stability of the leaving alkoxide; stability of the charge on phosphorus; and position, axial or equatorial, of the potential leaving group. The dimethylphenyl phosphite reactions with **3** and **4** appear to be somewhat anomalous in that the phenyl and methyl 2,2,4-trimethyl-3-oxobutyrates are formed in a manner unknown. In all other cases the indication is that migration is strictly intramolecular, since external alkoxide would readily polymerize the lactone. The question of migrational abilities will be explored more fully in the following paper.

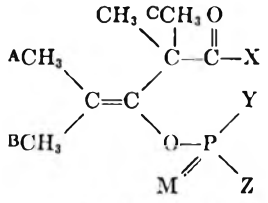
Experimental Section

Materials and Methods.—Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tenn., Schwarzkopf Microanalytical Laboratory, Woodside, N. Y., and at the Celanese Chemical Co., Technical Center.

Infrared spectra were obtained on Beckman IR-5A and Perkin-Elmer 421 spectrophotometers. Unless otherwise noted, reported ir bands are of strong or medium strength. Proton mag-

Table VI

Physical, Spectral, and Analytical Data for[a]



Compd[b]	X	Y	Z	M	Chemical shifts[c] (J_{HP} or J_{HH})[d] CH_{3A}	CH_{3B}	CH_{3C}	X[e]	Y, Z[e]	Solvent	Ir bands, cm^{-1}	Bp or mp, °C
9a	CH_3O	CH_3O	CH_3O		1.47 (d, 3.0)	1.67 (d, 1.5)	1.34 (s)	3.65 (s)	3.75 (d, 10)	Neat	2982, 2945, 1732, 1665 (w), 1457, 1392, 1280, 1260, 1195, 1150, 1123, 1080, 1035, 1022, 817, 750 (film)	64–66 (0.06 Torr)
9b	C_2H_5O	C_2H_5O	C_2H_5O		1.48 (d, 3.0)	1.70 (d, 1.5)	1.30 (s)	1.18, OCH_2CH_3 (t, 7) 4.0, OCH_2CH_3 (m)	1.23, OCH_2CH_3 (t, 7) 4.0, OCH_2CH_3 (m)	Neat	3000, 2950, 1730, 1670 (w), 1470, 1390, 1255, 1150, 1123, 1050, 945, 925, 812, 750 (film)	72–74 (0.1 Torr)
9c	n-C_3H_7O	n-C_3H_7O	n-C_3H_7O		1.48 (d, 3.0)	1.68 (d, 1.5)	1.30 (s)	0.95,[f] $OCH_2CH_2CH_3$ (m) 1.5, $OCH_2CH_2CH_3$ (m) 3.9, OCH_2CH_3 (m)		Neat	2960, 2900, 1730, 1675 (w), 1470, 1390, 1255, 1150, 1063, 1018, 980, 868, 809 (film)	100–103 (0.08 Torr)
15c	n-C_3H_7O	n-C_3H_7O	n-C_3H_7O	S	1.52 (d, 4.0)	1.74 (d, 3.0)	1.43 (s)	1.0,[f] $OCH_2CH_2CH_3$ (broad t, 7) 1.5, $OCH_2CH_2CH_3$ (m) 4.0, $OCH_2CH_2CH_3$ (m)		$CDCl_3$	2980, 1730, 1670 (w), 1465, 1380, 1245, 1143, 1055, 1000, 966, 900, 866, 758 (film)	
9d	n-C_4H_9O	n-C_4H_9O	n-C_4H_9O		1.48 (d, 3.0)	1.69 (d, 1.5)	1.32 (s)	0.9,[f] $OCH_2CH_2CH_2CH_3$ (broad t, 7) 1.1–1.9, $OCH_2CH_2CH_2CH_3$ (broad multiplet) 3.9, $OCH_2CH_2CH_2CH_3$ (broad m)		Neat	2950, 1730, 1670 (w), 1465, 1385, 1250, 1150, 1065, 1028, 968, 812, 775 (film)	115–118 (0.08 Torr)
15d	n-C_4H_9O	n-C_4H_9O	n-C_4H_9O	S	1.51 (d, 4.0)	1.72 (d, 3.0)	1.42 (s)	1.0,[f] $OCH_2CH_2CH_2CH_3$ (broad t, 7) 1.1–1.9 $OCH_2CH_2CH_2CH_3$ (broad m) 4.0, $OCH_2CH_2CH_2CH_3$ (m)		$CDCl_3$	2960, 1730, 1670 (w), 1465, 1380, 1248, 1145, 1115, 1055, 1025, 985, 898, 865, 807, 735 (film)	

15g	CH_3O	OCH_2–CH_2O	(S)	1.55 (d, 5.0)	1.73 (d, 3.5)	1.41 (s)	3.69, OCH_3 (s)	4.45, OCH_2CH_2O (m)	$CDCl_3$	2980, 2930, 1730, 1630 (w), 1465, 1385, 1250, 1190, 1150, 1110, 1075, 1030, 960, 925, 862, 814, 735, 690 (film)	84–85 (white solid)
16h	C_6H_5O	CH_3O	CH_3	O	1.65 (d, 4.0)	1.81 (d, 2.5)	1.58 (s)	7.2, C_6H_5O (m)	3.77, OCH_3 (d, 11.5) 1.58, PCH_3 (d, 18)	$CDCl_3$	2950, 1740, 1670 (w), 1590, 1490, 1315, 1250, 1198, 1165, 1118, 1074, 1042, 962, 933, 858, 813, 685, 643 (film)
16h′	CH_3O	C_6H_5O	CH_3	O	1.55 (d, 4.0)	1.81 (d, 2.5)	1.50 (s)	3.74, OCH_3 (s)	7.3, OC_6H_5 (m) 1.75, PCH_3 (d, 18)	$CDCl_3$	2950, 1730, 1670 (w), 1590, 1495, 1425, 1250, 1215, 1150, 1110, 1075, 962, 938, 858, 687, 645 (film)
16i′	OCH_3	CH_3	CH_3	O	1.42 (3.0)	1.52 (2.5)	1.65 (s)	3.38 (s)	1.17 (d, 14.0)	Benzene	2978, 2919, 1730, 1670 (w), 1480, 1397 (w), 1377 (w), 1305, 1310, 1280, 1265, 1260, 1205, 1163, 1130, 1022, 955, 932, 872, 830, 778 (film)

[a] All compounds are colorless liquids or oils, unless otherwise noted. [b] Satisfactory C, H, and P analyses (0.4%) were obtained for each of these compounds. **9d** was analyzed as its sulfur derivative **15d**. **16h** and **16h′** were analyzed as a mixture as were **15g** and **17-S**. [c] In ppm downfield from internal TMS. [d] Multiplicity and coupling constant (J_{PH} or J_{HH}) in parentheses below chemical shift value. [e] Resolution would not allow distinction between phosphorus and carbon attachment of certain groups because of a coincidental overlap of resonances.

netic resonance (pmr) spectra were obtained on Varian A-60 and A-56/60 instruments using tetramethylsilane (TMS) as internal standard. Reported chemical shifts are in δ, parts per million downfield from TMS. Multiplicity pf peaks is indicated by s, singlet; d, doublet; t, triplet; and m, multiplet. To resolve spectra complicated by overlapping peaks a technique was used which involved addition of incremental amounts of benzene to a $CDCl_3$ solution of the compound being analyzed. By observing the change in positions of peaks after each benzene addition, it was possible to sort out chemical shifts and coupling constants. Mass spectral data were taken on Consolidated Electrodynamics Corp. Type 21–110 and Perkin-Elmer Model 270 instruments.

Vpc analyses were run on an F & M Model 810 instrument and also on an Aerograph Model A90-P3 chromatograph, both thermal conductivity units. Analytical work was done on either column A, a 6 ft by 0.25 in. 20% SE-30 on 60–80 mesh Chromosorb W, or column B, a 6 ft by 0.25 in. 30% Celanese Ester No. 9 on the same solid support, both at 120 ml/min flow rate. Preparative vpc was accomplished with a 10 ft by $^3/_8$ in. 20% SE-30 on Chromosorb W column at 200 ml/min flow rate. Two analytical methods were used. **Method A.** A weighed amount of toluene or tetralin was introduced as internal standard following the reaction. The relative areas of standard and each component were measured by triangulation or planimetry. In several cases relative sensitivities were measured and shown not to vary by more than 10%. This is probably also a measure of overall accuracy of the measurement and in the relative yields are of most interest was deemed adequate for the purposes of the experiments. **Method B.** Under identical chromatographic conditions and injection sample sizes, the total area of reactants was determined before reaction and that of remaining reactants and of products formed after reaction. Percentage yields of products were calculated on the basis of starting materials consumed using the measured areas and assumed equal sensitivity of all peaks.

All reactants were reagent commercial materials, often distilled before use, or were prepared by standard reference procedures except for the following. Commerical phosphite samples were distilled from sodium before use. **2,2,4,4-Tetramethylcyclobutanone** was prepared from the dione using the procedure of Shechter.[21] 2,2,4,4-Tetramethyl-1,3-cyclobutanedione (100 g, 0.715 mol) was dissolved in 95% ethanol. Water was added until the solution turned turbid, and then ethanol was added until turbidity disappeared. Semicarbazide hydrochloride (200 g, 1.79 mol) and sodium acetate (200 g) were added to the solution which was then heated several hours on a steam bath. After sitting overnight at room temperature, the solid was removed by filtration and was washed several times with water. Drying under vacuum yielded the disemicarbazone, a white powder (197 g, 76% yield). Sodium (50.0 g, 2.17 mol) was dissolved slowly in ethylene glycol (500 ml). To the ethylene glycol solution in a three-necked 3-l. flask at 100° was added the disemicarbazone (65 g, 0.293 mol). Continued heating at 150° produced vigorous foaming. At 180° the foaming subsided and a pale yellow liquid distilled at 150°. The reaction mixture was maintained at 205° for 1.5 hr. After cooling, the solution was steam distilled. To the combined condensate from steam distillation and distillate collected during the heating process was added oxalic acid (150 g). The mixture was heated on a steam bath for several hours and then steam distilled. The condensate was extracted with three portions of chloroform. After being dried over calcium chloride, the solvent was removed using a rotary evaporator and an aspirator. Distillation yielded pure 2,2,4,4-tetramethylcyclobutanone, 10.2 g, 28% yield, bp 84–85° (158 Torr) [lit.[22] 77° (150 Torr)].

Methyl ethylene phosphite was prepared by heating a solution of trimethyl phosphite (125 g, 1.01 mol) and ethylene glycol (58.0 g, 0.935 mol), to which a small piece of sodium had been previously added, in a flask to which was connected a short column and distillation head. As the solution was heated and stirred, methanol distilled. When the evolution of methanol ceased, the solution was distilled from sodium through a Vigreux column to give methyl ethylene phosphite, 39.6 g, 0.325 mol, 35% yield, bp 62–65° (25 Torr). The pmr spectrum (benzene) corresponded to that given by Haake and coworkers.[23]

(21) H. Shechter, private communication. We thank Professor Shechter for making the details of this preparation available to us.

(22) H. L. Herzog and E. R. Buchman, *J. Org. Chem.*, **16**, 99 (1951).

(23) P. Haake, J. P. McNeal, and E. J. Goldsmith, *J. Amer. Chem. Soc.*, **90**, 715 (1968).

Dimethyl Phenyl Phosphite.—Phosphorus trichloride (50.0 g, 0.364 mol) and triethylamine (37.1 g, 0.366 mol) were mixed with 500 ml of ether in an ice-cooled flask. With constant stirring phenol (34.3 g, 0.364 mol) in 200 ml of ether was added dropwise (addition required 3 hr). Triethylamine (73.8 g, 0.728 mol) was added rapidly followed by dropwise addition of methanol (23.4 g, 0.728 mol) in 250 ml of ether. The mixture was refluxed for 1 hr after which the amine hydrochloride was removed by filtration, and the solvent was removed under reduced pressure on a rotary evaporator. Distillation through a wire spiral column yielded pure dimethyl phenyl phosphite, 24.8 g, 0.133 mol. 37% yield, bp 62–63° (0.25 Torr) [lit.[24] 86° (12 Torr)]. The pmr spectrum (neat) showed a 6 H doublet at 3.55 ppm (J_{HP} = 10.5 Hz) and a 5 H multiplet at 7.2 ppm.

General Procedure for Reactions of Phosphites with Lactone (4).—All reactions were run neat under N_2 and monitored by vpc. Conditions are given in Table V along with yields determined. Products (9) were isolated by vacuum distillation. In most cases derivatives were prepared by gently warming the product with sulfur or by reaction at room temperature with methyl iodide. Such derivatives were purified by preparative vpc.

Physical and spectral data and analyses appear in Table V for routine reactions. More detailed discussions of unusual cases and of formation of derivatives appear below.

Trimethyl Phosphite.—Further evidence for the structure of product **9a** was provided by results of its hydrolysis and methanolysis. Treatment of **9a** with excess methanol containing a trace of *p*-toluenesulfonic acid gave only trimethyl phosphite and methyl 2,2,4-trimethyl-3-oxovalerate as shown by vpc as did methoxide-catalyzed room temperature methanolysis. Similarly, hydrolysis with dilute HCl in methanol–water gave only the valerate in 24 hr at room temperature.

Triethyl Phosphite.—Product **9b** (0.5 g) was allowed to stand at room temperature with an excess (1.5 ml) of methyl iodide for 2 days. Complete conversion (vpc method B) of **9b** to **16b**, a colorless viscous liquid, was observed. Vpc analysis showed only the isomerization product **16b** and a low-boiling product, presumably ethyl iodide. **16b** was not further purified: ir (film) 795, 848, 892, 926, 965, 1038, 1074, 1113, 1142, 1247, 1310, 1395, 1465, 1665 (w), 1720, 2930, and 2980 cm^{-1}; pmr (50/50 benzene–$CDCl_3$) δ 1.41 and 1.21 (6 H, t J_{HH} = 7 Hz, CH_3CH_2O), 1.41 (3 H, d, J_{HP} = 17 Hz, PCH_3), 1.46 (6 H, s, gem CH_3), 1.46 (3 H, d, J_{HP} = 4.0 Hz, vinyl CH_3), 1.72 (3 H, d, J_{HP} = 2.5 Hz, vinyl CH_3), 4.0 (4 H, m, OCH_2CH_3).

Tri-*n*-butyl Phosphite.—Because of the overlap of broad methylene absorptions in the nmr of **9d** with those for the geminal and vinyl methyl precluded accurate integration of the spectrum, the structure was further characterized by conversion of a 5% solution of **9d** in 1-butanol, to which had been added a trace of Na, at 100° in 3 days to high yields of tri-*n*-butyl phosphite and *n*-butyl 2,2,4-trimethyl-3-oxovalerate. Products were verified by retention time comparison with authentic samples on vpc columns A and B.

Triisopropyl Phosphite.—Lactone (5.00 g, 35.7 mmol) and triisopropyl phosphite (14.9 g, 71.6 mmol), heated at 120° for 943 hr, gave an 84% conversion of lactone and a 22% conversion of phosphite to products as shown by vpc monitoring. The lactone was consumed more rapidly than the phosphite indicating that something other than a 1/1 adduct was being formed. The amount of the products observed on vpc did not account for all of the lactone consumed. Distillation yielded 16% of the original lactone, 68% of the original phosphite, and a small amount of a colorless viscous liquid [15% yield based on reacted lactone and 28% based on reacted phosphite, bp 80–90° (0.15 Torr)]. This liquid was not isolated in sufficient quantity or purity to allow complete characterization. However, ir and pmr spectra of impure samples indicated that it was analogous to **9c** formed from tri-*n*-propyl phosphite and the lactone and thus was assigned the structure **9e**: pmr (benzene) δ 1.16 (18 H, d, J_{HH} = 7 Hz, $CH(CH_3)_2$), 1.46 (6 H, s, gem CH_3's), 1.53 (3 H, d, J_{HP} = 3.0 Hz, vinyl CH_3), 1.78 (3 H, d, J_{HP} = 1.5 Hz, vinyl CH_3), 4.6 (3 H, m, $OCH(CH_3)_2$); ir (film) 2980, 1730, 1670 (w), 1475, 1385, 1265, 1148, 1110, 1078, 1010, 865 cm^{-1}.

9e was converted by gentle warming with sulfur into the thiophosphate which decomposed upon attempted purification by vpc at 230° isothermal.

A large amount of undistillable, very viscous, cloudy residue remained from the distillation. The ir spectrum of the viscous residue (film) showed important absorptions at 760, 800, 862, 954, 982, 1060, 1110, 1250, 1385, 1465, 1670 (w), 1725, 1730, 2950, and 3000 cm^{-1}. Column chromatography failed to give pure samples of this residue, but pmr analysis of several fractions indicated a material containing 2–3 units of the lactone to 1 unit from the phosphite.

Tri-*sec*-butyl Phosphite 3 (5.00 g, 35.7 mmol) and the phosphite (17.8 g, 71.2 mmol) were heated at 120°. Heating for 928 hr yielded a 45% conversion of lactone to product but only a 7% conversion of phosphite to product (determined by vpc method C and distillation of reaction solution to recover starting materials). Distillation yielded a colorless viscous liquid **9f** [0.67 g, 1.72 mmol, 11% yield based on reacted lactone, 32% yield based on reacted phosphite, bp 110–115° (0.15 Torr)]. This liquid was not isolated in sufficient quantity or purity to allow complete characterization. However, the ir and pmr spectra of impure samples indicated that the structure of **9f** was analogous to **9d** which was obtained for tri-*n*-butyl phosphite and lactone: pmr ($CDCl_3$) δ 0.96 (9 H, t, J_{HH} = 7 Hz, CH_2CH_3), 1.21 (9 H, d, J_{HH} = 7 Hz, $CHCH_3$), 2.5 (6 H, broad m, CH_2), 1.55 (6 H, s, gem methyls), 1.53 and 1.78 (3 H each, d, J_{HP} = 3.0 and 1.5 Hz, vinyl methyls), 4.3 and 4.8 ppm (3 H, m, OCH); important ir bands occurred at 796, 868, 996, 1030, 1072, 1112, 1150, 1375, 1460, 1665 (w), 1725, and 2950 cm^{-1}. **9f** was converted into the thiophosphate **15f** by warming with sulfur. The thiophosphate decomposed on attempted trapping on vpc column B at 275°.

A large amount of viscous cloudy residue was left from the distillation which appeared to be analogous to the polymeric material obtained from triisopropyl phosphite and lactone. The ir spectrum of the viscous residue (neat film) showed absorptions at 800, 876, 926, 945, 969, 996, 1058, 1115, 1230, 1255, 1382, 1462, 1670 (w), 1730, 1750, and 2950 cm^{-1}.

Dimethyl Phenyl Phosphite.—Lactone (3.35 g, 23.9 mmol) and the phosphite (8.90 g, 47.8 mmol) were heated at 120°. After 408 hr vpc analysis showed 80% conversion of lactone into a number of products of which the two major products were present in 35 (**16h**) and 40% (**9h'**) yields (based on reacted lactone and calculated using vpc method B). The ratio of the two major products did not change appreciably during the course of the reaction. Also present were the methyl and phenyl esters of 2,2,4-trimethyl-3-oxovaleric acid in 2 and 15% yields, respectively (identified by comparison of retention times on vpc column A with those of authentic samples), and a number of unidentified products in very small yields. Distillation failed to separate the major products [35% combined yield, bp 70–80° (0.3 Torr)]. Warming of the impure fractions with methyl iodide converted **9h'** to **16h'** and did not affect **16h**. **16h** and **16h'** were separated and collected at 220° isothermal on vpc column B. See Table VI for spectral data.

Methyl Ethylene Phosphite.—Phosphite (2.87 g, 0.0205 mol) and 4 (5.00 g, 0.410 mol) heated at 110° for 369 hr resulted in 65% consumption of lactone. Vpc analysis showed two products in 15 (**17**) and 80% (**9g**) yield based on lactone consumed and using vpc method B. Distillation of 2.91 g of product solution gave fractions containing the two products in various ratios (0.78-g total, 61% yield, bp 82–86° (0.006 Torr)]. A fraction rich in **9g** was transesterified in benzene by an excess of methanol in 16 hr at 60° to methyl ethylene phosphite, methyl 2,4,4-trimethyl-3-oxovalerate, and trimethyl phosphite as shown by pmr and vpc analysis (columns A and B) of the reaction solution using authentic samples for comparisons.

The product mixture was warmed 2 hr with sulfur to give the thiophosphates **15g** and **17-S** which were separated by preparative vpc at 230°. **17-S** was a white solid (mp 103.5–105°): pmr ($CDCl_3$) δ 1.50 (3 H, s, gem CH_3), 1.62 (3 H, s, gem methyl), 1.70 (3 H, d, J_{HP} = 3.5, Hz, vinyl CH_3), 1.82 (3 H, d, J_{HP} = 5.0 Hz, vinyl CH_3), 3.70 (3 H, d, J_{HP} = 14 Hz, CH_3OP), 3.7 to 4.8 (4 H, broad m, OCH_2CH_2O); ir (film) 2950, 1740, 1670 (w), 1450, 1390, 1365, 1265, 1155, 1126, 1078, 1045, 960, 926, 880, 860, 842, 828, 788, 763 cm^{-1}. Data for **15g**, also a white solid, mp 84–85°, appear in Table VI. **17-S** and **15g** were subjected to quantitative elemental analysis as a mixture (see Table VI).

Dimethyl Methylphosphonite.—The phosphonite was prepared from methyl phosphonous dichloride[25] by reaction of the

(24) G. Kamai and F. M. Kharrosova, *Tr. Kazan. Khim. Tekhnol. Inst.*, **23**, 122 (1957).

(25) B. J. Perry, J. B. Reesor, and J. L. Ferron, *Can. J. Chem.*, **41**, 2299 (1963).

latter with methanol in pentane in the presence of dimethylaniline. Lactone (0.15 g, 1.5 mmol) and methyl dimethylphosphonite (0.14 g, 1.5 mmol) were mixed neat under N_2. The reaction at room temperature, monitored by vpc, was complete in 48 hr. Volatiles were removed under vacuum at room temperature to leave reasonably pure (by pmr and vpc) **9i**: 0.25 g; 83% yield; pmr ($CDCl_3$) δ 1.35 (3 H, d, J_{HP} = 9 Hz, PCH_3), 1.33 and 1.36 (3 H each, s, $C(CH_3)_2C$), 1.49 (3 H, d, J_{HP} = 3.5 Hz, vinyl CH_3), 1.70 (3 H, d, J_{HP} = 1.5 Hz, vinyl CH_3). Treatment of **9i** with methyl iodide at 25° gave **16i**, isolated by preparative vpc.

Tri-*n*-butyl Phosphine.—Lactone **4** (10.0 g, 72 mmol) and the phosphine (18.5 g, 92.0 mmol) were heated at 100–120° for 2 weeks. On cooling, a light tan-colored solid precipitated from the dark brown reaction solution, 4.14 g, 41% yield, which was recrystallized from diglyme to give white powder, mp 193–195°. This was shown by spectral comparison to be identical with the polymer obtained on treatment of lactone with a trace of sodium methoxide (lit.[14] mp 198–200°). The polymer decomposed on melting to lactone.[14]

General Procedure for Reactions of Phosphites with Dione (3).—All reactions were run neat under N_2. Conditions and yields appear in Table I. Spectral, physical, and analytical data for products, all liquids or oils, appear in Table I. In all cases the reactions were monitored by vpc. At 150° (Table I), trimethyl phosphite gave only the product of Arbuzov isomerization, the phosphinate **10a**. However, when the reaction was run at 100° or in hexane at 120°, the unisomerized dimethylphosphonite **8a** was isolated. A solution of trimethyl phosphite 300 g, 2.42 mol) and the dione (85 g, 0.61 mol) heated at 100° for 30 days gave on distillation the phosphonite **8a**, a colorless liquid, bp 76–81° (0.03–0.05 Torr), 64.1 g, 0.243 mol (40% yield), along with 19.0 g (0.072 mol) of the phosphinate **10a**, (12% yield). See Table II for spectral and analytical data. Reaction of **8a** at room temperature with methyl iodide or when heated by itself for 9 hr at 150° converted **8a** into **10a**, mass spectrum 264 (parent). Both the trimethyl and triethyl phosphite reactions at 120° showed only the product **8a** and **8b** early in the reaction. Products **9a** and **9b** were formed in increasing proportions as the reactions progressed. The tri-*n*-butyl and triisopropyl phosphite reactions gave no vpc evidence for formation of **8c** or **8d** at any time.

Methyl Dimethylphosphonite.—**3** (0.15 g, 1.5 mmol) and phosphonite (0.14 g, 1.5 mmol) were heated neat under N_2 at about 80°. Vpc monitoring showed the reaction to be complete in 18 hr. Removal of volatiles under high vacuum gave **8i**, essentially pure by vpc, in quantitative yield: pmr ($CDCl_3$) δ 1.17 (3 H, d, J_{HP} = 7.5 Hz, PCH_3), 1.32 (6 H, d, J_{HP} = 12 Hz, $PC(CH_3)_2$), 1.37 (6 H, s, $(CH_3)_2CO$), 3.55 (3 H, d, J_{HP} = 13 Hz, $POCH_3$), 3.72 (3 H, s, CO_2CH_3). **8i** was converted with methyl iodide to the phosphine oxide for analysis.

Tri-*n*-butyl Phosphine.—A solution of dione **3** (5.0 g, 36 mmol) in the phosphine (8.3 g, 41 mmol) under nitrogen at 120° showed isomerization of **3** to **4** in 18 hr (vpc analysis). Polymerization of **4** then ensued.

Reactions of the Methylphosphinate (10a).—**10a** (4.0 g, 15 mmol) was refluxed with 30 ml of 10% aqueous NaOH for 8 hr. The reaction mixture was acidified and subjected to continuous ether extraction for a prolonged period. The ether was dried over Na_2SO_4 and removed to leave the phosphinic acid **14**: 2.8 g, 15 mmol (near-quantitative yield); a white solid; mp 62–64°; recrystallized from ethanol, mp 71.4–72.8°; pmr (CCl_4) δ 1.06 (6 H, d, J_{HH} = 6.5 Hz, $CH(CH_3)_2$), 1.40 (3 H, d, J_{HP} = 14 Hz, PCH_3), 1.47 (6 H, d, J_{HP} = 15.5 Hz, $C(CH_3)_2P{=}O$), 3.30 (1 H, sep, J_{HH} = 6.5 Hz, $CH(CH_3)_2$), 12.3 (1 H, s, POH); ir ($CHCl_3$) 2980, 2940, 2880, 2100–2800 (w, broad, POH), 1696, 1468, 1375, 1296, 1170, 1090, 1045, 1028, 1002, 963, 883, 720 cm^{-1}.

Anal. Calcd for $C_8H_{17}O_3P$: C, 50.0; H, 8.9; P, 16.1. Found: C, 49.8, 49.7; H, 8.9, 9.0; P, 16.1, 16.5.

10a (16 g, 0.061 mol) was shaken at room temperature with 120 ml of 10% aqueous NaOH, during which time the temperature of the solution rose to 40°. The solution was acidified and ether extracted. The dried ether layer on evaporation yielded 6.0 g of an oil (**12**) which crystallized on standing. The mother liquor was then subjected to a continuous ether extraction. The dried ether solution, cooled to −20°, gave another 2.9 g of crystals (**12**): total yield 8.9 g, 0.35 mol (57%); mp 119.4–120.0°; neut equiv 250 (theory 252); pK_a 3.3 (H_2O, 25°); pmr ($CDCl_3$) δ 1.42 (6 H, s, $OC(CH_3)_2CO$), 1.56 (6 H, d, J_{HP} = 16 Hz, $(CH_3)_2$-CP=O), 1.68 (3 H, d, J_{HP} = 14.5 Hz, PCH_3), 3.74 (3 H, d, J_{HP} = 10.5 Hz, $POCH_3$), 11.4 (1 H, s, CO_2H); ir (KBr) 2990, 2500–3600 (CO_2H), 1710, 1692, 1467, 1407, 1390, 1366, 1307, 1260, 1200, 1170, 1150, 1130, 1052, 1030, 1002, 957, 890, 810, 762, 720 cm^{-1}.

Anal. Calcd for $C_{10}H_{19}O_5P$: C, 48.0; H, 7.6; P, 12.4. Found: C, 48.0; H, 7.4; P, 12.3.

12 was decarboxylated on heating at 150° to a colorless liquid with spectral properties consistent with the structure **13**: mass spectrum *m/e* (intensity, >15% base peak), 206 (parent, 5), 136 (100), 135 (60), 94 (45), 93 (22), 79 (17), 63 (15), 43 (35), 41 (29), 27 (19), and 15 (16); pmr (CCl_4) δ 1.02 (6 H, d, J_{HH} = 6.5 Hz, $HC(CH_3)_2$), 1.35 (3 H, d, J_{HP} = 13.5 Hz, PCH_3), 1.39 (6 H, d, J_{HP} = 15 Hz, $C(CH_3)_2P$), 3.31 (1 H, m, J_{HH} = 6.5 Hz, $HC(CH_3)_2$), 3.69 (3 H, d, J_{HP} = 10.5 Hz, $POCH_3$); ir (CCl_4), 2974, 2942, 1700, 1470, 1375, 1295, 1225, 1045, 1000, 888 cm^{-1}

When **10a** (3.0 g, 12 mmol) was refluxed 72 hr with 5 ml of 1:1 (v/v) HCl–H_2O, a water-insoluble layer appeared atop the reaction mixture. This layer was separated by addition of ether without shaking. The ether layer was dried (Na_2SO_4), and removal of the ether gave 0.70 g, 6.1 mmol (50% yield), of diisopropyl ketone identified by mass spectral, infrared, and vpc comparisons with authentic ketone. Extraction of the water layer with several portions of ether yielded 0.1 g (0.49 mmol) of **14**.

Yield of 8a, 9a, and 10a as a Function of Time.—A solution containing **3** (0.90 g, 64 mmol) and trimethyl phosphite (1.0 g, 81 mmol) in 2.0 ml of *n*-heptane was sealed under nitrogen in several glass tubes which were heated at 150°. Tubes were removed at intervals and their contents monitored from time to time by vpc analysis on column A. A set of identical samples was heated at 120°.

Reaction of Trimethyl Phosphite and Tris(dimethylamino)-phosphine with 2,2,4,4-Tetramethylcyclobutanone.—A 1-mol excess quantity of phosphite and the lactone were heated without solvent for 3 weeks at 115°. No detectable starting material consumption or product formation could be detected by vpc. A similar reaction with the aminophosphine produced some cloudiness in the solution but no detectable product.

Reaction of Trimethyl Phosphite and Tris(dimethylamino)-phosphine with 3-Dicyanomethylene-2,2,4,4-tetramethylcyclobutanone.—Reaction with excess phosphine at 120° for 15 days and excess aminophosphine at 60° for several weeks gave complete consumption of both butanone and phosphorus reactant. The reactions became very dark colored. However, no products were detected by vpc.

Effect of Time and Solvent on 9b/8b Ratio.—Dione **3** (0.35 g, 2.5 mmol) and triethyl phosphite (0.50 g, 3.0 mmol) were mixed in four different tubes and sealed under nitrogen. In another set of tubes the same amounts of phosphite and dione were mixed with 1 ml of acetonitrile and sealed under nitrogen. In a third set of tubes, *n*-heptane was used in place of acetonitrile. All were placed in a bath at about 150°. At intervals, tubes were removed and their contents analyzed by vpc, column A. For analysis the contents of the tube were transferred to a 5-ml volumetric flask and to dissolve all dione were diluted to 5 ml with acetonitrile for the neat and acetonitrile experiments and with chloroform for the heptane experiments. The diluted solution (1 ml) was then mixed with 40 μl of decane as internal standard. This allowed a reasonably accurate determination of the per cent dione unreacted. Results appear in Table III.

Conversion of 8b to 9b.—A mixture of 7.0 g of **3** with 10 ml of triethyl phosphite was sealed under N_2 and heated at about 150° for 92 hr. During this time the contents of the tube were shaken at intervals to dissolve the dione which sublimes on to the sides of the tube. After removal of dione and phosphite under high vacuum, the residue was shown to contain only **8b** and **9b** in 1.98:1.00 ratio. Portions of this mixture were sealed under nitrogen and kept at room temperature, 120 or 150°. At intervals a tube was removed, and vpc analysis for ratio **9b**/**8b** carried out. Results appear in Table IV.

To one of the above samples which had been at room temperature for 1 week (**8b**/**9b** = 1.5), a portion of decane was added as internal standard, and the tube was resealed and heated at 150°. Relative areas of peaks assigned to **8b**, **9b**, and triethyl phosphite relative to decane of assumed area 1.0 also appear in Table IV. Large amounts of dione were also formed but reliable quantitative data could not be obtained, since **3** crystallized out of the reaction mixtures at room temperature. The figures in Table IV are based on soluble dione only. A small portion of **4**

was also formed in each case, amounting to about 6% of the area of the internal standard.

Registry No.—**3**, 32687-47-1; **4**, 32687-48-2; **8a**, 32674-59-2; **8b**, 32674-60-5; **8e**, 32674-61-6; **8f**, 32674-62-7; **8i**, 32674-63-8; **9a**, 14261-54-2; **9b**, 14261-50-8; **9c**, 32674-66-1; **9d**, 14261-51-9; **9e**, 32674-68-3; **9f**, 32674-69-4; **9g**, 32674-70-7; **9i**, 32674-71-8; **10a**, 32674-72-9; **10b**, 32674-73-0; **10e**, 32674-74-1; **10f**, 32674-75-2; **10h**, 32674-76-3; **10i**, 32674-77-4; **11e**, 32674-78-5; **12**, 32674-79-6; **13**, 32674-80-9; **14**, 32722-86-4; **15c**, 32674-81-0; **15d**, 32674-82-1; **15e**, 32674-83-2; **15f**, 32674-84-3; **15g**, 32674-85-4; **16b**, 32674-86-5; **16h**, 32674-87-6; **16h'**, 32674-88-7; **16i**, 32674-89-8; **17-S**, 32674-90-1; methyl ethylene phosphite, 32674-91-2; dimethyl phenyl phosphite, 32674-92-3.

Pentacovalent Phosphorus. II. Reactions of Dione and Lactone Dimers of Dimethylketene with Trivalent Phosphorous Acid Amides[1]

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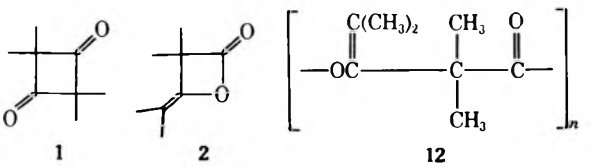
Reactions of the dione **1** and lactone **2** dimers of dimethylketene with the phosphoramidites $(CH_3O)_2PN(CH_3)_2$ (**3**), $CH_3OP[N(CH_3)_2]_2$ (**4**), and $C_6H_5OP[N(CH_3)_2]_2$ (**5**) and with trisdimethylaminophosphine (**6**) were investigated. Carboxy esters resulted from reactions of **3** and **4** with either dimer while **5** and **6** gave carboxamides. The structures of these products are similar to those formed from dimethylketene dimers on reaction with trialkyl phosphites. Except for reactions of **3**, identical products were formed from either **1** or **2** and a given phosphorus derivative. On reaction of **1** and **3**, three products are formed in relative proportions dependent on reaction temperature. These reactions are discussed in terms of a postulated mechanism involving nucleophilic attack by phosphorus on carbonyl carbon of **1** or **2**, followed either by ring expansion to a cyclic pentacovalent phosphorus intermediate or by ring opening to a phosphonium enolate species. Isomerization of **1** to **2** in the presence of **5** or **6** is also accommodated by the suggested reaction series. Possible kinetic control of carboxamide *vs.* carboxy ester formation is treated in terms of the structures and reaction patterns predicted for the postulated pentacovalent intermediates.

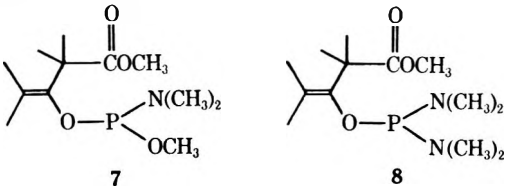
In the preceeding paper[3] we reported reactions of trialkyl phosphites and dimethyl methylphosphonite with the dimers (**1** and **2**) of dimethylketene. These results were interpreted in terms of transient pentacovalent phosphorus intermediates formed *via* ring expansion of the initial dimer–trivalent phosphorus adduct. Ultimate product formation was postulated to proceed *via* migration of an alkoxy group from pentacovalent phosphorus to the adjacent carbonyl group. Of interest in this regard is the question of the apparent relative migrational preference of different phosphorus substituents. This paper reports results of reactions of **1** and **2** with phosphorus amides having both methoxy and dimethylamino groups on phosphorus in the same molecule.



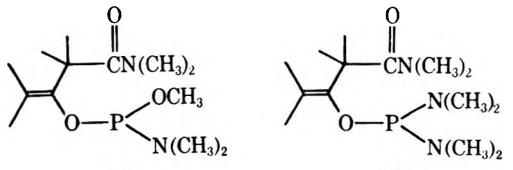
1 **2** **12**

Results

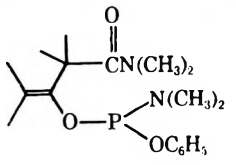
Reactions were carried out neat under nitrogen. The trivalent phosphorus derivatives used (**3**–**6**) are shown in Table I in which products and yields are also recorded for the lactone reactions. The lactone reactions proceeded in a rather straightforward manner giving reasonably high yields of vinyl products **7**–**11** similar to those which result with the trialkyl phosphites, as either the carboxamide or carboxylic ester. A side product in several instances is the same polymer **12** formed from lactone under the influence of methoxide.[4]



7 **8**



9 **10**



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Reactions of the mixed amide esters, phosphoramidites $(CH_3O)_2PN(CH_3)_2$ and $CH_3OP[N(CH_3)_2]_2$, gave almost exclusively carboxyl ester products. Only with the diamino compound **4** at 115° is any carboxamide **9** formed. By contrast $C_6H_5OP[N(CH_3)_2]$ yields exclusively the carboxamide **11**. Evidence for the structures of products **7**–**11** is given by their nmr and ir spectra and those of the sulfur and Arbuzov products (Table II). All show a weak ir band at about 1665 cm^{-1} for

(1) A portion of this work was published in preliminary form: W. G. Bentrude and W. D. Johnson, *Tetrahedron Lett.*, 4611 (1967). This work was supported by Public Health Service Research Grant No. CA-11045 from the National Cancer Institute.

(2) National Institutes of Health Predoctoral Fellow, 1966–1969. This work taken in part from the Ph.D. Thesis of W. D. Johnson, University of Utah, 1969.

(3) W. G. Bentrude, W. D. Johnson, W. A. Khan, and E. R. Witt, *J. Org. Chem.*, **37**, 631 (1972).

(4) R. H. Hasek, R. D. Clark, E. U. Elam, and J. C. Martin, *ibid.*, **27**, 60 (1962).

TABLE I
REACTIONS OF PXYZ WITH LACTONE 2[a]

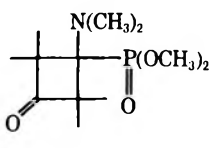
Reactant PXYZ	X	Y	Z	Mol of PXYZ/ mol of 2	T, °C	Time, hr	% convn	% yield[b]	Product
3	CH_3O	CH_3O	$(CH_3)_2N$	1.0	115	6.5	100	95 (62)[c]	7
								0	12
4	CH_3O	$(CH_3)_2N$	$(CH_3)_2N$	1.1	25	240	100	100 (65)[c]	8
								0	12
					115	7	100	70	8
								10	9
								(10)	12
5	C_6H_5O	$(CH_3)_2N$	$(CH_3)_2N$	2.0	120	350	80	65 (30)	11
								>10[d]	12
6	$(CH_3)_2N$	$(CH_3)_2N$	$(CH_3)_2N$	2.0	115	19	100	60 (37)	10
								>10[d]	12

[a] Reactions run neat under nitrogen. [b] Based on reacted lactone. [c] Isolated yield in parentheses. [d] Not measured quantitatively but estimated to be considerably more than from reaction of 4.

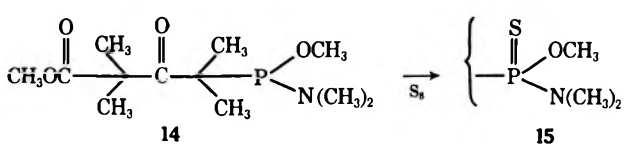
the olefinic bond and an intense carbonyl band at 1725–1730 (carboxylic acid esters) or 1635–1640 cm^{-1} (carboxamides). The trivalent derivatives have nmr absorptions readily assignable to vinyl methyls at δ 1.42–1.52 (J_{HP} = 3.0–3.5 Hz) and 1.64–1.76 (J_{HP} = 1.5–2.0 Hz) and geminal methyl absorptions at 1.28–1.41. The sulfur derivatives have similar absorptions at somewhat higher δ values. The *gem*-methyls sometimes appear as two peaks when phosphorus is an asymmetric center. The spectra of these products show them to be completely analogous to those formed from reactions of lactone with trialkyl phosphites which were well characterized in the preceeding paper.[3] Trivalent products **7**–**11** were very reactive with air (O_2) and sulfur. Quantitative elemental analyses were carried out on the sulfur derivative of each product **7**–**11**, designated as **7s**, **8s**, etc., except for **9** which was not isolated but was readily characterized by its nmr spectrum. Phosphonium salt derivatives of **8** and **10** were isolated from their reactions with methyl iodide.

Several reaction paths appear available in the dione–phosphoramidite reactions. With **4**, **5**, and **6** the same products result as in the lactone reactions including formation of **12**. Reactions of **5** and **6** showed buildup of large amounts of lactone at intermediate times. *E.g.*, with **6** at 80°, about half the dione had been isomerized to lactone in 124 hr even though complete conversion of lactone to **8** required 400 hr.

By contrast, **3** in reaction with dione gave two products (**13** and **14**) which were not formed with lactone.



13



14 **15**

The relative amounts of **13** and **14** are reduced compared to **7** at higher temperatures as shown in Table III.

The cyclobutanone derivative **13** is somewhat unusual, but its proposed structure is fully born out by its ir spectrum which showed an intense band at 1780 cm^{-1} expected for a cyclobutanone and absorptions at 1235 and 1250 cm^{-1}, one of which is likely a P=O stretching band. The nmr (C_6H_6) shows two sets of ring methyls at δ 1.38 and 1.48 and a dimethyl amino at δ 2.38 with J_{HP} of only 3.5 Hz. The reduced size of the coupling constant is consistent with the group not being directly bonded to phosphorus yet being in reasonably close proximity. Similar small J_{HP} values have been noted in analogous α-dimethylaminophosphonates.[5] The methoxyl groups on phosphorus appear in the expected range, δ 3.42 (J_{HP} = 11 Hz). The pentavalent structure of **13** was further shown by its failure to react with sulfur. Product **14** was isolated as its sulfur derivative **15**. Its structure was shown clearly by its pmr (C_6H_6) spectrum (see Experimental Section) which was very comparable to the product of trimethyl phosphite reaction with **1** whose structure was proved rigorously in the preceeding paper.[3] It also showed the intense carbonyl infrared absorptions at 1745 and 1685 cm^{-1} noted[3] for compounds of this type.

Discussion

These reactions involve essentially two features which deserve discussion: (1) the preservation or lack of preservation of dione or lactone structure in the products formed; (2) the distribution of products between carboxamides and carboxylic acid esters both of which could potentially result when both RO and $(CH_3)_2N$ are attached to the same phosphorus atom.

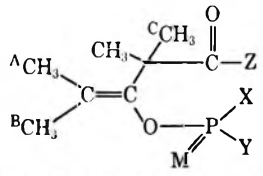
The first of the above aspects of these reactions may be treated in terms of a series of reactions (Scheme I) like that proposed[3] for the tertiary phosphite and dimethyl methylphosphonite reactions. Tables I and III show that, except for **3**, all nucleophiles (**4**–**6**) gave the same product (**24**) on reaction with either **1** or **2**. Reaction of dione **1** with **5** and **6** was accompanied by the formation of large amounts of **2**. We suggest that this probably occurs by the sequence **6** → **20** → **21** → **2**. It is well established[6] that the replacement of alkoxy substituents by amino groups in structures such as **17** and **20** stabilizes the ionic form **20** with the respect to the pentacovalent species **17**. This facilitates conversion of **1** to **2**. Completely consistent with these

(5) R. Burgada and J. Roussel, *Bull. Soc. Chim. Fr.*, 192 (1970); R. Burgada, *C. R. Acad. Sci., Ser. C*, **267**, 1854 (1968).

(6) D. B. Denney, D. Z. Denney, B. C. Chang, and K. L. Marsi, *J. Amer. Chem. Soc.*, **91**, 5243 (1969); F. Ramirez, C. P. Smith, J. F. Pilot, and A. S. Gulati, *J. Org. Chem.*, **33**, 3787 (1968).

TABLE II

SPECTROSCOPIC AND PHYSICAL DATA FOR



Product[a]	X	Y	Z	M	Chemical shifts (multiplicity, J_{HP}) CH_{3A}	CH_{3B}	CH_{3C}	X	Y	Z	Solvent	Ir frequency,[b] cm^{-1}	Physical data
7	CH_3O	$(CH_3)_2N$	CH_3O		1.43 (d, 3.5)	1.64 (d, 1.5)	1.28 (s)	3.37 (d, 13)	2.66 (d, 9.0)	3.63 (s)	Neat	2930, 1725, 1665, 1455, 1380, 1270, 1255, 1190, 1145, 1120, 1075, 1034, 970, 793, 740, 712, 683 (film)	Liquid, bp 68–70° (0.1 Torr)
7s	CH_3O	$(CH_3)_2N$	CH_3O	S	1.53 (d, 4.5)	1.71 (d, 3.5)	1.41 (s) 1.43 (s)	3.65 (d, 14)	2.90 (d, 13)	3.72 (s)	$CDCl_3$	2950, 1730, 1670 (w), 1465, 1385, 1250, 1190, 1147, 1113, 1076, 1035, 990, 856, 820, 752 (film)	Liquid
16	CH_3	$(CH_3)_2N$	CH_3O	O	1.41 (d, 3.5)	1.60 (d, 2.5)	1.30 (s)	1.41 (d, 16)	2.66 (d, 9.5)	3.60 (s)	CS_2	2930, 1725, 1665 (w), 1465, 1385, 1380, 1235, 1190, 1148, 1111, 1071, 992, 952, 907, 832, 775 (film)	Solid, mp 65–66°
8	$(CH_3)_2N$	$(CH_3)_2N$	CH_3O		1.42 (d, 3.5)	1.60 (d, 2.0)	1.26 (s)	2.60 (d, 9.0)	2.60 (d, 9.0)	3.54 (s)	Neat	2900, 1725, 1660 (w), 1450, 1380, 1270, 1192, 1135, 1110, 1068, 951, 778, 666 (film)	Liquid, bp 78–91° (0.15 Torr)
8s	$(CH_3)_2N$	$(CH_3)_2N$	CH_3O	S	1.52 (d, 4.5)	1.76 (d, 3.0)	1.42 (s)	2.75 (d, 12)	2.75 (d, 12)	3.73 (s)	$CDCl_3$	1730, 1670 (w), 1275, 1190, 1148, 1110, 1063, 988, 832, 760, 722 (Nujol)	Solid, mp 43–44°
10	$(CH_3)_2N$	$(CH_3)_2N$	$(CH_3)_2N$		1.43 (d, 3.0)	1.63 (d, 2.0)	1.25 (s)	2.63 (d, 9.0)	2.63 (d, 9.0)	2.92 (s)	Neat	2900, 1660 (s), 1640, 1470, 1390, 1275, 1200, 1112, 1068, 952, 797, 764, 744, 696, 666 (film)	Liquid, bp 87–88° (0.06 Torr)
10s	$(CH_3)_2N$	$(CH_3)_2N$	$(CH_3)_2N$	S	1.55 (d, 4.0)	1.76 (d, 3.0)	1.38 (s)	2.76 (d, 12)	2.76 (d, 12)	2.98 (s)	$CDCl_3$	1660 (s), 1630, 1295, 1190, 1110, 1070, 990, 980, 877, 848, 756, 738, 720 (Nujol)	Solid, mp 93.5–94.0°
11	C_6H_5O	$(CH_3)_2N$	$(CH_3)_2N$		1.52 (d, 3.5)	1.76 (d, 2.0)	1.38 (s) 1.41 (s)	7.1 (m)	2.74 (d, 9.5)	2.97 (s)	$CDCl_3$	2920, 1660 (s), 1630, 1580, 1485, 1390, 1220, 1110, 1068, 975, 860, 806, 763, 692 (film)	Liquid, bp 95–100° (0.1 Torr)
11s	C_6H_5O	$(CH_3)_2N$	$(CH_3)_2N$	S	1.56 (d, 4.5)	1.82 (d, 3.0)	1.62 (s) 1.74 (s)	7.2 (m)	2.58 (d, 12)	2.78 (s)	C_6H_6	2930, 1650 (s), 1635, 1580, 1490, 1390, 1208, 1110, 1100, 1068, 992, 916, 885, 856, 783, 762, 740, 688, 680 (film)	Liquid

[a] Satisfactory C, H, and P analyses were obtained for these compounds (±0.4%) with the following exceptions. **7** and **8**, which are readily air oxidized, were analyzed as their sulfur derivatives **7s** and **8s**. Only C and H analyses were obtained for **11s** and **16** (for **16**, calcd for H, 8.72; found, 8.20). [b] w indicates weak absorption; s signifies a shoulder.

SCHEME I

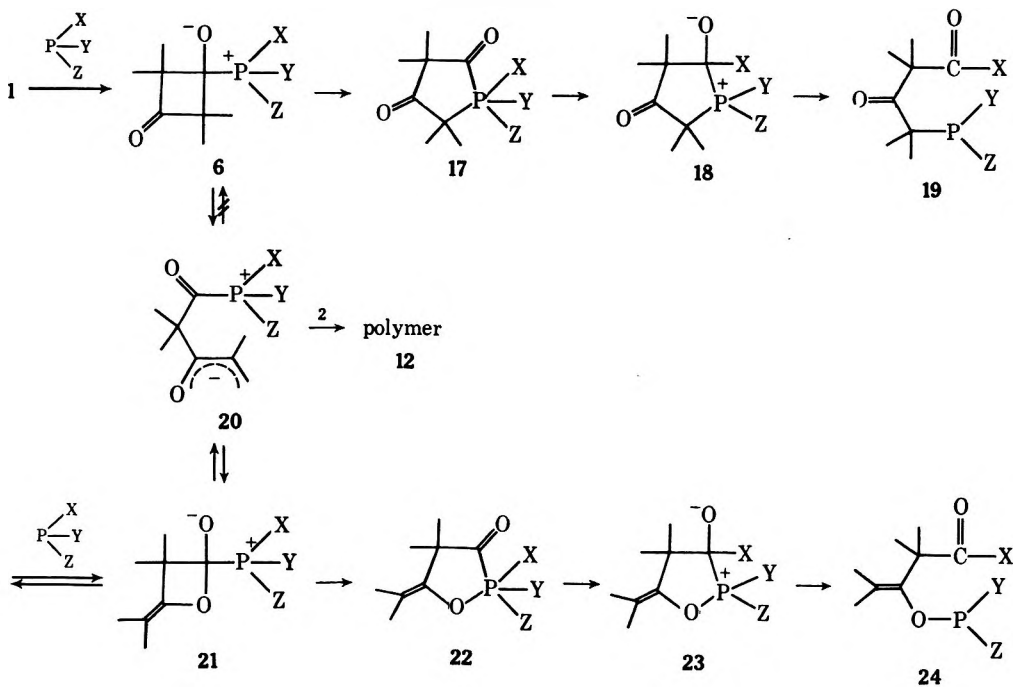


TABLE III
REACTIONS OF PXYZ WITH DIONE 1[a]

Reactant PXYZ	Mol of PXYZ/ mol of 2	T, °C	Time, hr	% convn	Product	% yield[b]
3	1.0	115	56	100	13	0
					14	0
					7	80
3	1.2	80	232	50	13	10
					14	45
					7	35
3	1.1	65	525	50	13	65
					14	10
					7	15
4	1.1	85	400	90	8	95
					12	Trace
5	2.0	120	350	40	11	45
					12	c
					2	45
6	1.1	80	400	100	10	60
					12	25[d]
					2	50[e]

[a] Reactions run neat under nitrogen. [b] Based on reacted dione using vpc method. [c] Not measured quantitatively but considerably more than a trace. [d] Isolated yield. [e] After 124 hr, 50% conversion of 1.

ideas about the effects of substituents on the relative stabilities of 17 and 20 is the observation that only with a single dimethylamino substituent (3) is formation of 19 observed and then only at reduced temperatures. With 4, 5, and 6, apparently the amino substituents favor the route through 20 by stabilizing 20 at the expense of 17.

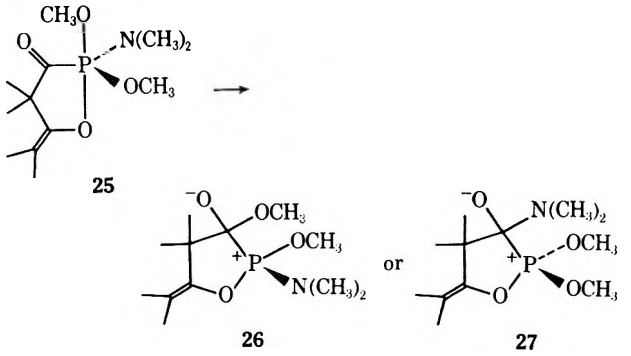
It will also be noted that the yield of polymer 12 from lactone is highest when intermediate 20, by which we believe 12 formation may be catalyzed, would be expected to be most readily formed from 21. A reasonable alternate explanation for the high degree of polymer formation in instances in which a positive charge is stabilized on phosphorus would be that 22 undergoes some dissociation to CH_3O^- or $(CH_3)_2N^-$ which then initiates the formation of 12.

Table I shows 3 is far more reactive toward the lactone than is trimethyl phosphite which requires 41 hr at 120° to completely convert lactone to product even when a 1-mol excess of phosphite is used.[3] This is consistent with the expected increased nucleophilicity of phosphorus on substitution of nitrogen in place of oxygen. Also consistent with phosphorus attack is the greatly reduced reactivity of the phenyl tetramethylphosphorodiamidite (5) with 2. In this instance 1 is converted to 2 and then only very slowly to 24 (11). Inspection of Table I shows in addition that 4 is also more reactive than trimethyl phosphite but no more reactive than 3. Substitution by a third dimethylamino (6) is accompanied by a decrease in reactivity compared to 3 and 4. At the same time, the amount of lactone which builds up on reaction of 6 with dione increases. These trends can be readily explained if the step 2 → 21 is normally endothermic and reversible. Dimethylamino substituents should lower the energy of 21 due to their electronic properties. This should speed up the process 2 → 21. At the same time increasing numbers of dimethylamino substituents may induce steric strain in intermediate 21. Thus, the rate of attack on 2 is maximized by replacing one or two methoxyls in trimethyl phosphite by dimethylaminos. A third dimethylamino results probably in a reduced rate of the reaction 22 → 23 (see later discussion) allowing the reverse of 2 → 21 to compete readily leading to a building of 2 on reaction of 6 with 1 as also occurs with 5. The reactivities of 3–6 with dione are not so readily comparable since they were not carried to similar levels of conversion. However, 6 is clearly more reactive than 4 as would be expected for nonreversible attack of more nucleophilic 6, both reactions giving rapid opening to 20. As expected 5 reacts very slowly.

The expected increase in phosphorus nucleophilicity in 3, 4, and 6 may also play a role in determining the relative amounts of 19 to 24 from the dione reactions. Product 19, if a stronger nucleophile, would be more likely to undergo isomerization to 24 *via* the reverse of

steps 6 → 17 → 18 → 19. This process is observed[3] with the dione products analogous to 19 from reaction with triethyl and trimethyl phosphite. A sample containing a 35/65 ratio of 7/14, heated for 24 hr, showed the amount of 7 to be little changed although 14 was partly consumed by Arbuzov rearrangement.

As noted above, reactions of 3–5 can lead to either a carboxamide or carboxy ester. Within the context of Scheme I, this appears to depend upon the relative ease of transfer of methoxy or dimethylamino in 17 → 18 and 22 → 23. This of course assumes kinetic control of product formation. Several factors may influence

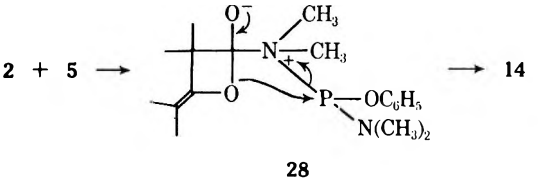


25 26 or 27

migrational aptitude. First, if the usual preference rules[7] for formation and reaction of pentacovalent phosphorus intermediates are obeyed, axial entrance and exit of substituents on phosphorus will be required. Second, the most electronegative substituent will occupy preferentially the axial position and thus be in a more favorable position to exit the bipyramid in migration. This suggests 25 as the most favored structure for the initially generated pentacovalent intermediate and predicts the observed migration of methoxy. A third factor could be the relative ease of ionization of a P–O and P–N bond. Consideration of stability of both the resulting anion and phosphonium ion predicts P–O cleavage to predominate. All of the above predict preferential methoxy migration as observed for reactions of 3 and 4.

Attempts to determine whether the variations in ratios of products of reaction of 4 with 2 result from kinetic or thermodynamic factors were not totally satisfying but indicated that 8/9 ratios were not readily changed once the products were formed. A mixture containing a 95/5 ratio of 8/9, heated at 115° for 18 hr, showed the ratios and amounts of 8 and 9 to remain unchanged even though at 115° the product ratio is usually about 85/15. However, a trace of $CH_3OP[N(CH_3)_2]_2$ and lactone were formed suggesting that 8 and/or 9 are formed reversibly. Similarly, an approximate 85/15 mixture, heated for about 300 hr at 60 and 92° showed little change in the 8/9 ratio although again a little of both 4 and 2 were formed. Thus, equilibration appears to be slow. A further indication that the carboxy ester is probably the product of kinetic control in reactions of 7 with 2 comes from consideration of bond strengths. The mean bond dissociation energies[8a] for P–O and P–N bonds to trivalent phosphorus favor the P–O bond by about 20 kcal/mol, whereas to dissociate the C–O bond in CH_3OCH_3 requires[8b] only about 10 kcal/mol more energy than it does to cleave the C–N bond in CH_3–$N(CH_3)_2$.

The formation of carboxamide in the reaction of 5 with 1 or 2 appears to be somewhat anomalous in terms of the above-discussed influences on migrational aptitude. One possibility is that the phenoxy substituent has rendered phosphorus of such low nucleophilicity in 5 that preferential attack by nitrogen now occurs (structure 28). This requires nitrogen attack to be much slower than phosphorus attack in reactions of 3, 4, and 6 since carboxamides are not generally formed.



28

It has been argued[9] that, in compounds like 3–6, nitrogen (a hard base) may be more nucleophilic than phosphorus (a soft base) toward carbonyl centers (medium hard acids). In fact, we also could explain reactions of 3 and 4 with 1 and 2 in terms of attack of oxygen rather than nitrogen or phosphorus. That nitrogen could be more nucleophilic than phosphorus is conceivable but that oxygen rather than phosphorus or nitrogen attack predominates seems untenable. The formation, which we report elsewhere,[10] of a stable phosphorane intermediate of type 22 in reaction of a cyclic derivative analogous to 4 with 2 to give ultimately an *N*,*N*-dimethylcarboxamide is strong evidence for the correctness of Scheme I involving P attack even when a carboxamide results. Further, if both 5 and 6 reacted with 2 *via* nitrogen attack, the tremendous difference in reactivities (Table I) would not be expected. Nitrogen attack on reaction with 5 cannot be completely ruled out, however, since phosphorus would have greatly reduced nucleophilicity.

The reaction of 1 and 3 which forms 13 may reasonably be written by two sequences of intermediates starting with 29 or 30, and both have been proposed[9a,b,11] in reactions of other ketones which give this type of product. The phosphorus attack route is favored by the Russian workers.[11] Apparently the lowest activation enthalpy process, that which forms the cyclobutanone derivative 13, predominates at 65°. At 80°, increasing amounts of ring expansion of intermediate 29 (or phosphorus attack if 30 is the intermediate giving 13) and ring opening occur leading to products of type 19 and 24. In regard to the question of whether 13 results *via* 29 or 30, it may be significant that no product of type 13 is found from 5 where reduced phosphorus nucleophilicity may have resulted in nitrogen attack.

Based on relative reactivities of the phosphorus nucleophiles, Hudson, *et al.*,[9a] have argued for nitrogen

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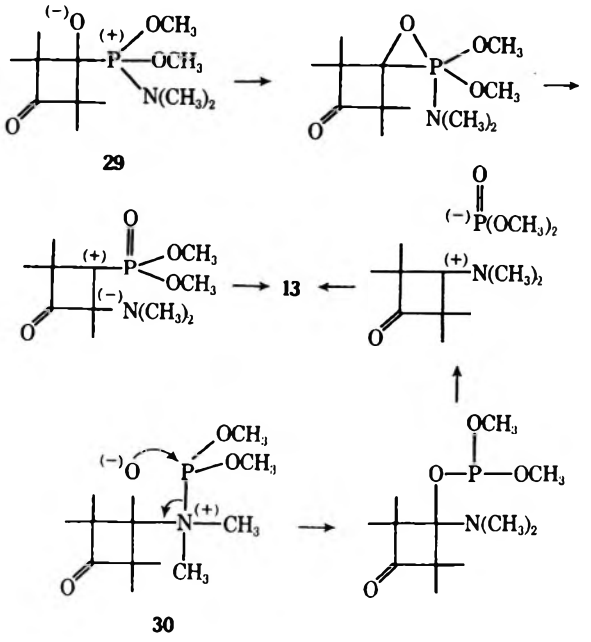
(10) W. G. Bentrude, W. D. Johnson, and W. A. Khan, *J. Amer. Chem. Soc.*, **93**, 923 (1971).

(11) A. N. Pudovik, I. V. Gur'yanova, S. P. Perevezentseva, and S. A. Terent'eva *Zh. Obshch. Khim.*, **39**, 337 (1969); V. P. Evdakov, L. I. Mizrakh, and L. Yu Sandalova, *Dokl. Akad. Nauk SSSR*, **162**, 573 (1965); A. N. Pudovik, S. A. Terent'eva, and E. S. Batyeva, *ibid.*, **175**, 616 (1967).



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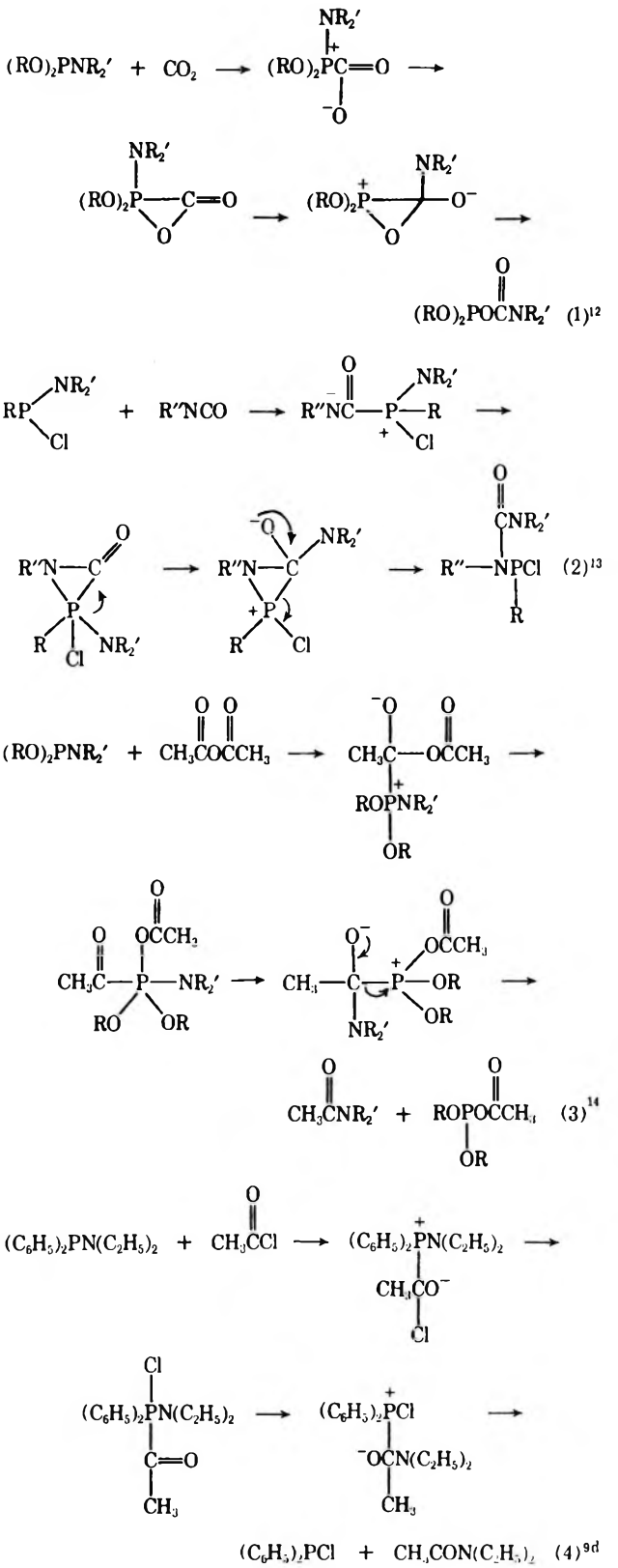
attack on carbonyl carbon in reactions with phenylisocyanate and benzaldehyde of **3** and its cyclic analog, 2-dimethylamino-1,3,2-dioxaphospholane. Rate-determining subsequent formation of a pentacovalent phosphorus intermediate was proposed. Apparently, some factor in our reaction system favors phosphorus attack at carbon in reactions of **3**, **4**, and **6**, as we have not been able to write reasonable mechanisms for carboxy ester formation *via* nitrogen attack. While we do not argue with the kinetic evidence for nitrogen attack, we think that it is interesting that it is possible to write reasonable mechanisms similar to that of Scheme I for many of the reactions for which nitrogen attack might be suggested but for which no supporting evidence is available. Reactions 1–4[9d,12–14] as written require dialkylamino rather than alkoxy migration contrary to what we observe in reactions 1 and 2. Unfortunately, the relative importance of kinetic *vs.* thermodynamic factors in reactions 1–4 are difficult to assess.

In a recent paper[15] it has been proposed that reaction of $(RO)_2PN(CH_3)_2$ (R = *i*-C_3H_7) with β-propiolactone gives $ROP(O)(NMe_2)CH_2CH_2CO_2R$ by phosphorus attack at saturated carbon and $(RO)_2P(O)CH_2CH_2CON(Me)_2$ by concerted P–N insertion in the lactone–C(=O)O– linkage followed by Arbuzov rearrangement. We believe that these results too could be accommodated *via* reactions similar to those of Scheme I. Further work relative to the importance of phosphorus *vs.* nitrogen attack in carbonyl systems appears needed.

Experimental Section

All chemicals were commercial materials with the exception of the trivalent phosphorus compounds.

Pmr spectra were taken on either a Varian A-60 or A-56/60 spectrometer. Chemical shifts are in δ, parts per million downfield from TMS as internal standard. Ir spectra were recorded on a Perkin-Elmer 5A infrared spectrophotometer. Unless otherwise noted, recorded bands (cm^{-1}) are of medium to strong intensity. Preparative vpc work was done with a Varian Aerograph A90-P3 gas chromatograph on a 10 ft by 3/8 in. 20% SE-30 on Chromosorb W column operated isothermally at 200 ml/min. Analytical vpc data were obtained with a thermal conductivity F & M 810 Model gas chromatograph using temperature programmed conditions, 120 ml/min flow and a 6 ft by 0.25 in. 20% SE-30 on 60–80 mesh Chromosorb W column. Quantitative estimates of reactant conversions and product yields were made by measuring the total area of reactants before reaction and that of remaining reactants and/or products formed. Identical injection sample sizes and chromatographic conditions



(1)[12]

(2)[13]

(3)[14]

(4)[9d]

(12) H. J. Vetter and H. Noth, *Chem. Ber.*, **96**, 1308 (1963); G. Oertel, H. Malz, and H. Holtschmidt, *ibid.*, **97**, 891 (1964).

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(14) V. P. Evdakov and E. K. Shlenkova, *Zh. Obshch. Khim.*, **35**, 1587 (1965).

(15) J. Koketsu, S. Kojima, and Y. Ishii, *Bull. Chem. Soc. Jap.*, **43**, 3232 (1970).

were utilized. Percentage yields of products were calculated on the basis of limiting starting material consumed using the measured areas and assumed equal sensitivity of all peaks. In some cases sensitivities were measured and found to be within 10% of each other. This accuracy was deemed sufficient for the purposes of the experiment in which, generally, relative yields of products of a given system under different conditions are of greatest interest.

Analyses were performed by the Schwartzkopf Microanalytical Laboratory, Woodside, N. Y., and by Galbraith Laboratories, Knoxville, Tenn. Melting points are uncorrected.

Dimethyl dimethylphosphoramidite (3) was prepared by mixing tris(dimethylamino)phosphine (50.0 g, 0.309 mol), 750 ml of benzene, and 1 g of dimethylamine hydrochloride and heating to reflux temperature. Methanol (19.8 g, 0.618 mol) in 250 ml of benzene then was added dropwise with constant stirring. After 17 hr of heating, vpc analysis showed that the reaction contained the optimum amount of desired product (~5% $CH_3OP[N(CH_3)_2]_2$). The solvent was removed under reduced pressure, and the residue was distilled through a heated helices-packed column to yield pure **3** (18.8 g, 0.137 mol): 44% yield; bp 86–89° (190 torr) [lit.[16] 50–51° 45 Torr)]; pmr (neat) δ 2.57 (6 H, d, J_{HP} = 9.0 Hz, $N(CH_3)_2$), 3.34 (6 H, d, J_{HP} = 12 Hz, $POCH_3$).

Methyl Tetramethylphosphorodiamidite (4).—Phosphorus trichloride (175 g, 2.00 mol), pyridine (158 g, 2.00 mol), and 1 l. of ether were mixed and cooled in an ice bath. Methanol (64.0 g, 2.00 mol) in 700 ml of ether was added dropwise with vigorous stirring. After the mixture was warmed to room temperature, the solid amine hydrochloride was removed by filtration, and the solvent was removed under reduced pressure. Distillation yielded CH_3OPCl_2: 60.0 g (0.452 mol); 23% yield; bp 42° (100 Torr) [lit.[17] 58° (300 torr)]. To the ice-cooled CH_3OPCl_2 (60.0 g) in 750 ml of ether was added dropwise with vigorous stirring dimethylamine (100 g, 2.22 mol) in 250 ml of ether. The addition funnel containing the dimethylamine solution was wrapped with aluminum foil which contained Dry Ice to prevent the dimethylamine from evaporating. After the mixture warmed to room temperature, the solid amine hydrochloride was removed by filtration, and the solvent was removed under reduced pressure. The residue was distilled twice through a heated helices-packed column to give the desired product (11.4 g, 0.0752 mol): 17% yield (based on CH_3OPCl_2); bp 95–96° (135 Torr) [lit.[18] 53–54° (24 Torr)]; pmr (neat) δ 2.51 (12 H, d, J_{HP} = 9.0 Hz, $PN(CH_3)_2$), 3.30 (3 H, d, J_{HP} = 12.5 Hz, $POCH_3$).

Phenyl Tetramethylphosphorodiamidite (5).—Tris(dimethylamino)phosphine (24.5 g, 9.15 mol) in 350 ml of anhydrous benzene was heated to reflux under nitrogen. Phenol (14.2 g, 0.15 mol) dissolved in 100 ml of anhydrous benzene was added dropwise. After addition, refluxing and stirring were continued for 15 hr. Benzene was distilled off under reduced pressure, and the residual liquid was distilled through a small Vigreux column to yield pure **5** (28.25 g, 0.133 mol): 86.6% yield; bp 52–53° (0.1 Torr); pmr (neat) δ 2.52 (12 H, d, J_{HP} = 9.0 Hz, $PN(CH_3)_2$), 7.0 (5 H, m, OC_6H_5). **5** was converted to its sulfide for analysis.

Anal. Calcd for $C_{10}H_{17}N_2OPS$: C, 49.17; H, 7.01; P, 12.68. Found: C, 48.68; H, 6.86; P, 12.80.

Reactions of Dione 1 with Phosphoramides 3–6.—The starting materials were mixed neat under a nitrogen atmosphere in a flask. The stopper was wired tightly in place and the flask was heated at the temperature indicated. At intervals the flask was opened under nitrogen, and the contents were monitored by vpc, 10°/min program rate. Details concerning these reactions appear below.

Phosphoramidite 3 (2.99 g, 21.4 mmol) and **1** (2.92 g, 21.4 mmol) were heated at 115° for 56 hr at which time vpc analysis showed reaction to be complete to give **7** in 80% yield based on dione. About 10% of an unidentified shorter retention time peak and several minor very long retention time products were noted. **7** was identified by its vpc retention time and by comparison of ir and pmr spectra of the reaction product mixture with those of authentic **7** from reaction of **3** with lactone **2**.

The same reactants (25.5 mmol of **3**, 21.4 mmol of **1**) gave predominantly product **7**, **14**, and **13** after 232 hr at 80° (50% conversion of **1**) in 35, 45, and 10% yields. Distillation [75–76° (0.15 Torr), 40% combined yield] failed to separate the products. Addition of sulfur and gentle warming gave products **15** and **7s** and left **13** unchanged. **15** and **7s** were separated by preparative vpc. **15**: pmr (C_6H_6) δ 1.48 and 1.59 (3 H each, s, $CO(CH_3)_2CO$), 1.53 (3 H, d, J_{HP} = 19 Hz, $PC(CH_3)_2$), 1.54 (3 H, d, J_{HP} = 17.5 Hz, $PC(CH_3)_2$), 2.62 (6 H, d, J_{HP} = 9.0 Hz, $PN(CH_3)_2$), 3.30 (3 H, d, J_{HP} = 13 Hz, $POCH_3$), 3.30 (3 H, s, CO_2CH_3); ir (film) 2950, 1745, 1720 (w), 1685, 1465, 1385, 1225, 1180, 1156, 1138, 1029, 990, 896, 806, 730, 679 cm^{-1}.

Anal. Calcd for $C_{12}H_{24}NO_4PS$: C, 46.58; H, 7.81; P, 10.01. Found: C, 46.37; H, 8.08; P, 9.57.

At 70° in 525 hr **3** (39.4 mmol) and **1** (35.7 mmol) gave approximately 50% conversion of **1** to **7**, **14**, and **13** in 15, 10, and 65% yield, respectively. Distillation yielded small amounts of **13**, bp 100–105° (0.15 Torr), purified by vpc: pmr (C_6H_6) δ 1.38 (6 H, s, ring CH_3), 1.48 (6 H, s, ring CH_3), 2.38 (6 H, d, J_{HP} = 3.5 Hz, $N(CH_3)_2$), 3.42 (6 H, d, J_{HP} = 11 Hz, $POCH_3$); ir (film) 2950, 1780, 1470, 1250, 1235, 1033, 830, 742 cm^{-1}.

Anal. Calcd for $C_{12}H_{24}NO_4P$: C, 51.98; H, 8.72; P, 11.17. Found: C, 51.82; H, 8.74; P, 11.05.

All the reactions showed the presence of a small amount of **2** formed in steady concentrations throughout the reaction.

Phosphoramidites 4, 5, and 6 reacted with **1** under conditions recorded in Table III in generally routine fashion to give the same products as they did with **2**. Reactions with **4** showed formation of a small amount (<5%) of lactone **2** which persisted throughout the reaction. With **5** at 40% conversion of **1**, a 45% yield of lactone **2** was noted by vpc along with the product **8** (45%) shown to be identical with that from **5** and **2** by vpc, ir, and pmr measurements. A small amount of solid **12** was observed to precipitate out of the reaction but was not isolated. Reaction with **6** (8.40 g, 5.15 mmol) showed half of **1** (6.82 g, 48.7 mmol) converted to **2** in 124 hr at 80°. Complete conversion of **1** to products took 400 hr at which time all **2** was consumed as well to a 60% yield of **10**. From the reaction was isolated 1.5 g (25% yield) of polymer **12** which was recrystallized from diglyme, mp 197–199° (lit.[4] mp 198–200°). **10** was distilled to give 3.2 g, 10.6 mmol (24% yield), of a viscous, colorless liquid, bp 92–93° (0.07 Torr).

Reactions of Lactone 2 with Phosphoramides 3–6.—The procedure was the same as with the dione, except as given below. Spectroscopic data for products appear in Table II. Products **7–11** were warmed with S_8 to convert them to the corresponding sulfides on which elemental analyses were obtained.

Phosphoramidite 3 (5.11 g, 3.65 mmol) and **2** (5.00 g, 3.65 mmol) at 100° for 6.5 hr gave 100% conversion of reactants to **7** in 95% yield by vpc. Distillation yielded pure **7** as a viscous, colorless liquid, 6.25 g, 22.5 mmol (62%), bp 68–70° (0.1 Torr). When heated gently with sulfur, **7** yielded the thio compound **7s**, collected by preparative vpc as a viscous, slightly yellow liquid. Reaction of **7** with excess methyl iodide at room temperature yielded the methylphosphonate **16** as a white solid, mp 65–66° (from hexane).

Dry air bubbled through **7** at room temperature for 4 hr gave an approximate 85% yield of what is probably the corresponding oxide, the phosphoramidate, a viscous, colorless liquid which was not further purified. A pmr spectrum of unpurified oxide differed from that of **7** only in slight changes in chemical shifts and coupling constants as expected for a simple oxidation at phosphorus.

Phosphoramidite 4 (3.00 g, 20.0 mmol) and **2** (2.50 g, 17.9 mmol) at room temperature for 10 days gave a 100% conversion of **2** to a quantitative yield of **8** (by vpc). Distillation yielded pure **8**, a colorless, viscous liquid, bp 79–81° (0.15 Torr). At 115° vpc analysis showed the same reactants to yield **8** (70%) along with material assigned structure **9** (10%). The latter was not obtained in pure, isolated form, but its structure was deduced from a pmr spectrum of **8** in which **9** was the only impurity. Peaks assignable to **9** were observed at δ 2.84 (s, $CON(CH_3)_2$) and 3.38 (d, J_{HP} = 13 Hz, $POCH_3$). Assignment was based on comparison with the pmr spectrum of **10**. **8** reacted readily with sulfur to give **8s**, white crystals, mp 43–44° (hexane). With excess methyl iodide at room temperature, **8** gave the methyl phosphonium salt, a white solid, which was washed six times with pentane: mp 130–132°; pmr ($CDCl_3$) δ 1.42 (6 H, s, gem CH_3), 1.61 (3 H, d, J_{HP} = 3.5 Hz, vinyl CH_3), 1.78 (3 H, d, J_{HP} = 3.0 Hz, vinyl CH_3), 2.42 (3, H, d, J_{HP} = 15 Hz, PCH_3), 2.97 (6 H, d, J_{HP} = 11 Hz, $N(CH_3)_2$), 3.76 (3 H, s, OCH_3); ir

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(Nujol) 1730, 1665 (w), 1320, 1245, 1170, 1145, 1103, 1072, 1013, 968, 923, 912, 880, 857, 834, 805, 770, 735 cm^{-1}.

Phosphoramidite 5 (2.00 g, 9.44 mmol) and **2** (0.66 g, 4.7 mmol) for 350 hr at 120° showed 80% conversion of **2** to **11** (65% yield by vpc) isolated by distillation as a viscous, colorless liquid (0.40 g, 1.1 mmol), 30%, bp 95–100° (0.1 Torr). A considerable amount of polymer **12** precipitated from solution during reaction but was not quantitatively measured. **11** reacted rapidly on warming with sulfur to give the thio compound **11s**, a pale yellow liquid isolated by preparative vpc.

Phosphoramidite 6 (11.6 g, 71.4 mmol) and **2** (5.00 g, 35.7 mmol) gave complete conversion of **2** to products in 19 hr at 115° yielding 60% of **10** (by vpc) and several minor unidentified products. A large amount of **12** also was formed. Distillation yielded pure **10**, a colorless viscous liquid, 4.0 g, 13 mmol (37%), bp 87–88° (0.06 Torr). Reaction of **10** with sulfur gave a solid which was recrystallized several times from hexane, mp 93.5–94°. With excess methyl iodide, **10** formed the methyl phosphonium salt, a white solid, which was washed several times with pentane to give a white solid: mp 175–177°; pmr ($CDCl_3$) δ 1.38 (6 H, s, gem CH_3), 1.64 (3 H, d, J_{HP} = 3.5 Hz, vinyl CH_3), 1.80 (3 H, d, J_{HP} = 2.5 Hz, vinyl CH_3), 2.45 (3 H, d, J_{HP} = 15 Hz, PCH_3), 2.98 (6 H, d, J_{HP} = 11 Hz, $PN(CH_3)_2$), 2.94 (6 H, s, $CON(CH_3)_2$); ir (Nujol) 1665, 1620 (w), 1315, 1255, 1175, 1111, 1095, 1059, 1011, 975, 950, 926, 910, 877, 859, 806, 734, 672 cm^{-1}.

Anal. Calcd for $C_{15}H_{33}N_3O_2PI$: C, 40.45; H, 7.47. Found: C, 40.54; H, 7.35.

Registry No.—**1**, 933-52-8; **2**, 3173-79-3; **3**, 20217-54-3; **4**, 17166-16-4; **5**, 26546-75-8; **6**, 1608-26-0; **7**, 20217-34-9; **7s**, 32687-54-0; **8**, 20217-52-1; **8** MeI, 32654-72-1; **8s**, 32687-56-2; **10**, 20217-33-8; **10** MeI, 32687-58-4; **10s**, 32687-24-4; **11**, 32687-25-5; **11s**, 32687-26-6; **13**, 32654-70-9; **15**, 32687-27-7; **16**, 32687-28-8.

Kinetic Analysis of Silver-Catalyzed Oxidative Cleavage Reactions by Peroxydisulfate Ions[1]

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Received July 20, 1970

The rates of the silver(I)-catalyzed oxidative cleavage reactions of pinacol (**1**), 2-methyl-2-hydroxy-3-butanone (**2**), and pyruvic acid (**3**) by potassium peroxydisulfate have been measured at various concentrations of the reactants. The observed rates indicate that two reaction paths are operative in these cleavage reactions. In path I, the oxidative cleavage is performed by silver(III). Path II is a free-radical chain reaction that involves silver(II) as the oxidative cleaving agent. Oxidative cleavage by path II is faster than path I and predominates at lower substrate concentrations, whereas the slower path I is more likely if the substrate concentration is high or if the substrate reacts rapidly with silver(III).

The silver(I)-catalyzed oxidative cleavage reactions of glycols by peroxydisulfate was demonstrated by Greenspan and Woodburn.[2] Kinetic studies of the cleavage reactions of α-hydroxy acids and esters show that the rate laws for the cleavage reactions are dependent on the concentrations of the reagents and, in some instances, the reaction rates are inversely related to the substrate concentration.[3-8] Our investigations were directed toward finding an explanation for the kinetic behavior of these oxidative cleavage reactions. A mechanistic rationale for the kinetics of the oxidative cleavage reactions of pinacol (**1**), 2-methyl-2-hydroxy-3-butanone (**2**), and pyruvic acid (**3**) yielding the products shown in eq 1, 2, and 3, respectively (see Experimental Section), is presented in this article.

$$\underset{\mathbf{1}}{(CH_3)_2C(OH)C(OH)(CH_3)_2} + S_2O_8^{2-} \xrightarrow{Ag^I} 2(CH_3)_2C{=}O + 2HSO_4^- \quad (1)$$

$$\underset{\mathbf{2}}{(CH_3)_2C(OH)COCH_3} + S_2O_8^{2-} \xrightarrow{Ag^I} (CH_3)_2C{=}O + CH_3CO_2H + 2HSO_4^- \quad (2)$$

$$\underset{\mathbf{3}}{CH_3COCO_2H} + S_2O_8^{2-} \xrightarrow{Ag^I} CH_3CO_2H + CO_2 + HSO_4^- \quad (3)$$

Kinetic Data.[3]—In the absence of Ag^I, the rate of reaction of the peroxydisulfate with compounds **1**, **2**, and **3** at 30° in a sulfate–bisulfate buffered solution (pH 1.4) is negligible. Upon addition of Ag^I, immediate reaction ensues. Preliminary studies by us, as well as the previously cited investigations by others,[3-8] showed that the rate laws for the reactions depended markedly on the relative concentrations of the reagents. Initial rates for the oxidative cleavage reactions of **1**, **2**, and **3** at various initial concentrations of Ag^I, the substrate, and peroxydisulfate are shown in Tables I, II, and III, respectively.

Examination of the oxidative-cleavage rates for pinacol in Table I reveal the following. (1) At the higher [Ag^I] and pinacol concentrations, the cleavage rates are essentially zero order in substrate and first order in Ag^I. (2) At the higher [Ag^I] but lower substrate concentrations, the reaction rates are half-order in both Ag^I and the substrate. (3) At the lowest [$S_2O_8^{2-}$], the reaction rates are zero order in pinacol and half order in [Ag^I]. (4) At low [Ag^I] but higher ($S_2O_8^{2-}$] and pinacol concentrations, the reaction rates are zero order in substrate but approach three-halves order in [Ag^I]. (5) The kinetic order of $S_2O_8^{2-}$ is considerably greater than unity except at low substrate concentrations. (6) At low [Ag^I], the reaction rate appears to be inversely related to the pinacol concentration.

The oxidative cleavage rates of the hydroxy ketone **2** and pyruvic acid (**3**) show some of the characteristics observed for the pinacol reaction. The most significant difference is that the inverse concentration effect

(1) This work was supported by a grant (AM-08517) from the National Institutes of Health.

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(3) D. D. Mishra and S. Ghosh, *J. Indian Chem. Soc.*, **41**, 397 (1964).

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(7) G. V. Bakore and S. N. Joshi, *Z. Phys. Chem.*, 250 (1965).

(8) G. D. Manghani and G. V. Bakore, *Bull. Chem. Soc. Jap.*, **41**, 2574 (1967).

TABLE I

INITIAL RATES[a] OF OXIDATIVE CLEAVAGE OF PINACOL (1) AT 30.0° [b]

$[S_2O_8^{2-}]$ × 10^2	$[Ag^I]$ × 10^3	[Pinacol] 0.30	0.15	0.075	0.018	0.0094
4.0	5.12	37.95	37.50	36.92		8.70
1.0	5.12	4.48	4.41	4.43	2.16	1.54
0.5	5.12	0.87	0.86	0.86		0.82
4.0	2.56	18.82	20.38	22.43		5.09
1.0	2.56	2.49	2.48	2.77	1.38	1.01
0.5	2.56	0.52	0.52	0.53		0.47
4.0	1.28	5.34	8.65	10.74		2.27
1.0	1.28	1.27	1.28	1.31		0.64
0.5	1.28	0.38	0.38	0.39		0.33
1.0	0.64	0.37	0.46	0.45	0.51	0.37
1.0	0.32	0.12	0.15	0.36	0.20	0.27

[a] All rates estimated from first 10% reaction of $S_2O_8^{2-}$ and are expressed in mol $l.^{-1}$ min^{-1} × 10^4. [b] Solutions buffered at pH 1.4 by 0.25 *M* Na_2SO_4 and 0.25 *M* $NaHSO_4$.

TABLE II

INITIAL RATES[a] OF OXIDATIVE CLEAVAGE OF 2-METHYL-2-HYDROXY-3-BUTANONE (2) AT 30.0° [b]

$[S_2O_8^{2-}]$ × 10^2	$[Ag^I]$ × 10^3	[2] 0.30	0.15	0.075	0.0187	0.0094
1.0	5.12	0.99	1.08	1.09	0.91	0.066
4.0	2.56	2.97		4.23		2.13
1.0	2.56	0.51		0.54		0.43
0.5	2.56	0.15		0.26		0.21
1.0	1.28	0.26	0.37	0.39	0.37	0.34
4.0	0.64	0.79		2.19		0.89
1.0	0.64	0.095		0.24	0.16	0.11
0.5	0.64	0.036		0.057		0.031

[a] All rates estimated from first 10% reaction of $S_2O_8^{2-}$ and are expressed in mol $l.^{-1}$ min^{-1} × 10^4. [b] Solutions buffered at pH 1.4 by 0.25 *M* Na_2SO_4 and 0.25 *M* $NaHSO_4$.

TABLE III

INITIAL RATES[a] OF OXIDATIVE CLEAVAGE OF PYRUVIC ACID (3) AT 30.0° [b]

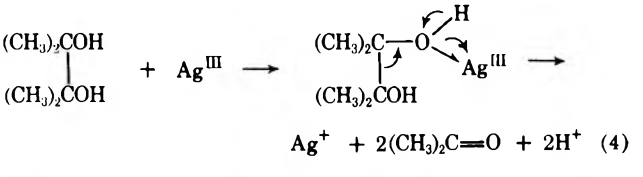
$[S_2O_8^{2-}]$ × 10^2	$[Ag^I]$ × 10^3	[Pyruvic acid] 0.075	0.0188	0.0094	0.0047
1.0	5.12	0.35	0.51	0.62	0.99
4.0	2.56	1.30	3.14		5.65
1.0	2.56	0.20	0.39		0.76
0.5	2.56	0.17	0.17		0.26
1.0	1.28	0.18	0.26	0.35	0.57
4.0	0.64	0.64	1.02		2.74
1.0	0.64	0.088	0.12		0.39
0.5	0.64	0.026	0.042		0.10

[a] All rates estimated from first 10% reaction of $S_2O_8^{2-}$ and are expressed in mol $l.^{-1}$ min^{-1} × 10^4. [b] Solutions buffered at pH 1.4 by 0.25 *M* Na_2SO_4 and 0.25 *M* $NaHSO_4$.

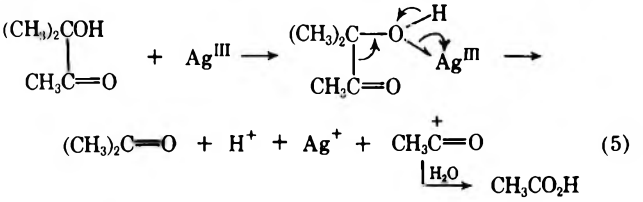
of the substrate on the reaction rates (item 6 above) is more pronounced and operative even at higher $[Ag^I]$.

These kinetic observations can be rationalized in terms of two paths for the oxidative-cleavage reactions. In path I, the cleavage is effected by Ag^{III} which is formed by oxidation of Ag^I by $S_2O_8^{2-}$.[9] Path II is a free-radical chain reaction involving Ag^{II} as the oxidative cleaving agent in a free-radical chain propagating process.

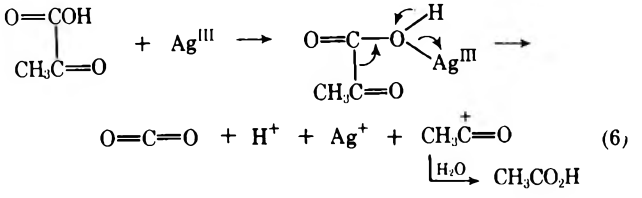
Path I.—Oxidative cleavage of the substrates **1**, **2**, and **3** may be performed by Ag^{III} as shown in eq 4, 5,



$$Ag^+ + 2(CH_3)_2C{=}O + 2H^+ \quad (4)$$



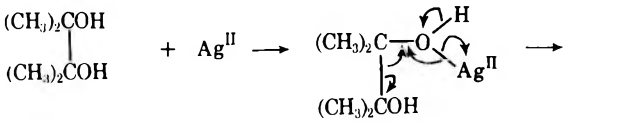
$$(CH_3)_2C{=}O + H^+ + Ag^+ + CH_3\overset{+}{C}{=}O \xrightarrow{H_2O} CH_3CO_2H \quad (5)$$



$$O{=}C{=}O + H^+ + Ag^+ + CH_3\overset{+}{C}{=}O \xrightarrow{H_2O} CH_3CO_2H \quad (6)$$

and 6.[10] The acylium ion formed in the cleavage reaction of the hydroxy ketone **2** and pyruvic acid (**3**) reacts with water producing the acetic acid observed as a reaction product in each case.

Path II.—In path II, the cleavage is performed by Ag^{II} as part of a free-radical chain reaction. In the case of pinacol, the cleavage by Ag^{II} produces an α-hydroxyalkyl radical which reacts with $S_2O_8^{2-}$ yielding another molecule of acetone and a chain propagating $SO_4\cdot^-$. Oxidation of Ag^I by $SO_4\cdot^-$ regenerates Ag^{II} (reaction 9) for the oxidative cleavage reaction. Oxida-



$$(CH_3)_2C{=}O + H^+ + Ag^I + (CH_3)_2\dot{C}OH \quad (7)$$

$$(CH_3)_2\dot{C}OH + S_2O_8^{2-} \longrightarrow (CH_3)_2C{=}O + H^+ + SO_4^{2-} + SO_4\cdot^- \quad (8)$$

$$SO_4\cdot^- + Ag^I \longrightarrow SO_4^{2-} + Ag^{II} \quad (9)$$

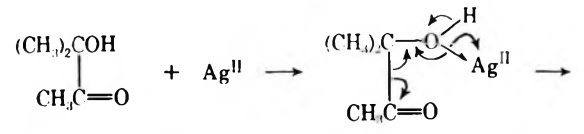
tive cleavage of the hydroxy ketone **2** and pyruvic acid in path II follows similar routes. An acetyl radical is formed in the cleavage reactions of **2** and **3** which propagates the chain by interaction with $S_2O_8^{2-}$ yielding both the chain carrying $SO_4\cdot^-$ and the acylium cation, the precursor of acetic acid. Both α-hydroxyalkyl radicals and acyl radicals have been proposed to react with peroxydisulfate[11] yielding the sulfate anion radical necessary to propagate the chain reaction by interaction with Ag^I as shown in eq 9.

Kinetic Analysis.—Support for these proposed mechanisms for the oxidative cleavage reactions is found in

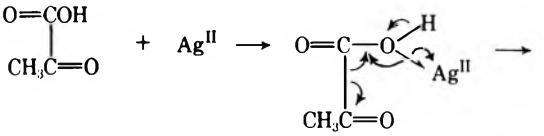
(9) For reviews of the chemistry of the higher oxidation states of silver, see J. A. McMillan, *Chem. Rev.*, **62**, 65 (1962); D. A. House, *ibid.*, **62**, 185 (1962).

(10) Although both Ag^{III} and Ag^{II} are able to form dsp^2-square-planar complexes with substrates capable of undergoing oxidative cleavage, our investigations of the oxidative cleavage rates of stereoisomeric cyclic 1,2 diols to be reported later indicate that formation of such complexes are not necessary for reaction to occur.

(11) J. O. Edwards, A. R. Gallapo, and E. McIsaac, *J. Amer. Chem. Soc.*, **88**, 3893 (1966).



$$(CH_3)_2C{=}O + H^+ + Ag^+ + CH_3\dot{C}{=}O \quad (10)$$



$$O{=}C{=}O + H^+ + Ag^+ + CH_3C{=}O \quad (11)$$

$$CH_3\dot{C}{=}O + S_2O_8^{2-} \longrightarrow CH_3\overset{+}{C}{=}O + SO_4^{\cdot-} + SO_4^{2-} \quad (12)$$

$$\overset{H_2O}{\longrightarrow} CH_3CO_2H$$

the kinetic data for the reaction given in Tables I, II, and III and the effects of allyl acetate in retarding the reaction rates.

Cleavage of the substrates by Ag^{III} in path I is possibly significant only at the higher $[Ag^I]$ and substrate concentrations. Under these conditions, particularly in the case pinacol and the hydroxy ketone 2, the reaction follows a rate law that is independent of the substrate concentration but is first order in $[Ag^I]$ and some higher kinetic order in $[S_2O_8^{2-}]$. This rate law is consistent with the sequence of reactions 13–15 in which formation of Ag^{III} (reaction 14) is the rate-determining step. The derived rate law for reaction 14 is given by eq 16 which indicates that the reaction is first

$$\text{(fast) } Ag^I + xS_2O_8^{2-} \underset{k_{-13}}{\overset{k_{13}}{\rightleftharpoons}} Ag^I(S_2O_8^{2-})_x \quad (13)$$

$$\text{(slow) } Ag^I(S_2O_8^{2-})_x + S_2O_8^{2-} \xrightarrow{k_{14}} Ag^{III} + 2SO_4^{2-} + xS_2O_8^{2-} \quad (14)$$

$$\text{(fast) } Ag^{III} + \text{substrate} \longrightarrow Ag^{III}(\text{substrate}) \xrightarrow{k_{15}} Ag^I + \text{products} \quad (15)$$

$$\text{rate} = \frac{d[Ag^{III}]}{dt} = \frac{k_{13}k_{14}[Ag^I][S_2O_8^{2-}]^{x+1}}{k_{14}[S_2O_8^{2-}] + k_{-13}} \quad (16)$$

order in $[Ag^I]$ and a kinetic order for $[S_2O_8^{2-}]$ that depends both on the extent of complexing of Ag^I with $S_2O_8^{2-}$ and the formation constant (k_{13}/k_{-13}) of the complex. If the complexing constant is low ($k_{-13} > k_{13}$), as might be expected for Ag^+ with oxygen functions, the contribution of k_{-13} to the rate of formation of Ag^{III}, and consequently the rate of cleavage by path I, may be significant and complexing of $S_2O_8^{2-}$ with Ag^I is consequently more extensive at higher $[S_2O_8^{2-}]$ and therefore the kinetic order of $S_2O_8^{2-}$ is greater at the higher concentrations of $S_2O_8^{2-}$.

The free-radical chain sequence for oxidative cleavage by path II is summarized in eq 17–19. This chain sequence is initiated by reaction of Ag^{III} produced in reaction 14 with Ag^I producing two Ag^{II} which start two chain sequences. Since reaction of Ag^I must compete with the substrate for Ag^{III} (reaction 15), initiation of the chain sequence by eq 20 should be favored by lower substrate concentrations. The inverse relationship of substrate concentration and the oxidative-cleavage rates suggests that reaction by the free-radical chain reaction in path II is faster than cleavage by path I. This effect is most pronounced in the reactions of pyruvic acid and is probably indicative of a faster rate of reaction of Ag^{III} with this substrate than with either pinacol or the hydroxy ketone 2. At low $[Ag^I]$, however, the inverse rate relationship is observable with both 1 and 2 because the balance between formation of Ag^{II} by reaction 20 and interaction of the substrate with Ag^{III} is more sensitive.

$$Ag^{II} + \text{substrate} \xrightarrow{k_{17}} Ag^I + \text{product} + \text{radical} \quad (17)$$

$$\text{radical} + S_2O_8^{2-} \xrightarrow{k_{18}} \text{product} + SO_4^{2-} + SO_4^{\cdot-} \quad (18)$$

$$SO_4^{\cdot-} + Ag^I \xrightarrow{k_{19}} Ag^{II} + SO_4^{2-} \quad (19)$$

$$Ag^{III} + Ag^I \longrightarrow 2Ag^{II} \quad (20)$$

Addition of allyl acetate to the reaction mixture indicates that the chain sequence in path II is operative to a significant extent in the pinacol and hydroxy ketone reactions (Table IV). The smaller effect of allyl acetate on the rate of cleavage of pyruvic acid is consistent with the suggestion made previously that path I may be operative to a greater extent than the free-radical path II for pyruvic acid because of its rapid reaction with Ag^{III}. It is interesting to note that the reaction rates of the inhibited reactions are essentially the same, an observation that supports the suggestion that the substrate is not involved in the rate-determining processes of path I.

TABLE IV

EFFECTS OF ALLYL ACETATE ON OXIDATIVE-CLEAVAGE RATES[a]

Substrate (M)	$[S_2O_8^{2-}] \times 10^2$	$[Ag^I] \times 10^3$	[Allyl acetate]	Rate[b]
Pinacol (0.075)	1	2.56	0	2.77
Pinacol (0.075)	1	2.56	2.5×10^{-2}	0.24
Pinacol (0.075)	1	2.56	1×10^{-1}	0.12
2-Methyl-2-hydroxy-3-butanone (0.075)	1	2.56	0	0.54
2-Methyl-2-hydroxy-3-butanone (0.075)	1	2.56	2.5×10^{-2}	0.13
2-Methyl-2-hydroxy-3-butanone (0.075)	1	2.56	1×10^{-1}	0.08
Pyruvic acid (0.075)	1	2.56	0	0.20
Pyruvic acid (0.075)	1	2.56	2.5×10^{-2}	0.12
Pyruvic acid (0.075)	1	2.56	1×10^{-1}	0.09

[a] All rates estimated from first 10% reaction of $S_2O_8^{2-}$ and are expressed in mol $l.^{-1}$ $min^{-1} \times 10^4$. [b] Solutions buffered at pH 1.4 by 0.25 M Na_2SO_4 and 0.25 M $NaHSO_4$.

The rate laws for oxidative cleavage by path II depend on the chain sequence 17–19, the initiation process 20, and the mode of termination of the chain reaction that may be operative. The termination reactions are bimolecular interactions of chain carrying free radicals and the particular chain-carrying radicals involved in termination depend to a significant extent on the relative steady-state concentrations of these species. These concentrations are dictated both by the reaction rate constants of the chain propagating reactions and

the relative concentrations of the reactants that participate in the chain sequence.[12]

It is apparent from the data in Table IV that an appreciable amount of the oxidative cleavage of pinacol and the hydroxy ketone 2 is likely occurring by path II in the reactant concentration range (high substrate and Ag^I concentration) where path I might be expected to occur. The observed oxidative cleavage rate law in this concentration range for pinacol and 2 is not only consistent for path I as indicated previously but would also be the rate law for path II under certain conditions. These conditions are met if the chain sequence is terminated by the interaction of a substrate derived radical with a sulfate ion radical. The derived rate law for

$$\text{radical} + SO_4\cdot^- \xrightarrow{k_{21}} \text{product} + SO_4^{2-} \qquad (21)$$

path II if reaction 21 is the termination reaction is given by

$$\text{rate} = \left(\frac{R_i}{k_{21}} k_{18}k_{19}[Ag^I][S_2O_8^{2-}]\right)^{1/2} \qquad (22)$$

R_i is the rate of initiation of the chain sequence. The rate of formation of Ag^{II} by reaction 20 is actually the rate of formation of Ag^{III} in reaction 14 and is given by rate eq 16. Substitution of 16 in 22 gives 23, a rate equation for path II which shows the oxidative cleavage rate is first order in $[Ag^I]$, zero order in the substrate, and some higher orders in $S_2O_8^{2-}$.

$$\text{rate} = \left(\frac{k_{13}k_{14}k_{18}k_{19}}{k_{21}(k_{14}[S_2O_8^{2-}] + k_{-13})}\right)[Ag^I][S_2O_8^{2-}]^{(x+2)1/2} \qquad (23)$$

Decreasing the concentration of the substrate has two effects on the course of the oxidative cleavage reaction. As pointed out earlier, partitioning of the available Ag^{III} favors reaction with Ag^I thereby increasing the amount of reaction occurring by path II relative to path I. Further, the termination of the free-radical chain sequence may take a different course at low substrate concentrations since the steady-state concentration of Ag^{II} would necessarily be greater than that encountered in higher substrate concentrations. This being the case, the sequence would be terminated by reaction 24 and the derived steady-state rate law

$$Ag^{II} + \text{radical} \xrightarrow{k_{24}} Ag^I + \text{product} \qquad (24)$$

for the reaction under such conditions is eq 25. The

$$\text{rate} = \left(\frac{k_{13}k_{14}k_{17}k_{18}[Ag^I][\text{substrate}][S_2O_8^{2-}]^{(x+2)}}{k_{24}(k_{14}[S_2O_8^{-2}] + k_{-13})}\right)^{1/2} \qquad (25)$$

derived rate law indicates the reaction rate is half order in both the substrate and Ag^I and is consistent with the observed rate law at low substrate concentrations.

At low $[Ag^I]$, the steady-state concentration of $SO_4\cdot^-$ is relatively greater than at higher concentrations of Ag^I. Termination of the chain sequence by reaction 26[13]

$$2SO_4\cdot^- \longrightarrow \text{termination product} \qquad (26)$$

is therefore more probable at low $[Ag^I]$. The derived steady-state rate law for path II when the chain sequence 17–19 is terminated by 26 is given in 27. The

$$\text{rate} = \left(\frac{k_{13}k_{14}[Ag^I][S_2O_8^{2-}]^{(x+1)}}{2k_{26}(k_{14}[S_2O_8^{2-}] + k_{-13})}\right) k_{19}[Ag^I] \qquad (27)$$

higher kinetic order of Ag^I observed at low $[Ag^I]$ is consistent with termination reaction 26 occurring at low $[Ag^I]$.

Termination of the chain sequence in a bimolecular interaction of two substrate derived radicals becomes significant if the steady-state concentration of these radicals is appreciably increased. Consequently, at low $[S_2O_8^{2-}]$, reaction 28 would be the expected path

$$2 \text{ radicals} \xrightarrow{k_{25}} \text{termination product} \qquad (28)$$

for termination of the chain sequence. The derived steady-state rate law for path II when termination does occur only by 28 is given in 29. This rate law

$$\text{rate} = \left(\frac{k_{13}k_{14}[Ag^I][S_2O_8^{2-}]^{(x+1)}}{2k_{28}(k_{14}[S_2O_8^{2-}] + k_{-13})}\right)^{1/2} k_{18}[S_2O_8^{2-}] \qquad (29)$$

predicts, as is observed at low $[S_2O_8^{2-}]$, that the reaction rate would be zero order in the substrate, half order in $[Ag^I]$, some some higher kinetic order in $S_2O_8^{2-}$.

It is of some significance that the observed rate laws for the oxidative cleavage reactions approach those predicted on the basis of the expected termination process when the concentration of a single reagent is appreciably decreased. At intermediate concentrations of the reagents, more than one termination reaction may be operative.

Experimental Section

Materials.—Pinacol was prepared by the procedure described by Vogel.[14] 2-Hydroxy-2-methyl-3-butanone and pyruvic acid were obtained from Aldrich and redistilled before using. Potassium peroxydisulfate (Fisher Certified Reagent) silver nitrate (Merck), sodium sulfate (Mallinkrodt Analytical Reagent), and sodium bisulfate (Baker and Adamson Reagent) were used without further purification. Allyl acetate (bp 100–102°, $n^{26}D$ 1.4011) was prepared by a Fisher ester synthesis from allyl alcohol and acetic acid.

Kinetic Measurements.—The reactions were performed in distilled water buffered to a pH of 1.4 by 0.25 *M* sodium sulfate and 0.25 *M* sodium bisulfate. The organic substrate and potassium peroxydisulfate were dissolved in the buffered solution and placed in a painted three-neck 500-ml flask. The flask was placed in a water bath maintained at 30 ± 0.1° and nitrogen was bubbled through the solution for 1 hr to remove any dissolved oxygen. An appropriate amount of 0.4 *M* silver nitrate was added and immediate reaction ensued. Aliquotes of the reaction mixture were removed at appropriate time intervals and the unreacted peroxydisulfate determined by the iodometric method described by Bartlett and Cotman.[15]

Product Distribution in Oxidative Cleavage Reactions.—A mixture consisting of 2-hydroxy-2-methyl-3-butanone (3.83 g, 0.0375 mol), potassium persulfate (6.76 g, 0.025 mol), and silver nitrate (0.106 g, 0.000625 mol) in 250 ml of water was allowed to react under a nitrogen atmosphere for 2 days. Gas chromatographic analysis of the reaction mixture on a 6 ft by $^1/_8$ in. column packed with Poropak Q (80–100 mesh) indicated the presence of 0.021 mol of acetone, 0.024 mol of acetic acid, and 0.015 mol of the unreacted hydroxy ketone. Extraction of the reaction mixture with ether afforded samples of acetic acid [mp

(12) For discussion see E. S. Huyser, "Free-Radical Chain Reactions," Wiley, New York, N. Y., 1970, Chapter 4.

(13) The nature of the product(s) in reaction 26 can only be speculated about but may be the result of interactions of $SO_4\cdot^-$ with H_2O producing hydroxy radicals which couple yielding H_2O_2. Provided the radical products of the $SO_4\cdot^-$ interactions, other than the chain propagating reaction 19, do not become involved in the chain reaction, the kinetic consequence is a bimolecular reaction of $SO_4\cdot^-$ radicals.

(14) A. J. Vogel, "Practical Organic Chemistry," 3rd ed, Longmans, London, 1956, p 349.

(15) P. D. Bartlett and J. D. Cotman, *J. Amer. Chem. Soc.*, **71**, 1419 (1949).

(p-bromophenacyl ester) 82° (lit.[16a] 85°)] and acetone [mp (2,4-dinitrophenylhydrazone) 124–125° (lit.[16b] 126°)].

In a reaction of 3.3 g (0.028 mol) of pinacol with 4.87 g (0.018 mol) of potassium peroxydisulfate and 0.042 g (0.00025 mol) of silver nitrate, 2.18 g (0.018 mol) of pinacol was recovered unreacted and 1.05 g (0.018 mol, 90% of theory) of acetone was formed as determined by gas chromatographic analysis of the reaction mixture.

(16) R. L. Shriner, R. C. Fuson, and D. Y. Curtin, "The Systematic Identification of Organic Compounds," 5th ed, Wiley, New York, N. Y., 1956: (a) p 311; (b) p 362.

Reaction of 0.88 g (0.010 mol) of pyruvic acid with 4.32 g (0.016 mol) of potassium peroxydisulfate and 0.042 g (0.00025 mol) of silver nitrate yielded 0.59 g (0.0098 mol, 98% of theory) of acetic acid as determined by gas chromatographic analysis of the reaction mixture. Carbon dioxide was evolved during the course of this reaction but not measured quantitatively.

Registry No.—**1**, 76-09-5; **2**, 115-22-0; **3**, 127-17-3; peroxydisulfate ion, 15092-81-6; allyl acetate, 594-87-7; $Ag^{(I)}$, 14701-21-4.

The Reductive Dimerization of Schiff Bases by Alkali Metals. Isomerization of the Dimeric Dianions

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Received August 9, 1971

The alkali metal induced reductive dimerization of substituted *N*-benzalanilines (ArCH=NPh) in ether solvents is examined. Particular attention is directed toward the isomerization of the diastereomeric mixture of dimeric dianions which are the primary products of the reaction. By means of cross-product experiments, it is shown that the isomerization results from an equilibrium between the dimeric dianions and the monomeric radical anion of the original *N*-benzalaniline. The observed effects of solvent and substituent groups correlate well with this conclusion.

The synthetic value of the reductive dimerization of carbonyl compounds or their derivatives is reflected in the variety of reagents which have been developed to effect this reaction.[1-10] A characteristic feature of the reaction is the formation of diastereomeric mixtures and this feature has stimulated efforts to elucidate the factors controlling the diastereomeric ratio.[11] Among the many examples of reductive dimerization, the reaction of *N*-benzalaniline with alkali or alkaline earth metals in anhydrous solvents has the intriguing feature that essentially only one diastereomer is formed, *dl*-*N*,*N*′,1,2-tetraphenylethylenediamine, under selected reaction conditions.[12,13] As has been shown,[12] the preponderance of the *dl* isomer arises from an isomerization of the diastereomeric dimeric dianions initially formed in the reductive dimerization, an isomerization which predominates in the *dl* dianion.

It was the intention of the present investigation to distinguish between the two mechanisms previously suggested[12] for the isomerization (see Scheme I). The first mechanism (path a, dissociative mechanism) depends on an equilibrium between the radical anion **2** and the dimeric dianions **3** to allow the kinetic product to isomerize to the thermodynamic one. The second mechanism (path b, carbanionic mechanism) relies on the abstraction of a benzylic proton by the basic amine anion **3**, forming a carbanion **4** which can then epimerize.

Should a mixture of two *structurally* different dimeric dianions **3** be present in solution, then the anionic mechanism would predict that the equilibrium mixture should consist essentially of the two *dl*-dimeric dianions. On the other hand, the dissociative mechanism would predict the formation of these and a cross dimer formed by the coupling of the two different radical anions present.

Such an experiment required two different diamines **5** whose anions were known to isomerize during formation and whose nmr spectra were sufficiently different that the reaction mixture could be analyzed. To optimize the formation of cross products, the *meso* isomer was preferred. In addition, a process was needed to convert the diamine to its corresponding dianion in order to induce isomerization.

With this purpose in mind, a number of substituted benzalanilines **1** were subjected to reductive dimerization with sodium in tetrahydrofuran (THF) or diethyl ether (DEE). The data pertaining to isomerization is summarized in Table I. Authentic samples of the dimeric diamines were isolated either from these reaction mixtures or from similar mixtures generated with aluminum amalgam. Table II summarizes the physical properties of the diamines and Table III the product composition from the aluminum amalgam reductions which, unlike the alkali metal reductions, contain large amounts of monomeric reduction products.

The stereochemistry of the dimeric diamines **5** is assigned on the assumption that the resonances of the benzylic protons in the *meso* isomer appear downfield from those of the *dl* isomer.[14,15] Such an assumption

(1) H. O. House, "Modern Synthetic Reactions," W. A. Benjamin, New York, N. Y., 1965, pp 50–77.

(2) R. Adams and E. W. Adams, "Organic Syntheses," Collect. Vol. II, Wiley, New York, N. Y., 1941, p 459, and references cited therein.

(3) M. S. Newman, *J. Org. Chem.*, **26**, 582 (1961).

(4) W. E. Bachman, *J. Amer. Chem. Soc.*, **53**, 2672 (1931).

(5) H. Thies, H. Schoenenberger, and K. H. Bauer, *Arch. Pharm. (Weinheim)*, **291**, 620 (1958).

(6) O. Anselmino, *Ber.*, **41**, 623 (1908).

(7) W. Stuhmer and G. Messwarb, *Arch. Pharm. (Weinheim)*, **286**, 221 (1953).

(8) W. Schlenk, J. Apprenrodt, A. Michael, and A. Thal, *Ber.*, **47**, 473 (1914).

(9) W. Schlenk and E. Bergmann, *Justus Liebigs Ann. Chem.*, **463**, 281 (1928).

(10) C. K. Mann and K. K. Barnes, "Electrochemical Reactions in Nonaqueous Systems," Marcel Dekker, New York, N. Y., 1970.

(11) J. H. Stocker, R. M. Jenevein, and D. H. Kern, *J. Org. Chem.*, **34**, 2810 (1969).

(12) J. G. Smith and C. D. Veach, *Can. J. Chem.*, **44**, 2497 (1966).

(13) J. J. Eisch, D. D. Kaska, and C.J. Peterson, *J. Org. Chem.*, **31**, 453 (1966).

(14) J. Wiemann, G. Dana, S. Thuan, and M. Brami, *C. R. Acad. Sci., Ser. C*, **258**, 3724 (1964).

(15) P. Beak and C. R. Payet, *J. Org. Chem.*, **35**, 3281 (1970).

SCHEME I

POSSIBLE MECHANISMS FOR THE ISOMERIZATION

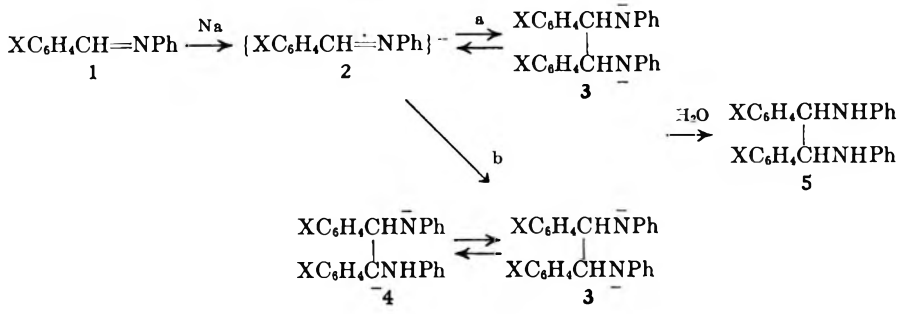
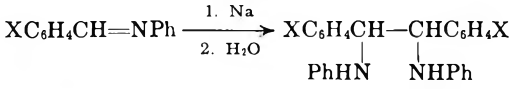


TABLE I

PRODUCT COMPOSITION FROM THE REACTION



X	% *dl*-5[a] in THF Initial[b]	Final[c]	$t_{1/2}$,[d] hr	% *dl*-5[a] in DEE Initial[b]	Final[c]	$t_{1/2}$,[d] hr
H	67	93	4.5	64	68	
o-Me	70	92	>1	43	85	13
m-Me	69	100	2.5	66	66	
p-Me	73	81	35[e]	59	59	
o-MeO	78	100	2		78	*f*
m-MeO	60	90	3	50	60	>50[e]
p-MeO	65	69		52	56	
m-Cl	100	100	>1	55	72	25

[a] Per cent of dimeric diamine; no significant amounts of the *N*-benzylaniline were detected. [b] At 0.5-hr reaction time. [c] At 24-hr reaction time. At longer reaction times, the *N*-benzylaniline began to appear. [d] Time for the product composition to reach a value halfway between the initial and equilibrium compositions. [e] Estimated assuming 90% *dl* at equilibrium. [f] Only 12% reacted in 24 hr.

is consistent with the stereochemistry of the one dimer of known stereochemistry,[7] is consistent with the melting points of the compounds, and is consistent with the observed isomerizations in which the isomer with the downfield proton isomerizes to the one with the upfield (*meso* → *dl*).

Conversion of the diamines to their corresponding dianions was successfully accomplished by treating them with the required amount of the disodium stilbene complex. This method[16] was selected in preference to phenylsodium or sodium hydride[17] since it utilized homogeneous solutions, and the reaction conditions were identical with the dimerization process itself. Control experiments with *N*,*N*′,1,2-tetraphenylethylenediamine (**5**, X = H) showed that the equilibrium composition was achieved on reacting either the *meso* or the *dl* isomer under these conditions.

For the cross-product experiment, the two dimeric diamines selected were **5** (X = H) and **5** (X = *o*-CH_3) since isomerization was observed in both cases and the chemical shifts of the benzylic protons of the *meso* and *dl* isomers of either compound were different. Anticipating the formation of a cross product, the expected reaction mixture was generated by reductively dimerizing a mixture of the two Schiff bases **1**, X = H and X = *o*-Me. The cross product, 1-(*o*-methylphenyl)-*N*,*N*′,2-triphenylethylenediamine (**6**), was easily observed in the nmr spectrum, the methyl resonance being clearly separated from the others and the benzylic protons appearing as an AB quartet. The isolation of this product was accomplished as well.

A mixture of *meso*-**5** (X = H) and *meso*-**5** (X = *o*-Me) when treated with an equivalent amount of disodium–stilbene complex produced the same reaction mixture as generated from the mixture of two Schiff bases. The mixed dimer **6** similarly treated formed the same reaction mixture. And, finally, in the simplest experiment of all, two *separate* reductive dimerizations using **1** (X = H) and **1** (X = *o*-Me) were carried to completion and the dimeric dianions so formed were mixed. Again, the isolated diamine mixture contained the cross product.

These three experiments establish that a dissociative mechanism is responsible for the isomerization observed in the reductive dimerization of Schiff bases by sodium metal. Since the dimeric dianions are themselves formed by the coupling of radical anions, the principal of microscopic reversibility[18] would dictate that dissociation of the dimeric dianions to radical anions (*i.e.*, path a, Scheme I) is occurring.[19] Szwarc[20a-c] has examined a related equilibrium involving the radical anion and dimeric dianion of 1,1-diphenylethylene. Two dissociation mechanisms were postulated. In the terminology used by Szwarc these equilibria are

$$^{-}DD^{-} \rightleftharpoons 2D^{-}$$

$$^{-}DD^{-} + D \rightleftharpoons D^{-} + {}^{-}DD\cdot \rightleftharpoons D + 2D^{-}$$

where D is the monomer, D^{-} the radical anion, and $^{-}DD^{-}$ the dimeric dianion.

Either of these equilibria (or both) would explain the observations recorded here. In addition, these equilibria coupled with the rapid electron transfer between radical anion and unsaturated monomer[20d,e] would predict that a Schiff base such as **1** (X = H) added to an equilibrating dianion such as **3** (X = *o*-Me) will result in the formation of mixed dimer **6**.

(16) The obvious choice of butyllithium was eliminated by the fact that the lithium salts of tetraphenylethylenediamine shows no isomerization (see ref 12).

(17) In control experiments with NaH, considerable amounts of *N*-benzylaniline were formed from tetraphenylethylenediamine (see also ref 12).

(18) C. K. Ingold, "Structure and Mechanism in Organic Chemistry," 2nd ed, Cornell University Press, Ithaca, N. Y., 1969, p 250.

(19) Attempts to observe an esr signal from these equilibrating systems were unsuccessful. We wish to thank Dr. T. Gough of this department for his assistance in these experiments. A similar failure has been reported by L. I. Petersen, *J. Amer. Chem. Soc.*, **89**, 2677 (1967).

(20) (a) S. Spach, H. Monteiro, M. Levy, and M. Szwarc, *Trans. Faraday Soc.*, **58**, 1809 (1962); (b) M. Szwarc and R. Asami, *J. Amer. Chem. Soc.*, **84**, 2269 (1962); (c) M. Matsuda, J. Jagur-Grodzinski, and M. Szwarc, *Proc. Roy. Soc., Ser. A*, **288**, 212 (1965); (d) J. Jagur-Grodzinski and M. Szwarc, *ibid.*, **288**, 224 (1965); (e) E. R. Zabolotny and J. F. Garst, *J. Amer. Chem. Soc.*, **86**, 1645 (1964).

TABLE II

PROPERTIES OF DIMERIC DIAMINES 5

X		Registry no.	Mp, °C	δ, ppm Benzylic	δ, ppm X	Found, % C	H	N	Cl
o-Me	*meso*	32979-86-5	139–141	5.16	1.97	85.57	7.30	7.23[a]	
	dl	32979-87-6	132–133	4.80	1.88	85.74	7.17	7.12	
m-Me	*meso*	32979-88-7	90–93	4.88	2.20	85.67	7.23	7.27	
	dl	32979-89-8	140–141	4.50	2.27	85.68	7.10	7.06	
p-Me	*meso*	27549-75-3	138.5–141	4.90	2.28	86.23	7.00	7.06	
	dl[b]	27549-69-5	131–131.5	4.55	2.27				
o-MeO	*dl*[c]	33021-00-0	168–170	5.03	3.63	79.49	6.69	6.66[d]	
m-MeO	*meso*	32979-92-3	122–123	4.95	3.62	79.10	6.52	6.60	
	dl	32979-93-4	110–112	4.53	3.63	79.34	6.66	6.69	
p-MeO	*meso*	32979-94-5	186–188	4.87	3.73	79.38	6.86	6.51	
	dl	32979-95-6	143–144	4.52	3.73	79.37	6.86	6.49	
o-Cl	*meso*	32979-96-7	172–174	5.53		72.35	5.07	6.40	16.33[e]
	dl	32979-97-8	140–142	5.24		72.12	5.24	6.42	16.39
m-Cl	*meso*	32979-98-9	136–139	4.91		71.83	5.11	6.36	16.53
	dl	32979-99-0	128–129	4.47		72.25	5.05	6.44	16.45
p-Cl	*meso*[f]	32980-00-0	198–199	4.94					
	dl[g]	32980-01-1	137	4.25					

[a] Theory: C, 85.88; H, 7.19; N, 7.14. [b] Reported mp 130°: H. Thies, H. Schonenberger, and K. H. Bauer, *Arch. Pharm.* (*Weinheim*), **291**, 620 (1958). [c] The *meso* isomer not isolated. [d] Theory: C, 79.21; H, 6.65; N, 6.60. [e] Theory: C, 72.06; H, 5.12; N, 6.47; Cl, 16.36. [f] Reported mp 194–195 (H. Thies, *et al.*, footnote *b*) and 195–196°: J. Huet, *Bull. Soc. Chim. Fr.*, 973 (1964). [g] Reported mp 136° (J. Huet, footnote *f*).

TABLE III

PRODUCT COMPOSITION FROM THE ALUMINUM AMALGAM REDUCTION OF SCHIFF BASES

$XC_6H_4CH{=}NPh$, X	Product composition, %[a] *meso*-5	*dl*-5	Monomer (δ)[b]
o-Me	33	38	29 (4.19)
m-Me	34	44	22 (4.12)
o-MeO	0	55	45 (4.31)
m-MeO	28	35	37 (4.21)
o-Cl	33	67	0 (4.30)
m-Cl	38	38	24 (4.25)
p-Cl	15	45	40 (4.04)

[a] Analyzed by nmr. [b] $XC_6H_4CH_2NHPh$ (chemical shift of benzylic proton).

This has been observed both with the dimeric dianion generated by reductive dimerization and by treatment of the diamine with disodium–stilbene.

Since any of these dissociations involves the radical ion (*e.g.*, path a, Scheme I), those factors which stabilize the radical anion would be expected to promote isomerization. Thus isomerization is more prevalent in THF, with its greater solvating power, than in DEE. In a relevant experiment, the addition of 10% hexamethylphosphoramide to THF effected isomerization in the reductive dimerization of 1 (X = *p*-MeO).

Substituents also modify the stability of the radical anion. Electron-donating substituents would be expected to destabilize the radical anion and indeed isomerization is inhibited by *p*-OCH_3 or *p*-CH_3. Electron-withdrawing groups, assisting the delocalization of electrons, should facilitate isomerization and a *m*-Cl substituent[21] does so. However, ortho substituents promote isomerization. Presumably this is due to the increased steric bulk[22] of the *o*-tolyl groups which assists the dissociation of the dimeric dianion to the radical anion.

(21) The *o*- and *p*-chloro analogs behave in a markedly different manner under these reaction conditions This behavior will be described in a later communication.

(22) W. Theilacker and M.-L. Wessel-Ewald, *Justus Liebigs Ann. Chem.*, **594**, 214 (1955).

Experimental Section[23]

Starting Materials.—The *N*-benzalanilines 1 were prepared from the freshly distilled substituted benzaldehyde and aniline according to a published procedure.[24] The properties of the Schiff bases produced agreed with the reported values. The solvents used for the reduction, after purification by distillation from lithium aluminum hydride, were stored over this reagent and distilled into the reaction vessel when needed. The reaction mixtures were analyzed by the procedure previously described.[12,13]

General Procedure for the Reductive Dimerization.—A modified Schlenk tube[25] was flushed with nitrogen, the Schiff base added (0.01 mol), and the solvent distilled in (75 ± 5 g). The tube was sealed and transferred to a drybox and the sodium metal (0.02 g-atom) was cut and added. After resealing and removing from the drybox, the mixture was shaken on a horizontal shaker. Reaction began almost at once as evidenced by streams of color flowing from the surface of the metal.

Aliquot samples of the solution were removed at 0.5, 1, 2, 4, 8, and 24 hr and quenched in water and the liberated sodium hydroxide was titrated with standard acid. With one exception, (1, X = *o*-MeO in DEE) all Schiff bases were completely converted to dimer (1 g-atom of Na per mole of Schiff base) in 2–4 hr. The titrated samples were then extracted with ether and the organic material was isolated and analyzed for its dimeric composition. These data are summarized in Table I.

Isolation of 1,2-Diaryl-*N*,*N*′-diphenylethylenediamines.—The *dl* isomers were isolated by recrystallization of those mixtures which isomerized. In one instance (5, X = *p*-MeO) isomerization was promoted by using tetrahydrofuran containing 10% hexamethylphosphoramide, the final composition being *dl*, 86.4%, and *meso*, 13.6%.

The *meso* isomers were obtained by crystallizing the DMF complex from solution.[26] This procedure operated most efficiently when the *meso*/*dl* ratio was no smaller than 0.5. Consequently, the alkali metal promoted reductions were often unsatisfactorily as sources of the *meso* isomers. With aluminum amalgam as a reducing agent, the products were protonated as rapidly as they formed and isomerization was avoided. This

(23) Melting points are uncorrected and were determined with a Mel-Temp apparatus in open capillaries. The nmr spectra were recorded on a Varian T-60 nmr spectrometer. The nitrogen used was Matheson purified grade further purified by passing through a benzophenone ketyl solution in refluxing xylene. Analyses are by M-H-W Laboratories, Garden City, Mich.

(24) L. A. Bigelow and H. Eatough, "Organic Syntheses," Collect. Vol. I, 2nd ed, Wiley, New York, N. Y., 1941, p 80.

(25) J. W. B. Reesor, J. G. Smith, and G. F. Wright, *J. Org. Chem.*, **19**, 940 (1954).

(26) (a) R. Jaunin, *Helv. Chim. Acta*, **39**, 111 (1956); (b) R. Jaunin and P. Courbat, *ibid.*, **43**, 2029 (1960).

proved to be a convenient source of material from which the *meso* isomers could be isolated. The physical properties of the isolated dimers are summarized in Table II and the composition of the reduction products formed in the aluminum amalgam reductions are shown in Table III.

Preparation of the Cross Dimer, 1-(*o*-Methylphenyl)-*N*,*N*'-,2-triphenylethylenediamine (6).—A solution containing 1.81 g (0.01 mol) of 1 (X = H) and 1.95 g (0.01 mol) of 1 (X = *o*-Me) in 200 ml of THF was treated with 0.92 g (0.04 g-atom) of sodium and shaken for 24 hr. The orange solution was drained from the excess sodium, treated with methanol, diluted with water, and extracted with ether. After removal of the solvent, the residue was analyzed by nmr by using the methyl resonances to determine the relative amounts of cross dimer 6, *dl* "homo dimer" 5 (X = o-Me), and the small amount of monomeric reduction product *N*-(*o*-methylphenyl)aniline. The contribution made by 5 (X = *o*-Me) and 6 to the area of the benzylic resonances was then calculated and subtracted from the total area to give the amount of *dl*-5 (X = H) (see Table IV).

TABLE IV
FORMATION OF THE CROSS DIMER

	Product anal, %				
		Homo dimers			
Reaction conditions[a]	Cross dimer 6	*dl*-5 (X = *o*-Me)	*dl*-5 (X = H)	*meso*-5 (X = H)	Monomer[b]
Mixed Schiff bases, 1 (X = H and *o*-Me)	51	19	27	<1	3
Mixed dimeric dianions, 3 (X = H and *o*-Me)	51	19	25	<1	5
Mixed diamines, *meso*-5 (X = H) and *meso*-5 (X = *o*-Me) + DSS[c]	54	18	22	<1	6
Cross dimer 6 + DSS[c]	47	17	34	2	<1
Dianion 3 (X = *o*-Me) treated with 2 equiv of 1 (X = H)	22	15	19	<1	5[d]
meso-5 (X = H) + DSS,[c] then treated with 1 equiv of 1 (X = *o*-Me)	27	10	40	<1	*e*

[a] 24-hr reaction time. [b] *N*-(*o*-Methylphenyl)aniline. [c] Disodium–stilbene. [d] Product contained 21% of 1 (X = H) and 19% of 1 (X = *o*-Me). [e] Product contained 13% of 1 (X = H) and 10% of 1 (X = *o*-Me).

Isolation of the cross dimer 6 was effected by recrystallization from methanol to remove the more soluble *dl*-5 (X = *o*-Me). The solid so obtained was recrystallized from DMF when the DMF complex of *dl*-5 (X = H) separated. The filtrate from this was acidified with 6 *N* HCl and the white precipitate was filtered, washed with water, dried, and recrystallized from absolute ethanol to give 6: mp 125–128°; nmr ($CDCl_3$, D_2O washed) δ 6.4–7.3 (m, 19 aromatic H), 4.81 (d, 1 H, CHCH, *J* = 8.0 cps), 4.54 (d, 1 H, CHCH, *J* = 8.0 cps), 2.03 (s, 3 H, CH_3).

Anal. Calcd for $C_{27}H_{26}N_2$: C, 85.67; H, 6.93; N, 7.40. Found: C, 85.68; H, 7.05; N, 7.32.

In an alternative procedure, each Schiff base in THF was treated with sodium in separate Schlenk tubes. After a 24-hr reaction time, the solutions were drained from the excess metal into the same nitrogen-filled flask and stirred for a further 24 hr. The isolated product was analyzed as described with the result shown in Table IV.

A similar cross product was prepared from 1 (X = H) and 1 (X = *m*-Me) and isolated by recrystallization from methanol: mp 120–121.5°; nmr ($CDCl_3$, D_2O washed) δ 6.4–7.4 (m, 19 aromatic H), 4.53 (broad s, 2 benzylic H), 2.33 (s, 3 H, CH_3).

Anal. Calcd for $C_{27}H_{26}N_2$: C, 85.67; H, 6.93; N, 7.40. Found: C, 85.89; H, 6.90; N, 7.58.

Isomerization with the Disodium–Stilbene Complex.—A solution of 0.005 mol of the selected diamine in 25 ml of THF was treated at room temperature under N_2 with a solution (THF) of 0.005 mol of the disodium–stilbene complex.[25] The color changed from the deep red of the stilbene complex to orange within 10–15 min. The solution was stirred 24 hr and quenched by the addition of methanol, and the product was isolated by diluting with water and extracting with ether.

Both *meso*- and *dl*-*N*,*N*',1,2-tetraphenylethylenediamine (5, X = H) so treated produced the equilibrium composition of 93% *dl* and 7% *meso*.

A mixture of 0.91[illegible] g (0.0025 mol) of *meso*-5 (X = H) and 0.981 g (0.0025 mol) of *meso*-5 (X = *o*-Me) was isomerized under these conditions (see Table IV). Similarly treated was a solution of 1.41 g (0.004 mol) of the cross dimer, 1-(*o*-methylphenyl)-*N*,*N*'-2-triphenylethylenediamine, in 25 ml of THF. Product composition is shown in Table IV.

Registry No.—6, 33021-01-1.

Acknowledgment.—The authors wish to acknowledge helpful discussions with Dr. D. Mackay of this department. This research was financially supported by the National Research Council of Canada.

Reactivity Differences in Competitive Metal Hydride Reductions of α,β-Unsaturated and Saturated Ketones

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Received July 30, 1971

Competitive reduction experiments involving mixtures of saturated and α,β-unsaturated six-membered ring ketones and lithium aluminum hydride or lithium tri-*tert*-butoxyaluminohydride have shown a large reactivity difference between the two types of ketones. Both hindered and unhindered ketone systems were employed as substrates. The unsaturated ketones were consistently less reactive than the saturated ketones. This reactivity difference is enhanced with the more selective tri-*tert*-butoxyaluminohydride reagent.

Competition experiments in which α,β-unsaturated and saturated six-membered ring ketones are made to compete for limited amounts of lithium aluminum hydride ($LiAlH_4$) or lithium tri-*tert*-butoxyaluminohydride (LTAH) reveal remarkable reactivity differences between the two types of ketones. The experiments described involve the inverse addition of standardized[1] solutions of $LiAlH_4$ in ether, or weighed amounts of LTAH in tetrahydrofuran (or ether), to stirred mixtures of two ketones. These experiments were the outgrowth of observations of the low reactivity of several cyclic enones toward $LiAlH_4$ reductions. The reactions carried out, together with the major products obtained, are listed in eq 1–3.

Analyses of the products were carried out by gas chromatography directly on the concentrated reaction products and also after catalytic hydrogenation with palladium on charcoal (except for the isophorone–dihydroisophorone competitive reduction, eq 1). Catalytic

(1) H. Felkin, *Bull. Soc. Chim. Fr.*, 347 (1950).

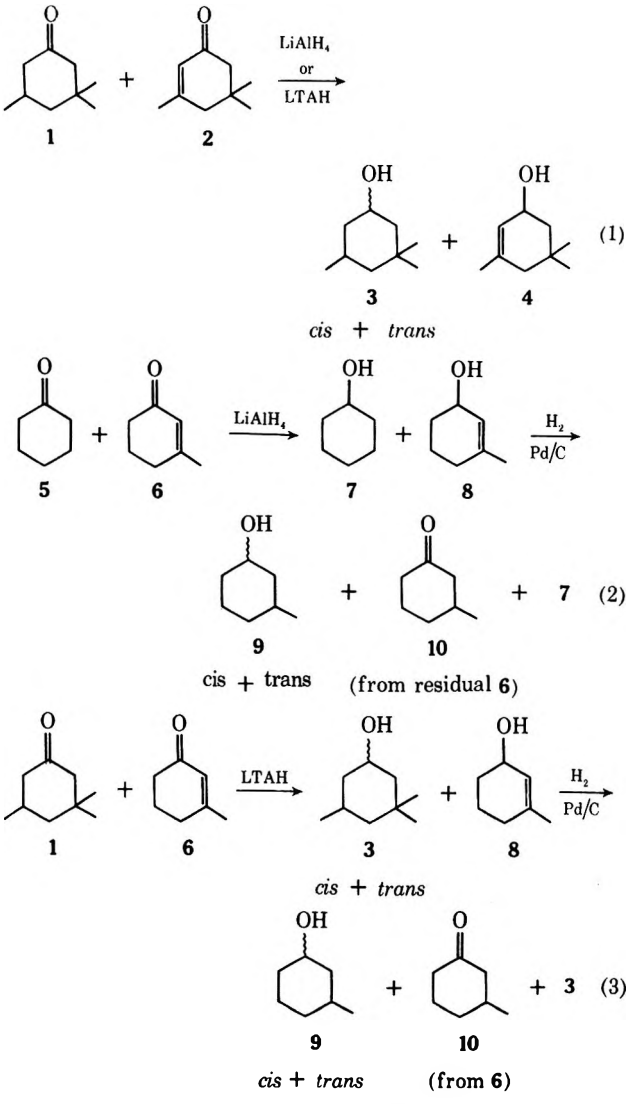
TABLE I

DIHYDROISOPHORONE (1)–ISOPHORONE (2) REDUCTIONS

Ketone mixture	Metal hydride	Product analysis,[a] % 1	3	2	4
1, 2 (0.030 mol each)[d]	$LiAlH_4$ (0.015 equiv)[e]	69.9[b]	30.1[b]	88	12
1, 2 (0.030 mol each)[d]	LTAH (~0.015 mol)[f]	61.9[g]	38.1[g]		0
		39.4[h]		60.6[h]	
1, 2 (0.030 mol each)[d]	LTAH (0.015 mol)[i]	59.5[j]	40.5[j]		0
		38.2[h]		61.8[h]	

[a] Analysis by glc on a 10 ft, 10% Carbowax 20M column at 150°, silanized, acid-washed. [b] 1 and 3 normalized to 100%. 3 was 57% *trans*, 43% *cis*. [c] 2 and 4 normalized to 100%. [d] In 100 ml of ether. [e] 0.73 *M* in ether added inversely. [f] In ether. [g] 1 and 3 normalized to 100%. 3 was 77% *trans*, 23% *cis*. [h] 1 and 2 normalized to 100%. [i] In 75 ml of tetrahydrofuran. [j] 1 and 3 normalized to 100%. 3 was 89% *trans*, 11% *cis*.

hydrogenation was necessary since the unsaturated alcohol **8** decomposed to a large extent during gas chromatographic analysis. Hydrogenation converted **8** to **9** which could be readily analyzed (see the Experimental Section).



Results and Discussion

The results of the competition between dihydroisophorone (**1**) and isophorone (**2**) are listed in Table I. Hydrogenation of the product was of course unfeasible in this case, and although some decomposition of the unsaturated alcohol **4** did occur during glpc analysis, satisfactory results were obtained by using selectivity factors derived from standard mixtures (*e.g.*, **2** and **4**) under carefully controlled analytical conditions.

Reductions of **1** to the epimeric *cis*- and *trans*-**3** occurred to the extent of 30% with $LiAlH_4$, while only 12% reduction of **2** occurred (first entry in Table I). The *unreacted* ketone composition for this experiment was found to be 46% **1** and 54% **2**, in very good agreement with that calculated (44% and 56%, respectively) on the basis of the relative extents of reduction for **1** and **2**. On the basis of the extent of total reduction, 86% of hydride was used. The second and third entries in Table I show that LTAH is much more selective than $LiAlH_4$, since reduction of **1** occurred, but no reduction of **2** was observed, In the second entry, the unreacted ketone composition was 39% **1** and 61% **2** (calculated values 38% **1** and 62% **2**), while for the third entry the observed ketone composition was 38% **1**, 62% **2** (calculated values 38% **1**, 62% **2**). These unreacted ketone ratios serve as additional analytical checks. The solubility of LTAH in ether is low, and its use in tetrahydrofuran is much more satisfactory. Separate experiments showed that reduction of the C=C double bond in **2** with $LiAlH_4$ was negligibly small as expected from previous studies.[2] The reduction of **1** with LTAH is a much more stereoselective process than with $LiAlH_4$, leading to a greater *trans*/*cis*-**3** ratio (*cf.* footnotes *b*, *g*, and *j*, Table I, and also footnotes *h*, *i*, Table II). Reductions in tetrahydrofuran are also more stereoselective than corresponding reductions in diethyl ether. These observations are in accord with previous reduction studies of **1** with $LiAlH_4$ and lithium alkoxyaluminohydrides.[3]

Steric and torsional factors[4] which have been used to explain relative reactivity in hydride attack on opposite faces of a carbonyl group in a given cyclohexanone do not appear to explain the reduced reactivity of **2** relative to **1**. In **1**, the almost equal amounts of *cis*- and *trans*-**3** obtained in reduction with $LiAlH_4$ is presumably due to opposing steric factors (axial methyl on C-3) and torsional effects (partial eclipsing of equatorial hydrogens on C-2 and C-6 with entering hydride). Inspection of Dreiding models[5] reveals that in **2** the steric factor is still present, while the torsional factor is reduced by elimination of one flanking CH_2 group by the presence of the C=C double bond. Therefore it appears that the reduced reactivity of **2** is inherent in the enone system, possibly arising from reduced conjugation of the two double bonds in going from the ground state to the transition state. However, the exact mechanism for

(2) M. R. Johnson and B. Rickborn, *J. Org. Chem.*, **35**, 1041 (1970).

(3) H. Haubenstock and E. L. Eliel, *J. Amer. Chem. Soc.*, **84**, 2363 (1962).

(4) M. Chérest, H. Felkin, and N. Prudent, *Tetrahedron Lett.*, 2199 (1968); M. Chérest and H. Felkin, *ibid.*, 2205 (1968).

(5) In structure **2** carbons 1, 2, 3, 4, and 6 are taken as coplanar, with carbon 5 below (or above) the plane.

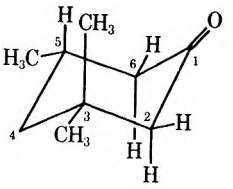
TABLE II

RESULTS OF OTHER COMPETITION REDUCTIONS

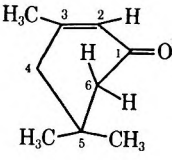
Ketone mixture	Metal hydride	Product analysis, %				
		5	7	6	10	9
5, 6 (0.020 mol each)[a]	$LiAlH_4$ (0.0116 equiv)[b]	66,[c] 65[d]	34,[c] 35[d]			
					82[d]	18[d,e]
		46[c]		54[c]		
		48[d]			52[d]	
		1	3	6	10	9
1, 6 (0.030 mol each)[f]	LTAH (0.0149 equiv)[g]	77,[c] 79[d]	23,[c,h] 21[d,i]			
					98[d]	2[d,e]
		44[c]		56[c]		
		45[d]			55[d]	

[a] In 60 ml of ether. Analyzed on 10 ft, 10% Carbowax 20M column at 135 and 120°. [b] 0.585 *M* in ether, added inversely. [c] Before hydrogenation. Normalized to 100%. [d] After hydrogenation. Normalized to 100%. [e] Mixture of cis and trans isomers. [f] In 100 ml of tetrahydrofuran. Analyzed on Carbowax 20M at 125°. [g] In 55 ml of tetrahydrofuran, added inversely. [h] **3** was 87% *trans*, 13% *cis*. [i] **3** was 92% *trans*, 8% *cis*.

reduction of enones is not yet established. Further competitive studies with conjugated and nonconjugated enone systems may be useful, and we intend to explore this further.



1



2

The first entry in Table II compares two unhindered ketones, **5** and **6** competing for $LiAlH_4$. The methyl group in **6** lies in the plane of the enone system and does not exert any significant steric hindrance in the reduction. Once again, considering possible steric and torsional factors, the enone **6** does not appear to be at a disadvantage relative to the saturated ketone **5**. As in the hindered ketone cases (*vide supra*), the enone is again less reactive, undergoing only 18% reduction compared with 35% reduction of **5**. As can be seen from Table II, the observed extent of reduction of **5**, and the relative ketone ratios both before and after hydrogenation, agree very well with each other. Also, the calculated remaining ketone composition is 45% **5**, 55% **6**, in good agreement with the observed 46–48% **5**, 52–54% **6** (or **10**).

The last entry in Table II compares the unhindered enone **6** with the relatively hindered ketone **1**. The reagent used was the more selective LTAH. Again, the saturated ketone **1**, even though more highly hindered, suffered more reduction (~22%), while the enone **6** was only 2% reduced. The observed unreacted ketone composition was 55–56% **6** (or **10**), 44–45% **1** (calculated 55% **6**, 45% **1**).

The fact that LTAH is more selective than $LiAlH_4$ might at first be ascribed to its greater "bulk." However, the nature of the active species in reductions with this reagent is uncertain,[6,7] and it is not always as stereoselective as its apparent size would suggest.[3,6] LTAH is less reactive than $LiAlH_4$[3] and kinetic studies of reductions with this reagent have been carried out.[8] The lower reactivity and higher selectivity of LTAH should prove useful in reductions of saturated ketones in the presence of conjugated enones.

Since the proportions of *cis*- and *trans*-**3**, obtained from reductions of ketone **1** (Tables I and II), agree well with previous values obtained in the reduction of **1** alone,[3] the present results are due to kinetic control, not to equilibrations.[9]

Experimental Section

Isophorone (**2**) and **10** were obtained from Matheson, and fractionally distilled. Dihydroisophorone (**1**) was prepared by oxidation[10] of the commercial alcohol mixture. 3-Methylcyclohex-2-en-1-one (**6**) was obtained from Aldrich. Samples of the known unsaturated alcohols **4**[11] and **8**[2] were prepared by $LiAlH_4$ reduction of the corresponding ketones, and the saturated alcohols **3** and **9** were similarly prepared by reduction of the corresponding ketones. LTAH was obtained from Ventron. Gas chromatographic analyses were carried out with a Hewlett-Packard 5750 chromatograph. Sensitivity factors derived from standard mixtures were determined for the various components. For example, in the analysis of two components 1 and 2, $K_2 = (A_2/A_1)(X_1/X_2)$; $K_1 = 1.0$, where K_1 and K_2 are relative sensitivity factors, A_1 and A_2 are experimentally determined areas (by the peak height–width at half-height methods), and X_1 and X_2 are the moles (or weights) of the components.

Reduction of Dihydroisophorone and Isophorone (1 and 2) with $LiAlH_4$.—A solution of **1** (4.23 g, 0.030 mol) and **2** (4.16 g, 0.030 mol) in 100 ml of anhydrous ether was added to a reactor equipped with a stirrer, reflux condenser, and addition funnel; 5 ml of 0.73 *M* $LiAlH_4$ in ether was transferred by pipet to the addition funnel and added dropwise to the well-stirred ketone solution. The reaction mixture was kept at room temperature overnight, and hydrolyzed (water and 10% sulfuric acid). The ether solution was washed (NaCl, $NaHCO_3$) and dried ($MgSO_4$) and the product was concentrated for glpc analysis by distillation of solvent (an oil bath was used, maximum temperature 85°).

Reduction of 1 and 2 with LTAH.—A solution of LTAH (3.8 g) was dissolved in 75 ml of tetrahydrofuran (distilled from $LiAlH_4$ through a helix-packed column) and added dropwise to a well-stirred solution of **1** (4.20 g, 0.030 mol) and **2** (4.18 g, 0.030 mol) in 100 ml of absolute ether. The work-up was carried out in the same manner as described above.

Reduction of 5 and 6 with $LiAlH_4$.—Ketones **5** (2.02 g, 0.021 mol) and **6** (2.21 g, 0.020 mol) in 60 ml of anhydrous ether were reduced by the dropwise inverse addition of 5 ml of 0.585 *M* $LiAlH_4$ in ether (0.0029 mol). After 3.5 hr of stirring, the reaction mixture was hydrolyzed with water and 10% sulfuric acid and worked up and concentrated in the usual manner, giving

(6) H. C. Brown and H. R. Deck, *J. Amer. Chem. Soc.*, **87**, 5620 (1965).

(7) D. C. Ayres, D. N. Kirk, and R. Sawdaye, *J. Chem. Soc. B*, 1133 (1970).

(8) J. Klein, E. Dunkelblum, E. L. Eliel, and Y. Senda, *Tetrahedron Lett.*, 6127 (1968).

(9) T. Toromanoff in "Topics in Stereochemistry," Vol. 2, N. L. Allinger and E. L. Eliel, Ed., Interscience, New York, N. Y., 1967, p 157. This review contains a discussion of the stereochemistry of hydride reductions of cyclohexenones.

(10) E. L. Eliel and H. Haubenstock, *J. Org. Chem.*, **26**, 3504 (1961).

(11) J. Klein and E. Dunkelblum, *Tetrahedron*, **24**, 5701 (1968).

22 g of concentrated product. A portion of the product (3.0 g) was retained for glpc analysis and the remainder was hydrogenated in 50 ml of anhydrous ethanol over 0.2 g of 5% palladium on charcoal using a Parr apparatus (initial pressure 43 psig). The solution of hydrogenated product was filtered and concentrated by distillation through a 12 in. helix-packed fractionating column (oil bath). The concentrated product was directly analyzed by glpc.

Reduction of 1 and 6 with LTAH.—Ketones 1 (4.22 g, 0.030 mol) and 6 (3.31 g, 0.030 mol) in 100 ml of tetrahydrofuran (distilled from $LiAlH_4$) were reduced by the dropwise inverse addition of LTAH (3.8 g, 0.015 mol) in 55 ml of tetrahydrofuran. Hydrolysis was effected in this case with water and 15% sodium hydroxide[12] after 2.5 hr of stirring. After concentration by distillation, a portion of the concentrated solution was directly analyzed by glpc while the remainder was hydrogenated over 0.3 g of 5% palladium on charcoal.

Control Experiments.—The fact that ketone ratios and ketone–alcohol ratios (of saturated compounds) did not vary significantly before and after hydrogenation lends confidence to the analytical procedure employed. In addition, a standard mixture of 1 and 10 was subjected to the hydrogenation and isolation procedures and was shown not to change in composition upon glpc analysis. Unsaturated ketones on hydrogenation also absorbed the exact amount of hydrogen (based on calibration of the apparatus) for conversion to the corresponding saturated alcohol.

(12) See L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis," Wiley, New York, N. Y., 1967, p 584.

Registry No.—**1**, 873-94-9; **2**, 78-59-1; **5**, 108-94-1; **6**, 16853-85-3; $LiAlH_4$, 17476-04-9.

Acknowledgment.—The author would like to thank Mr. P. Quezada for technical assistance.

The Addition of Lithium Dimethylcopper to Conjugated Cyclopropyl Enones

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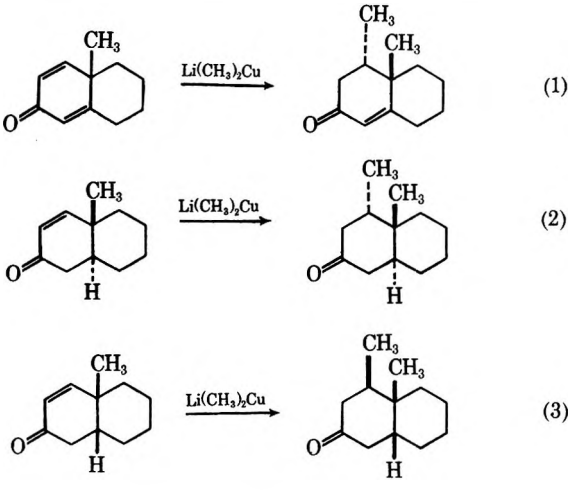
Received August 12, 1971

The addition of lithium dimethylcopper to 9,10-methano-1-octalin-3-one (**6**) affords a mixture of the expected 1,4 adducts (*ca.* 90% trans, 10% cis), a 1,6 adduct, 9-ethyl-4(10)-octalin-2-one (**8**), and a small amount of reduced cyclopropane cleavage product, 9-methyl-4(10)-octalin-2-one (**9**). Acid cleavage of the trans 1,4 adduct, *trans*-4-methyl-9,10-methanodecalin-2-one (**7a**), affords a 4:1 mixture of 4,9-dimethyl-*cis*-3-octalin-2-one (**19**) and *trans*-4,10-dimethyl-1(9)-octalin-2-one (**20a**), whereas the cis 1,4 adduct, *cis*-4-methyl-9,10-methanodecalin-2-one (**7b**), gives only *cis*-4,10-dimethyl-1(9)-octalin-2-one (**20b**) upon similar treatment. 5,10-Methano-1(9)-octalin-2-one (**16**), a cyclopropano enone isomeric with **6**, likewise affords 1,4- and 1,6-addition products upon treatment with lithium dimethylcopper.

The conjugate addition of lithium dimethylcopper(I)[2] to Δ^1-3-ones (eq 1–3) has been shown to proceed cleanly



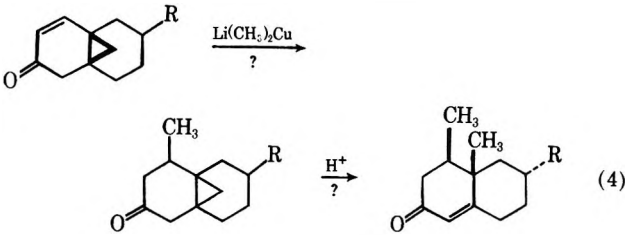
(1)

(2)

(3)

and stereoselectively. In the former two cases (eq 1 and 2) the methylation occurs trans to the angular methyl group to give *trans*-dimethyl products.[3] However, the cis-fused enone (eq 3) affords mainly the cis,-cis product.[4] The latter arrangement of *vic*-methyl groups is of particular interest in connection with the valencane–eremophilane family of sesquiterpenes, a class of compounds based on the *cis,cis*-1,9-dimethyldecalin framework.[5]

In the course of synthetic studies related to the sesquiterpene grapefruit flavor constituent nootkatone,[6] we decided to examine the conjugate methylation–cyclopropane cleavage sequence shown in eq 4. Our initial work was carried out on a model system designed to test the overall feasibility and stereochemistry of the above sequence. Accordingly, the known cyclopropyl alcohol **1** (Scheme I) was reduced (Li, NH_3, EtOH) *via* the methanesulfonate derivative **2** to the tricyclic olefin **3**.[7] Epoxidation followed by base-induced elimination afforded the allylic alcohol(s) **5**, oxidation of which gave the desired enone **6**.



(4)

Addition of lithium dimethylcopper(I) to enone **6** in ether solution at 0° afforded principally the 1,4 adduct **7** (55%) along with enones **8** (39%) and **9** (6%). The production of the latter two cyclopropane cleavage products was of special interest since a simple cyclopropyl ketone, bicyclo[4.1.0]heptan-2-one,[8] and a con-

(1) Predoctoral Fellow of the National Institutes of Health, Division of General Medical Sciences, Fellowship 5 FO1 GM 41100.

(2) H. O. House, W. L. Respess, and G. M. Whitesides, *J. Org. Chem.*, **31**, 3128 (1966).

(3) (a) T. M. Warne, Jr., "The Synthesis of (±)-Isonootkatone," Ph.D. Thesis, Northwestern University, Evanston, Ill., 1971, p 100; (b) R. M. Coates and J. E. Shaw, *Chem. Commun.*, 47 (1968); (c) R. L. Nale and L. N. Zalkow, *ibid.*, 1249 (1968).

(4) G. M. Cohen, unpublished results. *Cf.* J. A. Marshall and G. M. Cohen, *J. Org. Chem.*, **36**, 877 (1971).

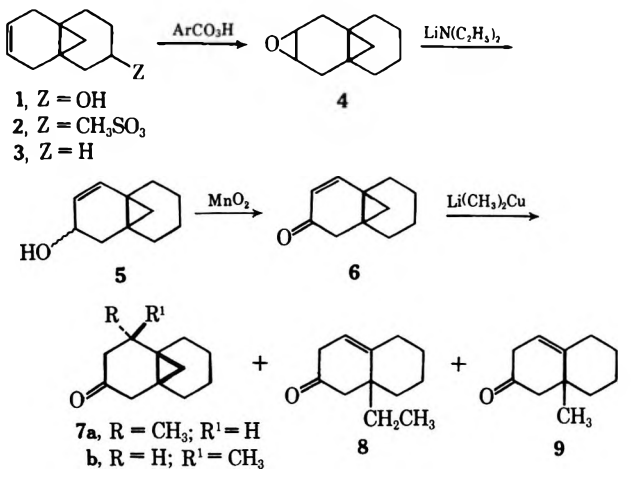
(5) *Cf.* J. A. Marshall and R. A. Ruden, *ibid.*, **36**, 594 (1971).

(6) W. D. Macleod, Jr., *Tetrahedron Lett.*, 4779 (1965).

(7) J. J. Sims, *J. Org. Chem.*, **32**, 1751 (1967).

(8) R. A. Ruden, "Stereoselective Total Synthesis of Racemic Nootkatone," Ph.D. Dissertation, Northwestern University, Evanston, Ill., 1971, p 66.

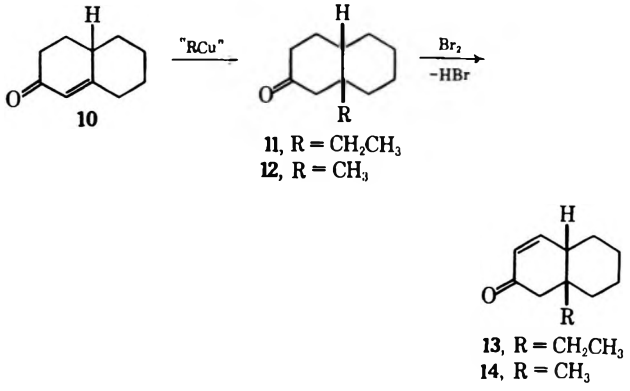
SCHEME I



jugated cyclopropyl cyclopentenone[9] failed to give cyclopropane cleavage products upon treatment with lithium dimethylcopper or phenylmagnesium bromide–cuprous iodide, respectively. In the present case, cyclopropane cleavage took place readily, even at −40°.

The structures of the cleavage products were ascertained through conversion with base to their conjugated isomers **13** and **14** which were synthesized independently as outlined in Scheme II.

SCHEME II



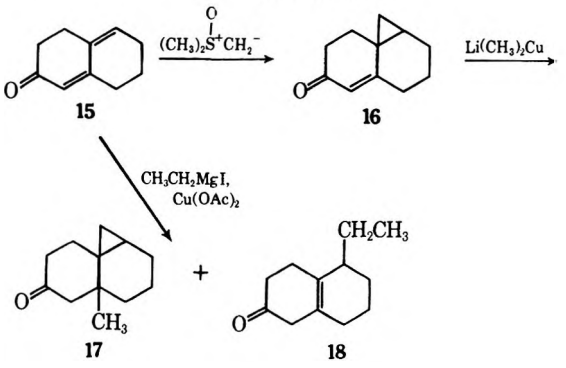
Hoping to find conditions more favorable to 1,4 addition, we conducted a brief study of temperature and solvent effects (Table I). The use of dioxane was suggested by our previous work on conjugate additions to a cyclohexadienone.[10] The present study indicated that in ether low temperature favors the cyclopropane cleavage reaction whereas in dioxane low temperature favors 1,4 addition. Under optimum conditions we obtained 72% of the 1,4 adduct, a 93:7 mixture of **7a** and **7b** (see below).

TABLE I
ADDITION OF $Li(CH_3)Cu$ TO CYCLOPROPYL ENONE 6

Solvent	Temp, °C	1,4 addition (7), %	1,6 addition (8), %	Reduction (9), %
Ether	−40	40	55	5
	0	55	39	6
	15	60	34	6
Dioxane	15	72	24	4
	40	61	33	6

Since the addition of an organocopper reagent to the cyclopropane ring of a cyclopropyl ketone had not previously been reported, we were interested to see if enone **6** was an isolated case or if the reaction would occur with related cyclopropyl enones.[11] Accordingly the work outlined in Scheme III was undertaken. Cyclopropanation of the dienone **15**[12] afforded the cyclopropyl enone **16**.[13] Addition of ethereal lithium dimethylcopper at 0° yielded the 1,4 adduct **17** (43%) and the cyclopropane-cleaved 1,6 adduct **18** (49%). The latter product was independently synthesized through 1,6 addition of ethylmagnesium iodide to dienone **15**. The stereochemistry of the 1,4 adduct **17** has not yet been examined.

SCHEME III



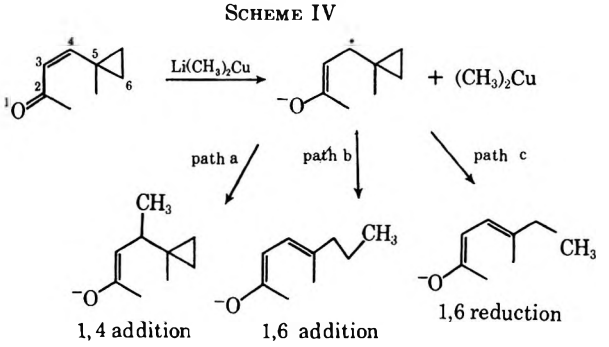
In ether higher temperature once again favored the 1,4 addition reaction (Table II).

TABLE II
ADDITION OF $Li(CH_3)_2Cu$ TO CYCLOPROPYL ENONE 16

Solvent	Temp, °C	1,4 addition (17), %	1,6 addition (18), %
Ether	−40	27	64
	0	43	49
	15	52	40

Scheme IV depicts a possible pathway for the observed addition reactions to cyclopropyl enones. Electron transfer from an organocopper species to a conjugated enone substrate leading to an intermediate radi-

SCHEME IV



(9) H. E. Zimmerman and R. L. Morse, *J. Amer. Chem. Soc.*, **90**, 954 (1968).

(10) J. A. Marshall and S. F. Brady, *J. Org. Chem.*, **35**, 4068 (1970).

(11) While this manuscript was in preparation, a report of a related cyclopropane cleavage of a cyclopentenone appeared: C. Frejaville and R. Jullien, *Tetrahedron Lett.*, 2039 (1971).

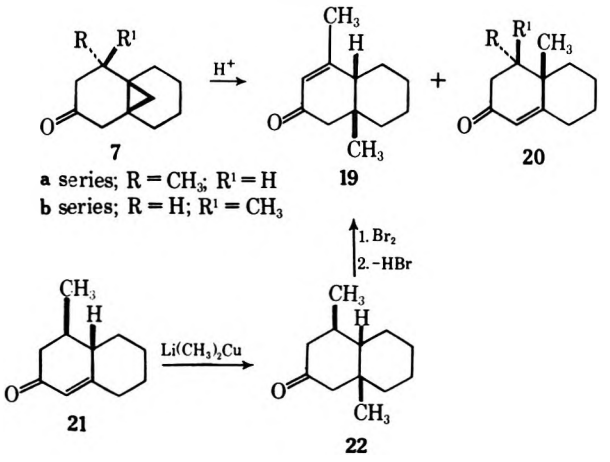
(12) N. N. Gaidamovich and I. U. Torgov, *Izv. Akad. Nauk SSSR*, 1903 (1961); *Chem. Abstr.*, **62**, 13197 (1962).

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

cal anion has been suggested by House and Fischer.[14] In the present case, the resulting radical anion could react directly with the organocopper *via* methyl transfer as postulated by House to give the 1,4 adduct (path a) or cyclopropane participation could take place leading to either the 1,6 adduct *via* methyl transfer (path b) or the reduction product *via* hydrogen transfer (path c), possibly from the solvent. The latter reactions may proceed directly from the radical anion with concerted cyclopropane cleavage or conceivably a prior cleavage could take place to give a new radical anion which could then react *via* methyl transfer or H transfer as noted above.

The stereochemistry of the 1,4 adduct **7** was ascertained through vpc analysis of the acid cleavage products, enones **20a** and **20b**, as shown in Scheme V. A

SCHEME V

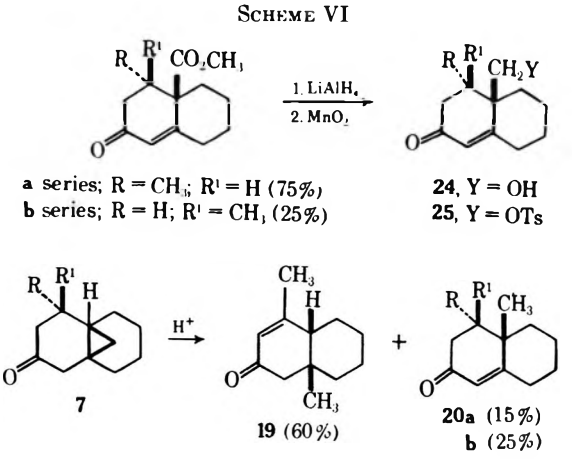


sample of ketone **7** obtained from the addition of lithium dimethylcopper to enone **6** appeared homogeneous by nmr and vpc criteria. However, upon treatment with acetic acid–HCl a mixture of three enones, **19** (75%), **20a** (18%), and **20b** (7%), was secured in 97% yield. The structure of enone **19** was confirmed by direct comparison with a sample obtained *via* the sequence outlined in Scheme V. Enones **20a** and **20b** were identified by direct comparison with authentic samples.[3]

The above findings indicate that at least 7% of the *cis*-methyl ketone **7b** must be formed in the 1,4 methylation of enone **6**. Since both **7a** and **7b** could give rise to enone **19** upon acid cleavage, and since they most likely would do so at differing rates, we could not utilize these results to deduce the relative amounts of methyl epimers obtained in the aforementioned 1,4 methylation. Attempts at direct analysis of this mixture were to no avail; so we decided to examine the acid cleavage of a known mixture of cyclopropyl ketones **7a** and **7b**. This mixture was prepared as shown in Scheme VI from a 3:1 mixture of keto esters **23a** and **23b**. Reduction with lithium aluminum hydride followed by MnO_2 oxidation afforded the keto alcohols **24a** and **24b** in 92% yield. The corresponding tosylate derivative **25** yielded the cyclopropyl ketones **7a** and **7b** in 98% yield upon treatment with zinc dust in aqueous acetic acid.[15] In view of the high yield of this step we assume that the ratio of ketones **7a** to **7b** is roughly the same (3:1) as

(14) H. O. House and W. F. Fischer, Jr., *J. Org. Chem.*, **33**, 949 (1968).
(15) S. Rakhit and M. Gut, *J. Amer. Chem. Soc.*, **86**, 1432 (1964).

SCHEME VI

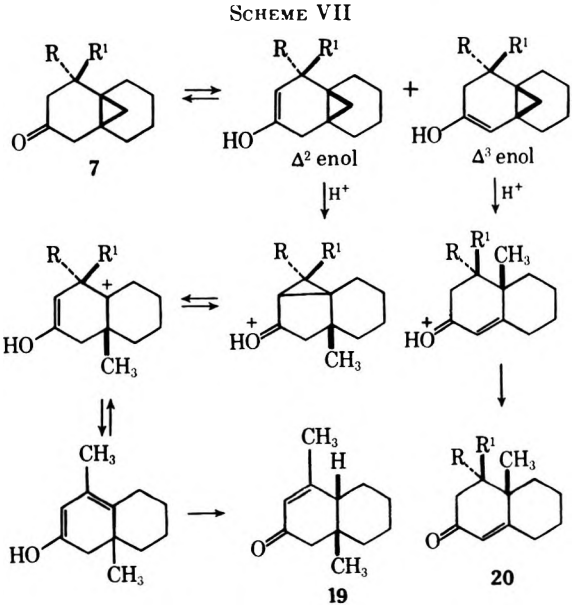


that of the starting keto esters **23** and the intermediates **24** and **25** (analyzed *via* integration of CH_3 doublets in the nmr spectra).

Cleavage of cyclopropyl ketones **7a** (75%) and **7b** (25%) with acetic acid–HCl afforded a 60:15:25 mixture of enones **19**, **20a**, and **20b** in 97% yield. Thus, ketone **7b** must cleave virtually unidirectionally to give enone **20b** under these conditions, whereas the epimeric ketone **7a** cleaves largely (4:1) in the opposite sense to give enone **19**.

The formation of enone **19** as the major cleavage product of ketone **7a** conforms to Sims's views on this reaction.[7] Accordingly, protonation of the cyclopropyl ketone conjugate acid will tend to give a dication intermediate with maximum charge separation. In the case of ketone **7b**, however, this direction of protonation is hindered by the *cis*-methyl grouping. An alternative explanation may be postulated (Scheme VII)

SCHEME VII

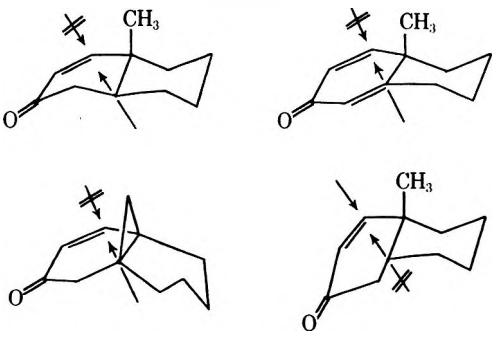


in which participation by the enolic double bond assists cyclopropane cleavage. Reaction through the Δ^2 enol (Scheme VII) may be less favorable in the b series owing to conformational changes which place the initially equatorial methyl grouping into the bowsprite position of a 1,4-cyclohexadiene-type boat conformation. The Δ^3 enol may also give rise to a ketone-protonated cyclopropane intermediate isomeric with that derived from

the Δ^2 enol. Formation of this intermediate (whose ultimate fate would be conversion to enone **19**) would appear geometrically unfavorable as judged by an examination of molecular models.

Thus, we have shown that the addition of lithium dimethylcopper to enone **6** gives largely (*ca* 90:10) the trans 1,4 adduct **7a**. This finding is somewhat surprising in view of the preferential formation of the cis 1,4 adduct from the cis-fused decalone analog of enone **6** (eq 3).[4] Evidently increased steric shielding of the top face of the double bond by the cyclopropane CH_2 plus the less concave geometry of enone **6** render trans addition more favorable than cis addition. The comparison of analogous systems is shown in Chart I.

CHART I



Finally, it should be noted that the acid cleavage of cyclopropyl decalones related to **7b** could be employed to generate compounds related to the valencane–eremophilane family of sesquiterpenes.[5]

Experimental Section[16]

9,10-Methano-2-octalin (3).—To a cooled (0°), stirred solution of alcohol **1**[7] (340 mg) in 3 ml of dry pyridine was added 0.23 ml of methanesulfonyl chloride. After 1 hr, the ice bath was removed and the solution was stirred at room temperature for 3 hr. Isolation with ether afforded the mesylate **2** as a pale yellow oil: λ_{max}^{film} 7.41, 8.52, and 10.09 μm. The crude mesylate was dissolved in 5 ml of ethanol and slowly added to a cooled (−78°) solution of NH_3 (80 ml) containing 1.2 g of lithium. The solution was stirred at −78° for 1 hr and at −33° for 0.5 hr. Cautious addition of 25 ml of 1:1 ethanol–pentane and evaporation of the ammonia followed by isolation with pentane and distillation [bath temperature 110° (10 mm)] afforded 190 mg (60%) of octalin **3** as a colorless oil: λ_{max}^{film} 3.31, 6.05, 6.92, and 9.86 μm; $\delta_{TMS}^{CCl_4}$ 5.44 (vinyl H, broad) and 0.37 ppm (cyclopropyl CH_2, $\Delta\nu_{AB}$ = 26 Hz, J_{AB} = 4 Hz). The analytical sample was obtained by preparative gas chromatography.

Anal. Calcd for $C_{11}H_{16}$: C, 89.12; H, 10.88. Found: C, 89.08; H, 10.94.

9,10-Methano-1-octalin-3-one (6).—A stirred solution containing 160 mg of alkene **3** in 5 ml of benzene was treated with 500 mg of *m*-chloroperoxybenzoic acid. After 12 hr at room temperature, isolation with benzene (a 10% KOH wash was used to remove acidic material) afforded 100 mg (56%) of the epoxide **4** as a colorless oil: λ_{max}^{film} 6.92, 9.86, and 12.48 μm; $\delta_{TMS}^{CCl_4}$ 2.80 (triplet, J = 3 Hz).

Lithium diethylamide was prepared by the dropwise addition of *n*-butyllithium (1.5 mmol) to a cooled ethereal solution (10 ml) of diethylamine (1.5 mmol).[17] After 10 min, 100 mg of epoxide in 3 ml of ether was aded, and the solution was heated at reflux for 24 hr. Isolation with ether afforded 67 mg (67%) of allylic alcohol **5**: λ_{max}^{film} 3.07, 3.39, 6.11, and 9.57 μm; $\delta_{TMS}^{CCl_4}$ 5.78, 5.76, 5.60, 5.58, 5.25, 5.10 (vinyl H, AB part of ABX pattern), 3.96 (CHOH, broad t, J = 8 Hz), and 0.52 ppm (cyclopropyl CH_2, $\Delta\nu_{AB}$ = 9.0 Hz, J_{AB} = 4.2 Hz).

To a solution of 1.0 g of allylic alcohol **5** in 100 ml of chloroform was added 10.0 g of activated manganese dioxide.[18] After stirring at room temperature for 20 hr, the solution was filtered and the filtrate was concentrated at reduced pressure. Distillation at 110° (bath temperature) at 0.05 mm afforded 0.81 g (80%) of enone **6**: λ_{max}^{film} 6.00, 6.96, 7.21, and 8.06 μm; $\delta_{TMS}^{CCl_4}$ 6.25 (vinyl H, $\Delta\nu_{AB}$ = 86 Hz, J_{AB} = 10 Hz), 2.54 (α-keto CH_2, $\Delta\nu_{AB}$ = 21.5 Hz, J_{AB} = 18 Hz), and 0.80 ppm (cyclopropyl CH_2, $\Delta\nu_{AB}$ = 36 Hz, J_{AB} = 4.0 Hz). This material was routinely purified for further use by preparative thick layer chromatography on silica gel using 1:1 ether–benzene as the solvent.

Anal. Calcd for $C_{11}H_{14}O$: C, 81.44; H, 8.70. Found: C, 81.20; H, 8.89.

Addition of Lithium Dimethylcopper to 9,10-Methano-1-octalin-3-one (6). A. In Ether at 0°.—A suspension of cuprous iodide (764 mg) in 25 ml of anhydrous ether was cooled to 0° with an ice bath and ethereal methyllithium (4.45 ml of 1.65 *M*) was added dropwide to the solution.[2] Enone **6** (180 mg) in 10 ml of ether was then added dropwise and the solution was stirred for 1 hr at 0°. The reaction mixture was poured into a rapidly stirred solution of saturated ammonium chloride. Isolation with ether (an ammonium hydroxide wash was used to remove suspended copper salts) and short path distillation afforded 180 mg (90%) of a colorless oil: bp 110° (bath temperature) at 0.1 mm; λ_{max}^{film} 5.85 μm. The gas chromatogram showed peaks at 8.2 min (6.9%) and 11.6 min (92%).

This material was subjected to preparative gas chromatography. The first peak eluted was identified as enone **9** by comparison with an authentic sample. The second peak eluted was shown to be approximately a 60:40 mixture of ketones **7** and **8**.

In another run, the material obtained from the addition of $LiMe_2Cu$ to enone **6** was treated with Na_2CO_3 in methanol according to the general equilibration procedure given below. The gas chromatogram showed peaks at 7.6 min (0.8%), 8.8 min (6%), 10.8 min (60%), and 11.9 min (33%).

This material was subjected to preparative gas chromatography. The first peak eluted was cyclopropyl ketone **7**: λ_{max}^{film} 5.85, 6.92, and 8.13 μm; $\delta_{TMS}^{CCl_4}$ 1.12 (CH_3 doublet, J = 6.2 Hz) and 0.53 ppm (cyclopropyl H, $\Delta\nu_{AB}$ = 19 Hz, J_{AB} = 6.0 Hz).

Anal. Calcd for $C_{12}H_{18}O$: C, 80.85; H, 10.18. Found: C, 80.89; H, 10.21.

The second peak to be eluted was identified as enone **13** by comparison with an authentic sample (see below).

Equilibration of the product mixture (31 mg) yielded 27 mg of ketones **9**, **14**, **7**, **8**, and **13**. From the percentages of these components it was determined that ketones **9**, **8**, and **7** were formed in a 5:55:40 ratio.

B. In Dioxane.—To a suspension of cuprous iodide (260 mg) in 4 ml of dioxane cooled to 15° was added 1.5 ml of 1.68 *M* ethereal methyllithium. After 0.5 hr, enone **6** (36 mg) in 6.0 ml of dioxane was added and the resulting solution was stirred at 15–20° for 6 hr. The reaction mixture was then poured into a rapidly stirred solution of ammonium chloride. Isolation with ether (an ammonium hydroxide wash was used to remove suspended copper salts) and short path distillation afforded 36 mg (90%) of a colorless oil. Equilibration of the addition products (23 mg) afforded 16 mg of a mixture whose composition indicated an initial composition of 4:24:72 for ketones **9**, **8**, and **7**.

Product Analysis.—Since the enone **8** and the cyclopropyl ketone **7** did not separate on the gas chromatogram, the product analysis was carried out on the conjugated enones **13** and **14** as follows. The mixture obtained from the addition of $LiMe_2Cu$ to enone **6** was dissolved in 10 ml of absolute methanol containing 20 mg of Na_2CO_3 and stirred for 8–10 hr at room temperature. Acetic acid was then added and the products were isolated with ether and distilled affording the equilibrated mixtures (yields 70–90%). The vapor phase chromatogram indicated that the

(16) Reactions were conducted under a nitrogen atmosphere using the apparatus described by W. S. Johnson and W. P. Schneider ["Organic Syntheses," Collect. Vol. IV, Wiley, New York, N. Y., 1963, p 132]. Reaction products were isolated by addition of water and extraction with the specified solvent. The combined extracts were washed with saturated brine and dried over anhydrous magnesium sulfate. The solvent was removed from the filtered solutions on a rotary evaporator.

(17) B. Rickborn and R. P. Thummel, *J. Org. Chem.*, **34**, 3583 (1969).

(18) O. Mancera, G. Rosencranz, and F. Sondheimer, *J. Chem. Soc.*, 2189 (1953).

per cent of conjugated enone in the equilibrium mixtures ranged from 85 to 90%, with 10–15% of the unconjugated isomers **8** and **9** remaining. Since the β,γ unsaturated enone **8** did not separate from the cyclopropyl ketone **7**, a correction factor was used to determine the exact ratio of components. Assuming that the ratio of $\alpha,\beta/\beta,\gamma$ double bond isomers for enone **9** would be similar to that of enone **8** and knowing the former ratio **9**:**14** = 0.1, we could determine the percentage of enone **8** present in the mixture.

Preparation of *trans*- and *cis*-1-Methyl-9,10-methano-1-octalin-3-one (3:1 7a/7b) from Keto Esters 23.—To a solution of 0.83 g of a 3:1 mixture of keto esters **23a** and **23b**[19] in 100 ml of ether was added portionwise with stirring 0.50 g of lithium aluminum hydride. The solution was heated at reflux for 18 hr and treated with 0.5 ml of 15% NaOH and 1.5 ml of water. The mixture was filtered after several hours and the filtrate was concentrated under reduced pressure affording 0.79 g of diol: λ_{max}^{film} 3.05 μm; $\delta_{TMS}^{CDCl_3}$ 5.51 (vinyl H), 1.00 (CH_3 doublet, J = 6.2 Hz), and 0.88 ppm (CH_3 doublet, J = 6.5 Hz).

The above diol in 100 ml of chloroform was stirred vigorously with 8.0 g of MnO_2[18] for 18 hr. The mixture was filtered and the filtrate was concentrated under reduced pressure affording 0.79 g of keto alcohol **24**: λ_{max}^{film} 3.00 and 6.04 μm; $\delta_{TMS}^{CDCl_3}$ 5.83 (vinyl H, two peaks), 1.04 (CH_3 doublet, J = 6.5 Hz), and 0.96 ppm (CH_3 doublet, J = 7.0 Hz).

A solution of the above ketol in 5 ml of pyridine at 0° was stirred for 1 hr at 0° and 16 hr at room temperature with 1.6 g of *p*-toluenesulfonyl chloride. The product was isolated by extraction with ether affording 0.57 g of tosylate **25**: λ_{max}^{film} 6.00, 7.38, 8.44, 8.52, and 10.40 μm.

The above tosylate in 100 ml of 1:1 aqueous acetic acid was stirred at reflux with 5.0 g of zinc dust.[15] The product was isolated *via* extraction with hexane and distilled affording 0.29 g (98% yield) of the cyclopropyl ketones **7a** and **7b** whose spectral properties closely matched those of the 93:7 mixture obtained *cia* conjugated methylation of enone **6** as described above.

***cis*-9-Ethyldecalin-2-one (11).**—A solution of ethylmagnesium iodide (prepared from 2.88 g of magnesium turnings and 16.8 g of ethyl iodide in 100 ml of ether) was cooled to −10° and a solution containing 5.0 g of 1(9)-octal-2-one (**10**) and 2.08 g of cupric acetate monohydrate in 150 ml of dry tetrahydrofuran was added over 0.5 hr with efficient stiring.[20] The dark mixture was allowed to warm to room temperature over 2 hr and was heated to reflux for 15 min. After excess aqueous ammonium chloride had been added to the mixture, the product was isolated with ether affording 4.2 g of a pale yellow oil: λ_{max}^{film} 2.91 (OH) and 5.84 μm. The crude mtaerial was chromatographed on 300 ml of alumina and 3.20 g (50%) of ethyldecalone **11** was eluted with 10% ether–hexane: λ_{max}^{film} 5.85, 6.87, and 8.19 μm; $\delta_{TMS}^{CCl_4}$ 1.40 (CH_2 quartet, J = 7.0 Hz) and 0.80 ppm (CH_3 triplet, J = 7.0 Hz).

Anal. Calcd for $C_{12}H_{20}O$: C, 79.94; H, 11.18. Found: C, 80.03; H, 11.38.

***cis*-9-Ethyl-3-octalin-2-one (13).**—To a cooled (0°), stirred solution of ethyldecalone **11** (1.0 g) in 50 ml of chloroform was added 0.96 g of bromine in 15 ml of chloroform over 5 min. After 0.5 hr at room temperature, isolation of the product with ether afforded 1.56 g of pale yellow bromo ketone, λ_{max}^{film} 5.80 μm. The crude material was dissolved in 50 ml of dimethylacetamide and 1.50 g of calcium carbonate was added.[21] The mixture was then heated at reflux for 1 hr. Isolation with hexane and short path distillation [bp 100° (bath temperature) at 0.05 mm] afforded 920 mg (92%) of the unsaturated ketone **13**: λ_{max}^{film} 5.97 μm; $\delta_{TMS}^{CCl_4}$ 6.18 (vinylic H's, ABX pattern, $\Delta\nu_{AB}$ = 47 Hz, J_{AB} = 10 Hz, apparent J_{AX} = 4.0 Hz, apparent J_{BX} = 1.9 Hz), 2.16 (CH_2CO, AB pattern, $\Delta\nu_{AB}$ = 2.46 Hz, J_{AB} = 15.0 Hz), and 0.81 ppm (CH_3 triplet, J = 6.3 Hz). The analytical sample was obtained by preparative gas chromatography.

Anal. Calcd for $C_{12}H_{18}O$: C, 80.84; H, 10.18. Found: C, 80.60; H, 10.23.

***cis*-9-Methyl-3-octalin-2-one (14).**—To a cooled (0°), stirred solution of decalone **12** (2.0 g) in 100 ml of chloroform was added 2.08 g of bromine in 30 ml of chloroform. After 0.5 hr, isolation with ether afforded the pale yellow bromo ketone, λ_{max}^{film} 5.80. The crude material was dissolved in 100 ml of dimethylacetamide and 1.50 g of calcium carbonate was added.[21] The mixture was heated at reflux for 1 hr. Isolation with hexane and short path distillation [bp 100° (bath temperature) at 0.05 mm] afforded 1.65 g (83%) of the unsaturated ketone **14**: λ_{max}^{film} 5.96 μm; $\delta_{TMS}^{CCl_4}$ 6.20 (vinylic H's, ABX pattern, $\Delta\nu_{AB}$ = 33 Hz, J_{AB} = 10 Hz, apparent J_{AX} = 4 Hz, apparent J_{BX} = 1.4 Hz), and 1.01 ppm (CH_3). The 2,4-dinitrophenylhydrazone derivative exhibited mp 140–143° (ethanol).

Anal. Calcd for $C_{17}H_{20}N_4O_4$: C, 59.29; H, 5.85; N, 16.27. Found: C, 59.39; H, 5.89; N, 16.39.

5,10-Methano-(1)9-octalin-2-one (16).—To a solution of dimethyloxosulfonium methylide (prepared from 7.35 g of trimethyloxosulfonium iodide and 1.27 g of 57% NaH dispersion)[13] in 30 ml of DMSO was added 3.17 g of dienone **15**[12] in 22 ml of DMSO. After 3 hr at room temperature, isolation with hexane and distillation afforded 1.17 g (30%) of ketone **16**: bp 90° (bath temperature) at 0.2 mm; λ_{max}^{film} 6.00, 6.21, 8.01, 11.38, and 13.18 μm; $\delta_{TMS}^{CCl_4}$ 5.72 ppm (vinyl H, s). This material was purified for further use by preparative thick layer chromatography on silica gel using 1:1 ether–benzene as the solvent. The 2,4-dinitrophenylhydrazone exhibited mp 185–187° (ethanol).

Anal. Calcd for $C_{17}H_{18}N_4O_4$: C, 59.64; H, 5.30; N, 16.37. Found: C, 59.41; H, 5.30; N, 16.47.

Addition of Lithium Dimethylcopper to Cyclopropyl Ketone 16.—To a cooled (0°) stirred suspension of CuI (260 mg) in 8 ml of ether was added 1.8 ml of 1.5 *M* ethereal methyllithium.[2] To this colorless solution was added 133 mg of cyclopropyl ketone **16**. After 1 hr at 0°, the reaction mixture was poured into a rapidly stirred solution of ammonium chloride. Isolation with ether (an aqueous ammonia wash was used to remove suspended copper salts) and short path distillation [bp 110° (bath temperature) at 0.1 mm] afforded 130 mg (90%) of addition products, λ_{max}^{film} 5.86 μm. The gas chromatogram showed peaks at 8.4 min (1.5%), 9.4 min (43%), 10.7 min (2.3%), 11.6 min (48%), and 12.8 min (4%).

The addition products were subjected to preparative gas chromatography. The first peak eluted was identified as ketone **17**: λ_{max}^{film} 5.84 μm; $\delta_{TMS}^{CCl_4}$ 1.00 (CH_3) and 0.45–0.20 ppm (cyclopropyl CH, complex).

Anal. Calcd for $C_{12}H_{18}O$: C, 80.85; H, 10.18. Found: C, 80.69; H, 9.98.

The second peak eluted was identified as enone **18** by comparison with an authentic sample (see below).

5-Ethyl-9-octalin-2-one (18).—To a solution of ethylmagnesium iodide (prepared from 3.35 g of ethyl iodide and 575 mg of magnesium in 20 ml of ether) was added 1.0 g of dienone **15**[12] and 415 mg of cupric acetate monohydrate in 30 ml of THF.[20] After 2 hr, excess aqueous ammonium chloride was added and the product was isolated with ether affording 1.10 g (92%) of ketone **18**. The analytical sample was secured *via* preparative layer chromatography on silica gel using 30:70 ether–benzene as the solvent: λ_{max}^{film} 5.85 and 6.91 μm; $\delta_{TMS}^{CCl_4}$ 2.60 (CH_2) and 0.84 ppm (CH_3 triplet, J = 6.8 Hz).

Anal. Calcd for $C_{12}H_{18}O$: C, 80.85; H, 10.18. Found: C, 80.81; H, 10.31.

Acid Cleavage of Cyclopropyl Ketone 7.—To 4 ml of 1:3 mixture of concentrated HCl–acetic acid was added 92 mg of cyclopropyl ketone **7** (a 3:1 mixture of **7a** and **7b**). The solution was heated at reflux for 4 hr. Isolation with ether and short path distillation [bp 110° (bath temperature) at 0.05 mm] afforded 90 mg (97%) of a mixture of enones **19**, **20a**, and **20b**: vpc 8.0 min (4.0%), 13.3 min (59%), 18.0 min (13%), and 19.2 min (24%). The 13.3-min peak was isolated by preparative vapor phase chromatography and identified as **19** on the basis of its spectral data: λ_{max}^{film} 5.98, 6.92, 7.29, and 8.02 μm; $\delta_{TMS}^{CCl_4}$ 5.60 (vinyl H, broad), 1.90 (vinyl CH_3, d, J = 1 Hz), and 0.98 ppm (CH_3).

The last two peaks were identified by coinjection with authentic samples. The peak at 18.0 min was the trans isomer **20a**[15] and the peak at 19.2 min was the cis isomer **20b**.[16]

4,9-Dimethyl-3-octalin-2-one (19).—To a cooled (0°) solution of 900 mg of decalone **22** in 50 ml of chloroform was added 0.28 ml of bromine in 15 ml of chloroform. After 0.5 hr at 0°, the solution was allowed to warm to room temperature over 0.5 hr. Isolation with ether afforded the crude bromo ketone as a pale yellow oil, λ_{max}^{film} 5.82 μm. This material was dissolved in 50 ml of dimethylacetamide, 1.50 g of calcium carbonate was added, and the solution was heated at reflux for 1 hr.[21] Isolation with hexane followed by short path distillation afforded 600 mg (66%) of enone **19**, bp 100° (bath temperature) at 0.1 mm. The spectral properties of this material exactly matched those of the major product of the acid-catalyzed rearrangement

(19) Reference 3a, pp 94–98.
(20) A. J. Birch and M. Smith, *Proc. Chem. Soc.*, 356 (1962).
(21) G. Green and A. Long, *J. Chem. Soc.*, 2532 (1961).

of cyclopropyl ketone **7**. The analytical sample was obtained by thick layer chromatography on silical gel using 1:1 ether–benzene as the solvent.

Anal. Calcd for $C_{12}H_{18}O$: C, 80.85; H, 10.18. Found: C, 80.62; H, 10.18.

4-Methyl-1(9)-octalin-2-one (21).—To a solution of 30 g of the pyrrolidine enamine of cyclohexanone in 200 ml of benzene was added 17.0 g of *trans*-3-penten-2-one.[22] The mixture was then heated at reflux for 24 hr.[22] A buffer solution made up of 25 ml of acetic acid, 25 ml of water, and 12.5 g of sodium acetate was added and the solution was heated at reflux for 4 hr. Isolation with benzene and distillation gave 13.8 g of octalone **21**, bp 88–90° (0.6 mm). This material was obtained as a mixture of α,β and β,γ double bond isomers. The pure conjugated isomer was obtained by cooling a hexane solution of the mixture in Dry Ice–acetone whereupon pure enone **21** crystallized and was obtained free of the β,γ isomer: λ_{max}^{film} 5.98 and 6.17 μm; $\delta_{TMS}^{CCl_4}$ 5.52 (vinyl H) and 1.06 ppm (CH_3, d, J = 6.0 Hz).

Anal. Calcd for $C_{11}H_{16}O$: C, 80.44; H, 9.82. Found: C, 80.63; H, 9.84.

4,9-Dimethyldecalin-3-one (22).—To a cooled (0°), stirred suspension of cuprous iodide (4.90 g) in 100 ml of anhydrous ether was added 35 ml of 1.6 *M* methyllithium.[2] To this clear solution was added 1.03 g of enone **21** in 15 ml of ether. After 1 hr, the mixture was poured into a saturated amonium chloride solution. Isolation with ether (an ammonium hydroxide wash was used to remove the suspended copper salts) and short path distillation afforded 1.04 g (90%) of ketone **22** as a colorless oil: bp 100° (bath temperature) at 0.2 mm; λ_{max}^{film} 5.85 μm; $\delta_{TMS}^{CCl_4}$ 1.12 (CH_3) and 0.98 ppm (CH_3, d, J = 6.0 Hz). The analytical sample was secured *via* a second distillation.

Anal. Calcd for $C_{12}H_{20}O$: C, 79.94; H, 11.18. Found: C, 80.15; H, 11.09.

(22) G. Stork, A. Brizzolara, H. K. Landesman, J. Szmuszkovicz, and R. Terrell, *J. Amer. Chem. Soc.*, **85**, 207 (1963).

Registry No.—**3**, 33021-03-3; **4**, 32970-11-9; **5**, 32970-12-0; **6**, 32970-13-1; **7a**, 32980-02-2; **7b**, 32980-03-3; **11**, 32980-04-4; **13**, 32980-05-5; **14**, 32980-06-6; **16**, 32970-14-2; **16** 2,4-DNP, 32970-15-3; **17**, 32970-16-4; **18**, 32970-17-5; **19**, 32980-07-7; **21**, 32980-08-8; **22**, 32980-09-9; **23a** diol derivative, 32980-10-2; **23b** diol derivative, 32971-05-4; **24a**, 32971-06-5; **24b**, 32971-07-6; **25a**, 32980-11-3; **25b**, 33015-67-7; lithium dimethylcopper, 32970-18-6.

Acknowledgments.—We thank the National Institutes of Health for their support of this work through a research grant (5 RO1 CA11089) and a predoctoral fellowship.

A Mercury Salt Pathway for the Degradation of Carboxylic Acids to Alkyl Halides Using Halogen and Mercuric Oxide[1]

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Received May 20, 1971

The degradation of carboxylic acids to alkyl halides using the halogens and mercuric oxide involves the initial formation of the mercuric salt of the acid, followed by a normal Hunsdiecker reaction of the salt with halogen. The relative insensitivity of the technique to water by comparison with the Hunsdiecker reaction of a silver salt is a consequence of the solubility of the mercury salts in the reaction medium (CCl_4). The synthetic applicability of the method is thus comparable with that of the Hunsdiecker reaction, with the additional limitation that those acids which fail to form mercury salts under the reaction conditions or which give insoluble salts cannot successfully be degraded.

Some time ago, Cristol and Firth reported the degradation of carboxylic acids to alkyl bromides using bromine and mercuric oxide.[2] The technique had as an advantage over the analogous Hunsdiecker reaction of silver carboxylates the avoidance of having to prepare the pure dry silver salts, which is often difficult owing to their thermal instability. Furthermore, there was no need to maintain scrupulously anhydrous reaction conditions; indeed, water is one of the reaction products (eq 1)

$$2Br_2 + 2RCO_2H + HgO \longrightarrow 2RBr + H_2O + HgBr_2 + 2CO_2 \quad (1)$$

Since this publication, scattered reports of the use of the reaction have appeared.[3-6] Davis and his coworkers showed[7] that CO_2 was evolved on treatment of a wide variety of acids with bromine and mercury oxide, and noted that although a very limited number of other metal oxides could replace mercury oxide in the reaction, the yields of CO_2 using these other oxides were consistently poor.

Concerning the mechanism of the reaction, Cristol and Firth proposed[2] that the function of the mercuric oxide was to oxidize bromine to a positive halogen intermediate, which then reacted with the carboxylic acid to yield an acyl hypobromite. Jennings and Ziebarth[8] have formulated this sequence as eq 2 and 3.

$$HgO + 2Br_2 \longrightarrow HgBr_2 + Br_2O \quad (2)$$

$$Br_2O + RCO_2H \longrightarrow RCO_2Br + HOBr \quad (3)$$

The proposed acyl hypobromite then decomposes to alkyl bromide by the decarboxylation sequence (eq 4–6) established for the Hunsdiecker reaction.[9-11]

$$RCO_2Br \longrightarrow RCO_2\cdot + Br\cdot \quad (4)$$

$$RCO_2\cdot \longrightarrow R\cdot + CO_2 \quad (5)$$

$$R\cdot + RCO_2Br \longrightarrow RBr + RCO_2\cdot \quad (6)$$

In this proposed sequence the intermediacy of the alkyl radical R· has been established with some cer-

(1) Presented at the 162nd National Meeting of the American Chemical Society, Washington, D. C., Sept 1971, Abstract ORGN 020.

(2) S. J. Cristol and W. C. Firth, *J. Org. Chem.*, **26**, 280 (1961).

(3) F. W. Baker, H. D. Holtz, and L. M. Stock, *ibid.*, **28**, 514 (1963).

(4) J. S. Meek and D. T. Osuga, *Org. Syn.*, **43**, 9 (1963).

(5) J. W. Wilt and J. A. Lundquist, *J. Org. Chem.*, **29**, 921 (1964).

(6) D. I. Davies and P. Mason, *J. Chem. Soc. C*, 288 (1971).

(7) J. A. Davis, J. Herynk, S. Carroll, J. Bunds, and D. Johnson, *J. Org. Chem.*, **30**, 415 (1965).

(8) P. W. Jennings and T. D. Ziebarth, *ibid.*, **34**, 3216 (1969).

(9) C. V. Wilson, *Org. React.*, **9**, 332 (1957).

(10) R. G. Johnson and R. K. Ingham, *Chem. Rev.*, **56**, 219 (1956).

(11) D. D. Tanner and N. J. Bunce in "The Chemistry of the Carbonyl Halides," S. Patai, Ed., Wiley-Interscience, New York, N. Y., to be published.

tainty. Cristol and his coworkers[2,12,13] showed that the ratio of exo and endo bromides from the degradation of an exo and endo pair of norbornane-2-carboxylic acids was the same whichever isomeric acid was used. Furthermore, the ratio was the same as that observed in the degradation of the silver salts of the same acids by the Hunsdiecker reaction,[14] in which the involvement of R· is well established.[9-11] It has also been shown[3] that in the degradation of bicyclo[2.2.2]-octane-1-carboxylic acid in carbon tetrachloride, the expected bromide was accompanied by the typical free radical by-product 1-chlorobicyclo[2.2.2]octane.

The purpose of the present study was to attempt to secure more evidence for the mechanism of the reaction for the steps in between the starting carboxylic acid and the formation of the penultimate product, the radical R·. Additional interest in the question was raised by observations[2,3,6,13] that iodine may replace bromine in the mercuric oxide–halogen reaction. If the sequence of eq 2–6 were being followed, this would demand the intermediacy of iodine monoxide, which has hitherto never been prepared. It was hoped that a study of the mechanism of the mercury oxide–halogen degradation might shed some light on the possible existence of the unknown iodine monoxide.

Results and Discussion

The first objective was to obtain evidence for intermediacy of the acyl hypohalite. This was achieved by trapping the hypohalite intermediate with an olefin; the interaction of acetic acid, mercury oxide, and iodine in the presence of cyclohexene afforded an excellent yield of 2-iodocyclohexyl acetate, the cyclohexene adduct of acetyl hypoiodite.[15] The reported isolation of iodolactones from two 2-norbornene-*endo*-5-carboxylic acids using mercury oxide and iodine[17] may likewise be viewed as intramolecular entrapment of an intermediate acyl hypoiodite.

Possible Routes to the Acyl Hypohalite.—Having placed the intermediacy of the acyl hypohalite on a reasonably secure foundation is good evidence in support of the partial reaction sequence 4–6 for the production of the alkyl halide, since this same intermediate is known to participate in the Hunsdiecker reaction.[9-11] However, this does not *a priori* prove the correctness of the complete reaction sequence 2–6. It was the purpose of this research to consider alternative possible reaction mechanisms, since, in any reaction in which three reactants are involved, it is likely that two of them combine before reaction with the third. Reasonable routes to the acyl hypohalite for the three possible combinations are shown in mechanisms A, B, and C.

$$\text{Mechanism A:}\quad RCO_2H + X_2 \rightleftharpoons RCO_2X + HX \qquad (7)$$

$$2HX + HgO \longrightarrow H_2O + HgX_2 \qquad (8)$$

$$\text{Mechanism B:}\quad HgO + 2X_2 \longrightarrow X_2O + HgX_2 \qquad (2)$$

$$X_2O + 2RCO_2H \longrightarrow 2RCO_2X + H_2O \qquad (9)$$

$$\text{Mechanism C:}\quad HgO + 2RCO_2H \longrightarrow (RCO_2)_2Hg + H_2O \qquad (10)$$

$$(RCO_2)_2Hg + 2X_2 \longrightarrow HgX_2 + 2RCO_2X \qquad (11)$$

There seems to be little evidence in support of mechanism A, in which the mercuric oxide serves simply to remove the HX formed in equilibrium 7. Equilibria of this type are known to be very unfavorable, positive halogen compounds of all kinds being rapidly destroyed by the halogen acids.[18-20] It would thus seen unlikely that so weak a base as mercuric oxide would be an efficient scavenger for mere traces of the halogen acid, and there would also seem to be no reason why other metal oxides could not replace mercuric oxide in this capacity; yet no other is as effective.[7] There is additional evidence pointing to the unfavorability of equilibria of type 7: acyl hypohalites are known to be particularly reactive in electrophilic aromatic substitution, more so than the elemental halogens;[21-24] yet solutions of chlorine and of bromine in acetic acid both halogenate exclusively by way of the elemental halogen.[25,26] This indicates that the concentration of the acetyl hypohalite is such solutions must be vanishingly small, and, on the basis of the above arguments, mechanism A was rejected from further consideration.

To help choose between mechanisms B and C, a series of experiments was carried out on the degradation of valeric, isobutyric, pivalic, and phenylacetic acids. The products of the degradation of the acids with mercury oxide and both bromine and iodine were studied, and the results were compared with the analogous degradations of the silver and the mercuric salts with the same halogens. The results of the study are summarized in Table I.

The case in support of mechanism B is the observation by Jennings and Ziebarth that bromine monoxide degrades valeric acid to 1-bromobutane, albeit in a yield inferior to that obtained in the mercury oxide–bromine reaction.[8] In mechanism B the original proposal has been amended by replacing eq 3 by eq 9; this takes account of the fact that more than 0.5 mol of alkyl bromide may be formed per mole of bromine. Several factors suggest that this mechanism is not being followed, however. First, since bromine monoxide is thermally very unstable, it might be expected that the reaction would be more successful at room temperature than at reflux, but such is not the case.

(12) S. J. Cristol, J. R. Douglass, W. C. Firth, and R. E. Krall, *J. Org. Chem.*, **27**, 2711 (1962).

(13) S. J. Cristol, L. K. Gaston, and T. Tiedeman, *ibid.*, **29**, 1279 (1964).

(14) Since the exo/endo ratio of bromides is also markedly dependent on the chain transfer reagent[13] this observation also constitutes indirect evidence for the participation of the acyl hypobromite as an intermediate.

(15) It could be argued that the formation of 2-iodocyclohexyl acetate does not demand the intermediacy of acetyl hypoiodite in this reaction, since the mercuration of cyclohexene is an alternative possibility.[16]

$$HgO + 2CH_3CO_2H \longrightarrow H_2O + (CH_3CO_2)_2Hg$$

$$(CH_3CO_2)_2Hg + C_6H_{10} \longrightarrow CH_3CO_2C_6H_{10}HgOCOCH_3$$

$$CH_3CO_2C_6H_{10}HgOCOCH_3 + I_2 \longrightarrow CH_3CO_2C_6H_{10}I + CH_3CO_2HgI$$

Even if this were the case, the substance of the proposal presented below for the degradation mechanism would not be altered, because this sequence of reactions also involves the mercuric carboxylate as a necessary intermediate.

(16) J. Chatt, *Chem. Rev.*, **48**, 7 (1951).

(17) A. J. Solo and B. Singh, *J. Org. Chem.*, **32**, 567 (1967).

(18) N. J. Bunce and D. D. Tanner, *J. Amer. Chem. Soc.*, **91**, 6096 (1969), and references cited therein.

(19) D. D. Tanner and M. W. Mosher, *Can. J. Chem.*, **47**, 715 (1969).

(20) C. Walling and B. B. Jacknow, *J. Amer. Chem. Soc.*, **82**, 6108 (1960).

(21) P. B. D. de la Mare and J. H. Ridd, "Aromatic Substitution, Nitration and Halogenation," Butterworths, London, 1959, Chapters 8–10.

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(23) Y. Ogata and K. Nakajima, *Tetrahedron*, **20**, 43, 2751 (1964).

(24) N. J. Bunce and L. O. Urban, *Can. J. Chem.*, **49**, 821 (1971).

(25) P. W. Robertson, *J. Chem. Soc.*, 1267 (1954).

(26) P. B. D. de la Mare and M. Hassan, *J. Chem. Soc.*, 1519 (1958).

TABLE I

COMPARISON OF SEVERAL METHODS OF DEGRADATION OF CARBOXYLIC ACIDS TO ALKYL HALIDES

Method[a]	X = Br, reflux: RBr, %	X = Br, reflux: RCO_2R, %	X = Br, 25°[b]: RBr, %	X = Br, 25°[b]: RCO_2R, %	X = I, reflux: RI, %	X = I, reflux: RCO_2R, %
			Valeric Acid[c]			
HgO/X_2	63	None	21	None	36	35
Hg^{2+} salt/X_2	81	None	61	None	64	21
Ag^+ salt/X_2[d]	85	None	73	None	67	33
X_2O[e]	14	None				
			Isobutyric Acid[c]			
HgO/X_2	47	None	20	None	1[e]	15
Hg^{2+} salt/X_2	63	None	56	None	<1[e]	30
Ag^+ salt/X_2[d]	75	4	77	<1	<1[e]	80
			Pivalic Acid[e]			
HgO/X_2	<1[c]	33[f]				
Hg^{2+} salt/X_2	<1[c]	18[f]				
Ag^+ salt/X_2[d]	<1[c]	25[f]				
X_2O	13[c]	None[f]				
			Phenylacetic Acid[f]			
HgO/X_2	None	28	<1	4	None	26
Basic Hg^{2+} salt/X_2	4	7	2	2		
Normal Hg^{2+} salt/X_2	34	18	40	None	16	63
Ag^+ salt/X_2[d]	58	21	26	2	6	73
X_2O[e]	7	None				

[a] Duplicate reactions on a 2–4 mmol scale in 10 ml of CCl_4 as solvent unless noted otherwise. [b] 25° implies room temperature; this was 25 ± 3°. [c] Products analyzed by vpc. [d] All data on silver salts from ref 27. [e] Solvent was Freon 113. [f] Analyzed by nmr.

Second, analysis of the by-products of the reaction shows that in addition to alkyl halides, the symmetrical esters RCO_2R are frequently formed. We have previously shown, in silver salt–halogen systems, that esters arise by a route involving the metal salt,[27] and it is hard to envision a pathway to these esters that involves bromine monoxide rather than the metal salt.

The strongest evidence against mechanism B is the observation that, whereas pivalic and phenylacetic acids give no more than traces of alkyl bromide on degradation with bromine and mercury oxide, the bromine monoxide reaction by contrast does afford detectable amounts of these bromides. There would seem to be no reason why all the acids studied should not react similarly if Br_2O were an intermediate. Particularly compelling is the case of pivalic acid; this acid is virtually impossible to degrade to bromide by a metal salt reaction, because the product is destroyed as it is formed in a rapid reaction with further metal salt.[27] This acid yields only ester on degradation with mercury oxide and bromine; yet, with preformed Br_2O, *tert*-butyl bromide (but not *tert*-butyl pivalate) is produced. The only previous report of a successful degradation of pivalic acid was also using a salt-free route, halogen exchange between pivalic acid and *tert*-butyl hypoiodite,[28] a process analogous to exchange with Br_2O. Thus the mercury oxide–bromine reaction, which gives ester but no *tert*-butyl bromide, behaves like a metal salt reaction rather than a positive halogen exchange process.

These arguments lead to the conclusion that mechanism C probably represents the reaction pathway.

(27) N. J. Bunce and N. G. Murray, *Tetrahedron*, **27**, 5323 (1971).

(28) D. H. R. Barton, H. P. Faro, E. P. Serebryakov, and N. F. Woolsey, *J. Chem. Soc.*, 2438 (1965).

There is a strong similarity in product distribution between the mercury oxide–halogen technique and the normal Hunsdiecker reaction using either the mercuric or the silver salts of the acids (the difference between the silver and mercuric salts of phenylacetic acid is taken up below). In favor of this pathway is the ease of reaction at reflux at which temperature bromine monoxide must be very quickly decomposed, and the lack of necessity of postulating the presumably even more unstable iodine monoxide as an intermediate. In control experiments it was found that, whereas mercury oxide and bromine react in solution only very slowly, incompletely, and at low temperature to afford bromine monoxide, the reaction between the oxide and, say, valeric acid to give the mercuric salt is rapid, especially at reflux, and essentially quantitative. It was observed that both the red and the yellow forms of mercury oxide were almost equally effective in promoting salt formation, as also they were in the degradation reaction.[7]

Effects of Water.—A curious feature of the mercuric oxide–halogen degradation is its relative insensitivity to moisture. Cristol and Firth were unable to explain this useful insensitivity, but argued on other grounds against a mercury salt pathway, and raised the possibility that a positive halogen intermediate might be involved.[2] Since the arguments above seem to favor the mercury salt route, the two views must be reconciled. The answer appears to lie in the fact that, unlike their silver counterparts, aliphatic mercury carboxylates are freely soluble in hot carbon tetrachloride, the usual reaction medium. Thus the mercury salt and the halogen may interact homogeneously, and in a different phase from the CCl_4-insoluble water. For the CCl_4-insoluble silver salts, both the salt and any water present are found at the solvent interface, where reaction with the halogen must occur. In this case the acyl hypohalite is very susceptible to attack by water as it is being formed. The arguments are illustrated for the valeric acid system in Table II.

TABLE II

INFLUENCE OF WATER ON THE DEGRADATION OF VALERIC ACID AND ITS SALTS TO 1-BROMOBUTANE

	RBr from HgO/Br_2, %	RBr from Hg^{2+} salt/Br_2, %	RBr from Ag^+ salt/Br_2, %
		CCl_4 at Reflux	
Dry	63	81	85
Wet[a]	61	60	17
		CCl_4 at 25°	
Dry	21	61	73
Wet[a]	18	17	4
		CH_3CN at Reflux	
Dry	14	42	39
Wet[a]	11	8	2

[a] Added water was in the amount of 0.1 ml (6 mmol) in 10 ml of dry solvent. The reactions were all on a scale of approximately 2 mmol of valerate, and were carried out in duplicate.

From Table II the notable features are (i) the similarity of behavior of the mercury salt and the silver salt in dry solvents; (ii) the similarity between the mercury salt and the mercury oxide system in wet

solvents; and (iii) the insensitivity of the mercury oxide system to added water. These may be explained as follows. In carbon tetrachloride at reflux neither mercury system is strongly influenced by water because the salt is soluble. At room temperature the acyl hypohalite presumably decomposes more slowly[24,29] and so in a wet solvent there is more chance for hydrolysis to occur. Thus the mercury oxide technique, in which water is a by-product, is at a disadvantage at room temperature even in the absence of added water. In acetonitrile, however, all three methods are strongly adversely affected by water because the acyl hypobromite and the water are present in a single phase; once again the mercury oxide method is less successful because of the water formed as a by-product.

Successful Degradation by HgO–Br_2 Correlated with Salt Formation.—If mechanism C indeed represents the reaction pathway, there must exist a parallel between those acids which give mercury salts (preferably soluble ones) under the reaction conditions and those that degrade successfully to alkyl halides. This question has been examined for a number of carboxylic acids of different structure with the results summarized in Table III.

TABLE III

CORRELATION OF BROMIDE FORMATION FROM RCO_2H–HgO–Br_2 WITH THE PRODUCT OF THE ACTION OF MERCURY OXIDE ON THE ACID

Acid	RBr, %	Hg^{2+} Salt Type[a]	Hg^{2+} Salt Solubility[b]
Valeric	69[c]	Normal	Soluble
Heptanoic	38[d]	Normal	Soluble
Nonanoic	70[d]	Normal	Soluble
Isodecanoic	42[d]	Normal	Soluble
Isobutyric	47[c]	Normal	Soluble
2-Ethylhexanoic	53[d]	Normal	Soluble
Pivalic	<1[c]	Normal	Soluble
Phenylacetic	<1[e]	Basic	Insoluble
Benzilic	79[d,f]	Normal	Soluble
		Basic	Insoluble
Benzoic	14[c]	Basic	Insoluble
p-Toluic	11[d]	?	Insoluble
p-Nitrobenzoic	42[d]	?	Insoluble
o-Nitrobenzoic	58[d]	Normal[g]	Insoluble
p-Chlorobenzoic	<1[c]	?	Insoluble
3,5-Dinitrobenzoic	None	No reaction	

[a] Normal $(RCO_2)_2Hg$; basic $(RCO_2)_2Hg \cdot HgO$. [b] In CCl_4. [c] Estimated by vpc. [d] Isolated material. [e] Estimated by nmr. [f] Product was benzophenone. [g] Probably normal; see Experimental Section.

From Table III may be noted the strong correlation between the acids that form soluble salts and those that degrade successfully. In general the most successful reactions were observed where the carboxyl group of the acid was bonded to aliphatic carbon. The only exceptions in this category were pivalic acid, discussed above, and phenylacetic acid, which forms a very insoluble basic salt. All the other acids in this group form normal salts, whose compositions were confirmed by elemental analysis. In the case of phenylacetic acid the normal salt was prepared by an alternative route, and was found to behave like the silver salt (Table I). However, the mercury oxide–halogen technique paralleled the behavior of the basic salt, which is formed under these conditions.

In the aromatic series the decarboxylation reaction was less generally successful, and correspondingly, insoluble mercury salts were usually formed. Indeed, because of the limited solubility of acids, salts, and mercury oxide in the reaction medium, it was difficult to isolate pure products from these acid–base reactions, and only one system, benzoic acid, was examined in detail. It was found that mercury oxide and benzoic acid give a basic salt upon refluxing in carbon tetrachloride. This material, $(PhCO_2)_2Hg \cdot HgO$, is formed over a wide range of initial benzoic acid–mercury oxide ratios when benzoic acid is in excess, and has a definite composition and melting point. Treatment of this basic salt with acetone, however, leads to extraction of the normal salt $(PhCO_2)_2Hg$ which may be recovered by filtration and removal of the acetone. This experience in the benzoic acid system made it impractical to attempt to separate the insoluble oxide–acid–mercury salt mixtures in the other aromatic series by extraction with solvents, for fear that the composition of these mixtures might be changed as a result. For most of the substituted benzoates it was ascertained simply that mercury-containing organic material had been formed. Interrelations between the mercury(II) benzoates are given in the Experimental Section.

Conclusions and Synthetic Considerations.—Comparison of the product distributions from the degradation of several acids by four methods (HgO–RCO_2H–Br_2; RCO_2Ag–Br_2; $(RCO_2)_2Hg$–Br_2; RCO_2H–Br_2O) and correlation of the success of the first of these with formation of mercuric salts under the same conditions indicate that the reaction pathway involves the formation of a mercury salt of the acid. This is then converted to alkyl halide and/or ester by the route established for the Hunsdiecker and Simonini reactions. From this mechanism the following predictions may be made as to successful synthetic conditions for other systems. (1) The acid should form a mercury salt under the reaction conditions, and this should be soluble in the reaction medium. (2) A water-immiscible solvent should be used. (3) An elevated temperature favors a higher yield of halide. (4) Limitations on the applicability of the Hunsdiecker reaction of the silver or mercury salts apply also to the mercuric oxide technique. Thus tertiary (other than bridgehead)[3] acids do not degrade to halide, and the use of iodine as halogen frequently leads to ester RCO_2R as the major reaction product.

Although requirement 1 for soluble salt formation excludes many, especially aromatic acids from successful use of the technique, for most aliphatic acids the simplicity of the method and avoidance of separately preparing the metal salt makes it an attractive alternative to the Hunsdiecker reaction. A further point is the ease of recovery of mercuric oxide from the spent mercury residues,[30] which could be an important cost factor in large scale use of the method. It should be noted, however, that the yields of halides are usually smaller than using the silver salt method (compare

(29) W. Bockemüller and F. W. Hoffmann, *Justus Liebigs Ann. Chem.*, **519**, 165 (1935).

(30) G. H. Cady, *Inorg. Syn.*, **5**, 156 (1957).

Table III with published[10] data for the Hunsdiecker reaction).[30a]

Experimental Section

Solvents were reagent grade materials and were dried using activated molecular sieves. Red and yellow mercuric oxide were obtained from British Drug Houses Ltd.; the organic acids were purchased from the same source or from Aldrich Chemicals Inc. Metal salts were prepared as described below, and were dried at 65° for several days prior to use. Microanalyses were performed by Mr. H. S. McKinnon of this department.

Estimation of products formed was carried out by nmr or vpc after adding a weighed quantity of a suitable standard substance to the reaction mixture. Reactions were carried out in duplicate for these purposes, and three independent analyses were carried out for each reaction mixture. The instruments used were a Varian Associates A-60A nmr, and a Varian Aerograph Model A90-P3 vapor phase chromatograph. Infrared spectra were measured on a Beckman IR-5A instrument.

Trapping of Acetyl Hypoiodite with Cyclohexene.—To a mixture of red mercuric oxide (2.0 g, 9 mmol) and cyclohexene (2.0 ml, 16 mmol) in glacial acetic acid (20 ml) was added iodine (2.0 g, 8 mmol). The mixture was stirred at room temperature for 0.5 hr, at which time the color of iodine was discharged. A control reaction in which the mercuric oxide was omitted was unreactive. After removal of mercuric iodide by filtration, the reaction mixture was poured into water (150 ml) and extracted with chloroform (four 25-ml portions). The organic phase was washed with sodium bicarbonate and with water and dried. The solvent was evaporated to leave a pale yellow oily residue (2.0 g) of 2-iodocyclohexyl acetate: ir ν_{max} 1735 cm^{-1} (ester); nmr (CCl_4) τ 4.9–5.5 (1 H, complex multiplet, >CHOAc), 5.7–6.2 (1 H, complex multiplet, >CHI), 8.0 (3 H, singlet, CH_3CO–), 7.5–9.0 (8 H, complex multiplet, four $>CH_2$ groups). A positive test for iodine was obtained.

Comparative Degradation of Acids by Different Reagents (Table I).—The following procedures are representative.

A. Valeric Acid with Iodine and Mercuric Oxide.—A mixture of red mercuric oxide (2.0 g, 9 mmol), valeric acid (0.418 g, 4.10 mmol), and carbon tetrachloride (12 ml) was heated to reflux, and iodine (0.732 g, 2.89 mmol) was added. Heating continued for 0.5 hr by which time the color of iodine was discharged. 1-Bromobutane (1.03 mmol) was added to the reaction mixture for analysis by vpc (10% SE-30 on acid-washed Chromosorb W, 90°). 1-Iodobutane (1.46 mmol) and *n*-butyl valerate (0.72 mmol) were formed.

B. Mercury Phenylacetate with Bromine at 25°.—To a mixture of mercuric phenylacetate (0.694 g, 1.47 mmol) and carbon tetrachloride (10 ml) was added 1.0 ml of a 2.38 *M* solution of bromine in carbon tetrachloride. The mixture was stirred for 2.5 hr, and then 1.0 ml of a 1.19 *M* solution of benzyl chloride in carbon tetrachloride was added. The mixture was evaporated down and the residue was analyzed by nmr. Comparison of the areas of the resonances due to $PhCH_2Cl$ (τ 5.6) with $PhCH_2Br$ (τ 5.7) and $PhCH_2CO_2CH_2Ph$ (τ 5.0 and 6.5) indicated that these compounds were formed to the extent of 0.98 and <0.01 mmol, respectively.

C. Pivalic Acid with Bromine Monoxide.—To a well-stirred mixture of bromine (5 ml) in dry Freon 113 (100 ml) cooled to 5° was added mercuric oxide (25 g) in 5-g portions at 10-min intervals. After a total reaction time of 1 hr, analysis of aliquots of the mixture[30] showed it to be 0.90 *M* in Br_2 and 0.11 *M* in Br_2O. A 15-ml aliquot of the Br_2–Br_2O solution was added to a mixture of pivalic acid (0.111 g, 1.09 mmol) and dry Freon 113 at reflux, and heat was supplied for 10 min. After the addition of 0.138 g (1.0 mmol) of 1-bromobutane, vpc analysis (SE-30, 55°) indicated that 0.14 mmol of *tert*-butyl bromide had been produced. Removal of the excess bromine and the solvent gave a residue (0.098 g) which on analysis by nmr was found to consist of pivalic acid [τ −1.8, CO_2H, and 8.8, $(CH_3)_3C$] and to be lacking in *tert*-butyl pivalate (τ 8.6 and 8.9).

Influence of Water on the Degradation of Valerate Derivatives (Table II).—The following procedure is typical. To a mixture of mercuric valerate (0.669 g, 1.66 mmol) in dry acetonitrile to which had been added 1% v/v water (10 ml) was added bromine (2.85 mmol). After heating to reflux for 0.5 hr, isoamyl bromide (1.79 mmol) was added to the cooled solution as a vpc standard. Vpc analysis (SE-30, 90°) indicated that 0.23 mmol of 1-bromobutane had been formed.

Small-Scale Degradations of Carboxylic Acids (Table III).—The following procedures are typical.

A. Heptanoic Acid.—A mixture of heptanoic acid (5.0 g, 38 mmol), mercuric oxide (11.0 g, 51 mmol), and CCl_4 (70 ml) was heated to reflux, and a solution of bromine (6.0 g, 37 mmol) in CCl_4 (10 ml) was added. After 15 min at reflux the mixture was filtered and the filtrate was washed with dilute sodium hydroxide and water, and dried. Removal of the solvent afforded 4.6 g of crude product, an oil, which was distilled to give 1-bromohexane (2.2 g, 38%), bp 154–157° (lit.[31] 156°).

B. *o*-Nitrobenzoic Acid.—A mixture of *o*-nitrobenzoic acid (1.0 g, 6 mmol), yellow mercury oxide (2.0 g, 9 mmol), and CCl_4 (20 ml) was heated to reflux, and bromine (1.0 g, 6.2 mmol) was added. After 3 hr at reflux, the cooled solution was filtered, washed, and evaporated as above to give a residue (0.70 g, 58%) of crude *o*-nitrobromobenzene which solidified on standing, mp 33–36°. Recrystallization from ethanol gave the pure product, mp 39–41° (lit.[31] 43°), whose ir spectrum was consistent with the assigned structure.

Preparation of Mercury Salts.—Interaction of the carboxylic acids and mercuric oxide was studied at reflux in CCl_4. The products of the reactions were in many cases known compounds, but were subjected to elemental analysis to confirm their constitutions.

Mercuric Valerate.—A mixture of yellow mercuric oxide (15 g, 69 mmol) and valeric acid (14 g, 138 mmol) was heated to reflux in CCl_4 (200 ml) for 2 hr, with the water formed in the reaction being removed by azeotropic distillation with CCl_4. The hot solution was filtered [when mercuric oxide (1.9 g) was recovered] and allowed to cool, when mercuric valerate (23.6 g, 85%), mp 93–95°, was obtained. *Anal.* Calcd for $C_{10}H_{18}O_4Hg$: C, 29.81; H, 4.47. Found: C, 29.81; H, 4.54.

Similar procedures were used to prepare the following mercuric carboxylates.

Mercuric isobutyrate, mp 103–105°. *Anal.* Calcd for $C_8H_{14}O_4Hg$: C, 25.60 H, 3.73. Found: C, 25.67; H, 3.89.

Mercuric pivalate, mp 234–236°. *Anal.* Calcd for $C_{10}H_{18}O_4Hg$: C, 29.81, H. 4.47. Found: C, 29.75; H, 4.65.

Mercuric heptanoate, mp 106–108°. *Anal.* Calcd for $C_{14}H_{26}O_4Hg$: C, 36.6; H, 5.66. Found: C, 36.69; H, 5.75.

Mercuric 2-ethylhexanoate, mp 66–71°. *Anal.* Calcd for $C_{16}H_{30}O_4Hg$: C, 39.45; H, 6.16. Found: C, 39.77; H, 6.43.

Mercuric nonanoate, mp 106–108°. *Anal.* Calcd for $C_{18}H_{34}O_4Hg$: C, 41.95; H, 6.60. Found: C, 42.57; H, 6.69.

Mercuric isodecanoate (oil) and mercuric benzilate, mp 66–70° dec, could not be freed completely from the parent acid, and were not obtained analytically pure. In the case of the reaction of benzilic acid with mercuric oxide, the insoluble basic salt was also obtained, mp 188–195° dec. *Anal.* Calcd for $C_{28}H_{22}O_7Hg_2$: C, 38.5; H, 2.53. Found: C, 38.87; H, 2.49.

A similar preparative procedure applied to other acids gave basic salts as follows. These compounds were generally very insoluble, and gave rather less satisfactory elemental analyses.

Basic mercury phenylacetate, $(PhCH_2CO_2)_2Hg \cdot HgO$, mp 200–205°. *Anal.* Calcd for $C_{16}H_{14}O_5Hg_2$: C, 27.9; H, 2.03. Found: C, 29.72, 30.01; H, 1.82, 1.85. The normal salt, $(PhCH_2CO_2)_2Hg$, mp 115–118°, was prepared alternatively by the action of a solution of mercuric nitrate in nitric acid on an aqueous solution of sodium phenylacetate which had been made neutral to litmus using dilute nitric acid. *Anal.* Calcd for $C_{16}H_{14}O_4Hg$: C, 40.7; H, 2.97. Found: C, 40.81; H, 2.88.

Basic mercuric benzoate $(PhCO_2)_2Hg \cdot HgO$, mp 171–172°. *Anal.* Calcd for $C_{14}H_{10}O_5Hg_2$: C, 25.5; H, 1.52. Found:

(30a) NOTE ADDED IN PROOF.—The results quoted in the tables were all obtained using equimolar amounts of Br_2 and RCO_2H. Improved yields of alkyl bromides may be obtained by increasing the mole ratio of Br_2 to 1.1 or 1.2; this probably offsets hydrolysis of RCO_2Br by the by-product water. For larger scale preparations the technique of J. Cason and D. M. Walba [*J. Org. Chem.*, **37**, 669 (1972)] in which the water formed is removed continuously by azeotropic distillation with solvent, would probably be most advantageous. These authors have come to similar conclusions regarding the probable mechanism of the RCO_2H–HgO–Br_2 reaction. The present author thanks Professor Cason for making available his results prior to publication.

(31) "Handbook of Chemistry and Physics," 49th ed, Chemical Rubber Co., Cleveland, Ohio, 1968.

C, 26.16; H, 1.54. (Another sample, Found: C, 24.24; H, 1.50.) Extraction of this material with acetone followed by filtration to remove mercuric oxide and evaporation of the solvent afforded the normal salt, $(PhCO_2)_2Hg$, mp 118–122°. *Anal.* Calcd for $C_{14}H_{10}O_4Hg$: C, 38.0; H, 2.26. Found: C, 39.07; H, 2.50. Another sample had mp 120–129°. Found: C, 38.38; H, 2.39. When aqueous acetone was used as the extraction agent, the product was mainly mercuric benzoate monohydrate, mp 140–149°. *Anal.* Calcd for $C_{14}H_{12}O_5Hg$: C, 36.4; H, 2.60. Found: C, 36.26; H, 2.21.

Mercuric benzoate monohydrate was formed by interaction of aqueous mercuric nitrate and sodium benzoate solutions, mp 161–163° (lit.[31] 165°). *Anal.* Calcd for $C_{14}H_{12}O_5Hg$: C, 36.4; H, 2.60. Found: C, 36.52; H, 2.21. An attempt to obtain the anhydrous salt by azeotropic distillation of the water with CCl_4 was unsuccessful.

Hydrolysis of Hydrated Mercuric Benzoate.—Suspension of hydrated mercuric benzoate (3.0 g) in boiling water (100 ml) for 1 hr gave an off-white solid (2.1 g, mp >360°) which analyzed for a basic mercuric salt $(PhCO_2)_2Hg \cdot 2HgO$. *Anal.* Calcd for $C_{14}H_{10}O_6Hg_3$: C, 19.2; H, 1.14. Found: C, 18.87; H, 1.07.

Hydrolysis of Basic Mercuric Benzoate.—Suspension of $(PhCO_2)_2Hg \cdot HgO$ (1.0 g) in boiling water caused hydrolysis to occur. The orange product (0.7 g) analyzed for $(PhCO_2)_2Hg \cdot 3HgO$ (*Anal.* Calcd for $C_{14}H_{10}O_7Hg_4$: C, 15.34; H, 0.91. Found: C, 14.60; H, 0.89.) but was apparently a mixture of starting material and mercuric oxide, mp 170–172°, undepressed by admixture with starting material. On cooling the filtered reaction mixture a small quantity (0.08 g) of hydrated mercuric benzoate was obtained, mp 161–165°. (Found: C, 36.18; H, 2.27.)

Basic (?) Mercuric *o*-Nitrobenzoate.—Interaction of *o*-nitrobenzoic acid and mercuric oxide in either CCl_4 or $CHCl_3$ gave, in addition to unreacted *o*-nitrobenzoic acid in solution and mercury oxide at the bottom of the flask, a yellow powder in suspension. The solution was decanted and the yellow powder was removed by filtration, mp 195–197° dec. Analysis indicated the composition $3(ArCO_2)_2Hg \cdot HgO$, but it is unclear whether the substance is a compound of this composition or is the normal salt, contaminated with mercuric oxide. (*Anal.* Calcd for $C_{42}H_{24}N_6O_{25}Hg_4$: C, 27.8; H, 1.32; N, 4.62. Found: C, 28.24; H, 1.26; N, 4.61.)

Registry No.—Mercuric oxide, 21908-53-2; 2-iodocyclohexyl acetate, 32865-61-5; mercuric valerate, 26719-05-1; mercuric isobutyrate, 19348-33-5; mercuric pivalate, 32276-77-0; mercuric heptanoate, 26719-06-2; mercuric 2-ethylhexanoate, 13170-76-8; mercuric nonanoate, 28043-55-2; mercuric benzilate, 32865-67-1; mercuric benzilate basic salt, 32839-01-3; $(PhCH_2CO_2)_2Hg \cdot HgO$, 32839-02-4; $(PhCH_2CO_2)_2Hg$, 14085-69-9; $(PhCO_2)_2Hg \cdot HgO$, 32839-03-5; $(PhCO_2)_2Hg$, 583-15-3; mercuric benzoate monohydrate, 32839-04-6; $(PhCO_2)_2Hg \cdot 2HgO$, 32839-05-7; $3(ArCO_2)_2Hg \cdot HgO$ (Ar = *o*-$NO_2C_6H_4$), 32839-06-8.

Acknowledgment.—The author thanks the National Research Council of Canada for generous financial support of this work.

Notes

Reaction Pathway in the Modified Hunsdiecker Reaction

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Received August 6, 1971

During the period since Cristol and Firth[1] published a simplified modification of the Hunsdiecker reaction for synthesis of bromides from carboxylic acid silver salts, the modified procedure, which utilizes a free carboxylic acid and mercuric oxide, has been used to advantage in several published investigations. The specific conditions employed in the published procedures have been rather diverse, as have the yields. In the initial report,[1] among the reactions carried out in boiling carbon tetrachloride solution was synthesis of heptadecyl bromide in 90% yield (crude) from stearic acid. In contrast, the "Organic Syntheses" procedure,[2] appearing subsequently, reported about 50% yield of cyclopropyl bromide, with tetrachloroethane as solvent at a temperature of 30–35°. In a procedure similar to that originally reported,[1] except that the acid and bromine were added concurrently to a boiling slurry of mercuric oxide in carbon tetrachloride, about 50% yield was again realized for a small-ring bromide;[3] however, this same procedure applied to the half-ester of an open-chain dicarboxylic acid has given 90% yield of bromo ester.[4]

Since the literature provides little evidence concerning the mechanism of the modified Hunsdiecker reaction, or the best way in which to carry out the synthesis, we have investigated its application to myristic acid. Our considerable and varied experience[5] with the classical Hunsdiecker reaction suggested that most of the difficulties are likely to be encountered with a moderately high molecular weight aliphatic structure. To this end, there was examined a procedure for tridecyl bromide which was based on the original successful method,[1] with some modification in recognition of the "Organic Syntheses" procedure.[2] Subsequent investigations revealed that the most important modification was operation at 25–30° rather than in boiling carbon tetrachloride. In 15 runs by different people,[6] the highest yield was about 5% (*cf.* Table I, run 4).

(1) S. J. Cristol and W. C. Firth, Jr., *J. Org. Chem.*, **26**, 280 (1961).
(2) J. S. Meek and D. T. Osuga, *Org. Syn.*, **43**, 9 (1963).
(3) K. B. Wiberg and G. M. Lampmann, *J. Amer. Chem. Soc.*, **88**, 4432 (1966).
(4) John I. Crowley, Ph.D. Dissertation, University of California, Berkeley, 1971.
(5) See, *inter alia*, J. Cason and R. L. Way, *J. Org. Chem.*, **14**, 31 (1949); J. Cason and R. H. Mills, *J. Amer. Chem. Soc.*, **73**, 1354 (1951); J. Cason, M. J. Kalm, and R. H. Mills, *J. Org. Chem.*, **18**, 1670 (1953); J. Cason and M. J. Kalm *ibid.*, **19**, 1836 (1954).
(6) For several specific procedures, multiple runs were carried out by students in the advanced organic laboratory course at Berkeley. Of particular value was the work of Richard P. Fisher, Howard B. Gamper, Maria del Carmen Kutas, Ronald M. Rodehorst, and Thomas M. Yarnell.

TABLE I
TRIDECYL BROMIDE FORMED IN VARIOUS PROCEDURES FOR THE MODIFIED HUNSDIECKER REACTION

Run no.	Procedure[a]	Total time, hr:min	Temp, °C[b]	Yield, %
1	A	1:35	BP	89
2	A[c]	1:45	BP	88
3	A[d]	2	BP	68
4	A	4	25–35	3–5
5	A	24	25	30
6	P	2	BP	90
7	C	2	BP	89
8	C[e]	1:30	BP	70
9	C	24	25	39
10	B	2	<30	0
11	B	2	30–70	18–35
12	B[f]	2	30–70	71–75

[a] Procedures are those described in the Experimental Section. [b] BP = boiling temperature of CCl_4. [c] Procedure altered by adding solution of bromine and myristic acid to slurry of HgO in boiling CCl_4. [d] Procedure same in same equipment except double size of run. [e] Half of bromine added at room temperature, with no evidence of reaction; heated cautiously until onset of exothermic reaction, which was controlled by an ice bath. Final half of bromine added as in run 7. [f] Molar ratio of myristic acid doubled.

More recently, Jennings and Ziebarth[7] have proposed that the initial step in the modified Hunsdiecker reaction is generation of Br_2O which reacts with the carboxylic acid to give the acyl hypobromite, an intermediate in the classical Hunsdiecker reaction. The following stoichiometry was proposed.

$$HgO + 2Br_2 \longrightarrow HgBr_2 + [Br_2O]$$

$$[Br_2O] + RCO_2H \longrightarrow [RCO_2Br] + HOBr$$

$$[RCO_2Br] \longrightarrow RBr + CO_2$$

It may be noted that the ratio required by these equations is $HgO:2Br_2:RCO_2H$, which contrasts with other published procedures that have used approximately equimolar amounts of bromine and carboxylic acid,[1-4] with somewhat more than 0.5 molar equiv of mercuric oxide. This divergence in ratio might be inferred to suggest something about 50% yields that have been reported; however, this interpretation is quite inconsistent with the 90% yield of Cristol and Firth.[1] A procedure for tridecyl bromide based on the stoichiometry and conditions required by the Br_2O intermediate has been examined.[6] When the reaction was run at temperatures below 30° (Table I, run 10), in recognition of the statement[7] that "Br_2O decomposes slowly at temperatures above −50°," no yield of tridecyl bromide could be detected. When the reaction mixture from mercuric oxide and bromine was heated after, or during, addition of the carboxylic acid, modest yields could be secured (run 11). When the higher temperature was used and the ratio of carboxylic acid was *doubled, yields were much higher (run 12), even though based on carboxylic acid as limiting reagent.*

Since the above cited observations appear to eliminate significant participation of the mechanism involving Br_2O as an intermediate, we have investigated the possibility that the modified Hunsdiecker reaction is what the name implies—a Hunsdiecker reaction on the mercury salt rather than the silver salt of a carboxylic acid. This proves to be the case and we have established conditions which give excellent yields. Intermediacy of the mercury salt was originally rejected[1] on the grounds that (a) water formed in generation of the mercury salt from mercuric oxide would destroy the intermediate acyl hypobromite; (b) the Hunsdieckers[8] originally reported that the mercury salt is quite inferior to the silver salt for higher molecular weight bromides. Nevertheless, the present investigation shows that, if the reaction is carried out in boiling carbon tetrachloride, the yield is the same (about 90%), whether the preformed mercury salt or carboxylic acid and mercuric oxide are used (*cf.* Table I, runs 1, 7).

Examination of the Hunsdieckers' paper reveals that no experimental evidence is included in support of the statement that the mercury salt is inferior in their reaction, in the case of higher molecular weight bromides; however, it is probable (judging from experimental procedures which were described[8]) that the reactions were run without stirring and at temperatures below the boiling point of carbon tetrachloride. This type of procedure would give poor results for higher molecular weight mercury salts, on account of low solubility in the solvent. At room temperature, with mercuric myristate, there is no evolution of either carbon dioxide or heat when bromine is added, and only partial reaction occurs after 24 hr (Table I, runs 5, 9). Results were similar whether or not the mercury salt was preformed. This contrasts sharply with the violent reaction, difficult to control, when the preformed mercury salt is used in boiling carbon tetrachloride.

Failure of water to interfere significantly with the modified Hunsdiecker reaction is most reasonably ascribed to a faster reaction of the acyl hypobromite with radicals such as bromine atoms, in preference to water present in a maximum of stoichiometric amounts.[9] Water is indeed formed in the reaction; it is evident on the coils of the condenser. Furthermore, in boiling carbon tetrachloride, with no provision for removing water, about one-third of the runs gave yields of 75–80%, and, when the size of run was doubled, a yield of about 70% resulted (Table I, run 3). These observations suggest that retention of water in the two-phase condensate in the reflux condenser is of some importance in reducing the concentration of water in the reaction mixture. Consistently high yields result when water is removed by azeotropic distillation as the reaction is carried out in boiling carbon tetrachloride (Experimental Section, procedure P; Table I, run 6). There is some evidence (*e.g.*, run 8) that yields are lower if the first part of the reaction is carried out at temperatures below the boiling point of carbon tetrachloride; however, at room temperature

(7) P. W. Jennings and T. D. Ziebarth, *J. Org. Chem.*, **34**, 3216 (1969).

(8) H. Hunsdiecker and C. Hunsdiecker, *Ber.*, **75**, 291 (1942).

(9) An investigation of the modified Hunsdiecker reaction, carried out by Dr. N. J. Bunce, *J. Org. Chem.*, **36**, 664 (1972), came to our attention as a result of his presentation of this material at the Washington meeting of the American Chemical Society, Sept 1971. Communication between Dr. Bunce and us has revealed that our investigations are along quite different lines, but we have arrived at the same conclusions regarding the reaction pathway. His explanation of the failure of water to seriously interfere with the modified Hunsdiecker reaction is somewhat different from ours, but reasonably so, since his investigations concentrated on mercury salts which are relatively soluble in CCl_4, whereas we are concerned with the rather insoluble mercuric myristate.

preformed mercury salt gave only slightly better yield than did carboxylic acid and mercuric oxide (runs 5, 9).

Experimental Section[10]

Tridecyl Bromide. Procedure A.—A dry flask equipped with a mechanical stirrer and a large inner spiral condenser (cooling water inside spiral) protected by a drying tube was charged with a solution of 17.2 g (0.075 mol) of myristic acid in 200 ml of dried CCl_4 and 10.2 g (0.047 mol) of red HgO. After the stirred mixture had been heated to boiling, heat was greatly reduced and a solution of 15 g (0.094 mol) of bromine in 10 ml of CCl_4 was added during about 35 min, during which time a small amount of heat was required to maintain reflux. After completion of addition, heating under reflux with stirring was continued for 1 hr. Mercury salts were removed from the cooled reaction mixture by filtration with suction through a Filter-Aid mat. The clear filtrate was extracted with 50 ml of 5% aqueous NaOH, and the coagulated precipitate which formed[11] was removed from the two-phase solution by suction filtration. After the CCl_4 phase had been washed with water, the tridecyl bromide was recovered by fractional distillation, or the solution was diluted to a measured volume, and yield was determined by glpc, using a response factor determined on distilled product. In three runs, yields were determined by both distillation and glpc; in one of these, yields were the same, in the other two yields by distillation were somewhat higher. Typical yields from this procedure, and modifications of it, are included in Table I.

Procedure B utilized a ratio of reagents and conditions consistent with the Jennings and Ziebarth[7] mechanism. In a closed system protected by a drying tube was stirred a slurry of 41 g (0.19 mol) of red HgO in 100 ml of CCl_4 as there was added at room temperature during about 10 min a solution of 60 g (0.37 mol) of bromine. There was insignificant evolution of heat. After this mixture had been stirred for an additional 5 min, there was added during about 15 min a solution of 34.3 g (0.15 mol) of myristic acid in 150 ml of CCl_4, at a temperature below 30°. Stirring was continued for 1 hr at room temperature or higher (*cf.* Table I). Work-up was similar to that described for procedure A.

Procedure C utilized preformed mercuric myristate. A mixture of 10.2 g of red HgO, 17.2 g of myristic acid, and 350 ml of CCl_4 was stirred and heated to reflux under a 50-cm Vigreux column so that the azeotrope of CCl_4 and water slowly distilled. After water evolution was no longer evident (about 2.5 hr), heating was continued for an additional 1 hr. Bromine (15 g) was then added to the stirred slurry of mercury salt as in Procedure A, except that, at reflux, about 1 hr was required for addition in order to keep the vigorous reaction under control by cooling in an ice bath. Work-up was as in procedure A.

Procedure P (Preferred).—A mixture of 20.4 g of red HgO, 34.3 g of myristic acid, and 250 ml of CCl_4 was heated under a 50-cm Vigreux column, with stirring, such that rate of distillation was about one drop/sec. After 15 min of distillation in this manner, addition was begun of a solution of 30 g of bromine in 100 ml of CCl_4. Addition was completed during 70 min; during the last few minutes, a majority of the bromine seemed to distil out as added; prior to this, only small amounts of bromine distilled. After bromine addition had been completed, an additional 100 ml of CCl_4 was added during 40 min, while distillation was continued as before. The cooled reaction mixture was worked up as described for procedure A (*cf.* Table I, run 6).

Registry No.—Tridecyl bromide, 765-09-3.

(10) Reagents used for the investigation were technical CCl_4, dried by azeotropic distillation of water (omission of drying had no significant effect); A.R. bromine; A.R. red HgO; reagent grade of myristic acid containing a total of <2% homologous fatty acids (glpc of resultant tridecylbromide). Microanalyses were by the Analytical Division, Department of Chemistry, University of California, Berkeley. Gas chromatographic analyses were on a 5-ft silicone column in an Aerograph A-90P, with reference to a response factor for tridecyl bromide determined on a pure sample.

(11) The salt precipitated by the NaOH wash, which was formed in larger amount in runs giving a lower yield of bromide, did not have the physical characteristics of a soap, and various elementary analyses were in major disagreement with the values for sodium myristate. Our investigations have not revealed the identity of this salt, and we have not determined whether its precursor is an intermediate in the reaction pathway to the bromide.

Synthetic Applications of Ylides Derived from 1-Dimethylamino-1-oxothioniacycloalkane Fluoroborates[1]

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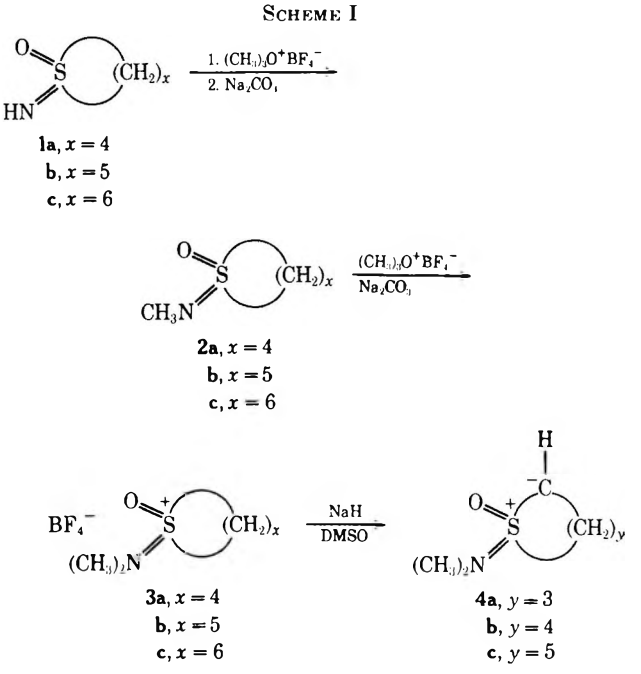
Received July 29, 1971

Several articles[2] from this laboratory have described some of the properties and uses of oxosulfonium ylides derived from salts of sulfoximines. The previous reports commented on the ease of handling, stability, ability to transfer alkyl groups larger than methyl, and the synthesis of optically active epoxides and cyclopropanes.

The present communication reports the transfer of alkyl groups functionalized with an ω-sulfinamide substituent. For this purpose the ylides **4a–c** were generated from a series of 1-dimethylamino-1-oxothioniacycloalkane fluoroborates (**3a–c**), Scheme I. The sulfoximines were prepared according to the earlier reports[2] from the sulfoxides and hydrazoic acid.[3] The sulfoximines were characterized by ir,[4] nmr, and elemental analysis of the hydrochloride salts.

SCHEME I



Reaction of the fluoroborates (**3a–c**) in dimethyl sulfoxide (DMSO) with sodium hydride at room temperature under nitrogen gave light yellow solutions of

(1) Part XXXVI in the series "Chemistry of Sulfoxides and Related Compounds." We gratefully acknowledge support by the National Science Foundation (GP 19623).

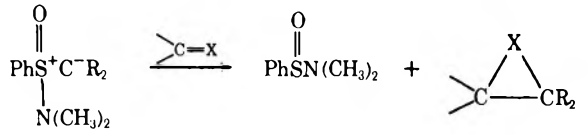
(2) (a) C. R. Johnson, E. R. Janiga, and M. Haake, *J. Amer. Chem. Soc.*, **90**, 3890 (1968); (b) C. R. Johnson and C. W. Schroeck, *ibid.*, **90**, 6852 (1968); (c) C. R. Johnson, R. F. Huxol, and E. R. Janiga, *ibid.*, **93**, 3771 (1971).

(3) (a) H. R. Bentley and J. K. Whitehead, *J. Chem. Soc.*, 2081 (1950); (b) J. K. Whitehead and H. R. Bentley, *ibid.*, 1572 (1952); (c) F. Misani, T. W. Fair, and L. Reimer, *J. Amer. Chem. Soc.*, **73**, 459 (1951).

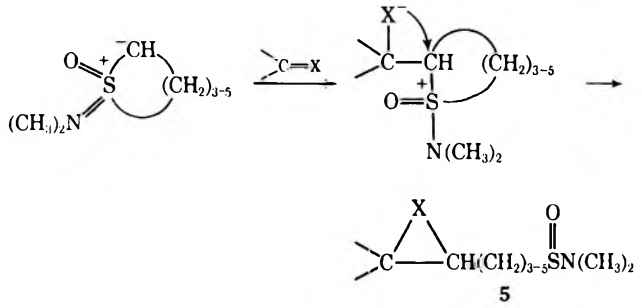
(4) The major absorption peaks agreed well with those found by N. Furukawa, K. Tsujihara, Y. Kawakatsu, and S. Oae, *Chem. Ind. (London)*, 266 (1969).

the ylides **4a–c**. Slow addition of a solution (DMSO) of an electrophilic reactant and stirring at ambient temperature for several hours completed the reaction.

In previous cases,[2] the reaction took the following course.

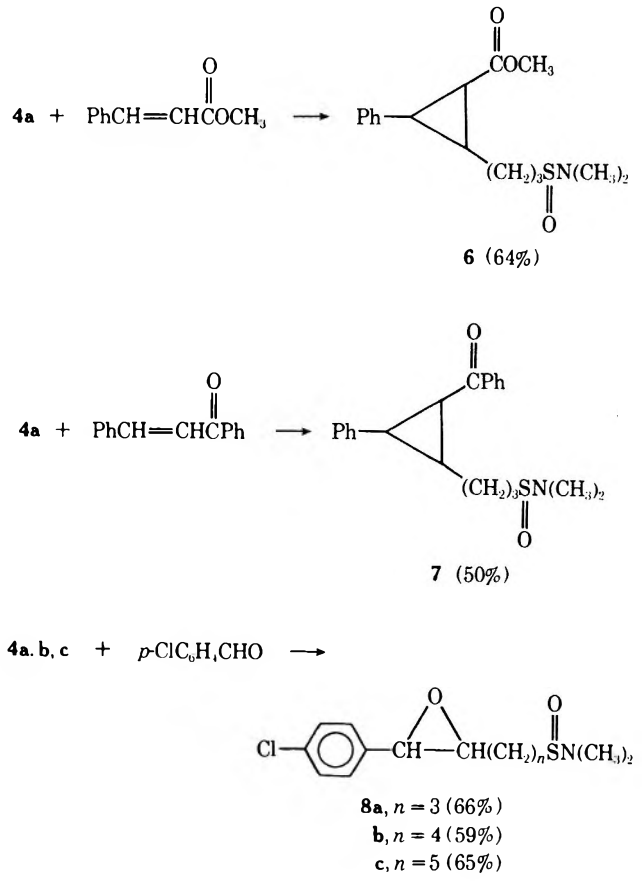


A cyclopropane or an epoxide was formed along with a sulfinamide. In the present case, both the small ring and the "by-product" are contained in the same molecule (**5**).



Thus, the reactions shown in Scheme II were completed (yield, per cent).

SCHEME II



In all cases the crude reaction products were viscous oils which were purified by elution chromatography on silica gel. A curious feature of the reaction of the ylides with *p*-chlorobenzaldehyde is the stereochemistry[5] of the epoxides: **8a** (100% trans), **8b** (80% trans), **8c** (66% trans). An investigation of models shows that ylide **4a** (five-membered ring) would allow facile formation of an erythro betaine, which would collapse to the trans epoxide. As the size of the alicyclic portion increases, the dimethylamino group would encounter increasing steric interference with the aromatic ring in the erythro betaine.

Experimental Section

Melting points were determined with a Thomas–Hoover capillary tube melting point apparatus and are uncorrected. The infrared spectra were measured on a Perkin-Elmer 137B Infracord and were standardized with the polystyrene band at 1601 cm^{-1}. Nuclear magnetic resonance spectra were obtained on a Varian Associates A-60A spectrometer employing tetramethylsilane as internal standard. Microanalyses were performed by Midwest Microlab, Inc., Indianapolis, Ind.

The cyclic dimethylaminooxosulfonium salts were prepared by the procedures outlined for open-chain compounds[2b,3] and were purified by recrystallization from methanol–ether.

1-(*N*,*N*,-Dimethylamino)-1-oxothioniacyclopentane fluoroborate (3a) was obtained in 76% yield: mp 78–79°; nmr (CD_3CN) δ 2.1–2.6 (m, 4), 3.15 (s, 6), 3.2–4.2 (m, 4).

Anal. Calcd for $C_6H_{14}BF_4NOS$: C, 30.66; H, 6.00. Found: C, 30.92; H, 5.93.

1-(*N*,*N*-Dimethylamino)-1-oxothioniacyclohexane fluoroborate (3b) was obtained in 37% yield: mp 129.5–130.5°; nmr (CD_3CN) δ 1.9–2.4 (m, 6), 3.1 (s, 6), 3.8–4.1 (m, 4).

Anal. Calcd for $C_7H_{16}BF_4NOS$: C, 33.76; H, 6.48. Found: C, 34.00; H, 6.63.

1-(*N*,*N*-Dimethylamino)-1-oxothioniacycloheptane fluoroborate (3c) was obtained in 61% yield: mp 102–103.5°; nmr (CD_3CN) δ 1.6–2.3 (m, 8), 3.1 (s, 6), 3.8–4.2 (m, 4).

Anal. Calcd for $C_8H_{18}BF_4NOS$: C, 36.52; H, 6.90. Found: C, 36.71; H, 7.09.

General Procedure.—Sodium hydride (1.25 equiv) dispersion in mineral oil in a round-bottomed side-armed flask was washed three times with dry pentane. The flask was immediately connected to a source of dry nitrogen and the fluoroborate salt (1 equiv) was added in one portion with stirring. Sufficient dry DMSO to prepare a 0.9–1.3 *M* solution of ylide was slowly introduced *via* syringe. After cessation of hydrogen evolution, the reaction was stirred for several more minutes. Then the substrate (1 equiv) was slowly introduced *via* syringe in DMSO or DMSO–THF solution and allowed to stir for 10–24 hr.

The work-up consisted of transferring the reaction mixture with water and ether to a separatory funnel and extraction of the aqueous phase with ether. The combined ether extracts were washed three times with water and once with saturated brine, and dried ($MgSO_4$). Filtration and concentration gave viscous oils, which were purified by chromatography on silica gel.

3-(2′-Carbomethoxy-3′-phenylcyclopropyl)-*N*,*N*-dimethylpropanesulfinimide (6) was obtained in 64% yield: nmr ($CDCl_3$) δ 1.3–2.7 (m, 9), 2.75 (s, 6), 3.75 (s, 3), 7.25 (m, 5), eluted with 4% methanol in methylene chloride.

Anal. Calcd for $C_{16}H_{23}NO_3S$: C, 62.11; H, 7.49. Found: C, 62.00; H, 7.65.

3-(2′-Benzoyl-3′-phenylcyclopropyl)-*N*,*N*-dimethylpropanesulfinimide (7) was obtained in 50% yield: nmr ($CDCl_3$) δ 1.3–2.2 (m, 6), 2.59 (s, 6), 2.65–3.2 (m, 3), 7.1–8.2 (m, 10), eluted with 2% methanol in ethyl acetate.

Anal. Calcd for $C_{21}H_{25}NO_2S$: C, 70.95; H, 7.09. Found: 70.57; H, 7.16. Molecular ion at *m/e* 355.

5-*p*-Chlorophenyl-4,5-epoxy-*N*,*N*-dimethylpentanesulfinamide (8a) was eluted with 5% methanol in ether: yield 66%; nmr ($CDCl_3$) δ 1.7–2.1 (m, 4), 2.6–3.1 (m, 3), 2.75 (s, 6), 3.61 (d, 1, J = 2 Hz), 7.2–7.5 (m, 4).

Anal. Calcd for $C_{13}H_{18}ClNOS$: C, 54.25; H, 6.30. Found: C, 54.43; H, 6.47.

6-*p*-Chlorophenyl-5,6-epoxy-*N*,*N*-dimethylhexanesulfinamide (8b) was obtained by elution with ethyl acetate and then with 1:1

(5) Calculated from the benzylic doublets in the nmr spectra. H. S. Gutowsky, M. Karplus, and R. M. Grant, *J. Chem. Phys.*, **31**, 1278 (1959); C. A. Reilly and J. D. Swalen, *ibid.*, **32**, 1378 (1960); C. A. Reilly and J. D. Swalen, *ibid.*, **34**, 980 (1961).

2-propanol–ethyl acetate: nmr ($CDCl_3$) δ 1.2–1.9 (m, 6), 2.74 (s, 6), 2.5–3.0 (m, 3), 3.6 (J = 2 Hz), 4.05 (d, 1, J = 4 Hz), 7.29 (m, 4).

Anal. Calcd for $C_{14}H_{20}ClNO_2S$: C, 55.71; H, 6.68. Found: C, 55.31; H, 6.83. Molecular ion at m/e 301.

7-*p*-Chlorophenyl-6,7-epoxy-*N*,*N*-dimethylheptanesulfinamide (8c).—The epoxide was prepared in 65% yield by the reaction of ylide **4c** and *p*-chlorobenzaldehyde. The oil was chromatographed on silica gel, developing with ethyl acetate. The infrared spectrum (neat) had peaks at 3050, 3920, 1490, 1450, 1175, 1065, 925, 828, and 778 cm^{-1}. The nmr ($CDCl_3$) had a multiplet at δ 7.28 (4 H, Ar **H**), a doublet at 4.03 (J = 4 Hz), and a doublet (J = 2 Hz) at 3.58 (combined area 1 H, Ar **CH** cis and trans), a three-proton multiplet at 3.1–2.6 (aliphatic –**CH** and CH_2S), a six-proton singlet at 2.73 [$N(CH_3)_2$], and at 1.8–1.1 [8 H, $-(CH_2)_4$] for the aliphatic chain.

Anal. Calcd for $C_{15}H_{22}ClNOS$: C, 57.04; H, 7.02. Found: C, 57.00; H, 7.24.

Registry No.—**3a**, 32846-71-2; **3b**, 32846-72-3; **3c**, 32846-73-4; **6**, 32846-69-8; **7**, 32846-70-1; **8a**, 32846-74-5; **8b**, 32846-75-6; *cis*-**8c**, 32846-76-7; *trans*-**8c**, 32958-92-2.

A New Synthesis of 3,4-(Difluoromethylenedioxy)benzaldehyde[1]

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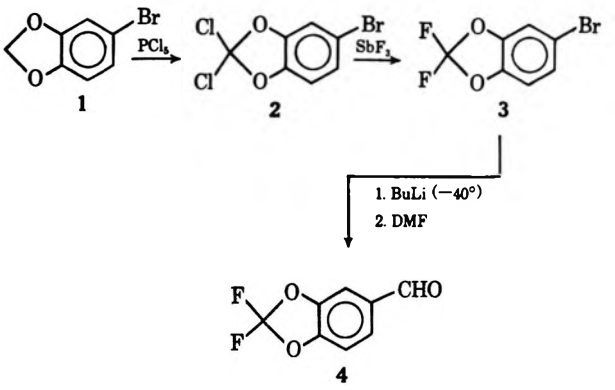
Received June 6, 1971

The methylenedioxyphenyl function is found in a broad spectrum of natural occurring materials[2] and appears to induce an enhancement or potentiation of biological activity.[3] The exchange of the methylene hydrogens for fluorine[4] represents an intriguing structural variation of biologically active substances containing this group. A particularly attractive intermediate for the introduction of this residue into organic molecules is 3,4-(difluoromethylenedioxy)benzaldehyde (**4**). Through a series of six synthetic steps Yagupol'skii[5] converted piperonylic acid into **4**, with an overall yield of approximately 30%. We wish to describe a much simpler three-step scheme to this valuable intermediate. The sequence of reactions is depicted below.

Chlorination of **1** with PCl_5 after the procedure of Barger[6] gave **2** in 83% yield. The exchange for fluorine was found to be very rapid and efficient if a solventless mixture of **2** and SbF_3 was heated under reduced pressure. In this manner, **3** distilled as it formed in a high state of purity. The chlorine–fluorine metathesis was considerably slower when the exchange was attempted in dioxane or hydrocarbon solvents.

Treatment of **3** with BuLi at −40° and subsequently adding freshly distilled dimethylformamide gave a 68% yield of **4**. An examination of the reaction products from this last step indicated that the halogen metal-interchange reaction occurred without loss of fluorine or rupture of the methylenedioxybenzene ring.[7]



In light of the ready formation of the aryllithium reagent from **3**, this reagent should also prove to be of value for the introduction of the 3,4-(difluoromethylenedioxy)phenyl functionality into organic substrates *via* the standard chemistry of organolithium reagents.

It is interesting to note that the alternative approach to **3**, *i.e.*, the exchange of methylene hydrogens for halogen prior to bromination, was ineffectual. Whereas the synthesis of (difluoromethylenedioxy)benzene was achieved without difficulty according to Yagupol'skii,[8] its bromination could not be realized without the destruction of the methylenedioxybenzene ring.

Experimental Section

3,4-(Dichloromethylenedioxy)bromobenzene (2).—Phosphorus pentachloride (400 g) and 112 g of 3,4-(methylenedioxy)-bromobenzene[9] were heated at 80° for 3 hr. Distillation gave an 83% yield of **3**, bp 107–109° (4 mm), $n^{20}D$ 1.5770.

Anal. Calcd for $C_7H_3Cl_2BrO_2$: C, 31.23; H, 1.12; O, 11.90. Found: C, 31.44; H, 1.10; O, 12.04.

3,4-(Difluoromethylenedioxy)bromobenzene (3).—Compound **2** (50 g) was heated with 50 g of SbF_3 at 20 mm. Redistillation of the collected liquid gave 35.3 g (80% yield) of **3**, bp 78–79° (20 mm), $n^{20}D$ 1.4722.

Anal. Calcd for $C_7H_3F_2BrO_2$: C, 35.47; H, 1.28; Br, 33.76. Found: C, 35.80; H, 1.30; Br, 33.69.

3,4-(Difluoromethylenedioxy)benzaldehyde (4).—To a solution of **3** (36.5 g) in 150 ml of Et_2O at −40° was added 100 ml of BuLi (1.6 M). After the addition was complete the reaction mixture was stirred for an additional hour at −40° and then treated with 33.6 g of DMF. The reaction was stirred for 1–2 hr at ambient temperature, treated with an exceess of NH_4Cl, and worked up in the usual manner. Vacuum distillation gave 19.6 g (68% yield) of **4**, bp 103–105° (20 mm).

Registry No.—**2**, 33070-31-4; **3**, 33070-32-5; **4**, 656-42-8.

(1) This work was supported by the U. S. Army Medicinal Research and Development Command under Contract No. DADA17-68-C-8103. This is Contribution No. 929 from the Army Research Program on Malaria.

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(3) C. F. Wilkinson, *J. Agr. Food Chem.*, **15**, 139 (1967); R. L. Metcalf, *Annu. Rev. Entomol.*, **12**, 299 (1967); J. E. Casida, J. L. Engel, E. G. Essac, F. X. Kemienski, and S. Kuwatsuka, *Science*, **153**, 1130 (1966).

(4) The rationale for exchanging hydrogen for fluorine in biologically active materials has been related to (a) altered electronic effects, (b) greater chemical stability, and (c) similarity in steric requirements. Discussions of these points are detailed by M. B. Chenweth and L. P. McCarty, *Pharmacol. Rev.*, **15**, 673 (1963); W. A. Sheppard and C. M. Sharts, "Organic Fluorine Chemistry," W. A. Benjamin, New York, N. Y., 1969, pp 454–463.

(5) L. M. Yagupol'skii and V. I. Troitskaya, *Zh. Obshch. Khim.*, **30**, 3129 (1960).

(6) G. Barger, *J. Chem. Soc.*, **93**, 566 (1908).

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(8) L. M. Yagupol'skii and V. I. Troitskaya, *Zh. Obshch. Khim.*, **34** (1), 307 (1964).

(9) Supplier: Frinton Laboratories, South Vineland, N. J.

The Influence of Conformation on Transmission of Electronic Effects in α,β-Unsaturated Ketones

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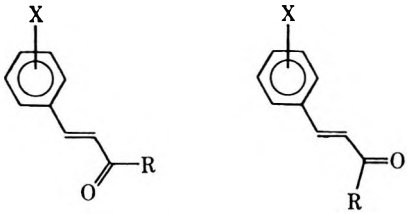
Received August 9, 1971

Only recently has the influence of conformation on transmission of electronic effects in α,β-unsaturated ketone systems been investigated. Perjéssy,[2] in a thorough investigation of substituent effects on the infrared stretching frequencies of chalcones, has concluded that s-trans conformers transmit more effectively than s-cis conformers on the basis of the magnitude of Hammett ρ values obtained when $\nu_{C=O}$ was plotted against σ^+. In the same report,[2] data previously reported by Dimmock,[3] *et al.*, for butyl styryl ketones were interpreted in a similar manner.

The previous investigations of transmission by s-cis–s-trans conformers of α,β-unsaturated ketones (Ia,b)



Ia, R = *n*-Bu
b, R = C_6H_5
c, R = H
d, R = CH_3

had as R groups *n*-butyl and phenyl groups which have rather large steric requirements. It seems likely that a significant amount of the difference in transmission of effects between s-cis and s-trans isomers for Ia and Ib may arise from differences in coplanarity of the two isomers. For example, examination of Dreiding models indicates that in the case of the s-cis isomer of Ia and Ib the R group and the α hydrogen are in close proximity and their interaction should alter the coplanarity of the styryl group and the carbonyl group. If the R group were smaller, there should be less interaction between it and the α hydrogen and hence it would be possible for a greater degree of coplanarity to be achieved. It might be expected that the transmission of electronic effects in the two conformations should become very nearly the same when the steric interaction of R and the vinyl hydrogens is reduced, if the degree of coplanarity of the styryl group and carbonyl group is important for transmission of electronic effects. The case Ic, in which R = H, should have minimum steric interactions; however, the conformational isomers of cinnamaldehyde cannot be detected by infrared spectroscopy.[4] Consequently, we have selected the system Id, methyl styryl ketones, R = CH_3, for study.

Although the steric requirements of the methyl group are considerable, they are significantly less than those of the *n*-butyl and phenyl groups which were used as R in the previous studies. When R is methyl (Id), there is a smaller interaction with the α hydrogen in the s-cis conformer; hence, if the degree of coplanarity is important to the efficiency of transmission, then a study of the methyl styryl ketone system should provide insight into its role. To test this point and as a part of our continuing investigation[5] of structure–reactivity relationships of α,β-unsaturated ketones, we have measured the carbonyl stretching frequencies of the s-cis and s-trans conformers of a series of substituted methyl styryl ketones.

Hayes and Timmons[4] have previously reported the assignment of the bands in the 1690-cm^{-1} region to the s-cis or nonplanar conformer and the bands in the 1670-cm^{-1} region to the s-trans conformers for **2** and **4**. The assignments reported here are based on analogy with their work. As anticipated, the lowest carbonyl frequencies were obtained for Id substituted with the strongest electron-withdrawing group and the highest frequencies were observed for Id substituted with the strongest electron donating group.

The methyl styryl ketones employed in this investigation are listed in Table I along with the values for carbonyl stretching frrquencies which were obtained in carbon tetrachloride solution. The frequencies for both conformers are correlated with σ^+ obtained from the tabulation of Ritchie and Sager.[6] Table II contains the results of the statistical analysis[7] of the correlations carried out according to the approach of Jaffé.[8] Figure 1 contains a graphical presentation of

TABLE I
METHYL STYRYL KETONES

Compd no.	Substituent	$\nu_{s\text{-}cis}$, cm^{-1}	$\nu_{s\text{-}trans}$, cm^{-1}
1	*p*-$(CH_3)_2N$	1688.9	1666.0
2	*p*-CH_3O	1693.2	1670.1
3	*p*-C_6H_5	1696.9	1674.0
4	*p*-H	1697.6	1674.8
5	*p*-Cl	1699.2	1677.2
6	*p*-Br	1699.3	1678.3
7	*p*-CN	1701.1	1680.0
8	*p*-NO_2	1702.0	1680.8

TABLE II
RESULTS OF STATISTICAL TREATMENT USING σ^+ CONSTANTS[a,b]

	n	ρ	*s*	*i*	*c*
s-cis-Id	8	5.38	0.48	1697.9	0.995
s-trans-Id	8	6.22	0.98	1675.9	0.984

[a] See ref 6. [b] *n* = number of points; ρ = slope as determined by method of least squares; *s* = standard deviation; *c* = correlation coefficient; *i* = intercept.

(1) American Chemical Society–Petroleum Research Fund Scholar.
(2) A. Perjéssy, *Chem. Zvesti*, **23**, 905 (1969).
(3) J. R. Dimmock, P. L. Carter, and P. D. Ralph, *J. Chem. Soc. B*, 698 (1968).
(4) W. P. Hayes and C. J. Timmons, *Spectrochim. Acta.*, **24A**, 323 (1968).
(5) (a) N. S. Silver and D. W. Boykin, Jr., *J. Org. Chem.*, **35**, 759 (1970); (b) R. W. Woodard and D. W. Boykin, Jr., *Chem. Commun.*, 628 (1970); (c) M. L. Ash, F. L. O'Brien, and D. W. Boykin, Jr., *J. Org. Chem.*, in press.
(6) C. D. Ritchie and W. F. Sager in "Progress in Physical Organic Chemistry," Vol. 2, Interscience, New York, N. Y., 1964.
(7) G. W. Snedecor and W. G. Cochran, "Statistical Methods," 6th ed, Iowa State University Press, Ames, Iowa, 1967.
(8) H. H. Jaffé, *Chem. Rev.*, **53**, 191 (1953).

TABLE III
RESULTS OF STATISTICAL TREATMENT USING F AND R CONSTANTS[a,e]

	n	f	r	i	E	c	% R
s-cis-Ia	5[b]	7.65 ± 0.78	16.14 ± 1.51	1694.9	0.53	0.994	46 ± 3
s-trans-Ia	5[b]	14.24 ± 1.47	29.72 ± 2.86	1675.0	1.0	0.994	46 ± 3
s-cis-Ib	9[c]	4.88 ± 1.26	6.24 ± 1.83	1672.2	1.30	0.945	40 ± 9
s-trans-Ib	9[c]	5.32 ± 1.52	10.86 ± 2.21	1653.0	1.57	0.959	56 ± 9
s-cis-Id	7[d]	3.27 ± 1.12	8.94 ± 1.90	1697.4	1.01	0.960	59 ± 10
s-trans-Id	7[d]	4.98 ± 1.54	10.16 ± 2.62	1674.5	1.39	0.953	52 ± 10

[a] Swain–Lupton field and resonance parameters; see ref 9. These correlations were made using a multiple linear regression program written using the statistical analysis described in ref 7. Calculations were made on an IBM 7094 computer. [b] The ν values were taken from ref 3; the substituents were *p*-H, *p*-Cl, *m*-Cl, *p*-CH_3, and *p*-CH_3O. [c] The ν values were taken from ref 2; the substituents were *p*-NH_2, *p*-CH_3O, *p*-CH_3, *p*-H, *p*-F, *p*-Cl, *m*-Cl, *p*-CN, *p*-NO_2. [d] The value of ν for the *p*-$(CH_3)_2N$ compound was not used in these calculations. [e] n = number of points; f = regression coefficient for field parameter; r = regression coefficient for resonance parameter; i = intercept; E = standard error of estimate; c = multiple correlation coefficient; % R = resonance contribution, calculations as in ref 5a.

the data. The correlations of the stretching frequencies with σ^+ are good for both isomers, for the s-cis $r = 0.995$ and, for s-trans, $r = 0.984$.

Comparison of ρ values for the two conformers of the methyl styryl ketones indicates that their abilities to transmit electronic effects are very similar. The ratio ρ-cis/ρ-trans is 0.86 for the methyl styryl ketones. This value is an increase over the values of the s-cis–s-trans of 0.76 and 0.78 for R = *n*-Bu and $-C_6H_5$ (Ia and Ib), respectively.[2] While the ratio does not reach unity, it is in good agreement with the value of 0.90 for the ratio reported for a series of 4′-substituted chalcones.[2] These results are in accord with the hypothesis that, as the two conformers approach similar degrees of coplanarity, their abilities to transmit electronic effects become similar.

The above results suggest that an important mode of transmission of electronic effects in these systems is by resonance. The linear free energy relationship reported by Swain and Lupton[9] provides a method by which the contribution of resonance to a correlation may be assessed. Table III contains the results of the correlations of the stretching frequency data for Ia, Ib, and Id with the Swain–Lupton expression. As has been noted previously[5a] for ir data, correlations with the two-parameter expression are generally poorer than those obtained with the Hammett expression. In general, and not unexpectedly, all systems give values for % R which are approximately the same. Unfortunately, the correlations are such that the error in the % R calculations is so high for Ib and Id that it is not possible to draw conclusions about trends. In order to rigorously determine the effect of conformation on the mode of transmission in these α,β-unsaturated systems, it will be necessary to find another more precise means of assessing them.

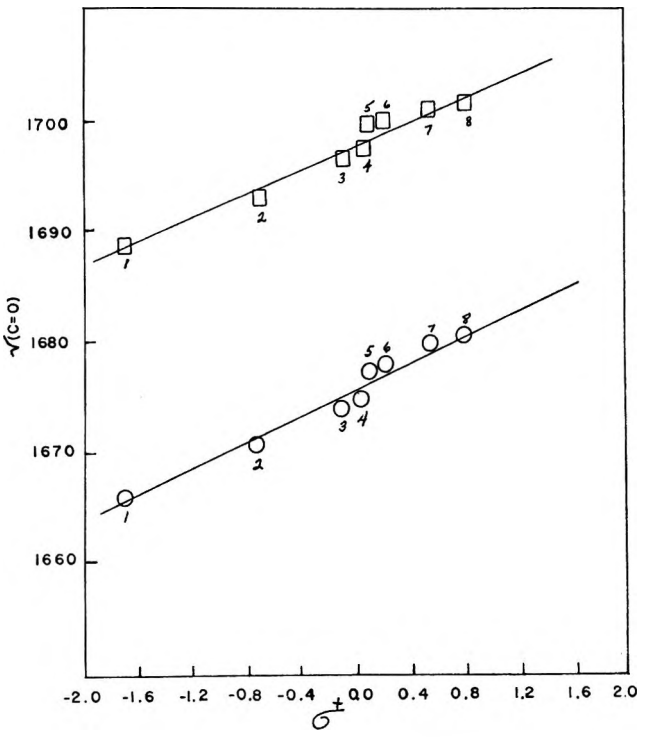


Figure 1.—Plots of $\nu_{C=O}$ *vs.* σ^+ for s-cis and s-trans conformers of para-substituted benzalacetones: □, s-cis conformers; ○, s-trans conformers.

Experimental Section

Methyl Styryl Ketones.—All of the ketones have been previously reported and were prepared as described by Johnston and Jones.[10] The compounds were purified by recrystallization, usually from hexane and their purity was checked by nmr. The compounds were dried *in vacuo* prior to measurement of their stretching frequency. Melting points are uncorrected and were obtained using a Thomas–Hoover Uni-Melt. The melting points observed followed by the literature values follow: 1, 135.5–136.5° (133–134°);[10] 2, 72–73° (72°);[11] 3, 134–135° (134.5°);[12] 4, 40–41° (40–41°);[10] 5, 58–59° (58–59°);[10] 6, 84.5–85.0° (83–84°);[13] 7, 105–106.5° (105–106°);[10] 8, 108–109° (106–107°).[10]

Infrared Frequencies.—The ir stretching frequencies for all the benzalacetones were determined using a Beckman IR-12 grating spectrometer operated in the expanded scale mode at scan rates of 8 cm^{-1} min, chart speeds of 1 in./min, and period setting of 8.[5a] The spectra of the benzalacetones were taken in solutions of spectral grade carbon tetrachloride at 35 ± 4°. The concentrations of the solutions were *ca.* 5% and a matched set of KBr cells with 0.05-mm path lengths were used. Band frequencies were taken at the half-width at 75% of the height of the s-cis band and at the half-width at 60% of the height of the s-trans band. All frequencies reported were obtained from averaging at least three different scans, all of which gave frequencies which were within 0.4 cm^{-1} of one another.

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(10) R. L. Johnston and L. A. Jones, *J. Chem. Eng. Data*, **16**, 112 (1971).

(11) Kalle A.-G., British Patent 943,266 (1963); *Chem. Abstr.*, **60**, 14697*a* (1964).

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Registry No.—**1**, 30625-58-2; **2**, 3815-30-3; **3**, 32979-83-2; **4**, 1896-62-4; **5**, 30626-03-0; **6**, 3815-31-4; **7**, 30626-00-7; **8**, 30625-98-0.

Acknowledgment.—Acknowledgment is made to the donors of The Petroleum Research Fund, administered by the American Chemical Society, for support of this research.

[4,5-*c*(*d*)]Pyrazolotropone. A New Aromatic Ring System

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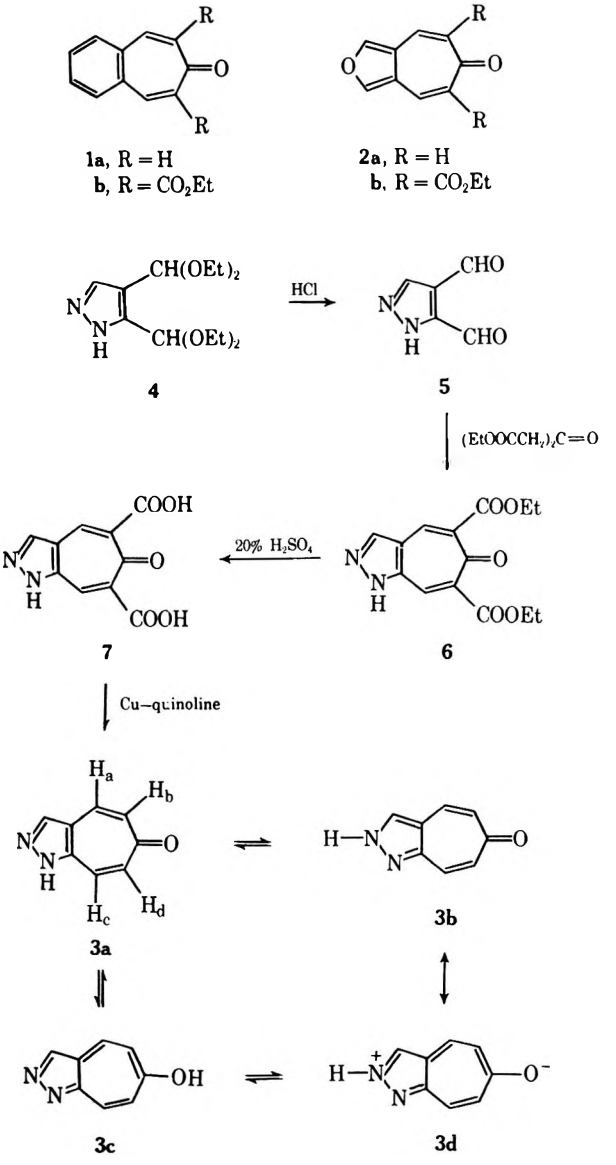
Received August 13, 1971

Heterocyclic analogs of 4,5-benzotropone (**1a**) were unknown until the recent preparations of 2-thiaazulen-6-ones,[2,3] 2-phenyl-1,3,5,7-tetramethyl-2-azaazulen-6-one,[3] and [4,5-*c*]furotropone (**2a**).[4] A hitherto unknown member of this series is [4,5-*c*(*d*)]pyrazolotropone (or 1,2-diaza-1*H*-azulen-6-one) (**3**), which could exist in any of several tautomeric structures **3a–d** (Scheme I). It was of interest to determine if the difference in basicity of the carbonyl group and the annular nitrogens would be relinquished for the stabilization which would result from further delocalization of the ten π electrons in the tautomer, 6-hydroxy-1,2-diazaazulene (**3c**).

A good yield of 2,7-dicarbethoxy[4,5-*c*(*d*)]pyrazolotropone (**6**)[5] was obtained as outlined in Scheme I. Its infrared spectrum (KBr) showed a broad band at 3226 cm^{-1} for the associated NH group in the pyrazole ring. The tropone ring carbonyl absorption was assigned to both bands at 1600 and 1520 cm^{-1} based on comparable bands reported[4] for the furotropone **2b** (1614 cm^{-1} in CH_2Cl_2) and the benzotropone **1b** (1625 and 1550 cm^{-1} in CH_2Cl_2). However, the intense band at 1600 cm^{-1} characteristic of the C=N absorption in pyrazoles[6] makes it difficult to definitely assign this band specifically as the carbonyl stretching frequency in **6**.

The ultraviolet absorption (methanol) at 222 nm (log ϵ 4.24) was attributed to the pyrazole ring, since alkyl-substituted pyrazoles absorb at 210–225 nm and arylpyrazoles at 250–280 nm.[6] The bands associated with the tropone ring (in isooctane at 225, 297, and 310 nm for tropone itself)[7] were shifted by the fused pyrazole chromophoric ring to 262 nm (log ϵ 4.43) and 316 (3.98), the latter band assigned to the conjugated keto function. Comparable absorptions were reported[4] for **2b**: λ_{max}^{EtOH} 219 nm (log ϵ 4.14) and 260 (4.49). The nmr spectra of **1**, **2**,[4] and **6** (*cf.* Experimental Section) were also very similar with respect to chemical shift values and absorption patterns for the tropone rings.

SCHEME I



Hydrolysis of **6** with 20% sulfuric acid gave 2,7-dicarboxy[4,5-*c*(*d*)]pyrazolotropone (**7**) in 87% yield. The parent structure was then obtained in 35% yield by decarboxylation of **7** at 205° with a copper–quinoline mixture. This represents a different, convenient, and improved method for decarboxylation of the precursor dicarboxylic acids to yield tropones. Usually acid hydrolysis in sealed tubes affords very low yields.[4]

The extent of aromaticity in **3** was estimated by a comparison of some spectral characteristics with the data available on the related unsubstituted systems, **1a** and **2a**. The bands at 1635 and 1582 cm^{-1} in the infrared spectra of tropones were previously considered carbonyl group vibrations. A study[8] on a number of tropones revealed that the lower frequency band was solvent dependent and therefore it was concluded that

(1) Taken from the Ph.D. dissertation of M. Pesce, St. John's University, June 1971.

(2) M. Winn and F. G. Bordwell, *J. Org. Chem.*, **32**, 1610 (1967).

(3) (a) A. V. El'tsov, A. A. Guinesina, and L. N. Kivokurtseva, *Zh. Org. Khim.*, **3**, 1343 (1967); *Chem. Abstr.*, **66**, 94581 (1967); (b) A. V. El'tsov, L. N. Kivokurtseva, and A. A. Guinesina, *Zh. Org. Khim.*, **4**, 907 (1968); *Chem. Abstr.*, **69**, 18958 (1968); (c) A. V. El'tsov, A. S. Guinesina, and L. N. Kivokurtseva, *Tetrahedron Lett.*, 735 (1968).

(4) M. S. Cook and E. J. Forbes, *Tetrahedron*, **24**, 4501 (1968).

(5) The nomenclature employed is analogous to that accepted for benzotropone and [4,5-*c*]furotropone,[4] the letters *c* and *d* referring to the numbering of the pyrazole ring in **3a** and **3b**, the numbers 4,5 referring to the side of the tropone ring fused to the pyrazole ring.

(6) A. N. Kost and I. I. Grandberg, "Advances in Heterocyclic Chemistry, Vol. 6, A. R. Katritzky and A. J. Boulton, Ed., Academic Press, New York, N. Y., 1966, pp 355–358, and references cited therein.

(7) W. von E. Doering and F. L. Detert, *J. Amer. Chem. Soc.*, **73**, 876 (1951).

(8) H. Goetz, E. Heilbronner, A. R. Katritzky, and R. A. Jones, *Helv. Chim. Acta*, **40**, 957 (1957).

this band was the carbonyl stretching mode. The lower frequency absorptions of furotropone **2a** and benzotropone **1a** were also found to be solvent dependent.[4] By correlating the frequency of this absorption with calculated bond orders it was inferred[4] that **2a** was less aromatic than tropone or **1a**. Since the carbonyl in **3** does not have a similar geometric disposition[9] to that in **1a** and **2a**, we were unable to compare the infrared absorptions at 1620–1590 cm^{-1} in the same manner.

The ultraviolet absorption bands of **3** (methanol) at 215 nm (log ϵ 4.01) for the pyrazole ring, 252 (4.40) for the tropone ring, and 320 (3.81) for the conjugated keto group compare well with those for benzotropone **1a** [λ_{max}^{EtOH} 231 nm (log ϵ 4.50), 272 (4.69), 332 (3.64), and 348 (3.45)] and for furotropone **2a** [λ_{max}^{EtOH} 211 nm (log ϵ 4.08), 216 (4.05), 250 (4.57), 255 (4.55), 292 (3.67), and 301 (3.67)]. We had an opportunity here to compare the extent of delocalization of the ring electrons by comparing the long-wavelength absorptions. The shift in maxima of about 47 nm toward the blue from the band for benzotropone was attributed[4] to a decrease in delocalization in furotropone. By analogy, the blue shift of only 28 nm by pyrazolotropone indicates the order of aromaticity to be benzotropone > pyrazolotropone > furotropone. The dipolar structure **3d** must make a significant contribution to the resonance hybrid of **3**.

In Table I, pyrazolotropone is compared with the other pertinent tropones with regard to their nmr properties. It is apparent that the three bicyclic structures can sustain an induced ring current. A comparison with tropone, which shows only a broadened singlet, reveals the bicyclic tropones to be less aromatic. Benzotropone and furotropone show their symmetry in the very similar absorption pattern for the peripheral protons. The unsymmetrical distribution of heteroatoms in **3** produces four absorptions consisting of two singlets and two doublets.

TABLE I
CHEMICAL SHIFTS FOR TROPONES[a]

Compd	Assignment, δ ppm: Fused ring protons	Tropone ring doublets
Tropone[b]		6.95 (broad singlet)
1a[c]	7.47 (4 H, s)	7.27 (2 H), 6.65 (2 H), J = 12 Hz
2a[c]	8.08 (2 H, s)	7.37 (2 H), 6.52 (2 H), J = 12 Hz
3	8.24 (NH, 1 H, s)	7.60 (H_c, s),[d] 6.64 (H_d, s)
	7.80 (CH, 1 H, s)	6.90 (H_a, d),[e] 6.40 (H_b, d)[e]

[a] The cross-conjugated 1,2,3,3a,8a-pentahydroazulen-6-one exhibited absorptions at δ 6.21 and 5.87 (J = 12.5 Hz) for the olefinic doublets: O. L. Chapman and T. H. Kock, *J. Org. Chem.*, **31**, 1042 (1966). [b] Data taken from D. J. Bertelli, C. Golino, and D. L. Dreyer, *J. Amer. Chem. Soc.*, **86**, 3329 (1964), solvent CCl_4. [c] Taken from ref 4, solvent not reported. [d] *Cf.* Scheme I for H symbols. [e] J = 2 Hz, solvent DMSO-d_6.

Experimental Section

All melting points, taken on a Mel-Temp apparatus, are uncorrected. Infrared spectra were measured on a Perkin-Elmer Infracord Model 137 using the potassium bromide pellet technique. Nuclear magnetic resonance spectra were recorded on a Varian A-60A using tetramethylsilane as an internal standard. Ultraviolet spectra were obtained with a Bausch and Lomb 505 spectrophotometer. Combustion analyses were performed by Schwarzkopf Microanalytical Laboratory, Woodside, N. Y., and Childers Microanalytical Laboratory, Milford, N. J.

Materials.—Diazomethane was prepared by Eistert's procedure,[10] and assayed by the method of Fieser.[11] The acetylenedialdehyde bis(diethyl acetal) was prepared according to the procedure of Wohl[12] and used in the procedure described by Henkel and Weygand[13] for the preparation of pyrazole-3(5),4-dicarboxyaldehyde, yield 81.8%, mp 202–203° (lit. 203–205°).

2,7-Dicarbethoxy[4,5-*c*(*d*)]pyrazolotropone.—To 4.96 g. (0.039 mol) of pyrazole-3(5),4-dicarboxaldehyde suspended in 55 ml of benzene was added 7.95 g (0.0044 mol) of diethyl acetonedicarboxylate and 0.5 ml of piperidine. The suspension was refluxed for 2 hr and cooled, and the solid was filtered and recrystallized from chloroform–pentane to yield 8.7 g (76.5%) of **6** as a white powder, mp 159–161°. Five preparations gave yields ranging from 43 to 77%: nmr ($CDCl_3$) δ 1.33 (t, 6, CH_3, J = 7 Hz), 4.38 (q, 4, CH_2), 8.22 (s, 2, tropone ring), 8.40 (s, 1, pyrazole CH), 12.80 (br, 1, NH).

Anal. Calcd for $C_{14}H_{14}N_2O_5$: C, 57.93; H, 4.86; N, 9.65. Found: C, 57.77; H, 4.97; N, 9.58.

2,7-Dicarboxy[4,5-*c*(*d*)]pyrazolotropone.—A suspension of the above dicarbethoxypyrazolotropone (16 g, 0.055 mol) in 200 ml of 20% sulfuric acid was refluxed for 1.5 hr and then stirred for 2 hr at room temperature. The cooled suspension was filtered and the residue was dried overnight in a desiccator at 100°. Recrystallization from absolute ethanol afforded 10 g (78%) of **7** as a tan solid, mp 259–261°. Five preparations gave the acid in 73–78% yields: uv λ_{max}^{MeOH} 213 nm (log ϵ 3.97), 272 (4.43), 333 (3.78); ir λ_{max} (KBr) 3226 (NH), 1709 (COOH), 1590 cm^{-1} (C=O tropone); nmr (DMSO-d_6) δ 8.00 (s, 1 H, pyrazole CH), 8.24 (s, 2 H, tropone), 10.25 (broad absorption, 3 H, NH and two COOH).

Anal. Calcd for $C_{10}H_6N_2O_5$: C, 51.29; H, 2.58; N, 11.96. Found: C, 51.72; H, 2.92; N, 11.65.

[4,5-c(*d*)]Pyrazolotropone.—To 4.6 g (0.0197 mol) of the above dicarboxypyrazolotropone was added 0.7 g of copper powder and 25 ml of quinoline. The solution was heated in an oil bath at 205° for 3.5 hr. The black suspension was poured into 30 ml of an ice-cold solution of 50% hydrochloric acid and the suspension was filtered. The filtrate was extracted with five 60-ml portions of ethyl acetate, and the extracts were dried ($MgSO_4$) and evaporated to a yellow solid. Solution in ethyl acetate and addition of pentane to the cloud point yielded 1.02 g (35.5%) of **3** as a light yellow solid, mp 223.5–225°. Eight preparations gave yields ranging from 10 to 36%. The product did not react with 2,4-dinitrophenylhydrazine reagent.

Anal. Calcd for $C_8H_6N_2O$: C, 65.74; H, 4.14; N, 19.17. Found: C, 65.70; H, 4.17; N, 19.25.

Registry No.—**3a**, 33015-60-0; **3b**, 33015-61-1; **3c**, 33015-62-2; **6a**, 33015-63-3; **6b**, 33015-64-4; **7a**, 33015-65-5; **7b**, 33015-66-6.

(9) O. L. Chapman and T. H. Kock, *J. Org. Chem.*, **31**, 1042 (1966).

(10) B. Eistert, "Organic Syntheses," Collect. Vol. II, A. H. Blatt, Ed., Wiley, New York, N. Y., 1967, p 165.

(11) L. F. Feiser and M. Feiser, "Reagents for Organic Synthesis," Wiley, New York, N. Y., 1967, p 191.

(12) A. Wohl, *Chem. Ber.*, **45**, 339 (1912).

(13) K. Henkel and F. Weygand, *Chem. Ber.*, **76**, 812 (1943).

The Electronic Effects of Oxygen in the 8-Oxabicyclo[4.3.0]non-3-ene Series

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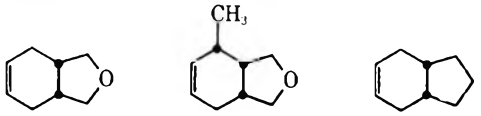
Received July 16, 1971

Replacement of a methylene group by an oxygen heteroatom has been shown to affect the chemistry of the molecule involved. A conformational effect has

been noted by Paquette in the solvolysis of oxocan-3-yl brosylate.[1] A retarding field effect has been demonstrated by Tarbell in the solvolysis of 4-tetrahydropyranyl tosylate.[2] Increased reactivity due to resonance participation has been observed in the hydroboration of 2,3-dihydrofuran.[3] We wish to report here some of our work which suggests the possibility of long-range nonbonded electronic participation in a rigid system.

Rickborn[4] has questioned whether the heteroatom in *cis*-8-oxabicyclo[4.3.0]non-3-ene (**1**) might contribute to the chemistry of the alkene bond. As a consequence of our work trying to establish whether a directive effect might be observed in the chemistry of the 8-oxabicyclo[4.3.0]non-3-ene series,[5] we investigated the reactivity of these molecules. The phthalans **1** and **2** and Δ^5-*cis*-tetrahydroindan (**3**) were subjected to competition experiments in order to evaluate the relative reactivities of the alkene bond.

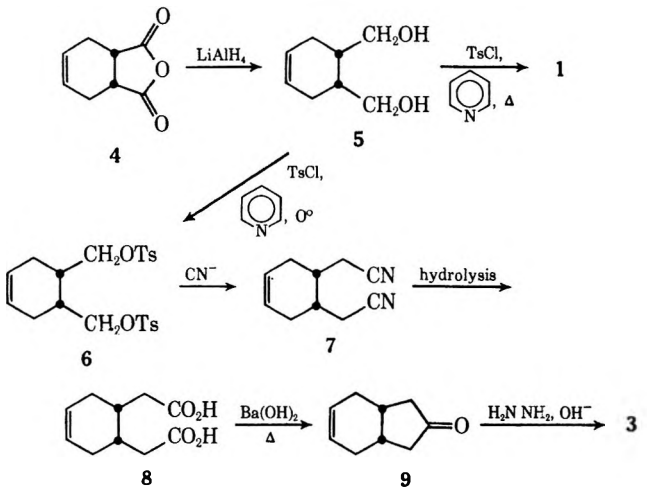


1 **2**

Results and Discussion

The synthesis of **1** and **3** are dilineated in Scheme I. The anhydride **4** was reduced to the 1,4-diol **5**, which in

SCHEME I



turn was readily cyclized to the tetrahydrofuranyl system by treating the diol with *p*-toluenesulfonyl chloride in refluxing pyridine. Formation of the ditosylate **6** was readily achieved by treating **5** with *p*-toluenesulfonyl chloride at 0°. The carbon chain lengthening was affected by a displacement of both tosylate functionalities with cyanide ion. The resulting dinitrile **7** was hydrolyzed to **8**, which under conditions of Ruzicka cyclization afforded the indanone derivative **9**. Wolff–Kischner reduction of **9** gave the desired Δ^5-*cis*-tetrahydroindan (**3**). The preparation of **2** has been reported.[5]

(1) L. A. Paquette, R. W. Begland, and P. C. Storm, *J. Amer. Chem. Soc.*, **92**, 1971 (1970).
(2) D. S. Tarbell and J. R. Hazen, *ibid.*, **91**, 7657 (1969).
(3) G. Zweifel and J. Plamondon, *J. Org. Chem.*, **35**, 898 (1970).
(4) B. Rickborn and S. Y. Lwo, *ibid.*, **30**, 2212 (1965).
(5) B. P. Mundy, A. R. DeBernardis, and R. D. Otzenberger, *ibid.*, **36**, 3830 (1971).

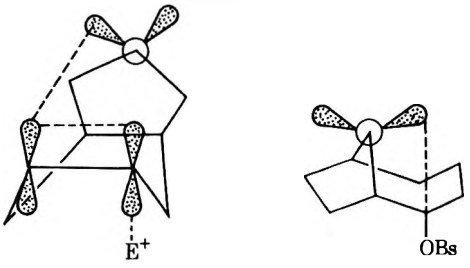
Each alkene was mixed with an equal molar amount of cyclohexene and was allowed to compete for a limited amount of mercuric acetate in THF–H_2O. The relative reactivities were ascertained by established methods[6] and are recorded in Table I.

TABLE I
RESULTS OF COMPETITION STUDIES

	Cyclohexene	1	2	3
Oxymercuration (K_{rel})	1.00	0.93	0.35	0.11
$AgNO_3$ equilibration (K_{eq})	0.018[a]	0.15	0.048	

[a] Reference 9.

The eightfold increase of reactivity of **1** as compared to **3** shows that the alkene bond is more reactive. Examination of various types of models suggests that the nonbonded electrons of the oxygen can stabilize any incipient charge which might result from electrophilic attack on the π system of the alkene. This interaction, as described by **10**, might be similar to the long-range oxygen participation reported by Paquette for **11**.[7]



10 **11**

The decrease in reactivity of **2** must be attributed to a "steric effect" of the methyl group.[8] It is interesting to note that the relative reactivities of cyclohexene *vs.* 3-methylcyclohexene are 1.0–0.36. The remarkable similarities of rate retardation due to a methyl group are of interest, particularly since **2** is conformationally more homogeneous than 3-methylcyclohexene. The directive effects found in the chemistry of **2** and 3-methylcyclohexene are also quite similar.[5]

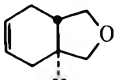
Comparison of the oxymercuration results with ease of silver nitrate complexing again suggests that the alkene bond of **1** is more susceptible to coordination with silver ion than cyclohexene (Table I). Distribution of **1** and **2** between carbon tetrachloride and aqueous silver nitrate[9] gave equilibrium constants whose ratio (K_2/K_1 = 0.32) is quite similar to the ratio of relative reactivities for oxymercuration.[10]

(6) S. L. Friess and A. Weissberger, Ed., "Techniques of Organic Chemistry," Vol. VIII, Interscience, New York, N. Y., 1953, pp 101–108.
(7) L. A. Paquette and P. C. Storm, *J. Amer. Chem. Soc.*, **92**, 4295 (1970).
(8) D. J. Pasto and J. A. Gontarz, *ibid.*, **92**, 7480 (1970).
(9) J. G. Traynham and J. R. Olechowski, *ibid.*, **81**, 571 (1959).
(10) We realize that the partition of alkenes between organic and aqueous silver nitrate phases is not always a reliable measure of K_{eq}. However, the similarity of the ratios of K_{eq} for **1** and **2** with the ratio of oxymercuration relative rates is an interesting observation[11] worthy of recording for other research workers.
(11) The question of mercurinium ions has received some attention recently. Pasto argues for their existance on stereochemical grounds.[8] Olah[12] has reported a direct observation of the mercurinium ion. Based on the stereochemical course of oxymercuration of **1**, the effect of oxygen heteroatoms[13] and the similarity between the relative rates of oxymercuration of **1** and **2** and the relative ease of argentation, we also suggest that mercurinium ions exist. Further work to substantiate this is in progress.
(12) G. A. Olah and P. R. Clifford, *J. Amer. Chem. Soc.*, **93**, 1261 (1971).
(13) (a) M. M. Jones, "Elementary Coordination Chemistry," Prentice-Hall, Englewood Cliffs, N. J., 1964, p 116; (b) R. W. Parry and R. N. Keller, "The Chemistry of the Coordination Compounds," J. C. Bailar, Jr., and D. H. Busch, Ed., Reinhold, New York, N. Y., 1956, p 123; (c) P. C. Chamberlain and G. H. Whitman, *J. Chem. Soc. B*, 1382 (1970).

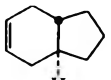
This unexpected similarity leads us to at least consider the possibility that, in both oxymercuration and complexing with silver nitrate, *the reactive site is the alkene bond* rather than the ether osygen.[11] A recent discussion of electrophilic addition of Ag^+ and Hg^{2+} to ethylene suggests that their modes of addition may be quite similar.[14] Further evidence supporting the suggestion that the silver did not coordinate with oxygen may be seen in the nmr spectrum of the silver nitrate complex. Comparison of **1** in D_2O with the complex in D_2O shows clearly that the π bond is being influenced by silver ion, altering the vinyl hydrogens chemical shift from δ 5.7 to 6.7. This is the same shift observed for cyclohexene.[15] In general it has also been reported that silver ion does not coordinate strongly with oxygen.[13a,b]

Another argument that might be posed against oxygen participation is one of prior complexing of mercury ion with the oxygen, followed by a rapid transfer to the alkene bond (an entropy effect). Several arguments can be formulated against this possibility. In general, oxygen does not coordinate well with mercury ion, and particularly ether–oxygen functions.[13c] Also, since THF is the solvent for this reaction one must question why the phthalan oxygen would be *specifically* superior to the THF oxygen for complexing, and specific exchange would be necessary to account for the increased reactivity. A recent analysis of oxymercuration of substituted cyclohex-2-enols concludes that there is probably little direct interaction between mercury and the hydroxyl group.[13c]

Lastly, one can reasonably suggest that rate differences are merely a reflection of differences in ring strain or steric requirements of methylene *vs.* oxygen. We have tried to rule these out by analyzing the relative reactivities in the trans series, **12** and **13**.[16] Here we



12



13

observe that **13** undergoes oxymercuration at about the same rate as **3** (k_{rel} = 0.15), while **12** oxymercurates about four times faster (k_{rel} = 0.4). Analysis of models demonstrates that **12** and **13** are conformationally similar and there is clearly little chance for participation by oxygen of **12**. At this time it is reasonable to suggest any increased reactivity as resulting from differences in strain. If we apply these arguments to the cis series, particularly **1** and **3**, it is not unreasonable to suggest that, *in the absence of participation by oxygen*, **1** and **3** should exhibit similar rates of oxymercuration. That **1** is considerably faster supports the concept of some sort of "oxygen-effect."[17]

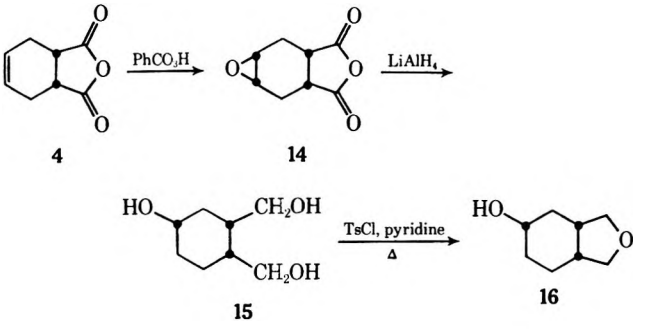
(14) R. D. Bach and H. F. Henneike, *J. Amer. Chem. Soc.*, **92**, 5589 (1970).

(15) F. A. Bovey, "Nmr Data Tables for Organic Compounds," Vol. I, Interscience, New York, N. Y., 1967, p 131.

(16) These compounds have been previously prepared by methods similar to those used for **1** and **3**.

(17) One might be concerned about differences in solubility as reflecting the rate differences. We have not analyzed the solubilities of the alkenes used in this study. However, we would expect **1** and **12** to have similar solubilities, as would **3** and **13**. If solubility were a major factor, we might expect **1** and **13** to exhibit similar reactivities, as we do observe. However, the greater reactivity of **3** than **12** again suggests some additional oxygen effect.

The major product resulting from oxymercuration of **1** is **16**. This was established by an unambiguous



synthesis of **16**. Epoxidation of **4** with perbenzoic acid yielded the known epoxide **14**.[18] Reduction of **14** with lithium aluminum hydride afforded the triol **15**, which was immediately treated with 1 equiv of *p*-toluenesulfonyl chloride in pyridine at reflux. The product from this synthesis must have the stereochemistry of **16** based on the history of the reaction sequence. That the product did not arise from cis addition during the oxymercuration process was established by analyzing the organomercurial resulting from methoxymercuration of **1**.[19]

Although the increased reactivity is not overwhelming, it does lend some support for Rickborn's questioning the use of perhydrophthalans as models for the more difficultly obtained perhydroindans.

Experimental Section

The infrared spectra reported here were obtained on a Beckman IR-5, using polystyrene as an external standard. The nuclear magnetic resonance spectra were obtained on a Varian Model A-60 instrument, using tetramethylsilane as an internal standard. Melting and boiling points are uncorrected. The competition studies were measured by utilizing the product ratios as observed from an F & M Model analytical gas chromatograph and the peak areas integrated with a Disc integrater.

Cyclohexene-4-*cis*-1,2-dimethanol (5).—A solution containing 30.4 g of *cis*-1,2,3,6-tetrahydrophthalic anhydride in approximately 1 l. of anhydrous ether was added to 8.0 g of lithium aluminum hydride in 600 ml of anhydrous ether. Work-up gave the colorless cis diol (15.1 g, 53%) boiling at 167–170° (0.25 mm) [lit. bp 165–170° (12 mm),[20] mp 34.5°[21]].

Cyclohexene-4-*cis*-1,2-dimethanol Di-*p*-toluenesulfonate (6).—A solution of **5** (17.5 g) in 50 ml of pyridine was added dropwise to a cooled (0°) solution of *p*-toluenesulfonyl chloride (78.5 g) in 100 ml of pyridine. After completion of the addition, the mixture was stirred for an additional 3 hr. The reaction mixture was then poured into 200 ml of cold water, and within a few minutes the white crystalline ditosylate had formed. Filtration yielded 55 g (99% yield) of the ditosylate, mp 97.5°.[20,21]

Cyclohexene-4-*cis*-1,2-diacetonitrile (7).—A mixture of **6** (53 g), potassium cyanide (26 g), and ethanol (500 ml) was refluxed for approximatly 60 hr. After cooling, 20 ml of water was added to dissolve the salts, and the ethanol was removed. The residue was extracted with methylene chloride, and the combined extracts were reduced in volume. Distillation of the crude product yielded a clear, yellow dinitrile (11.9 g, 63%) boiling at 195° (8 mm). The dinitrile was crystallized from methanol–water, mp 45–46° (lit.[21] mp 50°).

Cyclohexene-4-*cis*-1,2-diacetic Acid (8).—A solution of **7**

(18) See H. B. Henbest, *Proc. Chem. Soc.*, 159 (1963), for a concise report on some of the effects contributing to the course of epoxidation.

(19) W. Waters, *Tetrahedron Lett.*, 3769 (1969).

(20) E. Casadevall, C. Largeau, and P. Moreau, *Bull. Soc. Chim. Fr.*, 1514 (1968).

(21) D. C. Ayres and R. A. Raphael, *J. Chem. Soc.*, 1779 (1958).

(11.8 g) was refluxed until the evolution of ammonia ceased. After cooling the mixture was acidified with 87% phosphoric acid. The reaction yielded 10.0 g (68.5%) of white crystalline diacid (from acetonitrile) melting at 156–157° (lit.[21] mp 157°).

cis-4,7,8,9-Tetrahydroindan-2-one (9).—Cyclohexene-4-*cis*-1,-2-diacetic acid (5.0 g) was thoroughly mixed with iron powder (5.0 g) and barium hydroxide [0.6 g, $Ba(OH)_2 \cdot 8H_2O$]. This mixture was heated with an open flame while the ketone and water distilled. The crude ketone was separated from the water and redistilled to give 2.1 g (61.8%) of product boiling at 101° (11 mm). Spectral characteristics were consistant with the known product.[22]

Preparation of *cis*-4,7,8,9-Tetrahydroindan (10).—The Huang-Minlon modification of the Wolff–Kishner reduction was used.[23] A mixture of *cis*-4,7,8,9-tetrahydroindan-2-one (2.0 g), potassium hydroxide (2.8 g), 85% hydrazine (2.0 ml), and diethylene glycol (20 ml) was heated at 130° for 1.5 hr. The water and excess hydrazine were removed by distillation until the temperature reached 190–200°. The mixture was diluted with 200 ml of water and neutralized with 6 *N* hydrochloric acid. This mixture was extracted with methylene chloride, and the extracts were distilled to give the colorless hydrindan (1.0 g, 55.7%) boiling at 42–43° (9 mm). The infrared and nmr spectra were consistent with the structure.[22]

cis-8-Oxabicyclo[4.3.0]non-3-ene (1).—A solution of **5** (7.1 g) in 10 ml of pyridine was heated to reflux and a solution of *p*-toluenesulfonyl chloride (14 g) in 10 ml of pyridine was added dropwise with stirring. After the addition was completed, the mixture was refluxed for 1 hr. This solution was cooled and poured into an ice–sulfuric acid bath to neutralize the pyridine. The aqueous mixture was extracted with ether, and the combined ether extracts were dried over anhydrous magnesium sulfate. Distillation yielded the colorless product (4.8 g, 77.5%) boiling at 58–64° (9 mm) [lit.[24] bp 63–64° (13 mm)].

Preparation of **12** and **13**.—The trans series was prepared by methods similar to those outlined for **1** and **3**, except that cyclohexene-4-*trans*-1,2-dimethanol[20,21] was the starting material. Spectral and physical data for **12**[4] and **13**[25] were consistent with the reported values.

cis-1,3,6-Trihydro-8-oxabicyclo[4.3.0]non-3-ol (16).—**4** (3 g) was mixed with an equivalent amount of perbenzoic acid[26] in 50 ml of chloroform and the reaction mixture was maintained at 0° for 3 days. The crystalline product **12** was collected and recrystallized from ethyl acetate, mp 201–202°.[27] The epoxide (0.5 g) was dissolved in 10 ml THF and reduced with 0.25 g of lithium aluminum hydride. The crude triol **13** from this sequence (400 mg) was mixed with 25 ml of pyridine and 0.47 g of *p*-toluenesulfonyl chloride and was heated at reflux for about 2 hr. Evaporation of excess pyridine yielded the alcohol **14**, which was identical by glc (20% Carbowax 20M on Chromosorb W, 200°) with the major product of oxymercuration. The 3,5-dinitrobenzoate was crystallized from ethanol, mp 150–152°. *Anal.* Calcd for $C_{16}H_{16}N_2O_7$: C, 53.6; H, 4.8; N, 8.3. Found: C, 53.6; H, 4.8; N, 8.1.

Competition Studies.—The competition studies were performed by allowing a mixture of cyclohexene (the standard, 1.5 mmol) and other alkene (1.5 mmol) to compete for a limiting amount of mercuric acetate (0.8 mmol) in THF–water (1:1). Generally, the reactions were complete (as evidenced by the loss of yellow color in the mercuric acetate–water–THF mixture) within 1 or 2 min. After sodium borohydride reduction of the oxymercurials[28] the crude product mixture was analyzed for both product and unreacted alkene. The relative rates were calculated by

$$\frac{k_A}{k_B} = \frac{\ln (\text{fraction of A remaining})}{\ln (\text{fraction of B remaining})}$$

(22) J. C. Jallageas and E. Casasevall, *C. R. Acad. Sci., Ser. C*, **268**, 449 (1969).

(23) L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis," Wiley, New York, N. Y., 1967, p 431.

(24) E. L. Eliel and C. Pillar, *J. Amer. Chem. Soc.*, **77**, 3600 (1955).

(25) H. B. Henbest, W. R. Jackson, and B. C. G. Robb, *J. Chem. Soc. B*, 803 (1966).

(26) G. Braun, "Organic Syntheses," Collect. Vol. I, Wiley, New York, N. Y., 1941, p 431.

(27) A. P. Gray, D. E. Heitmeier and H. Kraus, *J. Amer. Chem. Soc.*, **84**, 89 (1962).

(28) The possibility of deoxymercuration accompanying reduction has not been eliminated. Future studies will attempt to analyze the problem.

Registry No.—**5**, 20141-17-7; **6**, 32970-96-0; **16** 3,5-dinitrobenzoate, 32970-97-1.

Acknowledgment.—We wish to express our appreciation to the Endowment and Research Foundation of Montana State University for its generous support of this work.

Acid-Catalyzed Rearrangement of Laureatin to Isolaureatin and Related Reactions[1]

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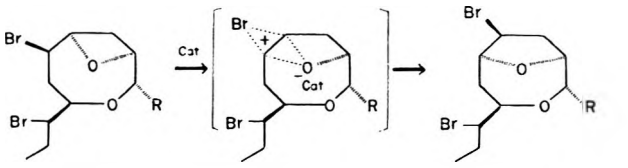
Received March 30, 1971

Laureatin (I) and isolaureatin (II) are naturally occurring bromo compounds containing oxetane and oxocane rings and oxolane and oxocane rings, respectively, from *Laurencia nipponica* Yamada.[2] In the course of studies aimed at selective cleavage of the oxetane ring of hexahydrolaureatin (III), we observed that on acid treatment (HBr–EtOH) III produced a trace of hexahydroisolaureatin (IV) besides a tribromo alcohol V, whose structure is discussed below. This finding prompted us to examine the reaction behavior of III and I under various acidic conditions. In this paper we report the rearrangement of these oxetane compounds (III and I) to the respective oxolane derivatives (IV and II) as well as related reactions.



I R = $-CH_2-CH=CH-C\equiv CH$ VII II R = $-CH_2-CH=CH-C\equiv CH$
III R = $n-C_5H_{11}$ IV R = $n-C_5H_{11}$

Compounds III and I were treated with Lewis acids and afforded IV and II, respectively, in moderate yields (maximum 76%) depending on the reaction conditions, as summarized in Table I.[3]

The same type of rearrangement was also observed when III was treated with H_2 in the presence of Pd/C at room temperature for 40 hr. Compounds IV, V, and a new monobromo alcohol VI[4] were produced in 38, 13, and 21% yields, respectively. Heating (*in vacuo*) in a sealed tube at 130–220°[5] resulted in recovery of III.[6] We emphasize that this rearrangement is noteworthy from the biogenetical point of view, since

(1) Part XVIII. Part XVII: M. Suzuki, E. Kurosawa, and T. Irie, *Tetrahedron Lett.*, 4995 (1970).

(2) T. Irie, M. Izawa, and E. Kurosawa, *Tetrahedron*, **26**, 851 (1970).

(3) The products were identified by comparison of their optical rotations and ir, nmr, and mass spectra, as well as R_f values in tlc, with those of authentic specimens.[2] The optical rotation of IV has been observed as $[\alpha]_D$ +8° in $CHCl_3$.

(4) Upon treatment with Raney Ni, VI afforded XI (see Experimental Section).

(5) Upon being heated above 230°, III decomposed with evolution of HBr.

(6) *Cf.* D. H. R. Barton, *et al.*, *J. Amer. Chem. Soc.*, **72**, 1066 (1950); *J. Chem. Soc.*, 1048 (1951); 4284 (1954); 4398 (1958).

TABLE I
REARRANGEMENT OF HEXAHYDROLAUREATIN (III) TO HEXAHYDROISOLAUREATIN (IV) AND OF LAUREATIN (I) TO ISOLAUREATIN (II)

Compd	Reagent	Reaction temp, °C	Reaction time, hr	Yield, % II	Yield, % IV	Yield, % V
III	HBr–EtOH	Reflux	24		10	51
III	KI–EtOH	Reflux	24		Trace	
III	KI–AcOH	Reflux	24		Trace	
III	KBr–AcOH	Reflux	21		39	
III	$ZnCl_2$–AcOH	80	17		42	
III	$ZnCl_2$–CF_3COOH–AcOH	40	53		76	
III	Br_2–CCl_4	Reflux	0.5		69	8
III	Br_2–EtOH	Reflux	0.5		13	65
I	$ZnCl_2$–AcOH	Reflux	24	19		
I	$ZnCl_2$–CF_3COOH–AcOH	40	48	33		

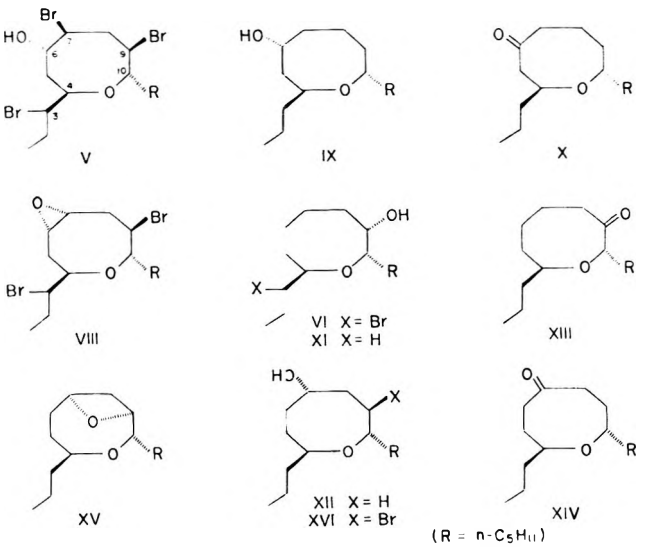
I and II have been isolated from the same alga.[2] The possibility was considered that II may have been formed by rearrangement of I during the isolation procedure. However, when an extraction procedure from alga was devised which rigorously excluded the conditions predicting rearrangement by heating or contacting with acid and alkali, I and II were isolated from the original extract in a ratio of 3:1 by neutral alumina chromatography. This fact supports the view that I and II are, indeed, naturally occurring compounds.

This rearrangement would certainly involve a synchronous shift of the Br atom and the oxido group oriented anti coplanar on adjacent carbon atoms, and relief of the oxetane ring strain in III or I would be, at least, a part of the driving force of this conversion.[7] A presumable structure VII for the intermediate, including an intimate ion pair, is favorable for this internal return.[8] This mechanistic pathway of the rearrangement is supported by the following evidence.

As shown in Table I, when III was refluxed with HBr or Br_2 in EtOH, compound IV in question was only a minor product (10–13%), and the main product (51–65%) proved to be a tribromo alcohol V (3,5-dinitrobenzoate, mp 162.5–163.5°). The structure of V, described later, suggests that both the relevant rearrangement and attack of the Br atom at C-9 leading to the formation of V would be concerted, probably *via* intermediate VII, because the oxolane ring of IV could not be cleaved under the conditions used.

The structure of V has been assigned on the basis of the spectral data (see Experimental Section) and the following evidence. (i) Treatment of V, its acetate, or its 3,5-dinitrobenzoate with 0.4 *N* NaOH–EtOH gave an epoxide (VIII) in a good yield, indicative of the trans disposition of the Br atom and the OH group on adjacent carbon atoms in V. (ii) Reduction of V with Raney Ni afforded a debromo alcohol (IX) which was oxidized with CrO_3–pyridine to yield the corresponding ketone (X). This alcohol IX was not identical with XI[2] and XII, the latter being prepared from hexahydrobisdebromolaureatin (XV)[2] *via* bromohydrin XVI (Br_2–EtOH, Raney Ni). Furthermore, ketone X proved to be different from XIII obtained by the oxidation of XI. The nmr spectral data of compounds IX–XIII are listed in Table II.

Contrary to expectation, oxidation of XII with CrO_3–pyridine gave no corresponding ketone XIV, yielding unidentified carboxylic acids. This anomalous behavior of XII could be explicable by the transannular effects, as shown below.[9]



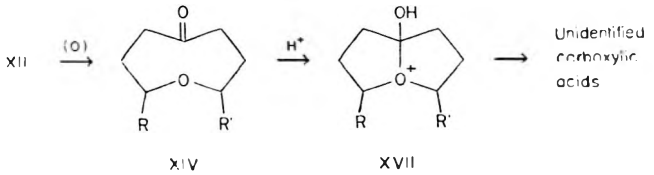


TABLE II
NMR DATA (τ) OF COMPOUNDS IX–XIII (60 MHz, IN CCl_4)

Compd	1-Me	15-Me	>CHOCH<	>CHOH	$-CH_2CO-$
IX	9.10 (br t)	9.10 (br t)	6.49 (2 H, m)	6.09 (1 H, m)	
X	9.05 (br t)	9.09 (br t)	6.52 (2 H, m)		7.78 (4 H, m)
XI	9.07 (br t)	9.07 (br t)	6.49 (2 H, m)	6.35 (1 H, m)	
XII	9.09 (br t)	9.09 (br t)	5.91 (2 H, m)	6.32 (1 H, m)	
XIII	9.07 (br t)	9.10 (br t)	6.39 (2 H, m)		7.21 (1 H, m)

Experimental Section[10]

General Procedure for the Rearrangement Reaction.—The sample (200–500 mg) was weighed in a tube, and a measured

(7) *Cf.* R. Hirshmann, G. A. Bailey, G. I. Poos, R. Walker, and J. M. Chemerda, *J. Amer. Chem. Soc.*, **78**, 4814 (1956); J. E. Herz, J. Fried, P. Grabowich, and E. F. Sabo, *ibid.*, **78**, 4812 (1956).

(8) P. de Mayo, "Molecular Rearrangements," Interscience, London, 1963, pp 3, 111; *cf.* P. G. Gassman and R. L. Cryberg, *J. Amer. Chem. Soc.*, **91**, 2047 (1969); F. Kohen, G. Adelstein, and R. E. Counsell, *Chem. Commun.*, 770 (1970); K. N. Houk, *J. Amer. Chem. Soc.*, **92**, 4144 (1970).

(9) N. J. Leonard, T. W. Milligan, and T. L. Brown, *J. Amer. Chem. Soc.*, **82**, 4075 (1960).

(10) Melting points are uncorrected. The purity of each compound was always checked by tlc. Optical rotations were determined in $CHCl_3$ solution. Ir spectra were obtained from a Nihon-Bunko IR-S spectrophotometer. Nmr spectra were taken with a Hitachi H-6013 spectrometer using TMS as internal standard in CCl_4. Mass spectra were obtained with a Hitachi RMU-6E mass spectrometer.

weight (200–300 mg) of catalyst and a measured volume (2–5 ml) of solvent were added. After being heated at the appropriate temperature, the reaction mixture was filtered and poured into water (50 ml) or evaporated *in vacuo* (in the case of EtOH solution). To the product was added 2 *N* aqueous NaOH (100 ml) and the whole was extracted repeatedly with ether. The ether solution was washed two times with 50-ml portions of 2 *N* NaOH solution and three times with 50-ml portions of water, dried over Na_2SO_4, and then evaporated. The oily substance thus obtained was purified by column chromatography on silica gel.

Rearrangement of Hexahydrolaureatin (III) to Hexahydroisolaureatin (IV) by Treatment with Zinc Chloride.—The solution of III[2] (227 mg) and anhydrous $ZnCl_2$ (287 mg) in a mixture of AcOH (3.0 ml) and CF_3COOH (0.2 ml) was heated at 40–42° for 53 hr. After being worked up as mentioned above, colorless oil (173 mg) was obtained, $[\alpha]D$ +8.3° (*c* 2.02, $CHCl_3$). The ir and nmr spectra were superimposable with those of an authentic sample of IV.[2]

Tribromo Alcohol V (3,7,9-Tribromo-4,10-epoxypentadecan-6-ol).—To a solution of III (2.69 g) in 99.5% EtOH (20 ml) was added Br_2 (1.0 ml) and the mixture was refluxed for 30 min. After being cooled, the solution was evaporated *in vacuo* and the residual oil was percolated with ether (*ca.* 100 ml). The ether solution was shaken successively with water, 10% $Na_2S_2O_3$ solution, and water and dried over Na_2SO_4. After removal of the solvent, the oily residue was purified by column chromatography on silica gel to give V (2.09 g) as a colorless oil: $[\alpha]D$ +14.8° (*c* 2.10, $CHCl_3$); ir (neat) 3450, 1041 cm^{-1}; nmr τ 9.09 (br t, 3), 8.91 (t, 3, J = 7 Hz), 8.71 (br m, 7), *ca.* 8.4–7.8 (br m, 4), 7.44 (br m, 4), 6.80 (br m, 1), 6.01 (br m, 5); mass spectrum *m/e* 359, 357, 355 ($M^+ - C_3H_6Br$), 329, 327, 325 ($M^+ - C_5H_{11}$ – HBr), 301, 299, 297 ($M^+ - C_6H_{11}O$ – HBr).

Acetate of V was obtained as a colorless oil: ir (neat) 1746, 1227, 1025 cm^{-1}; nmr τ 9.09 (br t, 3), 8.93 (t, 3, J = 7 Hz), 8.69 (br m, 6), *ca.* 8.4–8.0 (br m, 4), 7.98 (s, 3), 7.43 (br m, 4), 6.12 (br m, 4), 5.83 (m, 1), 4.77 (m, 1); mass spectrum *m/e* 401, 399, 397 ($M^+ - C_3H_6Br$).

3,5-Dinitrobenzoate of V was obtained as fine needles: mp 162.5–163.5°; ir ($CHCl_3$) 3100, 1745, 1630, 1602, 1551, 1463, 1347, 1273, 1165, 1076, 922 cm^{-1}; nmr τ 9.09 (br t, 3), 8.90 (t, 3, J = 7 Hz), 8.75 (br m, 6), *ca.* 8.4–7.8 (br m, 4), 7.28 (br m, 4), 5.09 (br m, 4), 4.60 (m, 1), 4.25 (m, 1), 0.83 (s, 3).

Anal. Calcd for $C_{22}H_{29}O_7N_2Br_3$: C, 39.25; H, 4.34; N, 4.16. Found: C, 39.51; H, 4.35; N, 4.34.

Epoxide VIII. A.—Compound V (746 mg) was eluted with benzene through a column packed with alumina (45 g), which was freshly shaken with 2 *N* NaOH and dried at 110°. The benzene eluate was evaporated *in vacuo* to give VIII (606 mg, 98%) as a colorless oil: $[\alpha]D$ −42.2° (*c* 2.25, $CHCl_3$); ir (neat) 1151, 1134, 1102, 1065, 964, 926, 905, 801, 762 cm^{-1}; nmr τ 9.10 (br t, 3), 8.95 (t, 3, J = 7 Hz), 8.75 (br m, 6), *ca.* 8.5–7.9 (m, 4), 7.69 (br m, 3), 7.35 (br m, 1), 6.90 (br m, 2), 3.86 (br m, 4); mass spectrum *m/e* 329, 327, 325 ($M^+ - C_5H_{11}$), 277, 275 ($M^+ - C_3H_6Br$), 235, 233, 219, 195 ($M^+ - C_3H_6Br$ – HBr).

B.—Hydrolysis of the acetate of V (274 mg) with 0.4 *N* NaOH–EtOH for 15 hr afforded VIII (157 mg) along with a small amount of unidentified by-product.

Alcohol IX (4,10-Epoxypentadecan-6-ol).—To a cold solution of V (194 mg) in EtOH (3 ml) was added freshly prepared W-7 Raney Ni (from 4 g of Al–Ni alloy). After being set aside for 3 hr, the reaction mixture was filtered and evaporated. The residual oil thus obtained was purified by column chromatography on silica gel to yield IX (85 mg) as colorless needles: mp 46.0–46.5° (from *n*-hexane); $[\alpha]D$ −20.6° (*c* 1.99, $CHCl_3$); ir ($CHCl_3$) 3350, 1130, 1080, 1054, 1033, 1009 cm^{-1}; nmr τ 9.10 (br t, 6), 8.70 (br m, 10), *ca.* 8.6–8.2 (br m, 10), 7.06 (br m, 1), 6.49 (br m, 2), 6.09 (br m, 1); mass spectrum *m/e* (rel intensity) 242 (0.2, M^+), 224 (3, $M^+ - H_2O$), 199 (17, $M^+ - C_3H_7$), 181 (11, $M^+ - C_3H_7 - H_2O$), 171 (19, $M^+ - C_5H_{11}$), 163 (17), 153 (13, $M^+ - C_5H_{11} - H_2O$), 141 (47), 123 (38), 113 (72), 95 (75), 83 (73), 81 (71), 69 (88), 55 (100), 43 (99).

Ketone X (4,10-Epoxypentadecan-6-one).—The alcohol IX (57 mg) was oxidized with CrO_3 (182 mg) in pyridine (1 ml) at room temperature for 4 days. After being worked up in the usual manner, the product was purified by chromatography on silica gel to yield X (52 mg) as colorless crystals: mp 35–37°; $[\alpha]D$ +32.6° (*c* 1.99 $CHCl_3$); ir ($CHCl_3$) 1700, 1128, 1071, 1038 cm^{-1}; nmr τ 9.09 (br t, 3), 9.05 (br t, 3), 8.68 (br m, 12), *ca.* 8.4–7.9 (m, 4), 7.78 (m, 4), 6.52 (br m, 2); mass spectrum *m/e* 240 (M^+), 197 ($M^+ - C_3H_7$), 169 ($M^+ - C_5H_{11}$), 157, 139, 129, 111, 85, 69, 55, 42.

Alcohol XI (4,10-Epoxypentadecan-9-ol).—This alcohol was prepared from III by treatment with Raney Ni in EtOH:[2] ir (neat) 3460, 1132, 1082, 1060 cm^{-1}; nmr τ 9.07 (br t, 6), *ca.* 6.5 (m, 3); mass spectrum *m/e* 242 (M^+).

Ketone XIII (4,10-Epoxypentadecan-9-one).—The alcohol XI (92 mg) was oxidized with CrO_3 (340 mg) in pyridine (2 ml) to give XIII (61 mg) as a colorless oil: ir (neat) 1710, 1129, 1085 cm^{-1}; nmr τ 9.10 (br t, 3), 9.07 (br t, 3), 8.63 (br m, 13), *ca.* 8.4–7.8 (br m, 6), 7.21 (m, 1), 6.39 (m, 2).

Bromohydrin XVI (9-Bromo-4,10-epoxypentadecan-7-ol).—To a solution of hexahydrobisdebromolaureatin (XV)[2] (250 mg) in EtOH (2 ml), Br_2 (0.2 ml) was added. After the mixture was allowed to stand for 2 days at room temperature, the solvent was removed *in vacuo* and the residue was percolated with ether. The ether solution was washed with 10% aqueous $Na_2S_2O_3$ and then with water, and dried. Removal of the ether followed by purification by silica gel chromatography afforded XVI (218 mg) as a colorless oil: ir (neat) 3400, 1085, 1025 cm^{-1}; nmr τ 9.09 (br t, 3), 9.06 (br t, 3), 8.63 (br m, 10), *ca.* 8.5–7.9 (m, 8), 7.73 (s, 1, OH), 6.30 (m, 1), 5.88 (m, 3).

The 3,5-dinitrobenzoate had mp 60.5–62.5°; ir (Nujol) 1737, 1629, 1600, 1549, 1274, 1168, 734, 725 cm^{-1}.

Anal. Calcd for $C_{22}H_{31}O_7N_2Br$: C, 51.27; H, 6.06; N, 5.44. Found: C, 51.20; H, 5.81; N, 5.27.

Alcohol XII (4,10-Epoxypentadecan-7-ol).—To a solution of XVI (125 mg) in EtOH (3 ml) was added freshly prepared W-7 Raney Ni (from 1 g of Al–Ni alloy). After being allowed to stand at room temperature for 3 hr, the catalyst and the solvent were removed and the residue was purified by column chromatography on silica gel to afford XII (80 mg) as colorless crystals: mp *ca.* 25°; ir (neat) 3350, 1085, 1055, 1030 cm^{-1}; nmr τ 9.09 (br t, 6), 8.69 (br m, 15), *ca.* 8.5–7.8 (br m, 5), 7.52 (s, 1, OH), 6.32 (m, 1), 5.91 (m, 2); mass spectrum *m/e* 242 (M^+), 224 ($M^+ - H_2O$), 199 ($M^+ - C_3H_7$), 171 ($M^+ - C_5N_{11}$).

Treatment of III with H_2 over Pd/C Catalyst.—In a hydrogenation vessel, III (668 mg) in AcOH (15 ml) was treated with H_2 over Pd/C catalyst at room temperature for 40 hr. After removal of the catalyst, the solution was neutralized and extracted with ether. The ether solution was dried and evaporated to yield a colorless oil. The product (672 mg) thus obtained was purified by column chromatography on silica gel to give IX (250 mg), V (107 mg), and VI (114 mg). Compound VI, colorless oil, $[\alpha]D$ + 14.3° (*c* 2.02, $CHCl_3$), showed ir spectrum 3450, 1123, 1110, 1085, 1050, 961, 803 cm^{-1}; nmr τ 9.09 (br t, 3), 8.95 (t, 3, J = 7 Hz), 6.54 (br m, 1), 6.24 (br m, 3); mass spectrum *m/e* 322, 320 (M^+), 241 ($M^+ - Br$), 224, 221 ($M^+ - C_6H_{12}O$), 199 ($M^+ - C_3H_6Br$).

Debromination of VI.—To a solution of VI (14 mg) in EtOH (0.5 mol) was added freshly prepared W-7 Raney Ni (from 0.5 g of Al–Ni alloy). After being worked up in the usual manner, colorless oil (8 mg) was obtained and identified as XI by a comparison of R_f value in tlc and ir spectrum with those of an authentic sample.[2]

Registry No.—I, 33122-30-4; II, 19897-64-4; III, 18762-31-7; IV, 19897-65-5; V, 33069-32-8; V acetate, 33069-33-9; V 3,5-dinitrobenzoate, 33069-34-0; VI, 33069-35-1; VIII, 33069-36-2; IX, 33069-37-3; X, 33069-38-4; XI, 33069-39-5; XII, 33069-40-8; XIII, 33069-41-9; XVI, 33069-42-0; XVI 3,5-dinitrobenzoate, 33069-43-1.

Acknowledgment.—The authors wish to express their thanks to Professor Tadashi Masamune for his helpful discussions. The authors' thanks are also due to Miss M. Shiozawa for her nmr measurements and to Miss Y. Imai for her measurements of mass spectra.

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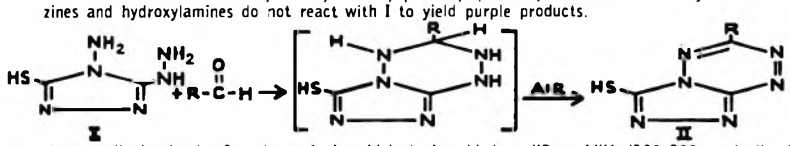

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(1) R. G. Dickinson and N. W. Jacobsen, Chem. Comm. 1719 (1970).

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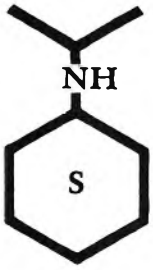

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M. W. Rathke and A. Lindert, J. Amer. Chem. Soc., *93*, 2318 (1971).

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1. W. H. Nutting, R. A. Jewell and H. Rapoport, J. Org. Chem. *35*, 505 (1970)

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