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THE JOURNAL OF Organic Chemistry®

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JANUARY 23, 1976

Synthesis and Cycloaddition Reactions of Acetylenic Iminium Compounds

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Received July 22, 1975

Phenyl, *tert*-butyl, and unsubstituted propiolamidium tetrafluoroborate salts, prepared from ready alkylation of acetylenic amides with triethyloxonium fluoroborate, undergo facile Diels–Alder cycloaddition with cyclopentadiene. Propiolamidium salts also react easily with tetraphenylcyclopentadienone, ethyl diazoacetate, and a mesoionic oxazolium compound. A qualitative comparison of the activation of multiple bonds toward cycloaddition by the amidium group with other known substituents is discussed.

Since electron-withdrawing substituents on acetylenes and olefins increase the rate of reaction with respect to the usual Diels–Alder addition,[2] it may be anticipated that in relation to carbonyl[3] and, in particular, nitro[4] groups, the iminium function, >C=N<$^+$, when substituted directly upon a multiple bond might exert a considerable inductive and mesomeric effect resulting in a facile Diels–Alder or 1,3-dipolar cycloaddition. The present study of iminium-activated acetylenes, previously unknown in the literature, shows that these compounds in fact rank among the best partners in Diels–Alder and 1,3-dipolar cycloaddition reactions.

Results and Discussion

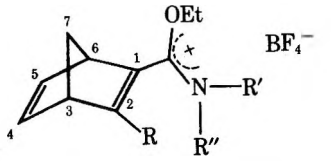
Of all the iminium-activated acetylenes represented by the general formula **1**, acetylenic iminium ethers (**1**, Z = OR‴) were the most easily accessible from phosgeneiminium salt chemistry,[5,6] and form the basis of the present study. Thus when the amide chloride of β-chlorocinnamic acid (**3**), initially formed from the condensation of acetophenone and phosgeneiminium chloride (**2**), was first hydrolyzed with saturated sodium bicarbonate yielding the β-chlorocinnamic amide **4**, followed by HCl elimination with sodium methoxide, *N,N*-dimethylphenylpropiolamide (**5**) was obtained in 76% yield. Then, treatment of **5** with triethyloxonium fluoroborate in methylene chloride at room temperature resulted in the formation of an air-stable, recrystallizable salt whose spectral and analytical data conform with the acetylenic amidium structure **6**. Analogously, *N,N*-dimethyl-*tert*-butylpropiolamide was converted into its alkylated salt **7** in 98% yield. Compound **7** is interesting in regard to *tert*-butylnitroacetylene, which was found to be much more reactive than the corresponding ester and nitrile derivatives.[4] The simplest and sterically least hindered propiolamidium tetrafluoroborate derivatives **8**–**10** were readily formed by analogous alkylation of unsubstituted propiolamides. Compounds **9** and **10** are yellow, crystalline, and isolable under an inert atmosphere. The less stable tertiary amidium **8** obtained in noncrystal-

6, R = C_6H_5; R′ = R″ = CH_3
7, R = $(CH_3)_3C$; R′ = R″ = CH_3
8, R = H; R′ = R″ = CH_3
9, R = R′ = H; R″ = CH_3
10, R = R′ = R″ = H

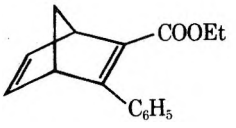
line form can be more conveniently generated in situ for use in further reactions.

A systematic comparison[7] of the ^{13}C spectra of acetylenic amides and corresponding amidium adducts indicates a considerable polarization of the amidium triple bond, i.e., a downfield shift of the β-acetylenic carbon together with an upfield shift of the α carbon, an expected result considering the conjugative effect of the iminium group. Such a polarization, explained in terms of perturbation molecular orbital theory,[8] might facilitate an unsymmetrical transition state within a cycloaddition reaction scheme, lower the energy requirements, and therefore produce a faster Diels–Alder or 1,3-dipolar cycloaddition. This has been found to be the case for acetylenic amidium compounds which exhibit a marked enhancement of reactivity when compared with their amides.

N,N-Dimethyl-*O*-ethylphenylpropiolamidium tetrafluoroborate (**6**) was treated with a slight excess of cyclopentadiene in CH_2Cl_2 at room temperature. After 24 hr the infrared absorption of the triple bond had diminished to one-half its initial intensity and after 70 hr it had completely disappeared. After evaporation of the solvent and excess diene and addition of ether, a compound whose spectral and analytical data are consistent with the norbornadiene derivative **11** was isolated. The cycloadduct **11** was characterized further by its hydrolysis to 1-carbethoxy-2-phenyl-3,6-*endo*-methylene-1,4-cyclohexadiene (**16**). The cycloadduct of cyclopentadiene and phenyl(trifluoromethanesulfonyl)acetylene occurs readily at room temperature whereas phenylpropioloyl chloride undergoes no appreciable reaction with cyclopentadiene.[2] Since an acid chloride substituent on acetylenes and olefins is more activating in cycloadditions than a nitrile, aldehyde, or ester, in that order,[2,9] it can be thus stated that *N,N*-dimethyl-*O*-ethylphenylpropiolamidium tetrafluoroborate (**6**) reacts faster than any of the corresponding carbonyl functionalized phenylacetylenes, and the amidium group activates more strongly than an acid chloride, nitrile, aldehyde, or ester group.



11, R = C_6H_5; R′ = R″ = CH_3
12, R = $(CH_3)_3C$; R′ = R″ = CH_3
13, R = R′ = H; R″ = CH_3
14, R = R′ = R″ = H
15, R = H; R′ = R″ = CH_3



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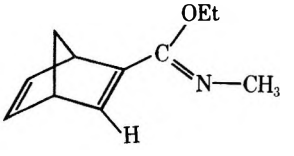

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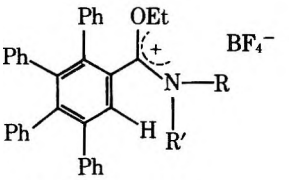
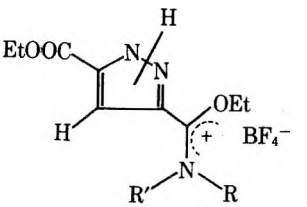
The reaction of cyclopentadiene with the *tert*-butyl acetylenic amidium compound **7** afforded after 2 weeks in methylene chloride at room temperature a stable 1:1 cycloadduct whose spectral and analytical data are consistent with its representation as **12**. In comparison with other *tert*-butyl acetylenes, the nitro-substituted derivative reacted fastest with cyclopentadiene, the completed reaction being observed after 2 hr at room temperature, but the corresponding ester and nitrile were inert to such conditions.[4] The lower reactivity of the *tert*-butyl derivative **7** toward cyclopentadiene as compared with its phenyl analogue **6** is apparently due to steric rather than electronic effects. The unsubstituted acetylenic amidium compounds **8–10** are therefore expectedly extremely reactive partners in Diels–Alder and 1,3-dipolar cycloadditions under these conditions.

Thus when the secondary propiolamidium compound **9** was initially treated in CH_2Cl_2 at room temperature with an excess of cyclopentadiene, an exothermic reaction ensued immediately upon addition. Complete disappearance of the triple bond was observed within 15 min; yet only an insoluble polymeric substance was obtained. However, when equimolar amounts of the two reactants were allowed to react, a product was isolated whose spectral characteristics are in agreement with the cycloadduct **13**. Both the ^1H and ^{13}C magnetic resonance spectra indicate that **13** exists in two forms, most likely owing to the orientation of the amidium group with respect to the norbornadiene C_1–C_2 double bond in a cis–trans arrangement. The hydrolysis of **13** with sodium carbonate produced an oil whose spectral data suggest the imino ether structure **17** since an NCH_3 resonance signal was observed at δ 3.01 and an imine absorption at 1660 cm^{-1} was recorded in the infrared spectrum. Noteworthy in the above reaction is the ease of cycloaddition reminiscent of the reactions of cyclopentadiene with dimethyl acetylenedicarboxylate[10] or propargyl aldehyde[11] at room temperature. Acetylene itself undergoes reaction[12] with cyclopentadiene only under increased pressure (1–6 atm) and at 325–435°. Even acetylacetylene requires heating at 90° for 6 hr in a sealed tube for reaction with cyclopentadiene.[13] Furthermore, the primary amidium derivative **10** was treated with cyclopentadiene at room temperature, yielding a 1:1 cycloadduct **14** in 71% yield. The NMR spectrum of **14** is easily interpretable. The H-2 olefinic proton resonated at δ 8.40 as a doublet ($J_{2,3}$ = 4.0 Hz) considerably shifted downfield with respect to the other vinylic protons H-4 and H-5 which were observed as a doublet of quartets at δ 6.92. This downfield shift is undoubtedly due to the adjacent amidium group at C-1. The allylic bridgehead protons H-3 and H-6 were found at δ 4.02 as a broad doublet and the bridge C-7 protons at δ 2.25 (bs). The NH_2 protons were nonequivalent arising at δ 8.74 and 9.17 as broad singlets and the remaining ethyl resonances were observed at δ 4.60 and 1.50. **8**, generated in situ, readily gave with cyclopentadiene the cycloadduct **15**.

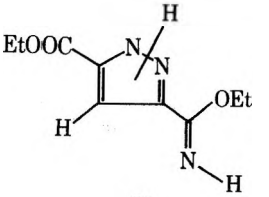
As a further example of their high reactivity, the monosubstituted acetylenic amidium derivatives **8** and **9** underwent ready cycloaddition with tetraphenylcyclopentadienone at room temperature, affording the substituted benzene derivatives **18** and **19**.



18, R = R′ = CH_3
19, R = H; R′ = CH_3



20, R = H; R′ = CH_3
21, R = R′ = H



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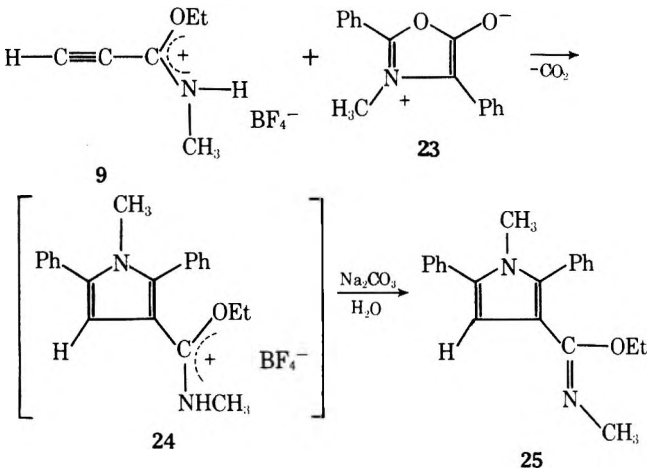
Derivatives **9** and **10** also underwent a facile 1,3-dipolar cycloaddition at room temperature. With ethyl diazoacetate and **9** or **10**, an exothermic reaction occurred and the amidium pyrazoles **20** and **21** were formed, respectively. Basic hydrolysis of **21** gave the imino ether derivative **22**. The 1,3 relationship between the carbethoxy and amidium groups is the expected[14] directiospecificity in such 1,3-dipolar cycloadditions.

Reaction of **9** with the azomethine 1,3-dipole contained in the oxazolium mesoionic compound[21] munchnone (**23**) afforded in a facile manner the imino ether pyrrole **25** via basic hydrolysis of the intermediate **24**.



The inability of **9** to undergo cycloaddition with anthracene or with tosyl azide gives an indication of the limits of reactivity of the monosubstituted acetylenic amidium derivatives.

When methyl propiolate as a reference and **8** and **9** were compared in reactivity to tetraphenylcyclopentadienone, only the acetylenic amidium salts reacted. Thus the monosubstituted acetylenic compounds are more reactive than the corresponding ester derivatives. In contrast to these highly reactive amidium salts, the corresponding propiolamides were unreactive under these conditions. Preliminary results on phenylpropiolamidinium perchlorate compounds (**1**, R = C_6H_5; Z = NHR; X = ClO_4) obtained by aminolysis of **3**, elimination of HCl, and protonation by perchloric acid, indicate that these derivatives are not very reactive in cycloadditions. The synthesis of less sterically hindered acetylenic amidinium compounds as well as other representative iminium-activated acetylenes (**1**, Z = H, alkyl, Cl) is currently under investigation and will be reported at a later date.

Experimental Section

Spectral characterizations were carried out on the following instrumentation: infrared spectra, Perkin-Elmer Model 257 spectrophotometer; NMR spectra, Varian DP-60, T-60, XL-100, and CFT-20 spectrometers, using Me_4Si as internal standard; mass spectra, Varian MAT-311 mass spectrometer at 70 eV. Melting points are uncorrected and were determined in capillaries in a "Dr. Tottoli" apparatus and all evaporations were carried out using a Rotovap apparatus. Microanalyses were performed by the Institut für Organische Chemie, Universität Wien, Vienna, Austria, and Instranal Laboratories, Rensselaer, N.Y.

Preparation of *N,N*-Dimethylphenylpropiolamide (5). To a stirred solution of *N,N*-dimethyl-β-chlorocinnamamide[6] (**4**) in dry methanol was added a methanolic solution of excess sodium methoxide at room temperature. After 5 min of stirring, the reaction was quenched with a small amount of water, solvent was evaporated, and the solid residue was extracted with CH_2Cl_2–H_2O. The organic layer was separated, dried over Na_2SO_4, and evaporated. **5** was recrystallized from cyclohexane as colorless needles (76%): mp 96–98° (lit.[15] mp 99, 101, 92°); ir ($CHCl_3$) 2220 (C≡C), 1625 cm^{-1} (CO); NMR ($CDCl_3$) δ 3.08, 3.33 [2 s, 6, $N(CH_3)_2$], 7.22–7.80 (m, 5, aromatic); mass spectrum *m/e* 173 ($M^{\cdot+}$), 129 (M − 44).

***N,N*-Dimethyl-*O*-ethylphenylpropiolamidium Tetrafluoroborate (6).** **5** (1.67 g, 0.01 mol) and triethyloxonium fluoroborate[16] (1.84 g, 0.01 mol) were stirred at room temperature in dry CH_2Cl_2 (20 ml) for 24 hr. The solvent was evaporated and the residue digested in anhydrous ether. Filtration, washing with ether, and drying afforded 2.39 g (85%) of a colorless, air-stable solid which could be recrystallized as colorless needles from ethanol (technical), but the recovery of **6** was low, possibly indicating reaction with solvent: mp 113–115°; ir (CH_2Cl_2) 2205 (C≡C), 1640 (amidium), 1060 cm^{-1} (BF_4^-); NMR ($CDCl_3$) δ 1.58 (t, *J* = 7.5 Hz, 3, OCH_2CH_3), 3.48, 3.73 [2 s, 6, $N(CH_3)_2$], 4.90 (q, 2, OCH_2CH_3), 7.34–8.08 (m, 5, aromatic).

Anal. Calcd for $C_{13}H_{16}NOBF_4$: C, 54.01; H, 5.58, N, 4.85. Found: C, 53.82; H, 5.40; N, 4.99.

***N,N*-Dimethyl-*O*-ethyl-*tert*-butylpropiolamidium Tetrafluoroborate (7).** Similarly, *N,N*-dimethyl-*tert*-butylpropiolamide[17] (0.95 g, 0.0062 mol) and triethyloxonium fluoroborate (1.2 g, 0.0063 mol) at room temperature in CH_2Cl_2 (25 ml) afforded an ether-insoluble product recrystallized as colorless prisms from ethanol–ether (1.32 g, 98%): mp 72–73°; ir (CH_2Cl_2) 2220 (C≡C), 1645 (amidium), 1060 cm^{-1} (BF_4^-); NMR ($CDCl_3$) δ 1.43 [s, 9, $C(CH_3)_3$], 1.52 (t, *J* = 7.0 Hz, 3, OCH_2CH_3), 3.41, 3.51 [2 s, 6, $N(CH_3)_2$], 4.70 (q, 2, OCH_2CH_3).

Anal. Calcd for $C_{11}H_{20}NOBF_4$: C, 49.09; H, 7.49; N, 5.21. Found: C, 48.87; H, 7.64; N, 5.37.

***N,N*-Dimethyl-*O*-ethylpropiolamidium Tetrafluoroborate (8).** *N,N*-Dimethylpropiolamide[18] (0.55 g, 0.006 mol) and triethyloxonium fluoroborate (1.20 g, 0.006 mol) were stirred in dry CH_2Cl_2 (15 ml) at room temperature for 19 hr. Solvent was removed in vacuo and the orange residual oil treated with anhydrous ether. After washing and decanting (all operations carried out under N_2) the oil was dried successively on water and oil vacuum pumps: yield 1.13 g (93% crude); ir (CH_2Cl_2) 3270 (HC≡C), 2120 (C≡C), 1655 (amidium), 1060 cm^{-1} (BF_4^-); NMR (CD_2Cl_2) δ 1.53 (t, *J* = 7.0 Hz, 3, OCH_2CH_3), 3.40, 3.63 [2 s, 6, $N(CH_3)_2$], 4.83 (q, 2, OCH_2CH_3), 4.93 (s, 1, HC≡C).

***O*-Ethyl-*N*-methylpropiolamidium Tetrafluoroborate (9).** *N*-Methylpropiolamide[18] (0.41 g, 0.005 mol) and Meerwein's reagent (0.94 g, 0.005 mol) were similarly allowed to react. After removal of solvent and addition of anhydrous ether, continued agitation produced a crystalline, yellow solid which was isolated (N_2 atmosphere) and dried under reduced pressure: yield 0.83 g (84%); ir (CH_2Cl_2) 3270 (HC≡C), 3220 (NH), 2130 (C≡C), 1665 (amidium), 1075 cm^{-1} (BF_4^-); NMR (CD_2Cl_2) δ 1.57 (t, *J* = 7.0 Hz, 3, OCH_2CH_3), 3.22 (d, *J* = 5.2 Hz, 3, $NHCH_3$), 4.70 (s, 1, HC≡C), 4.88 (q, 2, OCH_2CH_3), 10.2 (bs, 1, $NHCH_3$).

***O*-Ethylpropiolamidium Tetrafluoroborate (10).** Propiolamide[19] (0.66 g, 0.01 mol) and triethyloxonium fluoroborate (1.82 g, 0.01 mol) in dry CH_2Cl_2 (15 ml) were stirred overnight at room temperature. A light yellow oil insoluble in CH_2Cl_2 was formed. Solvent was evaporated and the oily residue was washed with anhydrous ether causing crystallization. The product (1.44 g, 82%) was dried under oil-pump vacuum. Owing to its insolubility spectral characterization could not be carried out.

1-(*N,N*-Dimethyl-*O*-ethylcarboxamidium)-2-phenyl-3,6-*endo*-methylene-1,4-cyclohexadiene Tetrafluoroborate (11). *N,N*-Dimethyl-*O*-ethylphenylpropiolamidium tetrafluoroborate (**6**, 0.2 g, 0.0007 mol) in CH_2Cl_2 (15 ml) was stirred at room temperature with an excess (~2 ml) of freshly distilled cyclopentadiene. After 70 hr the ir triple bond absorption had completely disappeared. The excess diene and solvent were evaporated and anhydrous ether added to the residual oil. Crystallization was induced by scratching after adding a trace of ethyl acetate, and recrystallization from ethyl acetate afforded colorless prisms (0.21 g, 85%): mp 122–123° dec; ir (CH_2Cl_2) 1645 (amidium), 1055 cm^{-1} (BF_4^-); NMR ($CDCl_3$) δ 1.31 (t, *J* = 7.0 Hz, 3, OCH_2CH_3), 2.20–2.56 (m, 2, H_7), 3.13, 3.41 [2 s, 6, $N(CH_3)_2$], 3.90–4.20 (m, 4, OCH_2CH_3, H_3 and H_6), 6.96–7.60 (m, 7, aromatic, H_4 and H_5).

Anal. Calcd for $C_{18}H_{22}NOBF_4$: C, 60.86; H, 6.24; N, 3.94. Found: C, 61.19; H, 5.96; N, 3.94.

Hydrolysis of 11. From **6** (0.2 g) and excess cyclopentadiene as described above was obtained the 1:1 cycloadduct **11** which was treated at room temperature with a saturated solution of potassium carbonate in H_2O with stirring and simultaneous extraction with ether. After all the solid had dissolved, the ether layer was isolated, the aqueous layer extracted once more with ether, and the ether extracts combined, dried ($MgSO_4$), and evaporated, leaving a light yellow oily residue which was distilled (horizontal bulbs,

130°, 0.1 mm) affording 1-carbethoxy-2-phenyl-3,6-*endo*-methylene-1,4-cyclohexadiene (**16**, 0.12 g, 72%): ir (film) 1700 cm^{-1} (CO); NMR ($CDCl_3$) δ 1.18 (t, J = 7.0 Hz, 3, OCH_2CH_3), 2.12 (m, 2, H_7), 3.95 (m, 2, H_3 and H_6), 4.08 (q, 2, OCH_2CH_3), 6.70–7.67 (m, 7, aromatic, H_4 and H_5); mass spectrum *m/e* 240 ($M^{\cdot+}$), 211 (M − Et·), 196 (M − CH_3CHO), 195 (M − EtO·), 175 (M − C_5H_5·), 129 ($PhC{\equiv}C{-}CO^+$).

1-(*N,N*-Dimethyl-*O*-ethylcarboxamidium)-2-*tert*-butyl-3,6-*endo*-methylene-1,4-cyclohexadiene Tetrafluoroborate (12). Over the period of 2 weeks was formed from **7** (0.5 g, 0.0018 mol) and excess cyclopentadiene in CH_2Cl_2 (15 ml) at room temperature, after evaporation and trituration with ether, a colorless solid recrystallized from ethyl acetate as colorless prisms (0.2 g, 32%): mp 135–140° dec; ir (CH_2Cl_2) 1655 (amidium), 1055 cm^{-1} (BF_4^-); NMR ($CDCl_3$) δ 1.08 (s, 9, *tert*-butyl), 1.45 (t, J = 7.0 Hz, 3, OCH_2CH_3), 1.90–2.26 (m, 2, H_7), 3.04, 3.33, 3.40, 3.43 [4 s, 6, $N(CH_3)_2$], 3.74–4.17 (m, 2, H_3 and H_6), 4.47 (q, 2, OCH_2CH_3), 6.66–7.23 (m, 2, H_4 and H_5).

Anal. Calcd for $C_{16}H_{26}NOBF_4$: C, 57.33; H, 7.82; N, 4.18. Found: C, 57.67; H, 7.87; N, 4.23.

1:1 Adduct of 9 and Cyclopentadiene. The secondary unsubstituted yneamidium compound **9** (0.65 g, 0.0033 mol) in dry CH_2Cl_2 (10 ml) was treated with an equivalent amount of freshly distilled cyclopentadiene (0.22 g, 0.0033 mol) at room temperature with stirring. After the reaction was followed by ir spectroscopy, solvent was evaporated 30 min later and the residue washed thoroughly (N_2 atmosphere) with anhydrous ether. The ether was decanted and the semisolid residue of 1-(*N*-methyl-*O*-ethylcarboxamidium)-3,6-*endo*-methylene-1,4-cyclohexadiene tetrafluoroborate (**13**) was dried under reduced pressure: ir (CH_2Cl_2) 3290, 3220 (NH), 1645 (amidium), 1060 cm^{-1} (BF_4^-); NMR (CD_2Cl_2) δ 1.46 (t, J = 7.0 Hz, 3, OCH_2CH_3), 2.38 (m, 2, H_7), 3.10, 3.26 (dd, J = 5.5 Hz, 3, $NHCH_3$), 3.95 (m, 2, H_3 and H_6), 4.50 (m, 2, OCH_2CH_3, nonequivalent methylene protons presented as a ten-line multiplet), 6.88 (m, 2, H_4 and H_5), 7.96 (m, 1, H_2), 9.05 (bs, 1, $NHCH_3$).

Hydrolysis of 13. Treatment of **13** (0.13 g, 0.0005 mol) with a saturated solution of Na_2CO_3, extraction with ether, drying, and evaporation afforded a crude orange oil whose spectral data were in accord with the norbornadienyl imino ether **17**: ir (film) 3000 region (CH aliphatic), 1660 cm^{-1} (C=N); NMR ($CDCl_3$) δ 1.25 (t, J = 7.0 Hz, 3, OCH_2CH_3), 1.92–2.17 (m, 2, H_7), 3.01 (s, 3, NCH_3), 3.55–3.92 (m, 2, H_3 and H_6), 3.96 (q, 2, OCH_2CH_3), 6.59–7.08 (m, 3, H_2, H_4, and H_5); mass spectrum *m/e* 177 ($M^{\cdot+}$).

1-(*O*-Ethylcarboxamidium)-3,6-*endo*-methylene-1,4-cyclohexadiene Tetrafluoroborate (14). To a suspension of the primary amidium compound **10** (0.74 g, 0.004 mol) in dry CH_2Cl_2 (20 ml) was added cyclopentadiene (0.27 g, 0.0041 mol) with stirring at room temperature. The initially insoluble **10** reacted gradually into solution (0.5 hr). After 3 hr the reaction mixture was filtered, the solvent evaporated, and dry ether added, effecting the crystallization of an air-stable cream solid (0.72 g, 71%): mp 120–123° dec; ir (CH_2Cl_2) 3440, 3180 (NH), 1680 (amidium), 1050 cm^{-1} (BF_4^-); NMR ($CDCl_3$) δ 1.50 (t, J = 7.5 Hz, 3, OCH_2CH_3), 2.25 (bs, 2, H_7), 4.02 (bd, 2, H_3 and H_6), 4.60 (q, 2, OCH_2CH_3), 6.92 (dq, J = 3.0, 14.0 Hz, 2, H_4 and H_5), 8.40 (d, $J_{2,3}$ = 4.0 Hz, 1, H_2), 8.74, 9.17 (2 bs, 2, NH_2).

1-(*N,N*-Dimethyl-*O*-ethylcarboxamidium)-3,6-*endo*-methylene-1,4-cyclohexadiene Tetrafluoroborate (15). To triethyloxonium fluoroborate (1.0 g, 0.0052 mol) in dry CH_2Cl_2 (20 ml) was added *N,N*-dimethylpropiolamide[18] (0.51 g, 0.0052 mol) with stirring. After 5 min at room temperature, cyclopentadiene (0.35 g, 0.0053 mol) was introduced. Solvent was evaporated after 20 min, and the residue was washed thoroughly with anhydrous ether and dried under reduced pressure (0.1 mm), yield 1.28 g (87%) of an orange oil contaminated by a small amount of Meerwein's reagent: ir (CH_2Cl_2) 1650 (amidium), 1600 (C=C), 1050 cm^{-1} (BF_4^-); NMR (CD_2Cl_2) δ 1.42 (t, 3, OCH_2CH_3), 2.04–2.40 (m, 2, H_7), 3.25, 3.33 [2 s, 6, $N(CH_3)_2$], 3.84–4.16 (m, 2, H_3 and H_6), 4.30 (q, 2, OCH_2CH_3), 6.84–7.17 (m, 2, H_4 and H_5), 7.60–7.73 (m, 1, H_2).

***N,N*-Dimethyl-*O*-ethyl-2,3,4,5-tetraphenylbenzamidium Tetrafluoroborate (18).** After triethyloxonium fluoroborate (1.25 g, 0.0066 mol) and **8** (0.64 g, 0.0066 mol) were stirred in dry CH_2Cl_2 (20 ml) for 10 min, tetraphenylcyclopentadienone (2.33 g, 0.0061 mol) was introduced and stirring continued for 18 hr. The solvent was then evaporated, anhydrous ether added, and crystallization induced by scratching, and **18** was recrystallized as colorless, irregular prisms from acetonitrile–ether (3.1 g, 83%): mp 248–250° dec (with gas evolution); ir (CH_2Cl_2) 1660 (amidium), 1060 cm^{-1} (BF_4^-); NMR (Me_2SO-d_6) δ 1.27 (t, J = 7.0 Hz, 3, OCH_2CH_3), 3.20, 3.40 [2 s, 6, $N(CH_3)_2$], 4.36 (m, 2, OCH_2CH_3), 6.96 (bs, 10, aromatic), 7.25 (s, 10, aromatic), 8.00 (s, 1, H_6).

Anal. Calcd for $C_{35}H_{32}NOBF_4$: C, 73.82; H, 5.67; N, 2.46. Found: C, 74.50; H, 5.26; N, 2.54.

***N*-Methyl-*O*-ethyl-2,3,4,5-tetraphenylbenzamidium Tetrafluoroborate (19).** **9** (0.5 g, 0.0025 mol) and tetracyclone (0.97 g, 0.0025 mol) were stirred in dry CH_2Cl_2 (20 ml) overnight. Solvent was evaporated and ether added, precipitating a solid, which was digested by agitation, filtered, and recrystallized from ethanol as colorless prisms (1.31 g, 94%): mp 209–211° dec (with gas evolution); ir ($CHCl_3$) 1665 (amidium), 1080 cm^{-1} (BF_4^-); NMR ($CDCl_3$) δ 1.18 (t, J = 7.0 Hz, 3, OCH_2CH_3), 2.88 (d, J = 5.0 Hz, 3, $NHCH_3$), 4.24 (q, 2, OCH_2CH_3), 6.50–7.34 (3 bs, 20, aromatic), 7.67 (s, 1, H_6), 9.92 (bs, 1, $NHCH_3$).

Anal. Calcd for $C_{34}H_{30}NOBF_4$: C, 73.52; H, 5.44; N, 2.52. Found: C, 73.68; H, 5.49; N, 2.49.

3-(*N*-Methyl-*O*-ethylcarboxamidium)-5-carbethoxypyrazole Tetrafluoroborate (20). A solution of ethyl diazoacetate (0.45 g, 0.004 mol) in CH_2Cl_2 (5 ml) was added dropwise to a stirred solution of the acetylenic amidium compound **9** (0.79 g, 0.004 mol). An exothermic reaction ensued and after stirring was continued for 1 hr, solvent was evaporated, anhydrous ether was added, and the resultant viscous oil was washed and vacuum dried (1.04 g, 84%): ir (CH_2Cl_2) 3200–3300 (b, NH), 1735 (CO), 1660 (amidium), 1080 cm^{-1} (BF_4^-); NMR (CD_2Cl_2) δ 1.00–1.92 (m, 6, OCH_2CH_3), 3.34 (d, J = 5.0 Hz, 3, $NHCH_3$), 4.42 (q, 2, $COOCH_2CH_3$), 5.05 (q, 2, OCH_2CH_3), 7.62 (s, 1, H_4), 9.75 (bm, 1, $NHCH_3$), 12.1 (bs, 1, ring NH).

3-(*O*-Ethylcarboxamidium)-5-carbethoxypyrazole Tetrafluoroborate (21). To a suspension of **10** (1.44 g, 0.0078 mol) suspended in dry CH_2Cl_2 (15 ml) was added dropwise ethyl diazoacetate (0.89 g, 0.0078 mol) with stirring at room temperature. After 30 min all starting material had reacted and stirring was continued for an additional 1 hr. The reaction mixture was filtered and evaporated and the residue digested in dry ether, yielding an air-stable light yellow solid (1.77 g, 76%): mp 80–83° dec; ir (CH_2Cl_2) 3000–3400 (NH, CH aliphatic, broad), 1740 (CO), 1690 (amidium), 1640 (CN), 1065 cm^{-1} (BF_4^-); NMR (Me_2SO-d_6) δ 1.38, 1.52 (2 t, 6, OCH_2CH_3), 4.45, 4.69 (2 q, 4, OCH_2CH_3), 7.79 (s, 1, H_4), NH not observed but addition of CF_3COOD yielded a peak of approximate integration of three protons.

Hydrolysis of 21. In the usual manner **21** (1.0 g, 0.0033 mol) was hydrolyzed with saturated Na_2CO_3–H_2O affording the imino ether **22** as light orange needles from ethyl acetate (0.6 g, 85%): mp 148–150°; ir (CH_2Cl_2) 3600 (NH), 3410 (NH), 1730 (CO), 1650 cm^{-1} (CN); NMR ($CDCl_3$) δ 1.38 (dt, 6, OCH_2CH_3), 4.38 (q, 4, OCH_2CH_3), 7.03 (s, 1, H_4), 10.1 (bs, 2, NH); mass spectrum *m/e* 211 ($M^{\cdot+}$), 210 (M − H·), 196 (M − CH_3·), 183 (M − CO).

Anal. Calcd for $C_9H_{13}N_3O_3$: C, 51.18; H, 6.20; N, 19.89. Found: C, 50.99; H, 5.92; N, 19.85.

Reaction of 9 with Munchnone.[21] To **9** (0.36 g, 0.0018 mol) in CH_2Cl_2 (15 ml) was added in small portions the oxazolium mesoionic compound **23** (0.46 g, 0.0018 mol) whereupon an immediate evolution of gas was observed (CO_2). After 1 hr of stirring at room temperature, solvent was evaporated but the oily residue could not be induced to crystallize and was directly hydrolyzed with saturated Na_2CO_3–H_2O in the usual manner, affording the imino ether pyrrole **25** as colorless needles from cyclohexane (0.51 g, 89%): mp 94–98° dec; ir (CH_2Cl_2) 1670 cm^{-1} (C=N); NMR ($CDCl_3$) δ 1.12 (t, J = 7.0 Hz, 3, OCH_2CH_3), 2.90 (s, 3, NCH_3), 3.52 (s, 3, NCH_3), 4.08 (q, 2, OCH_2CH_3), 6.40 (s, 1, H_4), 7.17–7.59 (m, 10, aromatic); mass spectrum *m/e* 318 ($M^{\cdot+}$), 317 (M − H·), 303 (M − CH_3·), 298 (M − CO), 289 (M − Et·), 273 (M − EtO·), 105 ($PhC{\equiv}O^+$), 77 (Ph^+).

Anal. Calcd for $C_{21}H_{22}N_2O$: C, 79.21; H, 6.97; N, 8.80. Found: C, 79.22; H, 6.98; N, 9.04.

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Bridgehead Nitrogen Systems. X. Cycloadditions with Thiazolium *N*-Ylides[1]

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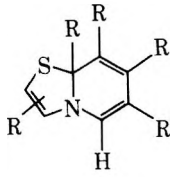
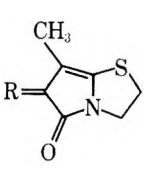
The thiazolium ylides, derived from 3-(2-aryl-2-oxoethyl)-4-methylthiazolium bromides and triethylamine, gave with dimethyl acetylenedicarboxylate and dibenzoylacetylene derivatives of the 1*H*-pyrrolo[2,1-c][1,4]thiazine system that were formed by rearrangement of the intermediate 5,7a-dihydropyrrolo[2,1-*b*]thiazole system. With ethyl propiolate a 1,2 adduct was formed by further reaction of a hydroxyl substituent in the thiazine system with ethyl propiolate and, in one instance, dibenzoylacetylene gave a dihydrothiazolo[3,2-*a*]azepine derivative. *N*-Phenylmaleimide also formed an adduct of the above pyrrolo[2,1-*b*]thiazole system but with phenyl isocyanate and phenyl isothiocyanate, ring closure of the initially formed 1,5-dipolar intermediate did not occur, these betaines being readily isolated.

Thiazole and its alkyl derivatives[2] undergo condensation with dimethyl acetylenedicarboxylate, giving 1:2 adducts. In contrast to the reaction of pyridine with acetylenic dienophiles, reactions of this type have recently been shown[3–5] to lead to isomeric rearrangement products such as **1**. Δ^2-Thiazolines also react[6] with acetylenic esters and an interesting variation occurs when 2-ethyl-Δ^2-thiazoline and the acetylenic ester react in the presence of 1 mol of an unsaturated compound such as methyl vinyl ketone. In this case the pyrrolo[2,1-*b*]thiazole derivative **2** was formed, with the ethylenic compound being involved in a transient quaternization of the thiazoline nitrogen atom.[7] Other 2-alkylthiazoles, converted into 3-acetonyl- and 3-phenacyl-2-alkylthiazolium salts, are cyclized with sodium acetate in aprotic solvents into pyrrolo[2,1-*b*]thiazoles.[8] Thiazole itself reacted[9] with tetracyanoethylene oxide to form the ylide **3** which, with dimethyl acetylenedicarboxylate, gave **4**. The ready quaternization of thiazoles suggested that deprotonation and subsequent 1,3-dipolar cycloaddition of the resulting ylide with dipolarophiles would be an attractive and versatile route to pyrrolo[2,1-*b*]thiazole derivatives with a variety of functional groups in the 6 and 7 positions. Our efforts to obtain these products, intermediates in the synthesis of analogues of the thieno[3,4-c]pyrrole system,[10] are described below.

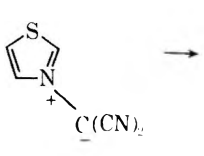


1



2

R = CH_3OOCCH



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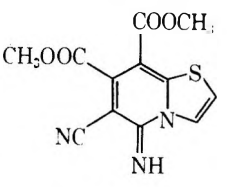
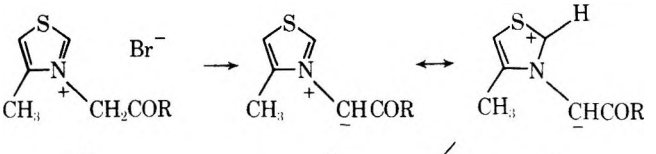
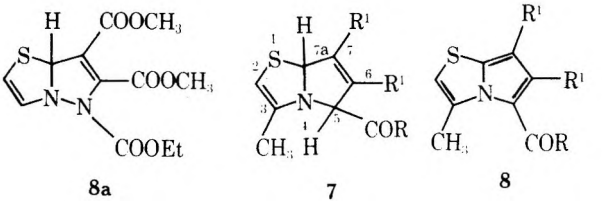


4

4-Methylthiazole and 2-bromoacetophenone, as well as 2,4′-dibromoacetophenone, reacted readily in boiling ethanol, giving the corresponding thiazolium salt **5** (R = Ph, *p*-BrC_6H_4, respectively). Similarly, ethyl bromoacetate in ether at room temperature gave the corresponding salt **5** (R = OEt). In the reactions described below the ylide **6** was generated in situ from the salt **5** and triethylamine in the

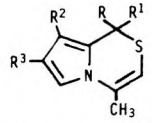


5 **6** **6a**



8a **7** **8**

Table I. Cycloadducts Derived from Thiazolium *N*-Ylides and Acetylenic Dipolarophiles



R	R^1	R^2	R^3	Mp °C	Yield %	Formula	Crystal Habit[a]	M^+	IR Data (KBr, cm^{-1})	UV Data $\lambda_{max}^{CH_3OH}$ nm (log ε)	NMR Data (δ) J (Hz)
Ph	OH	$COOCH_3$	$COOCH_3$	172	89	$C_{18}H_{17}NO_5S$	A[b]	359	3350 (OH) 1730, 1695 (CO)	214 (4.38)	7.66-7.22 (m, 5, aromatic), 7.40 (s, 1, H_6), 5.85 (bs, 1, H_3), 4.74 (s, 1, OH), 3.72 (s, 3, CO_2CH_3), 3.19 (s, 3, CO_2CH_3), 2.30 (bs, 3, 4-CH_3)[c]
p-BrC_6H_4	OH	$COOCH_3$	$COOCH_3$	182	61	$C_{18}H_{16}BrNO_5S$	A[d]	437	3350 (OH) 1725, 1685 (CO)		7.48 (s, 4, aromatic), 7.26 (s, 1, H_6), 5.86 (bs, 1, H_3), 4.53 (s, 1, OH), 3.80 (s, 3, CO_2CH_3), 3.36 (s, 3, CO_2CH_3), 2.35 (bs, 3, 4-CH_3)[c]
Ph	OH	COPh	COPh	165	89	$C_{28}H_{21}NO_3S$	B[b]	—	3325 (OH) 1625 (CO)	245 (4.40) 287 (4.10)	7.60-6.89 (m, 16, aromatic and H_6), 5.96 (bs, 1, H_3), 5.02 (s, 1, OH), 2.34 (bs, 3, CH_3)[c]
p-BrC_6H_4	OH	COPh	COPh	201-202	47	$C_{28}H_{20}BrNO_3S$	C[b]	—	3330 (OH) 1645 (CO)	235 (4.48) 285 (4.23)	7.77-7.0 (m, 15, aromatic and H_6), 6.23 (bs, 1, H_3), 2.42 (bs, 3, CH_3)[e]
Ph	OCH=$CHCOOC_2H_5$	H	$COOC_2H_5$	135-137	36	$C_{22}H_{23}NO_5S$	C[b]	413	1725, 1695 (CO) 1635 (C=C)	208 (4.33) 233 (4.29) 292 (4.43)	7.91-7.43 (m, 5, aromatic), 7.47 (d, 1, J = 1.5, H_6), 7.19 (d, 1, J = 1.5, H_8), 7.03 (d, 1, J = 10.0, OCH), 6.29 (bs, 1, H_3), 5.76 (d, 1, J = 10.0, vinylic), 4.29 (q, 2, J = 7.0, CH_2CH_3), 4.11 (q, 2, J = 7.0, CH_2CH_3), 2.29 (bs, 3, 4-CH_3), 1.34 (t, 3, J = 7.0, CH_2CH_3), 1.22 (t, 3, J = 7.0, CH_2CH_3)[c]
p-BrC_6H_4	OCH=$CHCOO_2H_5$	H	$COOC_2H_5$	170-172	47	$C_{22}H_{22}BrNO_5S$	A[b]	491	1725, 1720, 1685 (CO) 1635 (C=C)	293 (4.46)	7.80-7.54 (m, 4, aromatic), 7.49 (d, 1, J = 1.5, H_6), 7.14 (d, 1, J = 1.5, H_8), 7.00 (d, 1, J = 10.0, OCH), 6.26 (bs, 1, H_3), 5.77 (d, 1, J = 10.0, vinylic), 4.29 (q, 2, J = 7.0, CH_2CH_3), 4.12 (q, 2, J = 7.0, CH_2CH_3), 2.28 (bs, 3, 4-CH_3), 1.34 (t, 3, J = 7.0, CH_2CH_3), 1.23 (t, 3, J = 7.0, CH_2CH_3)[c]
Ph	OCH=$CHCOOC_2H_5$	$COOCH_3$	$COOCH_3$	152-153	37	$C_{23}H_{23}NO_7S$	D[d]	457	1720, 1695 (CO) 1635 (C=C)	238 (4.22) 290 (4.38)	7.93-7.20 (m, 5, aromatic), 7.41 (s, 1, H_6), 6.90 (d, 1, J = 10.0, OCH), 6.28 (bs, 1, H_3), 5.73 (d, 1, J = 10.0, vinylic), 4.16 (q, 2, J = 7.5, CH_2CH_3), 3.83 (s, 3, CO_2CH_3), 3.26 (s, 3, CO_2CH_3), 2.26 (bs, 3, 4-CH_3), 1.25 (t, 3, J = 7.5, CH_2CH_3)[c]
p-BrC_6H_4	OCH=$CHCOOC_2H_5$	$COOCH_3$	$COOCH_3$	141	86	$C_{23}H_{22}BrNO_7S$	E[d]	535	1740, 1720 (CO) 1640 (C=C)		7.73-7.40 (m, 4, aromatic), 7.33 (s, 1, H_6), 6.81 (d, 1, J = 10.0, OCH), 6.21 (bs, 1, H_3), 5.70 (d, 1, J = 10.0, vinylic), 4.13 (q, 2, J = 7.0, CH_2CH_3), 3.81 (s, 3, CO_2CH_3), 3.33 (s, 3, CO_2CH_3), 2.26 (bs, 3, 4-CH_3), 1.25 (t, 3, J = 7.0, CH_2CH_3)[c]
Ph	OCH=CHCOOH	H	COOH	232-234	70	$C_{18}H_{15}NO_5S$	E[b]	—	1695, 1680 (CO) 1640 (C=C)	235 (4.21) 290 (4.33)	7.86-7.55 (m, 6, aromatic and H_6), 7.41 (d, 1, J = 10.0, OCH), 6.95 (d, 1, J = 1.5, H_8), 6.70 (bs, 1, H_3), 5.81 (d, 1, J = 10.0, vinylic), 2.26 (bs, 3, 4-CH_3)[e]
p-BrC_6H_4	OCH=CHCOOH	H	COOH	265	92	$C_{18}H_{14}BrNO_5S$	F[f]	—	1675 (CO) 1640 (C=C)	260 (4.29) 287 (4.38)	7.87 (d, 1, J = 1.5, H_6), 7.80 (m, 4, aromatic), 7.48 (d, 1, J = 10.0, OCH), 7.06 (d, 1, J = 1.5, H_8), 6.77 (bs, 1, H_3), 5.88 (d, 1, J = 10.0, vinylic), 2.25 (bs, 3, 4-CH_3)[e]

[a] A = colorless needles; B = cream plates; C = plate yellow needles; D = colorless plates; E = colorless prisms; F = pale yellow prisms. Satisfactory analytical values (± 0.4% for C, H, N) were reported for all compounds in Table: Ed. [b] Crystallized from CH_3OH. [c] $CDCl_3$. [d] Crystallized from EtOH. [e] DMSO-d_6. [f] Crystallized from EtOH-H_2O.

Table II
^{13}C Chemical Shifts (ppm) for Products Obtained from 6 and Acetylenic Dipolarophiles[13]

Compd	Atom no. in 10									
	1	3	4	6	7	8	8a	C_4 CH_3	C_7 CO	C_8 CO
10 R = Ph; R^1 = $COOCH_3$	78.6	104.34	129.97	121.61	112.84	112.76	129.71	19.55	162.84	164.56
10 R = Ph; R^1 = COPh	78.98	104.52	131.26	123.46	122.54	119.31	130.00	19.38	188.23	191.50

presence of the dipolarophile, its presence being indicated by the deep-orange color of the reaction mixture.

Acetylenic Dipolarophiles. The ylide **6** (R = Ph, *p*-BrC_6H_4) readily gave 1:1 adducts with dimethyl acetylenedicarboxylate and dibenzoylacetylene in high yields expected to have structure **7** or its oxidation product **8** (R = Ph, *p*-BrC_6H_4; R^1 = $COOCH_3$). Analytical and mass spectral data (Table I) established a molecular composition for these products corresponding to **7**. However, a variety of oxidizing agents such as DDQ, tetrachloro-o- and -*p*-benzoquinone, $Pb(OAc)_4$, Ag_2O, and $Hg(OAc)_2$ could not convert **7** into the heteroaromatic system **8**, an oxidation that is extremely facile and often occurs on reaction work-up in related bicyclic systems.[11]

The principal ^{1}H NMR spectral characteristics of the 1:1 adduct from **6** (R = Ph) and dimethyl acetylenedicarboxylate interpreted in terms of structure **7** (R = Ph; R^1 = $COOCH_3$) were slightly broadened singlets at δ 5.85 (H_2) and 2.3 (3-CH_3) that on expansion were recognized as a quartet and a doublet, respectively ($J \simeq 1$ Hz, 100 MHz), and singlets at δ 7.4 (H_{7a}) and 4.74 (H_5), the last undergoing ready exchange with D_2O ($CDCl_3$ solution).

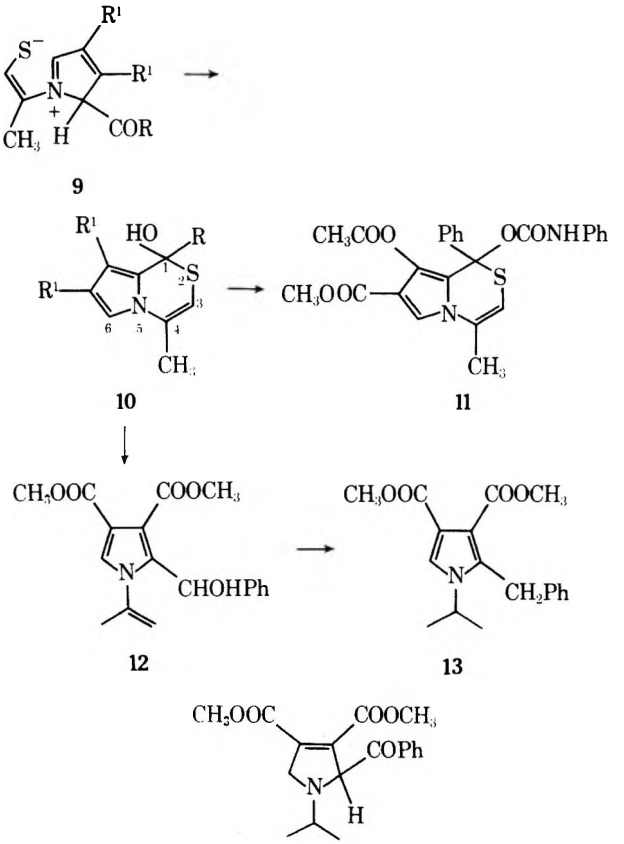
Although the chemical shift of H_2 at δ 5.85 is at higher field than the analogous proton in 2-methylthiazole itself (δ 6.83), the loss of ring current in **7** may account for this shift. Similarly, the chemical shift of H_{7a} at δ 7.4 approximates[12] that of H_{7a} in **8a** (δ 7.97).

The infrared spectrum of the product showed ν_{COOCH_3} at 1695 and 1730 cm^{-1} and a strong, broad absorption at 3350 cm^{-1} which was still retained even after extensive drying in vacuo. There was no absorption due to an aryl ketone.

These spectral and chemical properties make it very likely that the product obtained in this reaction is not the simple 1:1 adduct but rather some isomeric rearrangement product. In analogy to rearrangements observed in the thiazole[3] and benzimidazole systems,[5] the most likely bond to break in **7** is the C_{7a}–S bond. The intermediate vinyl sulfide formed, by rotation and condensation at the carbonyl group initially at C_5, would give rise to the hemithioketal **10** (R = Ph; R^1 = $COOCH_3$), the formation of the aromatic pyrrole nucleus no doubt providing driving force for the rearrangement.

Chemical evidence in support of structure **10** is twofold. Reaction of **10** with phenyl isocyanate gave the urethane **11**, characterized by ν_{NH} 3330 cm^{-1} and ν_{OCONH} 1740 cm^{-1}, and also by the disappearance in its ^{1}H NMR spectrum of the resonance at δ 4.74 which can be attributed to the OH group in **10**. In addition, treatment of **10** with W-2 Raney nickel resulted in desulfurization and formation of methyl 1-isopropyl-2-benzylpyrrole-3,4-dicarboxylate (**13**), probably via the intermediate product **12**, as tertiary alcohols have been observed[13] to undergo ready hydrogenolysis under these conditions. This last transformation excludes structure **7** as its desulfurization product would be anticipated to be the dihydropyrrole **13a**.

Structure **10** is consistent with both the ^{1}H NMR and ^{13}C NMR spectra. In the former resonances at δ 7.4, 5.85, and 2.3 are consistent with H_6, H_3, and 4-CH_3, respectively, and the exchangeable proton at δ 4.74 may be assigned to



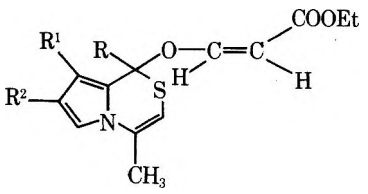
the 1-OH group. In Me_2SO-d_6 or $(CD_3)_2CO$ this proton undergoes an upfield shift, being obscured by the solvent water absorption. The ^{13}C spectrum[14] provided definitive evidence in support of structure **10**. Two resonances only were observed in the carbonyl region at 164.56 and 162.84 ppm attributable to the ester carbonyl groups, the remaining assignments being shown in Table II. Particularly important is the absence of an absorption that could be assigned to the tertiary C_5 in **7**, this absorption being anticipated[3] at ca. 65.5 ppm in analogy to that found for C_4 in tetramethyl 7,9-dimethyl-4*H*-quinolizine-1,2,3,4-tetracarboxylate.

Similarly, the reaction of **6** (R = *p*-BrC_6H_4) with DMAD gave an analogous adduct **10** (R = *p*-BrC_6H_4; R^1 = $COOCH_3$). Its ^{1}H NMR spectrum showed a readily exchangeable (D_2O) singlet at δ 4.53 assigned to the OH proton and the H_6 pyrrole proton was observed at δ 7.26, a chemical shift consistent with those reported[14] for pyrrole protons in similar environments.

Dibenzoylacetylene, a less reactive dipolarophile than DMAD, also gave 1:1 adducts with **6** (R = Ph, *p*-BrC_6H_4). The similarity of their spectral characteristics (Tables I and II) with those described above indicate that rearrangement also had occurred in this instance and that these products are best represented as **10** (R = Ph, *p*-BrC_6H_4; R^1 = COPh).

In contrast to the above acetylenes, ethyl propiolate un-

derwent reaction with the ylide **6** (R = Ph, *p*-BrC_6H_4) to yield a 1:2 adduct. The most important features of this product's infrared spectrum (KBr) was the absence of an OH absorption and the presence of a new strong olefinic absorption at 1635 cm^{-1}. Its ^1H NMR spectrum was likewise devoid of any resonance attributable to the OH proton while a characteristic cis olefinic coupling was observed at δ 7.03–5.76. These and the other spectral data (Table I) are in agreement with structure **14**. Two doublets (δ 7.49, 7.14;



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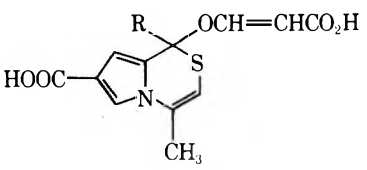

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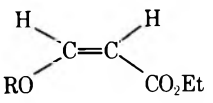

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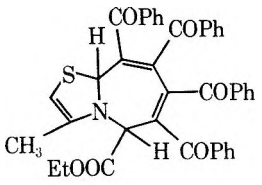
J = 1.5 Hz) assignable to H_6 and H_8 in the ^1H NMR spectrum of **14** (R = *p*-BrC_6H_4; R^1 = H; R^2 = COOEt) establish the mode of addition of the ylide **6** to ethyl propiolate. In **14** (R = Ph; R^1 = H; R^2 = COOEt) the H_6 proton occurred in the phenyl region at δ 7.47 (100 MHz). Hydrolysis of **14** resulted in formation of **15** (R = Ph, *p*-BrC_6H_4) described in Table I.

The formation of a 1:2 adduct from **6** and ethyl propiolate is no doubt due to the greater reactivity of this ester when compared to DMAD and dibenzoylacetylene. This was also illustrated by the conversion of **10** (R = Ph, *p*-BrC_6H_4; R^1 = $COOCH_3$) into **14** (R = Ph, *p*-BrC_6H_4; R^1 = R^2 = $COOCH_3$) with ethyl propiolate and triethylamine, providing additional evidence in support of **10**. The chemical shift of the OCH proton in **14** was observed in the range δ 7.03–6.81, consistent with the chemical shift[16] of the analogous proton in **16** [R = Ph, $(CH_3)_2CH$] at δ 6.85–6.45. It should also be noted that the addition of 2-propanol to ethyl propiolate in the presence of triethylamine results in formation of the cis product only.[16] In the reactions of **10** with ethyl propiolate described above only the cis product was obtained.

In contrast to the 1,5-dipolar cyclization and rearrangement described above, the reaction of **6** (R = OEt) with dibenzoylacetylene resulted in a 1:2 adduct assigned structure **17** and assumed to involve a 1,7-dipolar intermediate. Presence of a strong absorption at 1725 cm^{-1} due to the ester carbonyl group and absence of an OH absorption indicates that a rearrangement analogous to that described above has not occurred. Structures such as **18** and **19** can be excluded on the basis of the following ^1H NMR data. The chemical shift of H_5 was observed at δ 5.12 and those of H_2 and H_{9a} occurred at δ 6.36 and 6.56, respectively. Selective D_2O exchange of H_5 was not possible, base catalysis (Na_2CO_3 or $NaOCD_3$) causing exchange of all three protons. These chemical shifts are at too high field to be due to a pyrrole proton of **19** or to one in the side chain of structures **18** or **19**. In *trans*-dibenzoylethylene the chemical shifts of the olefinic protons are δ 8.09–7.90, in 1-(2-pyridyl)benzoylethylene the protons are in the range δ 8.0–7.5, and in 4-methylchalcone[17] the analogous protons are at δ 7.75–7.30.



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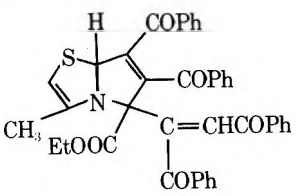

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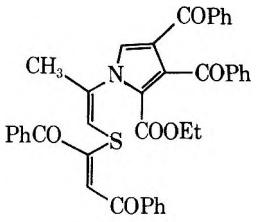

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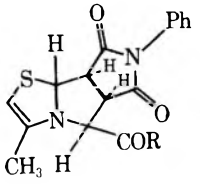
***N*-Phenylmaleimide Adduct.** A 1:1 adduct was readily obtained from **6** (R = Ph) and *N*-phenylmaleimide in DMF in the presence of triethylamine at room temperature. Structure **20** was assigned to this product on the basis of



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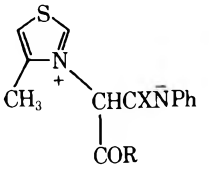

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the spectral data described in the Experimental Section. The chemical shift of the bridgehead proton at C_{7a} observed at δ 5.35 (d, J = 8.25 Hz) can only be accommodated by the assigned structure. Other olefinic dipolarophiles such as tetracyanoethylene, fumaronitrile, and *trans*-dibenzoylethylene did not yield any identifiable cycloadducts.

Heterocumulenes. Under conditions analogous to those above, phenyl isocyanate and phenyl isothiocyanate resulted in 1:1 adducts in which cyclization to a bicyclic ring system had not occurred. Spectral data favor structure **21** for these adducts. The features associated with the thiazolium nucleus in the initial salts **6** were present in **21** (X = O; R = Ph) but especially important was a D_2O-exchangeable proton singlet at δ 12.63, attributed to the side-chain methine hydrogen atom which, in addition to its β-diketone environment, is adjacent to a positive nitrogen atom. When X = S, this hydrogen underwent a downfield shift to δ 14.6. The absence of a NH absorption in the infrared spectrum also excludes this hydrogen atom being on the nitrogen atom.

Experimental Section[18]

General Procedure for Preparation of 4-Methylthiazolium Salts 5. 4-Methylthiazole (100 mmol), the bromo ketone (100 mmol), and absolute ethanol (50 ml) were refluxed for 2 hr. On cooling the salt separated and was recrystallized as below.

3-(2-Phenyl-2-oxoethyl)-4-methylthiazolium bromide (**5**, R = Ph) crystallized from dry ethanol as colorless needles: 84%; mp 210° dec; ir (KBr) 1680 cm^{-1} (CO); NMR (Me_2SO-d_6) δ 10.38 (d, 1, J = 2.8 Hz, H_2), 8.10 (m, 2, aromatic), 8.05 (d, 1, J = 2.8 Hz, H_5), 7.70 (m, 3, aromatic), 6.67 (s, 2, CH_2), 2.50 (s, 3, CH_3).

Anal. Calcd for $C_{12}H_{12}BrNOS$: C, 48.33; H, 4.06; N, 4.69. Found: C, 48.28; H, 4.05; N, 4.70.

3-[2-(4′-Bromophenyl)-2-oxoethyl]-4-methylthiazolium bromide (**5**, R = *p*-BrC_6H_4) crystallized from dry ethanol as cream needles: 58%; mp 244° dec; ir (KBr) 1690 cm^{-1} (CO); NMR (Me_2SO-d_6) δ 10.23 (d, 1, J = 2.8 Hz, H_2), 8.16–7.46 (m, 5, aromatic and H_5), 6.50 (s, 2, CH_2), 2.50 (s, 3, CH_3).

Anal. Calcd for $C_{12}H_{11}Br_2NOS$: C, 38.22; H, 2.94; N, 3.71. Found: C, 38.17; H, 3.16; N, 3.69.

3-(2-Ethoxy-2-oxoethyl)-4-methylthiazolium bromide (**5**, R = OEt) was prepared in anhydrous ether at room temperature and crystallized from dry ethanol–ether as colorless needles: 57%; mp 149–150°; ir (KBr) 1745 cm^{-1} (CO); NMR ($CDCl_3$) δ 11.30 (d, 1, J = 2.8 Hz, H_2), 8.15 (d, 1, J = 2.8 Hz, H_5), 5.98 (s, 2, NCH_2), 4.30 (q, 2, J = 7.0 Hz, CH_2), 2.63 (s, 3, 4-CH_3), 1.33 (t, 3, J = 7.0 Hz, CH_3).

Anal. Calcd for $C_8H_{12}BrNO_2S$: C, 36.09; H, 4.51; N, 5.26. Found: C, 35.94; H, 4.60; N, 5.24.

General Procedure for Reaction of 4-Methylthiazolium *N*-Ylides with Dipolarophiles. A stirred solution of the appropriate thiazolium salt and an equimolar amount of the dipolarophile in dry dimethylformamide was treated dropwise with an equimolar amount of triethylamine. A deep-orange color developed immediately and an exothermic reaction ensued. After stirring for 2 hr at room temperature, the reaction mixture was poured into ice–water and the precipitated solid was filtered, dried, and recrystallized from the appropriate solvent (Table I).

5-Ethoxycarbonyl-3-methyl-6,7,8,9-tetrabenzoyl-5,9a-dihydrothiazolo[3,2-*a*]azepine (**17**) was obtained as colorless needles after repeated recrystallization from chloroform–hexane: 62%; mp 230°; ir (KBr) 3115, 3050, 2975 (CH), 1725, 1685, 1670 cm^{-1} (CO); NMR ($CDCl_3$) δ 8.01–7.21 (m, 20, aromatic), 6.56 (s, 1, H_{9a}), 6.36 (bs, 1, H_2), 5.12 (s, 1, H_5), 3.67 (q, 2, J = 7.5 Hz, CH_2CH_3), 2.2 (bs, 3, 3-CH_3), 0.67 (t, 3, J = 7.5 Hz, CH_2CH_3).

Anal. Calcd for $C_{40}H_{31}NO_6S$: C, 73.50; H, 4.78; N, 2.14. Found: C, 73.08; H, 4.71; N, 2.45.

Reaction of the Pyrrolo[2,1-*c*][1,4]thiazines 10 with Ethyl Propiolate. An equimolar mixture of **10** and triethylamine in dry DMF was stirred and treated dropwise with an equimolar amount of ethyl propiolate. After 4 hr at room temperature, the reaction mixture was poured into ice–water and the product that separated purified by recrystallization or by PLC on silica gel (Table I).

Reaction of 1-Hydroxy-1-phenyl-4-methyl-1*H*-pyrrolo[2,1-*c*][1,4]thiazine-7,8-dicarboxylate (10) with Phenyl Isocyanate. A mixture of **10** (R = Ph; R^1 = $COOCH_3$) (0.2 g, 0.56 mmol), phenyl isocyanate (0.36 g, 3 mmol), benzene (2 ml) and a drop of pyridine was refluxed for 1 hr. The mixture was cooled, and hexane was added until the solution became cloudy. On cooling in ice a colorless solid separated which crystallized from benzene–hexane as colorless prisms (**11**): 0.27 g (0.56 mmol, 100%); mp 153°; ir (KBr) 3330 (NH), 1710, 1740 cm^{-1} (CO); NMR ($CDCl_3$) δ 8.06–7.08 (m, 12, aromatic, NH and H_6), 6.63 (d, 1, J = 1 Hz, H_3), 3.78 (s, 3, CH_3), 3.43 (s, 3, CH_3), 2.21 (d, 3, J = 1 Hz, 4-CH_3).

Anal. Calcd for $C_{25}H_{22}N_2O_6S$: C, 62.75; H, 4.63; N, 5.85. Found: C, 63.01; H, 4.68; N, 5.75.

Desulfurization of 10 (R = Ph; R^1 = $COOCH_3$) with Raney Nickel. The pyrrolothiazine (0.3 g, 0.85 mmol), freshly prepared Raney nickel (W-2)[19] (4 g), and ethanol (15 ml) were refluxed with stirring for 2 hr and filtered. Ethanol was evaporated from the filtrate and the residue was recrystallized from methanol, forming fine colorless needles of **13**: 0.15 g (56%); mp 101°; ir (KBr) 1718, 1700 cm^{-1} (CO); NMR ($CDCl_3$) δ 7.21 (s, 1, H_5), 7.18–7.08 (m, 5, aromatic), 4.21 (s, 2, CH_2), 4.16 (septet, 1, CH), 3.77 (d, 6, J = 1 Hz, CO_2CH_3), 1.16 (d, 6, J = 6.5 Hz, CH_3).

Anal. Calcd for $C_{18}H_{21}NO_4$: C, 68.55; H, 6.71; N, 4.44. Found: C, 68.54; H, 6.67; N, 4.40.

5-Benzoyl-3-methyl-*N*-phenyl-5,6,7,7a-tetrahydropyrrolo[2,1-*b*]thiazole-6,7-dicarboximide (20, R = Ph) was obtained as pale yellow prisms from acetone: 36%; mp 174–176°; ir (KBr) 3100, 3055 (CH), 1700 cm^{-1} (CO); λ_{max} (CH_3OH) 200 nm (log ϵ 4.38), 245 (4.22); NMR ($CDCl_3$) δ 9.05 (m, 2, aromatic), 7.20–7.70 (m, 8, aromatic), 5.83 (s, 1, H_2), 5.35 (d, 1, J = 8.25 Hz, H_{7a}), 4.92 (s, 1, H_5), 3.86 (d, 1, J = 8.25, 0.75 Hz, H_6), 3.55 (t, 1, J = 8.25 Hz, H_7), 1.87 (d, 3, J = 1.25 Hz, 3-CH_3); $M^{\cdot+}$ m/e 390 (34).

Anal. Calcd for $C_{22}H_{18}N_2O_3S$: C, 67.68; H, 4.65; N, 7.18. Found: C, 67.61; H, 4.63; N, 7.26.

anhydro-3-(1′-Benzoyl-2′-oxo-2′-phenylimino)-4-methylthiazolium hydroxide (**21**, R = Ph; X = O) was obtained as yellow plates from methanol: 87%; mp 187°; ir (KBr) 3025 (CH), 1610 cm^{-1} (CO); λ_{max} (CH_3OH) 242 nm (log ϵ 4.24), 296 (3.95); NMR (Me_2SO-d_6) δ 12.63 (s, 1, COCH), 9.95 (d, 1, J = 3 Hz, H_2), 7.83 (m, 1, H_5), 7.18–7.65 (m, 10, aromatic), 2.35 (s, 3, CH_3).

Anal. Calcd for $C_{19}H_{16}N_2O_2S$: C, 67.85; H, 4.80; N, 8.33. Found: C, 67.78; H, 4.63; N, 8.43.

anhydro-3-(1′-Benzoyl-2′-phenylimino-2′-thioxo)-4-methylthiazolium hydroxide (**21**, R = Ph; X = S) was obtained as pale yellow needles from methanol: 81%; mp 190° dec; ir (KBr) 3000, 2990 (CH), 1600 (CO), 1500 cm^{-1} (CS); λ_{max} (CH_3OH) 210 nm (log ϵ 4.31), 326 (4.43); NMR (Me_2SO-d_6) δ 14.60 (s, 1, COCH), 10.16 (d, 1, J = 2.0 Hz, H_5), 7.93 (d, 1, J = 2.0 Hz, H_5). 7.78 (m, 2, aromatic), 7.20 (m, 8, aromatic), 2.32 (s, 3, 3-CH_3).

Anal. Calcd for $C_{19}H_{16}N_2OS_2$: C, 64.77; H, 4.58; N, 7.95. Found: C, 64.93; H, 4.70; N, 7.90.

anhydro-3-[1′-(4-Bromobenzoyl)-2′-oxo-2′-phenylimino]-4-methylthiazolium hydroxide (**21**, R = *p*-BrC_6H_4; X = O) crystallized from benzene as pale yellow needles: 54%; mp 176–178° dec; ir (KBr) 3060, 2990 (CH), 1630 cm^{-1} (CO); λ_{max} (CH_3OH) 248 nm (log ϵ 4.28), 300 (4.28); NMR (Me_2SO-d_6) δ 12.53 (s, 1, COCH), 10.00 (d, 1, J = 3.0 Hz, H_2), 7.86 (s, 1, H_5), 6.90–7.70 (m, 10, aromatic), 2.36 (s, 3, 3-CH_3).

Anal. Calcd for $C_{19}H_{15}BrN_2O_2S$: C, 54.95; H, 3.64; N, 6.75. Found: C, 55.05; H, 3.68; N, 6.75.

Acknowledgments. We wish to express our appreciation to Dr. E. Williams, G. E. Corporate Research and Development Center, for her assistance with the ^{13}C spectra.

Registry No.—$C_{18}H_{17}NO_5S$, 57132-30-6; $C_{18}H_{16}BrNO_5S$, 57132-31-7; $C_{28}H_{21}NO_3S$, 57132-32-8; $C_{28}H_{20}BrNO_3S$, 57132-33-9; $C_{22}H_{23}NO_5S$, 57132-34-0; $C_{22}H_{22}BrNO_5S$, 57132-35-1; $C_{23}H_{23}NO_7S$, 57132-36-2; $C_{23}H_{22}BrNO_7S$, 57132-37-3; $C_{18}H_{15}NO_5S$, 57132-38-4; $C_{18}H_{14}BrNO_5S$, 57132-39-5; **5** (R = Ph), 6274-00-6; **5** (R = *p*-BrC_6H_4), 57132-40-8; **5** (R = OEt), 57132-41-9; **6** (R = Ph), 57132-42-0; **6** (R = *p*-BrC_6H_4), 57132-43-1; **6** (R = OEt), 57132-44-2; **7** (R = Ph; R′ = $COOCH_3$), 57132-45-3; **11**, 57132-46-4; **13**, 57132-47-5; **17**, 57132-48-6; **20** (R = Ph), 57132-49-7; **21** (R = Ph; X = O) 57132-50-0; **21** (R = Ph; X = S), 57132-51-1; **21** (R = *p*-BrC_6H_4; X = O), 57132-52-2; 4-methylthiazole, 693-95-8; 2-bromoacetophenone, 70-11-1; 2,4′-dibromoacetophenone, 99-73-0; ethyl bromoacetate, 105-36-2; dimethyl acetylenedicarboxylate, 762-42-5; dibenzoylacetylene, 1087-09-8; *N*-phenylmaleimide, 941-69-5; phenyl isocyanate, 103-71-9; phenyl isothiocyanate, 103-72-0.

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Formation of 2-Oxazolines by a Cyclization Involving the Displacement of Mercury

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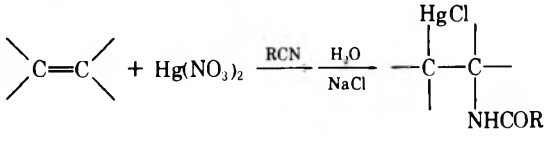
A series of *N*-acyl-2-aminoalkylmercuric chlorides has been synthesized by the reaction of olefins with mercuric nitrate monohydrate and nitriles followed by treatment with aqueous NaCl. This acylaminomercuration reaction was demonstrated to take place by way of trans addition. Thermal decomposition of the resulting *N*-acyl-2-aminoalkylmercuric chlorides at 180–240° in vacuo resulted in an intramolecular displacement of the chloromercury group with inversion of configuration to give the corresponding 2-oxazolines.

The facile reaction of olefins with mercuric nitrate and nitriles has recently been demonstrated to result in the formation of *N*-acyl-2-aminoalkylmercuric salts, which are conveniently isolated as the chlorides (eq 1).[2]



(1)

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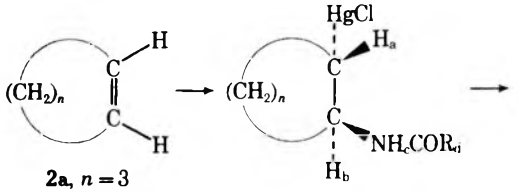
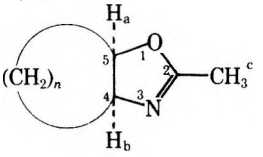
As a consequence of our interest in the synthetic potential of the organic compounds of mercury, we have undertaken the preparation of a series of these little-studied *N*-acyl-2-aminoalkylmercuric salts 1 in order to examine their chemical properties. It was felt that these salts might serve as a convenient and efficient source of 2-oxazolines.

A series of olefins was allowed to react at 0° with a mercuric nitrate monohydrate–nitrile system and the resulting mixture was treated with aqueous sodium chloride solution. In each case, a single *N*-acyl-2-aminoalkylmercuric chloride 1 was isolated. Cyclopentene (**2a**), cyclohexene (**2b**), and cycloheptene (**2c**) afforded the corresponding trans adducts **3a**, **3b**, **3c**, and **3d**. Similarly, trans-4-octene



2a, $n = 3$
b, $n = 4$
c, $n = 5$

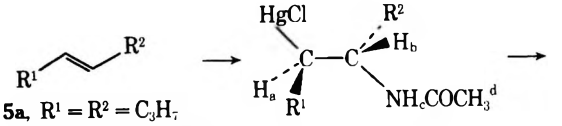
3a, $n = 3$; R = CH_3
b, $n = 4$; R = CH_3
c, $n = 5$; R = CH_3
d, $n = 4$; R = C_6H_5



4a, $n = 3$
b, $n = 4$
c, $n = 5$

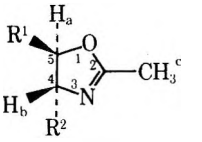
(**5a**) was converted to the erythro compound **6a**, and 1-octene (**5b**) was converted to **6b**.

The formation of *N*-acyl-2-aminoalkylmercuric salts 1 in the acylaminomercuration reaction (eq 1) has been rationalized in terms of nucleophilic attack by the nitrile on an intermediate mercurinium ion 8 (eq 2).[3] This, in turn, leads to a prediction that acylaminomercuration proceeds by way of trans addition. This prediction has not yet been adequately verified, however. The only experimental support



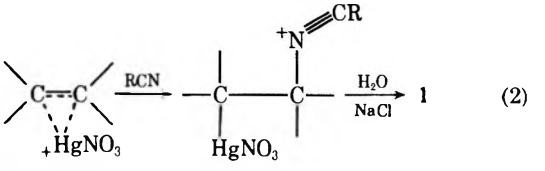
5a, $R^1 = R^2 = C_3H_7$
b, $R^1 = H$; $R^2 = C_6H_{13}$

6a, $R^1 = R^2 = C_3H_7$
b, $R^1 = H$; $R^2 = C_6H_{13}$



7a, $R^1 = R^2 = C_3H_7$
b, $R^1 = H$; $R^2 = C_6H_{13}$

for this prediction consists of a demonstration that halogen cleavage of the carbon–mercury bond in a series of *N*-acyl-



(2)

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2-aminocyclohexylmercuric chlorides yields the corresponding *N*-acyl derivatives of *trans*-2-bromo- and *trans*-2-chlorocyclohexylamine.[2c] An assignment of stereochemistry to the *N*-acyl-2-aminocyclohexylmercuric chloride substrates, which is founded on this evidence, requires an assumption that the halogen cleavage is a stereospecific electrophilic process which takes place with retention of configuration. Unfortunately, this assumption may be incorrect as a consequence of possible competition by a nonstereospecific radical cleavage process.[4] In addition, the very real possibility exists that the presence of a neighboring acylamino group may alter the stereochemical result of the halogenation reaction.[5] Consequently, it was of interest to obtain direct physical evidence that the acylaminomercuration of olefins does, in fact, take place by way of trans addition.

The NMR data set forth in Table I provide such direct physical evidence that the acylaminomercuration of cyclohexene (**2b**) and cycloheptene (**2c**) proceeds by way of trans addition. *N*-Acetyl-2-aminocyclohexylmercuric chloride (**3b**) and *N*-benzoyl-2-aminocyclohexylmercuric chloride (**3d**) have vicinal coupling constants J_{ab} of 9.6 and ca. 11 Hz, respectively. These values are of the magnitude expected for the coupling between two axial protons and are indicative of trans addition.[6] Similarly, *N*-acetyl-2-aminocycloheptylmercuric chloride (**3c**) has a vicinal coupling constant J_{ab} of 8.9 Hz which is also consistent with trans addition and a dihedral angle between the vicinal hydrogens of about 180°.[6a,7] First-order analysis of the H_a sextet

Table I
Physical Properties and NMR Spectra of *N*-Acyl-2-aminoalkylmercuric Chlorides

N-Acryl-2-aminoalkylmercuric Chloride	Yield, %	Mp, °C	Chemical shift, δ[a]			
			H_a	H_b	H_c	H_d
3a[b]	32	139–140[c]	*d*	4.17–4.80 (m) J_{ab} = ca. 7.7[e]	8.62 (d) J_{bc} = 6.2	1.99 (s)
3b	93	201–202[g]	2.48[h]	3.67–4.60 (br) J_{ab} = 9.6[f]	8.49 (d) J_{bc} = 6.6	1.94 (s)
3c	3.2[i]	185–186 dec[j]	2.79[k]	4.27–4.80 (br) J_{ab} = 8.9[f]	8.63 (d) J_{bc} = 6.8	1.99 (s)
3d	50	238–240 dec[l]	2.72[m] J_{ab} = ca. 11[n]	4.43–5.07 (br)	ca. 9.3[o]	7.37–7.78 (3 H, m), 8.23–8.75 (2 H, m)
6a	65	169–170[p]	2.67–3.37 (m)	4.37–4.93 (br)	8.88 (d) J_{bc} = 7.8	2.13 (s)
6b[b]	22	101–102[q]	1.97–2.60 (m)	4.33–4.93 (br)	8.84 (d) J_{bc} = 7.5	2.10 (s)

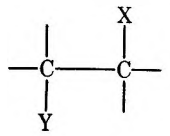
[a] In pyridine-d_5 with Me_4Si as internal standard. *J* values expressed in hertz. [b] Satisfactory elemental analyses and mass spectra were obtained for all new compounds. [c] Recrystallized from 50% aqueous ethanol. [d] Not measured. [e] Exchange of H_c with deuterium afforded a quartet of lines for H_b with J = 7.7 Hz. [f] Determined by exchange of H_c with deuterium followed by spin decoupling of the methylene protons coupled to H_b. [g] Lit.[2a] 201.5–202°. [h] Sextet. First-order analysis indicates coupling of ca. 10 Hz with two protons and ca. 4 Hz with a third. [i] After two recrystallizations from 95% ethanol. A 3.2% yield of elemental mercury was also obtained. [j] Lit.[2c] 172–175°. [k] Sextet. First-order analysis indicates coupling of ca. 9 Hz with two protons and ca. 3 Hz with a third. [l] Lit.[2c] 243°. [m] Sextet. [n] First-order analysis indicates coupling of ca. 11 Hz with two protons and ca. 4 Hz with a third. [o] Partially obscured by solvent. [p] Lit.[2c] 164–165°. [q] Recrystallized from 95% ethanol.

in the NMR spectrum of **3c** supports this conclusion. In view of the stereochemical results for cyclohexene (**2b**) and cycloheptene (**2c**), the stereochemistry of **3a** and **6a** has been assigned on the basis of an anticipated trans addition to the double bond of cyclopentene (**2a**)[8] and *trans*-4-octene (**5a**), respectively.

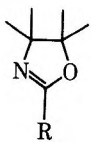
Jensen and Ouellette have demonstrated that the mercury of simple alkylmercuric salts can function as a leaving group under solvolytic conditions and have postulated that solvolysis involves ionization of the salt followed by loss of mercury to form a carbonium ion (eq 3).[9] In view of this,

$$RHgX \rightleftharpoons RHg^+ + X^- \qquad (3)$$
$$\searrow$$
$$R^+ + X^-$$

the interesting possibility exists that a chloromercury group might have value as a synthetically useful leaving group which is subject to displacement by an internal nucleophile. This prediction has been verified, in part, by the recent observation that 2-hydroxyalkylmercuric chlorides **9a** can be converted to epoxides in high yield under basic conditions.[10] In an effort to further extend the scope of this observation, we have examined a series of *N*-acyl-2-aminoalkylmercuric halides **1** in the expectation that they might possess chemical properties analogous to those of the corresponding *N*-acyl-2-aminoalkyl halides **9b**. The conversion of *N*-acyl-2-aminoalkyl halides **9b** to 2-oxazolines **10** is a facile and well-documented reaction[11] which is ordinarily carried out under basic conditions and proceeds via an internal displacement of halide ion with inversion of configuration.[12] Consequently, it appeared possible that *N*-acyl-2-aminoalkylmercuric chlorides **1** might also undergo decomposition to yield 2-oxazolines **10.**



9a, X = HgCl; Y = OH
b, X = Br or Cl; Y = RCONH



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Reaction of *trans*-*N*-acetyl-2-aminocyclohexylmercuric chloride (**3b**) with potassium *tert*-butoxide or sodium carbonate in inert solvents afforded oxazoline in only trace amounts. It was found, however, that with one exception, all of the *N*-acyl-2-aminoalkylmercuric chlorides **1** examined could be converted to 2-oxazolines in 10–30% yield by thermal decomposition at 180–240° under reduced pressure. Thus, **3a, 3b,** and **3c** afforded the *cis*-2-oxazolines **4a, 4b,** and **4c,** respectively, whereas **6a** yielded the corresponding *trans*-2-oxazoline **7a** and **6b** afforded **7b.** In all cases, deacylaminomercuration also took place as a major side reaction to give substantial amounts of the corresponding olefin. These results are set forth in Tables II and III. The stereospecificity of oxazoline formation was demonstrated by the fact that the resulting 2-oxazolines were found to be homogeneous both by gas chromatography and on the basis of their NMR spectra.

Table II
Pyrolysis of *N*-Acyl-2-aminoalkylmercuric Chlorides

N-Acyl-2-aminoalkylmercuric chloride	Pyrolysis temp, °C	Pyrolysis pressure, mm	Product yield, %[a]		
			Oxazoline	Olefin	Acetamide
3a[b]	178	9	31	60[c]	1.2
3b	240	3	25	60[d]	15
3c	200	0.2	11	*e*	*e*
3d	235	0.3	0	*e*	*e*
6a	180	9	16	*e*	*e*
6b	180	8	21	*e*	*e*

[a] Isolated yield unless otherwise specified. The formation of small amounts of elemental mercury could be detected visually in each case. [b] Treatment of the pyrolysis residue with aqueous ammonia resulted in a black coloration indicative of the presence of mercurous ion. [c] Cyclopentene determined by quantitative gas chromatography on a 15 ft × 0.25 in. column of 10% Silicone QF-1 on 60/80 Chromosorb P. [d] Cyclohexene determined by quantitative gas chromatography on a 15 ft × 0.25 in. column of 10% Silicone QF-1 on 60/80 Chromosorb P. [e] Not measured.

The assignment of cis and trans configurations to oxazolines **4c** and **7a,** respectively, is based on their NMR spectra (Table III). In a series of 4,5-dimethyl- and 4,5-diethyl-2-oxazolines of established configuration the coupling constant J_{ab} between the C-4 and C-5 protons is from 8.0 to

Table III
Physical Properties and NMR Spectra of 2-Oxazolines

Oxazoline[a]	Bp, °C (mm)	Chemical shift, δ[b] H_a	H_b	H_c
4a	47.5–48.0 (9)[c]			
4b	52.0–56.0 (2)[d]			
4c[e]	23.5–24.0 (0.1)	4.45–4.93 (m) J_{ab} = 9.8	3.93–4.47 (br) J_{ab} = 9.8	1.96 (d) J_{bc} = 1.5
7a	48.0–49.0 (3)	3.87–4.27 (m) J_{ab} = 6.0	3.37–3.83 (br) J_{ab} = 6.0	1.95 (d) J_{bc} = 1.2
7b	25.0–26.0 (0.02)	3.60–4.50 (m)		1.98 (s) $W_{1/2}$ = 2.4

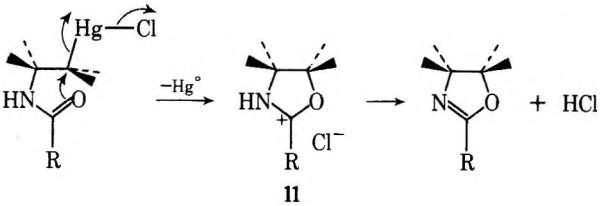
[a] Satisfactory elemental analyses and mass spectra were obtained for all compounds except where indicated. [b] In $CDCl_3$ with J values expressed in hertz. Values for J_{ab} determined by spin decoupling of the coupled methylene protons. [c] Lit.[13] 57.0–57.5° (13 mm). [d] Lit.[13] 75.5–76.5 (13 mm). [e] Satisfactory mass spectrum. Elemental analysis not carried out.

9.0 Hz for the cis compounds.[14] It has generally been observed that in five-membered rings which cannot deviate appreciably from planarity, such as the 2-oxazolines, J_{cis} is always appreciably larger than J_{trans}.[15] On this basis, **7a**, with a coupling constant J_{ab} of 6.0 Hz, may be unambiguously assigned a trans configuration. In the bicyclic oxazoline **4c**, the coupling constant J_{ab} is less definitive, however, as a result of the distortions introduced by the fused ring system. Nevertheless, the observed coupling constant J_{ab} for this bicyclic compound is consistent, on the basis of the Karplus relationship,[6a] with a cis configuration.

The assignment of configuration to oxazolines **4c** and **7a** finds further support in a consideration of the chemical shifts of the C-4 and C-5 hydrogen signals in the NMR spectra (Table III). It has been found in a series of 4,5-dimethyl- and 4,5-diethyl-2-oxazolines that the C-4 and C-5 hydrogens appear at about 0.5 ppm lower field in the cis compounds than in the trans isomers.[14] Specifically, in trans compounds the C-4 hydrogen is found in the range of δ 3.4–3.8 and the C-5 hydrogen is found at δ 4.0–4.2. In the cis compounds, the C-4 proton signal is observed at δ 4.0–4.1 and the C-5 proton is found at δ 4.4–4.7. This difference in chemical shift of the C-4 and C-5 protons in *cis*- and *trans*-2-oxazolines has been attributed to the shielding effect of the alkyl groups attached to the adjacent carbon atoms in the trans isomers, and has been found in many cis/trans isomer pairs of five-membered ring compounds.[16] The relatively flexible cycloheptyl ring associated with **4c** would be expected to produce similar shielding effects.[17] Comparison of these expected values with those set forth in Table III for **4c** and **7a** serves to confirm the assignment of stereochemistry to each of these compounds.

The formation of 2-oxazolines upon thermal decomposition of the *N*-acetyl-2-aminoalkylmercuric chlorides can be rationalized in terms of the mechanism set forth in Scheme I. A back-side displacement of mercury by the oxygen

Scheme I



11

atom of the amide carbonyl group would result in formation of the corresponding 2-oxazoline hydrochloride **11**, which could then undergo thermal decomposition to oxazoline and HCl. Such a reaction path would serve to explain the inversion of configuration observed during oxazoline formation. Inversion of configuration is also consistent with the related observation that epoxides can be generated by base treatment of both *trans*-2-hydroxycyclopentylmercuric chloride and *trans*-2-hydroxycyclohexylmercuric chloride.[10a] Such a stereochemical result, however, is at variance with the retention of configuration ordinarily observed in the electrophilic cleavage reactions of organomercurials.[18] Although 2-oxazolines form stable, isolable salts,[13,19] it has been demonstrated that 2-propyl-2-oxazolines can be distilled at 1 mm pressure and 185° from a reaction system that also produces phosphoric acid.[20] Consequently, it is not unreasonable to expect the oxazoline hydrochloride **11** to exist in equilibrium with HCl and free oxazoline at elevated temperatures. The HCl is then subject to removal by distillation in vacuo.[21]

The failure of *trans*-*N*-benzoyl-2-aminocyclohexylmercuric chloride (**3d**) to yield an oxazoline upon pyrolysis is surprising. The failure of potassium *tert*-butoxide and sodium carbonate to exert a favorable effect on the conversion of *trans*-*N*-acetyl-2-aminocyclohexylmercuric chloride (**3b**) to the corresponding 2-oxazoline is also unexpected. Although the analogous *N*-acyl-2-aminoalkyl halides **9b** are known to undergo thermal decomposition to yield 2-oxazoline salts,[19] these compounds are most conveniently converted to oxazolines in the presence of basic reagents.[11]

Experimental Section

All melting points and boiling points are uncorrected. Infrared spectra were determined either with a Beckman IR-8 or a Perkin-Elmer 257 infrared spectrophotometer. NMR spectra were recorded on a Varian T-60 spectrometer equipped with a T-6057 lock-decoupler. The mass spectra were obtained with a Varian MAT CH7 mass spectrometer. GLC analyses were carried out with either an Aerograph Model A-90-P or a Carle Model 8000 gas chromatograph. Microanalyses were performed by M-H-W Laboratories, Garden City, Mich.

***trans*-*N*-Acetyl-2-aminocyclohexylmercuric Chloride (3b).** The following procedure is representative of the general procedure employed for the preparation of the *N*-acyl-2-aminoalkylmercuric chlorides set forth in Table I. To a suspension of 137.0 g (0.40 mol) of mercuric nitrate monohydrate in 300 ml of acetonitrile at ice-bath temperature was added dropwise with mechanical stirring over a period of 27 min a solution of 32.8 g (0.40 mol) of cyclohexene (**2b**) in 100 ml of acetonitrile to give a clear, colorless solution. Stirring was continued at room temperature for 1 hr. The resulting clear yellow solution was poured into a mixture of 1 l. of water and 200 ml of saturated NaCl solution. The resulting white precipitate was separated by filtration, washed with 1 l. of water, and dried in vacuo to give 139.5 g (93%) of **3b**, mp 200.0–201.0°. Recrystallization from 2 l. of 95% ethanol afforded 100.0 g of **3b** as white, fibrous needles, mp 201.0–202.0° (lit.[2a] mp 201.5–202).

***cis*-2-Methyl-4,5-tetramethylene-2-oxazoline (4b).** The following procedure is representative of the general procedure employed for preparation of the 2-oxazolines set forth in Table III. *trans*-*N*-Acetyl-2-aminocyclohexylmercuric chloride (**3b**, 5.004 g, 13.29 mmol) was heated at an oil-bath temperature of 240° and a

pressure of 2.85 mm under a 10-cm Vigreux column, and the volatile product collected at dry ice–acetone bath temperature. The resulting volatile product consisted of 1.300 g of a colorless liquid which contained a suspended white solid. Crystallization of the crude product from ether afforded 0.116 g (15%)of acetamide as white needles, mp 81.5–82.5°. The filtrate was concentrated and the residual colorless oil subjected to short-path distillation (2.75 mm and 65° bath) to give 0.467 g (25%) of oxazoline **4b** as a colorless liquid.

Oxazoline **4b**, obtained from a large-scale preparative experiment, bp 52.0–56.0° (1.75–2.10 mm) [lit.[13] 75.5–76.5° (13 mm)], was homogeneous by gas chromatography on a 6 ft × 0.094 in. column packed with 8% Carbowax 1540 on 60–80 mesh calcined diatomite support. It was further characterized by conversion to its picrate, mp 165–169°.

Anal. Calcd for $C_{14}H_{16}N_4O_8$: C, 45.66; H, 4.38; N, 15.21. Found: C, 45.36; H, 4.18; N, 14.98.

The crude volatile product from a comparable experiment was found to contain 60% of cyclohexene (**2b**) by quantitative gas chromatography on a 15 ft × 0.25 in. column packed with 10% silicone (Fluro) QF-1 on 60–80 Chromosorb using *n*-octane as an internal standard.

Reaction of *trans*-*N*-Acetyl-2-aminocyclohexylmercuric Chloride (3b) with Potassium *tert*-Butoxide. A mixture of 5.001 g (13.3 mmol) of *trans*-*N*-acetyl-2-aminocyclohexylmercuric chloride (**3b**) and 1.490 g (13.3 mmol) of potassium *tert*-butoxide in 15 ml of diglyme (distilled from CaH_2) was heated at relfux in a nitrogen atmosphere for 3.5 hr. After cooling, the resulting brown solution was found to contain less than a 1% yield of *cis*-2-methyl-4,5-tetramethylene-2-oxazoline (**4b**) by quantitative gas chromatography on a 6 ft × 0.094 in. column packed with 8% Carbowax 1540 on 60–80, acid washed, silane treated, calcined diatomite support using 0.437 g of *o*-xylene as an internal standard.

Reaction of *trans*-*N*-Acetyl-2-aminocyclohexylmercuric Chloride (3b) with Sodium Carbonate. A mixture of 2.500 g (6.64 mmol) of *trans*-*N*-acetyl-2-aminocyclohexylmercuric chloride (**3b**) and 0.800 g (7.55 mmol) of anhydrous sodium carbonate in 50 ml of benzene was heated with shaking in a high-pressure steel reaction vessel at 250° for 2 hr. After cooling, the mixture was filtered and the filtrate concentrated to yield 0.213 g of dark brown oil. The infrared spectrum of this material indicated that little or no 2-oxazoline **4b** was present.

Registry No.—**2a**, 142-29-0; **2b**, 110-83-8; **2c**, 628-92-2; **3a**, 56943-31-8; **3b**, 31718-62-4; **3c**, 56943-32-9; **3d**, 19907-98-3; **4a**, 56943-33-0; **4b**, 23236-44-4; **4b** picrate, 56943-34-1; **4c**, 56943-35-2; **5a**, 14850-23-8; **5b**, 111-66-0; **6a**, 56943-36-3; **6b**, 56943-37-4; **7a**, 56943-38-5; **7b**, 56994-88-8; mercuric nitrate, 10045-94-0; NaCl, 7647-14-5; potassium *tert*-butoxide, 865-47-4; sodium carbonate, 497-19-8.

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Ring Expansion Reaction of 1,2-Dihydroquinolines to 1-Benzazepines

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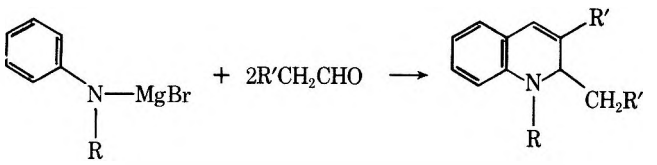
When 1-methyl-2,3-dialkyl-1,2-dihydroquinolines (**1a–c**) were treated with ethyl azidoformate, 1-methyl-2-ethoxycarbonylimino-3,4-dialkyl-2,3-dihydro-1*H*-1-benzazepines (**2a–c**) were produced in 30–80% yields. These benzazepines (**2a–c**) were obtained in 91–99% yields under a similar reaction condition from 1-methyl-2-alkylidene-3-alkyl-1,2-dihydroquinolines (**16a–c**) prepared from the corresponding 1,2,3-trialkylquinolinium chlorides (**18a–c**).

Attempts to expand smaller rings into a heterocyclic ring of 1-benzazepines have been achieved by many investigators; e.g., by the reaction of indoles with dimethyl acetylenedicarboxylate[1] or ethyl cyanoacetate,[2] by the Beckman[3] or Schmidt[4] rearrangement of tetralones, and by the treatment of 1,2-dihydroquinoline with dibromocarbene followed by the treatment of 1,2-dihydroquinoline with dibromocarbene followed by dehydrobromination.[5] The utility of azides in the azepine formation is well known.[6] This paper describes a new ring expansion reaction by ethyl azidoformate from 1-methyl-2,3-dialkyl-1,2-dihydroquinolines (**1**) to 1-methyl-2-ethoxycarbonylimino-3,4-dialkyl-2,3-dihydro-1*H*-1-benzazepines (**2**) via 1-methyl-2-alkylidene-3-alkyl-1,2-dihydroquinolines (**16**).

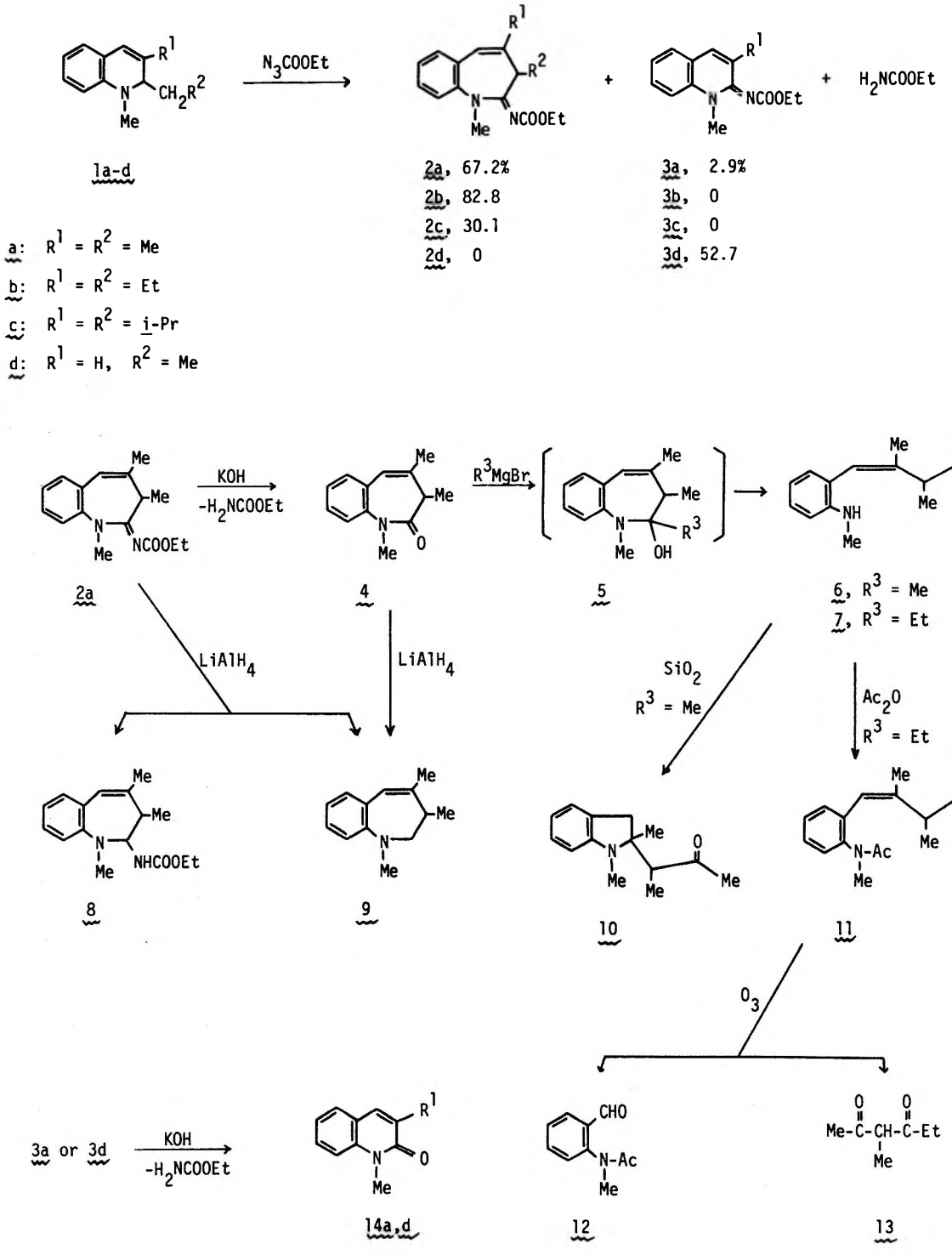
In a recent publication[7] we have reported that *N*-alkylanilinomagnesium bromides reacted with aliphatic aldehydes to give 1,2,3-trialkyl-1,2-dihydroquinolines in good yields. When the reaction of 1,3-dimethyl-2-ethyl-1,2-di-



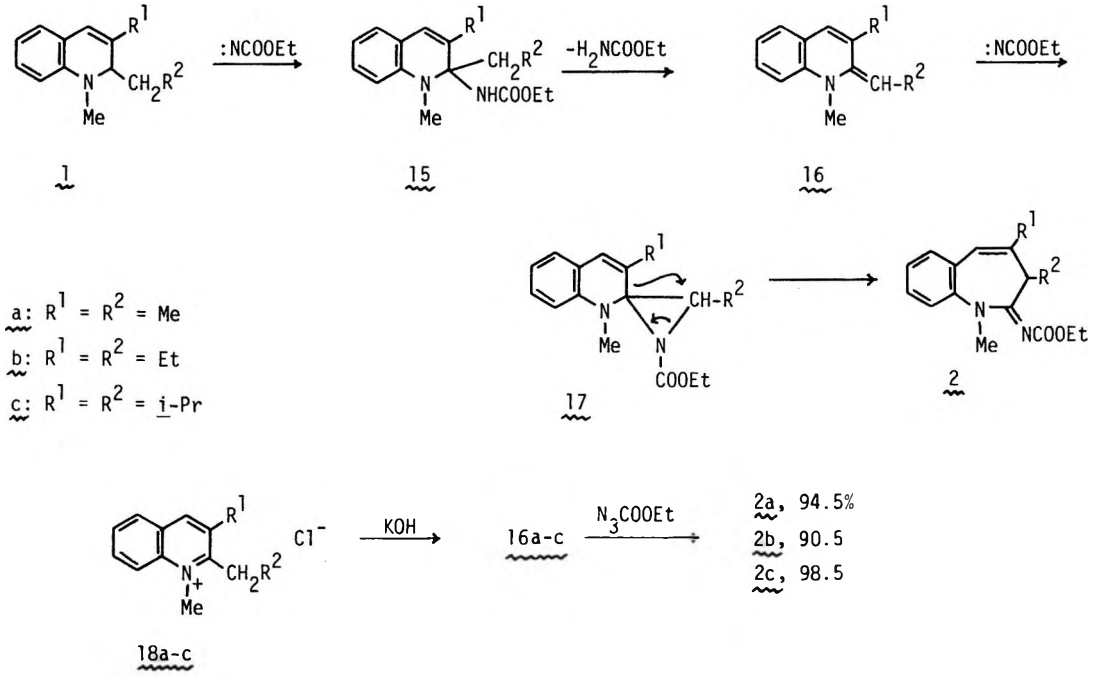
hydroquinoline (**1a**) with an excess of ethyl azidoformate was carried out in boiling ligroin, three products were produced: a yellow oil (**2a**, 67.2%), urethane (82.8%), and small amounts of crystals (**3a**, 2.9%). The NMR and ir spectra of the main product, $C_{16}H_{20}N_2O_2$ (**2a**), exhibited the presence of an ethoxycarbonylimino group, and a >CHCH$_3$ group instead of the C-2 ethyl group of the starting dihydroquinoline (**1a**). Alkali hydrolysis of **2a** produced high yields of urethane and a yellow oil (**4**) which showed lactam absorption at 1654 cm^{-1}. This carbonyl group was reduced to methylene by lithium aluminum hydride in a quantitative yield. The Grignard reaction product (**6** or **7**) of **4** with methyl- or ethylmagnesium bromide showed absorptions of a secondary amine (3410 cm^{-1}) and an acetyl or propionyl group (1705 cm^{-1}). The presence of these groups indicates that the alkylation reaction of **4** proceeded with the cleavage of the carbon–nitrogen bond.

Selective oxidation of the acetylated compound (**11**) of **7** was achieved by treatment with ozone to give aldehyde **12** (47.5%) and β-diketone **13** (26.0%). The aldehyde **12** was

Scheme I



Scheme II



identified as 2-(*N*-acetyl-*N*-methylamino)benzaldehyde, and the β-diketone (**13**) was identical with 3-methyl-2,4-hexadione,[8] by spectroscopic comparisons with authentic samples prepared by independent routes, respectively. These experimental results support that **2a** is 1,3,4-trimethyl-2-ethoxycarbonylimino-2,3-dihydro-1*H*-1-benzazepine and **4** is 1,3,4-trimethyl-2-oxo-2,3-dihydro-1*H*-1-benzazepine.

Lithium aluminum hydride reduction of **2a** gave a mixture of 1,3,4-trimethyl-2-ethoxycarbonylamino-2,3-dihydro-1*H*-1-benzazepine (**8**) and 1,3,4-trimethyl-2,3-dihydro-1*H*-1-benzazepine (**9**) which was also obtained from **4**. Silica gel column chromatography caused cyclization of **6** into 1,2-dimethyl-2-(1-methyl-2-oxopropyl)indoline (**10**).

The NMR and ir spectra of the minor product, $C_{14}H_{16}N_2O_2$ (**3a**), exhibited the presence of an ethoxycarbonylimino group. Alkali hydrolysis of **3a** formed 1,3-dimethyl-2-quinolone (**14a**)[7] and urethane in quantitative yields. Thus the structure of **3a** was determined as 1,3-dimethyl-2-ethoxycarbonylimino-1,2-dihydroquinoline.

A similar treatment of 1-methyl-2-propyl-3-ethyl-1,2-dihydroquinoline (**1b**) or 1-methyl-2-isobutyl-3-isopropyl-1,2-dihydroquinoline (**1c**) with ethyl azidoformate gave 1-methyl-2-ethoxycarbonylimino-3,4-diethyl-2,3-dihydro-1*H*-1-benzazepine (**2b**, 82.8%) or 1-methyl-2-ethoxycarbonylimino-3,4-diisopropyl-2,3-dihydro-1*H*-1-benzazepine (**2c**, 30.1%), respectively. From 1-methyl-2-ethyl-1,2-dihydroquinoline (**1d**) having no substituent on the C-3 carbon, however, the expected benzazepine derivative was not isolated, but 1-methyl-2-ethoxycarbonylimino-1,2-dihydroquinoline (**3d**, 52.7%) was obtained as a main product.

It is difficult to decide now whether the reaction proceeds by way of a nitrene intermediate or by an azide mechanism. If an excess of ethyl azidoformate used supplies carbethoxynitrene required during the reaction, the ring expansion reaction of dihydroquinoline may proceed in the following stages. (Of course, the same products could be formed by the azide mechanisms not involving the nitrene intermediate.[6b]) At first, carbethoxynitrene is inserted into a carbon–hydrogen bond at the C-2 position of **1** to give 1-methyl-2-ethoxycarbonylamino-2,3-dialkyl-1,2-dihydroquinoline (**15**), which is converted into 1-methyl-2-alkylidene-3-alkyl-1,2-dihydroquinoline (**16**) accompanied by the elimination of urethane. At the second stage, **16** reacts with nitrene again to give an aziridine ring (**17**). Then the benzazepine ring (**2**) is formed by the rearrangement of the aziridine.

Previously we reported[7] that unstable 1,3-dimethyl-2-ethylidene-1,2-dihydroquinoline (**16a**) was easily produced by the alkali treatment of 1,3-dimethyl-2-ethylquinolinium chloride (**18a**) in a quantitative yield. If 2-alkylidene-1,2-dihydroquinolines (**16**) are isolated from the corresponding 1-methyl-2,3-dialkylquinolinium chlorides (**18**), and allowed to react with ethyl azidoformate, the benzazepine formation will proceed more smoothly.

2-Alkylidene-1,2-dihydroquinolines (**16a, 16b,** and **16c**) were liberated by the alkali treatment of aqueous solutions of the corresponding quinolinium chlorides (**18a, 18b,** and **18c**) in a nitrogen atmosphere. Subsequently, they were extracted with ligroin and heated with ethyl azidoformate to give 90–99% yields of **2a, 2b,** and **2c,** respectively.

The reasons for the information of **3** and how the ethyl group is eliminated are still unclear. Further experiments are now in progress.

Experimental Section

Proton NMR spectra were recorded using a JNM-MH-100 (Jeol) spectrometer with tetramethylsilane as an internal standard. Infrared spectra were taken on a IR-A-2 (Jasco) spectrometer. Mass spectra were recorded using a RMU-6M (Hitachi) spectrometer. All melting points were measured on a Yanagimoto micro melting point apparatus, and are uncorrected.

1,3,4-Trimethyl-2-ethoxycarbonylimino-2,3-dihydro-1*H*-1-benzazepine (2a). Ethyl azidoformate (15.0 g, 0.13 mol) was added dropwise to a boiling solution of 1,3-dimethyl-2-ethyl-1,2-dihydroquinoline (**1a**, 8.427 g, 0.045 mol) in 20 ml of ligroin (bp 110–120°). The mixture was refluxed for 1 hr under a nitrogen atmosphere. Fractional distillation of the reaction mixture was repeated to give the following fractions.

Fraction a: bp 30–35° (0.1 mm), 3.298 g (82.8%) of urethane.

Fraction b: bp 130–132° (0.03 mm), 8.218 g (67.2%) of **2a**; ir (neat) 1680, 1614 cm^{-1}; NMR ($CDCl_3$) δ 0.90 (d, 3, J = 7.5 Hz, C-3 CH_3), 1.42 (t, 3, J = 7.5 Hz, ethoxy CH_3), 2.12 (s, 3, C-4 CH_3), 3.55 (s, 3, NCH_3), 4.25 (q, 1, J = 7.5 Hz, C-3 H), 4.35 (q, 2, J = 7.5 Hz, OCH_2), 6.48 (s, 1, C-5 H), and 7.00–7.43 (m, 4, aromatic H); mass spectrum *m/e* 272 (M^+, 77), 227 (42), 199 (44), 172 (32), 145 (100), and 129 (38).

Anal. Calcd for $C_{16}H_{20}N_2O_2$: C, 70.56; H, 7.40; N, 10.29. Found: C, 70.45; H, 7.53; N, 10.18.

Fraction c: bp 140–145° (0.03 mm), mp 52–53°, 0.320 g (2.9%) of 1,3-dimethyl-2-ethoxycarbonylimino-1,2-dihydroquinoline (**3a**); ir (KBr) 1685, 1642 cm^{-1}; NMR ($CDCl_3$) δ 1.34 (t, 3, J = 7.0 Hz, ethoxy CH_3), 2.28 (s, 3, C-3 CH_3), 3.73 (s, 3, NCH_3), 4.18 (q, 2, J = 7.0 Hz, OCH_2), and 7.02–7.48 (m, 5, C-4 H and aromatic H).

Anal. Calcd for $C_{14}H_{16}N_2O_2$: C, 68.83; H, 6.60; N, 11.47. Found: C, 68.80; H, 6.58; N, 11.49.

1-Methyl-2-ethoxycarbonylimino-3,4-diethyl-2,3-dihydro-1*H*-1-benzazepine (2b). In a similar manner as above for **2a**, the treatment of 1-methyl-2-propyl-3-ethyl-1,2-dihydroquinoline (**1b**, 9.702 g, 0.045 mol) with ethyl azidoformate (30 g, 0.26 mol) gave 11.111 g (82.8%) of **2b**: bp 140–145° (0.1 mm); ir (neat) 1685, 1610 cm^{-1}; NMR ($CDCl_3$) δ 0.76 (t, 3, J = 7.0 Hz, C-3 ethyl CH_3), 1.12 (t, 3, J = 7.2 Hz, C-4 ethyl CH_3), 1.20 (m, 2, C-3 ethyl CH_2), 1.23 (t, 3, J = 7.0 Hz, ethoxy CH_3), 2.35 (q, 2, J = 7.2 Hz, C-4 ethyl CH_2), 3.44 (s, 3, NCH_3), 3.66 (t, 1, J = 7.5 Hz, C-3 H), 4.19 (q, 2, J = 7.0 Hz, OCH_2), 6.32 (s, 1, C-5 H), and 6.90–7.22 (m, 4, aromatic H).

Anal. Calcd for $C_{18}H_{24}N_2O_2$: C, 71.97; H, 8.05; N, 9.33. Found: C, 71.83; H, 8.08; N, 9.42.

1-Methyl-2-ethoxycarbonylimino-3,4-diisopropyl-2,3-dihydro-1*H*-1-benzazepine (2c). In a similar manner as above for **2a**, the treatment of 1-methyl-2-isobutyl-3-isopropyl-1,2-dihydroquinoline (**1c**, 4.0 g, 16.4 mmol) with ethyl azidoformate (10.0 g, 86.9 mmol) gave 1.626 g (30.1%) of **2c**: bp 145–148° (0.05 mm); ir (neat) 1680, 1610 cm^{-1}; NMR ($CDCl_3$) δ 0.72 and 0.84 (d, 3 × 2, J = 6.5 Hz, C-3 isopropyl CH_3), 1.28 (d, 6, J = 7.0 Hz, C-4 isopropyl CH_3), 1.34 (t, 3, J = 7.5 Hz, ethoxy CH_3), 2.46 (m, 1, C-4 isopropyl CH), 3.48 (s, 3, NCH_3), 4.22 (q, 2, J = 7.5 Hz, OCH_2), 6.45 (s, 1, C-5 H), and 6.96–7.28 (m, 4, aromatic H).

Anal. Calcd for $C_{20}H_{28}N_2O_2$: C, 73.13; H, 8.59; N, 8.53. Found: C, 73.05; H, 8.67; N, 8.33.

1-Methyl-2-ethoxycarbonylimino-1,2-dihydroquinoline (3d). In a similar manner as above for **2a**, the treatment of 1-methyl-2-ethyl-1,2-dihydroquinoline (**1d**, 7.852 g, 45 mmol) with ethyl azidoformate (15.0 g, 130 mmol) gave 5.035 g (52.7%) of **3d**: mp 118–119°; ir (KBr) 1660, 1620 cm^{-1}; NMR ($CDCl_3$) δ 1.36 (t, 3, J = 7.5 Hz, ethoxy CH_3), 3.86 (s, 3, NCH_3), 4.22 (q, 2, J = 7.5 Hz, OCH_2), 7.56 (d, 1, J = 6.5 Hz, C-3 H), 7.76 (d, 1, J = 6.5 Hz, C-4 H), and 7.10–7.58 (m, 4, aromatic H).

Anal. Calcd for $C_{13}H_{14}N_2O_2$: C, 67.81; H, 6.13; N, 12.17. Found: C, 67.80; H, 6.14; N, 12.06.

1,3,4-Trimethyl-2-oxo-2,3-dihydro-1*H*-1-benzazepine (4). A solution of **2a** (0.870 g, 3.2 mmol) and potassium hydroxide (0.1 g) in 50% ethanol (20 ml) was refluxed for 5 hr. After removal of the ethanol, the aqueous solution was extracted with chloroform. The extract was washed with water, dried, and concentrated. Distillation of the residue gave 178 mg (62.3%) of urethane and 640 mg (99.7%) of **4**: bp 103–105° (0.025 mm); ir (neat) 1654 cm^{-1}; NMR ($CDCl_3$) δ 1.39 (d, 3, J = 7.0 Hz, C-3 CH_3), 2.06 (s, 3, C-4 CH_3), 2.80 (q, 1, J = 7.0 Hz, C-3 H), 3.51 (s, 3, NCH_3), 6.60 (s, 1, C-5 H), and 7.08–7.50 (m, 4, aromatic H); mass spectrum m/e 201 (M^+, 78), 185 (56), 158 (64), and 145 (100).

Anal. Calcd for $C_{13}H_{15}NO$: C, 77.58; H, 7.51; N, 6.96. Found: C, 77.43; H, 7.50; N, 6.73.

1,3,4-Trimethyl-2,3-dihydro-1*H*-1-benzazepine (9). A mixture of **4** (757 mg, 3.77 mmol) and $LiAlH_4$ (71.5 mg, 1.89 mmol) in dry ether (20 ml) was stirred for 1 hr at −10 to −5°. After the addition of 10 ml of saturated aqueous NH_4Cl the ether layer was separated, dried, and concentrated. Distillation of the residue gave 695 mg (97.7%) of **9**: bp 83–85° (0.03 mm); NMR ($CDCl_3$) δ 1.27 (d, 3, J = 7.5 Hz, C-3 CH_3), 2.02 (s, 3, C-4 CH_3), 2.54 (m, 1, C-3 H), 3.10 (s, 3, NCH_3), 3.20 (d, 2, J = 3.5 Hz, C-2 H), 6.30 (s, 1, C-5 H), and 6.68–7.31 (m, 4, aromatic H); mass spectrum m/e 187 (M^+, 100), 172 (32), 158 (32), 145 (46), 132 (94), and 117 (41).

Anal. Calcd for $C_{13}H_{17}N$: C, 83.37; H, 9.19; N, 7.48. Found: C, 83.13; H, 9.08; N, 7.51.

Lithium Aluminum Hydride Reduction of 2a. A solution of $LiAlH_4$ (180 mg, 4.74 mmol) in 10 ml of dry ether was added to a solution of **2a** (5.390 g, 19.82 mmol) in dry ether (40 ml). The mixture was stirred at −10 to −5° for 1 hr. After the addition of saturated aqueous NH_4Cl the ether layer was separated, dried, and concentrated. The residue was chromatographed on a silica gel column. The first fraction of benzene gave 2.316 g (62.5%) of **9**. The second fraction of benzene gave 1.450 g (26.7%) of 1,3,4-trimethyl-2-ethoxycarbonylamino-2,3-dihydro-1*H*-1-benzazepine (**8**): bp 98–102° (0.02 mm); ir (neat) 3420, 1720 cm^{-1}; NMR ($CDCl_3$) δ 1.26 (d, 3, J = 6.5 Hz, C-3 CH_3), 1.27 (t, 3, J = 7.0 Hz, ethoxy CH_3), 2.08 (s, 3, C-4 CH_3), 3.37 (s, 3, NCH_3), 3.62 (q, 2, J = 7.0 Hz, OCH_2), 4.14 (m, 1, C-3 H), 5.25 (s, 1, NH), 6.41 (s, 1, C-5 H), and 6.70–7.34 (m, 4, aromatic H).

Anal. Calcd for $C_{16}H_{22}N_2O_2$: C, 70.04; H, 8.08; N, 10.21. Found: C, 70.13; H, 8.07; N, 10.01.

***N*-Methyl-2-(2,3-dimethyl-4-oxo-1-pentenyl)aniline (6).** A solution of methylmagnesium bromide (40 mmol) in 20 ml of ether was added to a solution of **4** (7.990 g, 39.8 mmol) in dry ether (20 ml). The mixture was refluxed for 1 hr. After the addition of 10 ml of saturated aqueous NH_4Cl, the ether layer was separated, dried, and concentrated. Distillation of the residue gave 6.818 g (79.8%) of **6**: bp 72–76° (0.03 mm); ir (neat) 3410, 1707 cm^{-1}; NMR ($CDCl_3$) δ 1.10 (d, 3, J = 6.5 Hz, >CHC**H**$_3$), 1.70 (s, 3, =—CH_3), 1.91 (s, 3, $COCH_3$), 2.74 (s, 3, NCH_3), 3.48 (q, 1, J = 6.5 Hz, >C**H**–), 3.70 (s, 1, NH), 6.02 (s, 1, vinyl H), and 6.28–7.08 (m, 4, aromatic H).

Anal. Calcd for $C_{14}H_{19}NO$: C, 77.38; H, 8.81; N, 6.45. Found: C, 77.17; H, 8.82; N, 6.38.

***N*-Methyl-2-(2,3-dimethyl-4-oxo-1-hexenyl)aniline (7).** In a similar manner as above for **6**, the treatment of **4** (893 mg, 4.44 mmol) with ethylmagnesium bromide (5.0 mmol) in ether (20 ml) gave 566 mg (44.6%) of **7**: bp 75–78° (0.03 mm); ir (neat) 3410, 1705 cm^{-1}; NMR ($CDCl_3$) δ 0.93 (t, 3, J = 7.0 Hz, propionyl CH_3), 1.14 (d, 3, J = 6.5 Hz, >CHC**H**$_3$), 1.75 (s, 3, =—CH_3), 2.32 (q, 2, J = 7.0 Hz, $COCH_2$), 2.82 (s, 3, NCH_3), 3.59 (q, 1, J = 6.5 Hz, >C**H**–), 3.80 (s, 1, NH), 6.16 (s, 1, vinyl H), and 6.40–7.30 (m, 4, aromatic H).

Anal. Calcd for $C_{15}H_{21}NO$: C, 77.88; H, 9.15; N, 6.05. Found: C, 77.91; H, 9.14; N, 6.03.

1,2-Dimethyl-2-(1-methyl-2-oxopropyl)indoline (10). A solution of **6** (1.010 g, 4.65 mmol) in benzene or *n*-hexane was passed through a silica gel column. Distillation of the eluate gave 667 mg (50.9%) of **10**: bp 89–92° (0.03 mm); ir (neat) 1701 cm^{-1}; NMR ($CDCl_3$) δ 1.06 (d, 3, J = 7.0 Hz, >CHC**H**$_3$), 1.14 (s, 3, C-2 CH_3), 2.05 (s, 3, $COCH_3$), 2.54 and 3.40 (AB quartet, 2, J = 16.0 Hz, C-3 H), 2.61 (s, 3, NCH_3), 3.05 (q, 1, J = 7.0 Hz, >CH–), and 6.18–7.06 (m, 4, aromatic H).

Anal. Calcd for $C_{14}H_{19}NO$: C, 77.38; H, 8.81; N, 6.45. Found: C, 77.32; H, 8.80; N, 6.43.

***N*-Methyl-*N*-acetyl-2-(2,3-dimethyl-4-oxo-1-hexenyl)aniline (11).** A suspension of **7** (566 mg, 2.45 mmol), acetic anhydride (2 ml), and sodium acetate (50 mg) in 10 ml of dry benzene was refluxed for 5 hr. After the addition of 10 ml of water, the mixture was made slightly alkaline with sodium bicarbonate, and was extracted with benzene. Distillation of the extract gave 501 mg (74.8%) of **11**: bp 90–93° (0.03 mm); ir (neat) 1708, 1664 cm^{-1}; NMR ($CDCl_3$) δ 0.98 (t, 3, J = 7.0 Hz, propionyl CH_3), 1.26 (d, 3, J = 7.0 Hz, >CHC**H**$_3$), 1.77 (s, 3, =—CH_3), 1.81 (s, 3, $COCH_3$), 2.38 (q, 2, J = 7.0 Hz, $COCH_2$), 3.17 (s, 3, NCH_3), 3.82 (q, 1, J = 7.0 Hz, >C**H**–), 6.28 (s, 1, vinyl H), and 7.12–7.48 (m, 4, aromatic H).

Anal. Calcd for $C_{17}H_{23}NO_2$: C, 74.69; H, 8.48; N, 5.12. Found: C, 74.57; H, 8.49; N, 5.11.

Ozone Oxidation of 11. An excess of ozone (3% ozone in oxygen, flow rate 45 ml/min) was bubbled through a solution of **11** (871 mg, 3.77 mmol) in 30 ml of chloroform at −10 to 0° for 15 min. After stirring with 10 ml of 4% sodium bisulfite, the chloroform solution was separated, dried, and concentrated. Distillation of the residue gave 107 mg (26.0%) of 3-methyl-2,4-hexadione (**13**), bp 79–81° (21 mm) (lit.[8] bp 181–183°), and 270 mg (47.5%) of 2-(*N*-acetyl-*N*-methylamino)benzaldehyde (**12**): bp 75–79° (0.1 mm); ir (neat) 1688, 1663 cm^{-1}; NMR ($CDCl_3$) δ 1.81 (s, 3, $COCH_3$), 3.31 (s, 3, NCH_3), 7.32–8.06 (m, 4, aromatic H), and 10.18 (s, 1, CHO).

Anal. Calcd for $C_{10}H_{11}NO_2$: C, 67.78; H, 6.26; N, 7.91. Found: C, 67.73; H, 6.27; N, 7.90.

2-(*N*-Acetyl-*N*-methylamino)benzaldehyde (12). To a solution of 2-(*N*-methylamino)benzaldehyde[9] (220 mg, 1.63 mmol) in 5 ml of dry benzene was added acetyl chloride (160 mg, 2.04 mmol) and 2 drops of dry pyridine. The mixture was stirred for 10 min at 80°; then it was hydrolyzed with water. Distillation of the benzene extract gave 223 mg (77.3%) of **12**, bp 75–79° (0.1 mm).

Hydrolysis of 3a or 3d. A solution of **3a** (244 mg, 1.0 mmol) or **3d** (173 mg, 1.0 mmol) and potassium hydroxide (0.1 g) in 50% ethanol (10 ml) was refluxed for 1 hr. After removal of the ethanol, the aqueous solution was extracted with chloroform. The extract was washed with water and dried. Distillation of the extract gave 230 mg (100%) of 1,3-dimethyl-2-quinolone (**14a**), bp 105–109° (0.07 mm), mp 64–65° (lit.[7] mp 64–65°), or 153 mg (99.8%) of 1-methyl-2-quinolone (**14d**), bp 89–93° (0.05 mm), mp 73–74° (lit.[10] mp 74°).

Synthesis of 2 from 1-Methyl-2-alkylidene-3-alkyl-1,2-

dihydroquinolines (16a, 16b, and 16c). To a solution of 1,3-dimethyl-2-ethyl- (**18a**, 1.422 g, 6.44 mmol), 1-methyl-2-propyl-3-ethyl- (**18b**, 1.607 g, 6.44 mmol), or 1-methyl-2-isobutyl-3-isopropylquinolinium chloride (**18c**, 1.787 g, 6.44 mmol) in 10 ml of water was added 10 ml of 20% potassium hydroxide at 0–5°. Alkylidenequinoline (**16a, 16b,** or **16c**) was liberated immediately as a yellow oil, which was extracted with 40 ml of ligroin (bp 110–120°). To the boiling ligroin solution was added dropwise 1.496 g (13.0 mmol) of ethyl azidoformate. The mixture was refluxed for 1 hr. All procedures were carried out under a nitrogen atmosphere. Distillation of the reaction mixture gave 1.655 g (94.5%) of **2a**, 1.748 g (90.5%) of **2b**, or 2.083 g (98.5%) of **2c**, respectively.

Registry No.—**1a**, 51904-95-1; **1b**, 57091-58-4; **1c**, 57091-59-5; **1d**, 16021-59-3; **2a**, 57091-60-8; **2b**, 57091-61-9; **2c**, 57091-62-0; **3a**, 57091-63-1; **3d**, 57091-64-2; **4**, 57091-65-3; **6**, 57091-66-4; **7**, 57091-67-5; **8**, 57139-17-0; **9**, 57091-68-6; **10**, 57091-69-7; **11**, 57091-70-0; **12**, 57091-71-1; **16a**, 57091-72-2; **16b**, 57091-73-3; **16c**, 57091-74-4; **18a**, 55539-76-9; **18b**, 55539-77-0; **18c**, 55539-78-1; ethyl azidoformate, 817-87-8; methyl bromide, 74-83-9; ethyl bromide, 75-00-3; 2-(*N*-methylamino)benzaldehyde, 7755-70-6.

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Carbon-13 Nuclear Magnetic Resonance Spectra of Saturated Heterocycles. IV. *trans*-Decahydroquinolines

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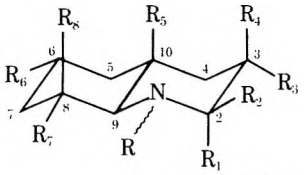
^{13}C NMR spectra of a number of methyl-substituted *trans*-decahydroquinolines and perhydrobenzo[*h*]quinolines are reported. Assignment of signals was accomplished by a combination of off-resonance decoupling, parametrization of substituent effects, and comparison with the spectra of a number of specifically deuterated analogues. Spectra of the *N*-methyl, *N*-ethyl, and *N*-isopropyl derivatives and of the hydrochlorides and trifluoroacetates of a number of the amines are tabulated. Parameters for methyl substitution, replacement of CH_2 by NH, and protonation have been calculated.

Stereochemical problems are increasingly being investigated by ^{13}C magnetic resonance techniques,[1] the chemical shifts constituting a very sensitive probe for conformational properties. Since the numerous signals of substances with high molecular weight can be assigned only with difficulty, an approach involving the recording of spectra of smaller model compounds which constitute subunits of the large molecules, combined with the tabulating of substituent effects, has been successfully applied[1] in a number of systems.

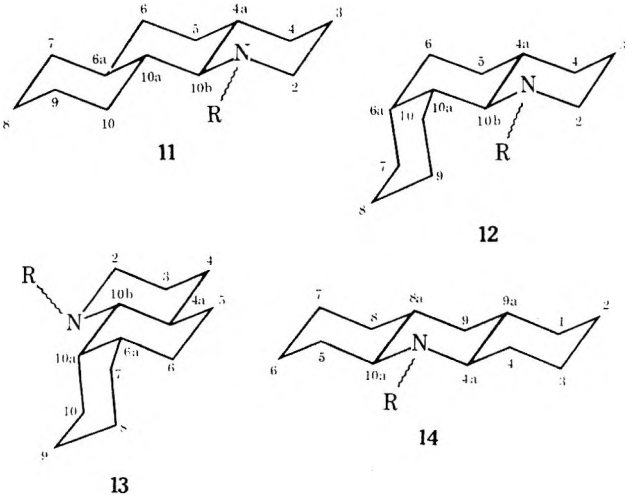
The *trans*-decahydroquinoline framework forms part of a considerable number of natural products. In order to acquire information on the conformational equilibrium of the NCH_3 group (axial–equatorial) in *N*-methylpiperidine and in *N*-methyl-*trans*-decahydroquinoline (**1**),[2] a series of methyl-substituted *trans*-decahydroquinolines[3] (Scheme I, **2–10**, R = H) and perhydrobenzo[*h*]quinolines (Scheme II, **11–13**, R = H), and their *N*-methyl, *N*-ethyl, and *N*-isopropyl derivatives [Schemes I, II, R = CH_3, CH_2CH_3 and $CH(CH_3)_2$] were synthesized[4–6] and their proton[6] and ^{13}C NMR spectra recorded. The conclusions concerning the NCH_3 equilibrium have been reported elsewhere;[2] here the complete ^{13}C NMR data of the compounds are presented and analyzed in terms of substituent parameters.

Scheme I



1. R_1-R_8 = H
2. R_1 = CH_3; R_2-R_8 = H
3. R_2 = CH_3; R_1, R_3-R_8 = H
4. R_3 = CH_3; R_1, R_2, R_4-R_8 = H
5. R_4 = CH_3; R_1-R_3, R_5-R_8 = H
6. R_5 = CH_3; R_1-R_4, R_6-R_8 = H
7. R_6 = CH_3; R_1-R_5, R_7, R_8 = H
8. R_7 = CH_3; R_1-R_6, R_8 = H
9. R_8 = CH_3; R_1-R_7 = H
10. R_6, R_7 = CH_3; R_1-R_4, R_5, R_8 = H

Scheme II



Configuration and Assignment of Signals. The ^{13}C

Table I
^{13}C Chemical Shifts[a] for *trans*-Decahydroquinolines[b]

Compd[c]		C-2	C-3	C-4	C-5	C-6	C-7	C-8	C-9[d]	C-10[d]	CH_3
Parent	1	47.33	27.29	32.46	32.64	26.29	25.64	34.00	62.09	43.34	
2α-Methyl	2	47.53	31.33	26.79	32.47	26.29	25.74	34.31	53.96	43.92	18.62
2β-Methyl	3	52.37	34.98	32.41	32.24	26.21	25.47	33.79	61.85	42.37	22.95
3α-Methyl	4	54.85	(32.79)	41.38	(32.59)	26.20	25.67	33.72	61.55	43.22	19.61
3β-Methyl	5	52.25	28.62	38.07	32.81	26.31	25.74	33.73	62.27	37.51	17.68
6α-Methyl	7	47.38	27.16	32.42	41.41	32.59	34.20	33.79	61.90	42.88	22.43
8α-Methyl	8	47.55	26.93	32.62	33.02	25.84	34.90	37.51	67.97	42.22	18.59
8β-Methyl	9	47.67	27.46	(33.02)	(33.29)	20.23	(32.87)	33.16	64.58	35.61	12.63
10-Methyl	6	48.13	22.97	(39.88)	(40.53)	21.48	25.97	28.88	64.31	33.94	15.60
8α-10-Dimethyl	10	48.64	22.87	(40.35)	(40.96)	21.31	35.52	31.72	70.65	33.98	18.95 (8) 16.75 (10)

[a] In $CDCl_3$, parts per million from Me_4Si. Parentheses indicate that assignments are not unambiguous. [b] For characterization of the *trans*-decahydroquinolines see ref 6. [c] *trans*-Decahydroquinoline; "β" means "on the same side of the ring as the hydrogen on C-10"; "α" means "on the side opposite to this hydrogen". [d] 9 and 10 are used in preference to 8a and 4a to allow unambiguous use of "a" for "axial".

spectrum of *trans*-decahydroquinoline has previously been recorded and discussed,[7] and the various signals have been assigned[7] by comparison with the corresponding data for *trans*-decalin and use of parameters derived by comparing piperidines with cyclohexanes. The signals for C-4 and C-5, previously reported[7] to have identical chemical shifts, were resolved by our instrument. To assign these signals, and a number of signals in several methyl-substituted compounds unambiguously, selectively deuterated analogues were synthesized as needed.[6] In the proton noise-decoupled spectrum of *trans*-decahydroquinoline-*2,3,3,4,9,10-d*$_6$ the signals for C-9 and C-10 (previously identified in *trans*-decahydroquinoline as doublets in the off-resonance decoupled spectrum; C-9, next to the nitrogen, resonating at lowest field) and for C-3 are not observed because of the absence of the nuclear Overhauser enhancement and by being dissipated into triplets and a quintet. C-2 and C-4 are seen as triplets, being substituted with one proton and one deuterium; C-2, next to the nitrogen, is also the most downfield triplet in the off-resonance decoupled spectrum of *trans*-decahydroquinoline.[7] The signals of C-5 and C-8 are shifted upfield by ~0.1 ppm in the deuterated compounds by the β effect of the deuterium[8] at C-9 and C-10, the signal of C-8 being diminished somewhat in intensity because of some deuterium substitution on this carbon.[6] Signals for C-6 and C-7 are practically unshifted by the deuteration, but a small additional signal for C-7, due to the small amounts of deuterium at C-8, is visible ~0.1 ppm upfield of the main signal. Thus the ^{13}C NMR spectrum of the hexadeuterated analogue of *trans*-decahydroquinoline corroborates the signal assignments previously made,[7] and, in addition, affords an unequivocal assignment of the now resolved C-4 and C-5 resonances.

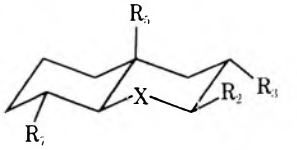
The configuration of compounds **4**–**10**[9] (trans fusion of the rings, equatorial or axial orientation of the CH_3 groups), which was previously inferred from their ^{1}H NMR spectra,[6] is now confirmed by the ^{13}C NMR data; while decahydroquinolines with cis ring fusion[3] have at least one ring ^{13}C NMR signal at higher field than 25 ppm because of γ-gauche interactions, among the trans isomers only **6, 9,** and **10** (Table I), the compounds with axial CH_3, show such high-field ring signals (due to γ-gauche interactions involving the methyl group). Moreover, the signals of the axial methyl groups (in **2, 5,** and **9**) are invariably at higher field than the corresponding equatorial signals (in **3, 4,** and **8**).

Ring carbon signals were assigned either by applying the parameters for methyl-substituted cyclohexanes[10a,b] and decalins[10c] to the parent compound **1** or by using parameters for replacement of CH_2 with NH[7] on appropriate decalins.[10c] Additional information was obtained by off-resonance decoupling and, for compounds **2, 3, 6, 8,** and **9**, by comparison with selectively deuterated analogues, as described for **1**. Some signals occurring in very narrow spectral ranges could not be assigned unambiguously; their tabulated values are parenthesized.

Assignment of the signals in the tricyclic compound **14** was accomplished by comparison of signal intensities, off-resonance decoupling, and comparison with **1** and *trans-syn-trans*-perhydroanthracene.[13] Configurational assignment and assignment of signals in the perhydrobenzo[*h*]quinolines (**11**–**13**) rests on comparison with **8** and **9**, with the corresponding perhydrophenanthrenes,[13] and also on the changes in chemical shifts upon N-methylation (see below).

Comparison with Carbocyclic Analogues. While the similarities of the compounds in Tables I and II with the corresponding methyl-*trans*-decalins and perhydrophenanthrenes, at least in the portion of the molecule remote from the nitrogen, are sufficient to make configurational assignments unambiguous, replacement of CH_2 by NH gives rise to considerable shift differences in the vicinity of the heteroatoms, as shown in Table III.

The C atoms α to the nitrogen are strongly deshielded but to a somewhat different extent; the tertiary carbon (C-9) is influenced less than the secondary (C-2). If C-2 is tertiary as in **3**, the effect is reduced (+19.2 ppm). The β effect is mildly shielding for C-8 and C-10; there is no consistent effect for C-3 and nearly no effect for Me(e)-2 (compare **3** and **15**).



	X	R_2	R_4	R_5	R_7
3	NH	CH_3	H	H	H
15	CH_2	CH_3	H	H	H
4	NH	H	CH_3	H	H
16	CH_2	H	CH_3	H	H
6	NH	H	H	CH_3	H
17	CH_2	H	H	CH_3	H
8	NH	H	H	H	CH_3
18	CH_2	H	H	H	CH_3

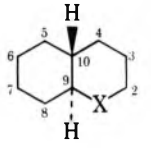
The upfield shift differences for C atoms γ to the site of replacement are in agreement with observations reported elsewhere[14] relating to upfield γ shifts by oxygen and nitrogen atoms. The shielding effect of the nitrogen on anti-per-

Table II
^{13}C Chemical Shifts[a] of Perhydrobenzo[*h*]quinolines[b] (11–13), Perhydroacridine[b] (14), and Their *N*-Methyl Derivatives (11m–14m)

C atom[c]	*trans-anti-trans*-PBQ		*trans-anti-cis*-PBQ		*trans-syn-cis*-PBQ		*trans-syn-trans*-PA	
	11	11m	12	12m	13	13m	14	14m
C-2	47.49	55.99	47.64	56.32	47.74	58.28	26.21	(25.83)
C-3	26.84	19.25	(27.10)	19.62	27.51	25.71	25.57	(26.10)
C-4	32.28	33.21	32.63	33.52	33.04	32.96	33.66	31.03
C-4a	41.81	31.75	(43.47)	31.52	35.99	34.56	62.10	69.28
C-5	32.75	33.56	28.33	28.99	33.15	33.47	33.66	31.03
C-6	34.11	34.45	32.05	32.50	25.45	25.28	25.57	(26.10)
C-6a	45.59	42.77	37.41	37.38	36.95	36.89		
C-7	33.73	33.79	26.72	26.69	32.33	32.56	26.21	(25.83)
C-8	(26.31)	(26.51)	(27.27)	(26.91)	21.60	21.65	32.34[d]	33.46[d]
C-8a							43.25[e]	40.99[e]
C-9	(26.33)	(26.55)	20.58	21.09	26.78	26.90	39.91	40.69
C-10	28.85	29.36	(27.18)	(26.88)	21.07	20.55		
C-10a	47.64	44.62	(41.46)	37.71	42.11	38.44	62.10	69.28
C-10b	66.09	69.11	57.14	60.39	65.40	72.77		
N-CH_3		33.15		33.02		42.34		36.07

[a] In parts per million, from internal Me_4Si in $CDCl_3$. Parentheses indicate that assignments are not unambiguous. [b] For characterization of compounds see ref 6. [c] For nomenclature see Scheme II. [d] Identical with C-1. [e] Identical with C-9a.

Table III
Shift Differences $\Delta\delta$[a] between *trans*-Decahydroquinolines[b] (X = NH) and *trans*-Decalins[c] (X = CH_2)



C atom	Effect	Shift difference[a]
C-2	α	+20.2 ± 0.5[d]
C-3	β	0.0 ± 0.4
C-4	γ	−2.3 ± 0.3
C-5	γ	−1.9 ± 0.3
C-6	δ	−0.9 ± 0.2
C-7	γ	−1.5 ± 0.4
C-8	β	−0.6 ± 0.3
C-9	α	+18.1 ± 0.4
C-10	β	−0.9 ± 0.6
Me(e)-2	β	+0.1[e]
Me(e)-3	γ	−3.2[e]
Me(e)-8	γ	−1.2[e]
Me(a)-10	γ	−0.2[e]
Me(e)-6	ϵ	−0.4[e]

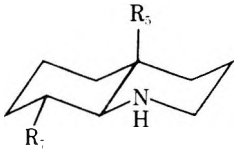
[a] In parts per million. A plus sign indicates that the signal in the NH compound is downfield from the signal in the CH_2 analogue. The differences reported are averages for all the pairs of compounds considered (see footnotes *b*, *c*) with their standard deviations. [b] Compounds 1, 3, 4, 6, 7, 8, 11, 12, 13, and 14, for which ^{13}C NMR spectra of CH_2 analogues are reported,[10c,13] were used in the calculation. [c] *trans*-Decalins,[10c] perhydrophenanthrenes,[13] and perhydroanthracene[13] corresponding to compounds in footnote *b* were used. [d] 3 was excluded. [e] Single occurrence. Data refer to resonance of methyl groups at position and in conformation indicated.

iplanar methyl groups ($\Delta\delta$ between **16**[10c] and **4**, −3.2 ppm) is more pronounced than on equally orientated methylene groups (C-5, −1.9; C-7, −1.5 ppm). Again (cf. ref 14) antiperiplanar methyl groups (−3.2 ppm) are more affected than gauche methyl groups ($\Delta\delta$ CH_3 between **17**[10c] and **6**, −0.2 ppm; between **18**[10c] and **8**, −1.2 ppm). The particularly large γ-gauche effect for C-4 (−2.3 ppm) suggests that at least part of the effect is transmitted through bonds, since C-4 is doubly γ to N-1. A similar explanation may apply to the comparatively large δ effect (−0.9 ppm).

The fact that the ^{13}C NMR spectra of the carbocyclic compounds in Table III were recorded as neat substances[10c,13] but the spectra of the amines were recorded in $CDCl_3$ introduces some uncertainty into the $\Delta\delta$ values because of potential solvent effects; however, comparison of the shift value of cyclohexane in $CDCl_3$ (27.15 ppm) with the literature value[10a] of the neat substance (27.38 ppm) suggests that the effect is not large. Reported[7] $\Delta\delta$ values for piperidine vs. cyclohexane suffer from the same shortcoming.

Shift Effects Produced by Methyl Substitution. Parameters were calculated for the shifts of the ring carbon atoms upon replacement of hydrogen by methyl substituents. The parameters used by Dalling, Grant, and Paul[10c] for the methyldecalins cannot be directly applied to the nitrogen analogues, since the position of the nitrogen relative to the methyl must be taken into account; this leads to a substantial increase in the number of parameters.[11,12] Starting with *trans*-decahydroquinoline, and developing α, β, and γ parameters for replacement of H by CH_3, one arrives at the results (column labeled "found") in Table IV. Comparison with values reported in the literature for the methylcyclohexanes[10b] (Table IV, column labeled "calcd") indicates that the effect of methyl substitution in the carbocycle and the nitrogen heterocycle are nearly the same. With but one exception the Dalling–Grant parameters[10b] predict the chemical shifts in *trans*-decahydroquinolines to within 2 ppm, quite frequently to within 1 ppm, the better agreement occurring, not unexpectedly, for substituents more remote from the nitrogen.

The values for γ_e (−0.4 ± 0.3 ppm), δ_e (−0.1 ± 0.4 ppm), and δ_a (+0.4 ± 0.2 ppm) are not included in Table IV because of their relatively small size. The δ_a value is deshielding and considerably larger than the value reported for the methylcyclohexanes[10b] (−0.06 ± 0.13 ppm). An equally large δ value is obtained by comparing the chemical shifts of the 8α-methyl groups (R_7 = CH_3) in **8** (18.56 ppm) and **10** (18.92 ppm): δ_{ae} = +0.36 ppm. The reverse effect (of the equatorial on the axial methyl group) is even larger (R_5 = CH_3 in **6**, 15.57 ppm; in **10**, 16.72 ppm; δ_{ea} = +1.5 ppm).



6. R_5 = CH_3; R_7 = H
8. R_5 = H; R_7 = CH_3
10. R_5 = R_7 = CH_3

Table IV
Effects of Methyl Substitution on ^{13}C Chemical Shifts in *trans*-Decahydroquinoline

Effect,[a,b] ring atom	Value Found	Value Calcd[b]	Compd
α_e, 2	+5.0	+6.0	3
α_e, 3	+5.5	+6.0	4
α_e, 6	+6.3	+6.0	7
$\alpha_e + \alpha_e\beta_e$, 8	+3.5	+3.5	8
$\alpha_e + \alpha_e\beta_e + \gamma_a + G_\gamma + \beta_e\gamma_a$, 8	−2.3	−1.7	10
β_e, 3	+7.7	+9.0	3
β_e, 2	+7.5	+9.0	4
β_e, 4	+8.9	+9.0	4
β_e, 5	+8.8	+9.0	7
β_e, 7	+8.6	+9.0	7
β_e, 7	+9.3	+9.0	8
$\beta_e + \delta_a$, 7	+9.9	+8.9	10
$\beta_e + \alpha_e\beta_e$, 9	+5.9	+6.5	8
$\beta_e + \alpha_e\beta_e + \beta_a + \alpha_e\beta_a + G_\beta$, 9	+8.6	+7.7	10
α_a, 2	+0.2	+1.4	2
α_a, 3	+1.3	+1.4	5
$\alpha_a + \alpha_a\beta_e$, 8	−0.8	−2.0	9
$\alpha + Q - T + 4V_g$,[c] 10	−9.4	−10.2[c]	6
$\alpha + Q - T + 4V_g + \gamma_e$,[c] 10	−9.4	−10.1[c]	10
β_a, 3	+4.0	+5.4	2
β_a, 2	+4.9	+5.4	5
β_a, 4	+5.6	+5.4	5
$\beta_a + \beta_a\gamma_e$, 7	+7.2	+7.0	9
$\beta_a + \alpha_e\beta_a$, 9	+2.5	+2.5	9
$\beta_a + \beta_a\gamma_e + G_\beta$, 4	+7.4	+5.7	6
$\beta_a + \beta_a\gamma_e + G_\beta$, 5	+7.9	+5.7	6
$\beta_a + \beta_a\gamma_e + G_\beta + \delta_e$, ≤	+7.9	+5.5	10
$\beta_a + \beta_a\gamma_e + G_\beta + \delta_e$, 5	+8.3	+5.5	10
$\beta_a + \alpha_e\beta_a + G_\beta$, 9	+2.2	+1.2	6
γ_a, 4	−5.7	−6.4	2
γ_a, 9	−8.1	−6.4	2
γ_a, 10	−5.8	−6.4	5
γ_a, 6	−6.1	−6.4	9
$\gamma_a + \beta_e\gamma_a$, 10	−7.7	−7.2	9
$\gamma_a + G_\gamma$, 3	−4.3	−4.4	6
$\gamma_a + G_\gamma$, 6	−4.8	−4.4	6
$\gamma_a + G_\gamma$, 3	−4.4	−4.4	10
$\gamma_a + \gamma_e + G_\gamma$, 6	−5.0	−4.4	10
$\gamma_a + \beta_e\gamma_a + G_\gamma$, 8	−5.1	−5.2	6

[a] In parts per million; plus sign indicates downfield from signal in *trans*-decahydroquinoline. [b] Parameters of Table IV, ref 10b, were used for calculated values, if not otherwise indicated. [c] Since no comparable parameter was given in ref 10b, the values from ref 10c are used for α, Q, T, and V_g

This is of some consequence since methyl substituents are frequently used as holding groups in monocyclic systems and their influence on δ positions is usually disregarded.

N-Methyl Derivatives. ^{13}C NMR spectra of the *N*-methyl derivatives[2] of compounds **1**–**14** (Schemes I, II, R = CH_3, **1m**–**14m**) were recorded in $CDCl_3$ and (in some cases) in C_6D_6. The data are collected in Tables II and V.

As in the case of the NH precursors, assignment of signals was accomplished by recording the off-resonance decoupled spectra, by comparison with the carbocyclic analogues[10c,13] and (in the case of **1m**, **2m**, **3m**, **6m**, **8m**, and **9m**) through selectively deuterated analogues. The NCH_3 signals were easily detected in the off-resonance decoupled spectra except for **8m**, **11m**, and **12m**, in which the NCH_3 resonances occur in a rather crowded spectral region; in the case of **8m** the NCD_3 analogue was therefore synthesized[2] in which the CD_3 signal disappeared because of loss of the NOE and dissipation of the signal through coupling with the deuterium.

While the *N*-methyl group in **1m**, **4m**, and **7m** is mobile, it is biased toward the equatorial position by the axial C–CH_3 in **5m**, **6m**, and **9m** and by C-10 in **13m**, and toward the axial position by the equatorial C–CH_3 in **8m** and by C-10 in **11m** and **12m**. By means of the equation $\delta = \delta_e n_e + \delta_a n_a$, the mole fractions of the axial and equatorial conformer in the mobile case (and therefore K and $-\Delta G°$) were calculated. These results are reported in detail elsewhere;[2] ≥95% of the NCH_3 are found to be in the equatorial position at room temperature in $CDCl_3$. Compounds **8m**, **11m**, and **12m** allow the calculation of the shift influences of an axial *N*-methyl group on the ring C atoms; compounds **5m**, **6m**, **9m**, and **13m** (and, if the ≤5% axial NCH_3 are neglected in a first approximation, also **1m**, **4m**, and **7m**) provide the analogous influence of an equatorial NCH_3. The effects are relatively constant; their averaged values are summarized in Table VI. Shielding and deshielding influences are qualitatively the same as in analogous methylcyclohexanes,[10a,b] but the effects in the *N*-methyldecahydroquinolines are generally larger. Most noticeable is the relatively large (−1.5 ppm) shielding γ_e effect. Since it occurs in the equatorially biased compounds as well as in the mobile ones, it cannot be due to a γ_a contribution. The effect is quenched by an axial methyl substituent at the ring carbon under consideration (C-3 in **5m** and C-10 in **6m**). The shielding of the γ_a effect is unusually large also: −7.5 ppm at C-3, −10.8 ppm at C-10 compared to −7.2 ppm for axial methyl in cyclohexane.[10b] Once again there is a sizable deshielding δ_a effect (0.9 ppm); this effect is negligible in methylcyclohexanes.[10b]

Since only a few ^{13}C NMR spectra of carbocyclic analogues of the *N*-methyl-*trans*-decahydroquinolines are reported,[10c] calculations of the effects resulting from replacement of C by N suffer from being based on insufficient data. The direction of such effects (deshielding for α, otherwise shielding) is, however, identical with that recorded in Table III for the secondary amines. The α effect on the methyl carbon is larger (+22.5 ppm) than on methylene and methine carbon (see above). The β effects on C-3 (−1.5 ppm) and C-10 (−2.0 ppm) are more upfield shifting than for the NH compounds. The chemical shifts in the spectra recorded in deuteriobenzene are 0.25–0.70 ppm more downfield from Me_4Si than the values obtained in $CDCl_3$. The solvent effect is largest at C-3 (average +0.44 ppm) and C-4 (average +0.49 ppm) and smallest at C–CH_3 (average +0.17 ppm) and N–CH_3 (average +0.04 ppm).

Comparison of the signals in *N*-methyl-*trans*-decahydroquinoline with **4m**–**7m** and **9m** allows calculation of parameters for *C*-methyl substitution; the values so obtained are similar to the ones in Table IV for *trans*-decahydroquinoline.

Because of the additional γ_g interaction to which the *N*-methyl group is subject in **2m**, **3m**, and **14m**, compared to the other model compounds, no conclusions on the axial-equatorial equilibrium can be drawn from the NCH_3 chemical shift. However, since the γ_a effects brought about by the NCH_3 group are fairly large (see Table VI), C-3 and C-10 in **2m** and **3m**, and C-8a and C-9a in **14m** should be considerably upfield shifted in comparison to the secondary amines if the axial NCH_3 conformer were present in appreciable amounts at equilibrium. The point is further discussed below.

A very large (−9.6 ppm) shielding effect on the axial CH_3 in **2** is observed upon N-methylation; a similar effect (−9.5 ppm) is seen for the analogously positioned C-8 in 3-α-methyl-*cis*-decahydroquinoline (**19**, R = H → R = CH_3).[3] This effect should be compared to the combination of the upfield shifting "γ_g" and "buttressing" effects seen in analogously substituted methylcyclohexanes[10a,b] (e.g., for the axial group in **20**) and methyldecalins[10c] (e.g., the carbocyclic analogue of **19** minus the 3-methyl group). The effect in the carbocycles is considerably smaller (−5.8 ppm in **20**; −6.33 ppm in 1-α-methyl-*cis*-decalin). There is thus an additional factor due to the nitrogen atom. The effect re-

Table V
^{13}C Chemical Shifts[a] of *N*-Methyl-*trans*-decahydroquinolines (1m–10m)[b]

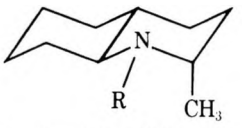
Compd[c]		C-2	C-3	C-4	C-5	C-6	C-7	C-8	C-9[d]	C-10[d]	C–CH_3	NCH_3
Parent	1m	57.94	25.80	32.59	33.06	26.01	25.87	30.47	69.25	41.84		42.59
		58.27	26.13	33.13	33.38	26.48	26.30	30.80	69.55	42.08		42.73
2α-Methyl	2m	55.97	31.62	26.92	32.94	26.21	26.03	30.94	60.03	42.51	9.08	39.53
2β-Methyl	3m	59.72	34.65	32.75	33.52	25.77	26.07	30.86	69.19	41.51	21.93	37.14
3α-Methyl	4m	65.56	30.95	41.35	32.96	25.95	25.76	30.29	68.57	41.65	19.68	42.39
		66.10	31.24	(41.94)	33.29	26.50	26.15	30.74	68.96	(41.97)	19.87	42.61
3β-Methyl	5m	63.57	28.51	38.22	33.12	26.05	25.80	30.14	70.11	36.23	18.77	43.01
		63.77	29.29	39.00	33.50	26.55	26.19	30.66	70.40	36.79	18.95	42.97
10-Methyl	6m	59.19	22.15	(40.32)	(40.67)	21.19	26.14	25.08	71.92	34.10	17.35	43.11
		59.36	22.56	(40.33)	(41.39)	21.56	26.45	25.44	71.85	34.48	17.49	42.93
6α-Methyl	7m	58.06	25.92	32.53	41.82	32.28	34.40	30.38	69.06	41.48	22.29	42.84
		58.32	26.36	33.06	42.06	32.59	34.71	30.78	69.28	41.76	22.54	42.92
8α-Methyl	8m	56.06	19.44	33.65	34.12	25.73	35.66	34.47	70.72	31.76	18.94	33.23
		56.34	19.88	34.22	34.38	26.08	35.92	34.77	70.78	31.74	19.02	33.28
8β-Methyl	9m	58.23	25.80	33.01	33.67	20.18	32.64	29.22	71.98	34.25	12.11	42.29
		58.32	26.23	33.42	33.92	20.61	32.63	29.71	71.98	34.53	12.02	42.33
8α,10-Dimethyl	10m	55.44	16.87	41.35	43.78	21.49	36.70	29.88	71.75	34.91	(19.97) (19.73)	35.26

[a] In parts per million, from internal Me_4Si. First line of signals: solvent $CDCl_3$. Second line of signals: solvent C_6D_6. [b] For characterization of compounds see ref 2 and 6. [c] *trans*-Decahydroquinoline. [d] For nomenclature see footnote *d*, Table I.

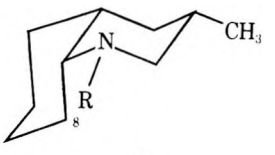
Table VI
Effect[a] of Axial[b] and Equatorial[c] NCH_3 Groups on Ring Shifts in *trans*-Decahydroquinoline

	Axial NCH_3			Equatorial NCH_3		
Ring atom[d]	Effect	Parameter	(Lit.)[e]	Effect	Parameter	(Lit.)[e]
C-2	+8.6 ± 0.1	$\beta_a + \beta_a\gamma_e$	(+7.0)	+10.8 ± 0.2	β_e	(+9.0)
C-3	−7.5 ± 0.1	γ_a	(−6.4)	−1.5 ± 0.4	γ_e	(+0.05)
C-4	+0.9 ± 0.1	δ_a	(−0.06)	+0.1 ± 0.2	δ_e	(−0.2)
C-5	+0.9 ± 0.2	δ_a	(−0.06)	+0.3 ± 0.1	δ_e	(−0.2)
C-6	*f*	ϵ_a		−0.3 ± 0.1	ϵ_e	
C-7	*f*	δ_a		+0.1 ± 0.2	δ_e	(−0.2)
C-8	−3.3 ± 0.3	γ_g	(−2.8)[g]	−3.6 ± 0.2	γ_g	(−2.8)[g]
C-9	+3.0 ± 0.2	$\beta_a + \alpha_e\beta_a$	(+2.5)	+7.4 ± 0.3	$\beta_e + \alpha_e\beta_e$	(+6.6)
C-10	−10.8 ± 0.8	$\gamma_a + \beta_e\gamma_a$	(−7.2)	−1.4 ± 0.1	γ_e	(+0.05)

[a] In parts per million. Plus sign indicates downfield shift. The values given are averages of the compounds considered (see footnotes *b*, *c*) with their standard deviations. [b] Compounds 8m, 11m, and 12m were used for the calculation. [c] Compounds 1m, 4m, 5m, 6m, 7m, 9m, and 13m were used for the calculation. [d] For nomenclature see Scheme I. [e] Parameters and their values (in parentheses) are those for methylcyclohexanes, ref 10b. [f] Values were too divergent for averaging. [g] The parameter is reported[11c,b] for a methyl group.



2, R = H 18.62 ppm
2m, R = CH_3 9.08 ppm



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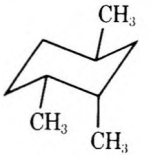

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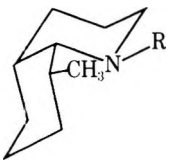
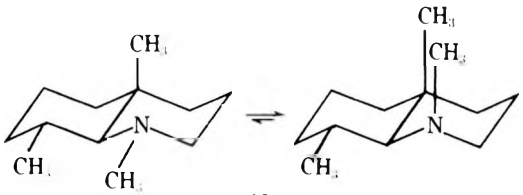
quires the presence of both the *N*-methyl group and the axial lone pair; it is absent in the NH analogs (which must exist with predominantly equatorial NH[15]) and it is reduced in the amine hydrochlorides, to a value even smaller than in the carbocyclic analogues ($2H^+Cl^- \rightarrow 2m_eH^+Cl^-$, $\Delta\delta = -3.57$ ppm).

The position of the NCH_3 group in **10m** cannot be estimated from the chemical shift of its signal since this group is compressed in both the axial and the equatorial position by either a syn-axial or a peri methyl group. Results[3] with 8α-methyl-*cis*-decahydroquinoline (**21**) and its *N*-methyl derivative (**21m**), in which the NCH_3 group cannot escape the per interaction, indicate that such an interaction is downfield shifting[16] [CH_3 (8α), **21** → **21m**, $\Delta\delta$ = +4.6 ppm]. The NCH_3 signal in **10m** has a chemical shift of 35.26 ppm;



21, R = H
21m, R = CH_3



10m

this points to a substantial contribution of downfield shifted axial NCH_3 rather than to a downfield shifted equatorial NCH_3 which should have a shift of ~45 ppm. Accordingly, the compressed CH_3(10) group is shifted downfield by 3.0–3.2 ppm (the two C-methyl groups in **10m** are too close for unambiguous assignment) but the essentially uncompressed CH_3(8α) group is shifted downfield by only 0.8–1.0 ppm. Also the γ effect on C-3 is large and upfield (−6.1

Table VII
^{13}C Chemical Shifts[a] of *N*-Ethyl- and *N*-Isopropyl-*trans*-decahydroquinolines

Compd[b]	C-2	C-3	C-4	C-5	C-6	C-7	C-8	C-9	C-10	C-CH_3	NCH	NCHCH_3	NCHCH_3
1-Et	52.63	25.91	32.80	33.26	26.05	25.91	30.10	65.29	42.07		46.29	9.18	
4-Et	60.33	30.93	41.54	33.14	26.00	25.85	29.99	64.55	41.90	19.78	46.12	9.03	
6-Et	53.55	22.25	(40.39)	(40.99)	21.20	26.24	24.84	67.55	34.23	17.31	46.41	8.58	
8-Et	49.64	18.73	33.80	34.53	25.76	35.80	34.20	72.19	33.37	19.05	36.63	13.92	
9-Et	52.58	25.78	33.21	33.86	20.19	32.64	28.73	67.63	34.52	12.41	45.58	9.20	
1-*i*-Pr	44.21	26.35	33.29	33.52	25.97	26.10	29.46	64.24	42.43		45.96	21.95	11.88
4-*i*-Pr	51.88	31.33	42.04	33.36	25.87	26.00	29.33	63.57	42.17	19.96	45.79	21.93	11.82
6-*i*-Pr	45.40	22.07	(40.32)	(41.70)	21.04	26.36	24.44	67.00	34.51	17.29	45.86	22.58	12.17
8-*i*-Pr	45.56	25.85	33.82	34.68	25.57	36.09	33.88	71.56	37.83	20.18	45.35	24.55	22.76
9-*i*-Pr	44.24	25.97	33.69	34.09	20.16	32.67	28.39	66.35	34.83	12.31	44.90	21.75	11.84

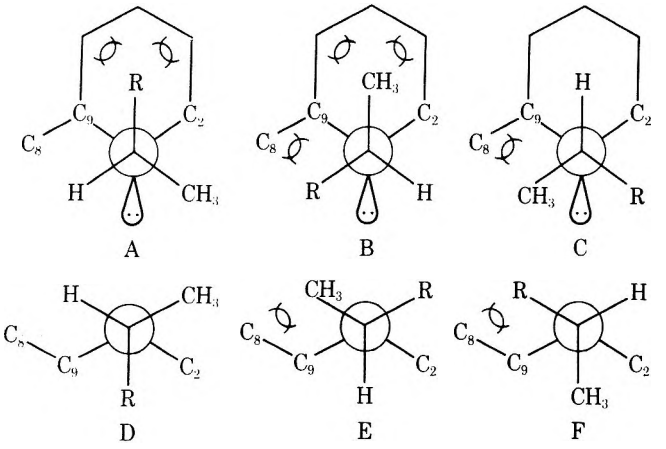
[a] In $CDCl_3$; parts per million from internal Me_4Si. [b] See Scheme I; Et, R = CH_2CH_3; *i*-Pr, R = $CH(CH_3)_2$. For melting points of derivatives and ^{1}H NMR data see ref 2.

ppm), indicating axial substitution on N. The same indication follows from the rather large downfield shifts of C-4 and C-5 (similarly as in **8m**). The combined force of these arguments indicates that the NCH_3 group in **10m** is largely axial. There is also confirmation, for the case of CH_3–CH_3 interactions, of the downfield shifting effect of syn-axial groups on each other reported elsewhere[16] in similar situations.

***N*-Ethyl and *N*-Isopropyl Derivatives.** The ^{13}C NMR spectra of the *N*-ethyl (Scheme I, R = C_2H_5) and *N*-isopropyl [Scheme I, R = $CH(CH_3)_2$] derivatives of **1, 4, 6, 8,** and **9** were recorded; the chemical shifts are collected in Table VII. Assignment of the methyl signals was done by off-resonance decoupling and, in the case of 4-*i*-Pr and 8-*i*-Pr, confirmed by recording the spectra of the $NCD(CD_3)_2$ analogues. Assignment of the signals of the ring C atoms in case of 1-Et, 8-Et, and 9-Et, and 1-*i*-Pr, 8- *i*-Pr, and 9-*i*-Pr, was confirmed by investigating the ring-deuterated compounds.

Comparison with the NCH_3 compounds shows that shift changes on C atoms remote from the nitrogen are relatively minor (an exception is 8-*i*-Pr, see below). Both C-2 and C-9 are less downfield shifted in 1-Et, 4-Et, 6-Et, and 9-Et compared to the NCH_3 analogues because of additional gauche interactions; the same is true for C-2 but not for C-9 in 8-Et, which exists in conformation A (R = H, Scheme III); a gauche interaction of C-9 with the methyl group would require contributions of the unfavorable rotamers B and C.

Scheme III



1-Et, 4-Et, 6-Et, 8-Et, 9-Et, R = H
1-*i*-Pr, 4-*i*-Pr, 6-*i*-Pr, 8-*i*-Pr, 9-*i*-Pr, R = CH_3

In 1-*i*-Pr, 4-*i*-Pr, 6-*i*-Pr, and 9-*i*-Pr, C-9 is still somewhat downfield shifted compared to the NH analogues by the β effect of the methine carbon, but the effect is nearly compensated by the gauche interactions with the methyl groups; C-2 is already upfield shifted. This suggests predominance of rotamer D in Scheme III (R = CH_3), where C-2 has two gauche interactions and C-9 only one. (Conformers E and F suffer from an *i*-Pr–Me/C-8 syn-axial interaction.)

In 8-*i*-Pr the methine carbon (45.35 ppm) of the isopropyl group is very much downfield compared to the methyl in **8m** (33.23 ppm) and the methylene in 8-Et (36.63 ppm); C-3, on the other hand, is much less shielded (relative to the NH compound, $\Delta\delta$ = −1.1 ppm) than **8m** ($\Delta\delta$ = −7.5 ppm) or 8-Et ($\Delta\delta$ = −8.2 ppm). Since the isopropyl methyl groups are encountering very severe sterical interactions in the isopropyl-axial conformations (see Scheme III) A–C, the possibility exists that the *N*-isopropyl group is partially in the equatorial position in spite of the peri interaction with the methyl group on C-8 that this would cause.

The diastereotopic isopropyl methyl groups in 1-*i*-Pr, 4-*i*-Pr, 6-*i*-Pr, and 9-*i*-Pr show shift differences of ~10 ppm; this finds its parallel in the proton spectra[2] of these compounds with shift differences of the methyl protons of ~0.3 ppm.

Ring-Deuterated *trans*-Decahydroquinolines. In connection with the earlier mentioned study of ring-deuterated *trans*-decahydroquinolines, the *2,3,3,4,9,10-*d_6 analogues of **1, 2, 3, 8,** and **9**, of their *N*-methyl derivatives, and of the *N*-ethyl and *N*-isopropyl derivatives of **1, 8,** and **9** were prepared. Compounds 1-d_6 and 9-d_6 and their *N*-alkyl derivatives contained small amounts of *2,3,3,4,8,9,10-*d_7 products because some exchange of the axial proton at C-8 occurred during synthesis, and 2-d_6 and 3-d_6 were admixed with substantial amounts of higher deuterated material owing to extensive exchange in the CH_3 group.[6]

The shift effects of the deuterium on the various carbon atoms are in agreement with results reported in the literature.[8,17,18] C atoms devoid of proton substituents (C-3, C-9, and C-10, and C-2 in 2-d_6 and 3-d_6) could not be detected in the proton noise-decoupled spectra, their signals being very small because of loss of the NOE, long relaxation times, and dissipation of the signals into triplets and quintets. C atoms substituted with one deuterium and one proton (C-4 in **1, 2, 3, 8,** and **9**, and C-2 in **1, 8,** and **9**) were split into triplets (J_{CD} ~ 20 Hz). C-2 was shifted upfield by 0.5–0.7 ppm, and C-4 by 0.6–0.8 ppm largely by the deuterium bound to it.

β effects of deuterium were seen on C-5 and C-8; the signals of these carbons were broadened by C–C–D coupling and shifted upfield by ~0.1 ppm relative to those of the protonated analogues. C-7 displayed a small satellite signal, ~0.1 ppm upfield of the main one, resulting from the minor amount of deuteration at C-8 which had occurred

Table VIII
^{13}C Chemical Shifts[a] of *trans*-Decahydroquinolinium Chlorides[b] and Trifluoroacetates[c]

Entry no.	Compd[d]	C-2	C-3	C-4	C-5	C-6	C-7	C-8	C-9	C-10	CH_3
1	$1H^+Cl^-$	44.85	22.50	30.09	32.12	24.94	24.84	29.87	61.29	39.11	
		−2.48	−4.79	−2.37	−0.52	−1.35	−0.80	−4.13	−0.80	−4.22	
2	$2H^+Cl^-$	48.43	27.50	24.75	32.01	24.94	24.94	29.72	54.44	39.44	14.61
		+0.90	−3.83	−2.04	−0.46	−1.35	−0.80	−4.59	+0.48	−4.48	−4.01
3	$3H^+Cl^-$	54.26	30.78	30.46	32.00	24.87	24.87	29.59	61.71	38.36	19.31
		+1.89	−4.20	−1.95	−0.24	−1.34	−0.60	−4.20	−0.14	−4.01	−3.64
4	$6H^+Cl^-$	45.04	18.78	38.02	39.50	20.50	25.21	25.21	63.28	33.61	16.06
		−3.09	−4.19	−1.86	−1.03	−0.98	−0.76	−3.67	−1.03	−0.33	+0.46
5	$8H^+Cl^-$	45.85	22.31	30.19	32.44	24.64	34.63	35.18	66.94	38.83	19.20
		−1.70	−4.62	−2.43	−0.58	−1.20	−0.27	−2.33	−1.03	−3.39	+0.61
6	$9H^+Cl^-$	45.56	22.24	30.71	32.85	19.09	31.85	30.19	64.29	32.49	13.24
		−2.11	−5.22	−2.31	−0.44	−1.14	−1.02	−2.97	−0.34	−3.12	+0.61
7	$1H^+TFA^-$	48.44	24.16	30.75	33.24	26.17	25.95	32.06	65.07	41.77	
		+1.11	−3.13	−1.71	+0.60	−0.12	+0.31	−1.94	+2.98	−1.53	
8	$6H^+TFA^-$	49.12	20.28	38.71	40.90	21.55	26.35	27.39	67.42	35.35	15.32
		+0.99	−2.69	−1.17	+0.37	+0.07	+0.38	−1.49	+3.11	+1.41	−0.28
9	$8H^+TFA^-$	48.80	24.01	30.78	33.57	25.78	35.61	37.39	70.82	41.42	17.90
		+1.25	−2.92	−1.84	+0.55	−0.06	+0.71	−0.12	+2.85	−0.80	−0.69
10	$9H^+TFA^-$	48.77	23.98	31.29	33.90	20.09	33.12	32.55	68.00	34.86	12.30
		+1.10	−3.48	−1.73	+0.61	−0.14	+0.25	−0.61	+3.42	−0.75	−0.35

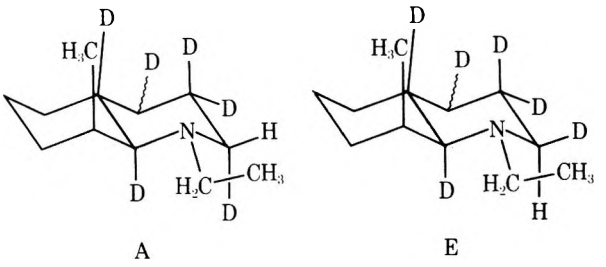
[a] First line of figures for each compound: shift in parts per million from internal Me_4Si. Second line: shift difference from the free amine in $CDCl_3$ (Table I) (salt − amine). A plus sign indicates that the signal in the salt is downfield from the signal in the free amine. [b] In $CDCl_3$. [c] In trifluoroacetic acid. [d] See Scheme I for compound identification. Cl^- indicates chloride; TFA^-, trifluoroacetate.

(vide supra). In compound 8, for the same reason, a deuterium satellite of the methyl resonance was seen.

Increase in line width for C atoms γ to the site of deuterium is generally small. However, broadening may occur,[8] due to a combination of long-range coupling and differential chemical shifting, especially in compounds which are either highly deuterated (coupling effect) or in which hydrogen and deuterium substitution coexist at the γ carbon (differential shift effect). Observation of such broadening allowed unambiguous assignment of the signals due to C-3 and C-6 in **6** and **6m**; the spectra of the *8,8,9-d*$_3$ analogues containing approximately 40% *8,9-d*$_2$ because of incomplete deuteration (the amount of d_2 compound could be estimated from the intensities of the two signals for C-7, 0.1 ppm apart) showed a threefold increase in line width for the signal of C-6 compared to the undeuterated compound whereas the signal for C-3 was unchanged.

The methyl group of the ethyl function in 1-Et-d_6 and 9-Et-d_6 (but not in 8-Et-d_6), and the upfield methyl group of the isopropyl function in 1-*i*-Pr-d_6 and 9-*i*-Pr-d_6 (but not in 8-*i*-Pr-d_6) showed two signals (shift difference 2.0 and 2.4 Hz for the ethyl and 0.7 and 0.9 Hz for the isopropyl methyl group). In the case of the ethyl compounds the larger of the two peaks was upfield, in case of the isopropyl, downfield. No doubling was seen for the downfield methyl in the isopropyl groups of 1-*i*-Pr-d_6 and 9-*i*-Pr-d_6, and only one signal could be detected for the corresponding methyl groups in 1-Et-*9*-d_1 and 1-*i*-Pr-*9*-d_1; admixture with undeuterated material still gave an unsplit signal. This finding, combined with the absence of any doubling in 8-Et-d_6 and 8-*i*-Pr-d_6 (or, of course, in any of the undeuterated compounds), forces one to the conclusion that the doubling of the methyl signals is caused by the deuterium at C-2. The hexadeuterated compounds are mixtures of isomers with axial or equatorial deuterium at C-2 and C-4 and since C-4 is quite distant from the *N*-alkyl groups, C-2 must be implicated in the doubling. In the presumably most favored rotational form of 1-Et or 8-Et, the CH_3 of the ethyl group is much closer to equatorial deuterium on C-2 (Scheme IV, E) than to axial deuterium (Scheme IV, A). The deuterium vs. proton shift effect may act through

Scheme IV



bonds (but this seems unlikely, since no effect is observed at the methylene carbon at the ethyl group, which is closer (γ) to the deuterium at C-2) or, more likely, it may act through space; no clear-cut decision can, however, be made on the basis of the available evidence.

Protonated *trans*-Decahydroquinolines.[19] The chemical shifts of a number of protonated *trans*-decahydroquinolines and *N*-methyl-*trans*-decahydroquinolines are collected in Tables VIII–X. Also recorded in these tables are the differences in chemical shift between the salts (protonated amines) and the free amines (in $CDCl_3$).[20]

Comparison of the data for the hydrochlorides and trifluoroacetates in Table VIII shows that for C atoms remote from the nitrogen (C-5, C-6, C-7) the shift differences $\Delta\delta$ (salt − free amine) for the two are quite similar (1.0–0.4 ppm), while close to the nitrogen they vary considerably. For example, for **1**, **6**, **8** (Table VIII, entries 1, 7; 4, 8; 5, 9), **6m**, **8m**, and **9m** (compare entries 18, 19, and 20 in Table IX with 27, 28, and 29 in Table X), the shift for C-2 upon formation of the hydrochloride is upfield, but for the trifluoroacetate it is downfield. The shift difference changes are brought about largely by the change in solvent and only in small part by the change of the gegenion; thus *N*-methyl-*trans*-decahydroquinoline hydrochloride and trifluoroacetate in $CDCl_3$ have very similar chemical shifts (Table IX, entry 11; Table X, entry 23). The same is true for the hydrochloride and trifluoroacetate in trifluoroacetic acid (Table IX, entry 13; Table X, entry 21). In contrast, the shifts for corresponding salts in $CDCl_3$ and CF_3COOH dif-

Table IX
^{13}C Chemical Shifts[a] of *N*-Methyl-*trans*-decahydroquinolinium Chlorides[b]

Entry no.	Compd[b]	C-2	C-3	C-4	C-5	C-6	C-7	C-8	C-9	C-10	CH_3	NCH_3
11	$1m_eH^+Cl^-$[c]	56.77	22.87	30.08	32.45	24.58	25.07	27.21	69.31	39.18		40.41
		−1.17	−2.93	−2.51	−0.61	−1.43	−0.80	−3.26	+0.06	−2.66		−2.18
12	$1m_aH^+Cl^-$[d]	54.15	18.19	30.31	32.73	24.88?	24.88?	28.16	65.62	33.38		32.82
13	$1m_eH^+Cl^-$[c,e]	59.71	24.80	31.03	33.69	25.88	26.28	29.41	73.19	42.33		42.14
		+1.77	−1.00	−1.56	+0.63	−0.13	+0.41	−1.06	+3.93	+0.49		−0.45
14	$2m_eH^+Cl^-$[f]	58.81	28.85	24.76	32.38	24.65	25.29	27.21	62.55	39.86	11.04	38.59
		+2.84	−2.77	−2.16	−0.56	−1.56	−0.74	−3.73	+2.52	−2.65	+1.96	−0.94
15	$2m_aH^+Cl^-$[d]	59.30	23.30	g	32.82	25.04?	25.04?	28.07	59.30	33.69	15.52	35.70
16	$3m_eH^+Cl^-$[f]	63.06	32.84	30.77	32.94	24.17	25.41	27.47	70.65	38.90	18.68	35.97
		+3.34	−1.81	−1.98	−0.58	−1.60	−0.66	−3.39	+1.46	−2.61	−3.25	−1.17
17	$3m_aH^+Cl^-$[d]	59.72	25.60	g	g	25.03?	25.03	28.15	67.51	31.60	17.74	25.81
18	$6m_eH^+Cl^-$	57.56	19.65	37.77	39.88	20.10	25.44	22.86	71.66	34.89	16.95	41.77
		−1.63	−2.50	−2.55	−0.79	−1.09	−0.70	−2.22	−0.26	+0.79	−0.40	−1.34
19	$8m_aH^+Cl^-$	55.67	18.13	30.36	33.03	24.52	34.68	33.59	71.22	33.51	18.88	32.71
		−0.39	−1.31	−3.29	−1.09	−1.21	−0.98	−0.88	+0.50	+1.75	−0.06	−0.52
20	$9m_eH^+Cl^-$	57.61	22.61	30.53	33.16	18.85	32.03	28.03	71.91	32.91	12.65	40.11
		−0.62	−3.19	−2.48	−0.51	−1.33	−0.61	−1.19	−0.07	−1.34	+0.54	−2.18

[a] First line of figures: shift in parts per million from Me_4Si. Solvent $CDCl_3$ if not otherwise indicated. Second line: shift difference from the unprotonated amine in $CDCl_3$ (Table V). [b] See Scheme I for compound identification. The symbol m indicates an *N*-methyl compound; the subscripts e or a refer to the equatorial or axial position of the *N*-methyl substituents. 1m, 2m, and 3m gave mixtures of hydrochlorides; the major component with the NCH_3 equatorial, the minor with NCH_3 axial. No second component could be detected in the hydrochlorides of 6m, 8m, and 9m. [c] The ⩽5% axial NCH_3 in the amine was neglected for the calculation of $\Delta\delta$ salt-amine. [d] Since the NCH_3 in the amine is predominantly equatorial, no $\Delta\delta$ was calculated. [e] Solvent trifluoroacetic acid. [f] The contribution of axial NCH_3 in the amine was neglected for calculation of $\Delta\delta$. [g] Overlaid by a signal of the major (NCH_3 eq) component.

Table X
^{13}C Chemical Shifts[a] of *N*-Methyl-*trans*-decahydroquinolinium Trifluoroacetates[b]

Entry no.	Compd[b]	C-2	C-3	C-4	C-5	C-6	C-7	C-8	C-9	C-10	CH_3	NCH_3
21	$1m_eH^+TFA^-$[c]	60.06	24.95	31.07	33.74	25.93	26.34	29.59	73.57	42.68		42.39
		+2.12	−0.85	−1.52	+0.68	−0.08	+0.47	−0.88	+4.32	+0.84		−0.20
22	$1m_aH^+TFA^-$[d]	57.54	19.27	31.29	34.11	26.13?	26.13?	30.45	69.99	35.27		34.80
23	$1m_eH^+TFA^-$[c,e]	57.09	23.01	30.11	32.49	24.70	25.14	27.37	69.95	39.54		40.54
		−0.85	−2.79	−2.48	−0.57	−1.31	−0.73	−3.10	+0.70	−2.30		−2.05
24	$1m_aH^+TFA^-$[d,e]	54.19	18.03	30.30	32.76	25.00?	25.00?	28.37	65.84	33.42		33.19
25	$3m_eH^+TFA^-$[f]	66.77	34.12	31.51	34.26	25.73	26.70	30.31	74.43	42.93	19.76	38.26
		+7.05	−0.53	−1.24	+0.74	−0.04	+0.63	−0.55	+5.24	+1.42	−2.17	+1.12
26	$3m_aH^+TFA^-$[d]	64.29	26.87	31.95	g	26.48	26.24	30.65	72.25	34.75	18.65	27.93
27	$6m_eH^+TFA^-$	60.89	(21.03)	38.77	41.44	(21.13)	26.65	24.56	75.70	36.48	16.20	42.60
		+1.70	−1.12	−1.55	+0.77	−0.06	+0.51	−0.52	+3.78	+2.38	−1.15	−0.51
28	$8m_aH^+TFA^-$	57.98	19.25	31.35	34.35	25.61	35.72	34.95	75.69	34.85	17.30	34.18
		+1.92	−0.19	−2.30	+0.23	−0.12	+0.06	+0.48	+4.97	+3.09	−1.64	+0.95
29	$9m_eH^+TFA^-$	60.30	24.67	31.34	34.40	20.03	33.29	29.73	76.12	35.71	11.56	41.93
		+2.07	−1.13	−1.67	+0.73	−0.15	+0.65	+0.51	+4.14	+1.46	−0.55	−0.36

[a] First line of figures: shift in parts per million from Me_4Si. Solvent trifluoroacetic acid if not otherwise indicated. Second line of figures: shift difference from the free amine in $CDCl_3$ (Table V). [b] See Scheme I for compound identification and footnote *b*, Table IX. 1m and 3m gave mixtures of salts; the major component with the NCH_3 group equatorial (m_e), the minor with the NCH_3 axial (m_a). 6m, 8m, and 9m gave only one set of signals in trifluoroacetic acid. [c] The ⩽5% axial NCH_3 in the free amine was neglected for the calculation of the shift difference salt — amine. [d] Since the NCH_3 in the amine was predominantly equatorial, no $\Delta\delta$ was calculated. [e] Solvent $CDCl_3$. [f] The contribution of axial NCH_3 in the free amine was neglected for the calculation of δ. [g] Overlaid with a signal of the major (NCH_{3e}) component.

fer considerably (Table IX, entries 11 and 13; Table X, entries 21 and 23) and by about the same amounts. This variation in chemical shift may be due to prevalence of ion pairs in the less polar solvent chloroform, but of solvated ions in the more polar solvent trifluoroacetic acid.

Comparison of hydrochlorides and unprotonated amines in the same solvent ($CDCl_3$) allows the calculation of protonation effects. Values taken from Tables VIII and IX are in agreement with data reported for piperidines,[22] piperidones,[23] and aliphatic amines.[19] Generally, the introduction of a positive charge at the nitrogen leads to shielding of both close-by and distant carbon atoms through polarization of the C–H bond. Exceptions occur for α carbons which bear methyl substituents (compounds **2**, **2m$_e$**, **3**, **3m$_e$**; entries 2 and 3 in Table VIII and 14 and 16 in Table IX); this is in accord with observations made in aliphatic amines.[19] However, C-9, though tertiary, is frequently shifted upfield in the *trans*-decahydroquinolines (Table VIII, entries 1, 3, 4, 5, and 6; Table IX, entries 18 and 20) although in other cases it displays the expected downfield shift (Table VIII, entry 2; Table IX, entries 11, 14, 16, and 19).

The carbon atoms β to the nitrogen become strongly shielded upon protonation, the effect being larger in the secondary (NH) than in the tertiary (NCH_3) amines, again in accord with what is seen in acyclic compounds.[19] The same difference has been observed in piperidines vs. *N*-methylpiperidines[21] and has been attributed to the allegedly preferred equatorial position of the lone pair in the NH (but not in the *N*-methyl) compound; in the light of other

work on the position of lone pair in piperidine[15] and in the light of the analogy with acyclic amines,[19] this explanation is no doubt incorrect.[24]

In agreement with earlier work[21] and with molecular orbital calculations,[25] we find an "alternating and attenuating" shift effect[21] upon protonation as one moves away from the ring nitrogen atom; the upfield shifts are $\alpha < \beta > \gamma < \delta$. In the case of the δ effect at C-6 this may, however, be an artifact resulting from the dual through-bond path (C-9–C-8–C-7–C-6 and C-9–C-10–C-5–C-6); results in the aliphatic series[19] in general show that C_γ is more upfield shifted than C_δ.

Whereas the *N*-methyl-*trans*-decahydroquinolinium chlorides (Table IX) are all conformationally homogeneous, this is not true of all of their amine precursors. In the case of **1m** (and probably also **2m** and **3m**) the *N*-methyl group is largely (≥95% in case of **1m**) equatorial and we felt justified in disregarding the axial component and to indicate $\Delta\delta$ (Table IX, entries 11, 14, and 16) as the difference between the equatorial salt and the mobile amine. Compounds **6m** and **9m**, on the other hand, are conformationally homogeneous and the $\Delta\delta$ values (entries 18 and 20) for these species are accurate for a *N*-methyl-*trans*-decahydroquinoline with equatorial *N*-methyl.

Compound **8m** has the novel feature of a conformationally homogeneous axial NCH_3 and displays slightly different shifts upon protonation (entry 19) than the equatorial analogues (β effect, lesser upfield shift at C-3 and C-8, larger downfield shift at C-10; enhanced γ-effect, larger upfield shift at C-4, C-5, and C-7). Other salts with axial NCH_3 ($\mathbf{1m}_aH^+$, $\mathbf{2m}_aH^+$, and $\mathbf{3m}_aH^+$; entries 12, 15, and 17 in Table IX) display similar absolute chemical shifts in those regions not directly affected by the substituent groups, suggesting little perturbation of the molecule by the methyl group at C-8.

In summary, the study of 14 *trans*-decahydroquinolines has enabled us to establish the effect of methyl substitution on the chemical shifts of various ring carbons and to compare shifts in saturated nitrogen heterocycles with those in analogous carbocycles. Deuteration, easily effected in this series, has proved extraordinarily helpful in signal assignment. A corresponding study of the *N*-methyl homologues has permitted assessment of the effect of conformationally homogeneous equatorial and axial *N*-methyl groups on ring carbon signals; in addition it has corroborated the effect of ring methyl substituents on the shifts of the ring carbon atoms in the parent *N*-methyl-*trans*-decahydroquinoline. A strongly upfield shifting effect of an equatorial *N*-methyl (axial lone pair) on an axial *C*-methyl on the adjacent carbon atom was discovered; this effect is similar to the known[26] effect on an axial proton. Axially and equatorially *N*-ethyl and *N*-isopropyl substituted *trans*-decahydroquinolines were also investigated. Finally, it proved possible to explore the effect of protonation on chemical shifts at α, β, γ, and δ positions in conformationally well-defined amines. While the nature of the acid (HCl, CF_3COOH) has little effect on the shift differences upon protonation, there is a strong effect of solvent, especially on those shifts (α, β) in the vicinity of the nitrogen; it is not permissible to compare shifts in trifluoroacetic acid with those in chloroform.

Experimental Section

Carbon-13 spectra were recorded on a Varian XL-100 pulsed Fourier transform nuclear magnetic resonance spectrometer operating at 25.16 MHz.[27] Samples were observed in 10-mm o.d. tubes, at 20 ± 5% solutions in deuteriochloroform or trifluoroacetic acid with 2–5% Me_4Si added as internal reference substance at 29 ± 1°C. The solvents provided the internal lock signal (deuterium or fluorine). 8-K, 16-K, or 32-K data point spectra were measured depending on the required degree of resolution; digital resolution was 0.6 Hz (0.025 ppm) at 8-K data points and 2500-Hz sweep width. The accuracy of the chemical shifts is estimated to be ± 0.03 to ± 0.05 ppm.[27]

The *trans*-decahydroquinolines and perhydrobenzo[*h*]quinolines were synthesized from 5,6,7,8-tetrahydroquinolines[5] and 5,6,6a,7,8,9,10,10a-octahydrobenzo[*h*]quinolines,[5] or from $\Delta^{1,9}$-octahydroquinolines,[6] through sodium–ethanol reduction.[6] Ring-deuterated analogues were prepared in an analogous way by reduction in ethanol-*O*-*d* with were prepared in an analogous way by reduction in ethanol-*O*-*d* with sodium.[6] *N*-Methyl, *N*-ethyl, and *N*-isopropyl derivatives were synthesized by known methods.[2] Preparative details, melting points of derivatives, and pertinent ^{1}H NMR data are reported elsewhere.[2,5,6]

The hydrochlorides were precipitated by passing gaseous HCl into the solutions of the amines in anhydrous ether. After evaporation of the solvent the hydrochlorides were dissolved in $CDCl_3$. The trifluoroacetates of the *N*-methyl compounds were prepared by adding the amine slowly into rapidly stirred, chilled excess trifluoroacetic acid.

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Registry No.—1, 767-92-0; 1 Cl^-, 4678-90-4; 1 TFA^-, 57288-91-2; **1m**, 875-63-8; **1m** Cl^-, 875-65-0; **1m** TFA^-, 57288-92-3; 1-Et, 771-30-2; 1-*i*-Pr, 19079-76-6; **2**, 18610-37-2; **2** Cl^-, 18610-38-3; **2m**, 18609-07-9; **2m** Cl^-, 18609-08-0; **3**, 18609-01-3; **3** Cl^-, 18609-02-4; **3m**, 18609-11-5; **3m** Cl^-, 18609-12-6; **3m** TFA^-, 57288-93-4; **4**, 52601-71-5; **4m**, 52008-63-6; 4-Et, 55970-19-9; 4-*i*-Pr, 55970-23-5; **5**, 52679-13-7; **5m**, 55970-11-1; **6**, 45846-79-5; **6** Cl^-, 57288-94-5; **6** TFA^-, 57289-06-2; **6m**, 52008-65-8; **6m** Cl^-, 57288-95-6; **6m** TFA^-, 57288-96-7; 6-Et, 55970-17-7; 6-*i*-Pr, 55970-21-3; **7**, 57288-97-8; **7m**, 55970-13-3; **8**, 52761-68-9; **8** Cl^-, 55905-31-2; **8** TFA^-, 57288-98-9; **8m**, 55970-12-2; **8m** Cl^-, 57288-99-0; **8m** TFA^-, 57289-00-6; 8-Et, 55970-18-8; 8-*i*-Pr, 55970-22-4; **9**, 52730-00-4; **9** Cl^-, 55905-28-7; **9** TFA^-, 57289-01-7; **9m**, 52008-64-7; **9m** Cl^-, 57289-02-8; **9m** TFA^-, 57289-03-9; 9-Et, 55970-16-6; 9-*i*-Pr, 55970-20-2; **10**, 55970-15-5; **10m**, 57289-04-0; **11**, 55925-21-8; **11m**, 57289-05-1; **12**, 55925-23-0; **12m**, 57345-27-4; **13**, 55925-22-9; **13m**, 57345-28-5; **14**, 16726-19-5; **14m**, 16726-26-4.

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Reaction of Geminal Diesters with the Amine Bases 1,5-Diazabicyclo[4.3.0]non-5-ene, 1,4-Diazabicyclo[2.2.2]octane, and 3-Quinuclidinol

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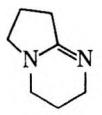
The bicyclic amidine base 1,5-diazabicyclo[4.3.0]non-5-ene (DBN, 1) transforms relatively hindered geminal diesters to either their corresponding monoesters or monoacids. The composition of the products (monoesters, or monoacids, or a mixture of monoesters and monoacids) can be determined by the reaction time. The bicyclic amine base 1,4-diazabicyclo[2.2.2]octane is useful for the selective decarbalkoxylation of a variety of geminal diesters. The failure to obtain acids as by-products is consistent with previous studies showing that Dabco (2) fails to cleave saturated esters under the same conditions. The bicyclic amine base 3-quinuclidinol (3) is useful for the decarbalkoxylation of a variety of geminal diesters to their corresponding monoesters. Decarbalkoxylation using DBN (1), Dabco (2), and 3-quinuclidinol in o-xylene is advantageous in cases where the usual hydrolytic conditions are precluded because of the presence of sensitive moieties, as well as for compounds not soluble in aqueous solvents.

We have reported[1] studies which indicate that the base 1,5-diazabicyclo[4.3.0]non-5-ene (DBN, 1) is useful for the



1

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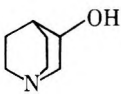

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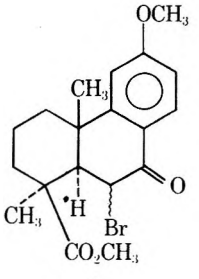
O-alkyl cleavage of hindered methyl esters and for the one-step conversion of bromo ketone **4** to the α,β-unsaturated ketone **5**. Similar results were obtained with 1,5-diazabicyclo[5.4.0]undecene-5.[2] Subsequent studies[3] with the base *N*-phenylbenzamidine indicated that treatment of bromo ketone **4** resulted in only dehydrobromination. Thus *N*-phenylbenzamidine was suggested as a relatively mild and selective dehydrobrominating agent. The base diazabicyclo[2.2.2]octane (Dabco, **2**) has been shown[4,5] to be effective for the decarbalkoxylation of β-keto and vinylogous β-keto esters. Similar results were obtained[6] with 3-quinuclidinol. Although a variety of reagents have been utilized[1,2,4,5,7] for cleaving β-keto and vinylogous β-keto esters, this represented the first report involving the use of a base which contains the bicyclic moiety found in quinine and related Cinchona alkaloids.[8] The suggestion was offered that since the cleavage reactions reported[6] are similar to those found in biological systems,[9] the possibility exists that reactions of this type could be catalyzed by amine bases (alkaloids) in plants.



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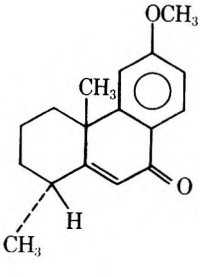


5

This paper describes an investigation into the reactivity and the relative selectivity of the amine bases DBN (1), Dabco (2), and 3-quinuclidinol (3) toward geminal diesters.

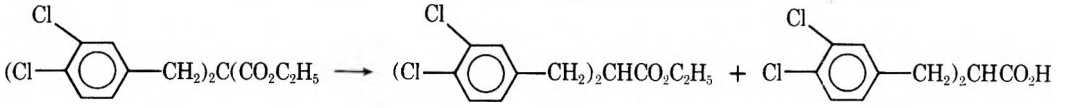
Results and Discussion

DBN (1). Initial studies with the base DBN involved the investigation of its reactivity with the geminal diester diethyl octadecylmalonate (**6**). Treatment of 1 equiv of **6** with 5 equiv of DBN (1) in 7 equiv of *o*-xylene at reflux for 6 hr gave white, crystalline compound **7** (52% yield) which was identical with an authentic sample of ethyl eicosanoate. The acidified aqueous extract of the reaction mixture yielded crystalline compound **8** (10% yield) which was shown to be eicosanoic acid.[10]

$$\underset{\mathbf{6}}{CH_3(CH_2)_{17}CH(CO_2C_2H_5)_2} \longrightarrow CH_3(CH_2)_{18}CO_2C_2H_5 + CH_3(CH_2)_{18}CO_2H$$

7 **8**

Table I
Reaction of DBN (1) with Ethyl Bis(3,4-dichlorobenzyl)malonate (9)



9 10 11

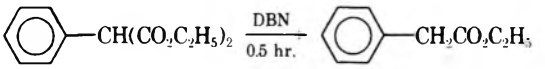
Molar ratio			Reaction	Yield, %		
Diester 9	DNB	o-Xylene	time, hr	Monoester 10	Acid 11	Diester 9
1	6	7	1.5	96[a]	None[b]	4[a]
1	10	15	4	68	29	None[a]
1	15	30	69	Trace[a]	89	None[a]
1	2	28	15	93[a]	None[b]	7[a]

[a] By GLC analyses. [b] By TLC analyses.

The obtainment of both the monoester **7** and monoacid **8** was not expected, since DBN (**1**) is known[1] to cleave esters to acids. These results led to experiments designed to investigate the possible utilization of DBN (**1**) as a reagent for the conversion of geminal diesters to either their corresponding monoester or monoacid. Presumably, the process involves decarbalkoxylation of the diester to the monoester and subsequent cleavage of the monoester to the monoacid, since DBN (**1**) has been shown to be an *O*-alkyl cleavage reagent.

The reaction of DBN (**1**) with ethyl bis(3,4-dichlorobenzyl)malonate (**9**) was studied (Table I) in order to optimize the conditions for obtaining either the monoester or monoacid from geminal diesters. Initially, a mixture of 1 mmol of diester **9** and 10 mmole of DBN (**1**) in 15 mmol of *o*-xylene was heated at reflux for 4 hr. The usual work-up gave a 68% yield of monoester **10** and a 29% yield of monoacid **11**. Compound **10** was identical with an authentic sample of ethyl bis(3,4-dichlorobenzyl)acetate. Compound **11**, mp 114.5–116.5°C, was consistent with bis(3,4-dichlorobenzyl)acetic acid. The results shown in Table I indicate that the optimum conditions for the obtainment of the monoester is a reaction time of 1.5 hr with a molar ratio of diester **9**:DBN:o-xylene of 1:6:7. Under these conditions **10** is obtained in 96% yield with no production of the corresponding acid. The use of the substantially longer reaction time (69 hr) and higher base to substrate molar ratio (15:1) results in the production of acid **11** in 89% isolated yield. Thus, conditions for the synthesis, in high yield, of either monoester **10** or acid **11** from geminal diester **9** were elaborated.

This reaction was extended to other substrates by treatment of 1 equiv of diethyl phenylmalonate (**12**) with 6 equiv of DBN (**1**) in 6 equiv of o-xylene at reflux for 30 min to yield (59%) ethyl phenylacetate (**13**).

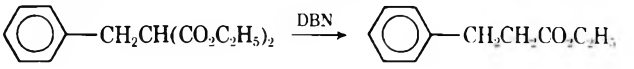


12 13

Treatment of 1 equiv of diester **14** with 5 equiv of DBN (**1**) in 7 equiv of o-xylene at reflux for 6 hr afforded a 21% yield of monoester **15** (Table II). Alternative reaction of 1 equiv of diester **14** with 2 equiv of DBN (**1**) in 10 equiv of o-xylene gave monoester **15** in 34% yield. The resulting monoester **15** was identified as ethyl benzylacetate.

A comparison of the yields obtained with substrates **9**, **12**, and **14** shows that the yield of monoester decreases as the steric bulk around the α carbon atom decreases. Geminal diesters with less steric bulk around the α carbon form products with a much higher retention time than the monoesters by GLC analysis. Preliminary evidence indicates that these components are a mixture of the Claisen

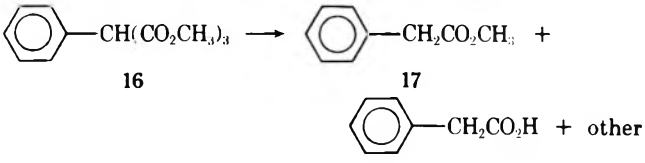
Table II
Reaction of DBN (1) with Diethyl Benzylmalonate (14)



14 15

Diester 14	DBN	o-Xylene	Reaction time, hr	Yield of monoester 15, %
1	5	7	6	21
1	2	10	25	34

Table III
Reactions of DBN (1) with Dimethyl Phenylmalonate (16)



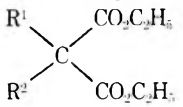
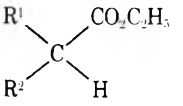
16 17 18

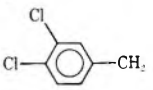
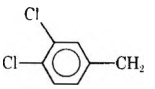
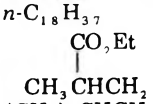
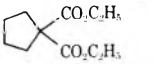
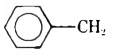
Diester 16	DBN	o-Xylene	Reaction time, hr	Yield, % Monoester 17	Yield, % Acid 18
1	5	6	0.5	34	Trace
1	5	6	2	Trace	29

and acyloin type condensation products which can be envisaged as forming from the monoester. A detailed study involving the characterization of all of these products and the possible utility of the bases DBN (**1**), Dabco (**2**), and 3-quinuclidinol (**3**) in catalyzing the condensation of monoesters is currently in progress.

The final reaction with DBN (**1**) was performed with dimethyl phenylmalonate (**16**) and is illustrated in Table III. This substrate was chosen to allow for comparison of the results obtained upon treatment of a dimethyl ester with DBN (**1**). Treatment of 1 equiv of dimethyl phenylmalonate (**16**) with 5 equiv of DBN (**1**) in 6 equiv of *o*-xylene at reflux for 0.5 hr gave a 34% yield of monoester **17** which was identical with methyl phenylacetate.[11] Similarly, treatment of the same molar ratio of reactants at reflux for 2 hr afforded a 29% yield of acid **18**, which was identical with phenylacetate acid.[11] In comparison with diethyl phenylmalonate (59% yield) under approximately the same conditions the yield of monoester **17** is lower (34% yield), which is probably a reflection of less steric bulk around the dimethyl ester and hence the formation of a larger quantity of condensations products. The majority of the monoester **17** formed is converted smoothly to acid **18** (29% yield) upon heating for an additional 1.5 hr. This is a reflection of the greater ease with which methyl esters are cleaved with

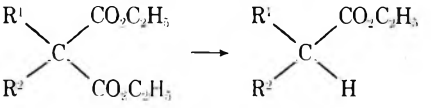
Table IV
Decarbethoxylation Reactions of Geminal Diesters Using Dabco (2)

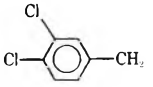
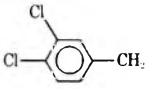



Geminal diester	Reactant R¹	Reactant R²	Refluxing time, hr	Product Monoester	Product Yield, %	Product Unreacted diester, %
9			4	10	79	None
6	n-$C_{18}H_{37}$	H	10.5	7	77	
19		CH_3	29	20	50	
21	$(CH_3)_2CHCH_2CH_2$	CH_3CH_2	48	22	62	13
23			48	24	73[a]	16[a]
25	CH_3CH_2	H	27	26	33[a]	3[a]
27		CH_3CH_2	10	28	31	20
14		H	6	15	42	

[a] Determined by GLC analyses.

Table V
Decarbalkoxylation Reactions Using 3-Quinuclidinol (3)



Geminal diester	R_1	R_2	Refluxing time, hr	Product Monoester	Product Yield, %
9			6	10	93
6	n-$C_{18}H_{37}$	H	7	7	96[b] 21[c]

[a] GLC analysis. [b] Base to substrate ratio 1:1; [c] Base to substrate ratio 10:1.

DBN (1) as compared with ethyl esters. Ethyl ester **9** required 69 hr at a base to subtrate ratio of 15:1 for complete conversion to the acid **11** and complete disappearance of the monoester **10**.

1,4-Diazabicyclo[2.2.2]octane (Dabco, 2). The ditertiary amine base Dabco (2) is useful for the cleavage of geminal diesters to their corresponding monoester as is shown by its initial reaction with diethyl bis(3,4-dichlorobenzyl)malonate (**9**). A mixture of 1 equiv of **9** and 10 equiv of Dabco (2) in 14 equiv of o-xylene was heated at reflux for 4 hr to yield (79%) white, crystalline monoester **10**.

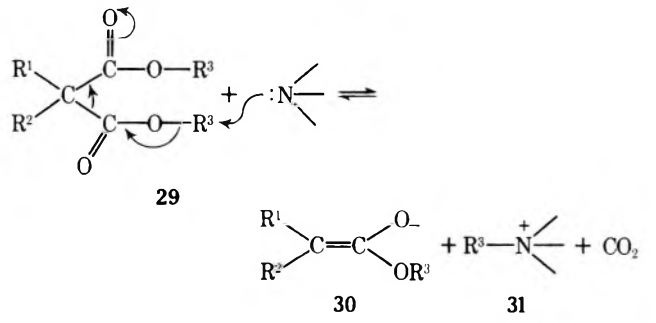
The generality of Dabco (2) as a reagent for cleaving geminal diesters is demonstrated by the results illustrated in Table IV. Typically, 1 equiv of the appropriate geminal diester was treated with 10 equiv of Dabco (2) in 30 equiv of o-xylene for an appropriate period of time to yield 30–80% of the corresponding monoester.

Examination of substrates **9**, **6**, **19**, and **21** in Table IV seems to indicate that as the electron-withdrawing ability of the α-substitution group decreases, the time required to complete the reaction increases. A GLC study of substrates **25**, **27**, **16**, and **14** (which gave low yields of the monoesters) showed peaks with a higher retention time than the monoesters. This result was suggestive (as previously indicated) of condensation of the monoesters formed in the reaction mixture. This is reasonable since Table IV shows that generally the amount of condensation product by GLC analysis increases as the steric bulk of the α-substitution alkyl group decreases. The fact that Dabco (2) does not cleave monoesters to their corresponding acids[4,5] eliminates the possibility of acids as by-products. Thus Dabco is a reagent which is useful for decarbalkoxylation of hindered geminal diesters to their corresponding monoesters in good yield.

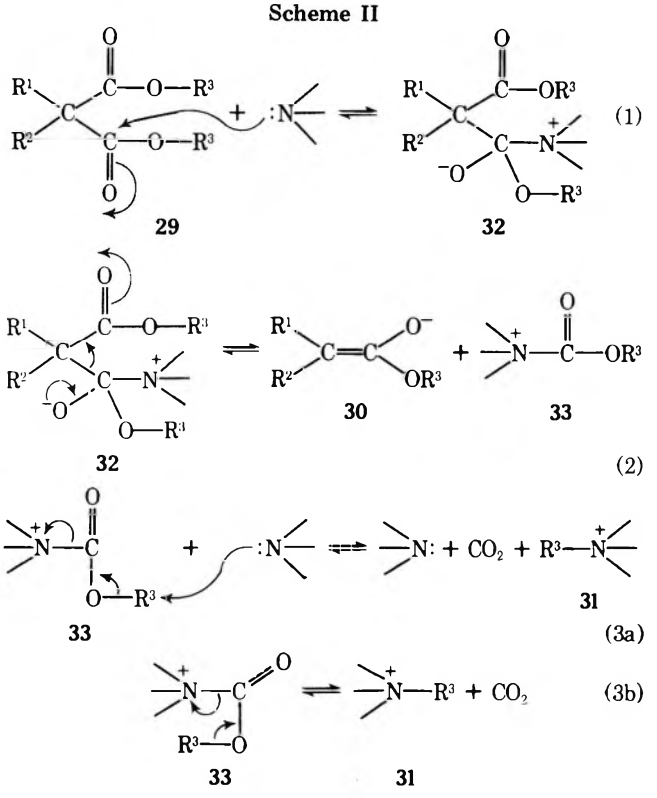
3-Quinuclidinol. The base 3-quinuclidinol (3), which contains a bicyclic moiety similar to that found in quinine and related Cinchona alkaloids, is useful for the cleavage of geminal diesters to the monoester as shown in Table V. Geminal diester **9** gave a 93% yield of product upon refluxing with 20 equiv of 3-quinuclidinol in 30 equiv of o-xylene. The attainment of a high yield (93%) of product **17** from geminal diester **16** required a much smaller base to substrate molar ratio (1:1). Using a large excess of 3-quinuclidinol results in a low yield of monoester because of the occurrence of condensation under these conditions for relatively unhindered esters as is shown for geminal diester **6** in Table V.

Postulated Mechanisms for Decarbalkoxylation Reactions. Two mechanisms are consistent with the facile cleavage of a variety of geminal diesters with amine bases DBN (1), Dabco (2), or 3-quinuclidinol (3) in o-xylene. These possible mechanisms are illustrated in Schemes I

Scheme I

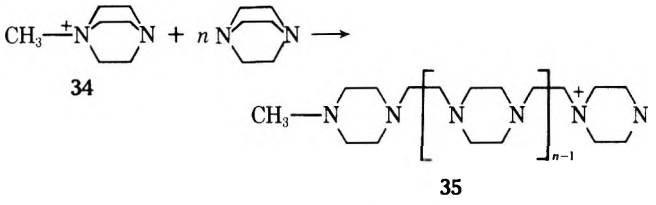


Scheme II



and II. Since DBN (1) is an *O*-alkyl cleavage reagent, it may operate through a mechanism such as that shown in Scheme I, while the bases Dabco (2) and 3-quinuclidinol may operate through another. However, it is possible that all bases (**1**, **2**, and **3**) may operate via the same mechanism for decarbalkoxylation.

The following observations are consistent with both mechanisms. First, carbon dioxide was evolved from all reactions and collected quantitatively as barium carbonate. Secondly, the rate of cleavage was enchanced by electron-withdrawing α-substituents (R^1 and R^2). Thirdly, methyl esters were cleaved faster under same reaction conditions than their corresponding ethyl esters.



All attempts to isolate alkylated bases as their salts failed. This could be due to the fact that the quaternary ammonium salt (e.g., **34**) reacted with other molecules of the base which was generally present in excess to form a polymer (e.g., **35**). This postulation is supported by a similar reaction observed by Viche.[12] Another reasonable explanation for the failure to isolate salt **32** is the ease with which tertiary amine salts have been reported[13,14] to dealkylate in excess base. The literature contains[13,14] references which seem to support the formation of salts such as **34**.

Conclusions

Reactions involving base-catalyzed[15] alkylation and acylation of malonic esters have significant roles in organic synthesis. Their products, geminal diesters, act as important intermediates in syntheses and are usually cleaved to the corresponding diacid by conventional methods which include aqueous acid or base hydrolysis. These methods[16] normally include subsequent decarboxylation by heating and then esterification to give the monoester. Alternatively, cleavage and subsequent decarboxylation of β-keto esters has been achieved in one step[7,17,18].

Cleavage of hindered geminal diesters using DBN (1) is advantageous, not only for the nonaqueous reaction conditions, but also for the selectivity of the products. Esters such as **9** provide a good yield of either the monoester or monoacid. The product obtained can be determined by the reaction time in a one-step reaction. The majority of known methods[16] have required two steps to achieve the monoacid and three steps to the monoester.

Decarbalkoxylation of hindered geminal diesters to monoesters with Dabco (**3**) is also advantageous because of the efficiency of the process (one-step). Furthermore, it is desirable in cases where the usual hydrolytic conditions are precluded because of the presence of acid- or base-sensitive functional groups, as well as for compounds which are not soluble in aqueous solvents.

Decarbalkoxylation reactions involving 3-quinucidinol (**3**) are efficient and advantageous in many instances for the reasons similar to those elaborated above for Dabco (**2**).

Since the cleavage reactions reported in this paper are similar to those found in biological systems,[9,19] the possibility exists that reactions of this type could be catalyzed by amine bases (alkaloids) in plants.

Experimental Section

Nuclear magnetic resonance spectra were obtained using a Jeolco Minimar spectrometer equipped with a spin decoupler. Tetramethylsilane was used as the internal standard and chloroform-*d*, 99.8% ($CDCl_3$), and acetone-d_6, 99+% (CD_3COCD_3), were used as solvents. Mass spectral data (MS, GLC–MS) were obtained using a Hewlett-Packard Model 5930, or a Perkin-Elmer Model 270 mass spectrometer. Infrared spectra were obtained using a Perkin-Elmer Model 137B Infracord, a Beckman IR5A spectrophotometer, or a Perkin-Elmer Model 521 grating infrared spectrophotometer. The spectra of liquids were taken on films formed between two sodium chloride plates; potassium bromide was used in preparing pellets of solid samples for infrared spectra. The band 1603 cm^{-1} of a polystyrene film (0.05 mm) was used as a reference peak. Column chromatography was performed in glass columns (wet or dry packed) with sintered glass using Woelm absorption silica gel (activity 1) of M. Woelm, Eschwege, Germany (distributed by ICN Pharmaceuticals) as the solid support. Thin layer chromatography (TLC) was performed using E. Merck (Darmstardt) silica gel G of Applied Science Laboratories, Inc., coated glass plates. Chromatoplates (20 × 20 cm and 5 × 20 cm) were prepared by using a Desaga spreader with thickness of 0.25 mm for qualitative TLC and 0.50 mm for preparative TLC. The plates were activated at 110°C for 1 hr. Potassium dichromate in sulfuric acid was used as the detecting agent. Gas–liquid chromatography (GLC) was performed using a Hewlett-Packard Model 402 gas chromatograph with a hydrogen flame detector. Glass columns (6 ft × 3.0 mm i.d.) and 12 ft × 3.0 mm i.d.) bent in a U shape were used. The column temperature, nitrogen flow rate, types and amount of liquid phase, and the retention time (t_R) are given in the Experimental Section for each sample. The column substrates and solid supports used in the GLC analyses were obtained from Applied Sciences Laboratories

or from Hewlett-Packard Analytical Instruments. Melting points were obtained on a Fisher-Jones apparatus and are uncorrected. Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn.

Reaction of DBN (1) with Geminal Diesters. A. Preparation of Ethyl Eicosanoate (7) and Eicosanoic Acid (8). A mixture of 0.412 g of geminal diester **6** (Aldrich reagent) and 0.635 g (5.1 mmol) of DBN (1) in 0.645 g (6.8 mmol) of *o*-xylene was heated at reflux for 6 hr. To the reaction mixture was added dilute sodium hydroxide which was followed by extraction with ether. The ether extract was washed with dilute acid, washed with water, dried over anhydrous sodium sulfate, and evaporated in vacuo to yield 0.177 g (52%) of monoester **7**. Monoester **7** was identical by ir, NMR, and GLC retention time (t_R 1 min 30 sec using a 6-ft 5% SE-30 on 80/100 mesh Chromosorb W column, nitrogen flow rate 11 ml/min, column temperature 292°C) on comparison with an authentic sample. The aqueous portion was acidified and extracted with ether. The ether extract was washed with water, dried over anhydrous sodium sulfate, and evaporated in vacuo to give 0.030 g (10%) of crystalline compound **8**, mp 73–75°C (lit.[10] 75–76°C). Compound **8** was identical by ir and MS comparison with authentic spectra of eicosanoic acid.[10]

B. Preparation of Ethyl Bis(3,4-dichlorobenzyl)acetate (10) and Bis(3,4-dichlorobenzyl)acetic Acid (11). A mixture of 0.479 g (1.0 mmol) of diester **9** (Alfred Bader Chemicals) and 1.241 g (10.0 mmol) of DBN (1) in 1.616 g (15.2 mmol) of *o*-xylene was heated at reflux (163°C) for 4 hr. The cooled reaction mixture was acidified with dilute acid and extracted with ether. The ether extract was washed first with saturated aqueous sodium chloride and then with water, dried over anhydrous magnesium sulfate, and evaporated in vacuo to give 0.391 g of solid materials.

The crude solid (0.391 g) was dissolved in a small amount of chloroform and transferred onto a glass column (2.54 cm o.d.) which was packed with 27 g of silica gel. The column was eluted with the following solvent ratios of ether in hexane (ml/ml): 0/50, 15/285, 35/315, 30/170. 40/160 60/140 80/120, 100/100, 250/0. A total of 30 fractions were collected, with 50 ml each for the first 27 fractions, 100 ml each for the 28th and 29th fractions, and 250 ml for the 30th fraction. Fractions 2–16 yielded 0.278 g (68%) of white, crystalline material, mp 75–76°C, which was identical by ir, NMR, and GLC retention time on comparison with an authentic sample of compound **10**. Fractions 17–30 were combined and treated with diazomethane to yield 0.109 (29%) of a white, crystalline compound **11**: mp 114.5–116.5°C; ir ν_{max} (KBr) 3571–2326 (broad, hydrogen bonding), 2857 (saturated C–H stretching), 1695 (–C=O), 1471, 1408 cm^{-1}; NMR ($CDCl_3$) δ 2.82 [5 H, broad, $ArCH_2CH(CO)CH_2Ar$], 6.75–7.14 (6 H, m, ArH); MS *m/e* (rel abundance) 379 (17), 377 (35), 375 (26), 219 (62), 217 (100), 201 (30), 199 (41), 161 (65), 159 (92).

Anal. Calcd for $C_{16}H_{12}Cl_4O_2$ (378.08): C, 50.83; H, 3.20. Found: C, 51.11; H, 3.23.

C. Preparation of Ethyl Bis(3-4-dichlorobenzyl)acetate (10). Procedure I. A mixture of 0.121 g (0.25 mmol) of diethyl ester **9** (Alfred Bader Chemicals), 0.164 g (1.47 mmol) of DBN (1), and 0.191 g (1.80 mmol) of *o*-xylene was heated at reflux for 1.5 hr. The ether extract of the acidified (0.6 *M* HCl) reaction mixture was washed with water, dried over anhydrous sodium sulfate, and evaporated under reduced pressure to obtain 0.090 g of a crystalline solid, mp 75–78°C, containing 96% of monoester **10** and 4% of starting diester **9** by GLC analysis (6 ft, 5% SE-30 on 80/100 mesh Chromosorb W column, nitrogen flow rate 10 ml/min, column temperature 300°C) on comparison with authentic standards. TLC analysis of the crude product showed the absence of acid **11**.

Procedure II. A mixture of 0.240 g (0.5 mmol) of geminal diester **9** (Aldrich reagent) and 0.132 g (1.1 mmol) of DBN (1) in 1.479 g (1.4 mmol) of o-xylene was heated at reflux for 15 hr. The ether extract of the acidified reaction mixture contained 93% monoester **10** and 7% starting diester **9** by GLC comparison with authentic standards. TLC analysis of this ether of the acidified reaction mixture failed to show the presence of acid **11**.

D. Preparation of Bis(3,4-dichlorobenzyl) acetic Acid (11). A mixture of 0.124 g (0.25 mmol) of diethyl ester **9** (Alfred Bader Chemicals) and 0.463 g (3.73 mmol) of DBN (1) in 0.798 g (7.52 mmol) of *o*-xylene was heated at reflux for 69 hr. The ether extract of the acidified (0.6 *M* HCl) reaction mixture was washed with water, dried over anhydrous sodium sulfate, and evaporated under reduced pressure to give 0.074 g (89%) of crude crystalline compound **11**, mp 108°C (pure **11**, mp 114.5–116.5°C), containing mainly bis(3-4-dichlorobenzyl)acetic acid (**11**) by TLC and GLC comparison with authentic standards.

E. Preparation of Ethyl Phenylacetate (13). A mixture of 0.239 g (1.0 mmol) of diethyl phenylmalonate (**12**) and 0.765 g (6.2 mmol) of DBN (1) in 0.643 g (6.0 mmol) of *o*-xylene was heated at reflux for 30 min. The ether extract of the acidified (0.6 *M* HCl) reaction mixture was washed with water, dried over anhydrous sodium sulfate, and evaporated in vacuo to yield 59% of monoester **13** (t_R 1 min 45 sec) and 9% of starting diester **12** (t_R 6 min 42 sec) upon comparison with authentic standard by GLC analysis (6 ft, 5% SE-30 on 80/100 mesh Chromosorb W column, nitrogen flow rate 11 ml/min, column temperature 140°C).

F. Preparation of Ethyl Benzylacetate (15). Procedure I. A mixture of 1.005 g (4.0 mmol) of diester **14** (Aldrich reagent) and 0.998 g (28.0 mmol) of DBN (1) in 4.239 g (40.0 mmol) of o-xylene was heated at reflux for 25 hr. The organic portion of the acidified (0.6 *M* HCl) reaction mixture was poured onto a glass column (2.54 cm o.d.) which was packed with 52.5 g of silica gel. The column was developed and eluted with hexane and 2% ether in hexane to yield 0.241 g (34%) of ester **15** which was identical by ir, NMR, and GLC retention time on comparison with an authentic sample.

Procedure II. A mixture of 0.251 g (1.0 mmol) of diester **14** (Aldrich reagent) and 0.621 g (5.0 mmol) of DBN (1) in 0.737 g (7.0 mmol) of o-xylene was heated at reflux for 6 hr. The ether extract of the acidified (0.6 *M* HCl) reaction mixture was washed with water, dried over anhydrous sodium sulfate, and evaporated to yield 21% of ester **15** (t_R 3 min 56 sec) on comparison with an authentic sample by GLC analysis (6 ft, 5% SE-30 on Chromosorb W column, nitrogen flow rate 11 ml/min, column temperature 146°C).

G. Preparation of Phenylacetic Acid (18.) A mixture of 0.420 g (2.0 mmol) of dimethyl phenylmalonate (**16**) (Aldrich reagents) and 1.242 g (10.0 mmol) of DBN (1) in 1.275 g (12.0 mmol) of *o*-xylene was heated at reflux for 2 hr. To the reaction mixture was added 10 ml of 5% sodium hydroxide. The reaction mixture was then extracted with chloroform. The aqueous portion was acidified with concentrated hydrochloric acid and extracted with ether. The ether extract was washed with water, dried over anhydrous sodium sulfate, and evaporated under reduced pressure to yield 0.078 g (29%) of a white, crystalline compound **18**, mp 77°C (lit.[11] 77°C). Compound **18** was identical by ir and NMR comparison with known spectra[11] of phenylacetic acid.

H. Preparation of Methyl Phenylacetate (17). A mixture of 0.840 g (4.0 mmol) of dimethyl phenylmalonate (**16**) (Aldrich reagent) and 2.496 g (20.1 mmol) of DBN (1) in 2.576 g (24.3 mmol) of o-xylene was heated at reflux for 30 min. The reaction mixture was acidified with cold dilute acid. The organic layer was separated and poured onto a silica gel column. The column was eluted with 1000 ml of hexane and 500 ml of 5% ether in hexane, respectively. Fractions with t_R 1 min 30 sec (column temperature 139°C, nitrogen flow rate 12 ml/min) were combined to yield 0.204 g (34%) of a colorless liquid compound **17**, which was identical by ir, NMR, and mass spectral comparison with literature value[11] of methyl phenylacetate.

Reaction of Dabco (2) with Geminal Esters. A. Preparation of Ethyl Bis(3,4-dichlorobenzyl)acetate (10). A mixture of 0.920 g (1.9 mmol) of geminal diester **9** (Alfred Bader Chemicals) and 2.212 g (19.2 mmol) of Dabco (**2**) in 3.017 g (28.4 mmol) of *o*-xylene was heated at reflux for 4 hr. A trap containing a solution of barium hydroxide was connected to the apparatus through a drying tube attached to the top of the condenser. A white precipitate of barium carbonate was collected. The ether extract of the acidified (0.6 *M* HCl) reaction mixture was washed with 5% bicarbonate and water, dried over anhydrous sodium sulfate, and evaporated in vacuo to give 0.620 g (79%) of white, crystalline compound **10**, which was purified further with the aid of a silica gel column to a compound with mp 75–75.5°C; ir ν_{max} (KBr) 3390 (w, ArH), 2857 (w, CH), 1724 (s, C=O), 1471 cm^{-1} (s); NMR ($CDCl_3$) δ 1.03 (3 H, t, $-OCH_2CH_3$), 2.80 (5 H, broad, $ArCH_2CH$), 3.90 (2 H, q, $-OCH_2CH_3$) 6.95 (6 H, m, ArH); MS *m/e* (rel abundance) 407 (5), 405 (3), 402 (2.1), 247 (57), 245 (100), 219 (17), 218 (23), 201 (23), 199 (33), 161 (40), 159 (63).

Anal. Calcd for $C_{18}H_{16}Cl_4O_2$ (406.13): C, 53.23; H, 3.97; Cl, 34.92. Found: C, 53.04; H, 4.07; Cl, 34.75.

B. Preparation of Ethyl Eicosanate (7). A mixture of 0.827 g (2.0 mmol) of geminal diester **6** (Alfred Bader Chemicals), 2.200 g (19.6 mmol) of Dabco (**2**), and 3.181 g (30.0 mmol) of *o*-xylene was heated with constant stirring at reflux in an oil bath for 10.5 hr. The resulting reaction mixture was acidified with 0.6 *M* cold hydrochloric acid and extracted with ether. The ethereal portions were separated, washed with saturated sodium chloride solution, washed with water, and then dried over anhydrous magnesium sulfate. The solvent was removed in vacuo to give 0.525 g (77%) of a

solid which was further purified with a silica gel column to yield white, crystalline ethyl eicosanoate (7).

Anal. Calcd for $C_{22}H_{44}O_2$ (340.60): C, 77.58; H, 13.02. Found: C, 77.46; H, 13.11.

C. Preparation of Diethyl 2,4-Pentanedicarboxylate (20). A mixture of 0.868 g (3.0 mmol) of ester **19** (Alfred Bader Chemicals) and 3.365 g (30.0 mmol) of Dabco (**2**) in 4.774 g (45.0 mmol) of *o*-xylene was heated at reflux for 29 hr. The progress of the reaction was monitored by GLC analysis with a 6-ft glass column packed with 5% SE-30 on 80/100 mesh Chromosorb W (nitrogen flow rate 11 ml/min, column temperature 200°C). The reaction mixture was acidified with cold 0.6 *M* hydrochloric acid and extracted with ether. The ethereal portions were separated, combined, washed with water, and dried over anhydrous magnesium sulfate. The solvent was removed in vacuo to give 0.348 g of crude product which yielded 50% compound **20** and 2% starting diester **19** by GLC analysis. The crude product was distilled (1.5 mm, 57°C) using a Kugelrohr distillation apparatus to give a colorless liquid compound **20:** ir ν_{max} (thin film) 2857 (saturated aliphatic C–H stretching), 1724 (–C=O), 1453 cm^{-1}; NMR ($CDCl_3$) δ 1.25–1.75 (14 H, m, $-CH_2CH_3$, $-CHCH_2CH$, $-CHCH_3$), 2.45 [2 H, quintet, $CH_3CH(CO)CH_2CH(CO)CH_3$], 4.05 (4 H, q, $-OCH_2CH_3$); MS *m/e* (rel abundance) 216 (1), 172 (100), 143 (75), 116 (85), 102 (55), 69 (55).

Anal. Calcd for $C_{11}H_{20}O_4$ (216.28): C, 61.09; H, 9.32. Found: C, 60.91; H, 9.37.

D. Preparation of Ethyl Ethylisoamylacetate (22) A mixture of 1.304 g (5.1 mmol) of geminal diester **21** (Alfred Bader Chemicals) and 5.780 g (51.6 mmol) of Dabco (**2**) in 8.309 g (78.4 mmol) of *o*-xylene was heated at reflux for 48 hr. The reaction mixture was acidified with cold dilute acid. The organic portion was separated and poured onto a dried column (2 cm i.d.) which was packed with 33 g of silica gel. The column was developed and eluted with pentane. All fractions were monitored by GLC analysis. A glass column (12 ft × 3 mm) packed with 10% silicon rubber OV-17 on 80/100 mesh Chromosorb W was used. The nitrogen flow rate was 11 ml/min. The column temperature was maintained at 245°C. Fractions containing more than one component were combined and rechromatographed (same column packed with 42.4 g of silica gel). All fractions containing the same compound were combined to give 0.170 g (13%) of diester **21** (identified by GLC analysis on comparison with starting material having t_R 7 min 30 sec) and 0.572 g (62%) of compound **22**. Compound **22** showed the following spectral properties: MS *m/e* (rel abundance) 186 (3), 116 (100), 101 (53), 73 (27), 71 (27), 57 (37); ir ν_{max} (thin film) 2857 (saturated aliphatic C–H stretching), 1724 (–C=O), 1471 cm^{-1}; NMR ($CDCl_3$) δ 0.90–1.32 [19 H, m, $CH_3CH_2CHCH_2CH(CH_3)_2$, $-OCH_2CH_3$], 2.16 [1 H, sextet, $-CH_2CH(CH_2)CO$], 4.10 (2 H, q, $-OCH_2CH_3$).

Anal. Calcd for $C_{11}H_{22}O_2$ (186.30): C, 70.92; H, 11.90. Found: C, 70.96; H, 11.74.

E. Preparation of Ethyl Cyclopentanecarboxylate (24). A mixture of 1.347 g (6.3 mmol) of diester **23** (Alfred Bader Chemicals) and 7.225 g (62.6 mmol) of Dabco (**2**) in 10.108 g (95.3 mmol) of *o*-xylene was heated at reflux for 48 hr. The reaction mixture was cooled and acidified with dilute hydrochloric acid.

The organic constituents of the acidified reaction mixture was separated through a glass column packed with 48 g of dry silica gel. The column was developed and eluted with 1500 ml of pentane and 600 ml of 5% ether in pentane, respectively, to give 0.370 g (liquid) of a mixture. Fractions containing mainly compound **24** were combined and rechromatographed twice to give 0.054 g of a colorless liquid compound **24:** ir ν_{max} (thin film) 2857 (aliphatic C–H stretching), 1724 cm^{-1} (–C=O); NMR ($CDCl_3$) δ 1.25 (3 H, t, $-OCH_2CH_3$), 1.70–1.80 (8 H, m, protons of cyclopentane ring except the one attached to the carbon next to carbonyl carbon), 2.65 (1 H, m, –CHCO), 4.05 (2 H, q, $-OCH_2CH_3$); MS *m/e* (rel abundance) 142 (9), 101 (53), 88 (53), 84 (82), 69 (76), 43 (100), 41 (51).

Anal. Calcd for $C_8H_{14}O_2$ (142.20): C, 67.57; H, 9.93. Found: C, 67.54; H, 9.77.

F. Preparation of Ethyl *n*-Butanoate (26). A mixture of 1.894 g (10.0 mmol) of diester **25** (Aldrich reagent) and 11.278 g (97.7 mmol) of Dabco (**2**) in 17.020 g (160.5 mmol) of o-xylene was heated at reflux for 27 hr. The organic constituents of the reaction mixture were separated through a glass column (2.54 cm o.d.) packed with 100 g of silica gel (Woelm, activity 1). The column was developed and eluted with 1500 ml of hexane and 300 ml of 5% ether in hexane to give 0.064 g (6%) of a colorless liquid compound **26.** The spectra (ir, NMR, and MS) of compound **26** were identical with those reported[21] for ethyl *n*-butanoate.

G. Preparation of Ethyl 2-Phenylbutanoate (28). A mixture of 2.007 g (7.6 mmol) of geminal diester **27** (Alfred Bader Chemicals) and 9.215 g (82.6 mmol) of Dabco (**2**) in 12.845 g (121.1 mmol) of *o*-xylene was heated at reflux for 10 hr. The cold reaction mixture was acidified with dilute hydrochloric acid. The organic portion was separated and poured onto a glass column (2 cm i.d.) packed with 38.2 silica gel (Woelm, activity 1). The column was eluted with 1200 ml of hexane, 600 ml of 5% ether in hexane, and 200 ml of 16.7% ether in hexane, respectively. The fractions were monitored by GLC analysis using a glass column (12 ft × 3 mm) packed with 10% OV-17 on 80/100 mesh Chromosorb W with a nitrogen flow rate of 11 ml/min. The column temperature was maintained at 260°C. Fractions with retention time of 5 min 12 sec were combined and the solvent was removed to give 0.421 g (31%) of liquid compound **28** which was distilled at 72°C and 3.6 mmHg pressure to give a colorless liquid compound **28:** ir ν_{max} (thin film) 3030 (aromatic C–H stretching), 2941 (saturated aliphatic C–H stretching), 1724 (–C=O), 1471 cm^{-1}; NMR ($CDCl_3$) δ 0.88 (3 H, t, $-CHCH_2CH_3$), 1.17 (3 H, t, $-OCH_2CH_3$), 1.94 (2 H, quintet, $-CHCH_2CH_3$), 3.42 [1 H, t, $-CH_2CH(C_6H_5)C=O$], 4.06 (2 H, q, $-OCH_2CH_3$), and 7.27 (5 H, s, ArH); MS *m/e* (rel abundance) 192 (21), 118 (16), 119 (79), 91 (100), 41 (13), 29 (18).

Anal. Calcd for $C_{12}H_{16}O_2$ (192.26): C, 74.97; H, 8.39. Found: C, 74.77; H, 8.30.

H. Preparation of Ethyl Phenylacetate (17). A mixture of 1.934 g (8.0 mmol) of diester **16** (Aldrich reagent) and 8.972 g (78.0 mmol) of Dabco (**2**) in 12.713 g (120.0 mmol) of o-xylene was heated at reflux for 10 hr. The acidified reaction mixture was separated through a glass column (2.54 cm o.d.) packed with 51.5 g of silica gel. The column was eluted with 1800 ml of hexane and 700 ml of 5% ether in hexane to give 0.557 g (43%) of methyl phenylacetate (**17**).

I. Preparation of Ethyl 3-Phenylpropionate (15). A mixture of 2.012 g (8.0 mmol) of diester **14** (Aldrich reagent) and 9.055 g (78.4 mmol) of Dabco (**2**) in 12.667 g (119.5 mmol) of o-xylene was heated at reflux for 6 hr. The usual organic portion of the work-up yielded 0.595 (42%) of 3-phenylpropionate (**15**).

Reaction of 3-Quinuclidinol with Geminal Diesters. A. Preparation of Ethyl Bis(3,4-dichlorobenzyl)acetate (10). A mixture of 0.121 g (0.25 mmol) of diethyl ester **9** and 0.630 g (5.0 mmol) of 3-quinuclidinol (**3**) in 0.794 g (7.5 mmol) of o-xylene was heated at reflux for 6 hr. The ether extract of the acidified (0.6 *M* HCl) reaction mixture was washed with water, dried over anhydrous sodium sulfate, and evaporated in vacuo to give compound **10** in 93% yield (0.087 g).

B. Preparation of Methyl Phenylacetate (17). A mixture of 1.663 g (8.0 mmol) of dimethyl phenylmalonate (**16**) (Aldrich reagent) and 1.016 g (8.0 mmol) of 3-quinuclidinol (**3**) in 8.486 g (80.0 mmol) of o-xylene was heated at reflux for 1 and 1.5 hr. The ether extract of the acidified (0.6 *M* HCl) reaction mixture was washed with water, dried over anhydrous sodium sulfate, and evaporated to yield 92% (GLC) of methyl phenylacetate (**17**).

C. Preparation of Ethyl Eicosonate (7). Procedure I. A mixture of 0.204 g (0.5 mmol) of diester **6** (Alfred Bader Chemicals) and 0.661 g (5.0 mmol) of 3-quinuclidinol (**3**) in 1.600 g (15.0 mmol) of *o*-xylene was heated at reflux for 7 hr. The cooled reaction mixture was diluted with 80 ml of ether and extracted with 5% sodium hydroxide. The ethereal portion was separated, washed with dilute acid, washed with water, dried over anhydrous sodium sulfate, and evaporated under reduced pressure to give 0.054 g of crude product. The crude product gave a 21% yield of monoester **7** which was identified as ethyl eicosonate. The ether extract was washed with water, dried over anhydrous sodium sulfate, and evaporated under reduced pressure to give 0.004 g of crystal containing equal amounts of two compounds with higher retention time (t_R 3 min 24 sec and 8 min 24 sec) than the starting diester **19** (t_R 3 min 6 sec) by GLC analysis (conditions were the same as above).

Procedure II. A mixture of 0.204 g (0.5 mmol) of diester **6** and 0.066 g (0.50 mmol) of 3-quinuclidinol (**3**) in 1.600 g (15.0 mmol) of *o*-xylene was heated at reflux for 7 hr. The cooled reaction mixture was diluted with 80 ml of ether and extracted with 5% sodium hydroxide. The ethereal portion was separated, washed with dilute acid, washed with water, dried over anhydrous sodium sulfate, and evaporated under reduced pressure to give 0.246 g of monoester **7**.

Acknowledgment. The author wishes to thank Mr. Douglas Crawford for the mass spectral data.

Registry No.—**1**, 3001-72-7; **2**, 280-57-9; **3**, 1619-34-7; **6**, 7154-71-4; **7**, 18281-05-5; **9**, 57197-27-0; **10**, 57197-28-1; **11**, 1610-66-8;

12, 83-13-6; 14, 607-81-8; 16, 37434-59-6; 19, 57197-29-2; 20, 21239-22-5; 21, 77-24-7; 22, 57197-30-5; 23, 4167-77-5; 24, 5453-85-0; 25, 133-13-1; 27, 75-67-5; 28, 119-43-7.

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Preparation and Reactions of 2,6-Di-*tert*-butyl-4-(9-fluorenylidene)-1,4-benzoquinone

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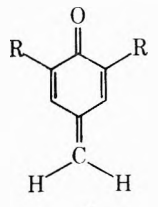
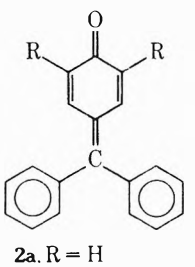
2,6-Di-*tert*-butyl-4-(9-fluorenylidene)-1,4-benzoquinone (**3**) was prepared from 2,6-di-*tert*-butyl-1,4-benzoquinone and fluorenylidenetriphenylphosphorane at 200°. In contrast to its α,α-diphenylmethylene analogue (**2b**), the 9-fluorenylidenequinone **3** smoothly undergoes electrophilic substitution reactions with phenols to give bisphenols. With anions as well as with amines, **3** reacts by 1,6 addition, yielding the correspondingly substituted phenols. Fluorenylidenequinone **3** was found to undergo a unique one-electron reduction with both hydrogen in the presence of platinum and with phenylmagnesium bromide. The acetyl derivative of the resulting 9-substituted fluorenyl radical was characterized by its ESR spectrum.

p-Methylenequinones of structure **1** play an important role as reactive intermediates in phenol oxidation.[1] Generally, they are easily reduced to the corresponding *p*-alkylphenols, they can dimerize by disproportionation, and they can undergo nucleophilic 1,6 addition resulting in aromatization.[1c] In the case of α,α-diphenylmethylene-substituted *p*-quinones (**2**, henceforth called fuchsones), disproportionation is structurally impossible, and reductive dimerization has not been encountered yet, probably because of the instability of the resulting hexaphenylethanes. Aromatization of fuchsones by acid-catalyzed 1,6 addition, however, occurs quite readily. For example, fuchsone itself (**2a**) rapidly adds water to give 4-hydroxytriphenylcarbinol.[2]



1
e.g., R = CH_3



2a, R = H
b, R = *tert*-butyl
c, R = CH_3

The chemistry of 3,5-di-*tert*-butylfuchsone (**2b**) has been the subject of detailed investigations.[3] This compound is easily reduced to give 3,5-di-*tert*-butyl-4-hydroxytriphenylmethane, and it readily aromatizes by addition of carbanions[4] as well as by photoinduced free-radical addition.[5] In contrast to **2a**, however, 3,5-di-*tert*-butylfuchsone does not add any nucleophiles in acid-catalyzed reactions and it does not undergo any electrophilic reactions with aromatic compounds such as phenols.[5b] Presumably, impaired protonation of the sterically hindered carbonyl group in conjunction with the steric hindrance of the methylene carbon caused by the out-of-plane position of the phenyl substituents may be responsible for the observed lack of reactivity. To test the validity of this assumption, it appeared interesting to replace the diphenylmethylene moiety in **2b** by the 9-fluorenylidene group and compare the chemistry of **2b** with that of its 9-fluorenylidene analogue. We have, therefore, prepared 2,6-di-*tert*-butyl-4-(9-fluorenylidene)-1,4-benzoquinone (**3**) and studied the effect of the rigidity of the fluorenylidene moiety and inherent planarity of **3** on its chemical properties.

Results and Discussion

A. Preparation of 2,6-Di-*tert*-butyl-4-(9-fluorenylidene)-1,4-benzoquinone. In contrast to the large number of known fuchsones, the synthesis of 9-fluorenylidenebenzoquinones has not been described before. The only 9-fluorenylidenequinones known are those derived from 1,4-naphthoquinone,[6] 9,10-anthraquinone,[7] and 9,10-phenanthrenequinone,[6] though little has been reported about their chemistry. The desired 2,6-di-*tert*-butyl-4-(9-fluorenylidene)-1,4-benzoquinone was most conveniently prepared in

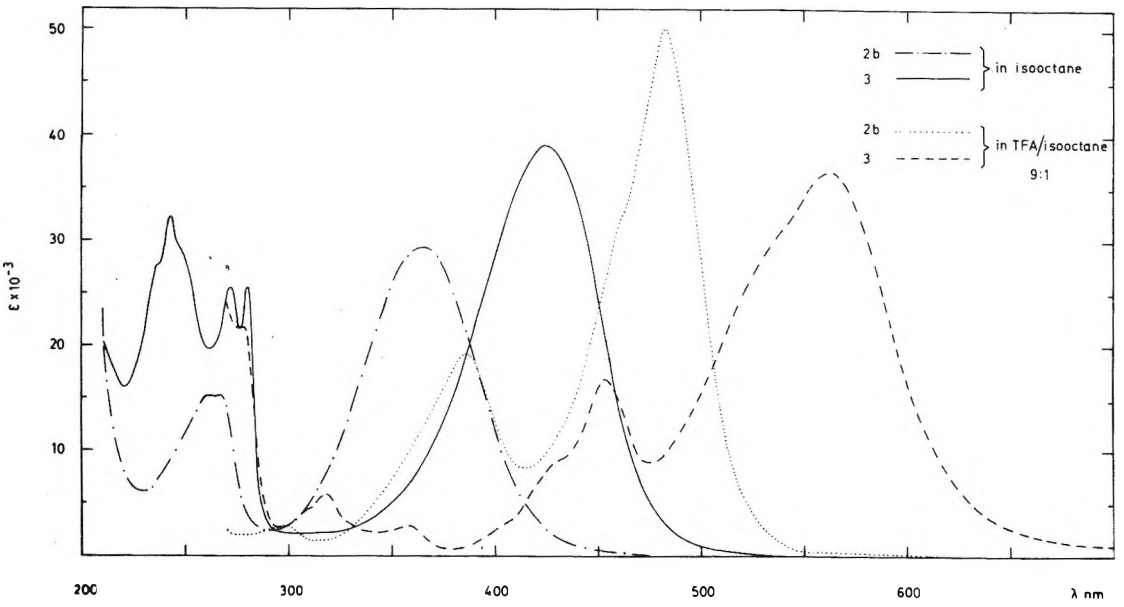
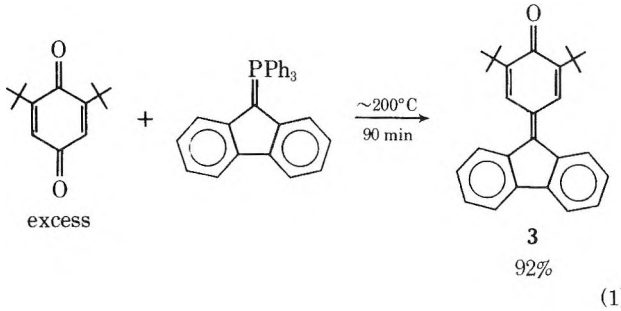


Figure 1. Electronic absorption spectra of **2b** and **3**.

Table I
Substitution of Aromatic Compounds by 3

4/5	Ar	Yield of 5, %
a	3,5-Di-*tert*-butyl-4-hydroxyphenyl	95
b	3,5-Dimethyl-4-hydroxyphenyl	82
c	3-*tert*-Butyl-4-hydroxy-5-methylphenyl	92
d	3,5-Diphenyl-4-hydroxyphenyl	95
e	3,5-Di-*tert*-butyl-2-hydroxyphenyl	91
f	3,5-Dimethoxy-4-hydroxyphenyl	56
g	4-Methoxyphenyl	65

92% yield from 2,6-di-*tert*-butyl-1,4-benzoquinone and fluorenylidenetriphenylphosphorane at 200° (reaction 1). The



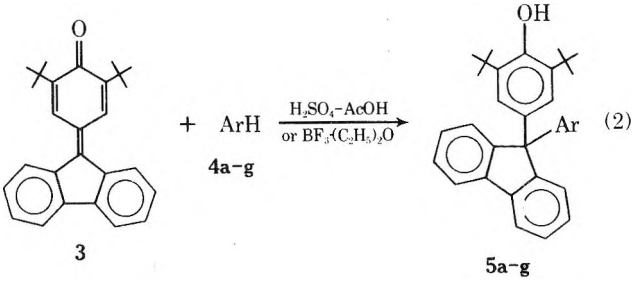
(1)

compound forms deep purple crystals which melt without decomposition at 227–228°. Its electronic absorption spectrum in the visible region exhibits its longest wavelength maximum at 424 nm, while a maximum at 364 nm is observed for 3,5-di-*tert*-butylfuchsone. The visible spectra of **2b** and **3** in trifluoroacetic acid, i.e., those of the corresponding triarylmethyl cations,[8] reveal a similar bathochromic shift (see Figure 1).

In the ir spectrum of **3** the strongest absorption attributed to the carbonyl group appears at 1592 cm^{-1} while the corresponding absorption in **2b** is found at 1602 cm^{-1}.[9]

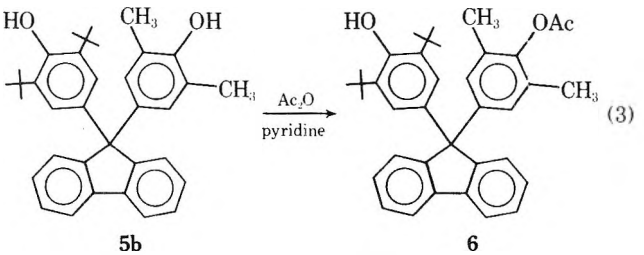
The NMR spectrum of **3** is in perfect agreement with the proposed structure. Different from the protons in the 3 and 5 positions of the 2,5-cyclohexadienone moiety in 3,5-di-*tert*-butylfuchsone at 7.20 ppm, the corresponding protons in the planar **3** give rise to a downfield singlet at 8.06 ppm since they are subject to the deshielding effect of the aromatic rings.[10] In its 270-MHz spectrum the protons of the fluorenylidene moiety give rise to a pair of doublets at 7.91 and 7.66 ppm and a pair of triplets centered at 7.36 and 7.29 ppm (see Experimental Section).

B. Acid-Catalyzed Additions to 2,6-Di-*tert*-butyl-4-(9-fluorenylidene)-1,4-benzoquinone. The reaction of fluorenylidenequinone **3** with 2,6-di-*tert*-butylphenol in acetic acid in the presence of sulfuric acid smoothly gives the symmetrical bisphenol **5a** which precipitates from the reaction mixture and can be isolated in 95% yield. The heretofore unknown asymmetrically 9,9-diaryl-substituted fluorenes **5b–g** were obtained by electrophilic substitution of **4b–g** under similar conditions (see Table I).



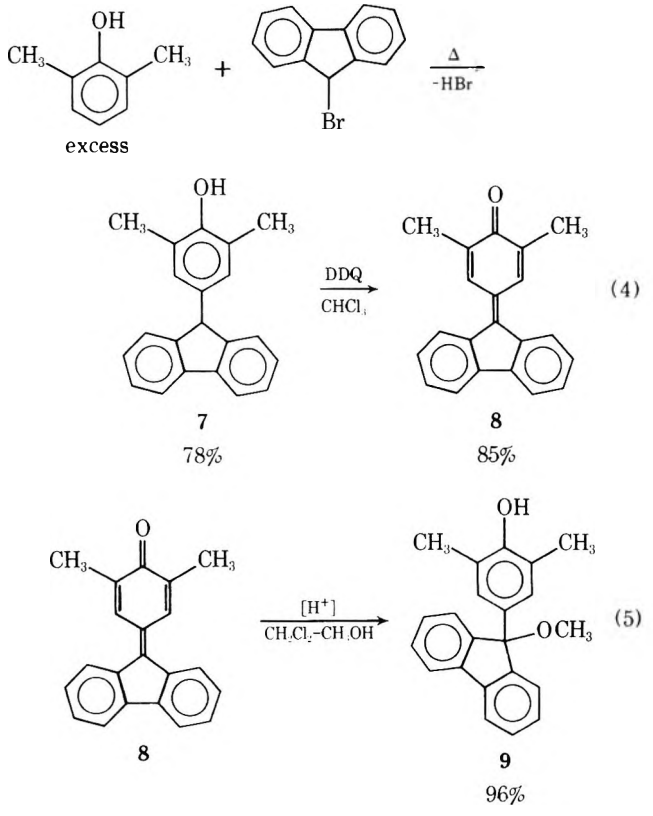
(2)

The structures of all new compounds are supported by their analytical and spectroscopic data (see Experimental Section) and by their chemical reactions. Bisphenol **5b**, for example, can be selectively acetylated at the less hindered phenolic site to give the corresponding monoacetate **6** (92% yield) (reaction 3).



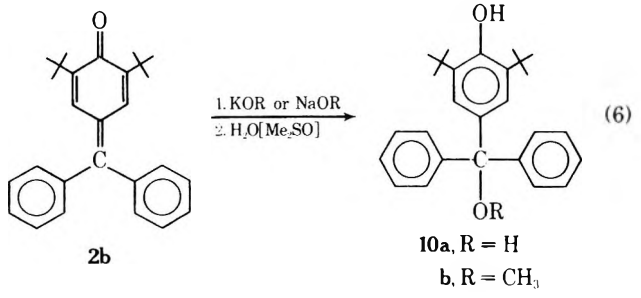
(3)

The driving force for the acid-catalyzed additions (reaction 2) most likely is due to the strained planarity of fluorenylidenequinone **3**, though the bulky *tert*-butyl substituents actually impair protonation of the carbonyl oxygen. The sterically less hindered 2,6-dimethyl-4-(9-fluorenylidene)-1,4-benzoquinone (**8**), which we prepared for comparison purposes (reaction 4), was found to undergo the 1,6



addition with methanol to give **9** (reaction 5) even in the absence of acid. Comparing the rates of the acetic acid catalyzed addition of methanol to fluorenylidenequinones **3** and **8** and the corresponding fuchsones **2b** and **2c**, the following order of relative reactivity was observed:[11] **8** ≫ **2c** > **3** ≫ **2b** (stable).

C. Anionic Additions to 2,6-Di-*tert*-butyl-4-(9-fluorenylidene)-1,4-benzoquinone. The reactions of anions with fluorenylidenequinone **3** were found to be analogous to the reactions of anions with 3,5-di-*tert*-butylfuchsone. Thus, with both water and methanol **2b** as well as **3** underwent base-catalyzed 1,6 additions in dimethyl sulfoxide solution to give the carbinols **10a** (reaction 6) and **11a**, and



their corresponding methyl ethers **10b** and **11b**, respectively. Similar 1,6 additions to **3** were observed with cyanide ion, methylsulfonyl carbanion, and 9-fluorenyl anion (reaction 7; see Table II).[12]

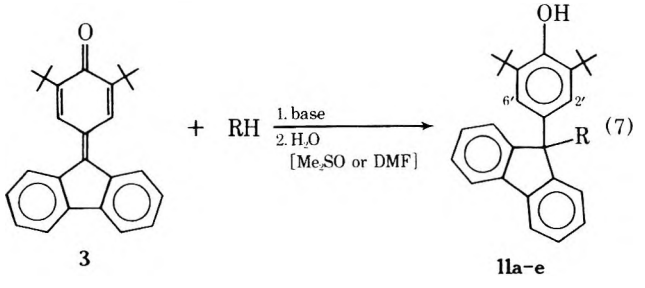


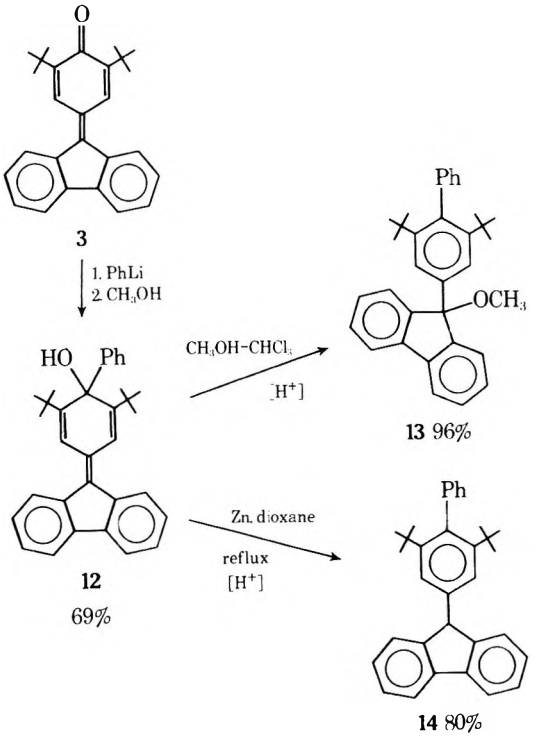
Table II
Base-Catalyzed Additions to 3 (Reaction 6)

11a–e	R	Yield, %
a	OH	86
b	OCH_3	85
c	CN	92
d	$CH_2SO_2CH_3$	75
e	9-Fluorenyl	81

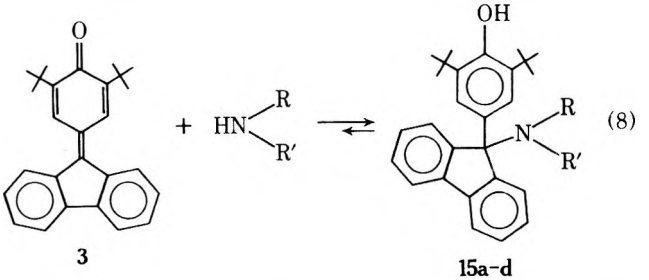
It is worth noting that in the NMR spectrum of the 9-aryl-9-fluorenylfluorene **11e**, two protons, most likely those in the 2′ and 6′ position, give rise to broad singlets at 6.05 and 6.18 ppm. Inspection of a Dreiding molecular model of **11e** suggests nonequivalence of the 2′,6′ protons because of hindered rotation about the aryl–C_9 bond.[13]

The 1,2 addition of phenyllithium to **3** followed the same exceptional course as had been found for 3,5-di-*tert*-butylfuchsone.[4] The structure of the 1,2-addition product **12** was established by its conversion into **13** and **14** (Scheme I). In the NMR spectrum of both **13** and **14** (see Experimental Section) the *tert*-butyl groups give rise to a singlet below 1 ppm, due to shielding by the phenyl substituent.

Scheme I



Interestingly, fluorenylidenequinone **3** was also found to undergo addition reactions with both primary and secondary amines (reaction 8; see Table III). The amine adducts

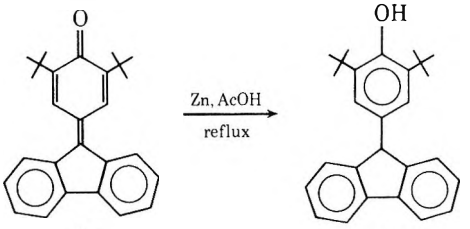


15a–d are colorless, crystalline compounds which are obtained in good yields when the amines are used as solvents. However, in chloroform solution and at elevated temperature the aminophenols **15** readily dissociate into their precursors.[14]

Table III
Addition of Amines to 3 (Reaction 8)

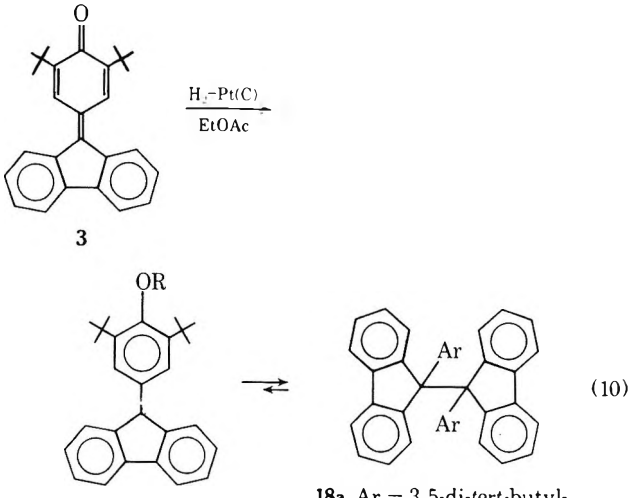
15a–d	R	R′	Yield, %
a	H	$CH(CH_3)_2$	87
b	H	c-C_6H_{11}	63
c		$-(CH_2)_2O(CH_2)_2-$	99
d		$-(CH_2)_4-$	91

D. Reductive Dimerization of 2,6-Di-*tert*-butyl-4-(9-fluorenylidene)-1,4-benzoquinone. Interesting and unexpected results were obtained when we studied the reduction of **3**. Zinc in boiling acetic acid smoothly reduces **3** to give the fluorenyl-substituted phenol **16** in 95% yield (reaction 9). During the course of the reaction, however, the



3 16 (9)

transient appearance of a colorless precipitate, which we presumed to be an unstable precursor of **16**, was noticed.[15] Upon catalytic hydrogenation at room temperature fluorenylidenequinone **3** indeed only consumed 0.5 molar equiv of hydrogen to give a colorless, crystalline product for which spectroscopic data (ir, NMR) are in agreement with the dimer **18a**. The NMR spectroscopic investigation revealed that the dimmer **18a** in solution decomposed to the fluorenylidenequinone **3** and the phenol **16**. Conceivably, the decomposition involves free-radical dissociation of dimer **18a** at the central carbon–carbon bond to give the fluorenyl radical **17a** which, because of the phenolic hydroxy group, is prone to undergo disproportionation. Perchloric acid catalyzed acetylation of dimer **18a** gives the



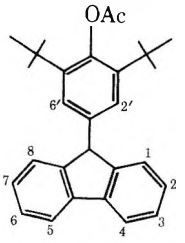
17a, R = H
b, R = Ac

18a, Ar = 3,5-di-*tert*-butyl-4-hydroxyphenyl
b, Ar = 3,5-di-*tert*-butyl-4-acetoxyphenyl (10)

fairly stable diaryl disubstituted 9,9′-bifluorenyl **18b**. Its structure was established by its conventional[16] preparation from fluorenylphenol **16** according to the following sequence of reactions (eq 11).

The equilibrium of dimer **18b** with the free radicals **17b** was studied by ESR spectroscopy.[17] The calculated spectrum of radical **17b**, based on coupling constants listed in

Table IV
Coupling Constants in 17b



17b

Position	a_H, G
1,8	3.27
2,7	0.62
3,6	3.40
4,5	0.83
2′,6′	1.95

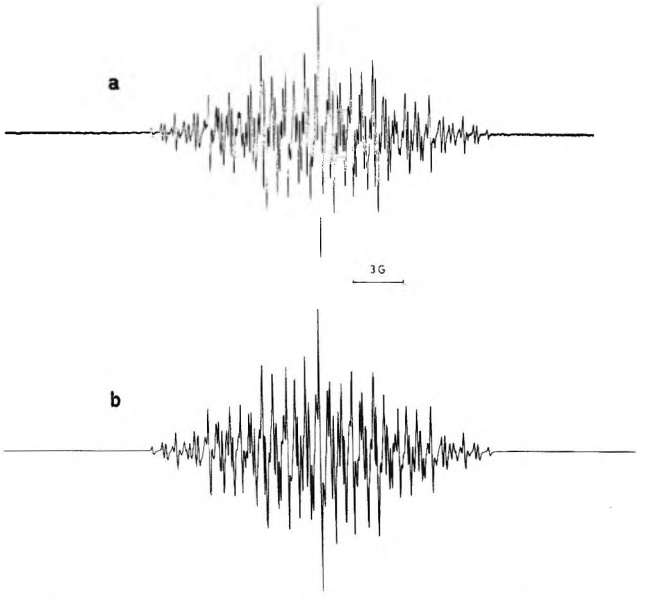
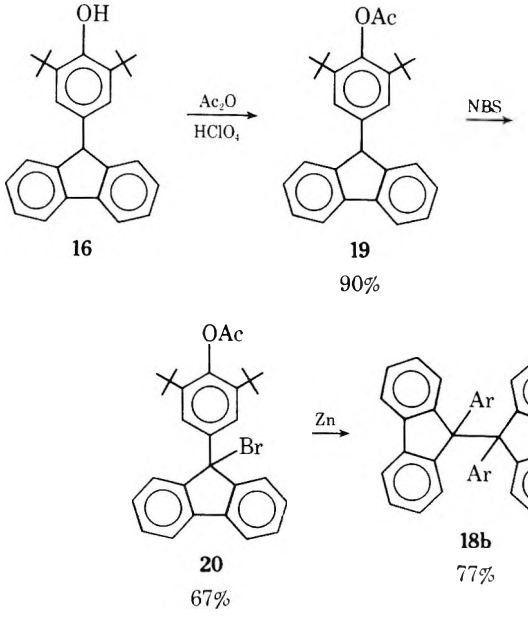


Figure 2. (a) ESR spectrum of radical **17b**; (b) simulated spectrum based on coupling constants in Table IV.

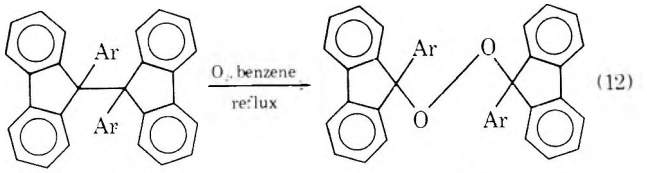


(11)

Table IV, is in excellent agreement with the experimentally found spectrum in xylene at 98° (see Figure 2). Based on the temperature dependence of the radical concentration,

the ΔH of equilibrium in anisole was found to be 25.8 ± 0.9[18] kcal/mol. For the equilibrium of the 9-phenylfluorenyl radical with its dimer a ΔH of 26.6 kcal/mol was observed.[17a]

As characteristic[16] for a 9-aryl substituted fluorenyl radical, **17b** rapidly reacts with oxygen to give the crystalline peroxide **21** whose structure is supported by analytical and spectroscopic data (see Experimental Section).



(12)

18b 21

90%

Quite unexpectedly, the reductive dimerization of fluorenylidenequinone **3** was also accomplished by phenylmagnesium bromide. This result is surprising in view of the 1,2 addition we observed with phenyllithium. The reductive dimerization indicates that **3** oxidizes the Grignard reagent by one-electron transfer[19] rather than undergoing the expected nucleophilic addition. This is of particular interest in view of the very recent discussion on the involvement of electron transfer steps in the Grignard reaction with ketones.[20]

Experimental Section

Melting points were determined on a hot-stage microscope and are uncorrected. Analyses were performed by NOVO Microanalytical Laboratory, Bagsvaerd, Denmark. Infrared spectra, in KBr pellets, were recorded on a Beckman IR9 instrument. Electronic absorption spectra were taken on a Beckman DK2 spectrophotometer. NMR spectra were recorded on Varian A-60 or Bruker WH 270 spectrometers using chloroform-*d*; chemical shifts are given in parts per million downfield from Me_4Si. ESR spectra were taken on a Varian E-9 instrument equipped for variable-temperature experiments.

2,6-Di-*tert*-butyl-4-(9-fluorenylidene)-1,4-benzoquinone (3). A stirred mixture of 2,6-di-*tert*-butyl-1,4-benzoquinone[21] (22.0 g, 0.1 mol) and fluorenylidenetriphenylphosphorane[22] (21.3 g, 0.05 mol) was kept for 90 min at 190–200°. The solid mixture obtained on cooling the red melt to room temperature was dissolved in warm methylene chloride. Addition of methanol gave a red crystalline precipitate. It was filtered off, washed with methanol, and dried at 120° to give 17.1 g (92%) of red-colored crystals, mp 227–228° (rods changing to plates at 215–218°). Recrystallization by dissolving in hot methylene chloride and adding methanol did not raise the melting point; ir 1590 (s), 1622 (w), 1640 cm^{-1} (w); uv (isooctane) λ ($\epsilon \times 10^{-3}$) 243 (32.4), 272 (25.4), 280 (25.4), 424 nm (39.0); NMR (270 MHz) 8.06 (s, 2), 7.91 (d, J = 7.5 Hz, 2), 7.66 (d, J = 7.3 Hz, 2), 7.36 (t, J = 7.3 Hz, 2), 7.29 (t, J = 7.5 Hz, 2), 1.41 ppm (s, 18).

Anal. Calcd for $C_{27}H_{28}O$ (368.49): C, 88.00; H, 7.66. Found: C, 87.77; H, 7.69.

Standard Procedure for the Preparation of Bisphenols 5a–f. Concentrated sulfuric acid (0.5 ml) was added dropwise to a stirred suspension of the phenol (3 mmol) and **3** (1.11 g, 3 mmol) in acetic acid (15 ml). The stirred reaction mixture was kept overnight at room temperature, yielding a colorless precipitate which was removed by filtration through a sintered glass funnel.

9,9-Bis(3′,5′-di-*tert*-butyl-4′-hydroxyphenyl)fluorene (5a): yield 1.64 g (95%); mp 274–275° (from petroleum ether, bp 80–110°) (lit.[23] 272–273°); ir 3640 cm^{-1}; NMR 7.85–7.65 (m, 2), 7.46–7.21 (m, 6), 6.98 (s, 4), 5.04 (s, 2), 1.30 ppm (s, 36).

9-(3′,5′-Di-*tert*-butyl-4′-hydroxyphenyl)-9-(3″,5″-dimethyl-4″-hydroxyphenyl)fluorene (5b): yield 1.22 g (82%); mp 229–230° (from boiling ethanol and drying for 1 hr at 140°); ir 3630, 3600 cm^{-1}; NMR 7.85–7.63 (m, 2), 7.51–7.21 (m, 6), 7.05 (s, 2), 6.77 (s, 2), 5.03 (s, 1), 4.44 (s, 1), 2.07 (s, 6), 1.30 ppm (s, 18).

Anal. Calcd for $C_{35}H_{38}O_2$ (490.69): C, 85.67; H, 7.81. Found: C, 85.83; H, 7.77.

9-(3′,5′-Di-*tert*-butyl-4′-hydroxyphenyl)-9-(3″-*tert*-butyl-4″-hydroxy-5″-methylphenyl)fluorene (5c): yield 1.48 g (92%); mp 208–209° (from acetic acid); ir 3620, 3570 cm^{-1}; NMR 7.85–7.65 (m, 2), 7.40–7.10 (m, 7), 7.01 (s, 2), 6.57 (m, 1), 5.02 (s, 1), 4.55 (br s, 1), 2.00 (s, 3), 1.30 ppm (s, 27).

Anal. Calcd for $C_{38}H_{44}O_2$ (532.77): C, 85.67; H, 8.32. Found: C, 85.39; H, 8.29.

9-(3′,5′-Di-*tert*-butyl-4′-hydroxyphenyl)-9-(3″,5″-diphenyl-4″-hydroxyphenyl)fluorene (5d): yield 1.76 g (95%); mp 232–233° (by dissolving in hot methylene chloride and adding ethanol); ir 3630, 3540 cm^{-1}; NMR 7.85–7.65 (m, 2), 7.52–7.10 (m, 20), 5.28 (s, 1), 5.04 (s, 1), 1.30 ppm (s, 18).

Anal. Calcd for $C_{45}H_{42}O_2$ (614.84): C, 87.91; H, 6.89. Found: C, 87.78; H, 6.86.

9-(3′,5′-Di-*tert*-butyl-4′-hydroxyphenyl)-9-(3″,5″-di-*tert*-butyl-2″-hydroxyphenyl)fluorene (5e). This compound was prepared from **3** (1.11 g, 3 mmol) and 2,4-di-*tert*-butylphenol (1 g, 4.85 mmol) in acetic acid (15 ml) and sulfuric acid (1 ml): yield 1.57 g (91%); mp 224–225° (from acetic acid); ir 3640, 3460 cm^{-1}; NMR 7.85–7.18 (m, 11), 6.73 (d, J = 2.5 Hz, 1), 5.25 (s, 1), 5.21 (s, 1), 1.40 (s, 9), 1.28 (s, 18), 1.08 ppm (s, 9).

Anal. Calcd for $C_{41}H_{50}O_2$ (574.85): C, 85.67; H, 8.77. Found: C, 85.62; H, 8.79.

9-(3′,5′-Di-*tert*-butyl-4′-hydroxyphenyl)-9-(3″,5″-dimethoxy-4″-hydroxyphenyl)fluorene (5f). The reaction according to the standard procedure resulted in an orange solution which was diluted with water and shaken with ether. The organic layer was washed with water and dried (magnesium sulfate) and the solvent was vacuum evaporated to give an oil which crystallized when treated with ether–*n*-hexane. Recrystallization from petroleum ether (bp 80–110°) gave 0.88 g (56%) of colorless crystals: mp 163–165°; ir 3640, 3540 cm^{-1}; NMR 7.89–7.69 (m, 2), 7.52–7.21 (m, 6), 7.05 (s, 2), 6.40 (s, 2), 5.40 (s, 1), 5.07 (s, 1), 3.67 (s, 6), 1.30 ppm (s, 18).

Anal. Calcd for $C_{35}H_{38}O_4$ (522.69): C, 80.43; H, 7.33. Found: C, 80.23; H, 7.60.

9-(3′,5′-Di-*tert*-butyl-4′-hydroxyphenyl)-9-(4″-methoxyphenyl)fluorene (5g). Boron trifluoride etherate (0.3 ml) was added to a suspension of **3** (1.11 g, 3 mmol) in anisole (15 ml). The stirred reaction mixture was kept for 1 hr at 75–80° and then diluted with benzene and washed with water. The organic layer was dried (magnesium sulfate) and the solvent was removed by evaporation in vacuo to give an oily residue which crystallized when treated with petroleum ether (bp 60–70°). Recrystallization by dissolving in hot ethanol and adding some drops of water gave 0.93 g (65%) of colorless crystals: mp 180–182°; ir 3640 cm^{-1}; NMR 7.85–7.65 (m, 2), 7.48–7.00 (m, 10), 6.72 (d, J = 9 Hz, 2), 5.05 (s, 1), 3.67 (s, 3), 1.29 ppm (s, 18).

Anal. Calcd for $C_{34}H_{36}O_2$ (476.66): C, 85.67; H, 7.61. Found: C, 85.48; H, 7.66.

9-(3′,5′-Di-*tert*-butyl-4′-hydroxyphenyl)-9-(4″-acetoxy-3″,5″-dimethylphenyl)fluorene (6). Pyridine (0.3 ml) was added to a stirred suspension of **5b** (500 mg) in acetic anhydride (10 ml). The solution thus obtained was kept for 10 hr at room temperature and then diluted with methanol. Vacuum evaporation of solvent gave a colorless, crystalline residue. It was triturated with aqueous methanol, removed by filtration, and recrystallized by dissolving in ether and adding petroleum ether (bp 80–110°): yield 500 mg (92%); mp 228–229°; ir 3610, 1755 cm^{-1}; NMR 7.83–7.65 (m, 2), 7.50–7.20 (m, 6), 7.03 (s, 2), 6.85 (s, 2), 5.06 (s, 1), 2.22 (s, 3), 2.00 (s, 6), 1.28 ppm (s, 18).

Anal. Calcd for $C_{37}H_{40}O_3$ (532.73): C, 83.42; H, 7.57. Found: C, 83.61; H, 7.57.

9-(3′,5′-Dimethyl-4′-hydroxyphenyl)fluorene (7). A molten mixture of 9-bromofluorene[24] (12.25 g, 50 mmol) and 2,6-dimethylphenol (30.5 g, 0.25 mol) was stirred for 16 hr at 45–50° and for an additional 24 hr at 80–90°. Excess 2,6-dimethylphenol was removed by vacuum sublimation at room temperature (0.1 mm) and the residue was recrystallized from methylene chloride–cyclohexane in the presence of charcoal: yield 11.1 g (78%) of colorless crystals; mp 158–160°; ir 3420 cm^{-1}; NMR 7.88–7.62 (m, 2), 7.51–7.18 (m, 6), 6.70 (s, 2), 4.90 (br s, 1), 4.48 (s, 1, exchangeable with D_2O), 2.13 ppm (s, 6).

Anal. Calcd for $C_{21}H_{18}O$ (286.37): C, 88.08; H, 6.34. Found: C, 87.87; H, 6.30.

2,6-Dimethyl-4-(9-fluorenylidene)-1,4-benzoquinone (8). A suspension of **7** (716 mg, 2.5 mmol) and 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (567 mg, 2.5 mmol) in ethanol-free chloroform (15 ml, filtered through activated basic alumina) was shaken for 3 hr under nitrogen. The precipitated hydroquinone was filtered off and washed with chloroform and the solvent was evaporated in

vacuo from the combined filtrates to give a red-colored crystalline residue which was recrystallized by dissolving in hot chloroform and addition of ether: yield 606 mg (85%) of red plates, mp 210–212°; ir 1595 (s), 1602 (s), 1628 cm^{-1} (w); uv (isooctane) λ ($\epsilon \times 10^{-3}$) 243.5 (30.8), 272.5 (25.0), 281 (24.8), 425 nm (38.2); NMR (270 MHz) 8.03 (s, 2), 7.91 (d, J = 7.5 Hz, 2), 7.64 (d, J = 7.4 Hz, 2), 7.36 (t, J = 7.4 Hz, 2), 7.28 (t, J = 7.5 Hz, 2), 2.19 ppm (s, 6).

Anal. Calcd for $C_{21}H_{16}O$ (284.36): C, 88.70; H, 5.67. Found: C, 88.63; H, 5.72.

9-(3′,5′-Dimethyl-4′-hydroxyphenyl)-9-methoxyfluorene (9). Acetic acid (1 ml) was added to a stirred solution of **8** (284 mg, 1 mmol) in methylene chloride (10 ml) and methanol (10 ml). After stirring for 45 min the pale yellow reaction mixture was concentrated by partial evaporation of solvent in vacuo. Addition of some drops of water gave a crystalline precipitate. It was recrystallized by dissolving in hot methylene chloride and addition of *n*-pentane: yield 303 mg (96%); mp 174–176°; ir 3460 cm^{-1}; NMR 7.80–7.25 (m, 8), 6.98 (s, 2), 4.51 (s, 1), 2.95 (s, 3), 2.13 ppm (s, 6).

Anal. Calcd for $C_{22}H_{20}O_2$ (316.40): C, 83.51; H, 6.37. Found: C, 83.16; H, 6.42.

3,5-Di-*tert*-butyl-4-hydroxytriphenylcarbinol (10a). This compound was prepared from **2b** (370 mg, 1 mmol) in the same way as described for **11a.** Recrystallization from petroleum ether (bp 80–110°) gave 255 mg (65%) of colorless crystals: mp 151–152° (lit.[25] 151–152°); ir 3635, 3575 cm^{-1}; NMR 7.28 (m, 10), 7.03 (s, 2), 5.20 (br s, 1), 2.76 (s, 1), 1.33 ppm (s, 18).

α,α-Diphenyl-α-methoxy-2,6-di-*tert*-butyl-*p*-cresol (10b). This compound was prepared from **2b** as described for **11b.** Recrystallization from methanol gave 330 mg (82%) of colorless to pale yellow crystals: mp 121–122°; ir 3640 cm^{-1}; NMR 7.58–7.13 (m, 12), 5.16 (s, 1), 3.06 (s, 3), 1.37 ppm (s, 18).

Anal. Calcd for $C_{28}H_{34}O_2$ (402.58): C, 83.54; H, 8.51. Found: C, 83.63; H, 8.43.

9-(3′,5′-Di-*tert*-butyl-4′-hydroxyphenyl)-9-fluorenol (11a). **3** (368 mg, 1 mmol) was added under nitrogen to a stirred solution of potassium hydroxide (2 g) in dimethyl sulfoxide (25 ml) and water (5 ml). After 30 min at 90–95° traces of unreacted starting material were removed by filtration. The filtrate was diluted with water (200 ml) and neutralized with acetic acid. The precipitate thus obtained was filtered off and dissolved in ether. The organic layer was dried (magnesium sulfate) and the solvent was partially evaporated in vacuo. Addition of petroleum ether (bp 60–70°) gave a crystalline precipitate which, after recrystallization from petroleum ether (bp 80–110°), gave 335 mg (86%) of colorless crystals: mp 171–172°; ir 3630, 3570 cm^{-1}; NMR 7.73–7.18 (m, 10), 5.12 (s, 1), 2.43 (br s, 1), 1.35 ppm (s, 18).

Anal. Calcd for $C_{27}H_{30}O_2$ (386.54): C, 83.90; H, 7.82. Found: C, 83.74; H, 7.69.

9-(3′,5′-Di-*tert*-butyl-4′-hydroxyphenyl)-9-methoxyfluorene (11b). Sodium methoxide (540 mg, 10 mmol) was added to a stirred suspension of **3** (368 mg, 1 mmol) in dimethyl sulfoxide (25 ml) under nitrogen. The mixture was kept for 15 min at 80°, then diluted with water (200 ml) and neutralized with acetic acid. The precipitate thus formed was recrystallized twice from aqueous ethanol (75%) to give 342 mg (85%) of colorless to pale yellow crystals: mp 141–142°; ir 3630 cm^{-1}; NMR 7.75–7.20 (m, 10), 5.07 (s, 1), 2.95 (s, 3), 1.34 ppm (s, 18).

Anal. Calcd for $C_{28}H_{32}O_2$ (400.57): C, 83.96; H, 8.05. Found: C, 83.74; H, 7.97.

9-(3′,5′-Di-*tert*-butyl-4′-hydroxyphenyl)-9-cyanofluorene (11c). Sodium cyanide (735 mg, 15 mmol) and **3** (1.11 g, 3 mmol) in dimethyl sulfoxide (50 ml) were stirred for 15 min at 80° under nitrogen. The resulting green solution was slowly diluted with water (200 ml) to give a colorless, crystalline precipitate which was recrystallized from aqueous ethanol: yield 1.10 g (92%); mp 181–182°; ir 3595, 2240 cm^{-1}; NMR 7.85–7.15 (m, 8), 7.08 (s, 2), 5.20 (s, 1), 1.32 ppm (s, 18).

Anal. Calcd for $C_{28}H_{29}NO$ (395.55): C, 85.02; H, 7.39. Found: C, 84.77; H, 7.40.

9-(3′,5′-Di-*tert*-butyl-4′-hydroxyphenyl)-9-[(methylsulfonyl)methyl]fluorene (11d). Potassium *tert*-butoxide (560 mg, 5 mmol) was added to a stirred suspension of **3** (1.11 g, 3 mmol) and dimethyl sulfone (942 mg, 10 mmol) in dimethyl sulfoxide (50 ml). The stirred reaction mixture was kept under nitrogen for 5 min at 70°. Dilution with ice–water and neutralization with acetic acid gave a crystalline precipitate. Recrystallization from ethanol in the presence of charcoal gave 1.05 g (75%) of colorless crystals: mp 218–219°; ir 3625, 1310, 1125 cm^{-1}; NMR 7.89–7.67 (m; 2), 7.62–7.18 (m, 6). 7.02 (s, 2), 5.15 (s, 1), 4.30 (s, 2), 2.00 (s, 3), 1.32 ppm (s, 18).

Anal. Calcd for $C_{29}H_{34}O_3S$ (462.66): C, 75.29; H, 7.41. Found: C, 75.10; H, 7.51.

9-(3′,5′-Di-*tert*-butyl-4′-hydroxyphenyl)-9-(9″-fluorenyl)fluorene (11e). Potassium *tert*-butoxide (460 mg, 4 mmol) was added to a solution of **3** (1.11 g, 3 mmol) and fluorene (670 mg, 4 mmol) in dimethylformamide (50 ml). The mixture was stirred for 30 min at 90° under nitrogen. Addition of ice gave a crystalline precipitate which was recrystallized by dissolving in warm acetone and adding aqueous ethanol (75%): yield 1.30 g (81%) of colorless crystals, mp 204–205°; ir 3620 cm^{-1}; NMR 7.66–6.66 (m, 16), 6.18 (br, s, 1), 6.05 (br s, 1), 5.33 (br s, 1), 5.15 (s, 1, exchangeable with D_2O), 1.40 ppm (s, 18).

Anal. Calcd for $C_{40}H_{38}O$ (534.74): C, 89.85; H, 7.16. Found: C, 89.56; H, 7.29.

3,5-Di-*tert*-butyl-4-hydroxy-4-phenyl-1-(9-fluorenylidene)-2,5-cyclohexadiene (12). Phenyllithium (6 ml, 2 *M* in benzene–ether, 70:30) was added to a stirred suspension of **3** (1.11 g, 3 mmol) in benzene (20 ml) under nitrogen. The mixture was kept for 1 hr at room temperature under nitrogen and the solvent was partially evaporated in vacuo. Slow dilution with methanol gave a yellow, crystalline precipitate which was recrystallized by dissolving in hot methylene chloride and adding methanol: yield 0.93 g (69%) of yellow crystals, mp 205–206°; ir 3570, 1640 cm^{-1}; NMR 8.08–7.08 (m, 15), 2.05 (s, 1), 1.18 ppm (s, 18); uv (methanol) λ ($\epsilon \times 10^{-3}$) 233 (34.3), 251 (42.0), 265 (sh, 21.2), 275 (sh, 16.7), 390 nm (36.6).

Anal. Calcd for $C_{33}H_{34}O$ (446.63): C, 88.74; H, 7.67. Found: C, 88.33; H, 7.58.

9-[(3′,5′-Di-*tert*-butyl-4′-phenyl)phenyl]-9-methoxyfluorene (13). Concentrated hydrochloric acid (0.2 ml) was added to a solution of **12** (150 mg, 0.34 mmol) in chloroform (5 ml) and methanol (10 ml). The reaction mixture was refluxed for 30 min and the resulting pale yellow solution was concentrated by partial evaporation of solvent in vacuo, giving a colorless precipitate. It was recrystallized by dissolving in hot methanol and adding water: yield 150 mg (96%); mp 174–175°; NMR 7.75–7.20 (m, 15), 2.16 (s, 3), 0.95 ppm (s, 18).

Anal. Calcd for $C_{34}H_{36}O$ (460.66): C, 88.65; H, 7.88. Found: C, 88.43; H, 7.74.

9-[(3′,5′-Di-*tert*-butyl)-4′-phenyl]fluorene (14). Concentrated hydrochloric acid was added dropwise to a refluxing mixture of **12** (200 mg, 0.45 mmol) and zinc powder (2 g) in dioxane (25 ml) until the solution was colorless. The mixture was filtered and the filtrate was concentrated (to ca. 5 ml) by vacuum evaporation of solvent. Addition of methanol and water gave a crystalline precipitate which was recrystallized by dissolving in ether and adding methanol to give 155 mg (80%) of colorless crystals: mp 173–174°; NMR 7.87–7.70 (m, 2), 7.66–7.22 (m, 13), 5.10 (br s, 1), 0.98 ppm (s, 18).

Anal. Calcd for $C_{33}H_{34}$ (430.63): C, 92.04; H, 7.96. Found: C, 91.70; H, 7.90.

9-(3′,5′-Di-*tert*-butyl-4′-hydroxyphenyl)-9-(*N*-isopropylamino)fluorene (15a). A suspension of **3** (555 mg, 1.5 mmol) in isopropylamine (20 ml) was stirred under nitrogen for 30 min at room temperature. The resulting yellow solution was concentrated to 5 ml by vacuum evaporation. Dropwise addition of water to the stirred mixture gave a pale yellow crystalline precipitate which was recrystallized by dissolving in isopropylamine and dropwise addition of water: yield 535 mg (87%) of colorless to pale yellow crystals, mp 133–134°; ir 3625 cm^{-1}; NMR 7.76–7.20 (m, 10), 5.03 (br s, 1), 2.43 (m, 1), 1.85 (br s, 1), 1.35 (s, 18), 0.75 ppm (d, J = 6 Hz, 6).

Anal. Calcd for $C_{30}H_{37}NO$ (427.64): C, 84.26; H, 8.72. Found: C, 83.96; H, 8.65.

9-(3′,5′-Di-*tert*-butyl-4′-hydroxyphenyl)-9-(*N*-cyclohexylamino)fluorene (15b). **3** (555 mg, 1.5 mmol) was dissolved in warm cyclohexylamine (15 ml). Upon cooling to room temperature, the red solution turned pale orange colored. Careful dilution with water gave a crystalline precipitate which was recrystallized by dissolving in warm cyclohexylamine and adding water: yield 440 mg (63%) of colorless to pale yellow crystals, mp 172–174°; ir 3625 cm^{-1}; NMR 7.72–7.19 (m, 10), 5.00 (br s, 1), 2.30–0.80 ppm (br m containing a sharp peak at 1.33, 30).

Anal. Calcd for $C_{31}H_{37}NO_2$ (455.64): C, 81.72; H, 8.19. Found: C, 81.83; H, 8.24.

9-(3′,5′-Di-*tert*-butyl-4′-hydroxyphenyl)-9-(*N*-morpholino)fluorene (15c). **3** (555 mg, 1.5 mmol) in morpholine (15 ml) was stirred for 30 min at 50–60° under nitrogen. Careful dilution with water gave a crystalline precipitate which was recrystallized by dissolving in warm morpholine and dropwise addition of water: yield 675 mg (99%) of colorless crystals, mp 230–231°; ir 3630

cm^{-1}; NMR 7.76–7.29 (m, 10), 5.10 (br s, 1), 3.67 (m, 4), 2.35 (m, 4), 1.35 ppm (s, 18).

Anal. Calcd for $C_{31}H_{37}NO_2$ (455.64): C, 81.72; H, 8.19. Found: C, 81.83; H, 8.24.

9-(3′,5′-Di-*tert*-butyl-4′-hydroxyphenyl)-9-(*N*-pyrrolidino)fluorene (15d). **3** (1.11 g, 3 mmol) was dissolved in pyrrolidine (30 ml) at room temperature under nitrogen. After 10 min, excess pyrrolidine was removed by vacuum evaporation, giving a yellowish crystalline residue. Recrystallization by dissolving in benzene and adding ethanol gave 1.21 g (91%) of pale yellow crystals: mp 219–221°; ir 3620 cm^{-1}; NMR 7.72–7.15 (m, 10), 5.00 (br s, 1), 2.40 (m, 4), 1.60 (m, 4), 1.35 ppm (s, 18).

Anal. Calcd for $C_{31}H_{37}NO$ (439.65): C, 84.69; H, 8.48. Found: C, 84.52; H, 8.45.

9-(3′,5′-Di-*tert*-butyl-4′-hydroxyphenyl)fluorene (16). A suspension of **3** (3.68 g, 10 mmol) and zinc powder (3 g) in concentrated acetic acid (150 ml) was refluxed for 45 min under nitrogen. The reaction mixture was filtered and the filtrate was diluted with water (200 ml) to give a colorless, crystalline precipitate. Recrystallization from ethanol gave 3.53 g (95%): mp 177–178°; ir 3615 cm^{-1}; NMR 7.89–7.70 (m, 2), 7.54–7.21 (m, 6), 6.95 (s, 2), 5.05 (s, 1, exchangeable with D_2O), 5.00 (br s, 1), 1.36 ppm (s, 18).

Anal. Calcd for $C_{27}H_{30}O$ (370.51): C, 87.52; H, 8.16. Found: C, 87.44; H, 8.15.

9,9′-Bis(3″,5″-di-*tert*-butyl-4″-hydroxyphenyl)-9,9′-bifluorenyl (18a). A suspension of **3** (1.12 g, 3.04 mmol) in ethyl acetate (140 ml) was hydrogenated over 10% platinum on charcoal, H_2 uptake 45 ml (at 20°, 745 mm; 1.55 mmol). Vacuum evaporation of solvent from the essentially colorless solution obtained after removal of catalyst gave a precipitate which was filtered off after addition of petroleum ether (bp 60–70°). Several washings with *n*-pentane left a pale yellow product, yield 795 mg (71%), mp 175–195° dec. Attempts to recrystallize the crude product (under nitrogen) resulted in considerable loss of material: NMR 7.68–6.54 (m, 20), 5.10 (s, 2), 1.30 ppm (s, 36).

9,9′-Bis(4″-acetoxy-3″,5″-di-*tert*-butylphenyl)-9,9′-bifluorenyl (18b). A. By Acetylation of 18a. **18a** (300 mg, 0.4 mmol) was added under stirring to a 2 *M* solution of acetic anhydride in ethyl acetate–$HClO_4$[26] (10 ml). The mixture was stirred for 30 min at room temperature and then diluted with ethanol (20 ml). Concentration by vacuum evaporation of solvent to a volume of 5 ml followed by addition of methanol (10 ml) and some drops of water gave a crystalline precipitate. Recrystallization from ethanol gave 260 mg (78%) of colorless crystals: mp 203–206° dec; ir 1762 cm^{-1}; NMR 7.60–6.50 (m, 20), 2.33 (s, 6), 1.18 ppm (s, 36).

Anal. Calcd for $C_{58}H_{62}O_4$ (823.14): C, 84.63; H, 7.59. Found: C, 84.31; H, 7.66.

B. From Reaction between Phenylmagnesium Bromide and 3. Ten milliliters of a phenylmagnesium bromide solution prepared from 1.10 g of magnesium turnings and bromobenzene (5 ml) in ether (50 ml) was added dropwise to a stirred suspension of **3** (1.11 g, 3 mmol) in ether (25 ml) under nitrogen. The light green suspension thus obtained was stirred for 20 min under nitrogen at room temperature and was then hydrolyzed with a saturated ammonium chloride solution under nitrogen blanketing and the organic layer was dried (magnesium sulfate) under nitrogen. Addition of petroleum ether (bp 60–70°) and evaporation of diethyl ether in vacuo gave a colorless to pale yellow precipitate which was removed by filtration. The crude product was acetylated with 50 ml of acetylating agent[26] as described under A. Vacuum evaporation of solvent to ca. 5 ml gave a colorless precipitate. It was recrystallized from ether–ethanol to give 630 mg (51%), mp 203–207°.

From the original petroleum ether filtrate of the Grignard reaction, 70 mg (30%) of diphenyl, mp 69–70° (no depression upon admixture of authentic material), was isolated by vacuum sublimation (0.1 mm) at room temperature.

C. From 9-(4′-Acetoxy-3′,5′-di-*tert*-butylphenyl)-9-bromofluorene (20) and Zinc Powder. A solution of **20** (200 mg, 0.4 mmol) in anhydrous benzene (15 ml) was shaken under nitrogen with zinc powder (2 g). After 1 hr, the reaction mixture was filtered, the inorganic material was washed with benzene, and the solvent was partially evaporated in vacuo. Addition of ethanol gave a colorless, crystalline precipitate, yield 127 mg (77%), mp 204–207° dec. The identity of the products obtained by procedures A–C was confirmed by NMR.

9-(4′-Acetoxy-3′,5′-di-*tert*-butylphenyl)fluorene (19). Compound **16** (500 mg, 1.35 mmol) was added to a stirred acetic anhydride solution in ethyl acetate–$HClO_4$[26] (20 ml). Addition of ethanol (30 ml) after 30 min followed by vacuum evaporation of solvents gave a colorless, crystalline precipitate which was washed with water. Recrystallization from boiling ethanol gave **19** (500 mg, 90%): mp 166–167°; ir 1760 cm^{-1}; NMR 7.90–7.70 (m, 2), 7.50–7.2- (m, 6), 7.08 (s, 2), 5.05 (br s, 1), 2.32 (s, 3), 1.25 (s, 18).

Anal. Calcd for $C_{29}H_{32}O_2$ (412.58): C, 84.42; H, 7.82. Found: C, 84.22; H, 7.82.

9-(4′-Acetoxy-3′,5′-di-*tert*-butylphenyl)-9-bromofluorene (20). A mixture of **19** (825 mg, 2 mmol), *N*-bromosuccinimide (400 mg, 2.2 mmol), and dibenzoyl peroxide (10 mg) in carbon tetrachloride (25 ml) was refluxed for 1 hr. Succinimide was filtered off and washed with carbon tetrachloride. Vacuum evaporation of solvent from the combined filtrates gave a solid residue which was dissolved in boiling petroleum ether (bp 80–110°) and filtered through Celite. The clear solution thus obtained was concentrated by vacuum evaporation of solvent, giving a crystalline precipitate. Recrystallization from *n*-hexane gave 660 mg (67%) of colorless crystals: mp 178–180°; ir 1760 cm^{-1}; NMR 7.77–7.23 (m, 10), 2.30 (s, 3), 1.28 ppm (s, 18).

Anal. Calcd for $C_{29}H_{31}BrO_2$ (491.47): C, 70.87; H, 6.36. Found: C, 70.59; H, 6.22.

9,9′-Bis(4″-acetoxy-3″,5″-di-*tert*-butylphenyl)-9,9′-bifluorenyl Peroxide (21). A stream of oxygen was passed into a solution of **18b** (150 mg, 0.182 mmol) in refluxing benzene (50 ml). After 1 hr about 90% of the benzene was removed by vacuum evaporation. Addition of ethanol (50 ml) followed by further vacuum evaporation of solvent gave a colorless, crystalline precipitate which was recrystallized by dissolving in methylene chloride and adding methanol to give 140 mg (90%) (after drying under vacuum at 100° for 2 hr): mp 209–211°; ir 1760 cm^{-1}; NMR 7.75–7.15 (m, 16), 6.93 (s, 4), 2.23 (s, 6), 1.07 ppm (s, 36).

Anal. Calcd for $C_{58}H_{62}O_6$ (855.14): C, 81.47; H, 7.31. Found: C, 81.13; H, 7.26.

ESR Measurements. The ESR spectrum (Figure 2) was obtained at 98° by using a degassed solution of dimer **18b** in xylene which had been distilled from sodium. The kinetic experiment was performed in anisole solution by measuring the signal intensity S as function of the temperature between 75 and 120°. The ΔH of the equilibrium between **17b** and **18b** was obtained from a plot of ln S vs. T^{-1} using the least-squares method.

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Registry No.—**2b**, 13131-76-5; **3**, 57196-25-5; **4a**, 128-39-2; **4b**, 576-26-1; **4c**, 2219-82-1; **4d**, 2432-11-3; **4e**, 96-76-4; **4f**, 91-10-1; **4g**, 100-66-3; **5a**, 57196-26-6; **5b**, 57196-27-7; **5c**, 57196-28-8; **5d**, 57196-29-9; **5e**, 57196-30-2; **5f**, 57196-31-3; **5g**, 57196-32-4; **6**, 57196-33-5; **7**, 57196-34-6; **8**, 57196-35-7; **9**, 57196-36-8; **10a**, 13145-53-4; **10b**, 57196-37-9; **11a**, 57196-38-0; **11b**, 57196-39-1; **11c**, 57196-40-4; **11d**, 57196-41-5; **11e**, 57196-42-6; **12**, 57196-43-7; **13**, 57196-44-8; **14**, 57196-45-9; **15a**, 57196-46-0; **15b**, 57196-47-1; **15c**, 57196-48-2; **15d**, 57196-49-3; **16**, 57196-50-6; **18a**, 57196-51-7; **18b**, 57196-52-8; **19**, 57196-53-9; **20**, 57196-54-0; **21**, 57196-55-1; 2,6-di-*tert*-butyl-1,4-benzoquinone, 719-22-2; fluorenylidenetriphenylphosphorane, 4756-25-6; acetic anhydride, 108-24-7; 9-bromofluorene, 1940-57-4; 2,3-dichloro-5,6-dicyano-*p*-benzoquinone, 84-58-2; methanol, 67-56-1; potassium hydroxide, 1310-58-3; sodium methoxide, 124-41-4; sodium cyanide, 143-33-9; dimethyl sulfone, 67-71-0; fluorene, 86-73-7; phenyllithium, 591-51-5; isopropylamine, 75-31-0; cyclohexylamine, 108-91-8; morpholine, 110-91-8; pyrrolidine, 123-75-1; phenylbromide, 108-86-1; *N*-bromosuccinimide, 128-05-8.

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Reaction of Substituted Malachite Green Cations with Cyanide Ion

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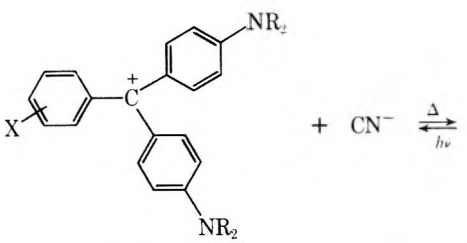
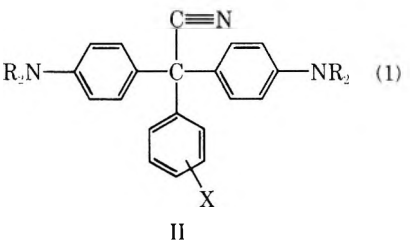
The reaction rate constants and the activation parameters for the reaction of cyanide ion with a variety of substituted triarylmethane carbocations have been measured in dimethyl sulfoxide (Me_2SO) containing 8% water by volume. The reaction is second order overall and first order with respect to each reactant. The nucleophilicity system parameter ($N_+ = 8.1$) indicates a nucleophilic system much like that found in pure Me_2SO. The slope of the Hammett plot ($\rho = 0.647$) and the large negative "salt effect" closely resemble the results found for reactions of these carbocations in water, indicating a similar transition state structure and mechanism.

The reaction of the stable triarylmethyl cations (i.e., primarily dye cations) with a variety of nucleophiles in a number of solvents has been studied extensively.[1] The reaction of the cyanide nucleophile with this class of dye carbocation (I) has been shown to be a kinetically straightforward anion–cation recombination, which can be easily followed by spectrophotometry at low concentrations because of the very high extinction coefficients of the cations (ϵ 10^5 M^{-1}). The relatively slow reaction to form the covalent triarylmethane leuconitrile (II) has been treated as a nucleophilic attack involving an ion pair at the transition state.[2] More recently it has been considered as a reaction involving the reorganization of the solvent structure around a one solvent separated ion pair,[3] as a critical factor at the transition state.

The present work will examine the reactions of cyanide ion with a variety of substituted triarylmethane cations (eq 1) in dimethyl sulfoxide containing 8% water by volume, in order to measure the activation parameters of these reactions and to determine further applicability of the linear free energy relationship to a series of triarylmethanes[4] carrying a larger number of substituents than the series studied by previous investigators.



I



II (1)

Results

The reactions of the carbonium ions with cyanide ions in dimethyl sulfoxide (Me_2SO) containing 8% water were studied by irradiating a solution containing the leuconitrile of the dye and potassium cyanide. The irradiation, which was carried out in a spectrophotometer, produced the desired dye cation in concentration of ca. 10^{-6} *M*. The reaction kinetics with excess cyanide (ca. 10^{-5}–10^{-3} *M*) are pseudo-first-order with respect to the dye, to at least 90% completion. The plots of the pseudo-first-order rate constants (k_{ps}) are linear in all cases with respect to the cyanide ion concentration over a wide range (20–500 ×), Figure 1. As would be expected, all the carbonium ions were found to follow excellent second-order kinetics in their reactions with cyanide ion.

Certain salts have been shown to cause retardation of the pseudo-first-order rates of this reaction, as shown by an inverse relation between k_{ps} and salt concentration.[2,5] Although we also found that some salts have a strong retarding effect on the rate (vide infra), potassium cyanide did not display such as effect, nor did it cause side reactions.

An 8% aqueous Me_2SO resolution containing potassium cyanide, even at the low concentrations used in the kinetic studies, will contain hydroxyl ions formed by the hydrolysis of the salt. The concentration of these ions was measured using apparatus similar to that described by Ritchie and Unschold.[6] The hydroxide ion concentration in this solvent was found to be similar to the calculated concentrations assuming a mixture of solvents. Over the range of potassium cyanide concentrations studied, the hydroxyl ion concentration is smaller than that of the cyanide ion by as much

Table I
Second-Order Rate Constants

Registry no.	Compd X	R_2	Temp, °C	n^a	$k_2{}^b$	r^c
7438-46-2	p-N(CH_3)$_2$	CH_3	15.00	5	44.37 (16.15)	0.992
			20.00	9	61.69 (10.29)	0.985
			28.00	3	104.3 (2.6)	0.9996
			30.00	3	134.7 (16.5)	0.998
			35.05	7	134.3 (58.5)	0.985
			40.00	3	190.2 (71.0)	0.994
			45.00	4	244.7 (41.7)	0.955
			50.00	8	669.1 (362.4)	0.950
57049-32-8	p-Phenoxy	CH_3	17.40	6	244.0 (51.5)	0.978
			30.00	7	404.3 (96.4)	0.982
			50.00	5	1133. (92.)	0.983
42297-53-0	p-CH_3O	CH_3	18.70	9	169.9 (37.2)	0.950
			40.00	7	592.7 (55.9)	0.990
			60.00	5	1908. (215.)	0.956
17717-39-4	p-CH_3	CH_3	17.50	8	194.4 (49.8)	0.962
			35.00	9	575.6 (112.9)	0.978
			50.80	7	1447. (204.)	0.967
10309-95-2	H	CH_3	20.00	3	259.6 (5.0)	0.985
			30.00	7	619.6 (32.5)	0.987
			40.00	3	1225. (63.)	0.999
42297-52-9	m-CH_3O	CH_3	17.50	6	159.7 (31.1)	0.989
			30.00	9	365.6 (81.9)	0.943
			35.00	7	641.6 (122.1)	0.975
			50.00	9	951.0 (43.9)	0.956
34101-54-7	m-CF_3	CH_3	17.40	6	604.4 (268.8)	0.985
			30.00	11	912.7 (219.6)	0.969
			50.00	5	2709. (329.)	0.973
34101-55-8	p-CF_3	CH_3	18.65	7	725.7 (111.3)	0.975
			30.00	2	1194. (23.)	*d*
			35.35	4	1581. (257.)	0.989
			50.10	3	2324. (8.)	0.910
25501-72-8	o-Cl	CH_3	17.00	4	18.00 (6.28)	0.962
			30.00	8	68.29 (13.57)	0.989
			50.00	3	130.0 (17.9)	0.994
			60.00	5	243.5 (35.7)	0.970
57049-33-9	H	H	19.50	7	263.3 (18.1)	0.980
			40.00	7	577.8 (14.7)	0.993
			60.00	15	1427. (475.)	0.907

[a] Number of runs. [b] Maximum of errors in parentheses. [c] Linear correlation coefficient for k_{ps} against CN^-. [d] Only one concentration measured at this temperature.

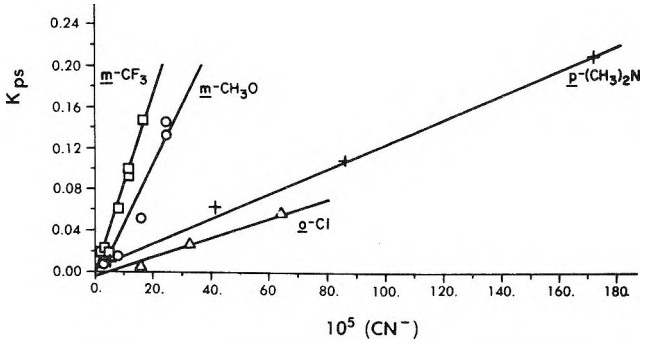


Figure 1. Dependence of the pseudo-first-order rate constants at 30°C for the conversion of I to II upon the concentration of cyanide ion. Experimental points are given for X = m-CF_3 (□), p-CH_3O (○), p-$(CH_3)_2N$ (+), and o-Cl (△).

as a factor of 25 at 10^{-3} *M* potassium cyanide, and approaches the cyanide ion only at very low (10^{-5} *M*) concentrations.

The expected effect of these ions, an increase in values of k_{ps}, was not apparent at the lowest cyanide concentrations ($<10^{-4}$ *M*), where the concentration of the hydroxyl ion approaches that of cyanide ion. A control run using the reaction of malachite green cation with hydroxide showed the relative nucleophilicity of hydroxide ion in 8% aqueous Me_2SO to be less than that of cyanide ion by a factor of ca. 5. Thus, the effect of hydroxide ion or any other nucleophile was not found; good linear correlation was obtained between k_{ps} and cyanide ion concentration for all the dyes at a given temperature. Thus, the kinetics of the reactions of the carbonium ions with cyanide could be studied without the use of buffer solutions, which themselves could cause difficulties by introducing their own salt effects.

At the higher temperatures with the more reactive compounds, there were indeed some indications of an increase in the rate constant leading toward plot curvature (k_{ps} vs. CN^-). However, this curvature did not cause unacceptable linear correlations, nor cause deviations from the excellent second-order kinetics at these concentrations. It is of interest that the cyanide ion concentrations studied ranged from 20-fold in the case of the most reactive compounds to 500-fold in the case of the least reactive dye cation. Over this extremely large range the data showed excellent correlation with the expected second-order kinetics and results were consistent with the rate law in eq 2.

$$\text{rate} = k_2 [\text{dye cation}^+] [CN^-] \quad (2)$$

The second-order rate constants (k_2) determined at a number of temperatures, are reported in Table I together with the linear correlation coefficients for the plot of k_{ps} against counterion concentration at each temperature.

Our rate constant values for the reaction of two of the dyes with cyanide, are, as expected from the earlier work by Ritchie,[5] substantially smaller than the rate constants in pure anhydrous Me_2SO by at least one order of magnitude, and larger than the rate in water by three orders of magnitude. In particular, when the rate constants at 25° for the

Table II
Activation Parameters for the Reaction of Triarylmethyl Cations with Cyanide Ion

Dye cation	Substituent X	Substituent R	r^a	E_a, kcal mol^{-1}	Log A	k_2 at 30°
Crystal violet	p-$N(CH_3)_2$	CH_3	0.986	11.0	10.0	134.7
	p-Phenoxy	CH_3	0.996	8.74	8.95	404.3
New green	p-CH_3O	CH_3	0.999	11.0	10.5	341.6[b]
	p-CH_3	CH_3	0.9999	11.2	10.7	431.7[b]
Malachite green	H	CH_3	0.999	14.5	13.2	619.6
	m-CH_3O	CH_3	0.988	10.4	10.1	365.6
	m-CF_3	CH_3	0.985	8.65	9.26	912.7
	p-CF_3	CH_3	0.997	6.81	7.97	1153.
	o-Cl	CH_3	0.976	11.5	9.96	68.29
Doebner's violet	H	H	0.998	7.14	7.75	400.3[b]

[a] Weighted linear correlation coefficient. [b] Calculated from the Arrhenius plot.

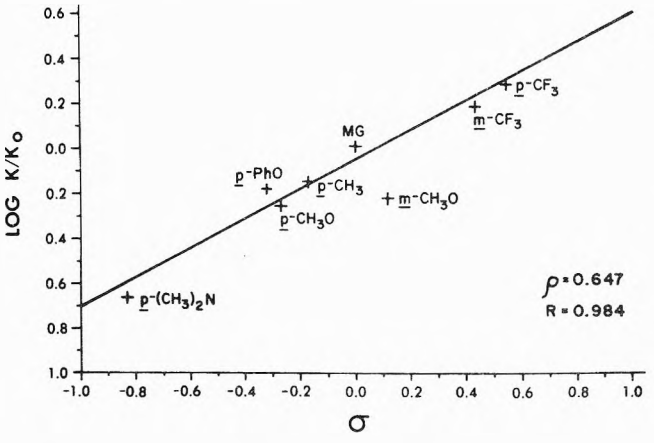


Figure 2. Correlation of the rates of combination at 30°C with the Hammett σ substitution parameters.

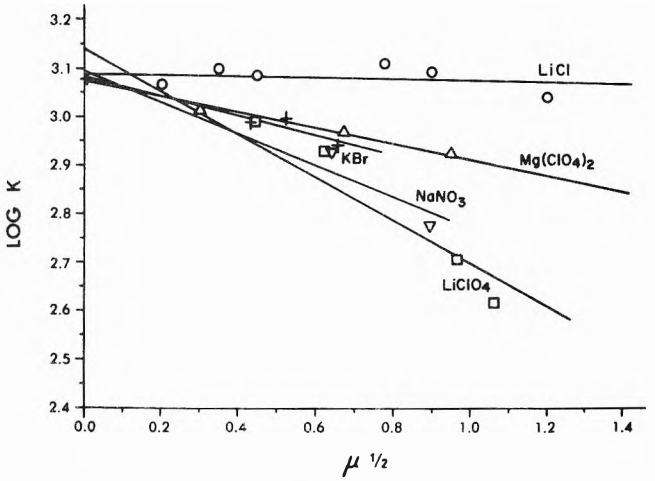


Figure 3. Effect of salts upon the reaction of p-CF_3 malachite green cation with cyanide ion at 30°C. Symbols follow: ○, LiCl; △, $Mg(ClO_4)_2$; +, KBr; ▽, $NaNO_3$; and □, $LiClO_4$.

malachite green and crystal violet cations were calculated from their Arrhenius plots (395.4 and 86.8 M^{-1} sec^{-1}, respectively), and were used with Ritchie's rate values for the reaction of these cations with water (3.8×10^{-6} and 6.3×10^{-7} M^- sec^{-1})[5], the values for N_+, the nucleophilicity system parameter of Ritchie,[3] were obtained.

$$N_+ = \log (k_n/k_{H_2O}) = \log \left(\frac{395.4}{3.8 \times 10^{-6}}\right) = 8.0 \quad (3)$$

$$\log \left(\frac{86.8}{6.3 \times 10^{-7}}\right) = 8.1 \quad (4)$$

These are consistent values which indicate a nucleophilic system much like that found by Ritchie with pure Me_2SO ($N_+ = 8.6$),[7,8] but with a reduced nucleophilicity, attributable to the presence of water, which solvates anions more effectively than the aprotic solvent.[10]

The activation parameters for the reaction of the carbocations examined are collected in Table II, together with the weighted linear correlation coefficients. The E_a values are slightly lower than those reported for other reactions of these dye cations indicating that the transition state is energetically favored in the present solvent system.[9]

Figure 2, the Hammett plot, shows that the reaction rate depends upon the electron density on the central carbon atom; electron-donating substituents decrease the rate while electron-withdrawing substituents increase it. The slope ($\rho = 0.647$) is very similar to that of the reaction of these dye cations with cyanide in water (0.693),[11] but less than that found in pure DMF or Me_2SO (1.11 and 1.12, respectively[11]).

The effect of salts upon the rate of reaction of the p-trifluoromethyl derivative of malachite green was also studied (Figure 3). This work was carried out at salt concentrations much higher than those for which theoretical treatments are applicable, but the plots of log k_2 against $\mu_{1/2}$ were linear for most salts. A "salt effect" was expected from the simple electrostatic treatment. It was found to be the same as reported for the reaction in aqueous solutions.[5] The large negative effect is much like that seen earlier by Bunton and Huang[1] at high salt concentrations for the reaction of trianisylmethane cation with hydroxide ion. Like them we found that the effect is most pronounced with lithium perchlorate, but our data, unlike theirs, indicate that $NaNO_3$ has a greater effect than LiCl, which has no detectable effect. The observed order upon the rate constant was $LiClO_4 < NaNO_3 < KBr < Mg(ClO_4)_2 <$ no salt = LiCl, whereas Bunton and Huang reported the order $LiClO_4 <$ LiCl $< NaNO_3 <$ no salt.

The results of this work are consistent with earlier investigations of nucleophilic attack upon stable carbocations. The activation parameters, the slope of the Hammett plot, and the large negative salt effects closely resemble the results found for the reaction of the triarylmethyl cations in water, indicating similar transition state structure and mechanism in the formation of leuconitrile from the dye cation.

Experimental Section[16]

Materials. Water was doubly distilled from potassium permanganate. Dimethyl sulfoxide (Fisher spectroanalyzed) was purged with nitrogen and used without further purification. The solvent was dimethyl sulfoxide containing 8% water by volume.

Potassium cyanide (ROC/RIC 99.5% grade) was used without further purification. The other inorganic salts were commercial reagent grade samples and were dried before use.

The leuconitriles of the triarylmethane dyes were prepared by

Table III
Physical Constants of the Triarylmethane Compounds

Substituents		Leucocarbinol		Dye		Leuconitrile[e]	
		mp, °C		95% EtOH	8% Me_2SO	mp, °C	
X	R	Obsd	Lit.	λ_{max} (10^5 ϵ)	λ_{max} (10^5 ϵ)	Obsd	Lit.
H	CH_3	160–162	163[b]	622 (10.63)	631.5 (9.63), 431 (1.84)[a] 631.5 (9.66), 431 (1.57)[h]	176–177	176–177[f]
p-$(CH_3)_2N$	CH_3		190[b]	589 (11.3)	603 (11.0)[h]	293	294–295.6[g]
p-CH_3O	CH_3	129–130	154[b]	610.5 (9.89)	621.5 (8.62), 466.5 (2.59)[a]	230–232	
p-Phenoxy	CH_3	147–148		616 (10.3)	628 (9.25), 458 (2.59)[a]	154–155	
p-CH_3	CH_3	157–159	151[b]	618 (10.6)	629 (9.82), 442.6 (1.59)[a]	211–212	
m-CH_3O	CH_3	149–151	151[b]	637 (9.89)	636.5 (8.79), 437.2 (1.42)[a]	145.5–147.5	
m-CF_3	CH_3	[d]	145–146[c]	634 (9.66)	641 (4.62), 428 (0.960)[i]	164–165	
p-CF_3	CH_3	187–188	181–182[c]	636 (9.93)	646.5 (7.49), 427 (1.16)[a]	201–202	
o-Cl	CH_3			640 (12.6)	642 (6.04)[h]	200.5	
H	H			564 (10.2)	584 (6.96), 404 (1.52)[h]	226–227	

[a] By acidification of alcohol. [b] Reference 4a. [c] Reference 4b. [d] Isolated as an oil. [e] Correct analyses were found for all new compounds (±0.4% for C, H, and N). [f] Reference 13. [g] L. Harris, J. Kamimsky, and R. G. Simard, *J. Am. Chem. Soc.*, 57, 115 (1935). [h] By irradiation of leuconitrile. [i] By chloranil oxidation.

treatment of dye cation with excess cyanide ion in dimethyl sulfoxide.[12]

The dye cation or its leucocarbinol (1 g) was dissolved in 25 ml of Me_2SO on the steam bath, and a double excess of hydrochloric acid (ca. 0.5 ml in 5 ml of water) was added. The resulting solution of dye was treated with 0.7 g (0.108 mol) of potassium cyanide and the mixture was stirred until the solution decolorized. At this time, the mixture was filtered, the filter pack washed with 10 ml of hot 95% ethanol, and the filtrate heated. Water (ca. 10 ml) was added slowly with stirring, to fog the resulting solution. The fogged mixture was then digested on the hot plate and cooled to give crystals. The crystals were separated, washed with water, and repeatedly recrystallized from a chloroform–ethanol mixture to give a constant melting point. Physical constants for the leuconitriles are shown in Table III.

Those dyes which were not commercially available could be obtained as their leucocarbinols (1) by the addition of the appropriate phenylsodium salt to Michler's ketone in toluene,[13] (2) by the addition of the phenyllithium salt in ether.[4b] When these one-step routes were unsuccessful, as in the case of Doebner's violet[14] and the m-trifluoromethyl compound, (3) the conventional condensation–oxidation method used by Ritchie[4a] was employed.

The dye cations were produced by three different methods and their absorbances then measured. The methods were (1) acidification of the dye leucocarbinol in 95% ethanol with a slight excess of hydrochloric acid; (2) irradiation[15] of the easily purified dye leuconitriles of Doebner's violet and the commercially obtained dyes; or (3) utilization of the quantitative[4c] chloranil oxidation to produce the cation in situ from the pure leucobase of the m-trifluoromethyl compound. The extinction coefficients (Table III) were determined by Beer's law linear regressions on the absorbance data of the cations and agree well with previously reported values.[4]

The spectra of the dye cations were then measured in 8% aqueous Me_2SO at different concentrations over the range used for kinetic studies. The extinction coefficients at the λ_{max} were determined by the same methods used with ethanol for the compounds. The absorption of the cations does not deviate from Beer's law in the concentration range measured. All spectra were measured on a Cary 17I spectrophotometer and the linear regressions on the data for the Beer's law were carried out on a Hewlett-Packard 9810A calculator.

Apparatus. Measurements of hydroxyl ion in aqueous Me_2SO were carried out using a Beckman Research pH meter, Model 1019, with H-cell similar to that described by Ritchie and Unschold,[6] a silver billet electrode (Beckman no. 39261), and Beckman E-2 electrode (no. 39099). The meter was operated on the millivolt scale and standardized with solutions of potassium hydroxide in 8% Me_2SO over a range of 10^{-5}–10^{-3} M base. In these cases good adherence to the Nerst equation was observed.

For the kinetic measurements, a Cary Model 17I spectrometer was equipped with a special compartment cover, and a thermostatted cell which could be kept ±0.05°C by means of water circulated from a constant-temperature bath. The cover contained a 100-W Hanovia high-pressure quartz mercury-vapor light source mounted in front of a parabolic reflector, with provision to insert a flint glass filter to remove the short-wavelength light. The cover had light-baffled venting and provision for air circulation to prevent overheating of the cell compartment and to prevent large ozone concentrations. In addition a heavy duty solenoid was mounted on this cover to close the shutter of the spectrophotometer detector to protect the detector when the mercury lamp was on.

Kinetics. Stock solutions of the leuconitriles and of the salts were prepared in Me_2SO containing 8% water by volume. These solutions were used to prepare reaction mixtures with concentrations of approximately 5×10^{-5} M in leuconitrile and with the desired concentrations of counterion (10^{-5}–10^{-3} M). The reaction was initiated by approximately 1-min irradiation with the mercury vapor lamp which produced the dye cation in a 5- or 10-cm thermostatted cell with less than a 10% conversion of the leuconitrile. At the completion of the decoloration reactions (i.e., when the absorbance had returned to zero) no absorbances that could be attributed to side products produced by irradiation were evident. Only after repeated or lengthy exposure of a solution did the absorbances due to decomposition become significant.

The change in absorbance was measured from the time the initiating lamp turned off until the reaction was completed. Three or more repetitions at each set of concentrations were carried out using fresh solutions. These were followed by measuring the change of absorbance at the wavelength of maximum absorbance of the dye at a known chart speed. These values were converted to concentrations using a digitizer and a Hewlett-Packard 9810A desk calculator, which was also used to calculate the rate constants using a linear regression technique. The data, when treated as pseudo-first-order, and as second order with respect to dye and cyanide concentrations, gave excellent correlations for up to 3 half-lives and greater than 90% completion of reaction. Correlation coefficients of at least 0.98 (usually 0.999) were obtained with data averaged from each set of replications. The second-order rate constant was calculated as the mean of all the rate constants obtained at a given temperature.

Acknowledgment. We wish to thank Drs. J. H. Cornell and M. Nakashima for their valuable discussions of the work with M. L. Herz. Our thanks also to Mr. T. Metcalf for his assistance in measuring the effect of salts on the reaction.

Registry No.—Leucocarbinol (X = H; R = CH_3), 510-13-4; leucocarbinol (X = p-$(CH_3)_2N$; R = CH_3), 467-63-0; leucocarbinol (X = p-CH_3O; R = CH_3), 10165-76-1; leucocarbinol (X = p-PhO; R = CH_3), 57049-34-0; leucocarbinol (X = p-CH_3; R = CH_3), 10249-42-0; leucocarbinol (X = m-CH_3O; R = CH_3), 10165-77-2; leucocarbinol (X = m-CF_3; R = CH_3), 28316-15-6; leucocarbinol (X = p-CF_3; R = CH_3), 28316-16-7; leucocarbinol (X = o-Cl; R = CH_3), 596-42-9; leucocarbinol (X = H; R = H), 57049-35-1; leuconitrile (X = H; R = CH_3), 4468-56-8; leuconitrile (X = p-$(CH_3)_2N$; R = CH_3), 4439-06-9; leuconitrile (X = p-CH_3O; R = CH_3), 57049-36-2; leuconitrile (X = p-phenoxy; R = CH_3), 57049-37-3; leuconitrile (X = p-CH_3; R = CH_3), 57049-38-4; leuconitrile (X = m-CH_3O; R = CH_3), 57049-39-5; leuconitrile (X = m-CF_3; R = CH_3), 57049-40-8; leuconitrile (X = p-CF_3; R = CH_3), 57049-41-9; leuconitrile (X = o-Cl; R = CH_3), 57049-42-0; leuconitrile (X = R = H), 57049-43-1; potassium cyanide, 151-50-8.

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Catalysis of the Reaction of Morpholine with Phenyl Benzenethiolsulfonate by Halide Ions and Thiocyanate. Possible Evidence for an Intermediate on the Reaction Coordinate in a Substitution at Sulfenyl Sulfur[1a]

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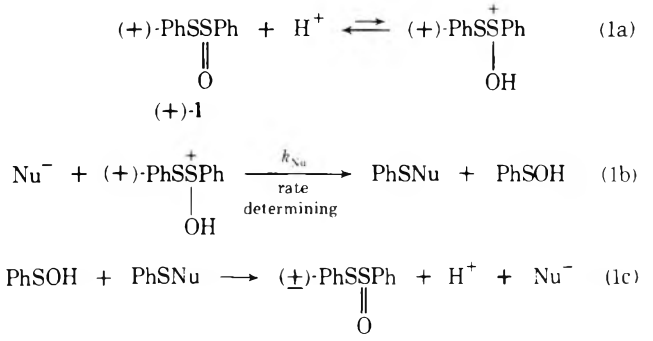
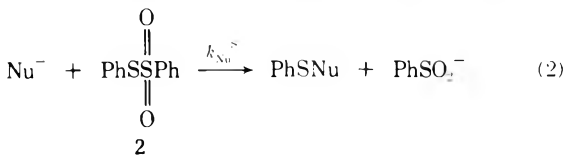
The reaction of morpholine with phenyl benzenethiolsulfonate (**2**) in aqueous dioxane to form the sulfenamide can be catalyzed by the addition of bromide, iodide, or thiocyanate ions. Data on their catalytic effectiveness can be used to measure the rates of attack of each of these three nucleophiles on the sulfenyl sulfur of **2**. One finds that SCN^- is 6.3 times more reactive than I^- and 19 times more reactive than Br^-. This reactivity pattern is markedly different than the one previously observed for attack of the same nuclophiles on the sulfenyl sulfur of $PhSS^+(OH)Ph$; there (k_{Nu}/k_{Br}) is SCN^-, 150; I^-, 400; Br^-, (1.0). It is shown that this marked change in reactivity pattern can be easily explained if nucleophilic attack on the sulfenyl sulfur of **2** by these nucleophiles involves an addition–elimination mechanism with an intermediate (**4**) on the reaction coordinate, and with loss of $PhSO_2^-$ from **4** being rate determining, while in the case of $PhSS^+(OH)Ph$ attack of the nucleophile is instead rate determining.

In aqueous dioxane optically active phenyl benzenethiolsulfinate, (+)-**1**, undergoes an acid- and nucleophile-catalyzed racemization via the mechanism shown in eq 1.[2] Both iodide and thiocyanate ion are much more reactive than bromide ion as catalysts for this reaction, k_{Nu}/k_{Br} being 400 for I^- and 150 for SCN^-.



Phenyl benzenethiolsulfonate (**2**) undergoes nucleophilic substitution reactions (eq 2) easily with many nucleophiles, and we have recently reported[3] kinetic data on the reactivity of 15 common nucleophiles toward **2** in aqueous dioxane.



Thiocyanate ion and the halide ions were not among the nucleophiles studied, however, because of several complications. First, benzenesulfenyl halides undergo hydrolysis easily in aqueous dioxane, and under some conditions[4] the hydrolysis product, the sulfenic acid PhSOH, can react readily with **2** to produce **1**; this has the potential for greatly complicating the kinetics. Second, the reaction of $PhSO_2^-$ with PhSX (reverse of eq 2 for Nu = X) can be fast enough compared to hydrolysis of PhSX so that, even if subsequent reactions of PhSOH produce no kinetic complications, reversal of attack of X^- on **2** can be kinetically significant, and one cannot equate k_X^S with the rate of disappearance of **2**, since attack of X^- on **2** will not be rate determining.

These several complications to determining the reactivity of halides and thiocyanate toward **2** can be circumvented if one can find some other nucleophile to add to the reaction medium which, at the concentration employed, is reactive enough toward PhSX compared to water or $PhSO_2^-$ so that it will capture essentially every PhSX produced by eq 2 before they can react with either water or $PhSO_2^-$. This added nucleophile should also react with PhSX to give a product which will be stable under the reaction conditions. The only other requirement is that the nucleophile added to trap PhSX must not itself react directly with **2** at too rapid a rate. If it does, the contribution of the X^--induced disappearance of **2** to the overall rate will be too small to be detected.

It appeared to us that morpholine might meet all the re-

Table I
Kinetics of the Nucleophile-Catalyzed Reaction of Morpholine with Phenyl Benzenethiolsulfonate (2) in 60% Dioxane at 25°[a]

Nucleophile	[Morpholine] = [morpholine H^+], M	[Nu^-], M	$10^3 k_{exp}$, sec^{-1}	k_X^S = ($k_{exp} - k_M$[morph])/[Nu^-], M^{-1} sec^{-1}
None	0.01	0.00	3.3	
SCN^-	0.01	0.01	6.8	0.25
		0.03	10.9	0.25
I^-	0.01	0.03	4.5 ± 0.1	0.039
		0.05	5.3 ± 0.1	0.038
Br^-	0.01	0.03	3.7 ± 0.1	0.013
		0.05	4.0 ± 0.1	0.013

[a] All runs at a constant ionic strength of 0.04 except those containing 0.05 M Br^- or I^-. In these runs the ionic strength is 0.06. Data for each set of conditions for iodide and bromide are average of several runs.

quirements just set forth. Thus, it would react readily with PhSX or PhSSCN to give a sulfenamide, and these are stable under the reaction conditions.[3] On the other hand, it is not too reactive toward 2.[3]

Indeed, we have found that it is possible to measure the reactivity of Br^-, I^-, and SCN^- toward 2 using morpholine to trap the reactive sulfenyl derivative formed in eq 2. The results are reported in this paper and are especially interesting because they indicate a quite different reactivity pattern for these three nucleophiles toward 2 than the one observed earlier[2] toward protonated 1. A possible explanation for this is presented.

Results

The kinetics of the disappearance of 2 (2×10^{-4} M) in 1:1 morpholine–morpholine H^+ buffers containing 0.01–0.04 M morpholine in 60% dioxane at 25° at a constant ionic strength of 0.04 have been previously measured.[3] In the present work the addition of 0.01–0.05 M bromide, iodide, or thiocyanate ion to such solutions was found to result in a definite increase in the rate of disappearance of 2. This was more marked with thiocyanate than with the two halide ions. Even though the concentration of $PhSO_2^-$ in these runs increases from zero at the start to a final value equal to $[2]_0$, there is no decrease during the course of a run in the experimental first-order rate constant for the disappearance of 2, showing that morpholine is trapping the reactive sulfenyl derivatives formed in eq 2 and preventing their return to 2 via reaction with the $PhSO_2^-$ produced. The experimental first-order rate constants for the disappearance of 2 under the various reaction conditions are summarized in Table I.

If the reaction scheme shown in Chart I applies under our reaction conditions, the experimental first-order rate constant for the disappearance of 2 in any given run will be given by

$$k_{exp} = k_M[\text{morph}] + k_X^S[X^-]$$

and for a given X^-

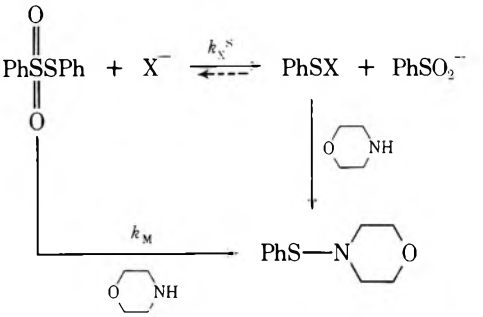
$$k_X^S = \frac{k_{exp} - k_M[\text{morph}]}{[X^-]}$$

should be a constant independent of the concentration of X^-. The last column of Table I shows that this is indeed the case. We therefore believe that the values of k_X^S shown in that column are accurate measures of the reactivity of Br^-, I^-, and SCN^- toward 2.

Discussion

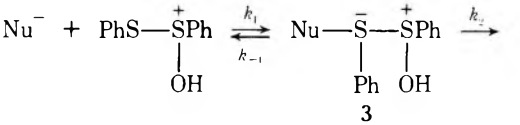
From the last column in Table I one sees that for eq 2 the reactivity toward 2 of I^- or SCN^-, as compared with Br^-, i.e., (k_{Nu}^S/k_{Br}^S), is SCN^-, 19; I^-, 3.0; Br^-, (1.0). This contrasts markedly with the reactivity pattern observed for these same three nucleophiles toward protonated 1, where (k_{Nu}/k_{Br}) for eq 1b is SCN^-, 150; I^-, 400; Br^-, (1.0). Particularly striking is the fact that SCN^- is more reactive than I^- toward 2 in the substitution at the sulfenyl sulfur in eq 2 while I^- is more reactive than SCN^- in the substitution at a sulfur of similar oxidation state in eq 1b. The only difference in the two substitutions is that in one the leaving group is $PhSO_2^-$ while in the other it is PhSOH.

Chart I
Mechanism of Catalysis of the Disappearance of 2 by Halide Ions and Thiocyanate in the Presence of Morpholine



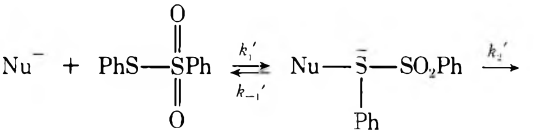
(X = Br^-, I^-, or SCN^-)

Can this peculiar change in the rate pattern be simply explained? We think that it can provided one assumes that the substitutions depicted in eq 1b and 2 do not actually involve synchronous bond making and bond breaking but instead occur in each case with the formation of an intermediate (3 or 4) as shown in eq 3a and 3b.



3

PhSNu + PhSOH (3a)



4

PhSNu + $PhSO_2^-$ (3b)

In eq 3a we feel that PhSOH will be a better leaving group than I^-, SCN^-, or Br^-, so that $k_2 > k_{-1}$ in all cases, with the result that attack of the nucleophile on protonated 1 (step k_1) will be rate determining, and the experimentally measured rate constants for the three nucleophiles will be directly proportional in each case to k_1.

On the other hand, in the reaction of Br^-, I^-, and SCN^- with **2** we think that each of these anions should be a better leaving group than $PhSO_2^-$, so that k_2'/k_{-1}' will be less than unity in all cases. In this situation step k_2', rather than attack of Nu^- on **2** (step k_1'), will be rate determining and k_{Nu}^S will be given by $k_1'k_2'/(k_{-1}' + k_2')$.

Furthermore, it would be reasonable to expect $k_2'/(k_{-1}' + k_2')$ to be considerably smaller for I^- than for the other two nucleophiles, because k_2' should be effectively independent of Nu^-, while k_{-1}' would probably be much larger for I^- than for either Br^- or SCN^-, since I^- is in all probability a considerably better leaving group than the other two anions. Thus, even though k_1' for I^- attacking **2** was larger than k_1' for SCN^- by about the same amount as in the attack of these two nucleophiles on protonated **1**, it would be easy for k_I^S to be significantly less than k_{SCN}^S, simply because $k_2'/(k_{-1}' + k_2')$ for I^- was so much smaller than $k_2'/(k_{-1}' + k_2')$ for SCN^-.

The presence of intermediates on the reaction coordinate in eq 3a and 3b and a change of rate-determining step from attack of Nu^- on protonated **1** to departure of $PhSO_2^-$ from **4** with a change in the leaving group ability of the group to be displaced in the substitution can thus provide a simple and straightforward rationalization for the marked difference in the reactivity pattern for Br^-, I^-, and SCN^- in eq 1b vs. eq 2. We recognize that other more complex explanations are doubtless conceivable. For this reason the difference in the reactivity pattern for the three nucleophiles toward the two substrates can be considered only as suggestive, rather than compelling, evidence for the presence of an intermediate on the reaction coordinate in the substitutions in question.

This is not the first occasion in which kinetic evidence of one type or another has been obtained suggestive of an intermediate being on the reaction coordinate in a simple nucleophilic substitution at sulfenyl sulfur. The work of Ciuffarin provides several additional examples.[5,6] While these, like the present example, are suggestive rather than compelling, and while there have been other cases[7,8] where the evidence seemed to point to synchronous bond making and bond breaking, rather than to an addition–elimination mechanism involving an intermediate, we feel that the present results and those of Ciuffarin,[5,6] together with the known ability of sulfur to expand its valence shell, make it generally desirable to picture nucleophilic substitutions at sulfenyl sulfur as proceeding through an intermediate, except in those specific cases where there is definite experimental evidence that bond making and bond breaking are synchronous.

Experimental Section

Preparation and Purification of Materials. The preparation and purification of phenyl benzenethiolsulfonate (**2**) and the purification of dioxane and morpholine followed previously described procedures.[3] Sodium thiocyanate, potassium iodide, potassium bromide, lithium perchlorate, and perchloric acid were all reagent grade and were used without further purification.

Procedure for Kinetic Runs. A 1:1 morpholine–morpholine H^+ buffer in 60% dioxane was prepared by adding a known amount of standard perchloric acid to a known amount of morpholine in 60% dioxane. To this was then added the appropriate amount of the catalyzing nucleophile (bromide, iodide, or thiocyanate) along with the amount of lithium perchlorate needed to bring the ionic strength up to the desired value. Four milliliters of this solution was thermostatted in a quartz uv cell in the cell compartment of a Perkin-Elmer Model 402 spectrophotometer. The reaction was then initiated by adding to this solution with efficient mixing 40 μl of a relatively concentrated stock solution of **2** in dioxane. The disappearance of **2** was then followed by monitoring the change in optical density at 272 nm. Plots of $\log (A - A_\infty)$ vs. time showed excellent linearity in every case and rate constants were reproducible to within ±3%. A run without added catalyzing nucleophile gave the same rate as previously observed by Kice, Rogers, and Warheit.[3]

Registry No.—**2**, 1212-08-4; morpholine, 110-91-8; thiocyanate, 302-04-5; iodide, 20461-54-5; bromide, 24959-67-9.

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New Synthesis of $S(Se)$-Alkylphosphorothio(seleno)lates from the Corresponding Phosphoroanilidates. Stereospecific Cleavage of the Phosphorus–Nitrogen Bond in Chiral Phosphoroanilidates

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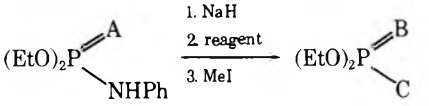
Reaction of sodio derivatives of phosphoroanilidates and their thio and seleno analogues with carbon disulfide or carbon dioxide, followed by treatment of the resulting phosphorothioate or phosphoroselenoate sodium salt with methyl iodide, gave the corresponding S or Se methyl esters. The stereochemistry of P–N bond cleavage was studied using optically active *O*-ethyl ethylphosphonoanilidate and *O*-ethyl ethylphosphonoanilidothioate and diastereoisomeric 2-*N*-phenylamino-2-oxo(-seleno, -thio)-4-methyl-1,3,2-dioxaphosphorinanes. In all cases P–N cleavage proceeds with high stereospecificity and retained configuration around the phosphorus atom. Chemical correlation of absolute configuration at phosphorus in a family of chiral ethylphosphonic acid derivatives is also described.

Although the reaction of anions derived from dialkyl phosphoroanilidates with carbonyl and thiocarbonyl compounds, leading to isocyanates, isothiocyanates, and carbodiimides, was described in the early sixties,[1] the fate of the

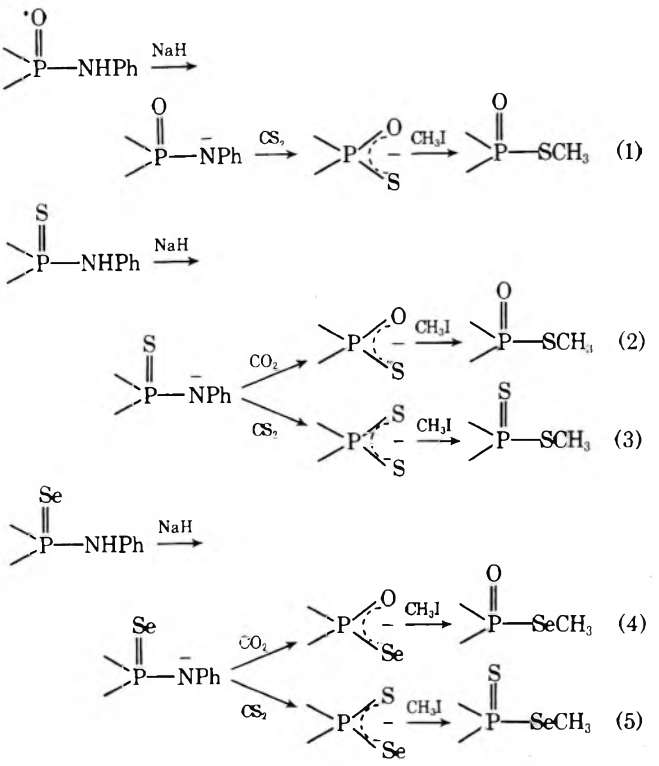
Table I



Expt	Substrate A	Mp or bp, °C (mmHg)	δ_{31P}, ppm	Ref	Reagent	Product B	C	Yield, %	Bp, °C (mmHg)	δ_{31P}, ppm	Ref
1	O	95–96	−2.3	23 mp 96.5°	CS_2	O	SCH_3	82	67–70 (1.5)	−28.5	25 bp 78.5–79° (3 mmHg)
2	S	114 (0.4)	−65.2	24 bp 136–137° (2.5 mmHg)	CO_2			71			
3					CS_2	S	SCH_3	74	50–52 (0.6)	−93.5	26 bp 53–55° (0.7 mmHg)
4	Se	122 (0.25)	−66.5	Anal. Calcd for $C_{10}H_{16}O_2PNSe$: C, 41.12; H, 5.52; P, 10.60; N, 4.79. Found: C, 41.58; H, 5.63; P, 10.96; N, 4.60.	CO_2	O	$SeCH_3$	76	88–90 (1.5)	−19.7	27 bp 100° (4 mmHg)
5					CS_2	S	$SeCH_3$	64	70–72 (0.6)	−83.5	Anal. Calcd for $C_5H_{13}O_2PSSe$: C, 24.28; H, 5.32; P, 12.54. Found: C, 24.17; H, 5.49; P, 12.84.

phosphorus residue and the stereochemistry of its formation has not, to our knowledge, been investigated. By analogy with the Wittig reaction[2] it was reasonable to assume that retention of configuration at phosphorus would accompany the conversion of a chiral anilide or thioanilide into the corresponding phosphorus-containing anion.

In this investigation we have studied the conversion of phosphoroanilidates and their thio and seleno analogues to the corresponding thiolo and selenolo esters summarized in eq 1–5.



The thiolo and selenolo esters obtained are reactive intermediates in their own right, very useful in synthesis of acid anhydrides or other products resulting from nucleophilic displacement at a phosphorus atom. Special attention has been paid to the stereochemistry of the phosphorus moiety in those cases where enantiomeric or diastereoisomeric compounds could be used.

The possibility of converting phosphoroamidates into phosphorus derivatives containing other functional groups was exploited to a limited extent.

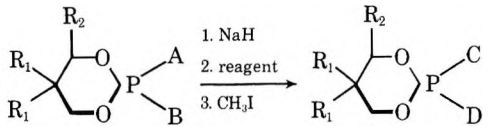
Earlier methods of cleavage of the P–N bond are those involving hydrogen chloride[3] or acidic solvolysis.[4] However, hydrogen chloride reacts stereospecifically only with sterically hindered 2-aminophosphetanes.[5] Acyclic, optically active *N*-benzylphenylmethylphosphinothioamidate reacts with hydrogen chloride with complete loss of optical activity of the resulting phenylmethylphosphinochloridothionate.[5] Recently reported results on methanolysis of methylphenylphosphinoanilidate indicate an acidity-dependent merged dissociative (A-1) and associative (A-2) mechanism for this process.[6] No complete racemization (100% A-1 mechanism) was observed even under strong acidic conditions. In optimal solvolytic conditions 78% stereospecificity, with inversion at phosphorus, was observed. Reaction of phosphorodianilidates with amyl nitrite, leading to the removal of the aniline moiety, has been applied in the field of phosphorylation of nucleosides.[7] It was not explored in cases where stereochemistry at chiral phosphorus molecule could be used.

Taking into account that cleavage of the P–N bond can be applied for preparation of optically active phosphorus derivatives via diastereoisomeric phosphoroamidates, we undertook to study the best conditions under which such reactions proceed.

Results and Discussion

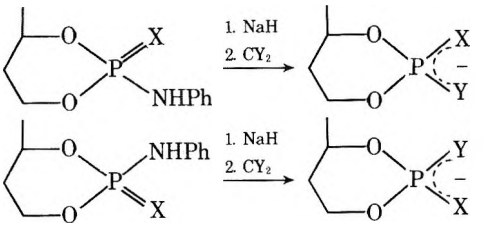
At first the reaction of diethylphosphoroanilidate anion with carbon disulfide, followed by alkylation of the resulting diethylphosphorothioate anion with methyl iodide (eq 1), was used as a simple achiral model. *O,O*-Diethyl-*S*-methyl phosphorothioate was isolated in 82% yield. Reactions of diethyl thio- and selenophosphoroanilidates were also carried out. The anion generated with sodium hydride in dioxane solution was allowed to react with carbon dioxide (eq 2, 4) and/or with carbon disulfide (eq 3, 5). Alkylation of the resulting sodium salts gave corresponding thiolo or selenolo esters in good yields, as shown in Table I. Similar results were obtained when 2-*N*-phenylamino-2-X-1,3,2-dioxaphosphorinanes (X = O, S, Se) were employed in our studies (see Table II). Reactions of *cis*- and *trans*-2-*N*-phenylamino-2-X-4-methyl-1,3,2-dioxaphosphorinanes (X = O, S, Se; Table II, expt 6–14) are of special interest.

Table II.



	Substrate							Reagent	Product						
Expt	R_1	R_2	A	B	Mp, °C	δ_{31P}, ppm	Ref		C	D	Yield %	δ_{31P}, ppm	SS,[b] %	Mp or bp, °C (mmHg)	Ref
1	CH_3	H	O	NHPh	167	+2.6	Anal. Calcd for $C_{11}H_{16}O_3NP$: C, 54.77; H, 6.68; N, 5.81; P, 12.84. Found: C, 54.91; H, 6.62; N, 5.91; P, 12.60.	CS_2	O	SCH_3	83	−22.5		81–82	28, mp 81–81.5°
2	CH_3	H	S	NHPh	175–176	−62.5	Anal. Calcd for $C_{11}H_{16}O_2NPS$: C, 51.35; H, 6.37; N, 5.48; P, 12.04. Found: C, 51.63; H, 6.42; N, 5.54; P, 12.31.	CO_2	O	SCH_3	57	−22.5		81–82	See expt 1
3								CS_2	S	SCH_3	68	−90.0		85–86	28, mp 85.5–86°
4	CH_3	H	Se	NHPh	175–176	−62.0	Anal. Calcd for $C_{11}H_{16}O_2NPSe$: C, 43.44; H, 5.29; N, 4.61; P, 10.15. Found: C, 43.14; H, 5.49; P, 10.51; N, 5.00.	CO_2	O	$SeCH_3$	76	−13.8		90–92	Anal. Calcd for $C_6H_{13}O_3PSe$: C, 29.65; H, 5.39; P, 12.74%. Found: C, 29.52; H, 5.58; P, 13.01.
5								CS_2	S	$SeCH_3$	72	−80.0		71–73	Anal. Calcd for $C_6H_{13}O_2PSSe$: C, 27.81; H, 5.08; P, 12.19. Found: C, 27.80; H, 5.15; P, 12.39.
6	H	CH_3	NHPh	O	173–175	+1.0	8, mp 174–176° δ_{31P} +1.1 ppm	CS_2	SCH_3	O	62	−23.5	100	110–115 (0.2)	29, δ_{31P}, −22.8 ppm
7	H	CH_3	O	NHPh	153–155	+4.5	8, mp 154–156° δ_{31P} +3.5 ppm	CS_2	O	SCH_3	58	−19.5	100	76–77	29, mp 77–77.5° δ_{31P} −18.1 ppm
8	H	CH_3	NHPh	S	91–92	−63.0	9, mp 91–92° δ_{31P} −63.0 ppm	CO_2	O	SCH_3	61	−19.5	100	76–77	See expt 7
9	H	CH_3	S	NHPh	171–172	−59.5	9, mp 171–172° δ_{31P} −59.5 ppm	CO_2	SCH_3	O	66	−23.5	100	104–106 (0.05)	See expt 6
10	H	CH_3	NHPh	Se	95–96	−62.5	9, mp 95–96° δ_{31P} −62.5 ppm	CO_2	O	$SeCH_3$	60	−12.5	100	58–59	30, mp 59–59.5° δ_{31P} −11.7 ppm
11	H	CH_3	Se	NHPh	166–167	−60.0	9, mp 166–167° δ_{31P} −60.0 ppm	CO_2	$SeCH_3$	O	57	−13.7	100	100 (0.01)	30, δ_{31P} −14.0 ppm
12	H	CH_3	NHPh	Se	See expt 10			CS_2	S	$SeCH_3$	52	−79.0 (437 Hz)[a]	100	56–57°	Anal. Calcd for $C_5H_{11}O_2PSSe$: C, 24.50; H, 4.53; P, 12.63. Found: C, 24.44; H, 4.50; P, 12.54.
13	H	CH_3	Se	NHPh	See expt 11			CS_2	$SeCH_3$	S	56	−88.0 (510 Hz)[a]	100	95 (0.2)	Anal. Found: C, 24.54; H, 4.67; P, 12.99.
14	H	CH_3	S	NHPh	See expt 9			CS_2	S SCH_3	SCH_3 S	66	−88.5 −95.5	69 31	105–110 (0.2)	31, δ_{31P} −88.5 ppm δ_{31P} −95.5 ppm

[a] In parentheses values of $^1J_{P-Se}$ are given. [b] SS = stereospecificity.



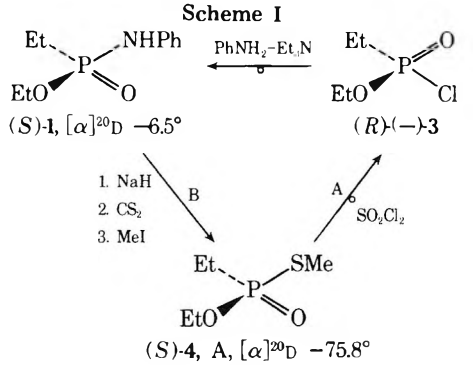
X = O, S, Se; Y = O, S

The synthesis and assignment of cis–trans geometry in the family of starting materials leading to models used in this study were reported recently from this laboratory.[8,9]

In this series of experiments we aimed to define the stereochemistry of the reactions investigated. Reaction mixtures prior to standard work-up preparative procedure were examined with the aid of ^{31}P NMR spectroscopy for determination of the cis–trans isomer ratio.

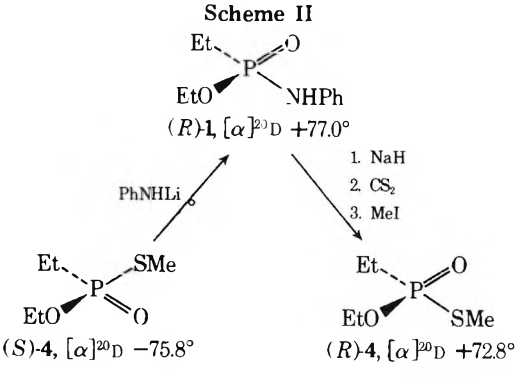
Reaction of a 2-thioanilidate anion (Table II, expt 14) with carbon disulfide, followed by alkylation with methyl iodide, is indicative of an axial preference of the methylthio substituent in diastereoisomeric tetracoordinated dioxaphosphorinanyl ring system or the higher nucleophilicity of sulfur in an axial disposition[10] in the ambident dithiophosphate anion. Detailed inspection of Table II reveals that the reactions under consideration are fully stereospecific and proceed with full retention of configuration at phosphorus (expt 6–13). Preparative yields are reported for products isolated by distillation or crystallization. Both *cis*- and *trans*-2-methylseleno-2-thiono-4-methyl-1,3,2-dioxaphosphorinanes (expt 12, 13) were previously unreported and cis–trans assignment, together with stereochemical course of reactions, was elucidated by comparison of spin–spin coupling constants between directly bonded phosphorus and selenium-77. In the light of recent data reported from this laboratory[11] the cis isomer, with equatorially oriented MeSe group, has a higher absolute value of $^{1}J_{^{31}P-^{77}Se}$ (510 Hz) than that of the trans isomer with MeSe group in axial disposition (437 Hz). It is also worthwhile to mention that methylation of ambident phosphoroselenothioate anion (Table I, expt 5; Table II, expt 12, 13) proceeds exclusively on selenium center, in accordance with previous findings reported from this laboratory.[12] Since several discrepancies in stereochemical course of reactions between cyclic and acyclic systems[13] have been reported, we decided to carry out the reaction of enantiomeric *O*-ethyl ethylphosphonoanilidate (1) and its thiophosphoryl analogue **2** with carbon disulfide and carbon dioxide, respectively, and to elucidate definitively the stereochemistry of the reactions in question. Stereochemical correlations are demonstrated in Schemes I–IV. It should be mentioned that the

Scheme I



stereochemistry of *O*-ethyl ethylphosphonoamidates and their thiono analogues have not been established previously and it was necessary to perform several transformations which would give a clear picture of the reactions investigated. *S*-(−)-**1**[14] was obtained in the reaction of optically active (*R*)-(−)-*O*-ethyl ethylphosphonochloridate (**3**) with aniline in the presence of triethylamine as shown in Scheme I. (*R*)-(−)-**3** was obtained from chlorinolysis of (*S*)-(−)-*O*-ethyl-*S*-methyl ethylphosphonothiolate (**4**) with sulfuryl chloride and was not isolated in a pure form prior to aminolysis. Reaction of the sodium salt of (−)-**1** with carbon disulfide followed by alkylation of the resulting *O*-ethyl ethylphosphonothioate anion with methyl iodide gave **4** with the same configuration as the starting thiolo ester used for chlorinolysis, although its specific rotation value was much lower. The transformations described above constitute, according to Cram's classification,[15] a podal, triligostatic, three-reaction cycle in which both chlorinolysis of phosphoryl thiolo esters[16] as well as aminolysis of phosphoryl chloroanhydrides[17] are known to proceed with inversion of configuration at phosphorus. On this basis we conclude that the third reaction, direct **1** → **4** transformation, proceeds with retention at phosphorus center. Although the observed loss of optical activity of **4** in the cycle was most likely caused by fast racemization of chloride **3** prior to its aminolysis,[18] we undertook additional studies in order to establish more definitely the stereospecificity of anilidate → thiolo ester conversion. Direct synthesis of anilidate **1** from thiolo ester **4** was performed. The reaction of (*S*)-(−)-**4** with lithium anilide yielded (+)-**1** which, after reaction with carbon disulfide, gave **4** of opposite sign of rotation to that of the starting material, with overall stereospecificity above 95% (see Scheme II). The rules of an antipodal, triligostatic, two-reaction cycle of the kind represented in Scheme II led us to the conclusion that nucleo-

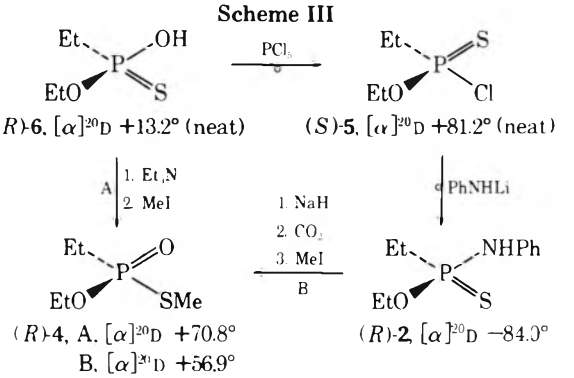
Scheme II



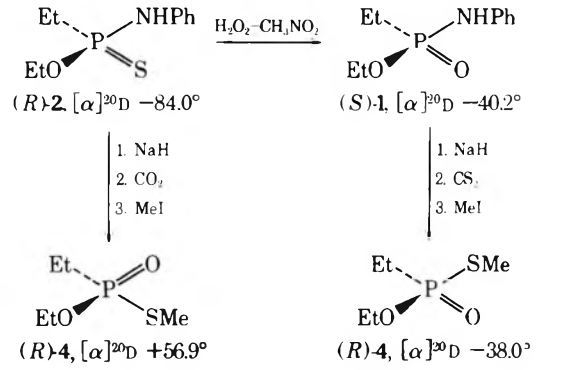
philic exchange (replacement) of a thiomethyl group at a phosphoryl center by lithium anilide proceeds, as in the case of oxo esters,[19] with full inversion of configuration at the phosphorus atom.

Similar results were obtained for the thioanilidate **2**, which was prepared by the reaction of *O*-ethyl ethylphosphonochloridothionate (**5**) with lithium anilide. The stereochemical correlation with the parent *O*-ethyl ethylphosphonothioic acid (**6**) is summarized in Scheme III. Since in the podal, diligostatic, four-reaction cycle the chlorinolysis of thio acid **6** with phosphorus pentachloride proceeds with inversion of configuration[20] and the alkylation of **6** does not affect the configuration at phosphorus, we can conclude that one of the remaining reactions must proceed with inversion and the other one with retention of configuration at phosphorus. Although aminolysis of chloride **5** with diethylamine and its lithium salt was previously described,[21] the stereochemical course of these reactions was obscure. Thus, we constructed another reaction cycle which correlates the configuration of anilidate **1** with that of thioanilidate **2** by means of direct oxidation of **2** with hydrogen peroxide (see

Scheme III



Scheme IV



Scheme IV). This antipodal, three-reaction cycle involves one ligand metathesis arising from substitution of sulfur atom by oxygen during the oxidation process. Since both conversion **1** → **4** (as proved above) as well as oxidation of thionophosphoryl amido esters with hydrogen peroxide[22] proceed without any change of configuration at phosphorus, the third reaction (e.g., direct **2** → **4** conversion) must proceed also with retention of configuration. This finding led us to the conclusion concerning the stereochemical course of substitution of the chlorine atom in chloridothionate **5** by the anilide anion (Scheme III). This reaction proceeds with inversion of configuration at phosphorus and stereospecificity exceeding 80%.

Two important conclusions can be drawn from these stereochemical correlations: (1) phosphorylation and thiophosphorylation of lithium anilide with phosphonothiolates or phosphorochloridothionates proceed with inversion of configuration at phosphorus; (2) the Wadsworth–Emmons type conversion[1] of phosphoroanilidates and their thio (seleno) analogues into the corresponding phosphorothio(seleno)lates is highly stereospecific and proceeds with retention of configuration at phosphorus.

Finally we tried to exploit the reaction of amidate anions with carbonyl compounds for the synthesis of chiral organophosphorus compounds via resolution of diastereoisomeric phosphonothioamidates. Reaction of racemic **5** with (−)-α-phenylethylamine gave a 1:1 mixture of diastereoisomeric *O*-ethyl-*N*-α-phenylethyl ethylphosphonothioamidate (**7**). Pure diastereoisomer **7** was isolated through fractional crystallization from *n*-hexane. However, its reaction with butyllithium, followed by reaction with carbon dioxide in boiling dioxane, failed to give the expected **4**. This means that the method of conversion of phosphoroamidates into phosphoryl thiolo esters described above is limited to "activated" amidates only.

Experimental Section

All melting points and boiling points are uncorrected. Solvents and commercial reagents were distilled and dried by conventional methods before use.

^{1}H NMR spectra were recorded at 60 MHz with a Jeol C-60H spectrometer equipped with Hetero-Spin-Decoupler JNH-SD-HC, with Me_4Si as an internal standard. ^{31}P NMR spectra were obtained on the same instrument at 24.3 MHz with external H_3PO_4 as the reference. Negative chemical shift values are reported for compounds absorbing at lower fields than H_3PO_4. Mass spectra were obtained on a LKB 9000S spectrometer at 70 eV ionizing energy. Optical activity measurements were made with a Perkin-Elmer 141 photopolarimeter in benzene solution, unless specified otherwise. Product purities were determined from integrated ^{1}H and ^{31}P NMR spectra and GLC (Varian Aerograph 1520) or TLC (Silufol UV 254 plates) analyses.

I. Starting Materials. A. Diethyl phosphoroanilidite was obtained according to Kabachnik and Gilarov[24] from diethyl phosphorochloridite and aniline in the presence of triethylamine in benzene solution: bp 120° (4 mmHg); n^{20}D 1.5203; $\delta_{^{31}P}$ −129.0 ppm; yield 63% [lit.[24] bp 120° (4 mmHg), n^{20}D 1.5254]. Its oxidation with *tert*-butyl hydroperoxide and addition of elemental sulfur or selenium gave corresponding diethyl phosphoroanilidate and its thiono and seleno derivatives. Their colligative and spectral parameters are given in Table I.

B. 2-*N*-Phenylamino-5,5-dimethyl-1,3,2-dioxaphosphorinane was obtained from the corresponding chlorophosphite[32] and aniline in the presence of triethylamine in benzene solution: mp 65–67°; $\delta_{^{31}P}$ −116.0 ppm (benzene); yield 46%. Anal. Calcd for $C_{11}H_{16}O_2NP$: C, 58.66; H, 7.15; P, 13.75; N, 6.22. Found: C, 58.50; H, 7.22; P, 13.75; N, 6.22. Corresponding 2-oxo-, 2-thio-, and 2-seleno-2-phenylamino-5,5-dimethyl-1,3,2-dioxaphosphorinanes were obtained by oxidation of cyclic anilidite with *tert*-butyl hydroperoxide, elemental sulfur, and selenium, respectively, and their characteristics are included in Table I.

C. Isomeric 2-*N*-phenylamino-2-X-4-methyl-1,3,2-dioxaphosphorinanes (X = lone pair, O, S, Se) were synthesized according to procedures described recently from our laboratory.[8,9]

D. *O*-Ethyl ethylphosphonothioic acid [6, bp 57–59° (0.08 mm Hg), n^{20}D 1.4909] was obtained and resolved into optical antipodes according to Aaron et al.[33]

E. *O*-Ethyl ethylphosphonochloridothionate [(*S*)-5, bp 20° (0.05 mmHg), n^{23}D 1.4912, $[\alpha]^{20}$D +81.2° (neat), $\delta_{^{31}P}$ −106 ppm] was obtained from optically active thio acid (*R*)-**6** [$[\alpha]^{20}$D +13.2° (neat)] according to the procedure described by Michalski and Mikolajczyk.[34]

F. *O*-Ethyl-*S*-methyl ethylphosphonothiolate [(*S*)-4, bp 55° (1 mmHg), n^{20}D 1.4782, $[\alpha]^{20}$D −75.8°, $\delta_{^{31}P}$ −61.5 ppm] was produced by S-alkylation of the triethylammonium salt of (*S*)-**6** [$[\alpha]^{20}$D −14.1° (neat)].[35]

G. Chlorinolysis of 4 and Reaction of Resulting *O*-Ethyl Ethylphosphonochloridate (3) with Aniline. Freshly distilled sulfuryl chloride (2.7 g, 0.02 mol) was added dropwise into a solution of (*S*)-**4** (3.4 g, 0.02 mol, $[\alpha]^{20}$D 75.8°) in benzene (50 ml) at 5°. Stirring at room temperature was continued for 15 min and a benzene solution of aniline (3.72 g, 0.04 mol) and triethylamine (4.08 g, 0.04 mol) was slowly added at 20° with stirring and external cooling. Stirring at room temperature was continued for 30 min and amine hydrochloride was filtered off and washed with benzene. The solvent was evaporated and the residue was chromatographed (300 g of silica gel 100–200 mesh) in benzene–acetone (1:1). The separation was followed by TLC. *O*-Ethyl ethylphosphonoanilidate [(*S*)-**1**] was isolated after evaporation of solvent, as an undistillable oil with a yield of 3.0 g (70.5%): $\delta_{^{31}P}$ −34.0 ppm (benzene); $[\alpha]^{20}$D −6.5° (Anal. Calcd for $C_{10}H_{16}O_2NP$: C, 56.20; H, 7.55; N, 6.58; P, 14.50. Found: C, 56.30; H, 7.61; N, 6.72; P, 14.50); ir (film) 1200 ($\nu_{P=O}$), 3155 cm^{-1} (ν_{N-H}); mass spectrum *m/e* (rel intensity) 93 (100), 213 (73), 185 (29), 139 (15), 120 (11), 111 (17.5), 105 (12), 65 (20).

H. Reaction of Lithium Anilide with 4. To a solution of butyllithium (0.08 mol) in ether (80 ml) was added at −10° with stirring and external cooling, under a dry nitrogen atmosphere, 7.5 g (0.08 mol) of aniline. The mixture was cooled to −40° and 12.5 g (0.075 mol) of (*S*)-**4**, $[\alpha]^{20}$D −75.8°, was added. Stirring at room temperature was continued for 1 hr and the resulting precipitate was filtered off. The filtrate was evaporated, dissolved in benzene, washed with cold, 1% HCl, dried over $MgSO_4$, and evaporated. The residue was chromatographed (200 g of silica gel 100–200 mesh) in benzene–acetone (1:1). The column chromatography was followed by TLC. Evaporation of solvent gave (*R*)-**1** as an undistillable, viscous oil, $\delta_{^{31}P}$ −34.0 ppm (benzene), $[\alpha]^{20}$D +77.0°, yield 3.1 g (19.5%). The ir and mass spectra were identical with these recorded for **1** described in section IF.

From another fraction of eluate 6 g (48%) of unchanged 4 was recovered.

I. Reaction of Lithium Anilide with 5. To a solution of butyllithium (0.05 mol) in ether (40 ml) was added at −10°, with stirring and external cooling, under a dry nitrogen atmosphere, 4.65 g (0.05 mol) of aniline. The resulting solution was cooled to −40° and 8 g (0.0465 mol) of (*S*)-**5**, $[\alpha]^{20}D$ + 81.2° (neat), was added. The reaction mixture was stirred for 1 hr at room temperature and then evaporated under reduced pressure. The residue was dissolved in benzene (50 ml) and washed with 2% HCl (2 × 50 ml). Water solutions were extracted with benzene (2 × 20 ml). Combined organic fractions were dried over $MgSO_4$ and evaporated. The residue was distilled under reduced pressure, giving 4.5 g (42%) of thioanilidate (*R*)-**2**: bp 115° (0.2 mmHg); $n^{26}D$ = 1.5652; δ_{31P} −85.0 ppm (benzene); $[\alpha]^{20}D$ = −84.0° (Anal. Calcd for $C_{10}H_{16}ONPS$: C, 52.50; H, 7.03; P, 13.50; N, 6.12. Found: C, 51.99; H, 7.28; P, 13.98; N, 6.19); ir (film) 3265 cm^{-1} (ν_{N-H}); mass spectrum *m/e* (rel intensity) 155 (100), 229 (64), 127 (68), 105 (56), 93 (55). As a lower boiling fraction 4.0 g (50%) of unchanged phosphonochloridothionate **5** was recovered, bp 30–35° (0.2 mmHg), $n^{20}D$ 1.4906, $[\alpha]^{20}D$ + 60.2° (neat).

J. Oxidation of 2 with Hydrogen Peroxide. To a solution of (*R*)-**2** (2.3 g, 0.01 mol), $[\alpha]^{20}D$ −84.0°, in nitromethane (50 ml) was added hydrogen peroxide (1 g, 80%). The mixture was gently heated and at 50° an exothermic reaction occurred. Heating at 60° was continued for 30 min. The mixture was evaporated and the residue was purified on silica gel (100–200 mesh) (100 g) with benzene–acetone (1:1) as an eluent. Evaporation of solvent gave 1.9 g (89%) of (*S*)-**1** as an undistillable, viscous oil, δ_{31P} −34.0 ppm (benzene), $[\alpha]^{20}D$ = −40.2°. The ir and mass spectra were identical with those recorded for **1** described in section IF.

K. *O*-Ethyl-*N*-α-phenylethyl Ethylphosphonothioamidate (7). To a solution of racemic **5** (38.5 g, 0.2 mol) in benzene (150 ml) was added, with stirring, a solution of α-phenylethylamine [24.5 g, 0.2 mol, $[\alpha]D$ −37.0° (neat)] and triethylamine (20.4 g, 0.2 mol) in benzene (50 ml). An exothermic reaction was observed and the temperature rose to 40°. Stirring at this temperature was continued for 3 hr and the resulting precipitate was filtered off and washed with benzene. The filtrate was evaporated and the residue was distilled under reduced pressure, giving **7** as a colorless liquid: bp 120–125° (0.2 mmHg); $n^{22}D$ 1.5450; $[\alpha]^{20}D$ −29.8°; yield 37 g (72%) (Anal. Calcd for $C_{12}H_{20}PNSO$: C, 56.00; H, 7.84; P, 12.05; N, 5.45. Found: C, 56.66; H, 8.26; P, 11.87; N, 6.04); mass spectrum *m/e* (rel intensity) 105 (100), 257 (63.8), 224 (29.6), 178 (21.8), 121 (47.2), 120 (100), 91 (29.1), 77 (49.2). Its ^{31}P NMR analysis (benzene) revealed the presence of two substances, **7a** (δ_{31P} −89.5 ppm) and **7b** (δ_{31P} −89.8 ppm), in the ratio 1:1. The product had solidified during the storage at room temperature. Its recrystallization from *n*-hexane caused an increase in **7a**:**7b** ratio and after repeated fractional crystallization pure **7a** (11.5 g) was obtained, δ_{31P} −89.5 ppm, mp 51–52°, $[\alpha]^{20}D$ = +12.8° (Anal. Found: C, 55.85; H, 7.95; P, 11.85; N, 5.32). From mother liquors the fraction containing 36% of **7a** and 64% of **7b** (^{31}P NMR analysis) was isolated (yield 15 g, $[\alpha]^{20}D$ −42°).

II. Conversion of Phosphoroanilidates $(RO)_2P(X)NHPh$ (X = O, S, Se) to Corresponding Thiolo(seleno) Esters. General Procedure. To a suspension of NaH (1.44 g, 0.06 mol) in dioxane (100 ml) was added, dropwise, at 50°, a solution of corresponding anilidate (0.05 mol) in dioxane (50 ml). Reaction was accompanied with evolution of hydrogen and formation of a white precipitate. The reaction mixture was stirred at 90° for the next hour[36] and CS_2[37] (20 ml) was added in small portions during 1 hr. An additional 1 hr of stirring at 90° was followed by solvent evaporation, the residue was shaken with 100 ml of benzene–hexane (1:5) solution, and the resulting precipitate was filtered off and washed with hexane. The precipitate was suspended in benzene (100 ml) and 14.2 g (0.1 mol) of methyl iodide was added. The suspension was refluxed for 2 hr and cooled and the precipitate was filtered off and washed with benzene. The filtrate was evaporated and the residue was examined by means of ^{31}P NMR. Pure product was isolated by distillation or crystallization, yield 50–80%. Further details are included in Table I.

III. Conversion of 1 to 4. The procedure described in section II was applied to **1** (3.1 g, 0.0145 mol, $[\alpha]^{20}D$ +77.0°) using CS_2 as the reagent. Pure **4** was isolated in 78% yield [1.9 g, bp 62° (2 mmHg), $n^{20}D$ 1.4782, $[\alpha]^{20}D$ +72.8°, δ_{31P} −61.5 ppm).

IV. Conversion of 2 to 4. The reaction of **2** (3.0 g, 0.013 mol, $[\alpha]^{20}D$ −68.5°) with NaH–CO_2–MeI was performed as described in section II. Pure **4** was isolated by distillation: bp 62° (2 mmHg); $n^{22}D$ = 1.4778; $[\alpha]^{20}D$ = +46.5°; δ_{31P} −61.5 ppm; yield 1.2 g (55%).

V. Attempted Conversion of 7a to 4. To a solution of **7a** (5.14 g, 0.02 mol, $[\alpha]^{20}D$ +12.8°) in dioxane (50 ml) was added at 20°, with stirring, under a dry nitrogen atmosphere, a solution of butyllithium[38] (0.021 mol) in ether (11 ml). An exothermic reaction was observed. Stirring at room temperature was continued for 10 min and dry CO_2 was bubbled through the solution for 1 hr at room temperature and then for 2 hr at 90°. The ^{31}P NMR spectrum showed an absorption band at −101 ppm and no signal in the region characteristic for thio acid (**6**) salt. Thus, the signal at −101 ppm was suspected to correspond to *N*-lithium salt of **7**. It has been proved by its hydrolysis and recovery of starting **7** (82%), bp 123–125° (0.2 mmHg), $[\alpha]^{20}D$ +10.3°.

Registry No.—(*S*)-**1**, 57237-61-3; (*R*)-**1**, 57237-62-4; (*R*)-**2**, 57237-63-5; (*R*)-**3**, 57287-75-9; (*S*)-**4**, 20698-84-4; (*R*)-**4**, 20698-85-5; (*S*)-**5**, 13547-42-7; *rac*-**5**, 13547-40-5; (*R*)-**6**, 4789-36-0; (*S*)-**6** Et_3N salt, 57237-64-6; **7** isomer 1, 57237-65-7; **7** isomer 2, 57237-66-8; diethyl phenylphosphoramidoselenoic acid, 57237-67-9; *O,O*-diethyl *Se*-methylphosphoroselenothioic acid, 50735-57-4; 2-oxo-2-phenylamine-5,5-dimethyl-1,3,2-dioxaphosphorinane, 57237-68-0; 2-thiono-2-phenylamino-5,5-dimethyl-1,3,2-dioxaphosphorinane, 57237-69-1; 2-seleno-2-phenylamino-5,5-dimethyl-1,3,2-dioxaphosphorinane, 57237-70-4; *cis*-2-seleno-2-phenylamino-4-methyl-1,3,2-dioxaphosphorinane, 57237-71-5; *trans*-2-seleno-2-phenylamino-4-methyl-1,3,2-dioxaphosphorinane, 57237-72-6; 2-methylseleno-2-oxo-5,5-dimethyl-1,3,2-dioxaphosphorinane, 52963-22-1; 2-methylseleno-2-thiono-5,5-dimethyl-1,3,2-dioxophosphorinane, 57237-73-7; *trans*-2-methylseleno-2-thiono-4-methyl-1,3,2-dioxaphosphorinane, 57237-74-8; *cis*-2-methylseleno-2-thiono-4-methyl-1,3,2-dioxaphosphorinane, 57237-75-9; sulfuryl chloride, 7791-25-5; lithium anilide, 20732-26-7; hydrogen peroxide, 7722-84-1; (−)-α-phenylethylamine, 2627-86-3.

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(36) When X = O an anion formation was so fast that additional heating was not necessary.
(37) When X = S, Se in some experiments, leading to phosphoryl compounds, dry CO_2 was bubbled through the reaction mixture at 90° for 2 hr.
(38) Sodium hydride did not react with **7** even in boiling dioxane as proved in a separate experiment.

Organophosphorus Compounds of Sulfur and Selenium. Stereochemistry of Oxidation of Thiono- and Selenophosphoryl Compounds with Hydrogen Peroxide

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The oxidation of 2-R-2-*S*(*Se*)-4-methyl-1,3,2-dioxaphosphorinanes with hydrogen peroxide to 2-oxo derivatives proceeds with net retention of configuration at the phosphorus atom. The same stereochemical course was observed in the case of enantiomeric *O*-ethyl-*O*-methyl ethylphosphonothionate. On the other hand, conversion of optically active phosphine sulfide into the corresponding oxide proceeds with inversion of configuration accompanied by racemization. In contrast the oxidation of enantiomeric phosphine selenide by hydrogen peroxide depends on the reaction conditions. Oxidation reactions of thio- and selenophosphoryl compounds with hydrogen peroxide are rationalized in terms of stability of pentacovalent intermediates, which depends on structure of reactants and reaction conditions.

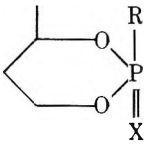
Better insight into the mechanism of oxidation of thio- and selenophosphoryl derivatives to their oxo analogues is of importance for stereochemical correlations, constructing new stereochemical cycles,[1] and better understanding of the metabolic pathways of some phosphoroorganic biocides which are known to involve PS → PO oxidation reactions.[2]

The stereochemistry of conversion of thiophosphoryl compounds into phosphoryl analogues has attracted attention in many research laboratories. It has been demonstrated that oxidizing agents such as potassium permanganate,[3] nitric acid,[4] dinitrogen tetroxide,[4] organic peracids,[5,6] ozone,[6] dimethyl sulfoxide,[7] and hydrogen peroxide[8] can smoothly oxidize thio- and selenophosphoryl compounds. The stereochemical course of the oxidation is dependent on the nature of oxidizing agent, reaction medium, and structure of thio- and selenophosphoryl moieties. Thus nitric acid oxidizes methylphenyl *n*-propylphosphine sulfide and *O*-ethyl-*O*-methyl ethylphosphonothionate with inversion of configuration,[4a] but retention was observed when diastereoisomeric 2-thiono-[4b] and 2-seleno-2-methoxy-4-methyl-1,3,2-dioxaphosphorinans[4c] were used as model compounds. Herriot has also demonstrated the reversal of stereochemistry in oxidation of diastereoisomeric *O*-menthyl methylphenylphosphinothionates by *m*-chloroperbenzoic acid.[5] Net retention was observed in neutral solvents. Addition of trifluoroacetic acid caused a dramatic change in stereochemistry and inversion was observed. The same relationship between stereochemistry and acidity of reaction medium was earlier reported from this laboratory for dinitrogen tetroxide oxidation of enantiomeric phosphine sulfide.[4a] However, dinitrogen tetroxide causes much racemization of the resulting phosphoryl compounds and determination of the particular reaction step responsible for this racemization must await further studies.[9]

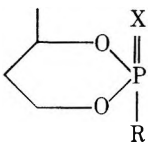
Hydrogen peroxide has also been used as an oxidizing agent[8] and oxidations of diastereoisomeric *O*-menthyl methylphenylphosphinothionate as well as optically active *O*-methyl *tert*-butylphenylphosphinothionate were described as fully stereospecific and proceeding with retention of configuration at phosphorus atom. This result seemed to be in disagreement with our preliminary findings on application of hydrogen peroxide for stereospecific PS → PO conversion. For this reason we undertook more detailed studies on this reaction employing various thio- and selenophosphoryl compounds and different reaction media.

Results

Diastereoisomeric 2-R-2-X-4-methyl-1,3,2-dioxaphosphorinanes (**1–6**), enantiomeric *O*-ethyl-*O*-methyl ethylphosphonates (**7, 8**), and thio, seleno, and oxo derivatives of

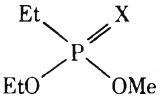


cis

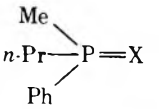


trans

1, X = S; R = OMe[4b,11]
2, X = Se; R = OMe[4c]
3, X = S; R = NMe_2[12]
4, X = Se; R = NMe_2[12]
5, X = O; R = OMe[13]
6, X = O; R = NMe_2[13]



7, X = S[14]
8, X = O[14]



9, X = S[3,15]
10, X = Se[4c]
11, X = O[3,15]

methylphenyl-*n*-propyl phosphine (**9–11**) were chosen as stereochemical models for our studies. Stereochemistry of these compounds has been well established. Information concerning models, reaction conditions (solvent, temperature, and time), and stereospecificities is collected in Tables I–IV.[10]

Table I
Oxidation of 2-R-2-X-4-Methyl-1,3,2-dioxaphosphorinanes with Hydrogen Peroxide

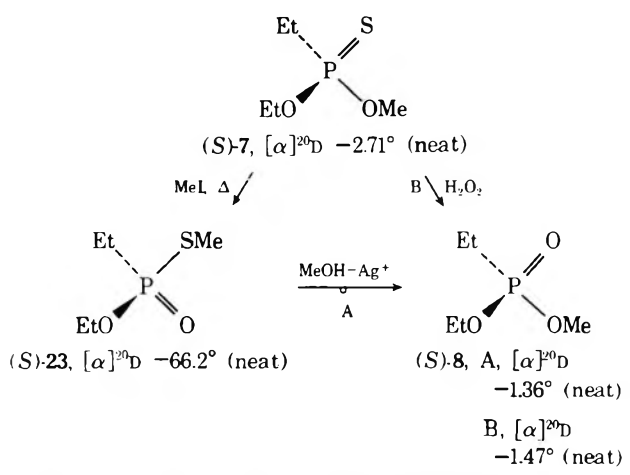
Expt	Starting material: Compd	Starting material: Isomer ratio	Reaction conditions	Product: Compd	Product: Yield, %	Product: Isomer ratio
1	1	6% cis 94% trans	Boiling methanol, 1 hr	5	70	20% cis 80% trans
2	1	86% cis 14% trans	Boiling acetone, 2 hr	5	65	75% cis 25% trans
3	3	90% cis 10% trans	Boiling nitromethane, 30 min	6	62	75% cis 25% trans
4	2	4% cis 96% trans	Methanol, 20°, 30 min	5	85	4% cis 96% trans
5	2	88% cis 12% trans	Acetone, 20°, 30 min	5	82	86% cis 14% trans
6	4	85% cis 15% trans	Acetone, 20°, 30 min	6	83	85% cis 15% trans

Table II
Oxidation of Optically Active *O*-Ethyl-*O*-methyl Ethylphosphonothionate (7) with Hydrogen Peroxide

Expt	$[\alpha]^{20}D$ (neat) of 7, deg	Reaction conditions	Yield of 8, %	$[\alpha]^{20}D$ (neat) of 8, deg
1	−2.71	Boiling methanol, 15 min	85	−1.35
2	−2.71	Boiling dioxane, 15 min	82	−1.47
3	−2.71	Boiling nitromethane, 15 min	78	−0.96

Inspection of Table I reveals that conversion of dioxaphosphorinanyl derivatives (**1–4**) to corresponding 2-oxo compounds (**5, 6**) proceeds with overall retention of configuration at phosphorus, but in the case of 2-thiono derivatives (**1, 3**) the products are partly epimerized (expt 1–3). Oxidation of 2-seleno derivatives (**2, 4**, expt 4–6) proceeds faster under milder conditions. Yields and stereospecificities are higher than those for 2-thiono compounds. Retention of configuration at phosphorus atom has also been found during oxidation of optically active phosphonothioate (**7**) (see Table II). Although the optical purity of **7** as well as the resulting *O*-ethyl-*O*-methyl ethylphosphonate (**8**) has not been precisely determined, on the basis of stereochemical correlations summarized in a form of the podal, three-reaction cycle, containing one ligand, metathesis (see Scheme I) we assume that the stereospecificity of oxidation is rather high.[16]

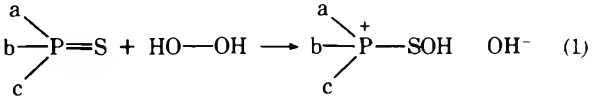
Scheme I



However, oxidation of the sulfide **9** with hydrogen peroxide is accompanied with net inversion of configuration at phosphorus atom, but the resulting methylphenyl-*n*-propylphosphine oxide (**11**) is highly racemized (Table III). Variations of solvents and temperature did not increase the stereospecificity of investigated reactions. Higher stereospecificity was achieved in oxidation of the optically active phosphine selenide **10**. The stereochemistry of this reaction distinctly depends on reaction conditions (see Table IV). When the process was carried out in primary alcohols such as methanol or ethanol, net retention was noted (expt 9–12). Other solvents such as acetone, pyridine, dioxane, nitromethane, *tert*-butyl alcohol, or water (reaction in a heterogenic medium) gave product **11** with inverted configuration (expt 1–8). The same stereochemical course was observed when reaction was carried out in methanol containing 10% trifluoroacetic acid (expt 13). It is of interest to note that in the nitromethane solution (expt 5, 6) the stereospecificity of the reaction does not depend on the reaction temperature. However, when the reaction was carried out in ethanol, the increase of the temperature (expt 9–11) improves its stereospecificity.

Discussion

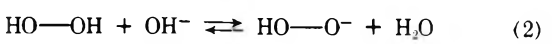
Taking into account the high stereospecificity of oxidation of chiral phosphinothionates[8] and structure- and solvent-dependent stereochemistry of oxidation of compounds under investigation the following rationale can be proposed. We assume that the first step in the reaction of thio(seleno)phosphoryl compounds with hydrogen peroxide, by analogy with other heterolytic reactions of peroxy compound with nucleophiles,[17] is the nucleophilic attack of sulfur (selenium) on the oxygen atom of hydrogen peroxide molecule with formation of ion pair **12** (eq 1).[18]



(1)

12

This is supported by the fact of higher reactivity of selenophosphoryl compounds than that of corresponding thio derivatives toward electrophilic reagents owing to higher polarizability of the selenium atom than that of sulfur. Also the fact that the oxidation of selenide **10** does not occur in the presence of strong base (5% NaOH solution) supports electrophilic activity of H_2O_2 molecule. The nucleophilic attack on anionic species **13** (coming from the equilibrium 2) seems unlikely.



(2)

13

The apparent acidic catalysis (see expt 7, Table III) can be also rationalized in terms of enhanced electrophilicity of protonated species **14**.

Table III
Oxidation of Optically Active Methylphenyl-*n*-propylphosphine Sulfide (9) with Hydrogen Peroxide

Expt	$[\alpha]^{20}D$ of 9 (methanol), deg	Reaction conditions	Yield of oxo compd (11), %	$[\alpha]^{20}D$ of 11 (methanol), deg	Stereospecificity[a]
1	−8.25	Boiling acetone, 20 min	82	+3.5	42.5% of inv
2	−8.25	Boiling methanol, 20 min	80	+1.8	22.0% of inv
3	−8.25	Boiling ethanol, 20 min	75	+1.3	16.0% of inv
4	−8.25	Boiling nitromethane, 10 min	74	+1.35	16.5% of inv
5	−8.25	Boiling dioxane, 10 min	68	+0.85	10.3% of inv
6	−8.25	Boiling pyridine, 60 min	69	+1.8	22.0% of inv
7	−8.25	10% CF_3COOH in dioxane, 50°, 10 min	72	+5.3	64.0% of inv

[a] The stereospecificity was calculated on the basis of specific rotations $[\alpha]^{20}D \pm 20°$ (methanol) given by Mislow[27] for 9 and 11.

Table IV
Oxidation of Optically Active Methylphenyl-*n*-propylphosphine Selenide (10) with Hydrogen Peroxide

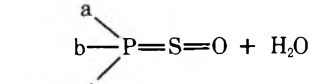
Expt	$[\alpha]^{20}D$ of 10 (methanol), deg	Reaction conditions	Yield of oxo compd (11), %	$[\alpha]^{20}D$ of 11 (methanol), deg	Stereospecificity[a]
1	−15.2	Acetone, 20°, 10 min	85	+8.1	52.0% of inv
2	−14.4	Dioxane, 20°, 10 min	74	+7.0	47.5% of inv
3	−15.2	Pyridine, 20°, 20 min	78	+4.3	28.0% of inv
4	−14.9	*tert*-Butyl alcohol, 30°, 10 min	81	+7.95	51.0% of inv
5	+19.4	Nitromethane, 20°, 10 min	76	−11.3	57.0% of inv
6	−15.6	Nitromethane, −20°, 30 min	82	+9.6	59.0% of inv
7	−15.2	10% CF_3COOH in dioxane, 20°, 10 min	85	+5.8	37.0% of inv
8[b]	−14.5	H_2O, 20°, 10 min	90	+12.5	83.0% of inv
9	−14.4	Ethanol, 20°, 10 min	80	−5.2	35.5% of ret
10	−15.6	Ethanol, −25°, 30 min	78	−0.5	3.1% of ret
11	−15.6	Boiling ethanol, 5 min	75	−10.55	65.0% of ret
12	−15.2	Methanol, 20°, 10 min	82	−8.4	54.0% of ret
13	−15.2	10% CF_3COOH in methanol, 20°, 10 min	85	+5.8	37.0% of inv

[a] The value ±19.8° of specific rotation $[\alpha]^{20}D$ (methanol) of 10[4c] served as a base of calculation of the stereospecificity of oxidation. [b] The reaction was performed by addition of fine powdered 10 into 30% H_2O_2.

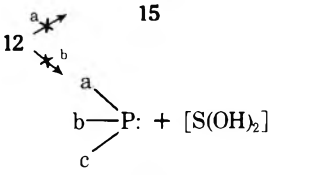
$$HO{-}OH + H^+ \rightleftharpoons HO{-}\overset{+}{O}\begin{matrix}H\\H\end{matrix} \quad (3)$$

14

The next step cannot be deprotonation of 12 by OH^- (eq 4a) because resulting intermediate 15 should decompose



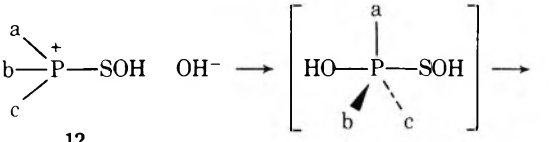
15 (4a)



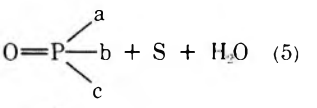
(4b)

with retention of configuration at phosphorus.[5] Displacement by OH^- at sulfur is also unlikely (eq 4b) because the intermediate P^{III} compound with at least one P–OR bond should readily hydrolyze in reaction conditions or act with H_2O_2 to give product with retained configuration.[3] Absence of hydrolysis products as well as inversion in the case of oxidation of phosphine sulfide (see Table III) rules out this possibility.

The most probable course of events seems to be, by analogy to base-catalyzed hydrolysis of alkoxy- and alkylthiophosphonium salts,[8,15] an attack of hydroxyl anion on phosphorus atom with formation of the pentacovalent intermediate 16. The mode of attack strongly depends on the environment of phosphorus atom. When a, b, c are alkyl or aryl ligands, the attack of OH^- is most likely to be directed on the a, b, c face of the tetrahedron along the axis of the P–S bond (eq 5).



12 16a



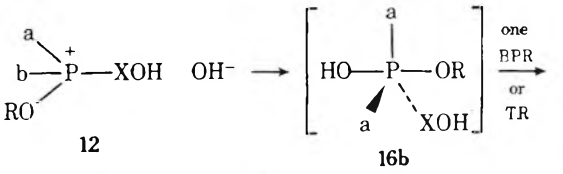
11 (5)

The five-coordinate intermediate 16a formed has the most apicophilic[19] groups (e.g., OH and SOH) in axial positions and should decompose giving elemental sulfur[20] and phosphine oxide 11 with inverted configuration. An experimental proof of net inversion at phosphorus atom during phosphine sulfide 9 oxidation has been documented (Table III).

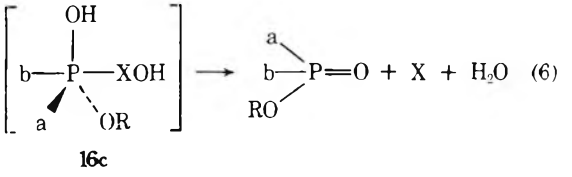
It has to be emphasized that the product 11 as well as other products, 5, 6 and 8, are stereochemically stable under the reaction conditions, indicating that any loss in the stereospecificity at phosphorus atom must have occurred prior to product formation. Although net inversion during oxidation of 9 was noticed, it seems to be reasonable to accept that the pseudorotation process of intermediate 16a is responsible for partial racemization.

In those cases, when at least one alkoxy group is attached to phosphorus in thio- or selenophosphoryl molecule, an attack of hydroxyl anion on electrophilic phosphorus center

is expected along the P–O axis from the opposite side to the most apicophilic[19] oxo ligand. This leads to formation of an intermediate **16b** in which the attacking group is in



12 **16b**



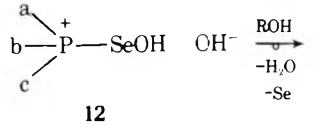
16c

X = S, Se

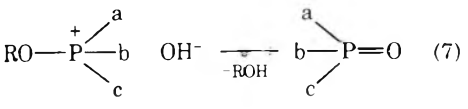
an axial and the leaving group in an equatorial position. Since the leaving group is required to reach the apical position in an intermediate of type trigonal bipyramid, one permutational isomerization can satisfy this condition, which in consequence leads to retention of configuration at phosphorus atom.

The approach presented above explains the stereochemical results listed in Tables I and II as well as those reported by Trippett,[8] and is in harmony with well-documented mechanistic considerations of base-catalyzed hydrolysis of alkoxy(alkylthio)phosphonium salts.[8] Observed partial epimerization in the case of cyclic thionophosphates **1** and thionoamidates **3** may be due to the subsequent pseudorotation process of intermediate **16c.** In the case of corresponding selenophosphoryl compounds (**2, 4**) such an intermediate is considerably less stable and its subsequent pseudorotation seems to be unlikely. An increase of the stereospecificity of oxidation of compounds **2** and **4** (see Table I) was indeed observed.

The summary of results concerning the oxidation of phosphine selenide **10,** presented in Table IV, requires special comment. Inversion observed, when the reaction was performed in solvents such as acetone, nitromethane, dioxane, pyridine, or *tert*-butyl alcohol, can be explained in the same manner as the oxidation of sulfide **9** (see eq 5). Higher stereospecificity may be due to the lower stability of the pentacovalent species of type **16a** for the selenium analogue and its faster decomposition to the products. Temperature has no effect on the stereospecificity of the oxidation process (compare expt 5 and 6, Table IV) carried out in the solvents mentioned above. Even more surprising results were noted when oxidation was performed in primary alcohol as reaction medium (Table IV, expt 9–13). Observed in this case net retention of configuration at phosphorus may be explained by assumption of direct assistance of solvent in the reaction mechanism. The intermediate ion pair **12** (see eq 1) can be attacked by solvent molecule with formation of the alkoxyphosphonium salt **17** of



12



17 **11**

inverted configuration (eq 7) in the manner described in eq 5 for oxidation of sulfide **9.** The lack of influence of the less nucleophilic and sterically hindered *tert*-butyl alcohol on the stereospecificity of the whole process speaks in favor of this explanation. A similar effect of lowering of nucleophilicity of alcohol was achieved by addition of trifluoroacetic acid to the reaction medium (expt 13, Table IV) where once again net inversion was observed. Similar considerable influence of primary alcohol on the stereochemistry of oxidation of methylphenyl-*n*-propyl phosphine with *tert*-butyl hypochlorite was earlier reported by Denney and Hanifin.[21] Striking dependence of the stereospecificity of oxidation of **10** with H_2O_2 on the temperature in those cases when the reaction was carried out in ethanol as a solvent (Table IV, expt 9–11) is of special interest. This fact may be rationalized by the assumption that influence of primary alcohol discussed above on reaction mechanism (eq 7) is more efficient at higher temperatures. At the lower temperatures direct influence of alcohol on the reaction mechanism can be less important and the inversion mechanism (eq 5) has to be considered. This is supported by the fact that sulfides **9** even in methanol solution are oxidized with net inversion owing to higher stability of the P–S bond as compared to the P–Se one, and contribution of solvent to the stereospecificity of the whole process can be neglected. As an alternative explanation of the influence of temperature on oxidation of selenide **10** in primary alcohol solution the pseudorotation of intermediate **16** may be considered because of its longer life-time at −20°. However, these various reaction paths cannot be distinguished at the present time.

Experimental Section

All solvents and commercial reagents were purified by the conventional method and distilled before use. NMR spectra were recorded on a Jeol C-60H instrument at 60 MHz observing frequency for ^1H and 24.3 MHz for ^{31}P nuclei. Chemical shifts were referred to internal Me_4Si (^1H NMR) and external H_3PO_4 (^{31}P NMR). Negative values were reported for compounds absorbing at lower fields than H_3PO_4. Heteronuclear Spin Decoupler JNM-SD-HC was used for chemical shift determination and integrations. GLC analyses were conducted with a Varian Aerograph 1520. Optical activity measurements were made with a Perkin-Elmer 141 photopolarimeter in methanol as a solvent (unless specified otherwise). Products purities were determined from integrated ^1H and ^{31}P NMR spectra and GLC analyses. Highly concentrated H_2O_2 solutions (80–90%, measured by manganometric titration) were obtained by careful evaporation of commercial 30% reagent under reduced pressure.

I. Starting Materials. 2-Chloro-4-methyl-1,3,2-dioxaphosphorinane (18) was prepared from 1,3-butanediol and PCl_3 in CH_2Cl_2 according to the Lucas[22] procedure.

***cis*-2-Methoxy-4-methyl-1,3,2-dioxaphosphorinane (19a)** was prepared from chlorophosphite **18** and methanol in the presence of 5% molar excess of triethylamine in ether at −20°: bp 44° (5 mmHg); $n^{21}D$ = 1.4480; yield 70% [lit.[11b] bp 20–22° (0.05 mmHg), $n^{21}D$ = 1.4468]. In repeated experiments the content of **19a** (δ_{31P} −132.6 ppm) in **19** was found to be in a range of 85–96%.

***trans*-2-Methoxy-4-methyl-1,3,2-dioxaphosphorinane (19b)** was obtained from **19a** by addition of a catalytic amount of benzene saturated with HCl and subsequent distillation: bp 65° (30 mmHg), $n^{20}D$ = 1.4418 (lit.[11b] bp 90–92° (60 mmHg), $n^{21}D$ = 1.4481. Prepared samples of **19** contained 94–100% of **19b** (δ_{31P} −129.5 ppm).

***cis*-2-Methoxy-2-thiono-4-methyl-1,3,2-dioxaphosphorinane (1a)** was obtained in 83% yield by addition of elemental sulfur to **19** (containing 90% of **19a**) at 5° in benzene, bp 68–70° (0.02 mmHg), $n^{20}D$ = 1.4892 [lit.[11b] bp 78–80° (0.3 mmHg), $n^{20}D$ = 1.4902]. The product contained 86% of **1a** (δ_{31P} −65.0 ppm) and 14% of **1b** (δ_{31P} −63.4 ppm).

***trans*-2-Methoxy-2-thiono-4-methyl-1,3,2-dioxaphosphorinane (1b)** was prepared in 85% yield by addition of elemental sulfur to **19** (containing 96% of **19b**) in benzene, bp 74–76° (0.02 mmHg), $n^{20}D$ = 1.4942 [lit.[11b] bp 76–80° (0.03 mmHg), $n^{22}D$ = 1.4913]. The product consisted of a mixture of **1a** and **1b** in the ratio 6:94, respectively.

***cis*-2-Methoxy-2-seleno-4-methyl-1,3,2-dioxaphosphori-**

nane (2a) was synthesized in 79% yield from **19** (**19a:b** 90:10) and elemental selenium at 5° in benzene, bp 85–87° (0.1 mmHg), $n^{20}D$ = 1.5216 (Anal. Calcd for $C_5H_{11}O_3PSe$: C, 26.22; H, 4.84; P, 13.53. Found: C, 26.32; H, 4.97; P, 13.41). GLC and ^{31}P NMR analysis revealed the presence of **2a** (88%, $\delta_{^{31}P}$ −68.5 ppm, $^1J_{P-Se}$ = 941 Hz) and **2b** (12%, $\delta_{^{31}P}$ −67.2 ppm). ^1H NMR ($CDCl_3$) δ_{CH_3} 1.41 ppm, $^3J_{HCCH_3}$ = 6.4 Hz, $^4J_{POCCH_3}$ = 2.2 Hz, δ_{OCH_3} 3.80 ppm, $^3J_{POCH_3}$ = 15.0 Hz.

***trans*-2-Methoxy-2-seleno-4-methyl-1,3,2-dioxaphosphorinane (2b)** was prepared in 81% yield by addition of elemental selenium to **19** (96% of **19b**) in benzene, bp 100–102° (0.2 mmHg), $n^{20}D$ = 1.5268 (Anal. Found: C, 26.30; H, 4.86; P, 13.28). GLC and ^{31}P NMR analysis showed the presence of **2a** (4%, $\delta_{^{31}P}$ −68.5 ppm) and **2b** (96%, $\delta_{^{31}P}$ −67.2 ppm, $^1J_{P-Se}$ = 978 Hz). ^1H NMR ($CDCl_3$) δ_{CH_3} 1.41 ppm, $^3J_{HCCH_3}$ = 6.4 Hz, $^4J_{POCCH_3}$ = 2.2 Hz, δ_{OCH_3} 3.70 ppm, $^3J_{POCH_3}$ = 14.5 Hz.

2-Dimethylamino-4-methyl-1,3,2-dioxaphosphorinane (20) was synthesized from chlorophosphite (**18**) and dimethylamine in benzene at 10°, bp 75° (20 mmHg), $n^{20}D$ = 1.4652, yield 71% (lit.[12] bp 71° (13 mmHg), $n^{20}D$ = 1.4650). The ^{31}P NMR analysis revealed the presence of *cis*-**20** (80%, $\delta_{^{31}P}$ −143.4 ppm) and trans isomer (20%, $\delta_{^{31}P}$ −139.2 ppm).

2-Dimethylamino-2-thiono-4-methyl-1,3,2-dioxaphosphorinane (3) was obtained in 83% yield by addition of elemental sulfur to **20** in benzene, bp 92–93° (0.3 mmHg), $n^{23}D$ = 1.5000 (Anal. Calcd for $C_6H_{14}O_2NPS$: C, 36.90; H, 7.23; N, 7.18; P, 15.87. Found: C, 37.43; H, 7.40; N, 7.52; P, 16.20). The ^{31}P and ^1H NMR analysis ($CDCl_3$) showed the presence of 90% *cis*-**3** ($\delta_{^{31}P}$ −73.5 ppm, δ_{NCH_3} 2.80 ppm, $^3J_{PNCH_3}$ = 11.3 Hz) and 10% of *trans*-**3** ($\delta_{^{31}P}$ −73.0 ppm, δ_{NCH_3} 2.50 ppm, $^3J_{PNCH_3}$ = 13.3 Hz). The product had solidified during the storage in the refrigerator. Its recrystallization from ether–hexane let us obtain pure *cis*-**3**, mp 37–38°. Anal. Found: C, 37.07; H, 7.25; N, 7.28; P, 15.83).

2-Dimethylamino-2-seleno-4-methyl-1,3,2-dioxaphosphorinane (4) was prepared in 79% yield from **20** and elemental selenium in benzene solution, bp 88–90° (0.2 mmHg), $n^{22}D$ = 1.5302 (Anal. Calcd for $C_6H_{14}O_2NPSe$: C, 29.75; H, 5.82;N, 5.78; P, 12.79. Found: C, 30.06; H, 6.10; N, 6.05; P, 1308). The ^{31}P and ^1H NMR analysis (benzene) revealed the presence of *cis*-**4** (85%, $\delta_{^{31}P}$ −79.0 ppm, $^1J_{P-Se}$ = 930 Hz, δ_{NCH_3} = 2.70 ppm, $^3J_{PNCH_3}$ = 12.0 Hz) and *trans*-**4** (15%, $\delta_{^{31}P}$ −79.8 ppm, $^1J_{P-Se}$ = 960 Hz, δ_{NCH_3} 2.30 ppm, $^3J_{PNCH_3}$ = 14.0 Hz). The product had solidified during the storage at room temperature. Its recrystallization from ether–hexane gave pure *cis*-**4**, mp 51–52° (Anal. Found: C, 29.84; H, 6.05; N, 5.98; P, 13.03).

***O*-Ethyl ethylphosphonothioic acid (21)** [bp 57–59° (0.08 mmHg), $n^{20}D$ = 1.4907] was obtained and resolved into optical antipodes according to Aaron et al.[23]

***O*-Ethyl ethylphosphonochloridothionate (22)** [bp 20° (0.05 mmHg), $n^{23}D$ = 1.4912, $[\alpha]^{20}D$ −65.8° (neat)] was prepared by chlorination of thio acid **21** [$[\alpha]^{20}D$ = −14.2° (neat)] with PCl_5 according to the procedure given by Michalski and Mikołajczyk.[24]

***O*-Ethyl-*O*-methyl ethylphosphonothionate (7)** [bp 46° (3 mmHg), $n^{20}D$ = 1.4662, $[\alpha]^{20}D$ = −2.71° (neat), $\delta_{^{31}P}$ −102.5 ppm)] was prepared by the reaction of **22** [$[\alpha]^{20}D$ = −65.8° (neat)] with sodium methoxide.[16]

***O*-Ethyl-*S*-methyl ethylphosphonothiolate (23)** [bp 62° (2 mmHg), $n^{22}D$ = 1.4776, $[\alpha]^{20}D$ = −66.2° (neat), $\delta_{^{31}P}$ −61.5 ppm] was synthesized from **7** [$[\alpha]^{20}D$ = −2.71° (neat)] by the reaction with methyl iodide under Pishschimuka reaction conditions.[16]

***O*-Ethyl-*O*-methyl ethylphosphonate (8)** [bp 50° (2.5 mmHg), $n^{20}D$ = 1.4129, $[\alpha]^{20}D$ = −1.36° (neat), $\delta_{^{31}P}$ −34.5 ppm] was prepared by methanolysis of **23** [$[\alpha]^{20}D$ = −66.2° (neat)] in the presence of silver nitrate according to the procedure described by Stec.[16]

Optically active methylphenyl-*n*-propylphosphine (24) was prepared by alkaline hydrolysis of diastereoisomeric benzylmethylphenyl-*n*-propylphosphonium dibenzoyl hydrogen tartrates[3,25] followed by reduction with $SiHCl_3$–Et_3N of the resulting phosphine oxide **11**:[26] bp 70° (1 mmHg); $n^{22}D$ = 1.5448; $\delta_{^{31}P}$ +37.6 ppm (benzene); δ_{CH_3} 1.26 ppm ($CDCl_3$), $^2J_{PCH_3}$ = 3.0 Hz [lit.[3] bp 73–74° (0.7 mmHg)].

Methylphenyl-*n*-propylphosphine sulfide (9) ($[\alpha]^{20}D$ = −8.25°) was prepared by addition of elemental sulfur to **24** [$[\alpha]^{20}D$ = −8.05° (toluene)]:[3,15] mp 65–75°; $\delta_{^{31}P}$ −37.3 ppm (benzene); δ_{CH_3} 2.12 ppm ($CDCl_3$), $^2J_{PCH_3}$ = 12.7 Hz.

Methylphenyl-*n*-propylphosphine selenide (10) ($[\alpha]^{20}D$ = −15.2°) was obtained by addition of elemental selenium to **24** [$[\alpha]^{20}D$ = −15.0° (toluene)]:[4c] mp 60–70°; $\delta_{^{31}P}$ −25.3 ppm (benzene); δ_{CH_3} 2.15 ppm ($CDCl_3$); $^2J_{PCH_3}$ = 12.7 Hz (Anal. Calcd for $C_{10}H_{17}PSe$: C, 49.00; H, 6.17; P, 12.63. Found: C, 49.22; H, 5.94; P, 12.42).

II. Oxidation of 1 with Hydrogen Peroxide. A. Hydrogen peroxide (2 ml) was added to a solution of **1** (3.64 g, 0.02 mol, **1a:b** 6:94) in methanol (20 ml). The mixture was refluxed for 1 hr, cooled, and evaporated. The residue was shaken with water and the resulting elemental sulfur was filtered off. The filtrate was extracted with $CHCl_3$ (5 × 10 ml). Combined $CHCl_3$ solutions were dried over $MgSO_4$ and evaporated. The residue was distilled, yielding 2.3 g (70%) of **5**, bp 115° (1.0 mmHg), $n^{22}D$ = 1.4388 [lit.[13] bp 90° (0.8 mmHg), $n^{20}D$ = 1.4365]. GLC and ^{31}P NMR analysis (neat) revealed the presence of **5a** (20%, $\delta_{^{31}P}$ +5.2 ppm) and **5b** (80%, $\delta_{^{31}P}$ +6.5 ppm).

B. The same procedure as in expt IIa performed in boiling acetone yielded from **1** (containing 86% of **1a** and 14% of **1b**) **5** containing 25% of **5a** and 75% of **5b** with overall yield 65%, bp 103–105° (0.6 mmHg), $n^{21}D$ = 1.4382 [lit.[13] bp 80–95° (0.5 mmHg), $n^{20}D$ = 1.4390].

III. Oxidation of 2 with Hydrogen Peroxide. A. Hydrogen peroxide (1 ml) was added dropwise, with stirring at 20°, to a solution of **2** (4.6 g, 0.02 mol, **2a:b** 4:96) in methanol (20 ml). An exothermic reaction was accompanied with precipitation of red selenium. Stirring at room temperature was continued for 20 min and the resulting selenium was filtered off. The filtrate was evaporated and the residue was distilled, yielding 2.8 g (85%) of **5**, bp 110° (0.8 mmHg), $n^{20}D$ = 1.4368. GLC and ^{31}P NMR analysis (neat) revealed the presence of **5a** (4%, $\delta_{^{31}P}$ +5.2 ppm) and **5b** (96%, $\delta_{^{31}P}$ +6.5 ppm).

B. The same procedure performed with **2** (containing 88% of **2a** and 12% of **2b**) in acetone yielded 82% of **5** (86% of **5a** and 14% of **5b**), bp 90° (0.3 mmHg), $n^{21}D$ = 1.4352.

IV. Oxidation of 3 with Hydrogen Peroxide. The procedure described in section II was performed with **3** (90% cis and 10% trans) in boiling nitromethane. The resulting phosphonoamidate **6** [bp 80° (0.3 mmHg), $n^{22}D$ = 1.4540, yield 62%] contained as the major component the cis isomer (75%, $\delta_{^{31}P}$ −12.3 ppm) contaminated with the trans isomer (25%, $\delta_{^{31}P}$ −6.4 ppm) [lit.[13] $\delta_{^{31}P}$ (*cis*-**6**) −7.5 ppm, $\delta_{^{31}P}$ (*trans*-**6**) −4.5 ppm].

V. Oxidation of 4 with Hydrogen Peroxide. The reaction was performed, as in section III, in acetone solution. Starting from the mixture of 85% of *cis*-**4** and 15% of *trans*-**4**, **6** was obtained with the same isomer ratio, bp 85° (0.4 mmHg), $n^{20}D$ = 1.4526, yield 81%.

VI. Oxidation of Phosphine Sulfide 9 with H_2O_2. General Procedure. Hydrogen peroxide (2 ml) was added to a solution of **9** (0.4 g, 0.002 mol) in appropriate solvent (20 ml). The solution was heated under reflux for 10–60 min. Solvent was removed under reduced pressure and the residue was dissolved in water (20 ml). The precipitated elemental sulfur was filtered off and the product **11** extracted with $CHCl_3$ and purified by distillation, bp 120° (0.6 mmHg), $\delta_{^{31}P}$ −32.5 ppm (benzene). The distillate had solidified in the form of white, extremely hygroscopic crystals, mp 55–58°, yield 70–80%.

VII. Oxidation of Phosphine Selenide 10 with H_2O_2. General Procedure. Hydrogen peroxide (0.022 mol) was added dropwise, with stirring and external cooling, to a solution of **10** (0.5 g, 0.002 mol) in appropriate solvent (20 ml). An exothermic reaction, accompanied with precipitation of red selenium, was observed. Stirring at room temperature was continued for 10–20 min and the resulting elemental selenium was filtered off. The filtrate was evaporated and the residue was distilled, yielding 75–90% of phosphine oxide **11**, bp 120° (0.6 mmHg), mp 55–58°, $\delta_{^{31}P}$ −32.5 ppm (benzene).

VIII. Oxidation of Thionophosphonate 7 with Hydrogen Peroxide. To a solution of **7** [3.36 g, 0.02 mol, $[\alpha]^{20}D$ = −2.71° (neat)] in dioxane (30 ml) was added hydrogen peroxide (2 ml, 90%). The solution was gently heated until an exothermic reaction took place. Heating under reflux was continued for the next 10 min and the mixture was evaporated and dissolved in water (20 ml). The resulting elemental sulfur was filtered off and the filtrate was extracted with $CHCl_3$ (8 × 10 ml). Combined $CHCl_3$ solutions were dried over $MgSO_4$ and evaporated. The residue was distilled, giving 2.5 g (82%) of **8**, bp 54° (3 mmHg), $n^{20}D$ = 1.4148, $[\alpha]^{20}D$ = −1.47° (neat).

Registry No.—**1a**, 23168-88-9; **1b**, 23168-89-0; **2a**, 33996-01-9; **2b**, 33996-02-0; *cis*-**3**, 40986-08-1; *trans*-**3**, 40986-07-0; *cis*-**4**, 57215-11-9; *trans*-**4**, 40986-11-6; **5a**, 33996-04-2; **5b**, 33996-03-1; *cis*-**6**, 41158-21-8; *trans*-**6**, 41158-20-7; **7**, 5152-73-8; **8**, 31660-62-5; **9**, 13153-91-8; (*S*)-(−)-**10**, 34641-79-7; (*R*)-(+)-**10**, 33995-97-0;

(*S*)-(−)-**11**, 1515-99-7; (*R*)-(+)-**11**, 17170-48-8; (±)-**11**, 2328-23-6; **18**, 6362-87-4; **19a**, 7735-85-5; **19b**, 7735-81-1; *cis*-**20**, 40781-04-2; *trans*-**20**, 40781-03-1; **21**, 4789-36-0; **22**, 4789-37-1; **23**, 20698-84-4; **24**, 13153-89-4; sodium methoxide, 124-41-4; benzylmethylphenyl-*n*-propylphosphonium dibenzoyl hydrogen tartrate isomer 1, 57215-13-1; benzylmethylphenyl-*n*-propylphosphonium dibenzoyl hydrogen tartrate isomer 2, 57215-15-3; hydrogen peroxide, 7722-84-1.

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(16) Assuming full retention in the Pishschimuka rearrangement of thionophosphonate **7** [J. Michalski, M. Mikolajczyk, and J. Omelańczuk, *Tetrahedron Lett.*, 3565 (1968)], one can calculate the stereospecificity of oxidation of **7** by comparison of the specific rotation of **8** obtained from oxidation with that of **8** resulting from silver ion promoted methanolysis [W. J. Stec, *Bull. Acad. Pol. Sci., Ser. Sci. Chim.*, **21**, 709 (1973)]. Such a solvolysis in the case of cyclic phosphorothiolates has been found to proceed with full inversion of configuration at phosphorus. However, in the case under consideration (see Scheme I) oxidation (B) seems to be more stereospecific than the methanolysis (A).
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1-Vinylcycloalkenes in the McCormack Cycloaddition with Phosphonous Dihalides. Stereochemistry of Some Resulting Bicyclic Phospholene Oxides[1]

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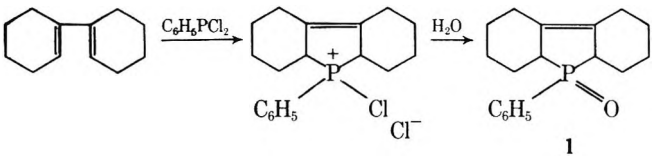
1-Vinylcyclohexene condenses at 25° with methylphosphonous dichloride. Hydrolysis of the cycloadduct gives the 3-phospholene oxide with a tetramethylene group at the 2,3 positions. The product consists of a mixture of stereoisomers (72% trans, 28% cis); their structures were assigned with the aid of ^{13}C, ^{31}P, and ^1H NMR spectral relations. 1-Vinylcyclohexenes containing bromine or chlorine on the α-vinyl carbon also participate smoothly in the cycloaddition. A new type of diene, containing a 2-trimethylsiloxy group, was used in the cycloaddition; 1-acetylcyclohexene gave such a siloxy diene with $LiN(i\text{-}Pr)_2$ and $(CH_3)_3SiCl$, and on hydrolysis of the cycloadduct formed with CH_3PCl_2 there was obtained a 3-keto phospholane derivative. The 4-vinyl derivative of 1,2-dihydronaphthalene also participated readily in the cycloaddition, giving a tricyclic phospholene oxide derivative. Two examples of further utilization of the bicyclic phospholene oxides are provided, namely, P-deoxygenation to the bicyclic phosphines and hydrogenation of the double bond to perhydrophosphindole derivatives.

The cycloaddition of conjugated dienes and trivalent phosphorus halides, first described by McCormack,[2] has proved to be an excellent route to derivatives of the phospholene ring system. To the present, however, this reaction has been used primarily to form monocyclic structures, although it has far greater potential through extension to the synthesis of multicyclic structures. McCormack did report[2] the use of 1,1′-biscyclohexenyl in the reaction with phenylphosphonous dichloride to form a tricyclic adduct which on hydrolysis gave phospholene oxide **1**, and the same compound was later obtained by other workers.[3] Phosphorus trichloride also adds to this diene.[4] Bridged phospholene



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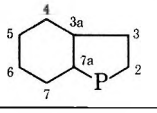
oxides (**2**) can be obtained by cycloaddition with cycloheptadienes.[5]

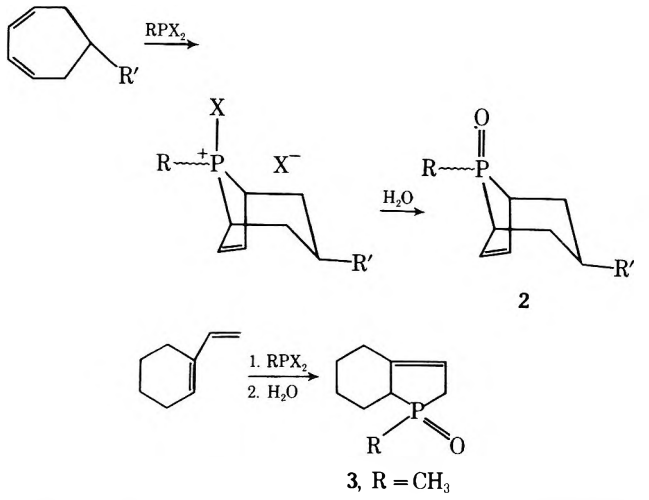
1-Vinyl cyclic alkenes are readily obtainable dienes, and should serve as valuable precursors of bicyclic phospholene derivatives. Thus, with 1-vinylcyclohexene, members of the hexahydrophosphindole family would be formed. While

Table I
^{13}C NMR Spectral Data[a]



Compd[b]	C-2	C-3	C-3a	C-4,5,6,7[c]	C-7a	PCH_3
3a	31.4 (60)	112.9 (11)	144.6 (13)	21.1–29.9	39.9 (68)	13.6 (63)
3b	30.1 (65)	113.8 (12)	143.5 (14)	21.1–29.9	40.8 (70)	9.6 (63)
6	24.8 (65)	28.5 (10)	144.1 (30)	20.4–22.6	130.3 (85)	15.9 (70)
trans-8	39.6 (60)	108.9 (10)	140.5 (10)	22.6–28.3	42.7 (70)	16.8 (63)
cis-8	38.5 (60)	109.3 (14)	139.4 (10)	22.6–28.3	43.6 (70)	12.6 (65)
13a	33.8 (10)	119.2 (3)	146.7 (3)	26.9–37.2	51.5 (10)	14.6 (18)
13b	33.2 (13)	120.7 (3)	144.0 (3)	26.9–37.2	44.0 (15)	9.2 (23)
15a	*d*	*d*	*d*	*d*	39.8 (70)	13.7 (60)
15b	*d*	*d*	*d*	*d*	38.1 (70)	17.3 (60)

[a] Chemical shifts are in parts per million downfield from Me_4Si. Values in parentheses are J_{P-C} in hertz. Solutions in $CDCl_3$ were used. [b] Samples of 3, 8, 13, and 15 were run as isomer mixtures. [c] Insufficiently resolved for firm assignments. [d] Occurred at δ 18.5–28.2.



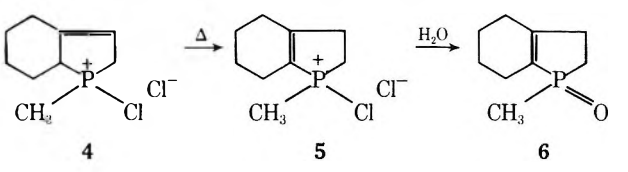
3, R = CH_3

McCormack's patent[2] included this diene among those said to undergo the cycloaddition, no examples were given, and no products were characterized; the process remains to be exploited for the synthesis of reduced phosphindoles. There are only a few examples known of such compounds;[6] they have been prepared by quite different methods and have different substitution and/or unsaturation patterns than those afforded by the McCormack route.

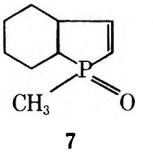
In this paper we will show that the McCormack reaction is eminently suitable for the synthesis of multicyclic phospholene derivatives. Both bicyclic and tricyclic derivatives have been obtained from appropriate 1-vinyl cyclic olefins, and the method appears quite capable of extension to other systems as well. Spectral techniques for unraveling the stereochemical consequence of fusing a cycloalkane ring onto a phospholene ring have also been developed in this study.

Synthesis of Bicyclic Phospholene Oxides. Under the mild conditions normally used for acyclic dienes in the McCormack reaction (room temperature in an alkane solvent), 1-vinylcyclohexene and methylphosphonous dichloride combined slowly to give a white, crystalline solid. After 25 days, the solid was hydrolyzed and the bicyclic phospholene oxide **3** was obtained in 37% yield. That the double bond was in the 3 position was readily apparent from the proton NMR spectrum; there was only a single olefinic proton (δ 5.43), showing the expected[7] large coupling to ^{31}P (29 Hz).

In an attempt to improve the yield in the cycloaddition, the reaction was conducted in refluxing hexane. Hydrolysis of the adduct that had precipitated after 42 hr gave a phospholene oxide in 64% yield, but the product proved to be isomeric with **3**. Since it gave no olefinic proton NMR signals, but had ir absorption for a double bond (1630 cm^{-1}), it was assigned structure **6**. Apparently, the initially formed cycloadduct **4** undergoes rearrangement on heating, forming **5**. The relationship between oxides **3** and **6** was confirmed by performing base-catalyzed rearrangement[7] of the double bond in the former into conjugation with the phosphoryl group. Of the two possible conjugated products, **6** and **7**, only **6** was formed (65%).



4 5 6



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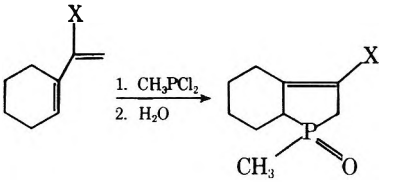
The ^{13}C NMR spectra (Table I) of oxides **3** and **6** confirmed the position of the double bond. The signals for carbons in the sp^2 region for **6** were very weak; these carbons are not coupled to hydrogen and their signals lack intensification of the nuclear Overhauser effect. That sp^2 carbon α to phosphorus was easily distinguished by its large coupling[8] to ^{31}P of 85 Hz. For **3**, stereoisomers were present, as is discussed in the next section. The two sp^2 carbons in each isomer had relatively small coupling to ^{31}P (11–14 Hz), proving their β location to phosphorus.

1-(α-Halovinyl)cyclohexenes, readily obtained by the reaction of aqueous hydrogen halides with 1-ethynylcyclohexene[9] or of thionyl chloride and pyridine on 1-ethynylcyclohexanol,[10] also condensed readily with methylphosphonous dichloride.

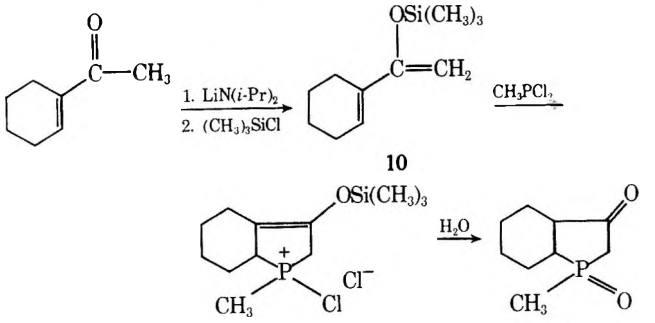


8, X = Br
9, X = Cl

Oxide **8** was established by ^{13}C NMR spectroscopy (Table I); the sp^2 carbons were easily distinguished, and from the small coupling to ^{31}P (10–14 Hz) it was obvious that both were located β to phosphorus. Also, in the proton

NMR spectrum, there was no signal for CH bearing bromine, as would be required for the rearranged structure corresponding to **6**. The latter point was useful in assigning structure **9** to the chloro derivative.

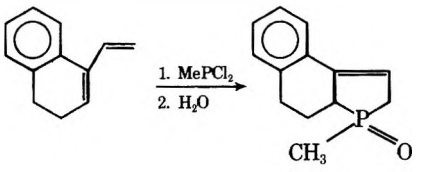
To demonstrate further the synthetic possibilities in the bicyclic system, we sought also the 3-keto derivative, which as for the monocyclic compound should be a useful intermediate to other structures. A new route to such ketones resulted from the present study. It employs a 1-acetylalkene as a starting material, which is converted to a siloxydiene by the lithium diisopropylamide–trimethylchlorosilane sequence.[12] Thus **10** was obtained as a distillable liquid in 60% yield. This siloxydiene participates in the McCor-



mack reaction, and the acidic medium developing on adduct hydrolysis causes simultaneous generation of the keto group. Recently, others[13] have also shown that siloxydienes are readily accessible from α,β-unsaturated ketones by silylation techniques, and it is quite possible that such compounds will be of general utility in 3-phospholanone synthesis. The overall route is very attractive since the desired phospholanone can be obtained in only two steps from the readily available α,β-unsaturated carbonyl compounds. Further investigation of this new method is in progress.

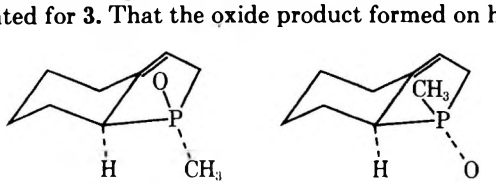
The bicyclic 3-phospholanone did not show spectral indications of any unusually high enol content. For the monocyclic compound, both ir and NMR spectra show clearly that large concentrations of enol can exist in equilibrium with the keto form.[11,14]

A 1-vinylcyclohexene bearing a benzo group was found to react especially readily with methylphosphonous dichloride, and demonstrates the great potential of the McCormack reaction for forming multicyclic phosphorus compounds. Hydrolysis after 10 days gave oxide **12** in 36% yield. The position of the double bond was established by



spectral features as used for the bicyclic compounds. Oxide **12** retains considerable water solubility in spite of its high carbon content.

Stereochemistry of Bicyclic Phospholene Oxides. 3-Phospholene oxides such as **3, 8, 9,** and **12** have two chiral centers and are capable of cis,trans isomerism.[15] These are illustrated for **3**. That the oxide product formed on hydrolysis of the diene–CH_3PCl_2 cycloadducts was a mixture of stereoisomers was evident from NMR spectral features; this was especially noticeable from signals associated with the CH_3–P unit, since steric differences are most pronounced at this site. Thus, the ^{13}C NMR spectrum of **3** (Table I) showed two CH_3 carbons (δ 13.6 and 9.6), with the downfield signal predominating (70:30). Also there were two methyl proton signals and two ^{31}P signals. The steric crowding from cis orientation of PCH_3 with a 2 substitutent causes an upfield shift of this CH_3 signal,[8] and thus the minor isomer of **3** with the upfield signal is assigned cis structure **3b**. The order of ^{31}P NMR signals resulting from this assignment (in D_2O, trans δ −70.5; cis, −77.1) is also that expected from monocyclic compounds; thus for 1,2-dimethyl-3-phospholene oxide, the trans signal is at −60.0 and cis is at −67.2.

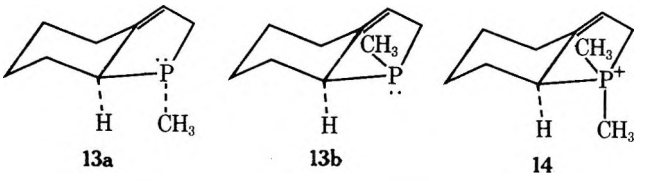


Tricyclic oxide **12** was obtained primarily (71%) in cis form, as judged from the ^{31}P NMR signals (major isomer δ − 77.1, minor −71.2). Stereoisomers were also obtained for halo compounds **8** and **9**, but in these cases, the isomer ratio was nearly 1:1. The isomer ratios from cycloadduct hydrolysis are not necessarily of mechanistic significance, since it is known that they may be influenced by conditions of the hydrolysis,[15] in ways that are yet to be defined.

The keto oxide **11** has three chiral centers, and the sample prepared is a mixture of the four possible cis, trans forms, as judged from the ^{31}P NMR spectrum with four close-lying signals (−44.8 to −49.2 ppm).

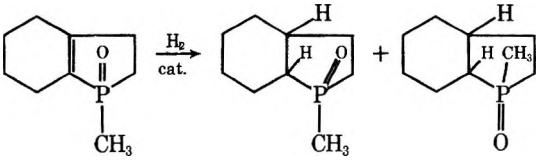
We have had some success in separating the mixture of isomers **3a** and **3b** by distillation through a short column of glass helices. The lower boiling trans isomer was obtained in 90% purity, leaving a cis-enriched pot residue. Pure samples seem obtainable, if desired, by this technique.

Stereochemistry of Other Bicyclic Phosphorus Derivatives. Phosphines. Oxide **3** was readily deoxygenated with trichlorosilane to form a mixture of stereoisomeric phosphines **13a** and **13b,** which gave the same quaternary salt **14** with methyl iodide. The reduction is known[16] to



proceed with retention of configuration, and thus the ratio of phosphines **13a** and **13b** remained the same as for the oxides **3a** and **3b**. That the major isomer indeed had the trans structure (**13a**) was confirmed by the ^{13}C NMR spectrum (Table I); this isomer had its CH_3 signal downfield (δ 15.4 ppm) from that of the minor isomer (δ 9.2), where the cis configuration caused steric crowding. The ^{31}P shifts (trans, δ +28.7; cis, +26.2) again were in the order expected from the monocyclic model, 1,2-dimethyl-3-phospholene[12] (trans, δ +28.2; cis, +16.7), as were the proton NMR shifts for the *P*-methyl groups (**13a,** δ 0.88, and **13b,** 0.73; the monocyclics had trans 0.83, cis 0.73).

Perhydrophosphindole Oxides. Cis addition of hydrogen to the double bond of the phospholene oxide **6** produced the perhydrophosphindole derivatives **15a** and **15b** in nearly equal amounts. That compound with the more



upfield ^{13}C methyl signal (Table I) was assumed to have structure **15a** on the basis of the greater steric crowding in this isomer. Catalytic hydrogenation is known to proceed by the cis addition of hydrogen, with attack on the less hindered face of the molecule where a choice is possible. In the case of **6**, hydrogen can approach a face where phosphoryl oxygen is present or a face where methyl is present. From the 1:1 mixture of products, it appears that the rates of approach to the two faces must be equivalent. This is, we believe, the first test of the relative directing influence of *P*-methyl vs. *P*-oxygen toward hydrogen in a 2-phospholene oxide system.[18]

Experimental Section

General. Melting points were taken on a Mel-Temp apparatus and are corrected; boiling points are uncorrected. All manipulations of phosphines were conducted under nitrogen in a glove bag. ^1H NMR spectra were taken with a JEOL MH-100 spectrometer; chemical shifts are relative to internal tetramethylsilane. ^{31}P NMR spectra were obtained on a Bruker HFX-10 system at 36.43 MHz with proton noise decoupling; chemical shifts are referenced to 85% H_3PO_4, with positive shifts upfield, negative downfield. Proton noise decoupled Fourier transform ^{13}C NMR spectra (Table I) were also obtained on the Bruker spectrometer, at 22.62 MHz, utilizing C_6F_6 in a 3-mm coaxial capillary as an external heteronuclear lock. Chemical shifts are given in parts per million downfield from Me_4Si as zero. Methylphosphonous dichloride was obtained from the Ethyl Corp. Elemental analyses were performed by commercial laboratories.

1-Methyl-$\Delta^{3(3a)}$-2,4,5,6,7,7a-hexahydro-1(*H*)-phosphindole 1-Oxide (3). To a wide-mouth, screw-cap brown bottle was added 37.8 g (0.35 mol) of 1-vinylcyclohexene, 32.2 ml (0.36 mol) of methylphosphonous dichloride, 1 g of copper stearate, and 100 ml of pentane. The bottle was sealed and allowed to stand for 2 months. The resulting cycloadduct was filtered off and washed with pentane (2 × 50 ml). The solid was added cautiously to 25 ml of water and the resulting mixture made slightly basic with solid $NaHCO_3$. The aqueous solution was then extracted continuously for 24 hr with chloroform. The chloroform extract was dried ($MgSO_4$) and concentrated on the rotary evaporator. Distillation of the residue gave 22.2 g of **3** (37%) as a colorless oil, bp 115–120° (0.2 mm), which crystallized on standing to a hygroscopic white solid: ^1H NMR ($CDCl_3$) δ 1.46 and 1.58 (each d, $^2J_{PH}$ = 13 Hz, for PCH_3 of **3b** and **3a**, respectively), 1.71–2.73 (m, ring $-CH_2-$), 5.42 (d, $^3J_{PH}$ = 29 Hz, >C=CH–); ir (neat) 1640 (C=C), 1205 cm^{-1} (P=O); ^{31}P NMR (D_2O, 50%) δ −70.5 (trans, 72%) and −77.1 (cis, 28%).

Anal. Calcd for $C_9H_{15}OP$: C, 63.52; H, 8.89; P, 18.19. Found: C, 63.18; H, 9.16; P, 17.80.

Twenty grams of a 70:30 mixture of **3a** and **3b** was distilled through a 0.25 × 12 in. column packed with glass helices. A total of nine equal-sized fractions was received over the range 90–106° (0.04 mm). It was found by GC and ^{31}P NMR that the trans isomer **3a** had been concentrated (90%) in the first several fractions. The last fraction and the pot residue contained the cis isomer **3b** in a purity of greater than 90%.

1-Methyl-$\Delta^{3a(7a)}$-2,3,4,5,6,7-hexahydro-1(*H*)-phosphindole 1-Oxide (6). To a heated (70°) mixture of 2.0 ml (22.3 mmol) of methylphosphonous dichloride, 500 mg of copper stearate, and 10 ml of *n*-hexane was added 2.0 g (18.5 mmol) of 1-vinylcyclohexene over a 90-min period. The resulting mixture was then refluxed for 42 hr. The flask was cooled (0°) and water (25 ml) was added. The solution was neutralized with solid $NaHCO_3$ and extracted continuously for 12 hr with chloroform. The chloroform extract was dried ($MgSO_4$) and concentrated on the rotary evaporator. Kugelrohr distillation of the residue at 110° (0.1 mm) gave 2.0 g of **6** (64%) as a colorless oil which crystallized on standing to a hygroscopic white solid: ^1H NMR ($CDCl_3$) δ 1.48 (d, $^2J_{PH}$ = 13 Hz, PCH_3), 1.40–2.70 (m, $-CH_2-$); ir (neat) 1630 (C=C), 1175 cm^{-1} (P=O); ^{31}P NMR δ −63.2 ($CDCl_3$, 50%) or −76.5 (D_2O, 50%).

The same compound was obtained by rearrangement of **3**. A mixture of 1 g (5.88 mmol) of **3** and 10 ml of 3 *N* NaOH was refluxed under N_2 for 72 hr. The resulting solution was cooled, neutralized, and extracted with chloroform (4 × 75 ml). The organic extracts were combined, dried ($MgSO_4$), and concentrated under vacuum. Distillation of the residual oil gave 620 mg of **6** (62%), bp 120–125° (0.2 mm), as a colorless oil which slowly solidified on standing; spectral properties were the same as those reported in the preceding paragraph.

Anal. Calcd for $C_9H_{15}OP$: C, 63.52; H, 8.89; P, 18.19. Found: C, 63.29; H, 9.10; P, 17.85.

3-Bromo-$\Delta^{3(3a)}$-1-methyl-2,4,5,6,7,7a-hexahydro-1(*H*)-phosphindole 1-Oxide (8). A mixture of 45 g (0.24 mol) of 1-(α-bromovinyl)-1-cyclohexene,[9] 22.5 ml (0.25 mol) of methylphosphonous dichloride, 2 g of copper stearate, and 200 ml of pentane was allowed to stand for 2 months. The resulting white solid was filtered off and washed with pentane. The solid was then added slowly to 100 ml of a saturated $NaHCO_3$ solution. The aqueous mixture was extracted continuously with chloroform for 12 hr. The chloroform was then dried ($MgSO_4$) and concentrated. Distillation gave 15.0 g of 8 (25%), bp 144–149° (0.02 mm), which solidified on standing: mp 77–82°; ^1H NMR ($CDCl_3$) δ 1.60 and 1.69 (each d, $^2J_{PH}$ = 12 Hz, PCH_3, for cis and trans isomers, respectively), 1.2–3.2 (m, $-CH_2-$); ir ($CDCl_3$ solution between salt plates) 1190 cm^{-1} (P=O); ^{31}P NMR (50% in D_2O) δ −67.2 (cis, 51%) and −61.6 (trans, 49%).

Anal. Calcd for $C_9H_{14}BrOP$: C, 43.40; H, 5.66; Br, 32.08; P, 12.44. Found: C, 43.36; H, 5.72; Br, 31.88; P, 12.43.

3-Chloro-$\Delta^{3(3a)}$-1-methyl-2,4,5,6,7,7a-hexahydro-1(*H*)-phosphindole 1-Oxide (9). A mixture of 14.2 g (0.1 mol) of 1-(α-chlorovinyl)cyclohexene,[10] 9.0 ml (0.1 mol) of methylphosphonous dichloride, 1 g of copper stearate, and 75 ml of pentane was allowed to stand for 3 weeks. The resulting white solid was filtered off and washed with pentane. The solid was then added slowly to 100 ml of a saturated $NaHCO_3$ solution. The aqueous mixture was extracted continuously with chloroform for 12 hr. The chloroform was then dried ($MgSO_4$) and concentrated. Distillation of the crude oil gave 6.1 g of **9** (30%), bp 133–138° (0.02 mm), as an oil which crystallized on standing to give a hygroscopic solid: mp 65–70°; ^1H NMR (D_2O) δ 1.65 and 1.73 (each d, $^2J_{PH}$ = 12.5 Hz, cis and trans PCH_3, respectively), 1.10–3.05 (m, $-CH_2-$); ir (Nujol) 1190 cm^{-1} (P=O); ^{31}P NMR (50% in D_2O) δ −66.4 (cis, 49.3%) and −60.7 (trans, 50.7%).

Anal. Calcd for $C_9H_{14}ClOP$: C, 52.81; H, 6.85; P, 15.16. Found: C, 53.05; H, 6.98; P, 15.08.

1-(α-Trimethylsiloxyvinyl)cyclohexene (10). To a cooled (−78°) solution of 2.12 g (0.21 mol) of diisopropylamine in 50 ml of tetrahydrofuran (THF) was added 87.5 ml of 2.4 *M* *n*-butyllithium (0.21 mol) in hexane. The lithium diisopropylamide precipitated from solution to form a white slurry. Stirring was continued for 15 min and then 25.1 g (0.20 mol) of 1-acetylcyclohexene in 10 ml of THF was added over a 10-min period. The slurry turned pale green; stirring was continued for 5 min at −78°. Chlorotrimethylsilane (27.2 g, 0.25 mol) was then added in one portion. The resulting mixture was stirred at −78° for 5 min and then at room temperature for 1 hr. The mixture was partitioned between pentane (250 ml) and saturated aqueous $NaHCO_3$ (200 ml). The layers were separated and the aqueous layer extracted with pentane (2 × 100 ml). The pentane extracts were combined, dried ($MgSO_4$), and concentrated to give a clear white oil. Distillation gave 24.1 g of **10** (60.2%): bp 111–115° (18 mm); ^1H NMR ($CDCl_3$) δ 0.20 [s, 9 H, $Si(CH_3)_3$], 1.60 (m, 4 H, $-CH_2-$), 2.11 (m, 4 H, allylic CH_2), 4.23 (d, *J* = 15 Hz, $-C=CH_2$), 6.20 (m, 1, H, $-CH_2CH=$); ir (neat) 1660 (internal C=C), 1610 cm^{-1} (terminal C=C).

1-Methyl-3-oxo-4,5,6,7-tetrahydrophosphindoline 1-Oxide (11). A solution of 4.2 g (0.02 mol) of diene **10**, 2.2 ml (0.025 mol) of methylphosphonous dichloride, 100 mg of copper stearate, and 50 ml of pentane was allowed to stand for 5 days. The resulting yellow solid was filtered off and washed with pentane (2 × 10 ml). The solid was added slowly to 10 ml of water and the resulting mixture stirred for 30 min. The solution was made slightly basic with 3 *N* sodium hydroxide and then extracted continuously with chloroform. The chloroform extract was dried ($MgSO_4$) and concentrated. The resulting gummy solid (1.8 g, 49%) was sublimed at 140° (0.5 mm) to give 1.02 g of 11 (37%): mp 77–82°; ^1H NMR ($CDCl_3$) δ 1.18–35 (complex multiplet, $-CH_2-$), 1.71 (d, $^2J_{PH}$ = 15 Hz, PCH_3), 1.74 (d, $^2J_{PH}$ = 14.5 Hz, PCH_3), 1.76 (d, $^2J_{PH}$ = 14 Hz, PCH_3), 1.78 (d, $^2J_{PH}$ = 14 Hz, PCH_3); ir ($CDCl_3$) 1715 cm^{-1} (C=O), 1180 cm^{-1} (P=O); ^{31}P NMR ($CDCl_3$) δ −44.8 (42%), −45.3 (32%), −46.2 (19%), and −49.2 (7%).

Anal. Calcd for $C_9H_{15}O_2P$: C, 58.07; H, 8.12; P, 16.64. Found: C, 57.97; H, 8.33; P, 16.38.

1-Methyl-$\Delta^{3(3a)}$-2,8,9,9a-tetrahydro-1(*H*)-benzo[*e*]phosphindole 1-Oxide (12). A solution of 6.61 g (42 mmol) of 1,2-dihydro-4-vinylnaphthalene prepared in 65% yield by the method of Robins and Walker,[20] 3.7 ml (42 mmol) of methylphosphonous dichloride, 1 g of copper stearate, and 50 ml of pentane was allowed to stand for 1 month. The resulting cycloadduct was filtered off and washed with pentane (2 × 50 ml). The solid was dissolved in

25 ml of water and the solution was made slightly basic with solid $NaHCO_3$. The aqueous mixture was then extracted with chloroform (4 × 50 ml). The organic extracts were combined, dried ($MgSO_4$), and concentrated to give 5.1 g (56%) of crude solid. Sublimation at 100° (0.05 mm) gave 3.30 g (36%) of **12**: mp 111–115°; ^1H NMR ($CDCl_3$) δ 1.44 (d, $^2J_{PH}$ = 12 Hz, PCH_3), 1.72 (d, $^2J_{PH}$ = 13 Hz, PCH_3), 1.90–3.62 (complex m, $-CH_2-$), 6.28 (d, $^3J_{PH}$ = 28 Hz, $-C=CH-$), 7.04–7.76 (4 H, aromatic); ^{31}P NMR (D_2O, 2 *M*) δ −77.7 (71%) and −71.2 (29%); ir (Nujol) 1200 cm^{-1} (P=O).

Anal. Calcd for $C_{13}H_{15}OP$: C, 71.55; H, 6.88; P, 14.20. Found: C, 71.49; H, 6.94; P, 14.41.

***trans*- (13a) and *cis*- (13b) 1-Methyl-$\Delta^{3(3a)}$-2,4,5,6,7,7a-hexahydro-1(*H*)-phosphindole.** To a solution of 5.1 g (30 mmol) of **3a** (60%) and **3b** (40%) in 200 ml of dry benzene at 0° was added a solution of 13.1 ml (130 mmol) of trichlorosilane in 25 ml of benzene over a 1-hr period. The ice bath was removed and the mixture was refluxed for 12 hr. It was cooled and carefully hydrolyzed by addition of 50 ml of a 20% NaOH solution. The layers were separated and the aqueous layer was extracted with benzene (4 × 25 ml). The organic extracts were combined and dried ($MgSO_4$) and the benzene was distilled off at atmospheric pressure. The remaining yellow oil was distilled to give 3.1 g of the isomers of **13** (68%) as a colorless liquid: bp 104–106° (16 mm); ^1H NMR ($CDCl_3$) δ 0.73 and 0.88 (each d, $^2J_{PH}$ = 3.5 Hz, PCH_3 for **13b** and **13a**, respectively), 1.10–2.85 (m, $-CH_2-$), 5.15–5.65 (m, $>C=CH-$); ^{31}P NMR (neat) δ +26.2 (**13a**, 56%) and +28.6 (**13b**, 44%).

The methiodide **14** was prepared by treating a small amount of the phosphine with excess methyl iodide. Recrystallization from methanol–ether gave white needles, mp 265° dec.

Anal. Calcd for $C_{10}H_{18}IP$: C, 40.54; H, 6.08; P, 10.47. Found: C, 40.71; H, 5.95; P, 10.28.

1-Methylperhydrophosphindole 1-Oxide (15a and 15b). A mixture of 1 g (5.8 mmol) of **6**, 100 ml of absolute ethanol, and 500 mg of 5% rhodium on alumina was placed in a Parr pressure bottle and shaken under H_2 (50 psi) for 13 hr. The catalyst was removed by filtration and the ethanol by rotary evaporation. The residual oil solidified and was sublimed at 70° (0.01 mm) to give 725 mg of **15** (73%): mp 88–94°; ^1H NMR (D_2O δ 1.57 and 1.62 (each d, $^2J_{PH}$ = 13 Hz, PCH_3), 1.15–2.60 (m, $-CH_2-$); ir (Nujol) 1160 cm^{-1} (P=O); ^{31}P NMR (50% in D_2O) δ −82.8 (49.5%) and −78.8 (50.5%).

Anal. Calcd for $C_9H_{17}OP$: C, 62.79; H, 9.88; P, 18.02. Found: C, 62.95; H, 10.05; P, 17.88.

Acknowledgment. We are grateful to Mr. William L. Orton for the preparation of **6** by the direct cycloaddition method.

Registry No.—**3a**, 57065-62-0; **3b**, 57065-63-1; **6**, 57065-64-2; *trans*-**8**, 57065-65-3; *cis*-**8**, 57065-66-4; *trans*-**9**, 57065-67-5; *cis*-**9**, 57065-68-6; **10**, 54781-35-0; **11** isomer A, 57065-69-7; **11** isomer B, 51728-59-3; **11** isomer C, 57128-60-6; **11** isomer D, 57128-61-7; **12**, 57065-70-0; **13a**, 57065-71-1; **13b**, 57065-72-2; **14**, 57065-73-3; **15a**, 57065-74-4; **15b**, 57128-62-8; 1-vinylcyclohexene, 2622-21-1; methylphosphonous dichloride, 676-83-5; 1-(α-bromovinyl)-1-cyclohexene, 57065-75-5; 1-(α-chlorovinyl)cyclohexene, 57065-76-6; 1-acetylcyclohexene, 932-66-1; chlorotrimethylsilane, 1,2-dihydro-4-vinylnaphthalene, 57065-77-7.

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Scope of the 1,6 Addition of Sulfur Dioxide to *cis*-3-Hexatrienes

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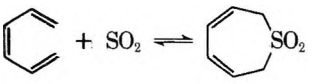
Reaction between *cis*-3-hexatriene and sulfur dioxide yields an adduct, 2,7-dihydrothiepin 1,1-dioxide. Similarly prepared were the seven-membered-ring sulfones with the following substituents: 3-isopropyl-6-methyl, 3,5-dimethyl, 2,4,6-trimethyl, and 3-acetoxymethyl. Sulfolenes only were obtained from *cis*-1,2-dicyclohex-1-enylethylene and 1,3,5-cyclooctatriene, as well as from 4,6-dimethyl-2,3,5-heptatriene. The structure of the adducts is described, and the influence of substituents on the course of the addition reaction is discussed.

The sulfolene reaction (the addition of sulfur dioxide to a conjugated diene) provides a valuable synthesis of five-membered-ring sulfones. Since the reaction is fully reversible, the sulfones have been exploited as intermediates for the modification and purification of dienes.[2] We have reported that the reaction between hexatriene and sulfur dioxide yields a seven-membered-ring sulfone, 2,7-dihydrothiepin 1,1-dioxide (**1**).[3] This transformation is also reversible. In this article we examine the generality of the cycloaddition with variously substituted trienes. The details of the mechanism of the reaction are considered elsewhere.[4]



1

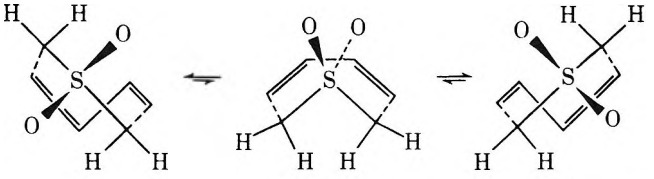
Results

2,7-Dihydrothiepin 1,1-Dioxide (1). The reaction of *cis*-hexatriene with excess sulfur dioxide gives an excellent

yield of 1. Its characterization has previously been described;[3] details are in the Experimental Section.[5] Several properties of this substance are worthy of comment. The adduct dissociates cleanly in the melt at 150–160° to regenerate *cis*-hexatriene (which distills from the reaction vessel) and less than 1% of *trans*-hexatriene or cyclohexadiene. Since 1 has an indefinite shelf life, it represents an attractive method of storing small quantities of this reactive triene for subsequent use. The kinetics and stereochemistry of the decomposition process have been examined.[4c,d]

Exchange in basic deuterium oxide yields α,α'-tetradeuterio-1, the availability of which facilitated analysis of the NMR spectrum of 1 (Experimental Section). In addition to providing a source of the specifically labeled triene, this demonstrates that 1 is the most stable of the isomeric dihydrothiepin dioxides, a result which has been confirmed by the conversion of 4,5-dihydrothiepin 1,1-dioxide into 1 under mildly basic conditions.[6]

Since the ring system of 1 is relatively unfamiliar, a comment regarding its possible conformations seems in order. Molecular models strongly suggest that the dihydrothiepin system exists exclusively in a twist form (**1a**), but that



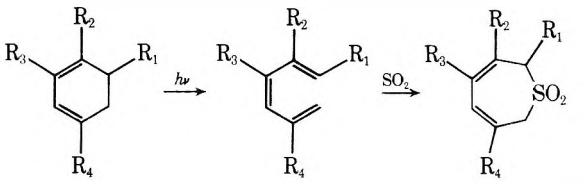
1a **1b** **1a′**

there should be a reasonably favorable pathway for its interconversion with an enantiomeric twist form (**1a′**).[7] In the course of this ring flipping it passes through a folded planar form (**1b**) which may represent a slight minimum (intermediate) on the energy profile for this process. Spectroscopic data supports this analysis. The ultraviolet absorption, uv max 227 nm (ϵ 5850), exhibits an attenuated intensity, attributable to nonplanarity in the diene. In this respect it resembles 1,3-cyclooctadiene, for which uv max 228 nm (ϵ 5600).[8] In support of this conformation is the NMR coupling constant between the 4 and 5 position protons, J = 4 Hz, which is reasonable for the presupposed dihedral angle (ca. 60°) between the planes of the double bonds in **1a**.[9] If the molecule were frozen in one of the twist forms (**1a** or **1a′**), then the geminal protons of methylene groups might be expected to experience different chemical environments.[7] However, this is not reflected in the NMR spectrum at temperatures as low as −50°. (The resonance of these protons remains a sharp doublet.) It can only be concluded either that these protons are accidentally magnetically equivalent ($\Delta\nu \ll J$) or that the barrier to ring flipping is lower than could be detected. Comparison with analogous systems[7] suggests that an activation energy for configurational inversion in the range of 10–20 kcal/mol would be reasonable for 1.

In agreement with the foregoing analysis is chemical evidence, specifically, the reluctance with which the conjugated system of 1 reacts with dienophiles. Diels–Alder addition could not be observed with maleic anhydride or tetracyanoethylene at temperatures below that which effected dissociation of 1. However, an adduct formed slowly in refluxing benzene with the highly reactive dienophile *N*-methyltriazolinedione. We suggest that cycloaddition to 1 proceeds through conformation **1b**, which is sparsely populated (or proceeds nonconcertedly).

Substituted Hexatrienes. As a class, 3-*cis*-hexatrienes represent a rather inaccessible and highly reactive type of

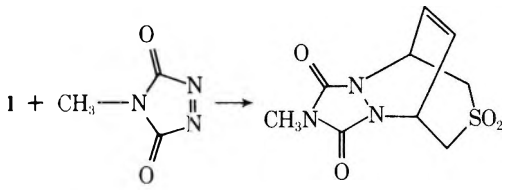
Table I
Substituted 2,7-Dihydrothiepin 1,1-Dioxides



2-5

Compd	R_1	R_2	R_3	R_4	Yield,[a] %
2	H	CH_3	H	i-C_3H_7	4
3	H	H	CH_3	CH_3	8
4	CH_3	H	CH_3	CH_3	6
5	H	CH_2OAc	H	H	14

[a] Yields are for both steps, and are based upon amount of cyclic diene submitted to the sequence.

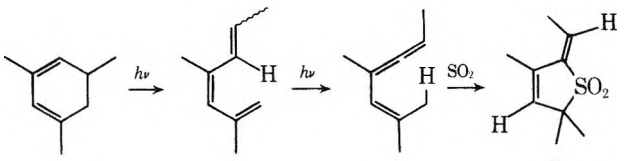


chemical entity. The characteristics of 1 suggested that the dihydrothiepin dioxide ring would be of synthetic utility in this regard. With this in mind, and with the intention of probing the mechanism of the cycloaddition, we undertook to examine sulfur dioxide addition with several trienes.

The paucity of methods for the preparation of acyclic trienes in which the central bond possesses cis geometry is well known to workers having need for such substances.[10] Most of our examples are based on photochemical ring opening of more readily available cyclohexadienes as listed in Table I. There is an inherent limitation in this approach, however. Cyclohexadienes and *cis*-hexatrienes absorb ultraviolet light at approximately the same wavelengths; although the ring opening proceeds with a satisfactory quantum efficiency, a steady state is soon achieved in which the cyclohexadiene component of the photoproduct mixture predominates (because the triene has a characteristically higher extinction coefficient). A further limitation is that thermal closure of the triene back to a cyclohexadiene may also take place (see Discussion). With certain substitution patterns on the triene, this may be so rapid (unimolecular reaction) as to compete effectively with cycloaddition by sulfur dioxide (bimolecular reaction). Our yields are low because of these factors and because no special effort to secure optimum conditions was attempted. In general, photolyses of cyclohexadienes were carried out with a 450-W mercury arc in ca. 0.03 *M* solution in ether at −20° until the reaction mixture showed no further rapid change upon irradiation as evidenced by uv or GLC analysis. Conditions for the addition of sulfur dioxide depended upon the propensity of the triene to reclose. After the reaction had gone to completion the product was generally obtained by column chromatography on silicic acid.

In the first example, the cyclohexadiene utilized was α-terpinene. In actuality the material submitted to photolysis was a commercial mixture containing ca. 25% of α-terpinene and the balance isomeric terpenes and aromatics as shown by GLC. The triene intermediate was quite unstable, reclosing to diene in a few minutes at room temperature. However, it was successfully intercepted with sulfur dioxide to give 3-isopropyl-6-methyl-2,7-dihydrothiepin 1,1-dioxide (**2**). Trienes from other components in the reaction mixture may have been present, but they did not lead

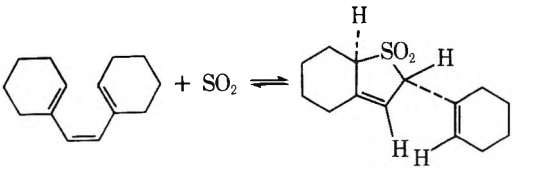
to isolable amounts of adducts. The next two cyclohexadienes were prepared by addition of methyl Grignard reagent to an appropriate ketone, followed by dehydration. In each case this led to a mixture of exocyclic and endocyclic dienes, which were submitted to photolysis without separation. A single product, 3,5-dimethyl-2,7-dihydrothiepin 1,1-dioxide (3), was obtained in the first instance. The intermediate triene did not recyclize so rapidly as in the case of the previous example. From the next cyclohexadiene and anticipated product, 2,4,6-trimethyl-2,7-dihydrothiepin 1,1-dioxide (4), was obtained as an oil, accompanied by a crystalline isomer. The latter was identified as 2-ethylidene-3,5,5-trimethyl-2,5-dihydrothiophene 1,1-dioxide (6). It most probably arose due to overphotolysis, since there is precedent for the production of an allene intermediate in this manner.[11] The orientation (cis–trans) of the ethylidene group is based upon steric considerations in the transition state, and the assignment is supported by a 1.5-Hz coupling (NMR) between the olefinic protons; this is reasonable for a five-bond coupling in a coplanar zigzag ("W") pattern. This product (6) is noteworthy on several



6

counts; it is a sulfolene derived from a vinylallene and as a sulfolene it possesses double substituents in an α position. Both of these features are novel; we have undertaken a broader investigation of allene–sulfur dioxide cycloadditions.[12] Thermal decomposition of the anticipated adduct, 4, gave back 2,4-dimethyl-1,*cis*-3,*trans*-5-heptatriene, indicating preferential formation of a triene with a trans terminal double bond as might be expected on steric or thermodynamic grounds.[4c] The final example in Table I (5) demonstrates the compatibility of the synthetic process with additional functionality, namely an acetoxyl group. The requisite cyclohexadiene was secured from the Diels–Alder adduct of 1-(diethylamino)butadiene and acrolein by diethylamine elimination followed by reduction and acetylation. We describe this route in detail in the Experimental Section since it would appear to be quite general and capable of modification to generate a variety of cyclohexadienes. The photolysis procedure with this diene gave 3-acetoxymethyl-2,7-dihydrothiepin 1,1-dioxide (5).

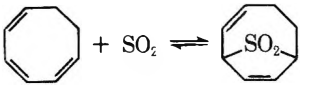
Finally, we shall briefly describe SO_2 adducts of two more trienes, which do not correspond to dihydrothiepin dioxide formation. The chief alternative synthesis of *cis*-hexatrienes involves partial hydrogenation over a poisoned catalyst of a dialkenylacetylene (or precursor thereof, such as an alkenylalkynylcarbinol[10c]). This method has severe practical limitations as regards yields and control of stereospecificity. Partial success is here demonstrated with the single example of dicyclohexenylacetylene. Hydrogenation of this material, brought about by Lindlar catalyst,[10a,c,d] afforded in our hands a complex mixture of hydrocarbons. Without attempted separation, these were treated directly with an excess of sulfur dioxide and the crude product mixture was submitted to column chromatography. By this sequence of operations low yields (<1%) of a sulfone of the correct composition ($C_{14}H_{20}O_2S$) could be obtained, although in several attempts no product at all was recovered. Spectral data for this material immediately demonstrated that it could not be a dihydrothiepin dioxide derivative. It lacked a uv absorption for the conjugated diene, and the NMR spectrum exhibited different chemical shifts for each of the two olefinic protons and for each of two methinyl protons occurring (probably) adjacent to the sulfonyl group. Consequently, the material is formulated as a 1,4 adduct (7). It was established that this material was not an



7

isomerized (via extensive hydrogen migration) dihydrothiepin dioxide (several of which might conceivably have given the observed spectra) by the fact that the sulfone readily dissociated on heating to give sulfur dioxide and triene. It might be suspected that the sulfone was formed from *trans*-dicyclohexenylethylene, a likely constituent of the hydrogenation mixture,[10c] since this material could only give a 1,4 adduct. However, the triene obtained upon thermolysis of the sulfone possessed ultraviolet absorption uv max 245 nm, the wavelength corresponding to the (apparently nonplanar) cis triene (trans triene uv max 260, 269, 281 nm).[10a] Consequently, we believe that in this case suprafacial 1,4 addition of sulfur dioxide to *cis*-dicyclohexenylethylene has occurred. However, a reservation must be made; the diversity of the components in the reactant mixture creates the possibility that 7 has an entirely different, unsuspected structure. Nevertheless, there is a strong indication that 1,4 addition of sulfur dioxide may compete effectively with 1,6 addition, depending on the nature of the triene.

The Experimental Section also carries the synthesis and characterization of 8, the product from sulfur dioxide and 1,3,5-cyclooctatriene. In this case formation of the (known[4b]) 1,6 adduct is disfavored by orbital symmetry considerations.[4d] A point of practical interest is that the crystalline adduct provides a particularly advantageous method of purification and storage of cyclooctatriene, since 8 dissociates on mild heating. In this regard it is competitive with the silver nitrate adduct (which we regard as less convenient).[13]



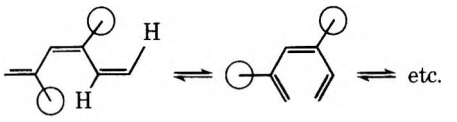
8

Discussion

The limited number of examples cited show that 1,6 cycloaddition of sulfur dioxide to 3-*cis*-hexatrienes apparently is a general reaction. Substituents in the β and γ positions (R_2, R_3, and R_4 in Table I) appear to facilitate the reaction. This is a qualitative observation, based on the fact that these trienes react rapidly in cold (and, in the case of 2, dilute) solution with sulfur dioxide whereas formation of the unsubstituted parent (1) requires more vigorous conditions. Substituents in the α position (R_1 in Table I) appear to suppress the reaction. Whereas a low yield of 4 was obtained with β and γ substituents to offset the effect of the α-methyl group, in several other cases which were attempted with one or two α substituents, either the reaction was diverted to 1,4 addition or no sulfone was obtained.[14] In this regard the reactivity of the trienes toward sulfur dioxide partially parallels the facility with which they recyclize to cyclohexadienes, although the aliphatic substituent effect appears small for the latter reaction (rate factors in the range of 1 to 3 have been suggested[10d]). We tentatively propose that these reactivity trends have a steric origin. The

presence of substituents at the internal positions (β, γ) favors conformations which place the terminal carbons of the triene in proximity; i.e., the cisoid conformation (or an approximating skew orientation) about both of the single bonds in a triene must be obtained before reaction can ensue. In the absence of substituents transoid conformations will be favored; however, steric bulk will destabilize the latter and lead to greater population of the reactive conformations (Scheme I). The retarding influence of the α

Scheme I



substituents (in the SO_2 addition only) may likewise be attributed to a steric origin, since they contribute congestion at the reaction site and possibly destabilize the product as well.[4d] An inductive effect of alkyl substituents might be expected to be relatively more important in the SO_2 reaction. A close correlation of structure–reactivity effects for the two reactions is unexpected in any event; the triene to cyclohexadiene electrocyclization proceeds suprafacially[10c] whereas the cycloaddition of SO_2 occurs antarafacially.[4a,c] The limited data recorded do not warrant further elaboration. Consideration of mechanistic aspects of the cycloaddition has been presented elsewhere.[4d]

Finally, we would mention the synthetic applicability of this reaction. On one hand, the adducts provide excellent precursors for other seven-membered-ring sulfones, particularly for the fully unsaturated thiepin dioxides.[3,15] More generally they appear to have limited use for the isolation and storage of hexatrienes. The most pertinent examples from this work would be the adduct from hexatriene itself (1) and the sulfolene from cyclooctatriene (8). Since the adducts are considerably less reactive than the trienes toward most reagents, the sulfone may be used as a temporarily protected derivative of the triene while manipulation is carried out elsewhere in the molecule. The triene functionality may be recovered subsequently by heating (although this may be accompanied by concomitant cyclization). A preparatively felicitous aspect of this fragmentation is the relative involatility of the sulfones compared to the products; consequently it is a simple matter to distill away the products as formed and thereby prevent (or suppress) their immediate further reaction. One independent and general synthesis (i.e., other than SO_2 addition) of the dihydrothiepin dioxide ring has been described.[4a,c,16] Other, more expeditious schemes, perhaps analogous to the sulfolene forming ylide reactions of McIntosh,[17] might largely overcome current practical restrictions on triene availability.

Experimental Section

General. Elemental analyses were by Galbraith Laboratories, Inc., Knoxville, Tenn., or Micro-Tech Laboratories, Inc., Skokie, Ill. Melting points were determined in open capillaries and are corrected. Nuclear magnetic resonance (NMR) spectra were obtained on a Varian A-60 instrument. Infrared (ir) spectra were obtained on a Perkin-Elmer Model 21 instrument. Ultraviolet (uv) spectra were obtained on a Cary Model 14 instrument. For gas chromatrography (GLC) a 1,2,3-tris(2-cyanoethoxy)propane column was used. Photolyses were carried out with a 450-W Hanovia mercury arc with a Vycor filter. The lamp was placed in a water-cooled immersion well which was placed in the reaction vessel (through which was bubbled a stream of inert gas for agitation) which was in turn placed in a refrigerator bath. The standard chromatographic isolation procedure referred to below involved the preparation of a 2.5-cm diameter column of 80 g of Mallinkrodt SilicAR CC7, 200-300 mesh, slurried in carbon tetrachloride. After application of the sample to the column, it was submitted to gradient elution involving in succession the following solvents: CCl_4 (100 ml); CCl_4–$CHCl_3$, 6:1 (70 ml), 2:1 (60 ml), 1:2 (60 ml); $CHCl_3$ (500 ml). Fractions were collected at 10-min intervals. Reactions products were located by TLC and spectroscopic analysis.

2,7-Dihydrothiepin 1,1-Dioxide (1). To a solution of 9.23 g (0.115 mol) of *cis*-hexatriene[18] (*trans*-hexatriene removed by formation of the maleic anhydride adduct) and 0.1 g of *tert*-butylcatechol in 18 g of ether in a combustion tube was added 40 g of sulfur dioxide at −80°. The container was sealed and the mixture was allowed to stand at room temperature for several weeks (alternatively, it may be heated at 50–55° for 48 hr). The tube was chilled and opened, and the solvent was allowed to evaporate. The residue was taken up in 60 ml of hot benzene and filtered, and was then diluted with 120 ml of hot hexane. Upon cooling the product separated and was collected. Concentration of the mother liquors afforded additional material. The combined product was sublimed at 100° (0.1 mm) to give 14.01 g (84.4%) of 1: mp 107–108°; ir ($CHCl_3$) 1310, 1120 cm^{-1}; uv max (C_2H_5OH) 227 nm (ϵ 5850); MS (70 eV) *m/e* 144. The NMR spectrum is not amenable to complete analysis. However, by comparing the spectra of various substituted dihydrothiepin 1,1-dioxides (here reported and unpublished)[9] chemical shifts and certain of the coupling constants for this ring may be deduced. The α protons (2,7 positions, adjacent to the sulfonyl group) occur at δ 3.5–4.0 ppm in various solvents; in the olefinic region, the β protons (3,6 positions) consistently occur upfield from the γ protons (4,5 positions), δ ca. 6.0 and 6.5 ppm, respectively. Coupling between the α and β positions is 6.8 Hz, that between β and γ is ca. 10 Hz, and that between two γ protons is ca. 4 Hz. All other couplings are ≤1 Hz. The spectrum (especially the methylene protons) was unchanged in $CDCl_3$ solution at temperatures down to −50°.[19] Similarly, nonequivalence in the α protons was not detectable (no broadening of line width at 40° and 60 MHz) in CCl_4, CS_2, C_6H_6, C_5H_5N, $C_6H_5NO_2$, $(CH_3)_2NCHO$, or CF_3CO_2H solutions.

Anal. Calcd for $C_6H_8O_2S$: C, 50.00; H, 5.60. Found: C, 50.00; H, 5.49.

Thermal Decomposition of 1. Quantitative recovery of *cis*-hexatriene from 1 may be carried out by heating the sulfone in a flask (under an inert gas sweep such that the triene is carried into a cold trap) with an oil bath (150–160°) or with a hot air blower. The pyrolysate was found to be free (<1%) of *trans*-hexatriene or 1,3-cyclohexadiene by GLC analysis.

Deuterium Exchange in 1. To a dioxane–deuterium oxide mixture containing 1 was added a catalytic amount of commercial potassium *tert*-butylate. The exchange reaction was conducted in an NMR tube so that it could be monitored. After warming for several hours, 1 was recovered by chloroform extraction and recrystallization from benzene–hexane, mp and mmp 107–108°. It was seen by NMR examination that the methylene hydrogens adjacent to the sulfonyl group (δ 3.7 ppm) were almost completely replaced by deuterium. The olefinic hydrogens remained; the resonance at δ 6.05 ppm was simplified to a broadened doublet.

Hexahydrothiepin 1,1-Dioxide.[20] A solution of hexamethylene sulfide in acetic acid was treated with excess peracetic acid for 24 hr at 25°. Solvent was removed on a rotary evaporator and the residue was recrystallized from benzene–hexane and then sublimed at 70° (2 mm) to give thiepane dioxide: mp 71–71.5° (recorded mp 68°);[20] ir ($CHCl_3$) 1313, 1294, 1120 cm^{-1}.

Anal. Calcd for $C_6H_{12}O_2S$: C, 48.64; H, 8.16. Found: C, 48.74; H, 8.03.

Hydrogenation of 1. Catalyst was prepared by prereducing 13 mg of 10% palladium on charcoal in 10 ml of ethyl acetate. To this was added 62 mg (0.43 mmol) of 1. After 10 min at 32° hydrogen absorption ceased; 2 molar equiv had been consumed. After filtration, evaporation, and recrystallization, hexahydrothiepin 1,1-dioxide (thiepane dioxide) was isolated in good yield, mp and mmp with authentic material 70–71°.

Diels–Alder Adduct of 1. A solution of 0.25 g (1.7 mmol) of 1 and 1.0 g of *N*-methyltriazolinedione in 20 ml of benzene was refluxed for 3.5 hr. After cooling, the precipitate was collected and recrystallized from acetic acid–benzene to give 0.34 g (76%) of the addition product: mp 280–282°; ir (KBr) 1775, 1710, 1330, 1320, 1125 cm^{-1}.

Anal. Calcd for $C_9H_{11}N_3O_4S$: C, 42.03; H, 4.31; N, 16.34. Found: C, 42.00; H, 4.10; N, 16.13.

3-Isopropyl-6-methyl-2,7-dihydrothiepin 1,1-Dioxide (2). A solution of 15 g of a terpene mixture containing ca. 25% of α-terpinene in 1.4 l. of ether was irradiated at 0° for 1.25 hr. After completion of the irradiation 15 g of sulfur dioxide was passed into the

solution, which was maintained at 0° for 3.5 hr and then allowed to warm slowly to 20° during the next 0.75 hr. After removal of the solvent on a rotary evaporator, any unreacted hydrocarbon was removed at 60° (0.1 mm). The remaining residue, a black tar, was taken up in carbon tetrachloride and treated with activated charcoal. After filtration the solution was concentrated to 10 ml and submitted to column chromatography. Fractions containing the product were combined and recrystallized from hexane at low temperature, giving 217 mg (4%) of **2**: mp 67.5–68.5°; ir (KBr) 1315, 1137, 1119 cm^{-1}; NMR ($CDCl_3$) δ 1.13 (d, 6, J = 7 Hz), 2.05 (s, 3), 2.55 (septet, 1, J = 7 Hz), 3.56 (s, 2), 3.62 (s, 2), and 6.21 ppm (s, 2).

Anal. Calcd for $C_{10}H_{16}O_2S$: C, 59.98; H, 8.05. Found: C, 59.91; H, 7.91.

3,5-Dimethyl-2,7-dihydrothiepin 1,1-Dioxide (3). Addition of methylmagnesium chloride to 3-methyl-2-cyclohexenone followed by acidic dehydration gave 1,3-dimethyl-1,3-cyclohexadiene.[21] A solution of 5.0 g (0.046 mol) of the diene in 1.4 l. of ether was irradiated at −10° for 1.25 hr. The solvent was removed upon a rotary evaporator at ca. 0° and the residue was transferred in the cold to a combustion tube. After cooling to −80°, 10 g of sulfur dioxide was added and the vessel was sealed and allowed to warm and maintained at 25° for 7 days. The tube was chilled and opened, and the solvent was allowed to evaporate. The residue was taken up in 10 ml of carbon tetrachloride and submitted to column chromatography by the standard procedure. Fractions containing the product were combined and recrystallized from hexane to give 0.63 g (8%)[21c] of **3**: mp 84–85°; ir (KBr) 1320, 1140, 1120 cm^{-1}; NMR ($CDCl_3$) δ 2.89 (broad s, 3), 2.99 (d, 3, J = 1.5 Hz), 3.58 (s, 2), 3.59 (d, 2, J = 7 Hz), 5.73 (t–q, 1, 7, J = 7, 1.5 Hz), 6.16 ppm (broad s, 1).

Anal. Calcd for $C_8H_{12}O_2S$: C, 55.80, H, 7.03. Found: C, 56.01; H, 7.09.

2,4,6-Trimethyl-2,7-dihydrothiepin 1,1-Dioxide (4) and 2-Ethylidene-3,5,5-trimethyl-2,5-dihydrothiophene 1,1-Dioxide (6). Addition of methylmagnesium chloride to 3,5-dimethyl-2-cyclohexenone followed by acidic dehydration gave a mixture of 1,3,5-trimethyl-1,3-cyclohexadiene[22] and 1,5-dimethyl-3-methylene-1-cyclohexene in approximately equal amounts (GLC analysis). A solution of 5.0 g (0.021 mol of endocyclic component) of diene in 1.4 l. of ether was irradiated at 0° for 1.25 hr. The ether was removed in the cold on a rotary evaporator. The residue was transferred with the aid of 10 ml of ether to a combustion tube and 0.1 g of *tert*-butylcatechol was added. At −80°, 15 g of sulfur dioxide was added and the vessel was sealed. After 24 hr at 25° the mixture was heated to 56° for 72 hr. After chilling the tube was opened and the solvent was allowed to evaporate. The residue was taken up in 10 ml of carbon tetrachloride and submitted to column chromatography by the standard procedure. Fractions containing sulfone product were combined and recrystallized from hexane at 0°. The mother liquors, containing an additional product, were reserved. The crystalline material, 0.70 g (18%), mp 110.5–111.5°, was assigned structure **6**: ir (KBr) 1282, 1155, 1116 cm^{-1}; uv max (C_2H_5OH) 242 nm (ϵ 15000); NMR ($CDCl_3$) δ 1.50 (s, 6), 2.19 (d, 3, J = 8 Hz), 2.27 (s, 3), 4.1 (m, 1), and 6.62 ppm (q–d, 1, J = 8, 1.5 Hz).

Anal. Calcd for $C_9H_{14}O_2S$: C, 58.05; H, 7.58. Found: C, 58.07; H, 7.59.

The hexane mother liquors from the recrystallization of **6** were chilled to −80°, whereupon an oil separated. After decantation the residue was taken up in pentane and the low temperature precipitation was repeated to afford 0.245 g (6%) of **4**, reasonably pure by NMR examination. For analysis the material was evaporatively distilled at 100° (0.01 mm): NMR (CCl_4) δ 1.43 (d, 3, J = 7 Hz), 1.83 (broad s, 3), 2.05 (d, 3, J = 1.5 Hz), ca. 3.3 (m, 1), 3.46 (s, 2), 5.35 (d–q, 1, J = 6, 1.5 Hz), and 6.07 ppm (broad s, 1).

Anal. Calcd for $C_9H_{14}O_2S$: C, 58.05; H, 7.58. Found: C, 58.45; H, 7.70.

Thermal decomposition of **4** was carried out in the manner described for **1**. In addition to sulfur dioxide, a single major hydrocarbon was obtained (GLC analysis), which had spectral properties in accord with its formulation as 2,4-dimethyl-1,*cis*-3,*trans*-5-heptatriene: ir (CCl_4) 970, 895 cm^{-1}; uv max (C_2H_5OH) 257, 267, 277 nm; NMR (CCl_4) δ ca. 1.8 (m, 9), 4.75 (m, 1), 4.92 (m, 1), 5.61 (m, 1), 5.64 (d–d, 1, J = 16, 6.5 Hz), and 6.60 ppm (broad d, 1, J = 16 Hz).

1-Hydroxymethyl-1,3-cyclohexadiene. The following synthesis should be adaptable to give a variety of cyclohexadienes.[23] To a solution of 80.3 g (0.64 mol) of 1-diethylaminobutadiene and 0.1 g of *tert*-butylcatechol in 100 ml of ether in an ice–salt bath and with magnetic stirring was added dropwise over a period of 0.5 hr a solution of 42 g of acrolein in 100 ml of ether. The mixture was stirred for 0.5 hr at 0° and then allowed to warm to 25° and stand for several hours. The ether was removed under vacuum and the residue was diluted with a cold mixture of 100 ml of concentrated hydrochloric acid and 500 ml of water. An aldehyde layer separated and the mixture was warmed briefly to complete diethylamine elimination. Organic material was extracted into ether, which was washed with water and saturated sodium chloride solution. The ether was removed under vacuum to give a residue (62 g) of cyclohexadienecarboxaldehyde,[23] which was submitted to reduction without purification. The product was taken up in 250 ml of methanol and the solution was stirred magnetically at 0° while 10 g of sodium borohydride in dilute sodium carbonate solution was added. After the initial reaction had subsided the mixture was allowed to warm to 25°. After several hours the mixture was diluted with water and extracted three times with ether–pentane. The organic extracts were washed with water and saturated sodium chloride solutions and dried over anhydrous sodium sulfate. The solvent was removed under vacuum and the residue was distilled at reduced pressure through a 20-cm Vigreux column to give 46 g (65%, based on diethylaminobutadiene) of 1-hydroxymethyl-1,3-cyclohexadiene,[23] bp 85–88° (14 mm).

Anal. Calcd for $C_7H_{10}O$: C, 76.32; H, 9.15. Found: C, 76.42; H, 9.17.

A tetracyanoethylene adduct was obtained, mp >200° dec without melting.

Anal. Calcd for $C_{13}H_{10}N_4O$: C, 65.53; H, 4.23; N, 23.52. Found: C, 65.40; H, 4.10; N, 23.59.

1-Acetoxymethyl-1,3-cyclohexadiene. To a mixture of 25 g (0.23 mol) of 1-hydroxymethyl-1,3-cyclohexadiene in 75 ml of pyridine at 0° was added slowly 50 ml of acetic anhydride. The mixture was allowed to come slowly to 25° and then to stand for several hours. The solution was treated with 300 ml of water and the ester was extracted into pentane. The organic extract was washed with dilute hydrochloric acid and with sodium bicarbonate solutions, and then was dried and the pentane was removed under vacuum. The residue was distilled under reduced pressure to give 31.3 g (90.5%) of 1-acetoxymethyl-1,3-cyclohexadiene, bp 58–60° (2 mm).

Anal. Calcd for $C_9H_{12}O_2$: C, 71.02; H, 7.95. Found: C, 70.94; H, 7.89.

A tetracyanoethylene adduct was obtained, mp 154.5–155°.

Anal. Calcd for $C_{15}H_{12}N_4O_2$: C, 64.27; H, 4.32; N, 19.99. Found: C, 64.26; H, 4.17; N, 20.08.

3-Acetoxymethyl-2,7-dihydrothiepin 1,1-Dioxide (5). A total of 30 g (0.197 mol) of 1-acetoxymethyl-1,3-cyclohexadiene, divided into 6-g batches, each dissolved in 1.4 l. of ether, was irradiated at −10 to −20° for 1.25 hr. From each batch the ether was removed below 20° and the residue was placed in a sealed tube with 15 g of sulfur dioxide, 0.1 g of *tert*-butylcatechol, and sufficient ether to effect transfer. After 4 days at 25° the tubes were opened, solvent was removed from the contents, and the residue was submitted to column chromatography by the standard procedure. Fractions found to contain the product from all batches were combined and recrystallized from large volumes of hexane to give a total of 6.2 g (14.5%) of **5**: mp 65–65.5°; NMR ($CDCl_3$) δ 2.11 (s, 3), 3.65 (d, 2, J = 6 Hz), 3.68 (s, 2), 4.73 (s, 2), 6.1 (m, 1), and 6.5 ppm (m, 2).

Anal. Calcd for $C_9H_{12}O_4S$: C, 50.00; H, 5.60. Found: C, 49.74; H, 5.70.

Adduct of Sulfur Dioxide and Dicyclohexenylethylene (7). This procedure was repeated many times, frequently without success. A solution of 4.61 g (0.025 mol) of dicyclohexenylacetylene[10a] in 50 ml of benzene was hydrogenated using 0.23 g of Lindlar catalyst; hydrogen uptake was interrupted after absorption of ca. 1 molar equiv. After filtration, the benzene was removed under vacuum and the residue, containing *cis*-dicyclohexenylethylene,[10a,c] was transferred with the aid of a little ether to a combustion tube. The vessel was cooled to −80°, 11 g of sulfur dioxide and 0.1 g of *tert*-butylcatechol were added, and the tube was sealed. After standing overnight at 25°, the mixture was heated to 56° for 1.25 hr. The tube was then chilled and opened, and the solvent was allowed to evaporate. The residue was triturated with warm hexane and the insoluble black precipitate was discarded. Removal of the hexane gave 4.84 g of a brown oil, which was submitted to column chromatography by the standard procedure. From appropriate fractions one could occasionally isolate, by low temperature crystallization from hexane, 10–15 mg (<0.2%) of a solid of the expected composition: mp 86–87°; ir (CCl_4) 1310, 1118 cm^{-1}; uv (C_2H_5OH) end absorption only, 235 nm (ϵ 46), 215 (4600); NMR ($CDCl_3$) δ 1–3 (m, 16), 3.5 (m, 1), 4.05 (m, 1), 5.5 (broad q, 1), and

5.65 ppm (m, 1); NMR (C_6H_6) δ 1–2.5 (m, 16), 3.35 (m, 1), 4.1 (m, 1), 5.3 (broad q, 1), and 5.7 ppm (m, 1). The foregoing spectral data exclude a dihydrothiepin dioxide structure for **7** but are in accord with its formulation as *trans*-2-cyclohex-1-enyl-2,4,5,6,7,7a-hexahydrobenzo[*b*]thiophene 1,1-dioxide. The latter sulfolene structure is further supported by the results of thermal decomposition of **7**, which liberates in addition to sulfur dioxide a triene (and/or cyclohexadiene), uv max (C_2H_5OH) 245 nm. This absorption corresponds to that reported for *cis*-dicyclohexenylethylene (uv 248 nm),[10a] and excludes the trans isomer (uv 260, 269, 281 nm)[10a] as the coreactant in the sulfur dioxide cycloaddition.

Anal. Calcd for $C_{14}H_{20}O_2S$: C, 66.64; H, 7.99. Found: C, 66.78; H, 8.05.

9-Thiabicyclo[4.2.1]nona-2,7-diene 9,9-Dioxide (**8**). This sulfone may be obtained from purified 1,3,5-cyclooctatriene prepared by reduction of cyclooctatetraene.[13] The procedure here given makes use of a currently more readily available hydrocarbon. A mixture of 105 g (0.97 mol) of 1,5-cyclooctadiene, 175 g (0.98 mol) of *N*-bromosuccinimide, and 2 g of benzoyl peroxide in 400 ml of carbon tetrachloride was refluxed overnight. After filtration there was obtained by distillation 94 g of "bromocyclooctadienes", bp 75–80° (25 mm). To this material in 260 ml of dimethylformamide at 0° was added portionwise 60 g of commercial potassium *tert*-butylate over 0.5 hr. Dilution with water, extraction with pentane, and distillation gave 37 g of "cyclooctatrienes",[24] bp 70–75° (60 mm). This material was placed in sealed tubes with approximately equal volumes of sulfur dioxide and a trace of *tert*-butylcatechol. After 12 hr at 100°, the tubes were chilled and opened, and the sulfur dioxide was allowed to evaporate. The residue was triturated with pentane and the crystalline material was collected. The filtrate was evaporated and the residual "cyclooctatriene" was again sealed with sulfur dioxide and heated for 12 hr. This was necessary since the reaction fails to go to completion under these preparative conditions (i.e., in the absence of a very large excess of sulfur dioxide).[4d] After several reaction cycles the product was combined and recrystallized from benzene–hexane to give 29.3 g (49% based on "cyclooctatriene") of **8**: mp 134–136° dec (rapid heating); ir ($CHCl_3$) 1308, 1127, 1108 cm^{-1}; NMR ($CDCl_3$) δ 2–3 (m, 4), 3.7 (broad t, 1), 4.05 (d–d–m, 1, J = 8, 4 Hz), ca. 5.6 (m, 1), ca. 5.9 (m, 1), 6.2 (d–d–m, 1, J = 8, 4 Hz), and 6.6 ppm (d–d–m, 1, J = 8, 4 Hz).

Anal. Calcd for $C_8H_{10}O_2S$: C, 56.46; H, 5.92. Found: C, 56.58; H, 5.86.

9-Thiabicyclo[4.2.1]non-7-ene 9,9-Dioxide. Into several combustion tubes were placed a total of 40 g (0.27 mol) of 1,3-cyclooctadiene, 0.5 g of *tert*-butylcatechol, 60 ml of ether, and 55–60 g of sulfur dioxide (at −80°). The tubes were sealed and maintained at 149–150° for 7 days (*caution:* explosion hazard). They were then chilled and opened, and the sulfur dioxide was allowed to evaporate. From the residue a crystalline product was obtained by dissolution in benzene and precipitation with hexane. This material was sublimed at 130° (0.01 mm) and recrystallized from benzene–hexane to give 5.0 g (8%) of adduct, mp 190–191°. This material also has been prepared indirectly from the sulfur dichloride addition product of 1,3-cyclooctadiene,[25] reported mp 190–191°.

Anal. Calcd for $C_8H_{12}O_2S$: C, 55.80, H, 7.03. Found: C, 55.68; H, 7.02.

9-Thiabicyclo[4.2.1]nonane 9,9-Dioxide. The cyclooctatriene–sulfur dioxide adduct (**8**) was hydrogenated in ethyl acetate solution using rather massive amounts of palladium on charcoal catalyst (in order to overcome an apparent poisoning effect). After filtration and solvent removal, the residue was sublimed at 150° (15 mm) to give the saturated bicyclic sulfone, mp 234–235° (reported mp 235–237°).[25] The same material (no mixture melting point depression) was obtained by hydrogenation of the cyclooctadiene adduct described in the preceding paragraph.

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Registry No.—**1**, 16301-86-3; 1 Diels–Alder adduct, 57196-79-9; **2**, 57196-80-2; **3**, 57196-81-3; **4**, 57196-82-4; **5**, 57196-83-5; **6**, 57196-84-6; **7**, 57196-85-7; **8**, 29294-06-2; hexahydrothiepin 1,1-dioxide, 6251-33-8; hexamethylene sulfide, 4753-80-4; *N*-methyltriazolinedione, 13274-43-6; α-terpinene, 99-86-5; 1,3-dimethyl-1,3-cyclohexadiene, 4573-05-1; 1,3,5-trimethyl-1,3-cyclohexadiene, 1731-26-6; 1,5-dimethyl-3-methylene-1-cyclohexene, 57196-86-8; 2,4-dimethyl-1,*cis*-3,*trans*-5-heptatriene, 57196-87-9; 1-hydroxymethyl-1,3-cyclohexadiene, 21203-48-5; 1-diethylaminobutadiene, 14958-13-5; 1-acetoxymethyl-1,3-cyclohexadiene, 32833-06-0; dicyclohexenylacetylene, 3725-09-5; *cis*-dicyclohexenylethylene, 52944-49-7; 1,3,5-cyclooctatriene, 1871-52-9; 9-thiabicyclo[4.2.1]non-7-ene 9,9-dioxide, 6522-52-7; 1,3-cyclooctadiene, 3806-59-5; 9-thiabicyclo[4.2.1]nonane 9,9-dioxide, 6522-53-8; *cis*-hexatriene, 2612-46-6; sulfur dioxide, 7446-09-5.

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Rearrangement–Substitution Reactions of a 2-(Arylsulfonyl)allyl System[1]

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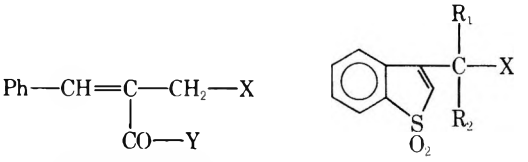
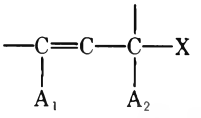
A synthetic route to substituted 2-(arylsulfonyl)allyl bromides (8) is reported. Reaction of allyl bromides 8 with primary and secondary amines in protic and aprotic solvents yielded rearrangement–substitution products (10). The product distribution and stability depend upon the steric requirement of the attacking alkylamine. When the kinetically favored amino sulfones (10, except for the *N,N*-diisopropylamino derivative) were allowed to stand in aprotic solvents of low polarity, rearrangement to the thermodynamically more stable isomeric amino sulfones (11) occurred. The aminotropic rearrangement was facilitated by added alkylamine, and a facile amine-exchange reaction occurred when 10d was treated with morphiline in aprotic solvents. Reaction of 8 with 2,4-dimethylimidazole yields the direct substitution product (11e) only. The significance of these observations with regard to the effect of polar substituents and structure of attacking amine on the mode of reaction of allyl systems is discussed.

There are few reports in the literature regarding rearrangement–substitution reactions of allyl systems bearing polar functional groups.[3] Cromwell and co-workers[4] showed that the 2-aroylallyl system 1 (Y = C_6H_5) reacts with primary and secondary amines in aprotic solvents to yield rearrangement–substitution products by a bimolecular mechanism. Rearrangement–substitution products were observed in two additional 2-carboallyl systems.[5,6] These observations constitute the only reported examples of SN2′-type product formation from primary allyl halides and amines. For this system (1) the product distribution is controlled by the *electron-withdrawing effect* of the carbonyl group.[7] Bordwell and Mecca[8] demonstrated that benzothiophene derivative 2 reacts via a bimolecular mechanism with a variety of nucleophiles, including charged ones, to yield SN2′-type products. It was shown that neither an α- nor γ-arylsulfonyl group (3a and 3b, respectively) is sufficient to promote rearrangement–substitution.[9]



1, Y = C_6H_5, CH_3, OCH_3 2



3a, A_1 = H; A_2 = SO_2Ar

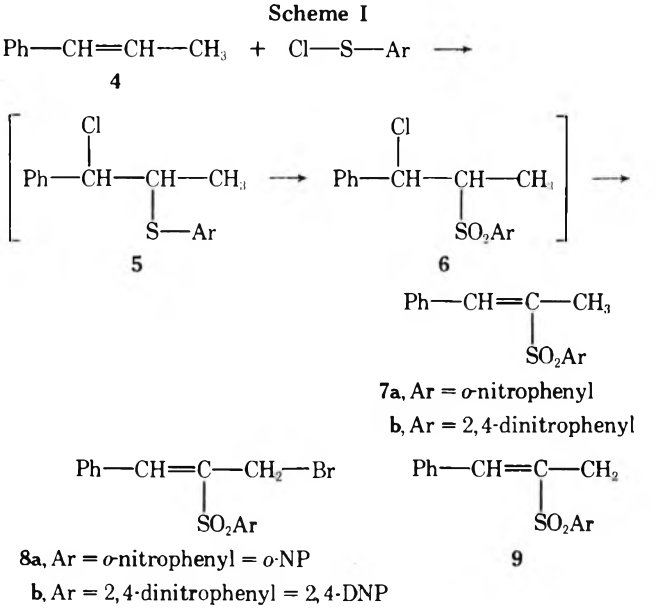
b, A_1 = SO_2Ar; A_2 = H

Thus, Bordwell concluded that an important effect of the sulfonyl group in promoting SN2′-type reactions of 2 is indirect electron withdrawal through the aromatic ring at the β position of the allyl chain. As part of a general program designed to elucidate factors that influence the reactivity of allyl systems, reactions of 2-(arylsulfonyl)allyl bromides (8) with amines were investigated. This report deals with the influence of the β-arylsulfonyl group on product distributions for nucleophilic substitution on the relatively simple allyl system 8. Allyl bromide 8 is analogous to Cromwell's β-aroylallyl system (1) and allows a comparison of the effectiveness of a β-arylsulfonyl vs. a β-aroyl substituent in promoting SN2′-type reactions.

Results and Discussion

Allyl bromides 8 were synthesized according to Scheme I. Thus treatment of 1-phenylpropene with an arenesulfenyl chloride yielded β-chloro sulfide 5.[10] The β-chloro sulfide

Scheme I



was oxidized to the corresponding β-chloro sulfone (6) with *m*-chloroperoxybenzoic acid in dichloromethane. Dehydrochlorination of 6a with *N*-methylpiperidine in benzene gave alkene 7a in 86% yield, wherein an arylsulfonyl group has been substituted for hydrogen (i.e., 4 → 7a). Alkene 7b was synthesized via the same sequence of reactions. The alkenes 7 were brominated with *N*-bromosuccinimide in refluxing carbon tetrachloride in the presence of benzoyl peroxide to yield the desired allyl bromides (8). This reaction was very slow and could be forced to completion only after prolonged heating, probably reflecting the strong electron-withdrawing effect of the 2-arylsulfonyl group in destabilizing the intermediate free radical 9. Thus carbonium ion type reactions of 8 would be expected to be inhibited by a similar mechanism during nucleophilic substitution.

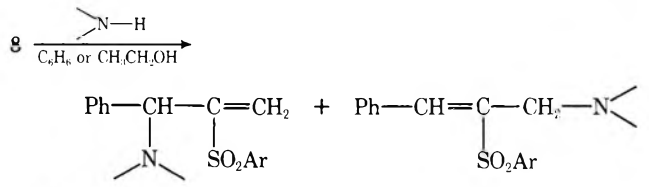
Treatment of 8a with morpholine, *tert*-butylamine, and diisopropylamine in benzene or ethanol yielded rearrangement–substitution products (10a, 10b, and 10c, respectively) along with direct substitution products (11) in varying amounts (Table I). When 10a and 10b were allowed to stand in deuteriochloroform at room temperature, facile rearrangements to the thermodynamically more stable isomers (11a and 11b, respectively) occurred. It is noteworthy that the time required for quantitative rearrangement of 10a to 11a is significantly less than that required for rearrangement of 10b to 11b. Also, 10c and 10d are stable toward rearrangement in the presence or absence of excess diisopropylamine. Thus 10d could be recovered after

Table I
Summary of Reactions of 2-(Arylsulfonyl)allyl Bromides 8 with Amines[a]

Registry no.	Nucleophile	Reaction time, hr	Solvent[b]	% 10[d]	% 11
110-91-8	OC_4H_8NH	0.05	Benzene (160)	100	0
	OC_4H_8NH	0.10	Ethanol (40)	100	0
75-64-9	t-$C_4H_9NH_2$	2	Brnzene (40)	80	20
	t-$C_4H_9NH_2$	17	Ethanol (40)	30	70
108-18-9	$[(CH_3)_2CH]_2NH$	24	Benzene (40)[c]	80	20
	$[(CH_3)_2CH]_2NH$	24	Benzene (20)[c]	83	17
	$[(CH_3)_2CH]_2NH$	24	Ethanol (20)[c]	33	67
930-62-1	2,4-Dimethylimidazole	2	Benzene (40)[c]	0	100

[a] Reactions were carried out using ca. 0.5 mmol of allyl bromide (8) and 2 equiv of amine. The first five entries involved 8a as reactant, in the latter three 8b was used. [b] The number in parentheses indicates ml solvent per mmol 8. [c] Unreacted bromide (8) remained. [d] Product ratios were determined by ^{1}H NMR analysis, and one isomer (10 or 11) was isolated and characterized for each reaction, except for entry 5.

standing at room temperature for weeks in deuteriochloroform and in chloroform containing added diisopropylamine. Amino sulfones **10a** and **10b** were relatively stable



10a, $>N = OC_4H_8N$; Ar = *o*-NP — **11a**

b, $>N = t$-C_4H_9NH; Ar = *o*-NP — **b**

c, $>N = [(CH_3)_2CH]_2N$; Ar = *o*-NP — **c**

d, $>N = [(CH_3)_2CH]_2N$; Ar = 2,4-DNP — **d**

e, $>N$ = 2,4-dimethylimidazolyl; Ar = 2,4-DNP — **e**

toward rearrangement when traces of free alkylamine were removed from solution, or as their hydrochloride salts. This suggested catalysis of the rearrangement by the free amine that acts as nucleophile (see Experimental Section). The diisopropylamino sulfone **10c** reacted with morpholine in chloroform to give **11a** in excellent yield. The isomeric diisopropylamino sulfone **11c** did not react with morpholine under the same conditions. Excess *tert*-butylamine facilitated the conversion of **10b** to the thermodynamically more stable isomer **11b**. While the 2-(arylsulfonyl)allyl system (8) mimics the behavior of the 2-aroylallyl system (1) in that both systems undergo facile amine exchange and rearrangement reactions, these systems differ in their reactivity toward diisopropylamine. Arylsulfonylallyl bromide **8a** reacts with diisopropylamine in benzene solution to give 80% rearrangement–substitution product **10c**, whereas aroylallyl bromide 1 gives only a trace of the SN2′-type product.[11,12]

We were unable to isolate **10a** or **10b** as crystalline materials. Thus, the structures of **10a** and 10b were assigned on the basis of ^{1}H NMR spectral analysis of their solutions. The progress of rearrangement of **10** to **11** was followed by observing the sets of signals for **10** decrease with a corresponding increase in signals for **11** (Table II). Upon completion of the rearrangement of **10** to **11**, the amino sulfones **11a** and **11b** were isolated as crystalline substances. The diisopropylamino sulfone **10d** was isolated in 37% yield as bright orange crystals from ether solution. The ^{1}H NMR spectra of isomerically pure compounds (**11a**, **11b**, and **10d**) were compared with spectra of the corresponding mixtures

Table II
Summary of Physical Data for Substituted 2-(Arylsulfonyl)allyl Derivatives[a,c]

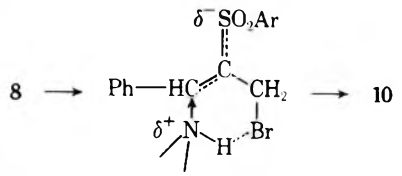
Compd	Mp, °C	H_a	H_b	H_c
7a	151			2.13
7b	155			2.17
8a	131			4.31
8b	144[b]			4.38
10a		6.43	4.09	
11a	152			3.51
10b		6.55	4.88	
11b	109			3.55
10d	138	6.60	5.25	
11d				3.71
11e	169			5.08

[a] H_a represents the vinyl protons of **10**, H_b represents the benzal proton, and H_c represents allyl protons of **7**, **8**, and **11**. The expected absorption bands were observed for the aromatic and alkyl protons of each compound. Chemical shifts are given in δ values relative to tetramethylsilane as internal standard in deuteriochloroform. [b] This sample was conaminated with a trace of **7b**. [c] Satisfactory analytical values (±0.3% for C, H, N) were reported for **7a,b**, **8a,b**, **11a,b,e**, and **10d**. Ed.

in order to confirm structure assignments and product distributions.

Previous studies have indicated that hydrogen bonding plays a role, of undetermined importance, in rearrangement–substitution reactions of allyl halides with amines in aprotic solvents.[13] In the present work, rearrangement–substitution products (**10**) were obtained from 8 and primary and secondary amines in both benzene and ethanol. The mild reaction conditions and aprotic environment for the reaction in benzene would be expected to favor a bimolecular mechanism.[7] We speculate that the presence of the amino proton provides a relatively low energy path for the rearrangement–substitution reaction, since a quasi-six-membered transition state is available through hydrogen bonding to the leaving bromide ion. The lower SN2′:SN2 product ratio in ethanol may be rationalized in terms of competing hydrogen bonding by solvent, or a faster amine exchange reaction in this solvent. In the case for reaction of 2,4-dimethylimidazole with **8b** an eight-membered transition state would be required (the proton is lost from the remote nitrogen atom), rendering the lower energy path inaccessible. The product distributions can be rationalized if one assumes a bimolecular mechanism; the less bulky amines would be expected to give a higher proportion of nucleophilic attack at the more hindered secondary carbon of the allyl chain (Table I). Thus, the transition state for formation of **10** from reaction of 8 with primary and secondary amines may be represnted by structure **12**, wherein

the arylsulfonyl group absorbs the developing negative charge. An analogous cyclic transition state (13) may be envisioned for the amine exchange reactions. Although the intervention of diamino adducts (14) was considered for



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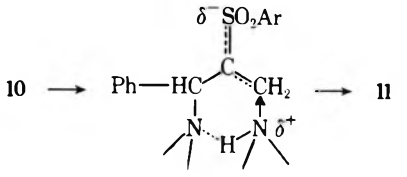

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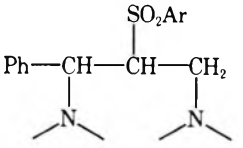

14

the latter reaction, no evidence for such intermediates was obtained upon close scrutiny of ^{1}H NMR spectra of reaction mixtures during the rearrangements. The inertness of **10d** toward reaction with diisopropylamine can be rationalized in terms of transition state **13**, since available evidence indicates that the bulky entering and leaving groups would require a cis relationship.[13]

In nonpolar aprotic solvents both **1**[4] and **8** probably react via a "variant of the SN2′" mechanism.[7] Since steric factors in **1** and **8** are practically identical, the difference in product distribution (for reactions in the same solvent) arises from the effect of the β-electron-withdrawing group. Data for reactions involving diisopropylamine (with **1** and **8**)[12] suggest that the β-arylsulfonyl group is more effective than the β-aroyl group in stabilizing the "SN2′-type" transition state for substitution in allyl halides. This parallels Taft σ constants for these substituents.[14] The arylsulfonyl group would be expected to more effectively stabilize a developing negative charge compared to an aroyl group, but the latter group is more effective in stabilizing a carbanion, judging from the relative acidities of ketones and sulfones.[15,16] Thus, we propose that the transition state for substitution in **8** lies along a continuum between a carbanionic intermediate and the classical SN2′ model.

Experimental Section[17]

2-(*o*-Nitrophenylsulfonyl)-1-phenylpropene (7a). A 19.0-g (0.10 mol) sample of *o*-nitrophenylsulfenyl chloride was allowed to react with 11.8 g (0.10 mol) of 1-phenylpropene in 200 ml of dichloromethane at room temperature for 24 hr. A 42.0-g (0.22 mol) sample of 85% *m*-chloroperoxybenzoic acid dissolved in 200 ml of dichloromethane was added slowly to the reaction mixture. Following reaction for 24 hr at room temperature, the reaction mixture was washed with saturated aqueous sodium bicarbonate solution, 10% aqueous sodium bisulfite, and again with sodium bicarbonate. The dried ($MgSO_4$) solution was evaporated under reduced pressure to yield a yellow oil. The oil was taken up in 300 ml of benzene and 15 g (0.15 mol) of *N*-methylpiperidine was added. The reaction was allowed to proceed at reflux temperature for 4 hr. The mixture was filtered while hot and washed with 300 ml of water and 300 ml of 1 *N* hydrochloric acid. Evaporation of the solvent yielded a yellow solid. This material was suction filtered with the aid of methanol as transfer agent. The desired product was obtained as an off-white powder, 26 g (86%), mp 142–145°. This compound was reasonably pure on the basis of its ^{1}H NMR spectrum and was used without further purification. The analytical sample was obtained upon several recrystallizations from methanol, mp 151°.

2-(2,4-Dinitrophenylsulfonyl)-1-phenylpropene (7b). The procedure that was used in the preparation of **7a** was applied to 23.5 g (0.10 mol) of 2,4-dinitrobenzenesulfenyl chloride and 11.8 g (0.10 mol) of 1-phenylpropene. Compound **7b** was obtained as a yellow, crystalline material from methanol, 16.3 g (47%), mp 154–155°.

2-(*o*-Nitrophenylsulfonyl)-3-phenylallyl Bromide (8a). A 10.0-g (0.033 mol) sample of **7a** and 7.0 g (0.039 mol) of *N*-bromosuccinimide were added to 150 ml of carbon tetrachloride and the mixture was brought to a gentle reflux. A solution of 0.5 g of benzoyl peroxide in 50 ml of carbon tetrachloride was added dropwise to the refluxing mixture over a 2-hr period. Refluxing was continued for 24 hr and the mixture was filtered while hot to remove suspended solids. Evaporation of the solvent under reduced pressure yielded a yellow oil that consisted of starting material (27%) and the expected allyl bromide **8a** (73%) by ^{1}H NMR analysis. The oil was treated with an additional 6.0-g (0.033 mol) sample of *N*-bromosuccinimide in the manner described above. After a 24-hr reflux period the solution was filtered while hot; a yellow-brown solid separated from the filtrate upon cooling. This solid consisted of the desired allyl bromide and excess *N*-bromosuccinimide, 9.2 g, mp 100–116°. Recrystallization from ethyl acetate yielded 5.6 g (44%) of yellow crystals, mp 130–131°.

2-(2,4-Dinitrophenylsulfonyl)-3-phenylallyl Bromide (8b). The procedure[18] that was used in the preparation of **8a** was applied to 9.3 g (27 mmol) of **7b** (i.e., the same approximate reaction time and reactant and solvent ratios). Compound **8b** was obtained as bright yellow crystals from ethyl acetate, 5.5 g (48%), mp 143–144°.

3-Morpholino-3-phenyl-2-(*o*-nitrophenylsulfonyl)propene (10a) and 3-Morpholino-2-(*o*-nitrophenylsulfonyl)-1-phenylpropene (11a). A 0.24-g (0.63 mmol) sample of **8a** and 0.12 g (1.4 mmol) of morpholine were mixed in 80 ml of benzene and allowed to react with stirring for 5 min. The benzene solution was washed with 50 ml of water and evaporated to dryness under reduced pressure. A ^{1}H NMR spectrum of the residue indicated the presence of direct substitution product **11a** only. This procedure was repeated, except that the reaction was terminated after 2 min by bubbling gaseous HCl into the benzene solution. The salt was removed by suction filtration, taken up in 50 ml of chloroform, and washed with aqueous saturated sodium bicarbonate. The organic phase was washed with water, dried ($MgSO_4$), and evaporated. The ^{1}H NMR spectrum indicated the presence of **10a** only (spectrum obtained approximately 3 hr after mixing of reagents).

A 0.24-g (0.63 mmol) sample of **8a** and 0.12 g (1.4 mmol) of morpholine were allowed to react in 20 ml of absolute ethanol for 10 min. Addition of 75 ml of diehhyl ether and treatment with gaseous HCl led to precipitation of an amine salt.[19] The free base was recovered as described in the preceding paragraph. ^{1}H NMR analysis of the product indicated the presence of **10a** (signals at δ 6.43 and 4.09) and the absence of **11a** (signal at δ 3.51 was absent).

Treatment of a 0.50-g (1.3 mmol) sample of **8a** with 0.26 g (3.0 mmol) of morpholine in 20 ml of benzene for 24 hr gave upon work-up (see above) a yellow oil that was recrystallized from a dichloromethane–petroleum ether mixture, 0.38 g (75%) of **11a**, mp 150–151°.

3-(*N*-*tert*-Butylamino)-2-(*o*-nitrophenylsulfonyl)-1-phenylpropene (11b). A 0.96-g (2.5 mmol) sample of bromide **8a** was added to 20 ml of benzene that contained 0.40 g (5.5 mmol) of *tert*-butylamine and the mixture was allowed to react at room temperature for 1.5 hr. The usual work-up gave an oil that consisted of a 50:50 mixture of **10b** and **11b**. Upon standing for 24 hr the amino sulfone **10a** rearranged to the direct substitution product (**11b**), judging from signals in the ^{1}H NMR spectrum at δ 6.55 and 4.88 for **10b** and at δ 3.55 for **11a**. The latter substance was recrystallized from dichloromethane–petroleum ether, yielding 0.41 g (44%) of bright yellow crystals, mp 108–109°. The proportion of substitution–rearrangement product was increased to 80% by altering reactant concentrations and reaction time (see Table I).

1-(*N*,*N*-Diisopropylamino)-2-(2,4-dinitrophenylsulfonyl)-1-phenylpropene (10d). A 1.0-g (2.6 mmol) sample of **8b** and 3.0 g (30 mmol) of diisopropylamine dissolved in 80 ml of benzene were allowed to react at room temperature for 4 days. The usual work-up gave a light brown oil that consisted of 83% **10d** and 17% **11d**. Crystallization of this material from ether gave 0.39 g (37%) of bright orange crystals of **10d**, mp 137–138°. The ^{1}H NMR spec-

trum ($CDCl_3$) showed peaks at δ 0.55 and 1.13 (d, 6 H, J = 7 Hz), 3.21 (heptet, 2 H, J = 7 Hz), 5.25 (s, 1 H), 6.5–8.5 (m, 10 H).

3-(*N,N*-Diisopropylamino)-2-(*o*-nitrophenylsulfonyl)-3-phenylpropene (10c) and 3-(*N,N*-Diisopropylamino)-2-(*o*-nitrophenylsulfonyl)-1-phenylpropene (11c). To a 0.24-g (0.63 mmol) sample of allyl bromide **8a** in 10 ml of benzene was added 0.13 g (1.4 mmol) of diisopropylamine in 10 ml of the same solvent. The reaction was allowed to proceed at room temperature with stirring for 24 hr. The benzene solution was washed with water and evaporated under reduced pressure to yield a brown, viscous oil. Examination of the ^1H NMR spectrum (signals at δ 6.53 and 5.25 for **10c**, and at δ 3.72 for **11c**) indicated the presence of **10c** and **11c** in a 4:1 ratio, plus starting material (**8a**). The signal for isopropyl protons in **11c** appeared at δ 0.55, while the isopropyl methyls of **10c** were nonequivalent, appearing at δ 0.77 and 1.13 (J = 7 Hz).

Reaction of 0.50 g (1.3 mmol) of **8a** with 1.0 g (9.9 mmol) of diisopropylamine in 20 ml of benzene for 4 days at room temperature gave **10c** and **11c** in a 4:1 ratio. Treatment of this mixture with 0.50 g (5.7 mmol) of morpholine in 20 ml of chloroform for 24 hr at room temperature yielded **11a** and **11c** in a 4:1 ratio (by ^1H NMR analysis). The solvent and excess morpholine were removed under reduced pressure and **11a** was crystallized from carbon tetrachloride, 0.23 g (48%), mp 151°. This compound was identical with **11a** that was obtained from **8a**.

3-(2,4-Dimethyl-1-imidazolyl)-2-(2,4-dinitrophenylsulfonyl)-1-phenylpropene (11e). A 0.50-g (1.3 mmol) sample of **8b** and 0.30 g (3.0 mmol) of 2,4-dimethylimidazole dissolved in 40 ml of benzene were allowed to react at room temperature for 3 days. The benzene layer was diluted to 60 ml and washed with two 50-ml portions of water. The dried ($MgSO_4$) solution was concentrated under reduced pressure. The bright yellow solid that resulted was recrystallized from dichloromethane–hexane, 0.26 g (50%), mp 168–169°. The ^1H NMR spectrum ($CDCl_3$) showed peaks at δ 1.70 (s, 3 H), 2.30 (s, 3 H), 5.07 (s, 2 H), 6.17 (s, 1 H), 7.2–8.5 (m, 8 H).

Aminotropic Rearrangements. A. 3-Morpholino-3-phenyl-2-(*o*-nitrophenylsulfonyl)propene (10a). In the presence of trace amounts of morpholine in benzene solution **10a** readily rearranged to **11a**. See the procedure for the preparation of **11a** and note that a short reaction time led to detection of **11a** only.

B. 3-(*N*-*tert*-Butylamino)-3-phenyl-2-(*o*-nitrophenylsulfonyl)propene (10b). A 4:1 mixture of **10b** and **11b** (from the reaction of 0.24 g of **8** with 2 equiv of *tert*-butylamine) was dissolved in approximately 2 ml of deuteriochloroform. The solution was divided into equal portions and placed in two ^1H NMR tubes. Into one of the ^1H NMR tubes, a drop of *tert*-butylamine was added. Four hours later, a ^1H NMR spectrum of the material in the tube containing the added amine showed no peaks at δ 6.55 or 4.88 while these absorption bands remained for **10b** in the other ^1H NMR tube. The latter mixture contained ca. 30% of **10b** after 4 hr.

C. 3-(*N,N*-Diisopropylamino)-3-phenyl-2-(2,4-dinitrophenylsulfonyl)propene (10d). A 0.50-g (1.2 mmol) sample of a 83:17 mixture of **10d** and **11d** was treated with 1.0 g (9.9 mmol) of diisopropylamine in 20 ml of 95% ethanol. The mixture was stirred at room temperature for 4 days. The mixture was added to 80 ml of water and extracted with three 50-ml portions of chloroform. The chloroform layer was washed with 50 ml of water, dried ($MgSO_4$), and evaporated under reduced pressure. The characteristic ^1H NMR absorption bands at δ 6.60 and 5.25 for **10d** remained, and comparison with the signal at δ 3.71 for **11d** indicated that the ratio of **10d** to **11d** remained unchanged.

To a ^1H NMR tube containing 0.19 g (0.43 mmol) of **10d** in 1.0 ml of deuteriochloroform was added 0.2 g (2.3 mmol) of morpholine. The contents of the tube were thoroughly mixed and allowed to stand at room temperature for 2 hr. ^1H NMR analysis of the mixture indicated quantitative conversion of **10d** to **11a'** (absence of ^1H NMR signals at δ 6.60 and 5.25 and appearance of a signal at δ 3.52 for the allyl protons of **11a'**).

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Registry No.—**4**, 637-50-3; **7a**, 57109-74-7; **7b**, 57109-75-8; **8a**, 57109-76-9; **8b**, 57109-77-0; **10a**, 57109-78-1; **10b**, 57109-79-2; **10c**, 57109-80-5; **10d**, 57109-81-6; **11a**, 57109-82-7; **11b**, 57109-83-8; **11c**, 57109-84-9; **11d**, 57109-85-0; **11e**, 57109-86-1; *o*-nitrophenylsulfenyl chloride, 7669-54-7; 2,4-dinitrobenzenesulfenyl chloride, 528-76-7; *N*-bromosuccinimide, 128-08-5.

References and Notes

(1) Presented in part at the 9th Great Lakes Regional Meeting of the American Chemical Society, St. Paul, Minn., June 1975.
(2) (a) Abstracted in part from the Senior Honors Paper of P.A.T., April 1975. (b) M.L.N. performed early experiments in this investigation.
(3) F. G. Bordwell, *Acc. Chem. Res.*, **3**, 281 (1970); (b) R. H. DeWolfe and W. G. Young, *Chem. Rev.*, **56**, 1076 (1950).
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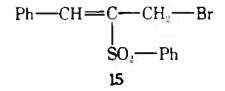
(12) On the basis of our work and data reported by Cromwell and co-workers,[11] the observed diisopropylamino product ratios reflect their kinetic distribution. The *o*-nitro group may play an important role in the reactivity of **8a**, since compound **15** gives only ca. 17% S_N2'-type product



15

upon treatment with diisopropylamine in benzene solution. However, **15** reacts with morpholine and *tert*-butylamine under comparable conditions to give S_N2' products in excellent yield (>80%). J. Neitzel, unpublished results.
(13) W. G. Young and H. L. Goering, *J. Am. Chem. Soc.*, **73**, 1076 (1951); G. Stork and W. N. White, *ibid.*, **75**, 4119 (1953); **78**, 4609 (1956).
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(17) Melting points were determined by the capillary method with a calibrated thermometer. Infrared spectra were obtained on a Beckman IR-5 and ^1H NMR spectra were determined on a Jeolco HL-60 NMR spectrometer. Elemental analyses were obtained from Heterocyclic Chemical Corp., Harrisonville, Mo., and Instranal Laboratory, Inc., Rensselaer, N.Y. A summary of physical data is given in Table II. Reactions were run at room temperature (ca. 25°) unless indicated otherwise.
(18) The authors wish to thank Charlotte Grove for repeating this procedure.
(19) We attempted to isolate and purify the hydrochlorides of amino sulfones **10a** and **10b** but these substances were hygroscopic. The free bases were regenerated after standing for 3 days at room temperature by treatment of the crude salts with dilute sodium bicarbonate solution. For **10b** that was recovered in this manner the product ratio was unchanged (ca. 80% **10b**) and complete rearrangement to **11b** required 3 days, whereas samples obtained by simply washing the benzene layer with water and evaporation required only ca. 24 hr for complete rearrangement under identical conditions.

9 ★ An exception to this generalization was reported recently : F. G. Bordwell and G. A. Pagani, ibid., 97, 118 (1975).

V.P.A.
25 April 1978

The Geometric Isomers of *O*-Alkylbenzohydroximoyl Chlorides. Synthesis, Identification, and Acid-Catalyzed Isomerization[1]

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Preparation of the *E* and *Z* isomers of nine *O*-alkylbenzohydroximoyl chlorides is described. The configurations of several of these geometric isomers were determined from dipole moment measurements. A correlation between configuration and the NMR chemical shift of the *O*-alkyl group hydrogens in these isomers was established. The acid-catalyzed (benzene–HCl, 40°) isomerization of a (*Z*)-hydroximoyl chloride went completely (within the detection limits of NMR spectroscopy) to the corresponding *E* isomer. In contrast, the acid-catalyzed (glacial acetic acid, 80°) isomerization of alkyl *O*-alkylbenzohydroximates gives significant amounts of the *Z* isomers (12–39%) at equilibrium. It is suggested that dipole moment effects may determine the relative stabilities of isomeric hydroximoyl chlorides and related compounds.

In connection with a study on the stereochemistry of nucleophilic substitution reactions in systems containing a carbon–nitrogen double bond, we undertook an investigation into the synthesis and identification of the geometric isomers of certain imidoyl halides.[3] The literature contains only a few examples of geometrical isomerism of imidoyl halides.[4–7] In fact, most of the well-documented reports concern preparation of isomeric imidoyl fluorides.[4,5] In other instances, attempts to isolate the geometric isomers of imidoyl halides have failed.[8,9] In these cases the preparation of both isomers may not be possible because of rapid isomerization of one of the isomers to the thermodynamically stable isomer. On the other hand, the stabilities of many types of imidoyl halides have not been investigated.

Geometrical isomerism due to restricted rotation around a carbon–nitrogen double bond is commonly observed in systems where an electronegative atom such as oxygen, nitrogen, or halogen is bonded to the imino nitrogen.[10,11] Consequently, we chose to investigate the stability of the geometric isomers of *O*-alkylbenzohydroximoyl halides. Numerous *O*-alkylbenzohydroximoyl chlorides have been reported in the early literature,[12–14] but it appears that no attempt has been made to prepare and identify the geometric isomers of these compounds.

The method of synthesis of the *E* and *Z* isomers of *O*-methylbenzohydroximoyl chloride (**3a** and **4a**) is outlined in Scheme I. Monomethylation of potassium benzohydroxamate (**1a**) resulted in the formation of methyl benzohydroxamate (**2a**). Reaction of **2a** with phosphorus pentachloride furnished *O*-methylbenzohydroximoyl chloride (**3a**). The NMR spectrum and gas chromatographic analysis of **3a** indicated that it was primarily a single stereoisomer (<1% contamination by the other geometric isomer). Ultraviolet irradiation of a hexane solution of **3a** gave a photostationary state mixture of **3a** and **4a** from which **4a** was separated by preparative gas chromatography. The ultraviolet irradiation produced along with **4a** a small amount of decomposition product which was identified as benzonitrile. Although pure samples of **4a** appear to be stable at room temperature, it is rather unstable in the crude photoreaction mixture. If this mixture is kept at room temperature without purification, the hydroximoyl chloride **4a** will isomerize to **3a** almost completely in about 1 week. This isomerization is probably catalyzed by hydrogen chloride which could be produced when the by-product benzonitrile is formed during the photoreaction. An attempt at deliberate thermal isomerization of **4a** in benzene at 50° failed to give any significant isomerization within a period of 1 week.

Using the methods outlined in Scheme I, eight other pairs of *O*-alkylbenzohydroximoyl chlorides (**3b–i** and **4b–i**) were synthesized. In addition, (*E*)-*O*-methylbenzohydroximoyl bromide (**3j**) was prepared in low yield by the reaction of **2a** with phosphorus tribromide. Ultraviolet irradiation of a hexane solution of **3j** failed to produce a detectable amount of the *Z* isomer.

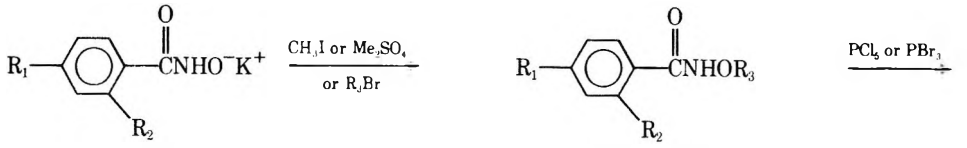
Table I
Dipole Moment Data for the *E* and *Z* Isomers of *O*-Methylbenzohydroximoyl Chlorides

Hydroximoyl chloride	Conformation	Theoretical dipole moment, D[a]	Experimental dipole moment, D[b]
3a	s-trans	1.25	1.38 ± 0.02 (1.40 ± 0.03)[c]
3a	s-cis	2.81	
4a	s-trans	1.78	
4a	s-cis	1.93	2.00 ± 0.04
3b	s-trans	3.52	3.58 ± 0.03
3b	s-cis	1.70	
4b	s-trans	3.18	
4b	s-cis	2.98	2.91 ± 0.04 (2.86 ± 0.08)[c]
3c	s-trans	1.57	1.73 ± 0.03
3c	s-cis	3.17	
4c	s-trans	2.10	
4c	s-cis	2.26	2.36 ± 0.04
3d	s-trans	1.03 (0.89)[d]	1.22 ± 0.03
3d	s-cis	1.02 (1.22)[d]	
4d	s-trans	1.03 (0.99)[d]	
4d	s-cis	0.98 (0.97)[d]	1.21 ± 0.05
3e	s-trans	1.72	1.87 ± 0.04
3e	s-cis	3.34	
4e	s-trans	2.30	
4e	s-cis	2.41	
3j	s-trans	1.16	1.40 ± 0.05
3j	s-cis	2.77	
4j	s-trans	1.69	
4j	s-cis	1.94	

[a] Calculated using the following bond (or group) moments and bond angles: CH_3–O, 1.04 D; N–O, 0.30 D; C=N, 1.80 D; C–Cl, 1.75 D; NO_2, 4.50 D; C–Br, 1.64 D; CH_3–C, 0.37; t-C_4H_9–C, 0.53; Ar–Cl, 1.60; 110° for N–O–CH_3(*E* and *Z* isomer); 114° for C=N–O (*E* and *Z* isomer); 115° for N=C–Cl (*E* isomer); 125° for N=C–Cl (*Z* isomer); 130° for N=C–C (*E* isomer); 120° for N=C–C (*Z* isomer). [b] The experimental dipole moments were determined in benzene at 25°; see the Experimental Section for details. [c] Duplicate determination. [d] The dipole moments in parentheses were calculated using the usual value of 1.60 D for Ar–Cl. The theoretical dipole moments based on an enhanced value for Ar–Cl of 1.80 D are outside the parentheses.

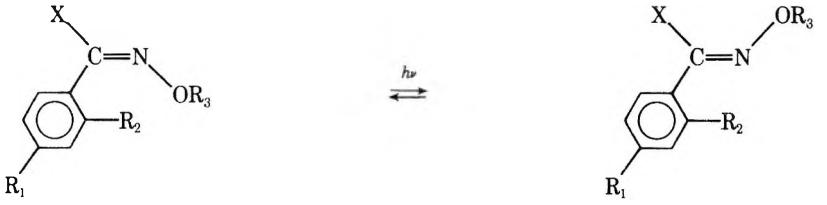
Configurational assignments for some of the hydroxi-

Scheme I



1a, $R_1 = R_2 = H$
b, $R_1 = NO_2$; $R_2 = H$
c, $R_1 = CH_3$; $R_2 = H$
d, $R_1 = Cl$; $R_2 = H$
e, $R_1 = t\text{-}C_4H_9$; $R_2 = H$
f, $R_1 = OCH_3$; $R_2 = H$
g, $R_1 = H$; $R_2 = CH_3$

2a, $R_1 = R_2 = H$; $R_3 = CH_3$
b, $R_1 = NO_2$; $R_2 = H$; $R_3 = CH_3$
c, $R_1 = R_3 = CH_3$; $R_2 = H$
d, $R_1 = Cl$; $R_2 = H$; $R_3 = CH_3$
e, $R_1 = t\text{-}C_4H_9$; $R_2 = H$; $R_3 = CH_3$
f, $R_1 = OCH_3$; $R_2 = H$; $R_3 = CH_3$
g, $R_1 = H$; $R_2 = R_3 = CH_3$
h, $R_1 = R_2 = H$; $R_3 = n\text{-}C_3H_7$
i, $R_1 = R_2 = H$; $R_3 = i\text{-}C_3H_7$



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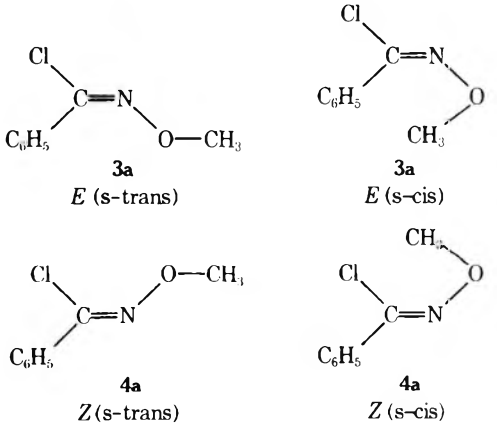
3 and 4f, $R_1 = OCH_3$; $R_2 = H$, $R_3 = CH_3$, X = Cl
g, $R_1 = H$; $R_2 = R_3 = CH_3$; X = Cl
h, $R_1 = R_2 = H$; $R_3 = n\text{-}C_3H_7$; X = Cl
i, $R_1 = R_2 = H$; $R_3 = i\text{-}C_3H_7$; X = Cl
3j, $R_1 = R_2 = H$; $R_3 = CH_3$; X = Br

4

3 and 4a, $R_1 = R_2 = H$; $R_3 = CH_3$; X = Cl
b, $R_1 = NO_2$; $R_2 = H$; $R_3 = CH_3$; X = Cl
c, $R_1 = R_3 = CH_3$; $R_2 = H$; X = Cl
d, $R_1 = X = Cl$; $R_2 = H$, $R_3 = CH_3$
e, $R_1 = t\text{-}C_4H_9$; $R_2 = H$; $R_3 = CH_3$; X = Cl

moyl chlorides **3** and **4** are based on dipole moment measurements (Table I). The theoretical dipole moments in Table I were calculated from bond moments[8a] and estimated bond angles. Various possible sets of bond angles were tried in these calculations. Although the resultant dipole moment is altered somewhat by small changes in bond angles, our configurational assignments are not affected. The bond angles chosen for Table I resulted in the best overall fit of the theoretical with the experimental dipole moments. These bond angles correspond to those used by Exner for his dipole moment calculations on (*E*)- and (*Z*)-benzohydroximoyl chloride.[8a,15]

Because of possible free rotation about the N–O bond axis in these compounds, calculations were made for the planar s-cis and s-trans conformations (as illustrated for **3a** and **4a**) of each compound. It is apparent from comparison



3a *E* (s-trans)

3a *E* (s-cis)

4a *Z* (s-trans)

4a *Z* (s-cis)

of the experimental dipole moments with the theoretical values that the phosphorus pentachloride reaction with a methyl benzohydroxamate (**2**) produces the *E* hydroximoyl chloride. Furthermore, it appears that the *E* hydroximoyl chlorides (**3**) exist in a planar s-trans conformation. The dipole moments of the *Z* hydroximoyl chlorides are in close agreement with the theoretical values for the s-cis conformation.[16] The assignment of a s-cis conformation to the *Z*

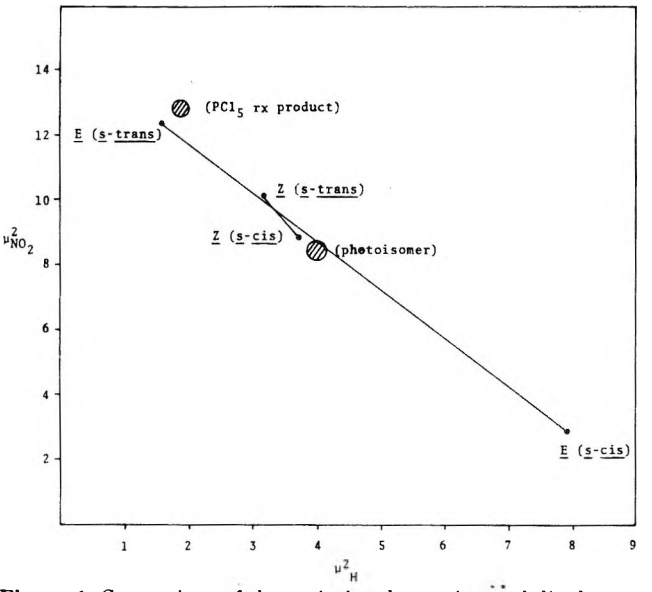


Figure 1. Comparison of theoretical and experimental dipole moments for the *E* and *Z* isomers of *O*-methylbenzohydroximoyl chloride (*x* axis, μ^2_H) and *O*-methyl-*p*-nitrobenzohydroximoyl chloride (*y* axis, $\mu^2_{NO_2}$); • represent theoretical values, ◍ represent experimental values.

isomers is somewhat uncertain since the theoretical dipole moments for *Z* (s-trans) and *Z* (s-cis) conformations differ at the most by only 0.2 D. To illustrate our conclusions, Exner's[17] method of graphical comparison of dipole moments is useful (Figure 1). In this graph the theoretical dipole moments for s-cis and s-trans conformations of the *E* and *Z* isomers of the unsubstituted compounds **3a** and **4a** (μ^2_H, plotted along the *x* axis) are compared to the dipole moments for the same conformations of the *E* and *Z* isomers of the *p*-nitro derivatives ($\mu^2_{NO_2}$, *y* axis). The tie lines between s-cis and s-trans conformations of the same geometric isomer represent the dipole moments for nonplanar conformations formed by rotation around the N–O bond axis.[18] An experimental point corresponds to the dipole moments of an unsubstituted and *p*-nitro hydroximoyl

Table II
Properties of Alkyl Benzohydroxamates, *O*-Alkylbenzohydroximoyl Chlorides, and Alkyl *O*-Alkylbenzohydroximates[a]

Compd	Method of preparation[b]	Yield, %	Mp or bp, °C	NMR, δ, ppm[c]	Ir, principal absorptions,[d] cm^{-1}	Uv max, nm (log ε)[e]
2a	A	47	mp 61–62[f] from ether–hexane	3.80 (s, 3 H), 7.4 (m, 3 H), 7.8 (m, 2 H)	3210, 1640, 1590, 1567 (Nujol)	
2b	B	42	mp 176–178[g] from ethanol–water	3.77 (s, 3 H), 8.0 (m, 2 H), 8.4 (m, 2 H), Me_2SO-d_6	3150, 1650, 1590 (Nujol)	
2c	B	70	mp 70–71 from ether–hexane	2.33 (s, 3 H), 3.80 (s, 3 H), 7.15 (d, J = 8 Hz, 2 H), 7.72 (d, J = 8 Hz, 2 H)		
2d	B	51	mp 106–109 from ethanol	3.74 (s, 3 H), 7.53 (ca. d, J = 8 Hz, 2 H), 7.80 (ca. d, J = 8 Hz, 2 H), Me_2SO-d_6		
2e	B[h]	74	Viscous oil[i]	1.31 (s, 9 H), 3.84 (s, 3 H), 7.41 (ca. d, J = 8 Hz, 2 H), 7.74 (ca. d, J = 8 Hz, 2 H)		
2f	B	77	mp 102–103 from water	3.79 (s, 6 H), 6.85 (d, J = 8.5 Hz, 2 H), 7.28 (d, J = 8.5 Hz, 2 H)	3160, 1640, 1600, 1565 (Nujol)	
2g	B	59	mp 105–106 from ether–hexane	2.38 (s, 3 H), 3.80 (s, 3 H), 7.25 (ca. s, 4 H)	3130, 1630, 1591 (Nujol)	
2i	C	29	mp 88–90 from ether–hexane	1.30 (d, J = 6 Hz, 6 H), 4.28 (septet, 1 H), 7.4 (m, 3 H), 7.8 (m, 2 H)	3140, 1623, 1564 (Nujol)	
3a	D (55°, 24 hr)	82	bp 53–54 (0.1 Torr)[j]	4.06 (s, 3 H), 7.4 (m, 3 H), 7.9 (m, 2 H)	1580, 1560	290 sh (2.88), 257 (4.11), 217 sh (3.96); 290 sh (2.76), 257 (4.08), 218 sh (3.94), 212 sh (4.03) in cyclohexane
4a	E		bp 43–44 (0.1 Torr)	3.92 (s, 3 H), 7.4 (m, 3 H), 7.7 (m, 2 H)	1595, 1580, 1565, 1553	254 (3.92), 217 sh (3.85), 256 (3.88), 218 sh (3.91) in cyclohexane
3b	D[k] (61°, 68 hr)	49	mp 121–122 from methanol	4.16 (s, 3 H), 8.10 (d, J = 8 Hz, 2 H), 8.30 (d, J = 8 Hz, 2 H)	1598 (w), 1590 (w), 1554, 1506 (Nujol)	296, (4.15), 227 (4.00)
4b	E[l]		mp 110–112 from methanol	4.04 (s, 3 H), 8.00 (d, J = 8 Hz, 2 H), 8.36 (d, J = 8 Hz, 2 H)	1595 (w), 1572 (w), 1510 (Nujol)	293 (3.98), 220 (3.94)

Table II
(*Continued*)

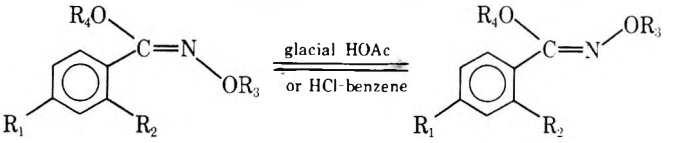
Compd	Method of preparation[b]	Yield, %	Mp or bp, °C	NMR, δ, ppm[c]	Ir, principal absorptions,[d] cm^{-1}	Uv max, nm (log ε)[e]
3c	D (60°, 2 hr)	66	bp 56–57 (0.06 Torr)	2.28 (s, 3 H), 4.02 (s, 3 H), 7.08 (d, *J* = 8.5 Hz, 2 H), 7.70 (d, *J* = 8.5 Hz, 2 H)	1603, 1580, 1575, 1552	293 sh (3.06), 262 (4.18), 219 sh (3.95), 212 (4.15)
4c	E			2.32 (s, 3 H), 3.91 (s, 3 H), 7.15 (d, *J* = 8 Hz, 2 H), 7.68 (d, *J* = 8 Hz, 2 H)	1601, 1582, 1579, 1555	261 (4.08), 220 sh (3.88)
3d	D (60°, 4 hr)	28	mp 28–29 from methanol	4.06 (s, 3 H), 7.29 (ca. d, *J* = 9 Hz, 2 H), 7.74 (ca. d, *J* = 9 Hz, 2 H)	1577, 1545 (w)	295 sh (3.19), 263 (4.24), 220 sh (3.98), 214 sh (4.14)
4d	E		mp <25	3.95 (s, 3 H), 7.35 (ca. d, *J* = 9 Hz, 2 H), 7.75 (ca. d, *J* = 9 Hz, 2 H)	1585	260 (4.04), 220 sh (3.88)
3e	D[m] (52°, 22 hr)	54	bp 82 (0.25 Torr)	1.30 (s, 9 H), 4.08 (s, 3 H), 7.41 (ca. d, *J* = 8.5 Hz, 2 H) 7.80 (ca. d, *J* = 8.5 Hz, 2 H)	1600, 1578	
4e	E			1.32 (s, 9 H), 3.98 (s, 3 H), 7.43 (ca. d, 2 H), 7.78 (ca. d, 2 H)		
3f	D (55°, 24 hr)	53	mp 51–53 from methanol	3.82 (s, 3 H), 4.06 (s, 3 H), 6.89 (d, *J* = 8.5 Hz 2 H), 7.80 (d, *J* = 8.5 Hz, 2 H)	1590, 1575	300 sh (3.54), 271 (4.29)
4f	E		mp 40–41	3.82 (s, 3 H), 3.95 (s, 3 H), 6.91 (d, *J* = 9 Hz, 2 H), 7.82 (d, *J* = 9 Hz, 2 H)	1596	271 (4.20), 215 sh (4.05)
3g	D (115°, 4 hr)	80	bp 55 (0.05 Torr)	2.42 (s, 3 H), 4.06 (s, 3 H), 7.3 (m, 4 H)	1585	242 (3.86)
4g	E			2.30 (s, 3 H), 3.88 (s, 3 H), 7.24 (s, 4 H)	1601, 1587	273 sh (2.98), 232 sh (3.81)
3h	D	Ref 20		0.99 (t, 3, *J* = 7 Hz, 2 H), 1.8 (m, 2 H), 4.24 (t, *J* = 6.5 Hz, 3 H), 7.4 (m, 3 H), 7.8 (m, 2 H)[n]	Ref 20	
4h	E			0.90 (t, *J* = 7 Hz, 2 H), 1.7 (m, 2 H), 4.10 (t, *J* = 6.5 Hz, 3 H), 7.4 (m, 3 H), 7.8 (m, 2 H)	1597, 1582, 1565, 1559	
3i	D (98°, 3 hr)	85	bp 48 (0.1 Torr)	1.35 (d, *J* = 6 Hz, 6 H), 4.56 (septet, *J* = 6 Hz, 1 H), 7.4 (m, 3 H), 7.9 (m, 2 H)	1580, 1557	

Table II
(*Continued*)

Compd	Method of preparation[b]	Yield, %	Mp or bp, °C	NMR, δ, ppm[c]	Ir, principal absorptions,[d] cm^{-1}	Uv max, nm (log ε)[e]
4i	E[o]			1.28 (d, J = 6 Hz, 6 H), 4.48 (septet, J = 6 Hz, 1 H), 7.4 (m, 3 H), 7.9 (m, 2 H)	1595, 1580, 1586	
3j	F	19	bp 66 (0.7 Torr)	4.13 (s, 3 H), 7.4 (m, 3 H), 7.8 (m, 2 H)	1581, 1560	
5a	H			3.80 and 3.84 (singlets, 6 H), 7.4 (m, 3 H), 7.7 (m, 2 H)	1618, 1595, 1571	
6a	G	68	bp 70 (0.3 Torr)	3.88 and 3.90 (singlets, 6 H), 7.4 (m, 3 H), 7.6 (m, 2 H)	1602, 1564	
5b	H			2.34 (s, 3 H), 3.80 (s, 3 H), 7.18 (d, J = 8.5 Hz, 2 H), 7.32 (d, J = 8.5 Hz, 2 H)		
6b	G	56	bp 75 (0.4 Torr)	2.34 (s, 3 H), 3.89 (s, 3 H), 7.15 (d, J = 8.5 Hz, 2 H), 7.56 (d, J = 8.5 Hz, 2 H)		
5c	H			2.23 (s, 3 H), 3.66 (s, 3 H), 3.76 (s, 3 H), 7.15 (s, 4 H)	1636, 1626, 1599	
6c	G	60	bp 62 (0.1 Torr)	2.37 (s, 3 H), 3.54 (s, 3 H), 3.87 (s, 3 H), 7.25 (s, 4 H)	1625	
5e	H			1.25 (d, J = 6 Hz, 6 H), 3.82 (s, 3 H), 4.27 (septet, J = 6 Hz, 1 H), 7.4 (m, 3 H), 7.8 (m, 2 H)	1612, 1592, 1558	
6e	G	76	bp 61–63 (0.1 Torr)	1.33 (d, J = 6 Hz, 6 H), 3.97 (s, 3 H), 4.36 (septet, J = 6 Hz, 1 H), 7.4 (m, 3 H), 7.7 (m, 2 H)	1604, 1565	

[a] Satisfactory elemental analyses (C, H, and N or C, H, N, and Cl) were reported for all new compounds listed in this table. Ed. [b] Obtained from reactions of the following types: A, a potassium benzohydroxamate with methyl iodide; B, a potassium benzohydroxamate with dimethyl sulfate; C, potassium benzohydroxamate with isopropyl bromide; D, alkyl benzohydroxamate with phosphorus pentachloride, reaction temperatures and times in parentheses; E, photoisomerization of the *E* isomer followed by preparative glc; F, methyl benzohydroxamate with phosphorus tribromide and purified by preparative GLC; G, (*E*)-*O*-alkylbenzohydroximoyl chloride with sodium alkoxide in alcohol (10%) and Me_2SO (90%); H, isomerization of the *Z* isomer in glacial acetic acid followed by preparative GLC. [c] Unless otherwise noted all NMR spectra were determined on $CDCl_3$ solutions. [d] Unless otherwise noted the ir spectra were determined on thin films of the neat liquids. The principal absorptions include NH, C=O, C=N, and aromatic absorptions. [e] Unless otherwise noted the uv spectra were determined on 95% ethanol solutions. [f] Reported mp 63.5–64.5° [J. H. Cooley, W. D. Bills, and T. R. Throckmorton, *J. Org. Chem.*, 25, 1734 (1960)]; 62° [O. Exner and B. Kakáč, *Collect. Czech. Chem. Commun.*, 28, 1656 (1963)]. [g] Reported mp 180° [O. Exner and J. Holubek, *Collect. Czech. Chem. Commun.*, **30**, 940 (1965)]. [h] Analytical sample prepared from reaction of thallium(I) *p-tert*-butylbenzohydroxamate with methyl iodide. See E. C. Taylor and F. Kienzle, *J. Org. Chem.*, 36, 233 (1971), for a similar procedure. [i] Distilled with a Kontes micromolecular distillation apparatus. [j] A compound with this structural formula (configuration not determined) has been prepared previously by the reaction of *O*-methylbenzamide oxime with sodium nitrite and hydrochloric acid, bp 225°: F. Tiemann and P. Kruger, *Ber.*, 17, 1665 (1884); 18, 727 (1885); P. Kruger, *ibid.*, 18, 1053 (1885). [k] Reaction carried out in chloroform solvent. [l] Separated from the *E*-isomer by preparative TLC (silica gel with 25:75 benzene–hexane eluent). [m] Reaction carried out in carbon tetrachloride solvent. [n] Correction of chemical shifts reported previously in ref 20. [o] Purified by preparative HPLC (Corasil column with hexane solvent).

Table III
Equilibrium Distributions of (*E*)- and (*Z*)-*O*-Alkylbenzohydroximates

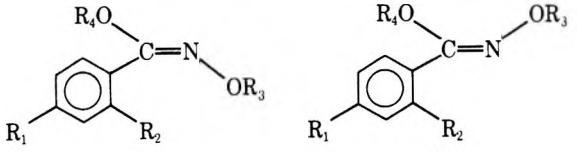


5 6

Isomers	R_1	R_2	R_3	R_4	Temp, °C	Solvent	% *Z* isomer (6)
5a and 6a	H	H	CH_3	CH_3	80	HOAc	32
5b and 6b	CH_3	H	CH_3	CH_3	80	HOAc	23
5c and 6c	H	CH_3	CH_3	CH_3	80	HOAc	12
5d and 6d	H	H	*n*-C_3H_7	CH_3	80	HOAc	30
5e and 6e	H	H	*i*-C_3H_7	CH_3	80	HOAc	32
5f and 6f	H	H	*n*-C_3H_7	C_2H_5	80	HOAc	39
5g and 6g	H	H	*n*-C_3H_7	*n*-C_3H_7	80	HOAc	39
5a and 6a	H	H	CH_3	CH_3	40	HOAc	27
5a and 6a	H	H	CH_3	CH_3	60	HOAc	29
5a and 6a	H	H	CH_3	CH_3	30	HCl–benzene	20
5a and 6a	H	H	CH_3	CH_3	40	HCl–benzene	23
5a and 6a	H	H	CH_3	CH_3	50	HCl–benzene	25

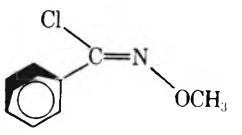
chloride that were obtained from the same kind of reactions, i.e., the phosphorus pentachloride reactions were assumed to give the same geometric isomer in both the unsubstituted and *p*-nitro cases. The position of the experimental values in relation to the theoretical points allows one to determine configuration and conformation along with the accuracy of the decisions. This graphical representation reinforces our configurational and onformational assignments for these compounds.

Having determined the configuration of several pairs of hydroximoyl chlorides (**3a–c** and **4a–c**) from dipole moment measurements, it was possible to establish a correlation of the configurations these compounds with their NMR spectra. In all of the compounds examined, the chemical shift of the *O*-methyl singlet (or *O*-alkyl multiplet) was further downfield in the case of the *E* isomer than in the corresponding *Z* isomer (Table II).[19] This correlation enabled us to make configurational assignments for compounds **3d–i** and **4d–i**. It is interesting to note that this correlation is the reverse of the NMR correlation established by us[20] for the *E* and *Z* isomers of alkyl *O*-alkylbenzohydroximates (**5** and **6**). In the isomeric pairs **5** and **6**, the *O*-



5 6

alkyl absorptions are further downfield in the *Z* isomer than in the *E* isomer. The downfield shift of the *O*-alkyl group hydrogens in a *E* hydroximoyl chloride is probably due to the shielding effect of the phenyl ring that is twisted out of the plane of the carbon–nitrogen double bond (as shown for **3a**).

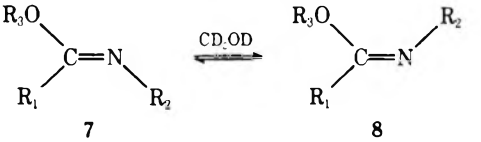


3a

In order to determine the relative stabilities of the hydroximoyl chlorides, the isomers **3a–g** and **4a–g** were equilibrated in hydrogen chloride–benzene (40°) solution. Within the detection limits of NMR spectroscopy it was found that in every case examined the *Z* isomer completely isomerized to the *E* isomer.

For purposes of comparison the *E* and *Z* isomers of several alkyl *O*-alkylbenzohydroximates[20] (**5** and **6**) were equilibrated (Table III). Unlike the hydroximoyl chlorides, equilibrium mixtures of benzohydroximates contain significant amounts of both isomers with the *E* isomer predominating. There seems to be little if any solvent affect on these equilibria since the equilibrium distribution (at 40°) of **5a** and **6a** is essentially the same in HCl–benzene and glacial acetic acid (Table II).

Various factors have been used to explain the equilibrium distributions of imino compounds including steric effects,[21,22] interorbital electron repulsions,[23,11b] and dipole moment effects.[22] In a recent report by Walter et al.,[22] it was proposed that the two factors determining the relative stability of imidates **7** and **8** are dipole interactions and steric effects. It was pointed out that in the absence of large steric effects (**7a** ⇌ **8a**), the isomer with the lowest dipole moment (**8a**) is found in the highest concentration. When the size of R_1 was increased by substitution with a *tert*-butyl group (**7b** ⇌ **8b**) a steric effect resulted in an increase in the equilibrium concentration of the *Z* isomer (**8b**).



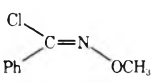
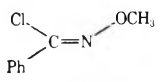
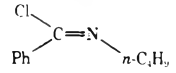
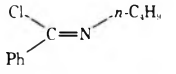
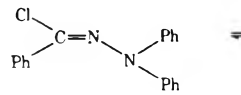
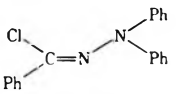
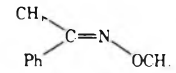
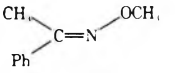
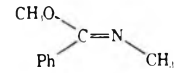
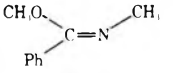
7 8

a, $R_1 = R_2 = R_3 = CH_3$ (*E*:*Z* 95:5)
b, $R_1 = t\text{-}C_4H_9$; $R_2 = R_3 = CH_3$ (*E*:*Z* 71:29)

Of the many factors that could contribute to the relative stabilities of the *E* and *Z* isomers of hydroximoyl chlorides, dipole interactions may be the most important. Considering only the isomeric pairs (**3a** and **4a**; **3c** and **4c**) that do not contain a para substituent with a large group moment (which masks the moment of the hydroximoyl chloride functional group) the stable *E* isomers have lower dipole moments than the *Z* isomers.

In contrast to hydroximoyl chlorides, where the stable isomer has the *E* configuration, dipole moment studies have shown that the only isolable isomer of a simple imidoyl chloride has the *Z* configuration (**10** in Table IV). In the case of imidoyl chlorides, the theoretical dipole moment for the *E* isomer (**9**) is higher than the experimentally

Table IV
Equilibrium Geometric Isomer Distributions for Compounds Containing a Carbon–Nitrogen Double Bond

Geometric isomers		Ref
		This work
3a (*E*)	4a (*Z*)	
μ = 1.38 D (exp)	μ = 2.00 D (exp)	
100% *E*	0% *Z*	
		8d
9 (*E*)	10 (*Z*)	
μ = 2.18 D (theory)	μ = 0.54 D (exp)	
0% *E*	100% *Z*	
		9
11 (*E*)	12 (*Z*)	
μ = 2.78 D (theory)[a]	μ = 0.91 D (exp)	
0% *E*	100% *Z*	
		24
13 (*Z*)	14 (*E*)	
μ = 1.25 D (s-trans, theory)[b]	μ = 1.10 D (s-trans, theory)[b]	
2% *Z*	98% *E*	
		25
15 (*E*)	16 (*Z*)	
μ = 1.29 D (exp)	μ = 2.32 D (s-trans, theory)	
100% *E*	0% *Z*	

[a] Calculation based on a planar diphenylamino group. [b] Calculated by us using the bond moments and bond angles in Table I.

determined dipole moment of the *Z* isomer (**10**). Dipole moment effects could also be responsible for the differences in the stabilities (Table IV) of isomeric *N,N*-diphenylbenzhydrazidoyl chlorides (**11** and **12**), *O*-methylacetophenone oximes (**13** and **14**), and methyl *N*-methylbenzimidates (**15** and **16**).

Experimental Section

Preparation of Compounds. Melting points are corrected and were determined on a Thomas-Hoover capillary melting point apparatus. All boiling points are uncorrected. Magnesium sulfate was employed as a drying agent for ether and chloroform extracts. Infrared spectra were determined with a Perkin-Elmer spectrophotometer, Model 225. The NMR spectra were determined at 60 MHz with a Varian Model A-60A spectrometer. The ultraviolet spectra were determined with a Cary Model 15 spectrophotometer. Compounds **3h, 5d, 6d, 5f, 6f, 5g,** and **6g** have been described in an earlier report.[20] The ultraviolet, infrared, and nuclear magnetic resonance spectra along with melting points or boiling points for all the other compounds prepared in this work are in Table II. The GLC (analytical and preparative) was carried out with a column (30 ft × 0.375 in.) consisting of 20% silicone gum rubber (SE-30) on 45–60 mesh Chromosorb W. Microanalyses were carried out by Atlantic Microlab, Atlanta, Ga. The potassium benzohydroxamates (**1a–f**) were prepared according to an organic synthesis procedure.[26,27] One representative example of each type of synthetic procedure is described in this section.

Methyl *p*-Methylbenzohydroxamate (2c). Dimethyl sulfate (34 ml) was added to a water (1000 ml) solution of potassium *p*-methylbenzohydroxamate (60.0 g) and potassium hydroxide (53 g). The solution was heated (75°) and stirred for 7 days, after which time it did not give a purple color with alcoholic ferric chloride solution. The solution was cooled in an ice bath and carefully acidified with cold glacial acetic acid. The crystals (37.0 g, 70%) which formed were filtered and dried, mp 55–69°. Several recrystallizations from ether–hexane gave colorless plates, mp 70–71°.

Anal. Calcd for $C_9H_{11}NO_2$: C, 65.44; H, 6.71; N, 8.48. Found: C, 65.22; H, 6.82; N, 8.34.

(*E*)-*O*-Methyl-*p*-methylbenzohydroximoyl Chloride (3c). Phosphorus pentachloride (18.2 g) was slowly added with stirring to methyl *p*-methylbenzohydroxamate (14.4 g) in an 100-ml round-bottom flask cooled in an ice bath. The flask was allowed to warm to room temperature and it was then heated at 56–60° for 2 hr. The flask was cooled to room temperature and the liquid product was poured slowly with stirring into cold water. The resulting mixture was extracted several times with chloroform. The combined chloroform extracts were washed alternately with 10% sodium bicarbonate solution, water, 6 *N* sodium hydroxide solution, and water. The chloroform solution was dried and the chloroform was removed by evaporation at aspirator pressure. The residual oil was distilled to give a colorless oil (9.50 g, 59%), bp 56–57° (0.06 Torr).

Anal. Calcd for $C_9H_{10}NOCl$: C, 58.87; H, 5.49; N, 7.63; Cl, 19.31. Found: C, 58.92; H, 5.53; N, 7.48; Cl, 19.47.

The oil did not form a white precipitate of silver chloride when added to an alcoholic silver nitrate solution, indicating the absence of phosphorus oxychloride. In most preparations of the (*E*)-hydroximoyl chlorides additional washing with 10% sodium hydroxide solution and redistillation was necessary in order to completely remove the phosphorus oxychloride.

(*Z*)-*O*-Methyl-*p*-methylbenzohydroximoyl Chloride (4c). Photoisomerization of 3c. A hexane (80 ml) solution of **3c** (2.0 g) was irradiated in quartz tubes for 3 hr using a Rayonet photochemical reactor, Model RPR-100 (The Southern New England Ultraviolet Co.) equipped with 2537-Å lamps. In order to prevent acid-catalyzed isomerization of **4c,** the hexane solution was shaken with solid, anhydrous sodium carbonate immediately after irradiation. The hexane was then removed by evaporation at aspirator pressure. The residual oil was analyzed by GLC and found to contain a 60:40 mixture of **3c** and **4c** along with a small amount of *p*-methylbenzonitrile. Pure **4c** was obtained by preparative GLC.

Anal. Calcd for $C_9H_{10}NOCl$: C, 58.87; H, 5.49; N, 7.63; Cl, 19.31. Found: C, 59.10; H, 5.57; N, 7.70; Cl, 19.08.

Isomerization of 4c in Benzene–Hydrogen Chloride Solution. A saturated solution (ca. 0.4 mol kg^{-1}) of hydrogen chloride in benzene was prepared by bubbling dry hydrogen chloride gas through anhydrous benzene for about 15 min. The hydroximoyl chloride **4c** (0.73 g) was added to the benzene–hydrogen chloride solution (1.00 g) in a NMR spin tube fitted with a rubber septum. The isomerization of **4c** to **3c** was followed by NMR spectroscopy (40°) until **4c** could no longer be detected (about 4 days).

Methyl (*Z*)-*O*-Methyl-*p*-methylbenzohydroximate (6b). A sodium methoxide solution prepared from 0.86 g of sodium and methanol (15 ml) was added to **3c** (4.5 g) dissolved in dimethyl sulfoxide (135 ml). The solution was heated at 45° for 25 hr and then poured into ice water (135 ml). Enough sodium chloride was added to saturate the aqueous layer and the mixture was extracted several times with ether. The ether extracts were dried and evaporated to give 4.15 g (94%) of oil. GLC analysis of the oil showed that it contained 98% **5b** and 2% **6b**. Distillation gave pure **6b** (2.48 g, 56%), bp 75° (0.4 Torr).

Anal. Calcd for $C_{10}H_{13}NO_2$: C, 67.02; H, 7.31; N, 7.82. Found: C, 67.18; H, 7.34; N, 7.91.

Methyl (*E*)-*O*-Methyl-*p*-methylbenzohydroximate (5b). Glacial Acetic Acid Isomerization of 6b. A glacial acetic acid (15 ml) solution of **6b** (1.34 g) was heated at 80° in a constant-temperature bath for 3.5 hr. The reaction solution was quenched by mixing with an excess of 6 *N* sodium hydroxide (50 ml) solution. The resulting mixture was extracted with ether (two 20-ml portions) and the ether extracts were dried and evaporated, yielding a clear oil. GLC analysis of the oil showed only two peaks due to **5b** and **6b** in a ratio of 77:23. Isomer **5b** was separated by preparative GLC.

Anal. Calcd for $C_{10}H_{13}NO_2$: C, 67.02; H, 7.31; N, 7.82. Found: C, 67.21; H, 7.35; N, 7.91.

For the equilibrium studies, the glacial acetic acid solutions of the *Z* or *E* hydroximates (**5**) were heated for various periods of time to determine when equilibrium had been reached. In all the isomerization reactions examined equilibrium had been attained within 3 hr.

Dipole Moment Measurements. Dipole moments were determined by the method of Guggenheim.[28] The dielectric constants were measured with a Kahl Scientific Type DM-01 Dipolmeter fitted with a DFL-1 sample holding cell (20-ml volume) which has a dielectric constant range of 1.0–3.4. The DFL-1 cell was calibrated in the D2 position of the dipolmeter with the following spectropho-

tometric grade liquids: cyclohexane (Baker), carbon tetrachloride (Aldrich), benzene (Baker), and toluene (Aldrich). These solvents had been stored over Linde type 4A molecular sieves at least 1 week prior to the measurements. Dielectric constants for these liquids have been reported.[28d] A calibration equation for conversion of the dipolmeter reading into dielectric constant was calculated by the method of least squares. Dielectric constants were measured on four or five benzene (Baker spectrophotometric grade kept over Linde type 4A molecular sieves) solutions of concentrations ranging from 0.005 to 0.06 weight fraction. The solutions were made up by weighing (Mettler semimicro analytical balance to the nearest 0.01 mg) the solute directly into a 25-ml volumetric flask and diluting to the mark with solvent. The flask was reweighed and the weight fraction of each solution was calculated. After the DFL-1 cell was filled with the solution to be measured the cell contents were allowed to stand for at least 5 min to allow the solution to reach thermal equilibrium. Five meter readings on the Dipolmeter were taken for each solution and the average was corrected with a correction diagram furnished with the instrument. After each measurement, the cell was rinsed thoroughly with acetone or methanol and dried by flushing with dry nitrogen. The cell was also rinsed with a few milliliters of the solution to be measured before the cell was filled. Immediately after measuring the dielectric constant, the refractive index of each solution was measured using an Abbe high-precision refractometer (Bellingham and Stanley Limited Model 60/ED) fitted with a 2-ml flow-through cell. The procedure previously described for cleaning and filling the Dipolmeter cell was used for the refractometer cell. Both the Dipolmeter and refractometer cells were maintained at 25.0 ± 0.1° by means of a circulating constant-temperature bath. The dipole moments were calculated from the equation

$$\mu^2 = \frac{27KT}{4\pi N}\frac{M(a_\epsilon - a_n)}{d(\epsilon_1 + 2)^2}$$

where K = Boltzmann's constant, N = Avogadro's number, T = temperature (K), M = molecular weight of the solute, d = density of the solvent, ϵ_1 = dielectric constant of the solvent, a_ϵ = slope of a line obtained by plotting $(\epsilon_{12} - \epsilon_1)$ vs. ω where ϵ_{12} is the dielectric constant of a solution and ω is the weight fraction of that solution, and a_n = slope of a line obtained by plotting $(n_{12}^2 - n_1^2)$ vs. ω where n_{12} is the refractive index of a solution and n_1 is the refractive index of the solvent. The values for a_ϵ and a_n were determined by least-squares evaluation of the data. The error limits in a_ϵ and a_n were estimated at the 95% confidence level. These errors limits were used to calculate the errors in the dipole moments given in Table I.

Acknowledgments. We gratefully acknowledge the financial support of this work by the Robert A. Welch Foundation. We are also grateful to Mrs. Nancy M. Silk and Dr. Pratibha V. Wakharkar for assistance in the preparation of some of the compounds and to Dr. Charles Weidig, who made some of the initial dipole moment measurements. Finally we wish to thank Dr. Evan P. Kyba, The University of Texas, for helpful discussions.

Registry No.—**1a,** 32685-16-8; **1b,** 57139-18-1; **1c,** 57139-19-2; **1d,** 57139-20-5; **1e,** 57139-21-6; **1f,** 57139-22-7; **1g,** 57139-23-8; **2a,** 2446-51-7; **2b,** 1613-79-2; **2c,** 25563-06-8; **2d,** 25563-14-8; **2e,** 57139-24-9; **2f,** 24056-08-4; **2g,** 57139-25-0; **2i,** 3532-27-2; **3a,** 41071-34-5; **3b,** 41071-36-7; **3c,** 57139-26-1; **3d,** 57139-27-2; **3e,** 57139-28-3; **3f,** 57139-29-4; **3g,** 57139-30-7; **3h,** 57139-31-8; **3i,** 57139-32-9; **3j,** 41071-43-6; **4a,** 41071-35-6; **4b,** 41071-37-8; **4c,** 57139-33-0; **4d,** 57139-34-1; **4e,** 57139-35-2; **4f,** 57139-36-3; **4g,** 57139-37-4; **4h,** 57139-38-5; **4i,** 57139-39-6; **4j,** 57139-40-9; **5a,** 41071-40-3; **5b,** 57139-41-0; **5c,** 57139-42-1; **5d,** 26889-19-0; **5e,** 57139-43-2; **5f,** 26889-20-3; **5g,** 26889-17-8; **6a,** 41071-39-0; **6b,** 57139-44-3; **6c,** 57139-45-4; **6d,** 26889-13-4; **6e,** 57139-46-5; **6f,** 26889-14-5; **6g,** 26889-11-2.

References and Notes

(1) Part of this work has been reported at the 27th Southwest Regional Meeting of the American Chemical Society, San Antonio, Texas, Dec 3, 1971, Abstract, p 99, and the International Symposium on Nucleophilic Substitution, Pocono Manor, Pa., April 15, 1975. A preliminary communication on a portion of this work has been published: J. E. Johnson, E. A. Nalley, and C. Weidig, *J. Am. Chem. Soc.*, **95,** 2051 (1973).
(2) Taken in part from the Ph.D. Dissertation of E. A. Nalley, Texas Woman's University, May 1975, and the M.A. Thesis of J. R. Springfield, Sam Houston State University, Dec 1970.
(3) For reviews on imidoyl halides see (a) H. Ulrich, "The Chemistry of Imidoyl Halides", Plenum Press, New York, N.Y., 1968; (b) R. Bonnett in "The Chemistry of the Carbon-Nitrogen Double Bond", S. Patai, Ed., Interscience, New York, N.Y., 1970, pp 628–642.
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(19) In addition, in every case examined the GLC retention time (SE-30) of an (*E*)-hydroximoyl chloride was greater than that of the corresponding *Z* isomer.
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New Reagents for the Intermolecular and Intramolecular Pinacolic Coupling of Ketones and Aldehydes

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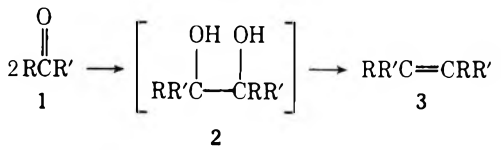
Studies are reported which extend considerably the scope and effectiveness of the pinacolic coupling reaction. Three reagents were found to be most useful: (1) magnesium amalgam–titanium tetrachloride, (2) cyclopentadienyltitanium trichloride–lithium aluminum hydride, and (3) the hexamethylbenzene complex of the well-defined Ti(II) species $(Cl_2AlCl_2)_2Ti$. Examples are given of intermolecular coupling reactions leading to *both* symmetrical and unsymmetrical pinacols. Some uses of the latter products in synthesis are illustrated. Several cases of intramolecular pinacolic reaction to form four-, five-, and six-membered rings are provided. Finally, a brief discussion is presented with regard to possible mechanisms for the titanium mediated pinacolic coupling.

The reductive coupling of carbonyl compounds constitutes an important method for the formation of carbon–carbon bonds.[1] The coupling of carboxylic esters (the acyloin reaction) has long been recognized as a powerful tool for intermolecular condensation and intramolecular cyclization. In contrast, the "pinacolic reduction" of ketones and aldehydes has seen limited application in complex synthetic problems. Aliphatic systems undergo coupling in poor yield and no general method for effective *intramolecular* pinacolic reduction has previously been reported.

Recently, Mc Murry[2] has demonstrated that a reagent (of undefined structure) derived from the interaction of titanium trichloride and lithium aluminum hydride induces coupling of carbonyl compounds. However, this reagent leads not to pinacols, but rather to the corresponding olefins as shown in Scheme I. Other low-valent transition metal reagents[3-5] have been reported to effect pinacolic coupling; however, these reagents do not effectively couple aliphatic ketones.

Scheme I



In connection with our interest in methods for constructing the D ring of gibberellic acid,[6] we have developed several highly efficient and *general* reagents for the pinacolic coupling of ketones and aldehydes. We report herein the results of this investigation, defining the power and scope of the pinacolic coupling process.

Intermolecular Reductive Coupling Reactions. Although Mukaiyama's $TiCl_4$–Zn reagent[4] successfully couples aromatic ketones and aldehydes, we found it less effective in aliphatic systems (vide infra). We have examined a variety of low-valent titanium compounds and have observed the nature and yield of products to be highly dependent on the precise Ti(II) species employed. *However, we have found that ketones and aldehydes are consistently coupled in excellent yield by the Ti(II) species generated by reaction of titanium tetrachloride and amalgamated 70–80 mesh magnesium.* Optimum yields are obtained by reaction at 0° for 1–15 hours in tetrahydrofuran (Table I). Substitution of other forms of aluminum, magnesium, or zinc or other solvent systems resulted in inferior yields. Table II compares our results with previously reported methods.

The potential pinacol rearrangement[8] of these reductive coupling products greatly extends their synthetic utility.

Table I
Intermolecular Reductive Coupling Reactions

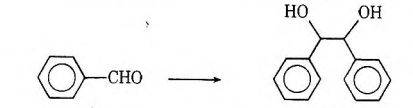
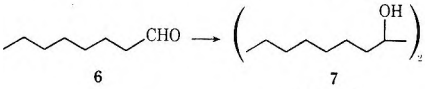
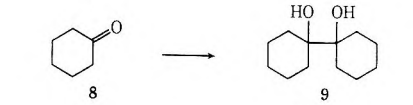
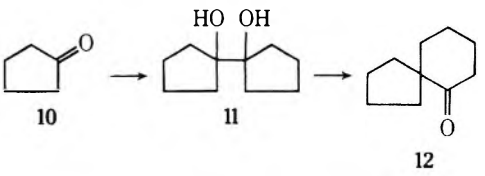
	% isolated yield
	84
	80
	93
	95

Table II
Comparison of Methods for Reductive Coupling of Cyclohexanone

Method	% isolated yield
$Mg(Hg)–TiCl_4$	93
$LiAlH_4–TiCl_3$[2]	(Olefin)
$Zn–TiCl_4$	24[a]
$Mg–TiCl_3$[5]	45
$Al(Hg)$[7]	55

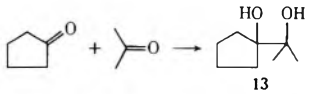
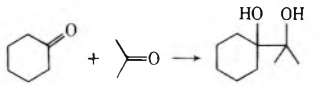
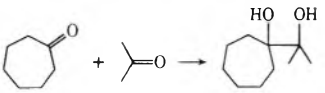
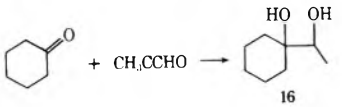
[a] This result was obtained following the procedure of Mukaiyama and coworkers.[4] The yield is corrected for unreacted starting material.

For example, diol 11 undergoes acid-catalyzed rearrangement providing spirodecanone **12**, now available in 82% overall yield from cyclopentanone.[9] This compound served as starting material in a recent total synthesis of perhydrohistrionicotoxin.[10]



We have extended the scope of the reductive coupling method to include the synthesis of *unsymmetrical* pinacols.[11] Thus, reaction of a cyclic ketone and 3 equiv of a low molecular weight carbonyl compound with the Mg(Hg)–$TiCl_4$ reagent affords a mixture from which the unsymmetrical pinacol is easily separated by chromatography in good yield (Table III). Although this method fails with low

Table III
Unsymmetrical Reductive Coupling Reactions

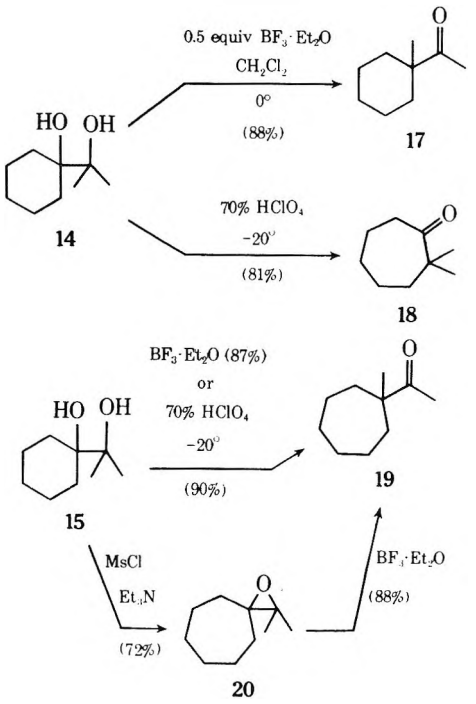
	% isolated yield[a]
 13	65[b]
 14	76[b]
 15	75[b]
 16	72[c]

[a] The yields are based on cyclic ketone. [b] The Mg(Hg)–$TiCl_4$ reagent was employed for this reaction. [c] The $CpTiCl_3$–$LiAlH_4$ reagent was employed for this reaction.

molecular weight aldehydes, excellent results are obtained using the reagent formed by reaction of cyclopentadienyltitanium trichloride and lithium aluminum hydride (vide infra).[12]

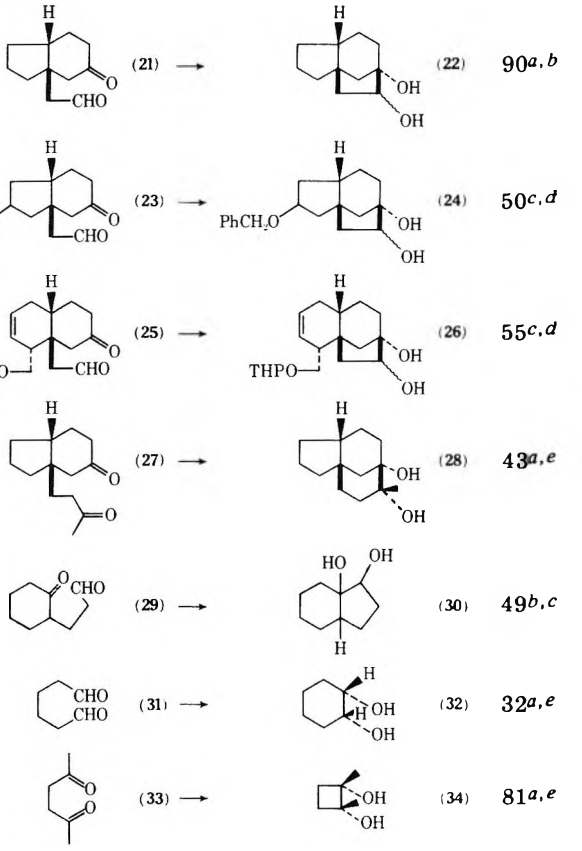
The unsymmetrical pinacols **13–16** are useful synthetic intermediates. Treatment with methanesulfonyl chloride and triethylamine affords epoxides in excellent yield. Both the pinacols and epoxides undergo ring expansion reactions and/or methyl group migration in high yields under mild conditions.[13] Scheme II details some of our results.

Scheme II



Intramolecular Reductive Coupling Reactions. Compounds **23** and **25** are key intermediates in studies directed toward the total synthesis of gibberellic acid being pursued in these laboratories. Our interest in methods for the intramolecular coupling of these molecules initiated this investigation. Classical conditions[6,7] proved totally ineffective for these reactions. Mc Murry's reagent succeeds only for pinacolic cyclizations in which deoxygenation of the initially

Table IV
Intramolecular Reductive Coupling Reactions

	% isolated yield
 (21) → (22)	90[a,b]
(23) → (24)	50[c,d]
(25) → (26)	55[c,d]
(27) → (28)	43[a,e]
(29) → (30)	49[b,c]
(31) → (32)	32[a,e]
(33) → (34)	81[a,e]

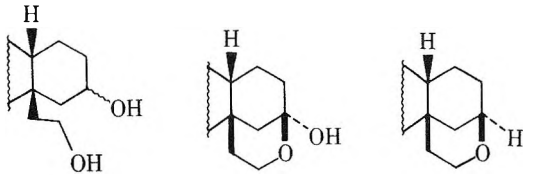
[a] The Mg(Hg)–$TiCl_4$ reagent was employed for this cyclization. [b] Obtained as a mixture of cis and trans diols (see Experimental Section for details). [c] The $CpTiCl_3$–$LiAlH_4$ reagent was employed for this cyclization. [d] Obtained in somewhat lower yield (40–45%) using Mc Murry's reagent ($TiCl_3$–$LiAlH_4$). [e] No trans diol could be detected.

formed pinacol would lead to highly strained bridgehead olefins. *We have found that reduction of cyclopentadienyltitanium trichloride with lithium aluminum hydride provides a new reagent which induces the intramolecular coupling of carbonyl compounds in fair to excellent yields.*[14] The Mg(Hg)–$TiCl_4$ reagent supplements this new species in less difficult cyclizations. Table IV illustrates our results.

Optimum reaction conditions involve reduction of 6 equiv of $CpTiCl_3$ with 4.5 equiv of $LiAlH_4$ at 50° in tetrahydrofuran followed by rapid addition of 1 equiv of carbonyl compound. High-dilution techniques are not necessary to inhibit intermolecular condensation. Other reactant ratios and solvent systems resulted in inferior yields. We have examined a large number of systems involving $TiCl_3$, $TiCl_4$, and $CpTiCl_3$ in combination with various reducing reagents for the coupling reaction of **21**. In addition to the previously described reagents, $TiCl_3$–*t*-BuLi, $TiCl_3$–*n*-BuLi, and $TiCl_3$–DIBAL furnish **22**, although in inferior yields. Some low-valent forms of other transition metals (Mo, W, Zr) were investigated but were found ineffective for intramolecular coupling.

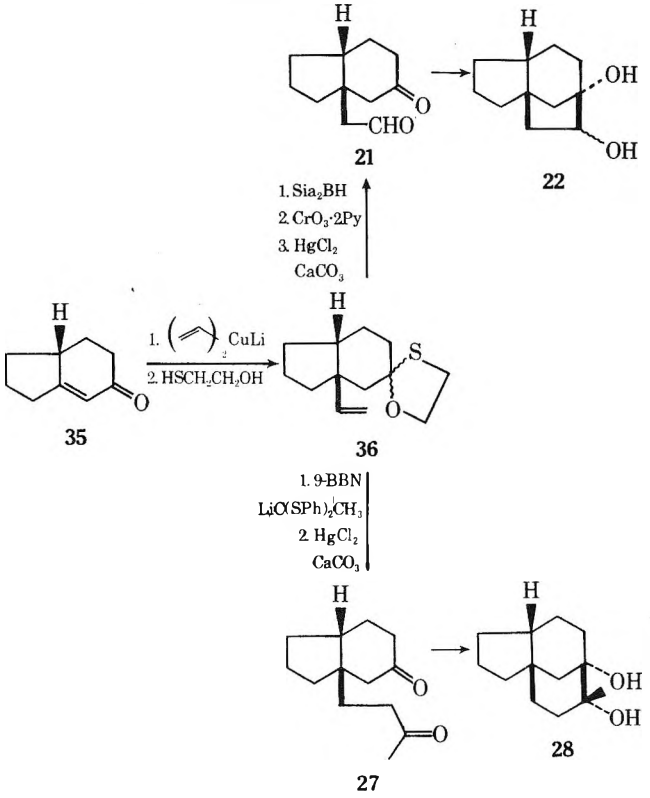
A complication encountered in applying previously described coupling conditions to the dicarbonyl substrates indicated in Table IV is competing intramolecular aldol condensation. This facile side reaction, which is particularly serious in the case of keto aldehydes **21**, **23**, and **25**, is mini-

mized by employing the $CpTiCl_3$–$LiAlH_4$ reagent. However, significant quantities of other products (both polar and nonpolar relative to pinacol) have been observed in certain instances. In the case of substrate **25**, these byproducts were shown to possess the following diol, ketol, and cyclic ether structures.



In conjunction with the conjugate addition of vinyl Gilman reagent,[6] the reductive coupling reaction provides a sequence for the *1,3 bridging of α,β-unsaturated ketones and aldehydes* (Scheme III). For example, functionalization of the vinyl appendage in **36** through hydroboration and oxidation allows the addition of a two-carbon 1,3 bridge (e.g., **35** → **22**). Alternatively, treatment of **36** with 9-BBN followed by an α-lithio thioacetal[15] leads to the addition of a three-carbon 1,3 bridge (e.g., **35** → **28**).

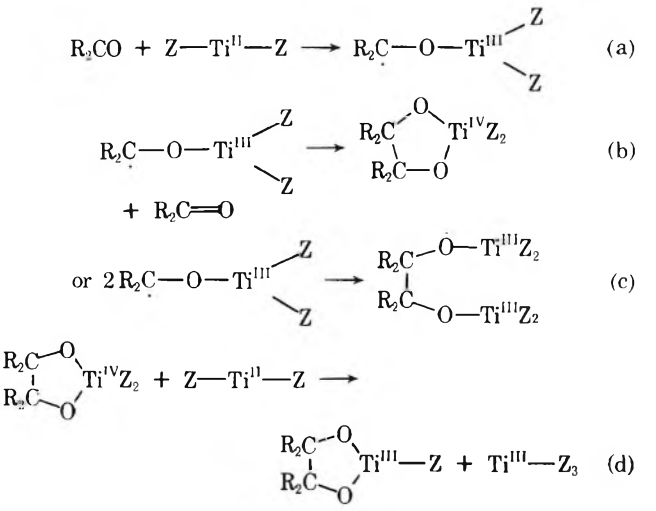
Scheme III



Of special note is the synthesis of a four-membered ring in high yield. Classical methods give cyclobutanediols in only very low yields.[17] Conia[18] has demonstrated the synthetic utility of these pinacols; thermal rearrangement of **34** affords 1,1-dimethylcyclobutanone while acid-catalyzed ring contraction provides methyl 1-methylcyclopropyl ketone in quantitative yield.

Mechanism of the Reductive Coupling Reaction. Mc Murry[2] has suggested that Ti(II) is the reactive species in these reductive coupling reactions. Based on this assumption a family of plausible mechanisms may be devised (Scheme IV). Reduction of the carbonyl group by the Ti(II) reagent gives a Ti(III) intermediate (eq a); two alternative paths for the coupling of this intermediate are shown. In eq b the Ti(III) intermediate participates in a cycloaddition

Scheme IV



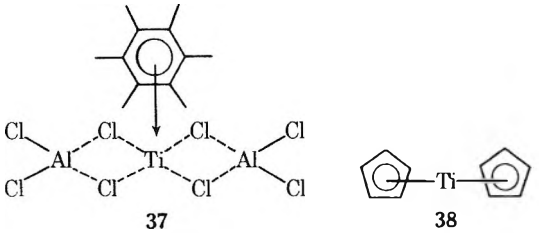
process to form a cyclic Ti(IV) derivative of the pinacolic product, whereas in eq c a pinacol bis-Ti(III) complex is formed by the coupling of two Ti(III) species.

In the case of intramolecular processes forming four- to six-membered carbocyclic systems, reaction by eq b would be expected to lead to cis 1,2-diols whereas the alternative pathway (eq c) could produce either cis or trans diols. The data in Table IV are consistent with the operation of either pathway for intramolecular coupling reactions, but suggest that in some instances (e.g., exclusive formation of cis diols **32** and **34**) the cycloaddition mechanism (eq b) may be favored.

In order to test the hypothesis embodied in Scheme IV, we examined the possibility of accomplishing pinacolic coupling using well-defined Ti(II) species. *We have found Ti(II) complexes of known structure which are capable of effecting the reductive coupling of carbonyl compounds.* The complex **37**,[19] prepared by reaction of Al–$AlCl_3$, $TiCl_4$, and hexamethylbenzene, is especially effective. Good yields of pinacols are obtained by reaction of **37** with acetone, cyclohexanone, and also the dicarbonyl compounds **21** and **33**.[20]

At least 2 molar equiv of **37** are required for complete reaction of carbonyl compound. This observation is consistent with pathways in which the Ti(II) reagent is transformed eventually into Ti(III) species. Such mechanisms include reaction by eq a and c and also the pathway expressed by eq a and b followed by reduction of the cyclic Ti(IV) pinacol ester by the Ti(II) reagent to two Ti(III) species (eq d).

Titanocene (**38**) was less effective as a pinacolic coupling reagent than **37** and therefore was not studied in any detail. For example, reaction of diketone **33** with titanocene, prepared by the method of Rausch and Alt,[21,22] gave a complex mixture from which **34** was isolated in 10% yield by preparative layer chromatography.



We are continuing to examine new titanium complexes in order to extend further the scope and efficiency of the reductive coupling reaction and to clarify the mechanism of these coupling reactions. The methods already described in

this report provide the chemist with powerful new synthetic tools for the formation of rings and chains.

Experimental Section

Instrumentation. Infrared spectra were obtained using a Perkin-Elmer Model 267 diffraction grating spectrophotometer. Proton magnetic resonance spectra were measured with Varian Associates T-60 and HA-100 spectrometers; chemical shifts are expressed in parts per million downfield from internal trimethylsilane. Mass spectra were observed with an AEI MS-9 spectrometer at an ionizing voltage of 70 eV. Melting points and boiling points are uncorrected.

Materials. Cyclopentadienyltitanium trichloride was obtained from Alfa Products and was stored and transferred under argon atmosphere in a glove bag. Titanium tetrachloride, methanesulfonyl chloride, and 2-mercaptoethanol were distilled under argon. Boron trifluoride etherate, diisopropyl sulfide, and acetonitrile were distilled from calcium hydride. Triethylamine was distilled from sodium hydride. Tetrahydrofuran (THF) and diethyl ether were distilled from sodium benzophenone ketyl. All reactions were carried out in flame-dried glassware under an atmosphere of argon.

Procedure for Intermolecular Reductive Coupling. Cyclohexanone. To a solution of mercuric chloride (0.044 g, 0.16 mmol) in 3 ml of distilled THF was added 70–80 mesh magnesium (0.144 g, 6.0 mmol), and the resulting mixture was stirred at room temperature under argon for 0.25 hr. The turbid supernatant liquid was withdrawn by syringe and the remaining amalgam was washed with three 2-ml portions of THF. The resulting dull gray amalgam was taken up in 5 ml of THF, cooled to −10°, and treated dropwise with titanium tetrachloride (330 μl, 0.570 g, 3.0 mmol) to give a yellow-green mixture. A solution of cyclohexanone (0.196 g, 2.0 mmol) in 5 ml of THF was added, and the purple reaction mixture was stirred at 0° for 0.5 hr. The reaction was quenched with 0.5 ml of saturated K_2CO_3 solution and stirred at 0° for 0.25 hr. The resulting dark blue mixture was diluted with ether and filtered through Celite. The filtrate was washed with saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated to afford 0.197 g of colorless crystals. Recrystallization from ether–petroleum ether gave 0.186 g (93% yield) of **9** as colorless crystals, mp 124–125° (lit.[23] mp 124.5–126.5°).

Reductive Coupling of Cyclopentanone. This reaction was carried out as described for cyclohexanone. Recrystallization of the crude product from ether–petroleum ether gave **11** as colorless crystals (95% yield), mp 111–112° (lit. mp 109–111° [23] and 111.4–112.4° [24]).

Reductive Coupling of Benzaldehyde. In an identical manner 1,2-diphenyl-1,2-ethanediol (**5**) was obtained in 84% yield.

Reductive Coupling of Octanal. This reaction was performed as described for cyclohexanone but required 13 hr at 0°. Recrystallization of the crude product from ether gave **7** (80% yield) as a white solid, mp 53–54° (lit.[25] mp 59–63°); an exact mass determination gave *m/e* 258.2558 (calcd for $C_{16}H_{34}O_2$, 258.2559).

Procedure for Unsymmetrical Reductive Coupling. Cyclohexanone and Acetone. To a solution of mercuric chloride (0.600 g, 2.21 mmol) in 10 ml of THF was added 70–80 mesh magnesium (1.92 g, 80.0 mmol), and the resulting mixture was stirred at room temperature under argon for 0.25 hr. The turbid supernatant liquid was withdrawn by syringe, and the remaining amalgam was washed with three portions of THF. Tetrahydrofuran (30 ml) was added, and the mixture was cooled to −10° and treated dropwise with titanium tetrachloride (4.4 ml, 7.6 g, 40.0 mmol). The walls of the reaction flask were washed with 10 ml of THF, and a solution of cyclohexanone (0.980 g, 10 mmol) and acetone (1.74 g, 30.0 mmol) in 10 ml of THF was added. The purple mixture was stirred for 1.5 hr at 0°, treated with 1.5 ml of saturated aqueous K_2CO_3 solution, and stirred for 0.25 hr further at 0°. Ether (100 ml) was added, and the mixture was filtered through Celite. The filtrate was washed with saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated to afford 2.81 g of a viscous oil. Column chromatography on silica gel (elution with 40% ether–petroleum ether) gave 1.160 g (76% yield) of **14** as colorless crystals: mp 82–83° (lit.[26] mp 83°); ^1H NMR ($CDCl_3$) δ 1.23 (s, 6 H) and 1.2–2.1 (m, 12 H); ir ($CHCl_3$) λ_{max} 2.76, 2.80, 2.9, 3.35, 3.40, and 3.49 μ; an exact mass determination gave *m/e* 158.1298 (calcd for $C_9H_{18}O_2$, 158.1306).

Reductive Coupling of Cyclopentanone and Acetone. Cyclopentanone (1.68 g, 20.0 mmol) was coupled with acetone (4.06 g, 70.0 mmol) according to the above procedure to afford **13** in 65% yield: mp 60–61° (lit.[27] 62°).

Reductive Coupling of Cycloheptanone and Acetone. Cycloheptanone (2.24 g, 20.0 mmol) was coupled with acetone (4.64 g, 80.0 mmol) according to the above procedure to afford 5.61 g of a viscous oil. Column chromatography on silica gel (elution with 40% ether–petroleum ether) gave 2.572 g (75% yield) of **15** as colorless crystals: mp 51–52°; ^1H NMR ($CDCl_3$) δ 1.23 (s, 6 H), 1.67 (broad s, 12 H), and 2.1–2.4 (m, 2 H); ir ($CHCl_3$) λ_{max} 2.76, 2.81, 2.9, 3.32, 3.40, and 3.49 μ; an exact mass determination gave *m/e* 172.1459 (calcd for $C_{10}H_{20}O_2$, 172.1463).

Reductive Coupling of Cyclohexanone and Acetaldehyde. To a solution of cyclopentadienyltitanium trichloride (1.315 g, 6.0 mmol) in 4 ml of distilled THF at 0° under argon was cautiously added lithium aluminum hydride (0.171 g, 4.5 mmol) in portions. The dark mixture was stirred at 50° for 1 hr, cooled to room temperature, and treated with a solution of cyclohexanone (0.098 g, 1.0 mmol) and acetaldehyde (0.176 g, 4.0 mmol) in 3 ml of THF. The resulting mixture was stirred for 2.5 hr at room temperature and then quenched with 0.5 ml of saturated aqueous K_2CO_3 solution. The blue mixture was stirred for 0.25 hr, diluted with ether, and filtered through Celite. The filtrate was washed with saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated to afford 0.251 g of a colorless oil. Preparative layer chromatography on silica gel (elution with ethyl acetate) gave 0.103 g (72% yield) of **16** as a colorless oil: ^1H NMR ($CDCl_3$) δ 1.15 (d, 3 H, J = 6 Hz), 1.3–2.2 (m, 10 H), 2.98 (broad s, 2 H, –OH), and 3.58 (q, 1 H, J = 6 Hz); ir (CCl_4) λ_{max} 2.94, 3.35, 3.41, and 3.49 μ; an exact mass determination gave *m/e* 144.1149 (calcd for $C_8H_{16}O_2$, 144.1150).

Ring Expansion of Diol 14. To 70% perchloric acid (15 ml) cooled to −20° was added in portions the diol **14** (0.158 g, 1.0 mmol), and the resulting solution was stirred for 0.25 hr at −20° under argon. Water was added, and the solution was extracted with ether. The combined organic layers were washed with saturated $NaHCO_3$ solution and saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated to afford 0.144 g of a pale yellow oil. Filtration through silica gel (elution with 5% ether–petroleum ether) gave 0.114 g (81% yield) of **18** as a colorless oil with spectral data identical with that previously reported.[28]

Rearrangement of Diol 14. To a solution of the diol **14** (0.158 g, 1.0 mmol) in 5 ml of CH_2Cl_2 at 0° under argon was added boron trifluoride etherate (0.071 g, 0.5 mmol), and the resulting solution was stirred for 0.25 hr at 0°. Ether was added, and the solution was washed with saturated $NaHCO_3$ solution, water, and saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated to yield 0.142 g of a pale yellow oil. Filtration through silica gel (elution with 5% ether–petroleum ether) gave 0.123 g (88% yield) of **17** as a colorless oil: ^1H NMR ($CDCl_3$) δ 1.10 (s, 3 H), 1.2–2.6 (m, 10 H), and 2.33 (s, 3 H); ir ($CHCl_3$) λ_{max} 3.23, 3.35, 3.43, and 5.86 μ.

Rearrangement of Diol 15. Exposure of diol **15** to 70% perchloric acid as described for diol **14** gave, after filtration through silica gel, the ketone **19** (90% yield) as a colorless oil. Similarly, treatment of **15** with BF_3·Et_2O as described above for **14** afforded **19** in 87% yield: ^1H NMR ($CDCl_3$) δ 1.10 (s, 3 H), 1.1–2.3 (m, 12 H), and 2.14 (s, 3 H); ir ($CHCl_3$) λ_{max} 3.39, 3.45, and 5.85 μ.

Preparation of Epoxide 20. To a solution of the diol **15** (0.344 g, 2.0 mmol) and triethylamine (1.01 g, 10.0 mmol) in 6 ml of methylene chloride at −20° under argon was added methanesulfonyl chloride (0.920 g, 8.0 mmol), and the resulting solution was stirred for 1.5 hr at −20° and 15 hr at 0°. The solution was washed with 5% aqueous acetic acid, water, and saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated to afford 0.282 g of yellow oil. Preparative layer chromatography on silica gel (elution with 50% ether–petroleum ether) gave 0.222 g (72% yield) of **20** as a colorless oil. The spectral data were identical with that previously reported for this compound.[28]

Rearrangement of the Epoxide 20. Treatment of the epoxide **20** with boron trifluoride etherate as described above for the diol **14** gave the ketone **19** in 88% yield.

Procedure for Intramolecular Reductive Coupling. Coupling of Keto Aldehyde 21. To 70–80 mesh magnesium (0.195 g, 8.0 mmol) in 3 ml of distilled THF under argon was added mercuric chloride (0.060 g, 0.22 mmol), and the mixture was stirred for 0.25 hr at room temperature. The solvent was withdrawn by syringe, and the amalgam was washed with three portions of THF. An additional 4 ml of THF was added, the mixture was cooled to −10°, and titanium tetrachloride (0.33 ml, 0.570 g, 3.0 mmol) was added dropwise. A solution of keto aldehyde[6] **21** (0.180 g, 1.0 mmol) in 4 ml of THF was introduced, and the mixture was stirred at 0° for 1.25 hr. The reaction mixture was treated with 0.5 ml of saturated K_2CO_3 solution at 0° for 0.25 hr, and the resulting blue-black mixture was filtered through Celite with the aid of ether.

The filtrate was washed with saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated to afford 0.165 g (90% yield) of **22** as colorless crystals (80:20 mixture of cis and trans diols). The cis and trans diols were separated by column chromatography on silica gel: trans diol, mp 107–109°; cis diol, mp 85–86°; ^1H NMR ($CDCl_3$) δ 1.3–2.0 (m, 15 H), 3.45 (broad m, –OH, 2 H), and 3.69 (d of d, 1 H, J = 3.5, 6.5 Hz); ir (tf) λ_{max} 2.95, 3.41, and 3.49 μ.

Reductive Coupling of Diketone 27. This compound was cyclized over 5 hr at 0° according to the above procedure to afford 0.281 g of a pale yellow oil. Preparative layer chromatography on silica gel (elution with ethyl acetate) gave the cis diol **28** (43% yield) as colorless crystals: mp 95–96°; ^1H NMR ($CDCl_3$) δ 1.18 (s, 3 H), 1.2–2.0 (m, 17 H), and 2.8 (broad s, –OH, 2 H); ir (tf) λ_{max} 2.93, 3.40, and 3.49 μ.

Reductive Coupling of Keto Aldehyde 25. To a solution of cyclopentadienyltitanium trichloride (0.207 g, 0.99 mmol) in 4 ml of distilled THF under argon was cautiously added a solution of lithium aluminum hydride in THF (1.12 M, 0.665 ml, 0.75 mmol). The reaction mixture was stirred at 50° for 1 hr and then a solution of keto aldehyde **25**[29] (0.050 g, 0.165 mmol) in 2 ml of THF was introduced. The mixture was stirred for 2 hr at 50°, cooled to room temperature, treated with 0.5 ml of saturated K_2CO_3 solution, and stirred for an additional 0.25 hr. The resulting dark blue mixture was filtered through Celite with the aid of ether, and the filtrate was washed with saturated NaCl solution, dried over Na_2SO_4, filtered, and concentrated to afford 0.048 g of a yellow oil. Preparative layer chromatography on silica gel (elution with ethyl acetate) gave 0.008 g of trans diol **26b**, mp 97–99° (15% yield), and 0.020 g of cis diol **26a** (40% yield): mp 87.5–89°; ^1H NMR ($CDCl_3$) δ 1.1–2.7 (m, 20 H), 3.0–4.2 (m, 5 H), 4.55 (s, 1 H), and 5.65 (s, 2 H); ir ($CHCl_3$) λ_{max} 3400, 3020, 1140, 1120, 1075, and 1035 cm^{-1}; an exact mass determination gave m/e 308.4184 (calcd for $C_{18}H_{28}O_4$, 308.4182).

Reductive Coupling of Keto Aldehyde 29. To a solution of cyclopentadienyltitanium trichloride (1.97 g, 9.0 mmol) in 10 ml of distilled THF at 0° under argon was cautiously added in portions lithium aluminum hydride (0.256 g, 6.75 mmol). The black mixture was stirred for 1 hr at 50°, and then a solution of keto aldehyde **29**[30] in 10 ml of THF was added dropwise. The resulting mixture was stirred for 2.5 hr at 50°, cooled to 0°, and treated with 1.0 ml of saturated K_2CO_3 solution, and stirred at room temperature for 0.5 hr. The reaction mixture was filtered through Celite with the aid of ether, and the filtrate was washed with saturated NaCl solution, dried over Na_2SO_4, filtered, and concentrated to afford 0.203 g of a yellow oil. Column chromatography on silica gel (elution with 10–60% tetrahydrofuran–hexanes) of this material and the product of another run gave four isomeric diols **30**[31] in yields of 12, 20, 11, and 6% (combined yield, 49%). The major isomer: mp 60.5–61°; ^1H NMR ($CDCl_3$) δ 1.3–2.6 (m, 15 H) and 3.7–4.0 (m, 1 H); ir ($CHCl_3$) λ_{max} 2.94, 3.41, and 3.50 μ; an exact mass determination gave m/e 156.1145 (calcd for $C_9H_{16}O_2$ 156.1150).

Reductive Coupling of Dialdehyde 31. The dialdehyde **31** was treated with the Mg(Hg)–$TiCl_4$ reagent at 0° for 2.5 hr according to the procedure described for keto aldehyde **21**. Preparative layer chromatography of the crude product on silica gel (elution with ethyl acetate) gave **32** (32% yield) as colorless crystals, mp 94–96° (lit.[32] mp 98°).

Reductive Coupling of Diketone 33. The diketone **33** was coupled with the Mg(Hg)–$TiCl_4$ reagent at 0° for 2.5 hr according to the procedure described for keto aldehyde **21**. Preparative layer chromatography of the crude product on silica gel (elution with ethyl acetate) gave **34** (81% yield) as colorless crystals, mp 29–30° (lit.[18a] mp 14°). The ^1H NMR, ir, and mass spectral data were identical with those reported;[18b] the bistrimethylsilyl ether was prepared and an exact mass determination gave m/e 260.1628 (calcd for $C_{12}H_{28}O_2Si_2$, 260.1628).

Addition of Vinyl Gilman Reagent to Enone 35. To a solution of 2.13 M vinyllithium (45.0 ml, 96 mmol) in 100 ml of ether at −50° under argon was added dropwise over 0.25 hr a solution of CuI[33] (9.90 g, 52 mmol) in diisopropyl sulfide (34.0 ml, 27.6 g, 234 mmol). This mixture was stirred for 0.25 hr at −25°, then cooled to −78°, and a solution of the enone **35** (5.45 g, 40.0 mmol) in 11 ml of ether was added dropwise over 0.25 hr. The resulting dark green mixture was stirred for 0.5 hr at −55° and then allowed to warm to −40° over 1 hr. The reaction mixture was poured into 200 ml of saturated aqueous NH_4Cl solution buffered to pH 8 with NH_4OH, stirred for 0.5 hr, and filtered through Celite with the aid of ether. The organic layer of the filtrate was extracted with saturated buffered aqueous NH_4Cl solution, water, and saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated to afford 12.481 g of a pale yellow oil. Chromatography on silica gel (elution with 5–15% THF–hexanes) gave 5.670 g (87% yield)[34] of the vinyl ketone **39** as a colorless oil: ^1H NMR ($CDCl_3$) δ 1.5–2.5 (m, 11 H), 2.37 (broad s, 2 H), 4.8–5.2 (m, 2 H), and 5.81 (d of d, 1 H, J = 10, 18 Hz); ir (tf) λ_{max} 3.21, 3.36, 3.45, 5.82, and 6.09 μ; GLC t_r 9.0 min (155°, 10 ft 5% Carbowax 20M); an exact mass determination gave m/e 164.1199 (calcd for $C_{11}H_{16}O$; 164.1201).

Preparation of Hemithioketal 36. A solution of the vinyl ketone **39** (4.00 g, 24.4 mmol) in 40 ml of ether was treated with distilled 2-mercaptoethanol (1.97 ml, 2.09 g, 26.8 mmol) and boron trifluoride etherate (3.0 ml, 3.46 g, 24.4 mmol) and then stirred at room temperature under argon for 1.5 hr. The reaction mixture was diluted with ether, extracted with half-saturated $NaHCO_3$ solution and saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated to afford 5.087 g (94% yield) of **36** (ca. 1:1 mixture of hemithioketal epimers) as a colorless oil used in the next step without purification: ^1H NMR ($CDCl_3$) δ 1.4–2.2 (m, 13 H), 3.00 and 3.04 (each a t, 2 H total, J = 6 Hz), 4.14 (t, 2 H, J = 6 Hz), 4.8–5.2 (m, 2 H), and 5.90 and 6.17 (each a d of d, 1 H total, J = 10, 18 Hz); ir (tf) λ_{max} 3.24, 3.40, 3.49, and 6.10 μ.

Hydroboration of 36. Disiamylborane was prepared by adding 2-methyl-2-butene (4.95 ml, 3.28 g, 46.8 mmol) to 1.17 M borane solution (in THF, 19 ml, 22.3 mmol) in 20 ml of THF at 0° under argon and stirring the resulting solution for 1 hr at 0° and 1 hr at room temperature. A solution of the hemithioketals **36** (2.50 g, 11.1 mmol) in 10 ml of THF was added, and the resulting solution was stirred for 14 hr at room temperature. The reaction mixture was cooled to 0° and treated dropwise with 15% NaOH solution (13.2 ml, 55.5 mmol) and 30% H_2O_2 solution (9.6 ml, 111 mmol). The mixture was then stirred for 1.5 hr at room temperature, poured into 10% Na_2SO_3–saturated NaCl solution, and extracted with ether. The combined organic layers were washed with saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated with the aid of toluene to afford 2.69 g of a colorless oil. Evaporative distillation (oven temperature 180°, 0.25 mm) gave 2.736 g (100% yield) of the alcohols **40** (mixture of hemithioketal epimers) as a colorless oil: ^1H NMR ($CDCl_3$) δ 1.4–2.0 (m, 16 H), 3.03 (broad t, 2 H, J = 6 Hz), 3.72 (broad t, 2 H, J = 6 Hz), and 4.13 (broad t, 2 H, J = 6 Hz); ir (tf) λ_{max} 3.00, 3.40, and 3.49 μ.

Oxidation of the Alcohol 40. To a mechanically stirred mixture of dipyridinechromium(VI) oxide[35] (4.14 g, 16 mmol) and purified, anhydrous Celite[36] (8.28 g) in 70 ml of CH_2Cl_2 at −20° under argon was added a solution of the alcohols **40** (0.373 g, 1.54 mmol) in 5 ml of CH_2Cl_2. The mixture was stirred for 1 hr at −20°, treated with powdered $NaHSO_4 \cdot H_2O$ (8.28 g, 60 mmol), and stirred for 0.5 hr at −20°. The resulting mixture was filtered through $MgSO_4$ with the aid of ether and CH_2Cl_2 and concentrated to afford 0.311 g (84% yield) of aldehyde **41** used in the next step without purification: ^1H NMR ($CDCl_3$) δ 1.5–2.2 (m, 15 H), 3.0 (m, 2 H), 4.10 (broad t, 2 H, J = 6 Hz), and 9.80 (m, 1 H); ir (tf) λ_{max} 3.40, 3.46, 3.65, and 5.80 μ.

Preparation of the Keto Aldehyde 21. A solution of hemithioketals **41** (0.115 g, 0.48 mmol) in 1.5 ml of H_2O and 6 ml of CH_3CN under argon was treated with $HgCl_2$ (0.287 g, 1.05 mmol) and $CaCO_3$ (0.120 g, 1.2 mmol) and stirred at room temperature for 10 min. The mixture was filtered through Celite with the aid of ether, and the filtrate was extracted with ice-cooled NH_4OAc solution (pH 7), ice–water, and saturated NaCl solution, dried over Na_2SO_4, filtered, and concentrated to afford 0.067 g (80% yield) of **21** as a colorless oil used in the next step without purification: ^1H NMR ($CDCl_3$) δ 1.7–2.7 (m, 15 H) and 10.0 (broad t, 1 H); ir (tf) λ_{max} 3.37, 3.41, 3.48, 3.65, and 5.82 μ.

Preparation of the Methyl Ketone 42. To a solution of the vinyl hemithioketals **36** (1.95 g, 8.7 mmol) in 50 ml of THF at room temperature under argon was added 0.5 M 9-borabicyclo[3.3.1]nonane (19.7 ml, 9.85 mmol). The resulting solution was stirred for 1.5 hr at room temperature and then cooled to −40°. To a solution of acetaldehydediphenylthioacetal[37] (2.64 g, 10.7 mmol) in 20 ml of THF at −40° under argon was added 2.13 M n-butyllithium solution (5.0 ml, 11.6 mmol). The yellow solution produced was added dropwise (using a cold finger cooled addition funnel at −50°) over 20 min to the borane solution. The reaction mixture was allowed to warm to 0° over 0.75 hr and was then treated with 15% NaOH solution (14 ml, 59 mmol) and 30% H_2O_2 solution (7.2 ml, 83.5 mmol) and stirred for 1 hr at 60° and 1 hr at room temperature. Ether, saturated NaCl solution, and 10% Na_2SO_3 solution were added, and the aqueous phase was extracted with ether. The combined organic layers were washed with saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated to afford 4.984 g of a yellow oil. Column chromatography on silica gel (elution with 5–15% THF–

hexanes) gave 1.53 g (68% yield) of **42** as a pale yellow oil: ^{1}H NMR ($CDCl_3$) δ 1.5–2.6 (m, 17 H), 2.17 (s, 3 H), 3.04 (two t, total 2 H, J = 6 Hz), and 4.14 (broad t, 2 H); ir (tf) λ_{max} 3.40, 3.49, and 5.83 μ.

Preparation of Diketone 27. A mixture of the hemithioketals **42** (1.53 g, 5.7 mmol), $HgCl_2$ (3.39 g, 12.5 mmol), and $CaCO_3$ (1.43 g, 14.3 mmol) in 52 ml of CH_3CN and 13 ml of distilled water was stirred at room temperature under argon for 10 min. The reaction mixture was filtered through Celite with the aid of ether, extracted with ice-cooled NH_4OAc solution, ice–water, and saturated NaCl solution, and then dried over $MgSO_4$, filtered, and concentrated to afford 1.17 g (99% yield) of **27** as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 1.4–2.5 (m, 17 H) and 2.12 (s, 3 H); ir (tf) λ_{max} 3.40, 3.49, and 5.84 μ; an exact mass determination gave m/e 208.1459 (calcd for $C_{13}H_{20}O_2$, 208.1463).

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Registry No.—**4,** 100-52-7; **6,** 124-13-0; **8,** 108-94-1; **10,** 120-92-3; **14,** 1124-96-5; **15,** 57132-07-7; **16,** 1123-26-8; **17,** 2890-62-2; **20,** 42393-59-9; **21,** 35730-87-1; *cis*-**22,** 35730-88-2; *trans*-**22,** 35730-89-3; **25,** 57132-08-8; **26a,** 57132-09-9; **27,** 57132-10-2; *cis*-**28,** 57132-11-3; **29,** 2568-20-9; **30** isomer a, 57132-12-4; **30** isomer b, 57132-13-5; **30** isomer c, 57527-69-2; **30** isomer d, 57527-70-5; **31,** 1072-21-5; **33,** 110-13-4; **35,** 1489-28-7; **36** isomer a, 57132-14-6; **36** isomer b, 57173-49-6; **37,** 12312-06-0; **39,** 35730-86-0; **40** isomer a, 57132-15-7; **40** isomer b, 57173-50-9; **41** isomer a, 57132-16-8; **41** isomer b, 57173-51-0; **42** isomer a, 57132-17-9; **42** isomer b, 57173-52-1; acetone, 67-64-1; cycloheptanone, 502-42-1; acetaldehyde, 75-07-0; methanesulfonyl chloride, 124-63-0; 2-mercaptoethanol, 60-24-2; diisoamylborane, 6838-83-1; mercuric chloride, 7487-94-7; magnesium, 7439-95-4; cyclopentadienyltitanium trichloride, 1270-98-0; lithium aluminum hydride, 16853-85-3; boron trifluoride etherate, 109-63-7; titanium tetrachloride, 7550-45-0.

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(37) Prepared in 94% yield by treatment of acetaldehyde with 5 equiv of thiophenol and 1 equiv of boron trifluoride etherate (ether, 0°, 9 hr).

A Palladium-Catalyzed Arylation of Allylic Alcohols with Aryl Halides

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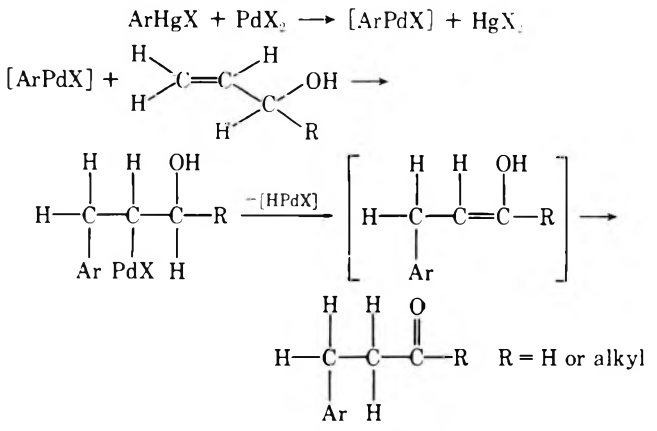
A convenient reaction for preparing 3-arylaldehydes and ketones from allylic alcohols and aryl halides is described. In some instances 3-arylallylic alcohols may also be obtained in varying yields depending upon the aryl halide used and the catalyst employed. The effects of substituents in both reactants on the reaction course are discussed. Homoallylic alcohols react similarly, giving substantial amounts of aryl ketones or aldehydes.

The previously reported allylic alcohol arylation with organopalladium compounds[1] was shown to be useful for the synthesis of 3-arylaldehydes and ketones when primary or secondary allylic alcohols, respectively, were allowed to react. The reaction required a molar amount of an organomercury compound to prepare, in situ, the organopalladium reagent with either an equivalent amount of a palladium(II) salt or a catalytic amount of this salt plus an equivalent amount of cupric chloride to regenerate the palladium after each reaction cycle. The addition of a hindered tertiary amine to the reaction mixtures also proved beneficial. Even under the most favorable conditions found, however, yields were never over 53% and were often considerably lower.

Table I
Arylation of Allylic Alcohols

Registry no.	Alcohol	Aryl halide (registry no.)	Catalyst	Reaction time, hr	Products[a] 3-Arylation Alcohol, %	3-Arylation Carbonyl compd, %	3-Arylation Alcohol/carbonyl	2-Arylation Alcohol, %	2-Arylation Carbonyl compd, %	2-Arylation Alcohol/carbonyl	Other products (yield)	Total yield, %	% 3-aryl addition
107-18-6	CH_2=$CHCH_2OH$	C_6H_5I (591-50-4)	$Pd(OAc)_2$	0.5[b]		84			16			71	84
	CH_2=$CHCH_2OH$	C_6H_5I	$Pd(OAc)_2(PPh_3)_2$	5.5[c]		76			24			74	76
	CH_2=$CHCH_2OH$	C_6H_5I	$PdBr(Ph)(PPh_3)_2$	26[c,d]		78			22			72	78
6117-91-5	CH_2CH=$CHCH_2OH$	C_6H_5I	$Pd(OAc)_2$	12[b]		74			26			84	74
556-82-1	$(CH_3)_2C$=$CHCH_2OH$	C_6H_5I	$Pd(OAc)_2$	12[c]		51		34	2	17	$C_6H_5C_6H_5$ (6.5) Unknown (6.5)	25	59
	$(CH_3)_2C$=$CHCH_2OH$	C_6H_5I	$Pd(OAc)_2$	96[c]		62		19	3	6.3	$C_6H_5C_6H_5$ (7) Unknown (9)	51	74
	$(CH_3)_2C$=$CHCH_2OH$	C_6H_5I	$Pd(OAc)_2$	12[b]		16		29	7	4.1	$C_6H_5C_6H_5$ (48)	44	31
	$(CH_3)_2C$=$CHCH_2OH$	C_6H_5HgOAc (62-38-4)	$Pd(OAc)_2$	7[g]		24		76				42	24
513-42-8	CH_2=$C(CH_3)CH_2OH$	C_6H_5I	$Pd(OAc)_2$	8[b]		96			4			95	96
598-32-3	CH_2=$CHCHOHCH_3$	C_6H_5I	$Pd(OAc)_2$	5[b]	Trace	90			10			95	90
	CH_2=$CHCHOHCH_3$	C_6H_5I	$Pd(OAc)_2(PPh_3)_2$	6[c]	14	76	0.18	4	6	0.67		96	90
	CH_2=$CHCHOHCH_3$	C_6H_5I	$Pd(OAc)_2$ + $18PPh_3$	14[c,e]	10	77	0.13	6	7	0.86		71	87
	CH_2=$CHCHOHCH_3$	C_6H_5I	$Pd(OAc)_2(PPh_3)_2$	62[c,f]	7	85	0.08	2	6	0.33		97	92
	CH_2=$CHCHOHCH_3$	4-$CH_3OC_6H_4I$ (696-62-8)	$Pd(OAc)_2$	12[b]		87			12		4-$CH_3OC_6H_4CH$=$CHCH$=CH_2 (1)	96	88
	CH_2=$CHCHOHCH_3$	C_6H_5Br (108-86-1)	$Pd(OAc)_2(PPh_3)_2$	35[c]	40	50	0.8	8	2	4.0		95	90
	CH_2=$CHCHOHCH_3$	C_6H_5Br	$Pd(OAc)_2$ + $4PPh_3$	50[c]	47	39	1.2	12	2	6		94	86
	CH_2=$CHCHOHCH_3$	C_6H_5Br	$Pd(OAc)_2$ + $18PPh_3$	144[c,f]	58	26	2.2	14	2	7		74	84
	CH_2=$CHCHOHCH_3$	C_6H_5Br	$PdCl_2(PPh_3)_2$	30[c]	38	51	0.75	9	2	4.5		92	89
	CH_2=$CHCHOHCH_3$	C_6H_5Br	$PdBr_2(PPh_3)_2$	35[c]	36	50	0.72	9	2	4.5	C_6H_5CH=$CHCH$=CH_2 (3)	93	89
	CH_2=$CHCHOHCH_3$	C_6H_5Br	$PdI_2(PPh_3)_2$	40[c]	40	48	0.83	9	3	3.0		90	88
	CH_2=$CHCHOHCH_3$	4-$CF_3C_6H_4Br$ (402-43-7)	$Pd(OAc)_2(PPh_3)_2$	44[c]	25	69	0.36	5	1	5.0		93	94
	CH_2=$CHCHOHCH_3$	4-$CH_3C_6H_4Br$ (106-38-7)	$Pd(OAc)_2$ + $3PPh_3$	48[c]	53	36	1.5	11				75	89
	CH_2=$CHCHOHCH_3$	2-$CH_3C_6H_4Br$ (95-46-5)	$Pd(OAc)_2$ + $3PPh_3$	2 weeks[c]	71[h]	17	4.2	10			2-$CH_3C_6H_4CH$=$CHCOCH_3$ (2)	88	90
115-18-4	CH_2=$CHCOH(CH_3)_2$	C_6H_5I	$Pd(OAc)_2$	5[b]	8			1			C_6H_5CH=$CHC(CH_3)$=CH_2 (91)	99	99
	CH_2=$CHCOH(CH_3)_2$	C_6H_5I	$Pd(OAc)_2(PPh_3)_2$	4[c]	98			1			C_6H_5CH=$CHC(CH_3)$=CH_2 (1)	98	99

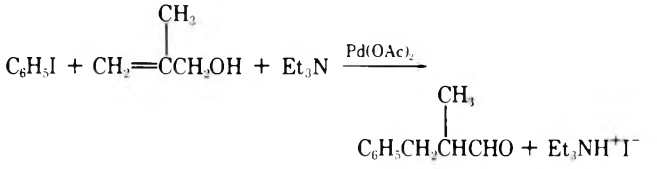
[a] Product yields were determined by GLC and were based on the aryl halide used. All reactions were carried out in capped glass tubes under argon at 100° except where noted. [b] Reaction solution consisted of 25 mmol of allylic alcohol, 20 mmol of aryl halide, 0.06 mmol of palladium complex, 25 mmol of triethylamine, and 6.5 ml of acetonitrile. [c] Reaction solution consisted of 25 mmol of allylic alcohol, 20 mmol of aryl halide, 0.06 mmol of palladium complex, and 10 ml of triethylamine. [d] Carried out at 60°. [e] Carried out at 50°. [f] Used 0.20 mmol of the palladium complex, instead of 0.06 mmol, and 1.0 g of PPh_3. [g] Reaction mixture consisted of 2 ml of allylic alcohol, 10 ml of acetonitrile, 50 mmol of phenylmercuric acetate, and 55 mmol of palladium acetate at 0–25° as described in ref 1. [h] 69% *E* isomer and 2% *Z* isomer.



Recently we have found that organopalladium compounds can be made more practically from aryl halides and that a combination of an aryl halide, a catalytic amount of a palladium salt, and a tertiary amine will arylate alkenes.[2] It seemed likely that this reaction could also be applied to the arylation of allylic alcohols. We report herein the results of a study of this reaction.

Results and Discussion

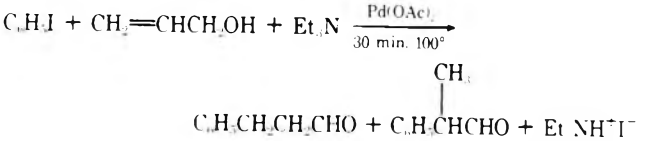
Preliminary studies of the reaction of 2-methyl-2-propen-1-ol with iodobenzene under the usual olefin arylation conditions[2,3] revealed that the major product formed was the expected 2-methyl-3-phenylpropanal. Further exploration of the reaction, however, showed that differences existed from the reactions previously investigated. Since the reaction appeared to be of potential synthetic utility, a thorough investigation of reaction variables with several different allylic alcohols and two homoallylic alcohols was undertaken.



Allylic Alcohol Reactions. The allylic alcohols studied and the results obtained are summarized in Table I. We chose to look at reactions of allyl alcohol, *trans*-crotyl alcohol, 2-methyl-2-propen-1-ol, 3-buten-2-ol, 2-methyl-3-buten-2-ol, 3-methyl-2-buten-1-ol, and 2-methyl-3-buten-2-ol. Generally, the reactions were carried out at 100° in capped bottles under argon where the time required for disappearance of the aryl halide reactant varied from less than 1 to more than 50 hr depending upon the reactants and reaction conditions. In some examples, long reaction times decreased the yields of products obtained. As we had observed with simple olefins,[2] aryl iodides underwent the reaction with palladium acetate as catalyst while aryl bromides required triphenylphosphine to be present, also. The iodide reactions often gave significantly different product mixtures when triphenylphosphine was present. It appeared to make no difference in which of several possible forms the catalyst was added. The dihalobisphosphinepalladium derivative behaved essentially the same as the diacetatobisphosphine or the halobisphosphine(phenyl) complexes.

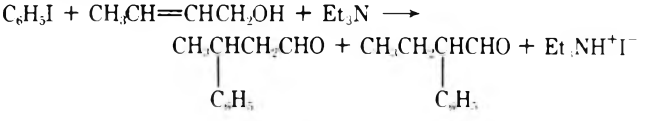
In the reactions of aryl iodides where phosphines were not added, reactions were carried out with acetonitrile as solvent. Without this solvent or with only excess triethylamine as solvent, the product triethylammonium iodide crystallized out during the reactions. In these cases the crystals apparently removed the palladium metal catalyst as they precipitated and consequently these reactions did not go to completion. Acetonitrile dissolves the salts. When triphenylphosphine was present the palladium apparently remained in solution until the reactions were essentially complete even if amine salt crystallized out.

The reaction of iodobenzene with allyl alcohol gave a maximum yield of products (71%) after only 30 min at 100°. The reaction was quite exothermic and became uncontrollable if more than about 0.3 mol % of catalyst based upon the aryl halide present, was used. The products formed were 84% 3-phenyl- (3-arylation) and 15% 2-phenylpropionaldehyde (2-arylation). Apparently, the phenylpalladium group added in both possible directions to the double bond and both adducts eliminated metal hydride to ultimately form aldehydes. The 2-phenylpropionaldehyde formation may require two intermediate steps, the initial elimination, a readdition of the hydride in the reverse direction, and then another elimination of metal hydride toward the hydroxyl bearing carbon. These steps apparently occur with ease with the palladium acetate catalyst, since neither of the possible intermediate phenylallyl alcohols (3-phenyl-2-propen-1-ol and 2-phenyl-2-propen-1-ol) were observed as products.

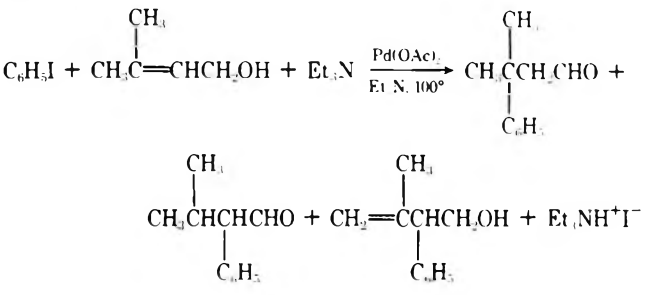


There is no advantage to adding triphenylphosphine to this reaction, since it only slows it down and slightly decreases the yield of 3-arylaldehyde relative to the 2-aryl derivative. Bromobenzene reacts poorly with allyl alcohol because it reacts considerably slower than the iodide does and the 3-phenylpropionaldehyde product suffers decomposition during the reaction, presumably by undergoing the aldol condensation.

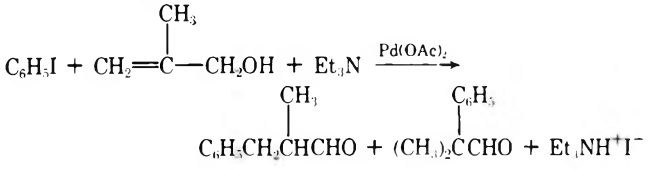
trans-Crotyl alcohol and iodobenzene with a palladium acetate catalyst react in 12 hr at 100° to give an 84% yield of a mixture containing 74% 3-phenylbutyraldehyde and 26% of the 2-phenyl isomer. The addition of the terminal methyl group to allyl alcohol in this case considerably slowed down the rate of the reaction and increased the amount of 2-arylation from 16 to 26%.



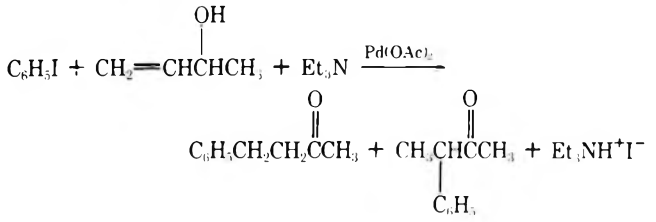
Even the presence of two terminal methyl groups in 3-methyl-2-buten-1-ol is not enough to cause phenylation to occur exclusively at the 2 carbon of the alcohol. This reaction, with iodobenzene and palladium acetate as catalyst at 100°, gave a mixture of an allylic alcohol and two isomeric aldehydes. Because the allylic alcohol formed, 3-methyl-2-phenyl-3-buten-1-ol, contained a more reactive double bond than the starting alcohol, it disappeared during the reaction. At about 25% reaction, approximately 40% of the products were formed by 2-arylation and 60% by 3-arylation.



The addition of a methyl group to the second carbon of allyl alcohol to form 2-methyl-2-propen-1-ol produced a more significant product change than the addition of the 3-methyl did. In the reaction with iodobenzene and palladium acetate, 2-methyl-2-propen-1-ol produced, in 95% yield, a mixture containing 96% of the 3-phenylaldehyde and only 4% of the 2-phenylaldehyde. This reaction also occurred slightly more rapidly than did the corresponding reaction of *trans*-crotyl alcohol.



We also looked at reactions of the 1-methylated allyl alcohol, 3-buten-2-ol. With iodobenzene and a palladium acetate catalyst we obtained, in 95.4% yield, a mixture composed of 90% of the terminal 3-phenyl ketone and 10% of the 2-phenyl ketone. This alcohol was a little more reactive than 2-methyl-2-propen-1-ol but less reactive than allyl alcohol. Thus, the 1-methyl group exerted a small effect raising the percent of terminal 3-phenyl product formed from 84 to 90%.



When the above reaction was carried out with diacetatobis(triphenylphosphine)palladium(II) as catalyst substantial amounts of two unsaturated alcohols were obtained in addition to the same two carbonyl products. The presence of the triphenylphosphine apparently stopped or at least reduced the tendency for the palladium hydride to readd to the unsaturated alcohol intermediates. Larger amounts of triphenylphosphine than two per palladium had little further effect, other than slowing the reaction and decreasing the total yield of products. The decreased yield is due to the palladium(II)-catalyzed reaction of the excess phosphine with some of the iodobenzene forming tetraphenylphosphonium iodide. Lowering the reaction temperature from 100 to 60° decreased the reaction rate considerably, but it did not alter the ratio of the 2- to 3-arylation products formed. There were small but significant changes in the alcohol to carbonyl ratios observed, however. At 100° the ratio of 3-aryl alcohol to 3-aryl ketone was 0.18 while at 60° the ratio was 0.086. The corresponding ratios for the 2-aryl alcohol to the 2-aryl ketone were 0.61 and 0.32, respectively. Thus, lowering the temperature decreased substantially the amounts of unsaturated alcohols and increased the amounts of saturated ketones produced.

p-Iodoanisole was also treated with 3-buten-2-ol with a palladium acetate catalyst. The *p*-methoxyl group had very little effect upon the distribution of reaction products. The ratio of 3- to 2-aryl additions was only slightly lower than in the reaction of iodobenzene. This contrasts with the results obtained previously in the reaction of phenyl- and *p*-anisylmercuric acetates with palladium acetate and propylene at 0° where the methoxyl group caused about 17% more addition of the aryl group to the more substituted carbon of the double bond.[4]

The reaction of bromobenzene with 3-buten-2-ol with the diacetatobis(triphenylphosphine)palladium catalyst proceeded in high yield in 35 hr at 100° in contrast to the corresponding reactions with primary allylic alcohols, where the products were not completely stable under the reaction conditions. The 3-buten-2-ol reaction with bromobenzene produced in 95% overall yield a mixture of alcohols and ketones with about 90% of the products arising from addition of the aryl group to the third carbon and 10% from addition to the second carbon. The total 2 and 3 isomer yields were the same as obtained with iodobenzene. The 3-aryl products consisted of 50% 4-phenyl-2-butanone and 40% 4-phenyl-3-buten-2-ol. The 2-aryl products were 2% 3-phenyl-2-butanone and 8% 3-phenyl-3-buten-2-ol. The addition of more than 2 equiv of triphenylphosphine per palladium as catalyst in this reaction slowed it down and caused a significant change in the product distribution. The maximum effect was caused with an 18:1 ratio of phosphine to palladium. However, as noted above, the excess phosphine also lowered the total yield by an amount approximately equivalent to the excess phosphine (to 71%) indicating that some bromobenzene was being converted into tetraphenylphosphonium bromide under the reaction conditions. The yields of 3-aryl alcohol are increased from 40 to 58% by the excess phosphine compared with the reaction containing only two phosphines per palladium while the 3-aryl ketone yield is reduced from 50 to 26%. A similar change occurred with the 2-phenyl products; the 2-phenyl alcohol yield increased from 8 to 14% while the 2-phenyl ketone yield remained about the same, 2%. The total amount of addition to the 3 carbon was now 84% compared to 90% with only 2 mol of phosphine.

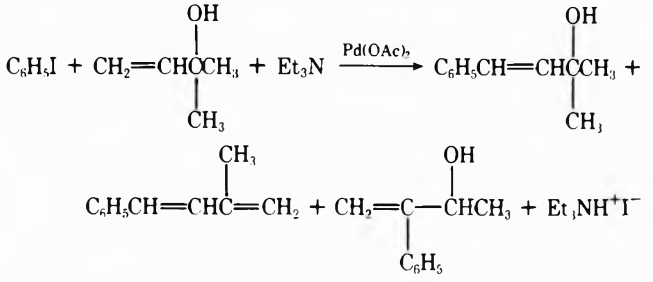
We have also noted in the reaction of bromobenzene with 3-buten-2-ol that it made essentially no difference whether acetate, chloride, bromide, or iodide ions were present as the anions in the catalyst.

The reaction of *p*-trifluoromethylbromobenzene with 3-buten-2-ol was investigated in order to observe the effect of an electron-withdrawing group on the product distribution. The reaction was a little slower than with bromobenzene. The total yield of products was 93% of which 94% was from aryl addition to the third carbon. Thus, 3-aryl addition was increased about 4% by the trifluoromethyl group compared with phenyl. The trend is explicable on the basis of electronic effects[4] and is consistent with the reverse effect found above in the *p*-iodoanisole reaction and with the arylmercuric acetate reactions studied previously.[4] The effect is less, however, than the previous example, probably mainly because of the higher reaction temperature used. The trifluoromethyl group also changed the alcohol to ketone ratio obtained. The ratio of the 3-phenyl alcohol to 3-ketone went from 0.79 to 0.34 with the CF_3 group and from 4.4 to 4.25 for the 2-aryl products, respectively. These results suggest that the more hydridic hydrogen tends to be eliminated but the effect is minor.

The addition of o-bromotoluene to 3-buten-2-ol was investigated to assess the importance of steric effects in the arylating group. For comparison purposes the *p*-bromotoluene reaction with 3-buten-2-ol was also carried out. As expected from the related reactions in Table I, the yields of products from the *p*-bromotoluene reaction were quite similar to those formed in the bromobenzene reaction except that they were *p*-methyl derivatives. Thus, the *p*-bromotoluene reaction produced 53% 4-*p*-tolyl-3-buten-2-ol (3-alcohol), 30% *p*-tolyl-2-butanone (3-carbonyl), 11% 3-*p*-tolyl-3-buten-2-ol (2-alcohol), and no 3-*p*-tolyl-2-butanone (2-carbonyl). In contrast, the products obtained from a similar reaction carried out with o-bromotoluene consisted of 71% 4-o-tolyl-3-buten-2-ol (3-alcohol), 17% 4-o-tolyl-2-butanone (3-carbonyl), 10% 3-o-tolyl-3-buten-2-ol (2-alcohol), and no 3-o-tolyl-2-butanone (2-carbonyl). Thus, the *o*-

methyl group caused a significant increase in the 3-alcohol to 3-carbonyl product ratio (1.5 to 4.2).

The effect of the presence of two α methyl groups in allyl alcohol upon the reaction products with iodobenzene is now predictable. The large steric effect of the tertiary alcohol group would be expected to substantially increase the amount of addition of phenyl to the third carbon. This proved to be the case. The reaction proceeded to completion in 4 hr at 100°, giving in 98% yield a mixture consisting of 99% of 3-phenylated products, 97% 2-methyl-phenyl-3-buten-2-ol, 1% 1-phenyl-3-methyl-1,3-butadiene, and 1% of the 2-aryl product, 2-methyl-3-phenyl-3-buten-2-ol.

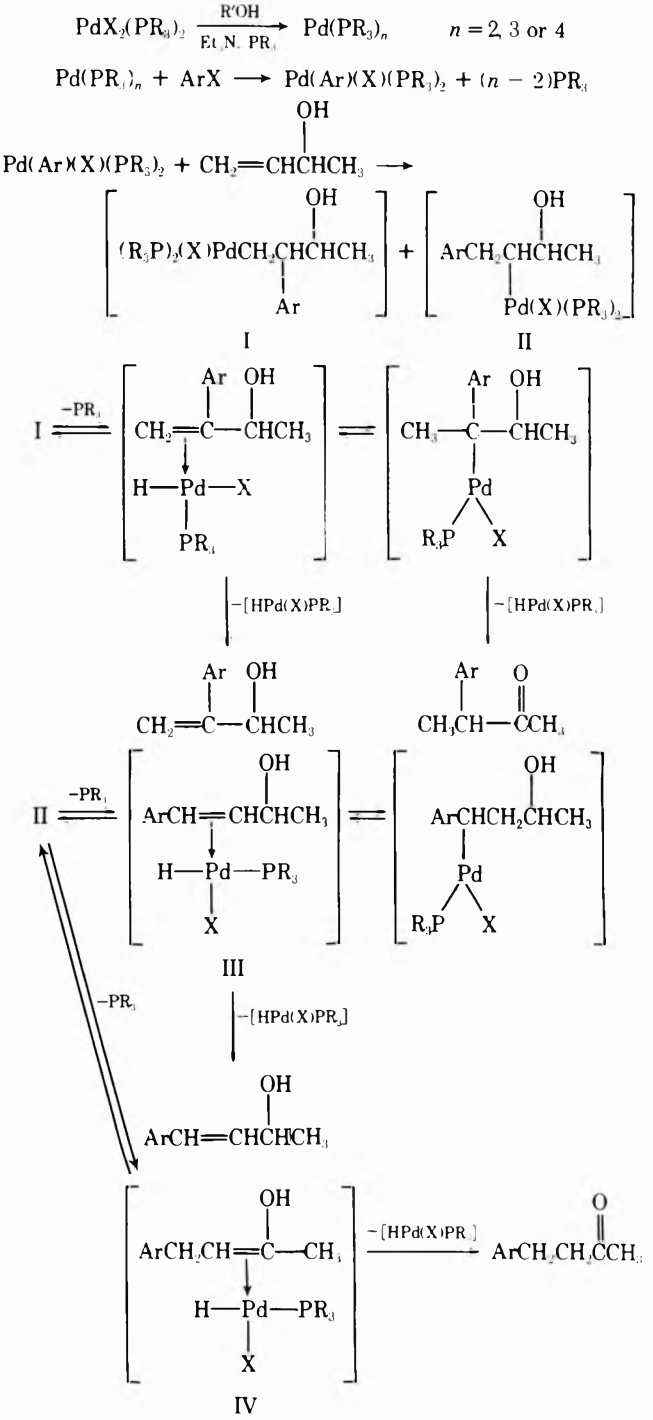


Mechanism of Reaction. The products obtained in the allylic alcohol arylations can be accounted for by the reactions shown in Scheme I, exemplified with 3-buten-2-ol. The scheme is similar to the one proposed for the related olefin arylation reaction.[2] Initially, the palladium(II) catalyst is believed to be reduced by the allylic alcohol to the true catalyst, a palladium(0)–triphenylphosphine complex or in the palladium(II) acetate reactions simply to finely divided palladium metal. In the latter reactions the precipitation of the metal can be seen when the reactants are mixed together. The palladium(0) species then oxidatively adds the aryl halide to form an arylpalladium complex. The last complex then adds to the allylic double bond in both possible directions to give adducts I and II. These adducts next undergo elimination of a hydridopalladium group to form olefin π complexes with the hydride. Dissociation at this stage produces the 2-aryl alcohol from I and either 3-aryl alcohol or the 3-aryl carbonyl product (in the enol form) from II. The presence of triphenylphosphine increases the rate of dissociation presumably by displacing the olefinic group from the metal in a second-order reaction. If dissociation does not occur then readdition and elimination reactions of the hydride group occur, leading ultimately to the carbonyl derivative, at which point the reaction becomes essentially irreversible. The dissociated, free hydride apparently rapidly decomposes, since once formed the unsaturated alcohols are generally stable in the reaction mixtures.

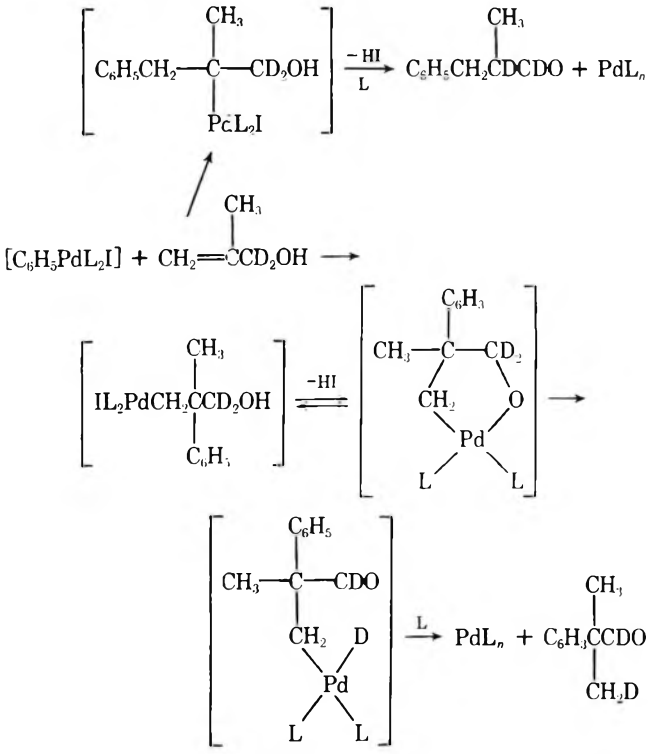
In the reaction of *o*-bromotoluene with 3-buten-2-ol the formation of less 3-aryl carbonyl and more 3-alcohol product than from *p*-bromotoluene is very probably the result of the sterically accelerated decomposition of complex III in Scheme I caused by the *o*-methyl group. Thus, more dissociation of III to alcohol occurs; consequently, less rearrangement to the carbonyl product can take place. If this explanation is correct it also indicated that elimination of the hydridopalladium group in II occurs initially mainly to π complex III rather than to IV, at least in the bromotoluene reactions.

The hydride addition–elimination sequence, however, is clearly not the only mechanism to be considered by which allylic alcohols are converted into carbonyl compounds. A direct metal assisted one–three hydrogen shift through a chelated alkoxide intermediate is another possibility. The formation of some 2-methyl-2-phenylpropionaldehyde (4%) in the phenylation of 2-methyl-2-propen-1-ol must have occurred by an alternative route, since the hydride 1:2 addition–elimination mechanism is not possible in this case. In order to gain more information about the origin of this alcohol we carried out the reaction of 2,2-dideuterio-2-methyl-2-propen-1-ol with iodobenzene and determined the fate of the deuterium. The major product, the 2-methyl-3-phenylpropanal, was found by NMR to contain essentially only one deuterium, on the aldehyde group, indicating that the 1,2-hydride addition–elimination mechanism was operating, since the other deuterium would have ended up on the carbon α to the aldehyde group and would have been lost by exchange in the aqueous isolation procedure employed. The minor product, the 2-methyl-2-phenylpropanal, contained two deuteriums, one in the aldehyde group and the other at least partly if not exclusively on a methyl group. The answer is not more definite be-

Scheme I
Mechanism of Arylation 3-Buten-2-ol



cause analyses were performed by mass spectroscopy and there was an appreciable amount of deuterium in the phenyl$^+$ and the $C_6H_7^+$ peaks. This was probably due to rearrangements but we did not establish this with model compounds. In any case the deuterium shift in the compound is exclusively intramolecular. It may occur by a direct 1:3 shift or more probably it occurs, at least partially, through an alkoxide intermediate as shown below.



In order to assess the importance of the cyclic alkoxide mechanism in the arylation of another allylic alcohol, we studied the reaction of iodobenzene with 2-deuterio-3-buten-2-ol. No deuterium was found in the terminal methyl group of the 3-phenyl-2-butanone produced and less than 10% of the benzylic position was deuterated. Deuterium was no doubt lost from this position by exchange during the isolation of the products. Thus, it appears that the 1,2-metal hydride addition–elimination mechanism for hydrogen shift is much preferred over the direct 1,3 shift.

Homoallylic Alcohol Reactions. Two homoallylic alcohols were treated with iodobenzene to determine how much carbonyl product would be formed in these cases. The results appear in Table II. 4-Penten-2-ol with a $Pd(OAc)_2$ catalyst gave a mixture of 44% 5-phenyl-2-pentanone, 38% *trans*- and 1.5% *cis*-5-phenyl-4-penten-2-ol, 9% 4-phenyl-2-pentanone, and 7% 4-phenyl-penten-2-ol. Thus, 44% of the aryl carbonyl product was formed. It is noteworthy that no more than ca. 1% of the possible intermediate 5-phenyl-3-penten-2-ol was detected. Presumably, the intermediate metal hydride π complex of this alcohol does not dissociate to an appreciable extent during the reaction. The total per-

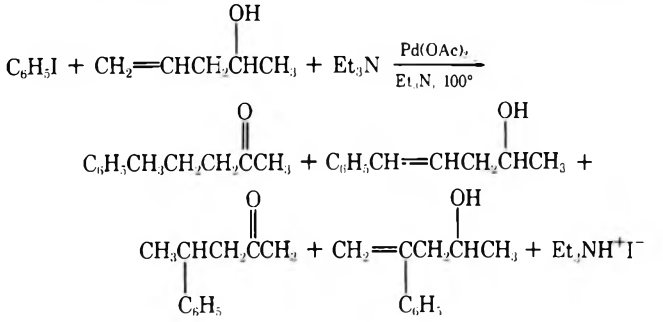


Table II
Arylation of Homoallylic Alcohols

Registry no.	Alcohol	Aryl halide	Reaction time, hr	Products									
				4-Arylation			3-Arylation				Other products (yield)	Total yield, %	% 4-aryl addition
				Alcohol, %, *E*/*Z*	Carbonyl compd, %	Alcohol/ carbonyl	Alcohol, %	Carbonyl compd, %	Alcohol/ carbonyl				
627-27-0	CH_2=$CHCH_2CH_2OH$	C_6H_5I	1[a]	30/0	49	0.6	4	17	4			70	79
625-31-0	CH_2=$CHCH_2CHOHCH_3$	C_6H_5I	6.5[a]	38/2	44	0.9	7	9	0.8		Unknown[b] (trace)	96	84
	CH_2=$CHCH_2CHOHCH_3$	C_6H_5Br[c]	24	63/9	7	10	16	1	16		Unknown[b] (4)	81	83

[a] Reaction solution consisted of 25 mmol of homoallylic alcohol, 20 mmol of aryl halide, 0.06 mmol of palladium acetate, 25 mmol of triethylamine, and 6.5 ml of acetonitrile at 100° in capped tubes under argon. [b] Unknown, believed to be 5-phenyl-3-penten-2-ol. [c] Catalyst was $Pd(OAc)_2(PPh_3)_2$.

cent terminal phenyl addition in this case (84%) is the same as found in the similar reaction carried out with allyl alcohol.

As expected from our previous results, the use of bromobenzene in this reaction with diacetatobis(triphenylphosphine)palladium(II) as catalyst gave about the same percent terminal phenyl addition but the 4-phenyl alcohol to 4-phenyl carbonyl ratio was much higher, 10.4 vs. 0.90 in the iodobenzene–palladium acetate reaction.

The second homoallylic alcohol allowed to react with iodobenzene was 3-buten-1-ol. The reaction proceeded about six times faster than the reaction with 4-penten-2-ol. The reaction products consisted of 49% 4-phenylbutanal, 30% 4-phenyl-3-buten-1-ol, 17% 3-phenylbutanal, and 4% 3-phenyl-3-buten-1-ol. Again, little of the possible intermediate 4-phenyl-2-buten-1-ol was formed. The percent terminal addition was 79% in this case. The fact that this value is 5% lower than found for allyl alcohol and 4-penten-2-ol suggests that some of the 4-phenylbutanal decomposed by aldol condensation during the reaction. Even using the experimental value, however, it is clear that somewhat more rearrangement to the carbonyl product occurred with the primary homoallylic alcohol than with the secondary one (49% vs. 44%). The fact that 17% of 3-phenyl carbonyl product was formed along with only 4% of the 3-phenyl alcohol from the phenylation of 3-buten-1-ol indicates that the palladium group is able to move over three carbons under these conditions easily.

Preparative Reactions. The reactions listed in Table I have all been carried out in capped tubes or bottles. Since this is not convenient for larger scale preparations, we investigated some of the reactions at reflux temperatures at atmospheric pressure. This was found to be a very useful procedure. While the reactions proceeded more slowly, since reflux temperatures were usually below 100°, the progress of the reactions could be observed simply by noting the temperature of the boiling reaction mixtures. It usually rose by 5° or more as reactants were used up. When the boiling point stopped increasing, the aryl halide usually had all reacted. The products then were easily isolated from the cooled reaction mixtures by adding ether and water and then separating, washing, and distilling the ether extracts. The yields were good to excellent. Some reactions with methyl acrylate and acrylonitrile were also successfully carried out by this procedure. The results of the preparative scale experiments are summarized in Table III.

The physical properties of all of the products prepared in this investigation are given in Table IV, which will only appear in the microfilm edition of this journal. (See paragraph at end of paper regarding supplementary material.)

Experimental Section

Reagents. Alcohols. Allyl and crotyl alcohol were distilled before use and stored over Linde 4A molecular sieves. 3-Methyl-2-buten-1-ol was prepared by the lithium aluminum hydride reduction of 3-methyl-2-butenoic acid. 3-Buten-1-ol was used as received from the Aldrich Chemical Co. All other alcohols were commercial products that were dried over molecular sieves before use.

Other Materials. The triethylamine was distilled and dried over molecular sieves before use. Iodobenzene and 4-bromobenzotrifluoride were only dried before use but the other liquid aromatic halides were distilled before drying. The solid, 4-iodoanisole, was used as received from Aldrich. Acetonitrile was used as received from Baker while 2-butanol was dried over 4A molecular sieves before use. Palladium acetate was prepared by the procedure of Wilkinson,[5] as was its complex with triphenylphosphine.[5] The triphenylphosphine was recrystallized from methanol. Other palladium complexes were prepared as noted previously.[6]

General Procedure for Small-Scale Allylic Alcohol Arylations. Reactions were carried out in 20-ml heavy-walled Pyrex tubes. The palladium catalyst, internal standard (naphthalene, 1-

Table III
Preparative Scale Reactions

Olefinic reactant (mol)	Aryl halide (mol)	Catalyst (mmol)	Amine (mol)	Solvent	Bp change, °C (reaction time, hr)	Isolated products (% yield)	% purity by GC
2-Methyl-3-butene-2-ol (0.25)	C_6H_5I (0.20)	$Pd(OAc)_2(PPh_3)_2$ (0.60)	Et_3N (0.52)	None	96–105 (6)	4-Phenyl-2-methyl-3-buten-2-ol (88)	98
2-Methyl-2-propen-1-ol (0.25)	C_6H_5I (0.20)	$Pd(OAc)_2$ (0.60)	Et_3N (0.25)	2-Methyl-1-propanol (65 ml)	107–113 (14)	3-Phenyl-2-methylpropanal (60)	98
3-Buten-2-ol (0.25)	C_6H_5I (0.20)	$Pd(OAc)_2$ (0.60)	Et_3N (0.25)	Acetonitrile (65 ml)	80–88 (10)	4-Phenyl-2-butanone (85)	>99
(*E*)-Methyl 2-butenoate (0.25)	C_6H_5Br (0.20)	$Pd(OAc)_2(PPh_3)_2$ (2.0)	Et_3N (0.25)	None	105–115 (72)	(*E*)-Methyl 3-phenyl-2-butenoate (54)[a]	99
Acrylonitrile (0.19)	C_6H_5I (0.15)	$Pd(OAc)_2(PPh_3)_2$ (1.5)	Et_3N (0.19)	None	81–100 (4)	*cis*-Phenylacrylonitrile (29) *trans*-Phenylacrylonitrile (59)	*b*
Methyl acrylate (0.19)	C_6H_5Br (0.15)	$Pd(OAc)_2(PPh_3)_2$ (1.5)	Et_3N (0.19)	None	87–~97 (68)	Methyl cinnamate (88)	99
Methyl acrylate (0.19)	1-$C_{10}H_7Br$ (0.15)	$Pd(OAc)_2(PPh_3)_2$ (1.5)	Et_3N (0.19)	None	96–~106 (120)	Methyl 3-(1′-naphthyl)-propenoate (62)	99

[a] Also formed in this reaction were 1.5% (*Z*)-methyl 3-phenyl-2-butenoate, 3% methyl 3-phenyl-3-butenoate, 2% (*E*)-methyl 4-phenyl-3-butenoate, and 0.5% (*Z*)-methyl 2-phenyl-2-butenoate. [b] Not determined.

methylnaphthalene, 2,3-dimethylnaphthalene, or benzophenone), and aryl halide were weighed into the tube. The air in the tube was replaced by argon and the tube was capped with a rubber-lined metal cap with two small holes in it for syringe needles. The alcohol, triethylamine, and solvent, if any, were then introduced from syringes. The tube was placed in a thermostated bath or the steam bath for 100°. Samples were removed by microsyringe for GLC analyses periodically. Analyses were carried out generally on 0.25 in. × 6 ft SE-30 or Carbowax 20M on Chromosorb W columns.

Products were isolated by diluting the cooled reaction mixtures with water and ether. The ether phase was separated, washed several times with water, dried over anhydrous magnesium sulfate, and concentrated. Alcohols were separated from carbonyl compounds where necessary by liquid chromatography on silica gel. The concentrated eluates were then separated by GLC using 0.25 in. or 0.5 in. columns.

General Procedure for Preparative Scale Reactions. The olefinic reactant, the aryl halide, solvent, if any, and the triethylamine were combined in a round-bottomed flask and the catalyst was added. The flasks were then connected to a condenser with a mercury bubbler attached at the top and flushed out with nitrogen. The solution was then heated to boiling in an oil bath keeping a slight nitrogen pressure on the flask. The boiling point of the solution was observed by means of a thermometer inserted into one of the necks of the flask. Stirring was not necessary. When the boiling point stopped increasing, the reaction mixture, now containing crystalline amine salt, was cooled and diluted with water and ether. The ether phase was separated, washed five times with water, dried over anhydrous magnesium sulfate, and then distilled under reduced pressure. The reactions carried out are listed in Table III. A detailed example is given below.

Preparation of 4-Phenyl-2-butanone. To a 250-ml three-necked round-bottomed flask equipped with a condenser and a thermometer was added 40.8 g (0.20 mol) of iodobenzene, 18.0 g (0.25 mol) of 3-buten-2-ol, 35 ml (0.25 mol) of triethylamine, 65 ml of acetonitrile, and 0.135 g (0.6 mmol) of palladium acetate. The solution formed was heated to boiling in an oil bath. The boiling point rose slowly from 80 to 88° over a period of 10 hr and then remained constant. The reaction mixture was now cooled and diluted with water and ether and the ether layer was separated. After the ether phase was washed five times with water, it was dried over anhydrous magnesium sulfate, filtered, concentrated, and distilled through a Nester-Faust spinning band distillation column, bp 114–116° (16 mm). There was obtained an 85% yield of greater than 99% pure (GLC) 4-phenyl-2-butanone.

Reaction of 1,1-Dideuterio-2-methyl-2-buten-1-ol with Iodobenzene. The deuterated alcohol was prepared by reducing methyl methacrylate with $LiAlD_4$ in ether. The NMR spectrum of the deuterated product in $CDCl_3$ was as follows: δ 6.08 (dd) (1 H), J = 11 and 18 Hz; 5.45 (d) (1 H), J = 2 Hz; 5.1 (m) (1 H), 4.18 (s) (1 H), and 1.23 (s) (3 H).

A mixture of 25 mmol of the deuterated alcohol, 20 mmol of iodobenzene, 25 mmol of triethylamine, 6.5 ml of acetonitrile, and 0.06 mmol of palladium acetate was heated under argon in a capped tube at 100° for 8 hr. The cooled reaction mixture was diluted with ether and water. The ether phase was separated, washed with water, and distilled under reduced pressure. The distillate was then separated into the two carbonyl products by preparative scale GLC. The NMR spectrum of the 2-methyl-3-phenylpropanal showed less than 10% deuterium on the 2 carbon and 100% on the aldehyde carbon. The minor alcohol, 2-methyl-2-phenylpropanal, was analyzed only by mass spectroscopy. The deuterated product showed a molecular ion at m/e 150 and a phenyldimethyl carbon ion at m/e 120 indicating that the aldehyde group contained one deuterium and the rest of the molecule one. The phenyl ion and the protonated benzene ion peaks were also strong as were their monodeuterated derivatives (ca. 1:1 ratios of protonated to monodeuterated ions).

Reaction of 2-Deuterio-3-buten-2-ol with Iodobenzene. The deuterated alcohol was prepared by reduction of 2-buten-3-one with $LiAlD_4$ in ether. The product had the following NMR spectrum in $CDCl_3$: δ 4.93 (m) (1 H), 4.79 (m) (1 H), 4.72 (s) (1 H), and 1.69 (d) (3 H), J = 1 Hz. The alcohol was treated with iodobenzene and palladium acetate exactly as in the preceding experiment with about 5 hr reaction time at 100°. Products were isolated as described above also. The 4-phenyl-2-butanone contained less than 10% deuterium and the 3-phenyl-2-butanone contained about 30% deuterium on the 3 carbon and about 15% on the 1 carbon. There was no detectable amount of deuterium on carbon 4 in either product.

Isolation of Tetraphenylphosphonium Iodide from the Phenylation of 3-Buten-2-ol. A reaction mixture consisting of 20 mmol of iodobenzene, 0.2 mmol of palladium acetate, 25 mmol of 3-buten-2-ol, 10 ml of triethylamine, and 3.8 mmol of triphenylphosphine was heated in a capped tube under argon for 10 hr at 100°. After cooling the crystalline solid present was removed by filtration, washed with hexane, and recrystallized from methylene chloride–ethyl acetate. There was obtained 1.1 g (61% based upon the triphenylphosphine) of tetraphenylphosphonium iodide, identified by ir and ^{31}P NMR (−23.2 ppm, authentic material −23.2 ppm, from H_3PO_4).

Acknowledgments. The mass spectral data were kindly obtained by Barbara Jelus. This project was supported by a grant from the National Science Foundation.

Registry No.—(*E*)-Methyl 2-butenoate, 623-43-8; acrylonitrile, 107-13-1; methyl acrylate, 96-33-3; 3-phenylpropanal, 104-53-0; 2-phenylpropanal, 93-58-3; 3-phenylbutanal, 16251-77-7; 2-phenylbutanal, 2439-43-2; 3-methyl-3-phenylbutanal, 1009-62-7; 3-methyl-2-phenyl-3-buten-1-ol, 29290-99-1; 3-methyl-2-phenylbutanal, 2439-44-3; biphenyl, 92-52-1; 2-methyl-3-phenylpropanal, 5445-77-2; 2-methyl-2-phenylpropanal, 3805-10-5; (*E*)-4-phenyl-3-buten-2-ol, 36004-04-3; 4-phenyl-2-butanone, 2550-26-7; 1-phenyl-1,3-butadiene, 1515-78-2; 3-phenyl-3-buten-2-ol, 6249-81-6; 3-phenyl-2-butanone, 769-59-5; 4-(4′-methoxyphenyl)-2-butanone, 104-20-1; 1-(4′-methoxyphenyl)-1,3-butadiene, 30448-78-3; 3-4′-methoxyphenyl)-2-butanone, 7074-12-6; (*E*)-4-(4′-trifluoromethylphenyl)-3-buten-2-ol, 57132-18-0; 4-(4′-trifluoromethylphenyl)-2-butanone, 57132-19-1; 3-(4′-trifluoromethylphenyl)-3-buten-2-ol, 57132-20-4; 3-(4′-trifluoromethylphenyl)-2-butanone, 57132-21-5; (*E*)-4-(4′-tolyl)-3-buten-2-ol, 57173-53-2; 4-(4′-tolyl)-2-butanone, 7774-79-0; 3-(4′-tolyl)-3-buten-2-ol, 57132-22-6; (*E*)-4-(2′-tolyl)-3-buten-2-ol, 57132-23-7; (*Z*)-4-(2′-tolyl)-3-buten-2-ol, 57132-24-8; 4-(2′-tolyl)-2-butanone, 57132-25-9; 1-(2′-tolyl)-1,3-butadiene, 57132-26-0; 4-(2′-tolyl)-3-buten-2-one, 16927-82-5; 3-(2′-tolyl)-3-buten-2-ol, 57132-27-1; (*E*)-2-methyl-4-phenyl-3-buten-2-ol, 57132-28-2; 3-methyl-1-phenyl-1,3-butadiene, 21919-51-7; 2-methyl-3-phenyl-3-buten-2-ol, 25982-72-3; (*E*)-4-phenyl-3-buten-1-ol, 770-36-5; phenylbutanal, 18328-11-5; 3-phenyl-3-buten-1-ol, 3174-83-2; (*E*)-5-phenyl-4-penten-2-ol, 54985-34-1; (*Z*)-5-phenyl-4-penten-2-ol, 54985-29-4; 5-phenyl-2-pentanone, 2235-83-8; 4-phenyl-4-penten-2-ol, 57132-29-3; 4-phenyl-2-pentanone, 17913-10-9; (*E*)-methyl 3-phenyl-2-butenoate, 8461-50-5; (*E*)-phenylacrylonitrile, 140-10-3; (*Z*)-phenylacrylonitrile, 102-94-3; (*E*)-methyl cinnamate, 1754-62-7; (*E*)-methyl 3-(1′-naphthyl)propenoate, 22837-81-6; $Pd(OAc)_2$, 3375-31-3; $Pd(OAc)_2(PPh_3)_2$, 14588-08-0; $PdBr(Ph)(PPh_3)_2$, 33381-14-5; $PdCl_2(PPh_3)_2$, 13965-03-2; $PdBr_2(PPh_3)_2$, 23523-33-3; $PdI_2(PPh_3)_2$, 23523-32-2.

Supplementary Material Available. Complete NMR spectra, physical properties, and observed molecular weights for the products prepared in this investigation (10 pp) will appear following these pages in the microfilm edition of this volume of the journal.

References and Notes

(1) R. F. Heck, *J. Am. Chem. Soc.*, **90**, 5526 (1968).
(2) H. A. Dieck and R. F. Heck, *J. Am. Chem. Soc.*, **96**, 1133 (1974).
(3) Preliminary experiments were carried out by D. J. Renn in these laboratories.
(4) R. F. Heck, *J. Am. Chem. Soc.*, **93**, 6896 (1971).
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(6) A. Schoenberg, I. Bartoletti, and R. F. Heck, *J. Org. Chem.*, **39**, 3318 (1974).

Palladium-Catalyzed Vinyl Substitution Reactions. I. A New Synthesis of 2- and 3-Phenyl Substituted Allylic Alcohols, Aldehydes, and Ketones from Allylic Alcohols

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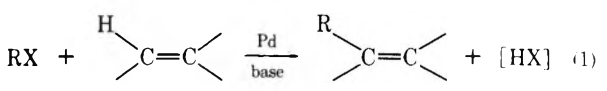
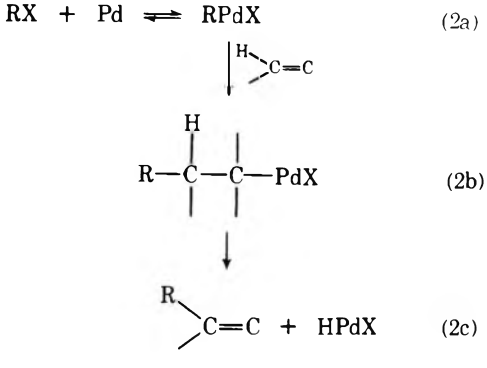
The palladium-catalyzed arylation of olefins has been extended to allylic alcohols. Aldehydes are formed from primary, ketones from secondary, and aryl-substituted allylic alcohols from tertiary allylic alcohols. With iodobenzene, a variety of organic and inorganic bases may be employed, but with bromobenzene, sodium bicarbonate is preferred.

The palladium-catalyzed substitution of vinylic hydrogen by aryl and vinyl halides was discovered by Mizoroki and co-workers[1] and Heck et al.[2,3] (reaction 1).

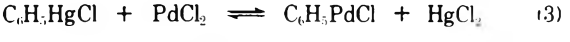


The reaction was reported to tolerate a variety of functional groups and examples were given of aryl halides with the substituents OMe, COOMe, NO_2, Cl, and C_6H_5. The olefins employed were limited to styrene, 4-nitrostyrene, 1-phenyl-1-propene, ethylene, propylene, 1-hexene, and methyl acrylate. Yields were reported to be low for olefins having methylene groups adjacent to the double bond.[2]

The mechanism of the reaction involves the formation of an organopalladium halide by an oxidative addition followed by addition to the olefin and elimination of HPdX.

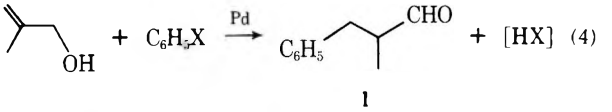


The organopalladium species may be generated by other means, such as reaction 3, which was used earlier by Heck.[4]



Under the mild conditions possible with 3, the phenylpalladium species was capable of reacting with a wide variety of olefins and in particular gave aldehydes and ketones with allylic alcohols.[5] We therefore were intrigued with the possibility of achieving a similar successful synthesis of aldehydes and ketones by the use of allylic alcohols in reaction 1.

Since reaction 2a requires considerably higher temperatures than reaction 3, we expected problems with side reactions, particularly those induced by base. Tertiary amines could deactivate the catalyst either by competing with the olefin for coordination sites, promoting the formation of inactive π-allyl complexes, or by catalyzing aldol condensations in the product aldehydes. We therefore first examined the effect of a variety of bases on the reaction of methallyl alcohol with bromo- and iodobenzene with the hope of achieving the following reaction.



Upon finding satisfactory conditions for reaction 4 a variety of allylic alcohols were then treated with iodobenzene and bromobenzene. A subsequent paper will discuss the effect of substituents on the aryl halide and the reaction of halobenzenes with nonallylic unsaturated alcohols.

Results

1. Reaction of Halobenzenes with Methallyl Alcohol. Table I gives results for reaction 4 where X = I and X = Br, respectively. Reasonable yields were obtained under a variety of conditions and this flexibility was later of value when the reaction was extended to other unsaturated alcohols and substituted aryl halides which imposed greater restraints on the synthesis.

The greatest reactivity was found for X = I, and when a hindered tertiary amine was used there was a spontaneous exotherm when the reaction was raised to 100°. Biphenyl was a side product whose yield was promoted by the presence of the polar aprotic solvent hexamethylphosphoramide (HMP) when diisopropylethylamine was used as base. In the absence of solvent, a good yield of 1 was obtained using diisopropylethylamine (85%). Lower yields were obtained with less hindered tertiary amines (e.g., morpholine, 60%). For the weaker bases the reaction was much slower. Diethylaniline gave rise to a weak exotherm and gave 40% conversion in 30 min at 130° but thereafter both 1 and the amine decreased in concentration, presumably owing to a condensation between the two. Para-substituted diethylanilines (-CN, -COPh) gave no reaction. Pyridine and 2,6-lutidine also gave no significant reaction, probably owing to the formation of complexes which were too stable to be catalytically active. Some sodium salts of weak acids were also successfully used as bases, providing that polar aprotic solvents were used (e.g., HMP or *N*-methylpyrrolidinone, NMP). Sodium bicarbonate gave significantly faster rates and yields than sodium acetate. The addition of triphenylphosphine made little difference to these reactions.

By contrast, only traces of 1 were formed from bromobenzene when triethylamine was used as base. Slightly better results were obtained with the more hindered base, diisopropylethylamine, but in both cases the principal product was an unidentified mixture of high-boiling materials. These were not, however, formed by a simple base-catalyzed condensation of the aldehyde which was found to be stable to tertiary amines at the temperatures used. A vari-

Table I
Reaction of Iodobenzene and Bromobenzene with Methallyl Alcohol[a]

Base	Halogen	Temp, °C	Time, hr	Solvent	Conversion,[b] %	Yield[c] PhPh, %	Yield of 1,[c,d] %
i-Pr_2NEt[e]	I	130	1	None	97	3	85
Bu_3N[e]	I	130	1	None	97	3	58
$N(CH_2CH_2)_3N$[f]	I	130	1	None	50	0	31
i-Pr_2NEt[e]	I	130	1	HMP	94	47	47
$NaHCO_3$	I	130	2	NMP	100	4	95[g]
NaOAc	I	140	7	HMP	75	3	23[h]
Et_3N	Br	130	2	DMF	81	0	Trace
Et_3N	Br	110	5	None	42	0	6
i-Pr_2NEt	Br	130	20	HMP	25	0	18
i-Pr_2NEt	Br	120	20	None	40	0	12
$NaHCO_3$	Br	130	2	DMF	100	0	100
$NaHCO_3$[i]	Br	130	2	DMF	100	0	84
Na_2CO_3	Br	130	10	DMF	91	0	73
Na_2CO_3[i]	Br	130	4	DMF	99	0	88
$Na_3PO_4 \cdot 12H_2O$	Br	110	10	DMF	79	0	63
$Na_3PO_4 \cdot 12H_2O$[i]	Br	110	10	DMF	77	0	54
$MgCO_3$	Br	140	10	DMF	33	0	20
$MgCO_3$[i]	Br	140	10	DMF	32	0	28
NaOAc	Br	130	6	DMF	24	0	10
NaOAc[i]	Br	130	6	DMF	37	0	14

[a] 50 mmol of C_6H_5X, 75 mmol of methallyl alcohol, 60 mmol of base, 0.45 mmol of $PdOAc_2$ and 20 ml of solvent under N_2. When X = Br, 0.9 mmol of PPh_3 added also. [b] Conversion of C_6H_5X by GC, internal standard. [c] Based on 100% conversion of C_5H_5X, GC internal standard. [d] Product identified by MS, NMR, C, H, analysis, bp 96° (10 mm) [lit.[5] 71–75° (3 mm)]. [e] 50 mmol of base. [f] 25 mmol of base. [g] 60% yield isolated in a similar experiment in HMP. [h] Isolated yield. [i] 0.1 g of Et_3N added.

ety of other conditions with diisopropylethylamine and other tertiary amines including diethylaniline, 2,6-lutidine, and 1,5-diazabicyclo[5.4.0]undec-5-ene, were unproductive.

A variety of inorganic bases were then tried for the bromobenzene reaction. Outstanding among these was sodium bicarbonate, which, in a polar aprotic solvent, gave the product rapidly in high yield. Further, the product was found to be stable to continued heating in the reaction mixture. Other carbonates were not as successful, especially the less soluble ones such as $CaCO_3$, which in 18 hr at 130° gave only a 20% conversion. If this is due to the insolubility of the carbonates, a small amount of a tertiary amine could catalyze their reaction. In agreement with this, it was found that a trace of triethylamine increased the initial rates of reaction by a factor of ~2 for all the inorganic bases except $Na_3PO_4 \cdot 12H_2O$ and NaOAc. The latter was found to have a detectable solubility in dimethylformamide while the solubility of the phosphate would be increased by the presence of the water of crystallization. Water in small amounts was also found to increase the rate of reaction when Na_2HPO_4 or Na_2CO_3 was used as base. The latter combination was as effective as Na_2CO_3 with a catalytic amount of triethylamine.

Since sodium bicarbonate decomposes at reaction temperatures, the mixture of Na_2CO_3 and H_2O which would be formed was compared with $NaHCO_3$. The latter was clearly superior, demonstrating that its effectiveness was inherent to sodium bicarbonate itself and not its decomposition products. The combination of Na_2CO_3 and H_2O gave a high initial rate which slowed greatly after attaining ~40% conversion in 30 min at 130°.

Catalyst deactivation could have many causes. For sodium acetate it is probably a result of the ability of the acetic acid produced to compete for Pd^0 and deactivate it by reaction 5.

$$HOAc + Pd^0 \rightleftharpoons HPdOAc \quad (5)$$

Acetic acid is known to have a retarding effect on reaction 1.[1] Tertiary amine hydrohalides may also be sufficiently acidic to react with Pd^0 species. The formation of catalytically inactive palladium species, especially π-allyl complexes, is probably a factor with some of the stronger bases. In some cases, however, catalyst deactivation appeared to be related to the decomposition of organopalladium intermediates to the elemental metal. When X = I, red-brown catalytic intermediates were formed which were stable to the end of reaction in the absence of phosphines. When X = Br, and $NaHCO_3$ was used as base, reaction 4 occurred in the absence of triphenylphosphine. Without the stabilizing effect of phosphines, however, palladium began to precipitate at an earlier stage of the reaction and the rate slowed down, making it difficult to achieve 100% conversion. In the absence of phosphines, the reaction was also quite solvent sensitive. Thus, with NMP as solvent, conversion of bromobenzene was only 50% after 5 hr at 145° to give equal amounts of biphenyl and 1. In HMP at 145°, however, bromobenzene was 98% converted after 3 hr, 1 was isolated in 72% yield, and only a trace of biphenyl was formed. Thus, while triphenylphosphine appears to be necessary to reaction 1 when X = Br,[2,3] it is not essential for reaction 4.

In the presence of triphenylphosphine, variation of the solvent had less effect and 1 was consistently produced in high yield in a variety of solvents such as DMF, HMP, NMP, tetramethylurea (TMU), and dimethylacetamide (DMAC). At higher temperatures (>140°), catalyst deactivation by precipitation of palladium metal occurred and the reaction stopped at high conversion. This was particularly apparent with DMF. An important factor in the choice of solvent appears to be the solubility of sodium bicarbonate, since the reaction was also found to proceed in ethylene glycol, but not in diethylene glycol dimethyl ether unless 5% water was added. Protic solvents gave poorer yields of 1 than the polar aprotic solvents. Chlorobenzene has been reported to give only traces of product in reaction 1[3] and our work confirmed this for reaction 4.

The product aldehyde 1 has been synthesized earlier by the related palladium-catalyzed reaction between phenylmercuric chloride and methallyl alcohol.[5] Although only one product was reported, we also obtained 5% of an isomer which was separated and identified by NMR as dimethylphenylacetaldehyde. Apparently addition of phenylpallad-

Table II
Reaction of Iodobenzene and Bromobenzene with Allylic Alcohols[a]

Registry no.	Alcohol	Time, hr	Halogen	Conversion, %	Products, % 3-Arylcarbonyl GC[b]	3-Arylcarbonyl Yield, %	2-Arylcarbonyl GC[b]	2-Arylcarbonyl Yield, %	Other products GC[b]
107-18-6	CH_2=$CHCH_2OH$	2	I	100	81	23[c]	19	10[c]	
513-42-8	CH_2=$C(CH_3)CH_2OH$	4	I	100	95	95[d]	5		
	CH_2=$C(CH_3)CH_2OH$	4	Br	100	95	86[d]	5		
6117-91-5	CH_3CH=$CHCH_2OH$	1	I	100	69	69	31	24	
	CH_3CH=$CHCH_2OH$	1.5	Br	93	69	45[c]	31	21[c]	
598-32-3	CH_2=$CHCH(CH_3)OH$	2	I	100	100	89[d]			
	CH_2=$CHCH(CH_3)OH$	2	Br	100	70	e			Unknown[f] 30
1569-50-2	CH_3CH=$CHCH(CH_3)OH$	20	I	99	80	50[c]	20		
556-82-1	$(CH_3)_2C$=$CHCH_2OH$	10	I	77	36		16		Biphenyl 31
									Unknown[g] 17
	$(CH_3)_2C$=$CHCH_2OH$	4	Br	27			19		Biphenyl 19
									Unknown[g] 35
115-18-4	CH_2=$CHC(CH_3)_2OH$	12	I	53					PhCH=$CHC(CH_3)_2OH$[h]
	CH_2=$CHC(CH_3)_2OH$	4	Br	65					
110-64-5	$HOCH_2CH$=$CHCH_2OH$	0.5	I	95					3-Phenyl-2,3-dihydrofuran[h]
	$HOCH_2CH$=$CHCH_2OH$	2	Br	100					

[a] 50 mmol of halobenzene, 75 mmol of allylic alcohol, 60 mmol of $NaHCO_3$, 0.45 mmol of $PdCl_2$, in 20 ml of solvent (NMP at 130° for X = I and HMP at 140° for X = Br), 1.35 mmol of PPh_3 added when X = Br. [b] Product distribution from GC. [c] Isolated yield. [d] From GC, based on internal standard. [e] In a similar experiment in which 0.45 mmol of $(Ph_2PCH_2)_2$ was substituted for PPh_3, the yield was 80% (GC) and 63% isolated. [f] This compound was subsequently isolated and identified as (*E*)-4-phenyl-3-buten-2-ol.[13] [g] This compound was subsequently isolated and identified as 3-methyl-2-phenyl-3-buten-1-ol.[13] [h] See text.

ium bromide to the double bond can occur in both senses.

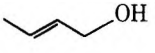
Having established optimum conditions for reaction 4, the scope of the reaction was then investigated for a variety of other allylic alcohols.

2. Variation of the Allylic Alcohol. Using the optimum conditions found for the reaction of halobenzenes and methallyl alcohol, a wide variety of allylic alcohols were treated with iodo- and bromobenzene. Results are given in Table II. Where isolated yields were not obtained, the products were isolated by preparative GC and identified by NMR, ir, and MS. Where authentic samples were available, yields were sometimes obtained from GC data by the use of an internal standard. NMR data not previously reported[5] are given in Table III.

Although reactions of iodobenzene were conveniently fast at 130° with allyl alcohol and monosubstituted allylic alcohols, disubstitution severely retarded the rate. Reactions of bromobenzene at 145° in the presence of triphenylphosphine proceeded at least as easily as when using iodobenzene at 130°.

In the absence of triphenylphosphine, the reactions stopped after a partial conversion (i, 31% after 1 hr; ii, 25% after 1 hr; iii, 0% after 1.5 hr).

i



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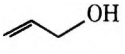


iii

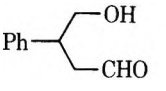
The reason for this is not yet clear, but it is likely that it is related to the precipitation of metallic palladium. Precipitation of palladium metal was almost immediate in the reaction of allyl alcohol and bromobenzene and no significant amount of products were formed. Running the reaction at lower temperatures did not help significantly. Even at 80°C, palladium metal was formed rapidly and the reaction was slow, resulting in deactivation of the catalyst at a very low conversion. Addition of triphenylphosphine helped to reactivate the catalyst in some of these cases.

Secondary reactions were important in the formation of the product from 2-butene-1,4-diol. The initial product was expected to be iv. This cyclized to the hemiacetal v, however, which dehydrated upon distillation to give the isolated product vi.

Table III
NMR Spectra[a]

Registry no.	Compd	δ, multiplicity (no. of protons), coupling constant in hertz
93-53-8	2-Phenylpropanal	9.60 d (1) *J* = 1.5; 7.35 m (5); 3.65 qd (1) *J* = 7, 1.5; 1.4 d (3) *J* = 7
104-53-0	3-Phenylpropanal	9.70 t (1) *J* = 1; 7.25 s (5); 3.1–2.6 m (4)
3805-10-5	2-Methyl-2-phenylpropanal	9.50 s (1); 7.28 s (5); 1.40 s (6)
1528-39-8	3-Phenyl-2-pentanone	7.23 s (5); 3.47 t (1) *J* = 7; 1.97 s (3), 2.4–1.2 m (2), 0.8 t (3)
2439-44-3	3-Methyl-2-phenylbutanal	9.74 d (1) *J* = 3; 7.3 m (5); 3.5–3.1 m (1); 2.4–1.8 m (1), 1.04 d (3) *J* = 6; 0.75 d (3) *J* = 6
1009-62-7	3-Methyl-3-phenylbutanal	9.53 t (1) *J* = 3; 7.35 m (5); 2.67 d (2) *J* = 3; 1.43 s (6)
56718-06-0	3-Phenyl-2,3-dihydrofuran	7.20 s (5); 6.50 m (1); 5.00 m (1); 4.7–4.0 m (3)

[a] 60 MHz in CCl_4 with Me_4Si. Spectra of other compounds agreed with published spectra.[5]



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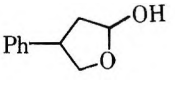

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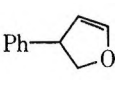


vi

Minor products (~5% or less) are not included in Table II. Where only one product is noted, the isomer resulting from the addition of the phenylpalladium species to the

Table IV
Reaction of Bromobenzene (50 mmol) with Allyl Alcohol (75 mmol)[a]

Time, hr	Conversion,[b] %	Yield[c] of $PhCH(CH_3)CHO$, %	Yield[c] of $PhCH_2CH_2CHO$, %
0.5	47	7	30
1.0	67	10	37
2.0	98	11	20
4.0	100	10	3

[a] With 60 mmol of $NaHCO_3$, 0.45 mmol of $PdCl_2$, and 1.35 mmol of PPh_3 in 20 ml of NMP under N_2 at 140°. [b] Conversion of C_6H_5Br by GC, internal standard. [c] Based on conversion by GC, internal standard.

Table V
Reaction of Halobenzene with Allyl Alcohol[a]

Halogen	Base	Solvent	Temp, °C	Time, min	Conversion[b] %	Yield,[c] % $PhCH(CH_3)CHO$	Yield,[c] % $PhCH_2CH_2CHO$
I	Et_3N	none	100	60	97	13	27
I	Et_3N	PhOPh	135	45	91	12	56
Br	$NaHCO_3$	HMP	110	240	90	13	12
Br	$NaHCO_3$[d]	HMP	110	120	87	9	22
Br	$NaHCO_3$[d]	NMP	100	60	51	4	6
Br	$NaHCO_3$[d]	NMP	130	10	46	6	23
Br[e]	$NaHCO_3$[d]	NMP	140	25	100	13	36
Br[e]	Na_2CO_3[d]	NMP	120	50	90	13	34

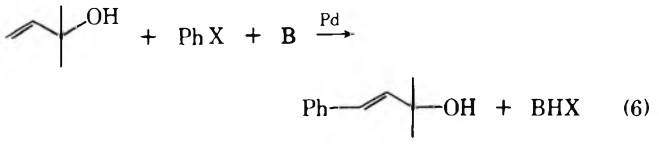
[a] 50 mmol of C_6H_5X, 75 mmol of allyl alcohol, 60 mmol of base, 0.45 mmol of $PdOAc_2$ and 20 ml of solvent. When X = Br, PPh_3 added, 0.9 mmol for first two cases and 1.35 mmol subsequently. [b] Conversion of C_6H_5X by GC, internal standard. [c] Based on 100% conversion (GC, internal standard). [d] A catalytic amount (0.2 g) of diisopropylethylamine added. [e] Allyl alcohol added gradually during reaction.

double bond in the reverse sense was not a significant product, although it may be formed. Where two major products were formed, the distribution did not appear to vary with the halogen used, the solvent, or the presence, amount, and nature of the phosphine. With the exception of methallyl alcohol, the only reactions which were optimized to any extent were those of allyl alcohol and 2-methyl-3-buten-2-ol, both of which suffered from competing side reactions.

3. Reaction of Halobenzenes with Allyl Alcohol. The product distribution from the reaction of allyl alcohol appeared to change with time in favor of 2-phenylpropanal. Aldehyde yields were therefore monitored continuously using an internal standard and the changing product distribution traced to a preferential destruction of 3-phenylpropanal (Table IV). Presumably this is due to a base-catalyzed aldol condensation.

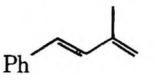
Table V shows that the destruction of 3-phenylpropanal can be minimized. For iodobenzene, a tertiary amine could be used and in this case a nonpolar solvent improved yields (tertiary amines are very poor aldol catalysts).[6] For bromobenzene an inorganic base was necessary with a polar aprotic solvent but a catalytic amount of a tertiary amine increased the rate and decreased aldehyde destruction. Generally these palladium-catalyzed reactions were best carried out at as low a temperature as possible to avoid catalyst and product decomposition. In the case of allyl alcohol, however, 3-phenylpropanal destruction was more pronounced at lower temperatures in the range 100–140°. Yields were further improved by adding the allyl alcohol gradually during the reaction so that its concentration (or that of the corresponding alkoxide) was minimized.

4. 2-Methyl-3-buten-2-ol. Reaction 6 was unaccountably slow with sodium bicarbonate and gave low yields for both X = I and X = Br.



(6)

With a tertiary amine, however, iodobenzene gave an 84% conversion in only 30 min at 120° (no solvent). The product consisted of the alcohol (90%) and the corresponding olefin vii (10%). As time increased, the ratio of olefin to alcohol increased, e.g., vii/viii = 4 at 2.5 hr and ∞ at 6 hr.



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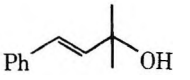


viii

This transformation was attributed to the catalytic effect of the amine hydroiodide or the small amount of acid in equilibrium with it. Although the amine gave a faster reaction than sodium bicarbonate, it had the disadvantage of causing the dehydration of the product. Fortunately it was possible to combine the advantages of amine and bicarbonate by using a catalytic amount of amine with the usual excess of sodium bicarbonate. In this case, a 90% conversion resulted after 30 min at 120° and the ratio of olefin to alcohol remained constant at 0.1 for 5.5 hr. The yield of alcohol was then determined by GC to be approximately 92% by the use of an internal standard.

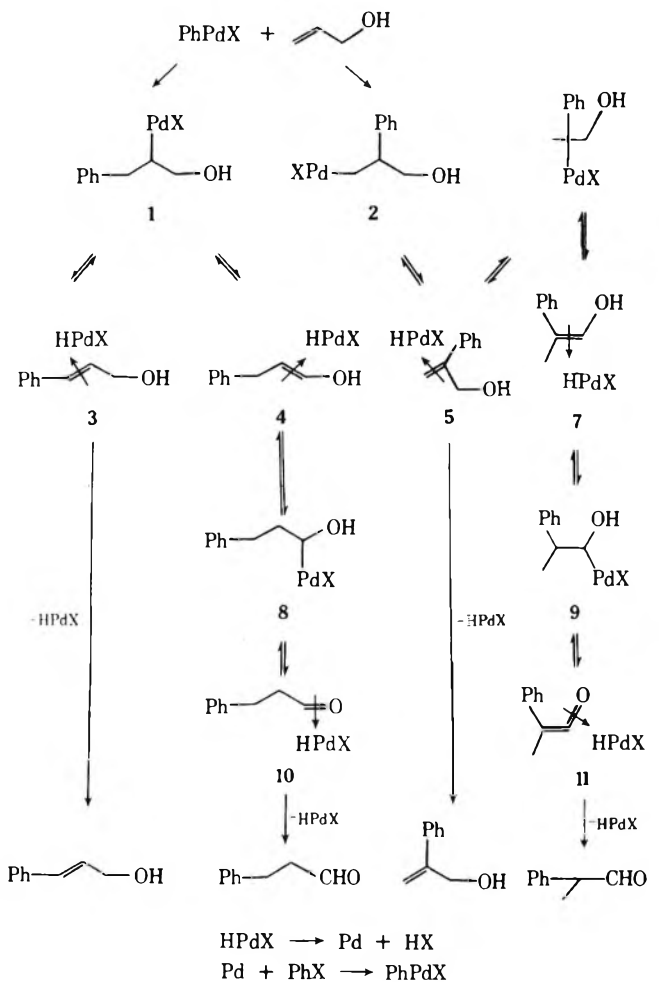
When the same combination of sodium bicarbonate with a catalytic amount of a tertiary amine was used for bromobenzene (PPh_3/Pd = 2), an 83% yield of the alcohol was obtained after 3 hr at 120° (solvent DMF).

Discussion

A common mechanism has been proposed for the arylation of olefins by phenylmercuric salts[7] and by aryl halides.[2,3] A comparison between the present work and the arylation of allyl alcohols by phenylmercuric salts[5] is therefore appropriate.

In both cases, arylpalladium halides are generated and these are expected to add to allyl alcohol to give intermediates 1 and 2 of Scheme I. These would be in equilibrium with intermediates 3, 4, and 5 which could give the free olefins by exchanging with other neutral ligands in solution. Since 5 is the enol form of 3-phenylpropanal, it would be

Scheme I



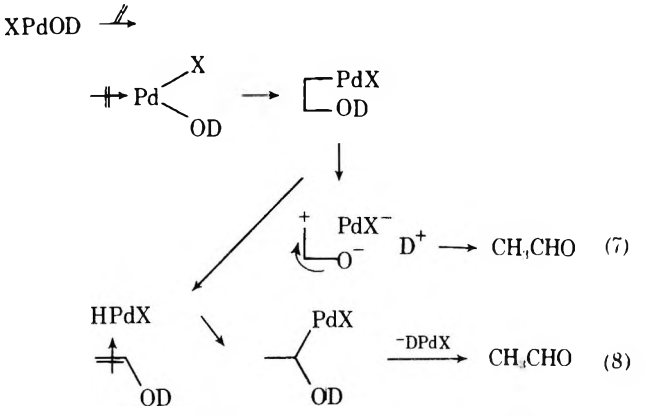
formed together with cinnamyl alcohol and 2-phenylallyl alcohol. If however, readdition of HPdX is fast compared to olefin exchange, intermediates **6**–**11** would also be formed. Of these, **10** and **11** would be aldehyde complexes which, being less stable than olefin complexes, would rapidly exchange and thereby favor formation of carbonyl products.

Two extreme cases may thus be distinguished: case A, in which coordinated olefins exchange rapidly and products are formed in a stepwise fashion (this favors the formation of unsaturated alcohols which could then slowly isomerize to carbonyl products); case B, in which a multistep olefin isomerization within the coordination sphere of the metal complex is faster than olefin exchange (in this case, carbonyl products would be favored).

Heck examined the reaction between phenylmercuric salts and allyl alcohol and found only 3-phenylpropanal, allylbenzene, and cinnamyl alcohol in the ratio 10:3:1. The last product suggests case A. However, in the reaction between crotyl alcohol and phenylmercuric salts, both the 2- and 3-phenylaldehydes were found, consistent with case B.

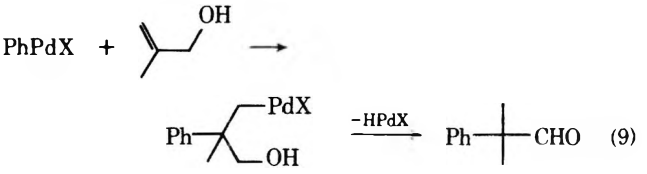
In our work the major products from allyl alcohol were 2- and 3-phenylpropanol, suggesting case B. In view of the differences found between allyl alcohol and crotyl alcohol in the earlier work, we also repeated the stoichiometric reaction between phenylmercuric acetate, palladium acetate, and allyl alcohol and found the dominant products to be biphenyl > 3-phenylpropanal > 2-phenylpropanal. The ratio of 3 to 2 addition was approximately 15. The large amount of biphenyl explains why phenylmercuric salts gave lower yields of aldehydes than the present synthesis.

Case B has been invoked in the past to explain results obtained in certain metal-catalyzed isomerizations.[8] One such result pertaining to the Wacker oxidation of ethylene to acetaldehyde is particularly relevant, since similar catalytic intermediates arise by a completely different reaction. Here, a stepwise mechanism involving the intermediacy of vinyl alcohol[9] was eliminated by the discovery that deuterium was not incorporated into the acetaldehyde when the reaction was carried out in D_2O.[10] Reaction 7 is the most commonly accepted explanation.[11] This involves the elimination of D^+ and PdX^- combined with a 1,2 hydride shift. A variant is reaction 8, in which the hydride shift is facilitated by palladium.



The latter mechanism was suggested by Heck[12] and led us to suggest the related mechanism (case B) for the present synthesis.

The reaction of methallyl alcohol with halobenzenes produced 5% of a product, 2-methyl-2-phenylpropanal, which cannot be explained by case B but requires a 1,3 hydride shift (reaction 9).



Palladium cannot facilitate this reaction via a π-olefin complex. Possible intermediates are a palladium π-cyclopropane intermediate or a cyclic palladium alkoxide.[13]

When this work was concluded we learned that Melpolder and Heck had been working along related lines and we are grateful to them for a copy of their paper prior to publication.[13] In common with us, they were unable to obtain stable products from aryl bromides and primary allylic alcohols when tertiary amines were used as bases. With the secondary alcohol, 3-buten-2-ol, they were more successful and obtained good yields of products. With this alcohol we found that sodium bicarbonate promoted a very much faster reaction than tertiary amines under our conditions. We attribute this difference to the products of the neutralization of the base. With tertiary amines, the amine hydrohalide which is formed probably dissociates to form the free acid in sufficient amount to partially deactivate the catalyst by reacting with it. Sodium acetate behaves similarly, since the catalyst is apparently basic enough to react with acetic acid. Sodium bicarbonate, however, has the virtue of liberating carbonic acid, which is expelled from the system as carbon dioxide.

(*E*)-4-Phenyl-3-buten-2-ol was a major product under the conditions used by Melpolder and Heck. This caused us to reexamine the corresponding reaction which we had run using sodium bicarbonate. Here we also found (*E*)-4-phe-

nyl-3-buten-2-ol but in lesser amount. The ratio of products for 3 substitution was carbonyl/alcohol = 0.4 in our case vs. 0.8 in theirs. In the reactions of 3-methyl-2-buten-1-ol, unsaturated alcohols were also found as products and this additional information is noted in Table II. Case A products, therefore, appear to become significant with certain structures. However, case B products are favored under our conditions and we have obtained carbonyl compounds as major products from some unsaturated alcohols in which the double bond and hydroxyl function are well separated, e.g., 4-methyl-4-penten-1-ol. Even 1-decen-10-ol gave significant amounts of aldehyde products. We will report further on the reactions of nonallylic unsaturated alcohols in a subsequent paper.

Experimental Section

Reagents, catalysts, and solvents were commercial products and were used without purification.

Reactions were carried out under a nitrogen blanket in a flask equipped with a serum cap for the removal of GC samples. When conversion reached 100% or ceased, the reaction mixture was stirred with a five- to tenfold excess of water and extracted with toluene. The products were then distilled from the toluene extract or separated by preparative GC. In some cases, yields were obtained by GC during or at the end of the experiment, by the addition of an internal standard. A typical example follows. Deviations from this procedure are noted in the Results section.

3-Phenyl-2-methylpropanal. $PdCl_2$ (0.80 g) was dissolved in 200 ml of hexamethylphosphoramide at 140° and cooled, and 79 g of bromobenzene, 54 g of methallyl alcohol and 50 g of sodium bicarbonate added. The mixture was heated under nitrogen while stirring and monitored by GC. After 3 hr the reaction mixture was cooled, 200 ml of toluene was added, and the mixture was extracted twice with 1 l. of water. The toluene solution was then evaporated to give 63 g of liquid which was distilled under nitrogen at 10 mm pressure to give 53 g of 3-phenyl-2-methylpropanal (72% yield).

(1) Conversions and yields may frequently be improved by the addition of triphenylphosphine, e.g., 2.4 g (2 mol/mol $PdCl_2$).

(2) Rates may be increased by the addition of a small amount of a tertiary amine, e.g., 1 g of triethylamine.

(3) Satisfactory results have also been obtained in some cases when the concentration of the palladium catalyst was decreased by a factor of 0.2 and even 0.04.

Registry No.—Iodobenzene, 591-50-4; bromobenzene, 108-86-1; 3-phenylbutanal, 16251-77-7; 2-phenylbutanal, 2439-43-2; 3-phenyl-2-butanone, 769-59-5; 2-methyl-4-phenyl-3-buten-2-ol, 25625-21-2.

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Hydroboration of Monoterpene Alcohols

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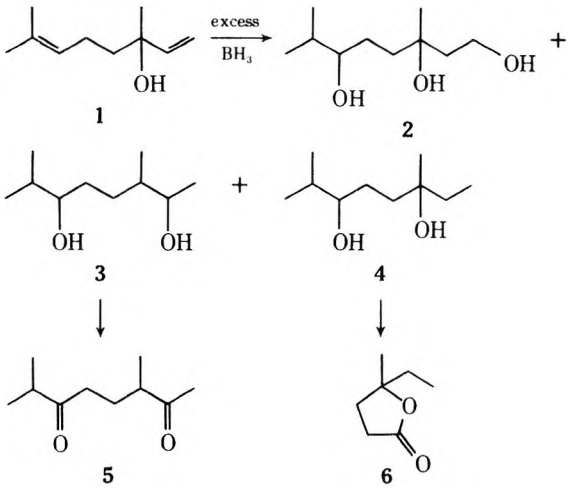
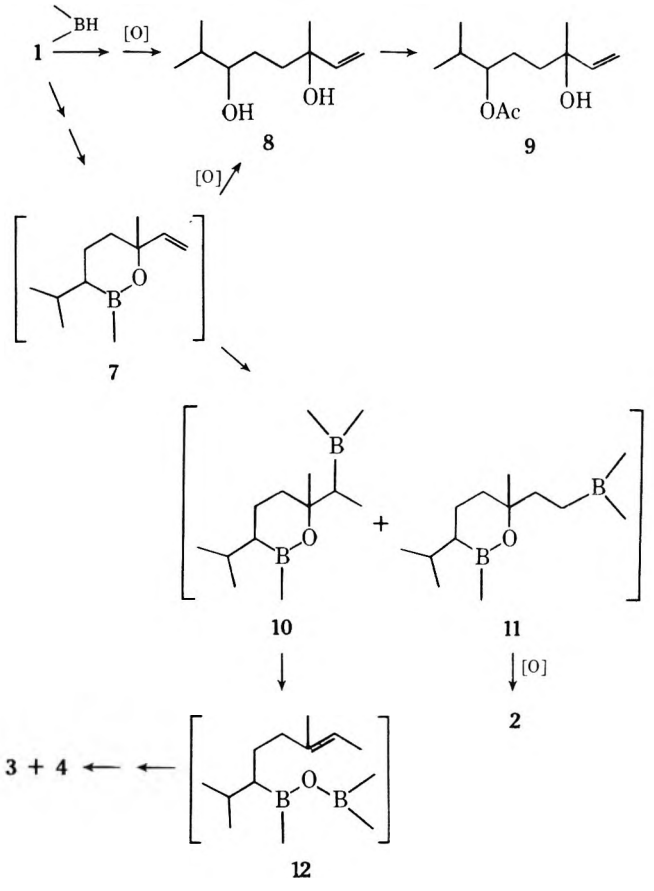
The reaction of linalool (**1**) with excess borane in tetrahydrofuran at ambient temperature affords 3,7-dimethyl-2,6-octanediol (**3**) and 3,7-dimethyl-1,3,6-octanetriol (**2**), while treatment of **1** with 0.67 equiv of borane produces 3,7-dimethyl-1-octen-3,6-diol (**8**). Hydroboration of linalool (**1**) with disiamylborane yields 3,7-dimethyl-6-octen-1,3-diol (**13**). The reaction of geraniol (**15**) or citral (**14**) with borane in THF yields after oxidation a mixture of **2** and 3,7-dimethyl-1,2,6-octanetriol (**18**). Distillation of the intermediary boranes yields 22% of 8-isopropyl-5-methyl-1-bora-2-oxabicyclo[3.3.0]octane (**16**). The remainder of the organoboranes undergo β-elimination upon heating to afford, after oxidation, 3,7-dimethyl-1-octen-6-ol (**20**) and 3,7-dimethyl-1,6-octanediol (**21**).

Cornforth[1] has reported that the hydroboration–oxidation of linalool (**1**) results in the formation of 30% of an unidentified diol in addition to 60% of 3,7-dimethyl-1,3,6-octanetriol (**2**), even when an excess of borane is used. We have confirmed these observations using a 50% excess of borane in THF and find that the diol is a 4:1 mixture of 3,7-dimethyl-2,6-octanediol (**3**) and 3,7-dimethyl-3,6-octanediol (**4**). Jones oxidation of the diol mixture afforded 3,7-dimethyl-2,6-octanedione (**5**) and 4-methyl-4-hydroxyhexanoic acid lactone (**6**).[2]

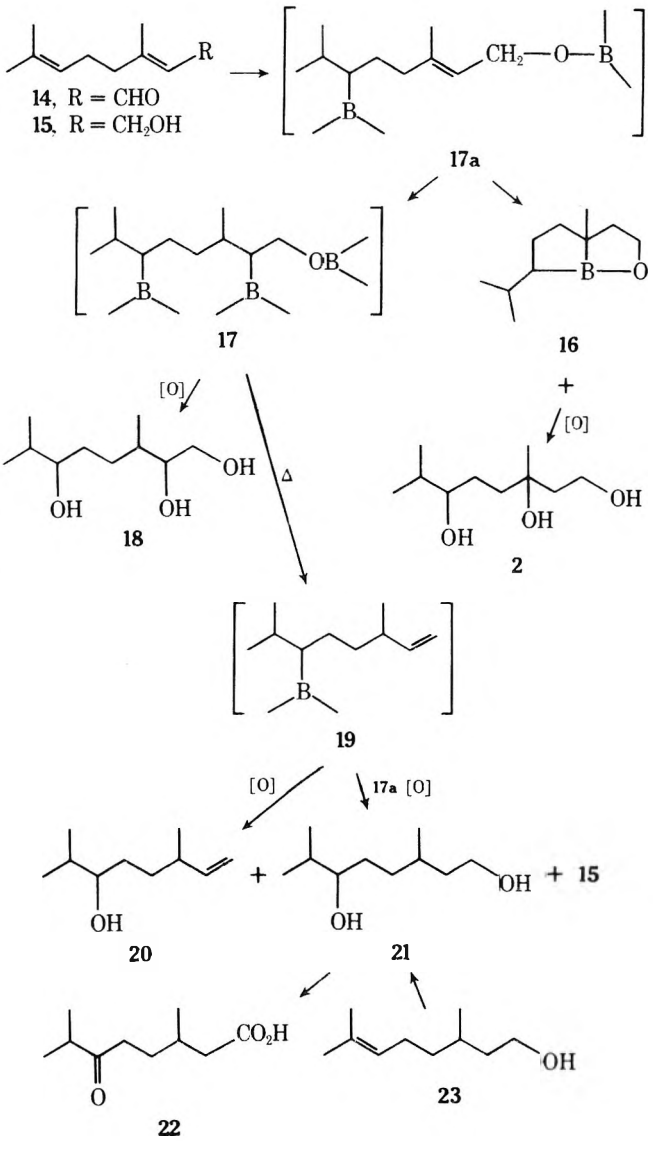
In order to gain an insight into the formation of diols **3** and **4**, linalool (**1**) was treated with 0.67 equiv of borane. Oxidation afforded recovered linalool (28%), triol **2** (9%), and 34% of 3,7-dimethyl-1-octene-3,6-diol (**8**) which was converted to the known monoacetate **9**[3] using acetic anhydride and pyridine. The formation of the 3,6-diol **8** to the exclusion of the 1,3-diol **13** is most likely the result of ini-



Scheme I



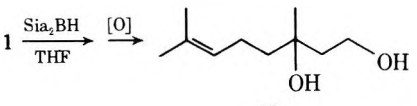
Scheme II



tial reaction of borane with the alcohol group[4] to afford an alkoxyborane which chooses to react in an intramolecular fashion to form oxaborinane **7**, which upon oxidation is converted to diol **8**.

In the presence of excess borane, intermediate **7** is apparently attacked at C-2 and C-1 to give **10**[5] and **11**. Borane **11** is stable and leads ultimately to triol **2**. The β-substituted organoborane **10** presumably undergoes a facile 1,2-elimination to **12**.[6] Reaction of **12** with more borane (boron attack at the secondary carbon atom), or intramolecular B–H addition permitting attachment of boron at the tertiary carbon,[7] leads ultimately to **3** and **4**, respectively (Scheme I).

In contrast to the above-mentioned results, the reaction of linalool (**1**) with the more sterically hindered disiamylborane[9] occurs exclusively at the C-1 position of the vinyl group to afford a 66% yield of 3,7-dimethyl-6-octene-1,3-diol (**13**).



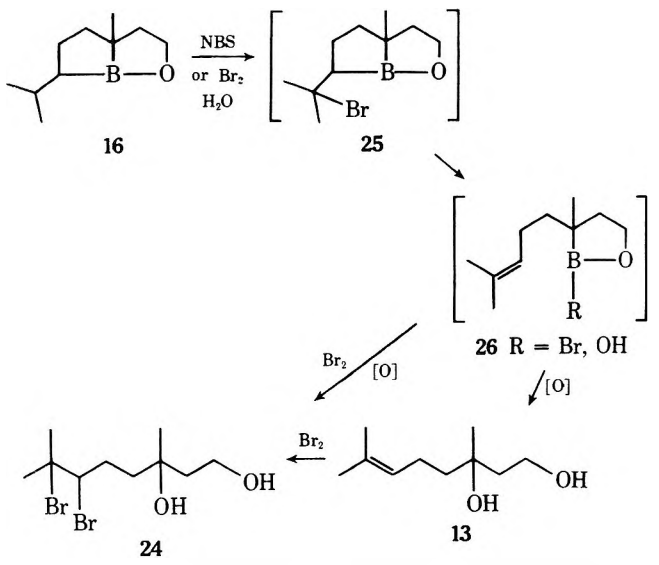
Hydroboration–oxidation of citral (**14**)[10] gave 3,7-dimethyl-1,2,6-octanetriol (**18**) containing 30% of the 1,3,6-triol **2**. Distillation of the alkylboranes formed from the hydroboration of citral (**14**) or geraniol (**15**)[11] with borane in THF afforded a 22% yield of 8-isopropyl-5-methyl-1-bora-2-oxabicyclo[3.3.0]octane (**16**), bp 78° (0.7 mm), which crystallized upon standing, mp 48–51°. Oxidation of **16** afforded 3,7-dimethyl-1,3,6-octanetriol (**2**) (Scheme II).

Oxidation of the nonvolatile organoboranes which remain after the distillation of borabicyclooctane **16** (pot temperatures of 185° were attained) gave 70% (46% yield) of 3,7-dimethyl-1-octen-6-ol (**20**) and 20% (13% yield) of 3,7-dimethyl-1,6-octanediol (**21**), along with ca. 10% of geraniol (**15**). The identity of **20** was confirmed by NMR analysis and by comparison of its ir spectrum with that published by Mitzner.[12] The structure of **21** was confirmed by oxidation to keto acid **22** using the Jones procedure and by comparison of spectral data with an authentic sample prepared via the hydroboration of citronellol (**23**). These products may be explained in terms of a thermal elimination reaction[6] (100–185°) of **17** to **19**. Monoalcohol **20** arises from oxidation of the elimination product **19**. Transfer of boron[13] from **17a** to **19** would afford boranes which upon oxidation would give diol **21** and geraniol (**15**).

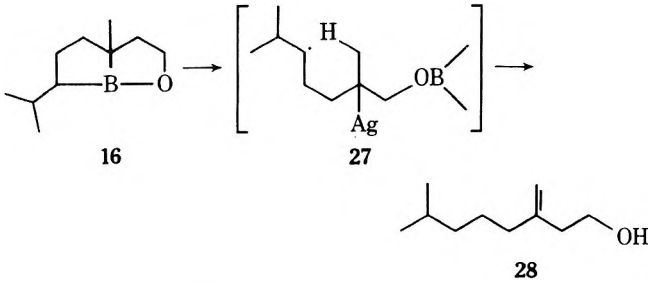
Several unsuccessful attempts were made to apply known methods for carbon–carbon bond formation to borane **16** in an effort to produce the cyclobutane carbon skeleton of grandisol.[14] Reaction of **16** with bromine or NBS in the presence of water[15] followed by oxidation afforded **24** and **13**, respectively. Bromination must take place preferentially at the tertiary carbon affording **25**, which is followed immediately by a β-elimination of the β-haloborane[4,16] to **26**, which in turn goes on to the observed products as shown in Scheme III.

An attempted free-radical coupling[17] of **16** by reaction with silver oxide using a variety of conditions also proved unsuccessful, as disproportionation product **28**[18] accounted for 40% of the material recovered, along with 40% of a mix-

Scheme III



ture of saturated and unsaturated diols and 20% of dimers. No trace of a cyclobutane derivative was found.



Experimental Section[19]

Hydroboration of Linalool (1) with Excess BH_3. To 5.0 g (32 mmol) of linalool (1) in 20 ml of dry THF at 0° under nitrogen was added dropwise 15 ml of 3 *M* BH_3 in THF (45 mmol). The solution was allowed to warm to room temperature overnight and was oxidized by the careful addition of 30 ml of 3 *N* NaOH and 20 ml of 30% H_2O_2 (176 mmol). After 3 hr, the layers were separated and the aqueous phase extracted with ether. The organic solution was washed with water and dried ($MgSO_4$) and the solvent was removed, leaving 4.55 g of viscous liquid (76%). A 3-g portion of the liquid was distilled, yielding two fractions. The first fraction, 0.4 g, bp 120° (0.1 mm), $n^{20}D$ 1.4594, contained 3,7-dimethyl-2,6-octanediol (**3**) contaminated by approximately 20% of the 3,6-diol (**4**): ir 3.0 (OH), 6.75, 7.25, 9.5, 10.15, 10.7, and 11.25 μ; NMR ($CDCl_3$) 0.90 (d, 9, J = 7 Hz, $CHCH_3$), 1.13 (d, 3, J = 6 Hz, $CHCH_3$), 1.16 (s, $HOCCH_3$, compound 4), 1.3–1.9 (m, 6), 2.75 (m, 2, OH), 3.30 (m, 1, CHOH), 3.70 ppm (m, 1, $HOCHCH_3$).

The second fraction, 2.0 g, bp 135° (0.1 mm), contained 70% of 3,7-dimethyl-1,3,6-octanetriol (**2**) and 30% of diol **3** by NMR analysis. The residue, 0.5 g, was pure triol **2**: $n^{20}D$ 1.4689; ir 3.0, 8.8, 9.5, and 9.9 μ; NMR ($CDCl_3$) 0.91 [d, 6, J = 6 Hz, $CH(CH_3)_2$], 1.21 (s, 3, $HOCCH_3$), 1.3–2.0 (m, 7), 3.30 (m, 1, CHOH), 3.80 (t, 2, J = 6 Hz, CH_2OH), 4.5 ppm (m, 3, OH).

Oxidation of Diols 3 and 4 with Jones Reagent. A few drops of diols **3** and **4** were dissolved in 5 ml of acetone and titrated with Jones reagent at room temperature. Isopropyl alcohol and ether were added and the liquid was decanted, washed with water and sodium bicarbonate solution, and dried ($MgSO_4$). The solvents were removed, affording a nonviscous liquid consisting of two components which were separated by thin layer chromatography (50% ether–pentane). 3,7-Dimethyl-2,6-octanedione (**5**), 70% of the crude mixture as determined by NMR analysis, showed R_f 0.60; ir 5.80 (C=O), 6.85, 7.35, 8.05, and 8.6 μ; NMR ($CDCl_3$) 1.08 [d, 6, J = 7 Hz, $CH(CH_3)_2$], 1.10 (d, 3, $CHCH_3$), 1.80 (m, 2, CH_2), 2.12 (s, 3, $COCH_3$), 2.35–2.75 ppm (m, 4). 4-Methyl-4-hydroxyhexanoic acid lactone (**6**), 25% by NMR, displayed R_f 0.35; ir 5.65 (C=O), 6.85, 7.25, 8.08, 8.6, 8.85, 9.1, 9.45, and 10.70 μ; NMR ($CDCl_3$) 0.97 (t, 3, J = 7.5 Hz, CH_2CH_3), 1.37 (s, 3, CH_3), 1.71 (q, 2, J = 7.5 Hz, CH_2CH_3), 1.9–2.3 (m, 2, CH_2), 2.60 ppm (m, 2, CH_2CO); mass spectrum[20] *m/e* (rel intensity) 128 (1), 113 (14), 99 (82), 84 (9), 73 (18), 71 (15), 69 (22), 57 (18), 56 (22), 55 (25), 43 (100), 42 (10), 41 (25), 39 (17).

Preparation of 3,7-Dimethyl-1-octene-3,6-diol (8). To 10.0 g (65 mmol) of linalool (**1**) in 40 ml of dry THF was added dropwise at 0° 14.6 ml (43.8 mmol) of 3 *M* BH_3 in THF. After stirring overnight at room temperature, oxidation and work-up were effected in the usual manner. Distillation afforded 2.8 g (28%) of recovered linalool (**1**), bp 48–70° (0.2 mm), and 3.8 g (34% yield) of a viscous oil, bp 80° (0.1 mm), identified as 3,7-dimethyl-1-octene-3,6-diol (**8**): ir 3.0 (OH, intensity ≃ to CH), 6.1 w (C=C); NMR ($CDCl_3$) 0.90 [d, 6, J = 6 Hz, $CH(CH_3)_2$], 1.27 (s, 3, $HOCCH_3$), 1.35–1.80 (m, 5), 3.32 (m, 3, OH and CHOH) or 3.28 (m, 1, CHOD with D_2O), 4.86–5.38 (m, 2, $CH{=}CH_2$), 5.65–6.20 ppm (m, 1, $CH{=}CH_2$). The residue, 0.9 g (9%), contained 3,7-dimethyl-1,3,6-octanetriol (**2**) by ir analysis.

The monoacetate **9**, prepared by heating 700 mg of diol **8** with 1.2 ml of pyridine and 550 mg of acetic anhydride at 80° for 1 hr, showed $n^{20}D$ 1.4490, and ir and NMR spectra consistent with those reported by Demole and Enggist.[3]

Preparation of 3,7-Dimethyl-6-octene-1,3-diol (13). To 16.9 ml (11.2 g, 160 mmol) of 2-methyl-2-butene in 50 ml of dry THF was added 26.6 ml of 3 *M* BH_3 in THF (80 mmol). The solution was stirred at ambient temperature for 2 hr, followed by the addition of 5.0 g (32 mmol) of linalool (**1**) at 0°. The reaction mixture was stirred for 0.5 hr at 0° and then for 2.5 hr at 25°. After oxidation and work-up, distillation afforded 1.8 g (36%) of unreacted linalool (**1**), bp 48° (0.1 mm), and 2.1 g (38%) of 3,7-dimethyl-6-octene-1,3-diol (**13**): bp 100° (0.1 mm); $n^{20}D$ 1.4690 [lit.[21] bp 149–150° (10 mm), $n^{20}D$ 1.4737]; ir 3.0 (OH), 6.9, 7.3, 9.0, and 9.5 μ; NMR ($CDCl_3$) 1.22 (s, 3, $HOCCH_3$), 1.35–2.3 (m, 6), 1.62 and 1.69 [s, 6, $C{=}C(CH_3)_2$], 3.5 and 3.9 (m, 2, OH, disappears with D_2O), 3.83 (t, 2, J = 6 Hz, CH_2OH), 5.13 ppm (m, 1, C=CH); mass spectrum *m/e* (rel intensity) 170 (2), 154 (19), 121 (37), 109 (41), 95 (25), 81 (35), 71 (39), 69 (93), 68 (20), 67 (30), 59 (20), 55 (42), 43 (100), 41 (88), 39 (31), 18 (29). The residue (0.2 g) appeared to be mainly 1,3,6-triol **2**.

Hydroboration–Oxidation of Citral (14). To 5.0 g (33 mmol) of citral (**14**) in 30 ml of dry THF at 0° was added 11 ml of 3.0 *M* BH_3 in THF (33 mmol) and the reaction mixture was stirred under a nitrogen atmosphere. Aliquots withdrawn from the reaction mixture and hydrolyzed indicated that 7.6% of the hydride remained after 5 min, and only 0.9% after 3 hr. The boranes were oxidized by the usual procedure to give 5.3 g of viscous oil. Distillation afforded 0.5 g of geraniol–nerol (**15**), bp 65–95° (0.2 mm), an intermediate fraction, 1.0 g, bp 100–140° (0.2 mm), and 2.5 g (63% yield) of a very viscous colorless liquid, determined by NMR analysis to contain 30% of 3,7-dimethyl-1,3,6-octanetriol (**2**) and 70% of the corresponding 1,2,6-triol **18**: bp 142° (0.1 mm); $n^{20}D$ 1.4705; ir 2.98 μ (OH, stronger than CH); NMR ($CDCl_3$) 0.90 (d, 9, J = 6 Hz, $CHCH_3$), 1.22 (s, $HOCCH_3$, triol **2**), 1.3–1.9 (m, 6), 3.2–4.0 ppm (m, 7).

Anal. Calcd for $C_{10}H_{22}O_3$: C, 63.12; H, 11.66. Found: C, 63.41; H, 11.60.

The presence of a 1,2-diol was confirmed by a positive periodate test.

Preparation of 8-Isopropyl-5-methyl-1-bora-2-oxabicyclo[3.3.0]octane (16). To 110 ml of 3.0 *M* BH_3 in THF (0.33 mol) and 200 ml of dry THF at 0° was added over 1 hr 50 g (0.325 mol) of geraniol (**15**, a 7:3 mixture of *E* and *Z* isomers) in 70 ml of THF. The solution was allowed to warm to room temperature over 2 hr followed by the addition of 3 ml of methanol to destroy excess hydride. Removal of solvent under reduced pressure and distillation afforded two fractions which distilled slowly at pot temperatures between 135 and 185°. The first fraction was borane **16**, a very viscous, air-sensitive oil, 11.70 g (22% yield), bp 78° (0.7 mm), which formed white crystals upon standing, mp 48–51°: ir ($CDCl_3$) 3.42 (CH), 7.4 br, and 12.6 μ; NMR ($CDCl_3$) 0.90 (m, 9), 1.2–2.3 (m, 8), and 3.6–4.2 ppm (m, 2). A portion of the crystalline organoborane **16** was oxidized by the usual procedure yielding 3,7-dimethyl-1,3,6-octanetriol (**2**), $n^{20}D$ 1.4670.

The second fraction, 3.72 g (7%), bp 120° (0.8 mm), was a nonviscous liquid which displayed ir (neat) 3.1, 3.4, 6.1 w, 6.85, 7.0–8.5, 10.01, and 11.05 μ; NMR ($CDCl_3$) 0.92 (m, 9), 1.1–2.3 (m, 8), 3.5–6.0 ppm (m, 2). A 1.0-g portion of the liquid was oxidized by the standard procedure, yielding 1.0 g of a material which was separated by preparative thin layer chromatography (60% ether–pentane) to afford 40% of 3,7-dimethyl-1-octen-6-ol (**20**), R_f 0.80: ir 3.0 (OH), 6.1, 10.05, and 11.0 μ (identical with the spectrum published

by Mitzner[12]); NMR ($CDCl_3$) 0.91 [d, 6, J = 6 Hz, $CH(CH_3)_2$], 1.0 (d, 3, J = 6 Hz, $CHCH_3$), 1.3–2.2 (m, 6), 3.35 (m, 1, CHOH), 4.7–5.1 (m, 2, $CH{=}CH_2$), 5.4–6.0 ppm (m, 1, $CH{=}CH_2$), and ca. 50% of an unidentified material, R_f 0.27, which gave a negative periodate test and was tentatively identified as a diol on the basis of its R_f value: ir 3.0 (OH, weaker than CH) and 9.50 μ; NMR ($CDCl_3$) 0.89 (d, 3, J = 6 Hz), 0.90 (d, 3, J = 6.5 Hz), 1.1–1.9 (m, 10), 3.0–4.0 ppm (m, 4).

The nonvolatile alkylborane residue (**17**, 39 g) which had been heated to 185° during the distillation of **16** was dissolved in 150 ml of THF, oxidized with alkaline hydrogen peroxide, and worked up by the usual procedure. Distillation afforded 16.7 g (46% yield) of **20**, bp 70° (1.0 mm), n^{20}D 1.4538, which was found to be contaminated by ca. 10% of geraniol (**15**) by GLC analysis using a 150-ft OS-138 column at 185°. A second fraction, 6.0 g (13% yield), bp 102–106° (0.1 mm), n^{20}D 1.4638, was purified by thin layer chromatography (60% ether–pentane) to give pure 3,7-dimethyl-1,6-octanediol (**21**), R_f 0.29: ir 3.0 (OH, weaker than CH), 6.85, 7.25, and 9.50 μ (CH_2O); NMR ($CDCl_3$) 0.90 (d, 9, $CHCH_3$), 1.1–1.8 (m, 8), 3.28 (m, 1), 3.64 ppm (t, 3, J = 6 Hz, CH_2OH).

Anal. Calcd for $C_{10}H_{22}O_2$: C, 68.91; H, 12.73. Found: C, 68.16; H, 12.72.

A few drops of diol **21** were dissolved in 5 ml of acetone and titrated with Jones reagent. The usual work-up gave a pale yellow oil identified as 3,7-dimethyl-6-oxooctanoic acid (**22**): ir 2.8–4.0 and 5.85 μ; NMR ($CDCl_3$) 0.97 (d, 3, J = 6 Hz, $CHCH_3$), 1.08 [d, 6, J = 7 Hz, $CH(CH_3)_2$], 1.4–1.8 (m, 3), 2.0–2.8 ppm (m, 5).

Preparation of 3,7-Dimethyl-1,6-octanediol (21). To 5.0 g (32 mmol) of citronellol (**23**) in 20 ml of THF at 0° under nitrogen was added dropwise 10.7 ml of 3.0 M BH_3 (32 mmol). The solution was stirred at room temperature for 2 hr, cooled to 0°, and oxidized by the usual procedure. Work-up and distillation yielded 4.0 g (72% yield) of **21**, bp 105° (0.1 mm), n^{20}D 1.4615, whose ir and NMR spectra were identical with those of the sample of **21** described above.

Reaction of 16 with Bromine. To a mixture of 1.76 g (10.6 mmol) of **16** in 20 ml of methylene chloride and 7.5 ml of H_2O at 0° under nitrogen was added 0.65 ml (1.90 g, 11.9 mmol) of bromine. The solution was allowed to warm to room temperature, and after 7 min the bromine color had dissipated. The mixture was again cooled to 0° and 16 ml of 3 N NaOH was added followed by 15 ml of ethanol and 3.5 ml of 30% H_2O_2 (32.6 mmol). The solution was stirred at 0° for 0.5 hr and then refluxed for 1.5 hr. The organic layer was separated, washed with saturated salt solution, and dried ($MgSO_4$) and the solvents removed, leaving 2.40 g of viscous yellow oil containing 75% of 3,7-dimethyl-6,7-dibromo-1,3-octanediol (**24**) by NMR and thin layer chromatographic analyses.

A pure sample of **24** was obtained by thin layer chromatography: ir 3.0 (OH), 3.4, 6.84, 7.30, 9.1, and 9.4 μ; NMR ($CDCl_3$) 1.29 (s, 3, $HOCCH_3$), 1.5–2.5 (m, 6), 1.83 and 2.00 [s, 6, $BrC(CH_3)_2$], 2.71 (s, 2, OH), 3.92 (t, 2, J = 6 Hz, CH_2OH), 4.1–4.3 ppm (m, 1, CHBr). The NMR and ir spectra were identical with those of an authentic sample of **24** prepared by the addition of bromine to **13**.

Anal. Calcd for $C_{10}H_{20}O_2Br_2$: C, 36.17; H, 6.07; Br, 48.12. Found: C, 35.85; H, 5.61; Br, 47.90.

Reaction of 16 with *N*-Bromosuccinimide. To 1.0 g (6.02 mmol) of borabicyclooctane **16** in 20 ml of CCl_4 under nitrogen was added 1.07 g (6.02 mmol) of NBS. The mixture was refluxed for 1 hr and cooled to 0°, and 10 ml of water was added. After stirring for 10 min, 6 ml of 3 N NaOH, 15 ml of ethanol, and 2.5 ml of 30% H_2O_2 were added, and the mixture was refluxed for 1 hr. The aqueous phase was extracted with CCl_4, the organic solution was washed (NaCl solution) and dried ($MgSO_4$), and the solvent was removed, leaving 0.8 g of yellow liquid. The products were separated by preparative thin layer chromatography (40% ether–pentane). The first band, R_f 0.88 (20%), appears to be a mixture of partially oxidized organoboranes as the compound burns with a bright green flame characteristic of boron. The second band, R_f ≤0.1, was reeluted using a 2:3:2 mixture of methanol, ether, and pentane to yield 50% of 3,7-dimethyl-6-octene-1,3-diol (**13**) containing a minor impurity which displayed an isopropyl doublet at 0.90 ppm. The NMR and ir spectra of **13** were identical with those of an authentic sample prepared by the hydroboration of linalool (**1**) with disiamylborane.

Reaction of Borabicyclooctane 16 with Silver Oxide. To an aqueous suspension of alkaline silver oxide (25 mmol) under nitrogen at 0° was added 1.8 g (10.8 mmol) of **16** in 12 ml of THF. The brown color of the silver oxide turned gray-black as silver formed. The mixture was stirred at ambient temperature for 2.5 hr, the silver was removed by filtration, and 5 ml of 30% hydrogen peroxide was added. The mixture was refluxed for 1 hr, cooled, and extracted with pentane. The organic solvents were removed, leaving 1.1 g of yellow oil which was distilled affording (a) 0.4 g, bp 56–60° (0.5 mm), n^{20}D 1.4541; (b) 0.4 g, bp 96–100° (0.5 mm), n^{20}D 1.4625; and (c) 0.2 g of residue. GLC of the low-boiling fraction on a OS-138 capillary column indicated that 80% of the fraction was comprised of one compound. A pure sample of 7-methyl-3-methylene-1-octanol (**28**) was obtained by GLC using a 12-ft DC-200 column at 200° (retention time 10 min) and showed ir 3.02, 6.08, 6.82, 7.25, 7.32, 9.55, and 11.25 μ; NMR ($CDCl_3$) 0.87 [d, 6, J = 6 Hz, $CH(CH_3)_2$], 1.1–2.1 (m, 8), 2.30 (t, 2, J = 6.5 Hz, $C{=}C{-}CH_2CO$), 3.68 (t, 2, J = 6.5 Hz, $-CH_2OH$), and 4.85 ppm (2, $-C{=}CH_2$). The mass spectrum showed a molecular ion at m/e 156.

The higher boiling fraction was a viscous oil which appeared to be a mixture of saturated and unsaturated diols as indicated by ir and NMR analysis.

Registry No.—**1**, 78-70-6; **2**, 57196-95-9: **3**, 31206-60-7; **4**, 57196-96-0; **5**, 57196-97-1; **6**, 2865-82-9; **8**, 57196-98-2; **13**, 27415-10-7; **14**, 5392-40-5; (*E*)-**15**, 106-24-1; (*Z*)-**15**, 106-25-2; **16**, 57196-99-3; **17**, 57197-00-9; **18**, 57197-01-0; **20**, 18479-56-6; **21**, 53067-10-0; **22**, 589-60-6; **23**, 106-22-9; **24**, 57197-02-1; **28**, 57197-03-2; 2-methyl-2-butene, 513-35-9; bromine, 7726-95-6; *N*-bromosuccinimide, 128-08-5.

References and Notes

(1) R. H. Cornforth, J. W. Cornforth, and G. Popják, *Tetrahedron*, **18**, 1351 (1962).
(2) Lactone **6** may be formed via dehydration and oxidation of a γ-lactol[3] formed from the anticipated hydroxy ketone.
(3) E. Demole and P. Enggist, *Helv. Chim. Acta*, **54**, 456 (1971).
(4) H. C. Brown and O. J. Cope, *J. Am. Chem. Soc.*, **86**, 1801 (1964).
(5) Brown has observed that the hydroboration of allyl alcohol occurs with 24% of the attack by boron at the 2 position.[4]
(6) H. C. Brown and R. M. Gallivan, *J. Am. Chem. Soc.*, **90**, 2906 (1968), and references cited therein.
(7) An intermolecular addition of B–H to **12** is not likely to take place at the tertiary carbon, since diborane is known to attack the tertiary position of 2-methyl-2-butene only to the extent of 2%.[8]
(8) H. C. Brown, "Boranes in Organic Chemistry", Cornell University Press, Ithaca, N.Y., 1972, p 265.
(9) H. C. Brown and G. Zweifel, *J. Am. Chem. Soc.*, **82**, 3222 (1960).
(10) Citral is a 2:1 mixture of the *E* and *Z* isomers geranial and neral.
(11) Geraniol and nerol are the *E* and *Z* isomers of 3,7-dimethyl-2,6-octen-1-ol, commonly referred to as geraniol. Varying the relative proportions of the isomers had little effect on the yield of **16**.
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(18) Compound **28** can be viewed as arising via an intramolecular hydrogen transfer in a radical such as **27**.
(19) All melting and boiling points are uncorrected. Refractive indices were determined on a Bausch and Lomb Abbe-3L refractometer and are uncorrected. NMR spectra were determined with Varian Associates A-60 and Perkin-Elmer R32 spectrometers. Infrared spectra were recorded on a Perkin-Elmer Infracord spectrometer. Mass spectra were recorded at 70 eV on a Hitachi RMU-6A mass spectrometer. Thin layer chromatography was carried out using 20 × 20 cm plates (Brinkman silica gel PF-254, 1 mm thickness). Microanalyses were performed by Dr. C. S. Yeh and associates.
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Thallium in Organic Synthesis. XLII. Direct Oxidation of 4-Substituted Phenols to 4,4-Disubstituted Cyclohexa-2,5-dienones Using Thallium(III) Nitrate[1]

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Oxidation of hydroquinones with 1 equiv, and 2,6-disubstituted phenols with 2 equiv, of thallium(III) nitrate (TTN) in methanol gives the corresponding *p*-benzoquinones in high yield. Oxidation of a variety of 4-alkyl- and 4-alkoxyphenols with 1 equiv of TTN in either methanol or trimethyl orthoformate (TMOF), on the other hand, gives 4-alkyl-4-methoxy- and 4,4-dimethoxycyclohexa-2,5-dienones in moderate to excellent yield. Formation of cyclohexadienones under these conditions is postulated to proceed via ipso thallation.

There have been a number of reports during the last few years on the oxidations of phenols with thallium(III) salts, and examination of the results indicates that the type of product which is formed depends both on the nature of the thallium reagent employed and on the structure of the phenol. Mel'nikov and Gracheva found that thallium(III) chloride oxidized hydroquinone to a mixture of *p*-benzoquinone and quinhydrone,[2] while Kabbe claimed that conversion of hydroquinone into *p*-benzoquinone was complete within 3 min when thallium(III) acetate was used.[3] This claim has since been shown to be specious,[4] but it has been established that hydroquinones are oxidized to *p*-benzoquinones almost instantaneously and in excellent yield when the more powerful oxidant thallium(III) trifluoroacetate (TTFA) is used.[5] The same reagent has been shown to oxidize a wide variety of 4-substituted phenols HOArX (X = *t*-C_4H_9, Cl, Br, I, CH_3COO) to the corresponding *p*-benzoquinones, and the synthetic utility, scope, and limitations of these processes have been defined.[5] The use of thallium(III) oxide in ethanol for the conversion of certain types of hydroquinone monesters into *p*-benzoquinones has also been described.[6]

Oxidation of 4-substituted phenols to 4,4-disubstituted cyclohexa-2,5-dienones by thallium(III) was first reported by Hecker and Lattrell, who succeeded in isolating quinol ethers and acetates in low yields from the boron trifluoride catalyzed reactions of a number of 4-alkylphenols with thallium(III) acetate in methanol and acetic acid, respectively.[7] Coombs and Jones subsequently showed that oxidation of estrone with TTFA gave 10β-trifluoroacetoxy-19-norandrost-1,4-diene-3,17-dione in high yield,[8] while, more recently, Yamada et al. have converted 5-hydroxyindan and 6-hydroxytetralin into the corresponding *p*-quinols in good yield by use of thallium(III) perchlorate in aqueous acid.[9] Analogous reactions have been reported by Schwartz et al.[10,11] and by Kupchan and Liepa,[12] who have utilized TTFA as a reagent for intramolecular oxidative phenol coupling.

With the exception of the one detailed investigation noted[5] above, no serious attempt has been made either to study the scope and limitations of these oxidations or to postulate reasonable mechanisms for the various conversions. Few of the phenols which have been oxidized are structurally simple, and the range of substrates which has been examined is very restricted; consequently, it is impossible to assess the synthetic utility of these oxidations as applied to simple monocyclic phenols.

The efficacy of thallium(III) salts TlX_3 as oxidants is known to be directly related to the nature of the anionic group X, and it has been adequately demonstrated for a wide range of reactions that the oxidizing power of the commonly available and easily handled thallium(III) salts is in the order nitrate > trifluoroacetate > acetate > chloride.[13] We now report the results of a detailed investigation of the reactions of a wide range of phenols with thallium(III) nitrate (TTN). These show that, as expected, oxidation of hydroquinones to *p*-benzoquinones by TTN in methanol takes place rapidly and proceeds in excellent yield. Of greater interest are the observations that 2,6-disubstituted phenols are also smoothly oxidized to *p*-benzoquinones, while many 4-alkyl- and 4-alkoxyphenols can readily be converted in excellent yield into 4-alkyl-4-methoxy- and 4,4-dimethoxycyclohexa-2,5-dienones, respectively.

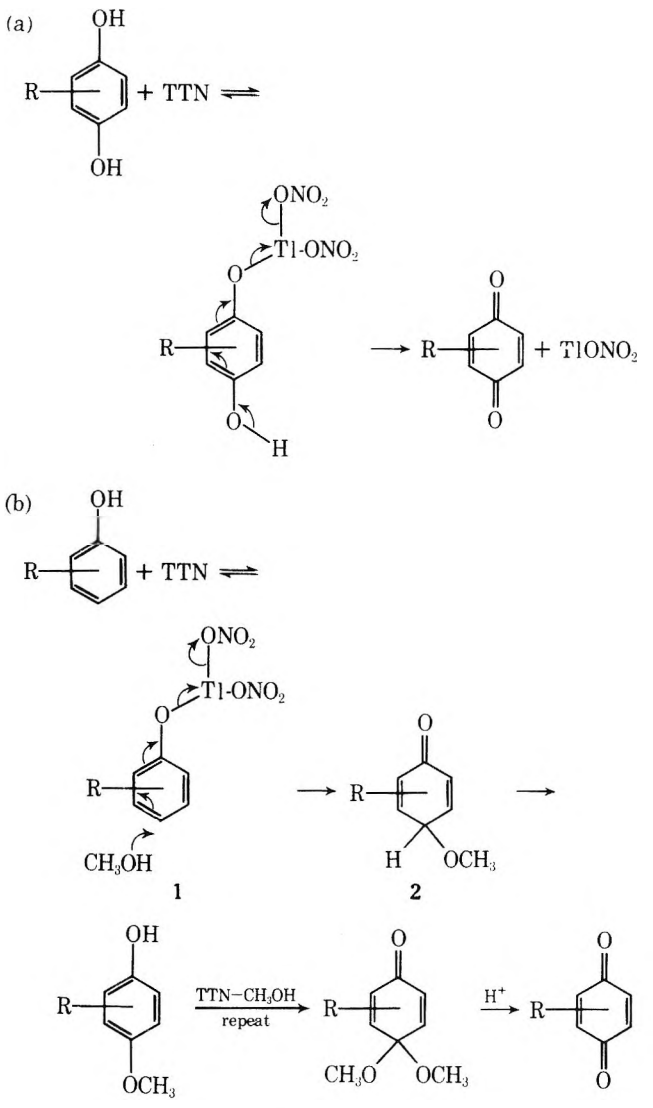
Discussion

Treatment of hydroquinone with 1 equiv of TTN in methanol resulted in almost instantaneous oxidation to give *p*-benzoquinone in 78% yield. 2-*tert*-Butyl-, 2,5-di-*tert*-butyl-, 2-methyl-, and 2,3,5-trimethylhydroquinone reacted analogously and the corresponding *p*-benzoquinones were isolated in 88, 96, 89, and 98% yield, respectively. Oxidation of a number of 2,6-disubstituted phenols with 2 equiv of TTN in methanol also proceeded smoothly, and again the corresponding *p*-benzoquinones were formed. Thus, 2,6-di-*tert*-butylphenol was converted into 2,6-di-*tert*-butyl-*p*-benzoquinone in 83% yield, 2,6-diisopropylphenol was smoothly oxidized to 2,6-diisopropyl-*p*-benzoquinone in 77% yield, 2,6-dimethylphenol gave a mixture of 2,6-dimethyl-*p*-benzoquinone (72%) and 3,3′,5,5′-tetramethyldiphenoquinone (6%), and 2,6-dimethoxyphenol gave 2,6-dimethoxy-*p*-benzoquinone in 80% yield.

In mechanistic terms these oxidations are, at first sight, apparently straightforward. A plausible mechanism for the oxidation of hydroquinones is outlined in Scheme I (a) which involves (1) ligand exchange between one of the phenolic hydroxyl groups and TTN to give an aryloxythallium(III) intermediate, and (2) oxidation of the aromatic ring as shown, with concomitant reduction of thallium(III) to thallium(I). A related mechanism can be postulated for the oxi-

dation of 2,6-disubstituted phenols [Scheme I (b)]. We now believe, however, that these mechanisms, together with

Scheme I

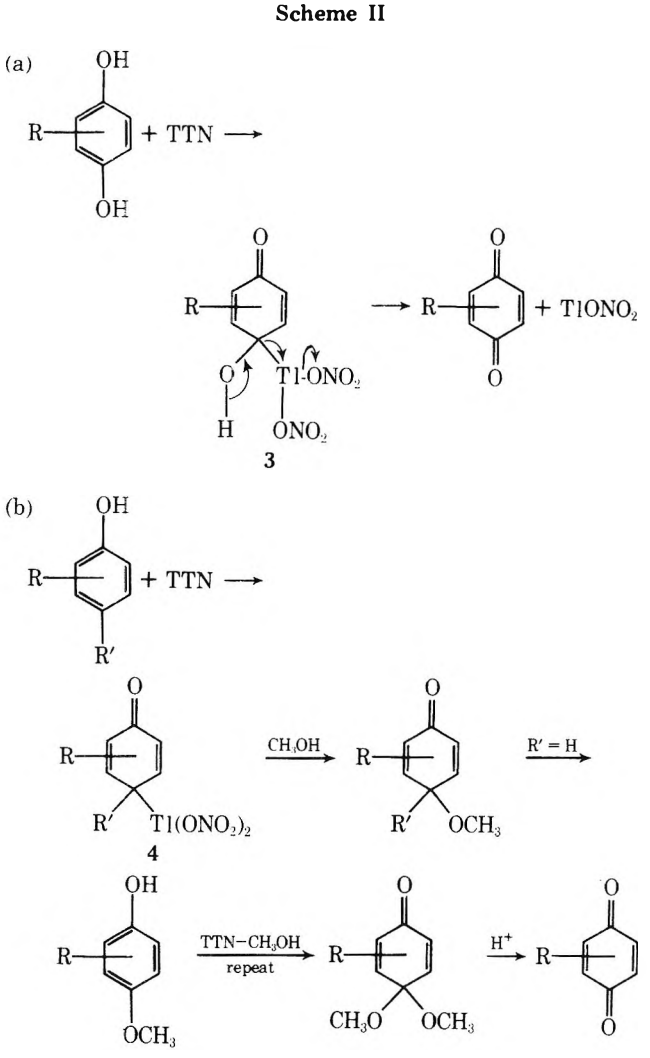


that postulated previously for the oxidation of 4-*tert*-butylphenols with TTFA,[5] are incorrect.

There are three major objections which can be raised with respect to the reactions postulated in Scheme I. (1) There is no precedent for ligand exchange between phenols and TTN and all attempts to prepare $ArOTl(ONO_2)_2$ compounds either by ligand exchange processes or by metathetical reactions have proved totally unsuccessful.[14] On the contrary, it can readily be demonstrated that phenol reacts smoothly with TTN at low temperature to give the expected product of electrophilic aromatic thallation, 4-hydroxyphenylthallium dinitrate. This compound can be isolated and characterized spectroscopically, and readily gives 4-iodophenol on treatment with aqueous potassium iodide.[15] (2) Ligand exchange between 2,6-disubstituted phenols, particularly 2,6-di-*tert*-butylphenol, and a bulky thallium(III) salt is highly unlikely on steric grounds; yet these phenols are smoothly and rapidly oxidized by both TTN and TTFA. (3) The reaction 1 → 2 in Scheme I (b) is *nucleophilic* attack on a phenol derivative, for which again there is no sound precedent. Schwartz et al. tentatively suggested in 1973 that reaction of phenols with TTFA might involve generation of a phenoxonium ion ArO^+,[10] but there is no evidence to substantiate facile formation of these high-energy intermediates under such mild reaction conditions.

Simple alternative mechanisms for the oxidations of hydroquinones and phenols with TTN are outlined in Scheme II. That is, the initial step is ipso thallation; decomposition

Scheme II

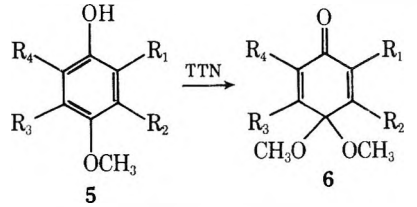


of intermediates of the type **3** in the manner shown is unexceptional (path a), while nucleophilic displacement of the thallium substituent from the intermediate cycloalkylthallium dinitrate **4** by methanol (path b) is a type of reaction for which there is abundant precedent in organothallium chemistry.[13] Ipso substitution is now a well-recognized phenomenon,[16] and 4,4-disubstituted cyclohexa-2,5-dienones have frequently been obtained as the products of electrophilic aromatic substitution reactions (especially nitration and halogenation) of phenols and their derivatives. The major difference between ipso thallation and ipso nitration or halogenation is that in the former case the initially formed organometallic compounds would be expected to be highly unstable, and hence the products which are isolated are those derived from a secondary reaction, namely attack of a nucleophilic species at the developing electrophilic center created by heterolysis of the very weak C–Tl bond. Hence treatment of 4-unsubstituted phenols with TTN would not normally be expected to give stable arylthallium derivatives but, provided sufficient oxidant were used, should lead to quinones, i.e., the situation generally found in practice.

A further logical consequence of the ipso-thallation mechanism is that oxidation of 4-substituted phenols with

1 equiv of TTN in methanol should, depending on the electronic nature of the 4-substituent group, lead directly to 4-methoxy 4-substituted cyclohexa-2,5-dienones. This proved to be the case, and from examination of the reactions of a wide range of substituted phenols we have been able to define the scope and limitations of this synthetic method. Moreover, the results obtained provide indirect evidence that the reaction proceeds via an electrophilic substitution process.

Thus, the 4-methoxyphenols **5a–h** were smoothly converted into the 4,4-dimethoxycyclohexa-2,5-dienones **6a–h** on treatment with TTN in either methanol or a mixture of methanol and trimethyl orthoformate (TMOF).[17] All of

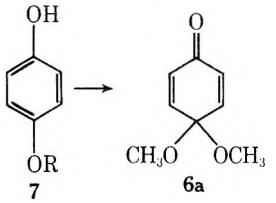


5 **6**

a, $R_1 = R_2 = R_3 = R_4 = H$, 97%
b, $R_1 = CH_3$; $R_2 = R_3 = R_4 = H$, 89%
c, $R_1 = R_4 = CH_3$; $R_2 = R_3 = H$, 87%
d, $R_1 = R_4 = t\text{-}C_4H_9$; $R_2 = R_3 = H$, 96%
e, $R_1 = R_4 = H$; $R_2 = R_3 = OCH_3$, 95%
f, $R_1 = H$; $R_2 = R_3 = OCH_3$; $R_4 = COCH_3$, 92%
g, $R_1 = Cl$; $R_2 = R_3 = R_4 = H$, 97%
h, $R_1 = Br$; $R_2 = R_3 = R_4 = H$, 91%

these oxidations proceeded rapidly at temperatures in the range −20 to 0°, and the chromatographically pure cyclohexadienone products were readily isolated from the reaction mixtures.

Attempts were then made to extend this type of oxidation to the preparation of unsymmetrical monoketals of *p*-benzoquinones. Thus, the simple hydroquinone monoethers **7a–f** were treated with TTN under conditions identical with those used for the oxidation of **5a–h**; compounds **7a–d** reacted smoothly, but the product formed in each case was 4,4-dimethoxycyclohexa-2,5-dienone (**6a**). Oxidation of the

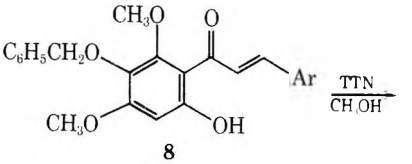


7 **6a**

a, $R = C_2H_5$, 94%
b, $R = CH(CH_3)_2$, 78%
c, $R = (CH_2)_3CH_3$, 91%
d, $R = (CH_2)_6CH_3$, 89%
e, $R = CH_2C_6H_5$, 19%
f, $R = C_6H_5$, 26%

benzyl and phenyl ethers, **7e** and **7f**, gave complex mixtures of products in each case, and again **6a** was formed, albeit in rather low yield. We assume that formation of **6a** in these reactions takes place in two discrete steps, namely initial production of the unsymmetrical ketal followed by rapid thallium(III) induced transketalization,[18] and standard control experiments provided supporting evidence for this hypothesis. Thus, freshly prepared **6a** was recovered unchanged if (1) dissolved in ethanol and the solution allowed to stand overnight at room temperature; (2) dissolved in ethanol containing thallium(I) nitrate and the mixture allowed to stand overnight at room temperature; and (3) dissolved in ethanol and the solution chromatographed on basic alumina (compounds **6a–h** were isolated and purified by chromatography). When, on the other hand, 1.5 mmol of TTN was added to a solution of 10 mmol of **6a** in 5 ml of ethanol and the mixture allowed to stand at room temperature for 10 min, examination of the NMR spectrum of the products obtained after chromatography of the reaction mixture on basic alumina clearly revealed that transketalization had occurred and that some 65–70% of 4,4-diethoxycyclohexa-2,5-dienone had been produced under these conditions.

In contrast to the above results obtained with the simple monoethers of hydroquinone, formation of mixed monoketals of *p*-benzoquinones was observed when 4-alkoxy 3,5-disubstituted phenols were oxidized with TTN. Thus, treatment of the chalcone **8** with TTN at 65° for 30 min gave the mixed ketal **9a** in 36% yield as a stable, yellow, crystalline solid.[19] When the oxidation was allowed to pro-



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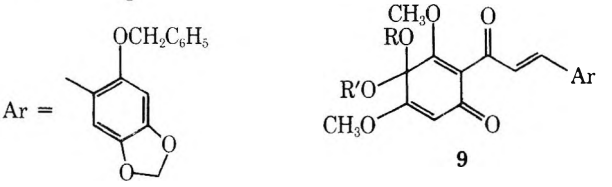
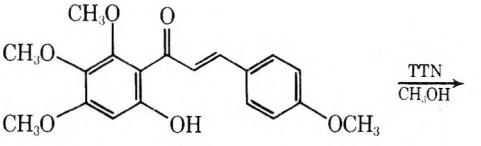


9

a, $R = CH_2C_6H_5$; $R' = CH_3$
b, $R = CH_2C_6H_5$; $R' = H$
c, $R = H$; $R' = CH_3$

ceed for a longer time, however, the initially formed mixed ketal **9a** underwent gradual acid-catalyzed hydrolysis to the hemiketal **9b**, and this compound was isolated in 21% yield after a reaction time of 1 hr. The alternative hemiketal **9c** was prepared in 58% yield by treatment of **9b** with a mixture of methanol and hydrochloric acid. Oxidation of the chalcone **10** with TTN in methanol at 65° also proceeded smoothly to give the hemiketal **11** in 70% yield.



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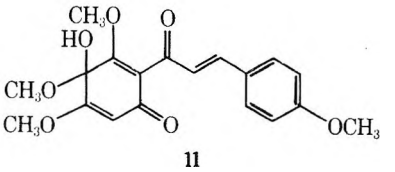
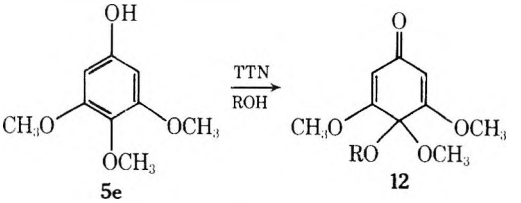


11

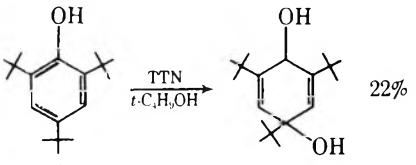
Formation of mixed monoketals and hemiketals in the above chalcone cases is presumably a consequence of steric hindrance both to ketalization and transketalization, and similar results were obtained with a variety of structurally simpler phenols. Thus, oxidation of 3,4,5-trimethoxyphenol (**5e**) with TTN in ethanol, 2-propanol, and *tert*-butyl alco-



5e **12**

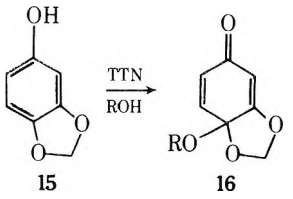
a, $R = C_2H_5$, 30%
b, $R = CH(CH_3)_2$, 29%
c, $R = C(CH_3)_3$, 29%

hol gave the mixed monoketals **12a–c**, respectively. Reaction of 2,4,6-tri-*tert*-butylphenol (**13**) with *tert*-butyl alcohol under the same conditions, on the other hand, gave only the quinol **14**; in this case it is unlikely on steric



13 14

grounds that *tert*-butyl alcohol would readily substitute into the 4 position, and hence water assumes the role of nucleophile (TTN is a trihydrate, and participation of the water of crystallization as a nucleophile has been noted in other reactions involving TTN[20]). Oxidation of 3,4-methylenedioxyphenol (**15**) with TTN in methanol or ethanol gave the mixed monoketals **16a** and **16b**, respectively, pro-

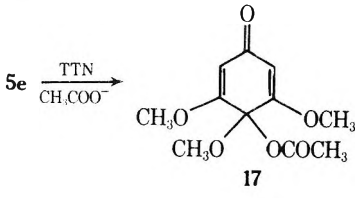


15 16

a. R = CH_3, 45%
b. R = C_2H_5, 59%

vided that the reaction mixtures were worked up immediately after oxidation was complete. These 3-substituted monoketals are considerably less stable than the 3,5-disubstituted compounds **9a** and **12a–c**; if they are allowed to stand in the reaction mixture, which contains nitric acid, or if they are treated with solutions of nitric acid in methanol or ethanol, they are rapidly converted into 2-methoxy- and 2-ethoxy-*p*-benzoquinone, respectively.[21]

We have examined briefly the possibility of utilizing nucleophiles other than alcohols in these oxidations. Treatment of **5e** with TTN and sodium acetate in a mixture of acetic acid and ethyl acetate, for example, gave 3,4,5-trimethoxy-4-acetoxycyclohexa-2,5-dienone (**17**) in poor (19%) yield, while reaction of **13** under the same conditions gave a mixture of the quinol **14** (25%) and the acetate **18** (10%). In



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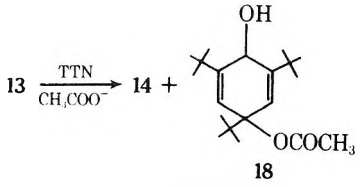
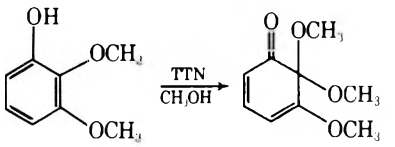


18

view of the low yields encountered in these reactions, and the few nucleophiles other than carboxylate anions which are compatible with TTN, no further effort was expended on these transformations.

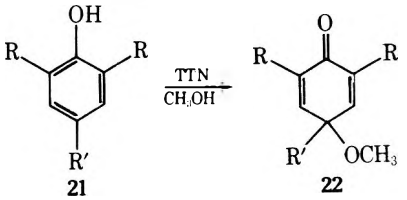
A number of attempts were also made to oxidize 2-methoxyphenols, as there is no simple procedure available for the preparation of 6,6-dimethoxycyclohexa-2,4-dienones. Treatment of 2-methoxyphenol with TTN in methanol gave a complex mixture of products from which no pure materials could be isolated, but oxidation of 2,3-dimethoxyphenol (**19**) under the same conditions gave the expected product **20** in 25% yield. Vanillin, isovanillin, and o-vanillin



19 20

were also smoothly oxidized to cyclohexadienones under the same conditions; these initially formed products could not be isolated in a pure state, however, as they rapidly underwent Diels–Alder cycloaddition reactions to give crystalline dimers.[22]

Following from the above results with methoxyphenols, the reactions of TTN with phenols carrying a substituent group other than an oxygen-containing group in the 4 position were investigated. 4-Alkylphenols reacted markedly more slowly than the corresponding 4-methoxy compounds and, except in cases where there were also substituent groups in the 2 and 6 positions, gave complex mixtures of products which proved impossible to separate. The 2,4,6-trialkylphenols **21a–c**, on the other hand, were smoothly converted into the cyclohexadienones **22a–c**. Phenols con-



21 22

a. R = R′ = CH_3, 72%
b. R = *t*-C_4H_9; R′ = CH_3, 90%
c. R = R′ = *t*-C_4H_9, 87%

taining an electron-withdrawing substituent in the 4 position (Cl, COOH, $COOCH_3$, NO_2) reacted very slowly with TTN; little of the reagent has been consumed even after reaction for 4 days at room temperature, while attempts to effect oxidation at 65° resulted in extensive decomposition of the phenols and production of tars.

In a qualitative sense, all of the above results are fully consistent with a mechanism for oxidation which involves electrophilic substitution of the aromatic ring, and the ipso thallation processes outlined in Scheme II satisfactorily account for the experimental observations. Unfortunately, all attempts to isolate organothallium intermediates of the type **4** proved totally unsuccessful. As mentioned earlier, however, ipso substitution has frequently been observed in the nitration and halogenation of phenols, and while most of the well-documented examples involve the use of polysubstituted phenols, the results of a recent study by Nilsson, Ronlán, and Parker on the chlorination of *p*-cresol are complementary to those of the present investigation and illustrate how the mechanism of substitution of simple phenols can vary dramatically with the reaction conditions.[23] Thus, treatment of *p*-cresol with $SbCl_5$ at room temperature gave a mixture of chlorinated phenols, but if the reaction was carried out at −50° under carefully controlled conditions 4-chloro-4-methylcyclohexa-2,5-dienone was obtained in 92% yield.

From a synthetic point of view it is obvious from the above results that oxidation of 4-methoxyphenols with TTN in methanol constitutes a convenient and manipulatively simple procedure for the direct preparation of a wide variety of 4,4-dimethoxycyclohexa-2,5-dienones. As far as we are aware there is no general procedure available for the synthesis of these interesting and highly reactive polyfunctional dienones. The parent compound **6a** has been pre-

pared previously by oxidation of 4-methoxyphenol in methanol either by cerium(IV)[24] or electrolytically,[23] and by controlled hydrolysis of *p*-benzoquinone bis(dimethyl ketal).[25] The 2,6-di-*tert*-butyl derivative **6d** has been obtained in excellent yield by treatment of 2,6-di-*tert*-butyl-4-methoxyphenol with copper(I) chloride in a methanol–pyridine mixture,[26] while the 2,3,5,6-tetramethyl[27] and 2,6-dichloro-3,5-dimethyl[28] analogues have been prepared by indirect methods.

Experimental Section

Melting points were determined on a Kofler hot-stage microscope melting point apparatus and are uncorrected. Microanalyses were performed by Mr. A. R. Saunders and Mr. J. Robinson of the University of East Anglia and by Mrs. I. Balogh-Batta of the Technical University, Budapest. Infrared spectra were recorded on a Perkin-Elmer Model 257 grating infrared spectrophotometer and on a Spectromom Model 2000 spectrophotometer using the standard Nujol mull, potassium bromide disk, and liquid film techniques. Nuclear magnetic resonance spectra were determined as solutions in either $CDCl_3$ or CCl_4 on Perkin-Elmer R12 60-MHz and Varian XL100 100-MHz spectrometers using tetramethylsilane as internal standard.

Starting Materials. All of the phenols used in this study were either commercially available or were prepared by standard literature procedures. All were purified by either distillation or crystallization prior to use.

General Method for the Preparation of 4,4-Dialkoxy- and 4-Alkyl-4-alkoxycyclohexa-2,5-dienones. A. Using TTN in Alcohols. A solution of TTN (5 mmol) in the appropriate alcohol (15 ml) was added to a stirred, cooled (−20°) solution of the phenol (5 mmol) in the same alcohol (15 ml) and the reaction mixture allowed to warm to room temperature. Petroleum ether (60 ml, bp 60–80°) was then added, the thallium(I) nitrate which precipitated was removed by filtration, and the filtrate was passed down a short column of basic alumina (8 × 1 in.) using either petroleum ether or dichloromethane as eluent. Evaporation of the eluate gave the product which, in almost all cases, was chromatographically and spectroscopically pure as isolated. Most of the compounds could be crystallized from either methanol or petroleum ether, preferably at −70°, but only with attendant losses in material of up to 75%.

B. Using TTN in Methanol–Trimethyl Orthoformate (TMOF). The phenol (5 mmol) was added to a stirred solution of TTN (5 mmol) in a mixture of methanol (15 ml) and TMOF (15 ml) cooled to −70°, the cooling bath was removed, and the mixture was allowed to warm to room temperature. Petroleum ether (50 ml) was then added, and the products were isolated in exactly the same way as described in A above.

Yield and physical data for the cyclohexadienones prepared in this way are listed in Table I (see paragraph at end of paper regarding supplementary material).

General Procedure for the Oxidation of Hydroquinones and 2,6-Dialkylphenols with TTN. A solution of the hydroquinone (5 mmol) in methanol (10 ml) was added dropwise to an ice-cold solution of TTN (5 mmol) in methanol (15 ml). After addition had been completed the reaction mixture was stirred for a further 10 min, the thallium(I) nitrate which had precipitated was removed by filtration, and the filtrate was partitioned between dichloromethane and saturated aqueous sodium chloride solution. The organic layer was separated, dried (Na_2SO_4), and evaporated under reduced pressure. The crude *p*-benzoquinone thus obtained was purified by chromatography on silica gel or neutral alumina using benzene or benzene–dichloromethane as eluent.

Oxidation of 2,6-dialkylphenols to *p*-benzoquinones was carried out in exactly the same manner except that the reaction was performed at room temperature and 10 mmol of TTN was used.

4-Benzyloxy-2-[3-(2-benzyloxy-4,5-methylenedioxyphenyl)acryloyl]-4-hydroxy-3,5-dimethoxycyclohexa-2,5-dienone (9b). 2,5′-Dibenzyloxy-2′-hydroxy-4′,6′-dimethoxy-4,5-methylenedioxychalcone (**8**,[19] 1 mmol) was oxidized by the general method A but at 65° and for 1 hr; during this time the initially formed ketal **9a**[19] was slowly hydrolyzed to **9b**. The reaction mixture was neutralized with sodium methoxide and evaporated to dryness and the residue chromatographed on silica gel using benzene–acetone (4:1) as eluent. This gave 110 mg (21%) of pure **9b** as red prisms: mp 128–130°; NMR ($CDCl_3$) δ 3.46 (s, 3, 5-OCH_3), 3.84 (s, 3, 3-OCH_3), 4.68 and 4.71 (inner lines of an AB quartet, 4-$OCH_2C_6H_5$), 5.13 (s, 2, 2′-$OCH_2C_6H_5$), 5.60 (s, 1, 6-H), 5.98 (s, 2, $-OCH_2O-$), 6.57 and 7.26 (s, 1 each, 3′,6′-H), 7.43 and 7.41 (s, 10, 2′,4-$OCH_2C_6H_5$), 8.04 (d, 1, J = 16 Hz, COCH=CH), 8.50 (d, 1, J = 16 Hz, COCH=CH).

Anal. Calcd for $C_{32}H_{28}O_9$: C, 69.06; H, 5.07. Found: C, 68.91; H, 5.07.

2-[3-(2-Benzyloxy-4,5-methylenedioxyphenyl)acryloyl]-4-hydroxy-3,4,5-trimethoxycyclohexa-2,5-dienone (9c). A solution of **9b** (100 mg) in a mixture of methanol (30 ml) and 10% hydrochloric acid (0.5 ml) was heated under reflux for 2 hr. The solution was then concentrated to ca. 15 ml by distillation under reduced pressure, when the crude product crystallized. This was collected by filtration, and recrystallization from methanol gave 50 mg (58%) of pure product as brick red needles, mp 168–170°, NMR ($CDCl_3$) δ 3.40 (s, 6, 3,5-OCH_3); the remainder of the signals corresponded to those for **9b**.

Anal. Calcd for $C_{26}H_{24}O_9$: C, 64.99; H, 5.04. Found: C, 64.92; H, 5.64.

3,4,5-Trimethoxy-4-hydroxy-2-[3-(4-methoxyphenyl)acryloyl]cyclohexa-2,5-dienone (11). 2′-Hydroxy-4,4′,5′,6′-tetramethoxychalcone (**10**,[29] 1.5 g) was oxidized at 65° as described for 8 above. Recrystallization of the crude product from methanol gave 1.1 g (70%) of pure **11** as yellow needles: mp 139–140°; NMR ($CDCl_3$) δ 3.42 (s, 3, 4-OCH_3), 3.85 and 3.87 (s, each 3, 3,5-OCH_3), 5.62 (s, 1, 6-H), 6.90 (d, 2, J = 8 Hz, 3′,5′-H), 7.60 (d, 2, J = 8 Hz, 2′,6′-H), 7.94 (d, 1, J = 16 Hz, COCH=CH), 8.21 (d, 1, J = 16 Hz, COCH=CH).

Anal. Calcd for $C_{19}H_{20}O_7$: C, 63.33; H, 5.59. Found: C, 63.37; H, 5.70.

4-Methoxy-3,4-methylenedioxycyclohexa-2,5-dienone (16a). Oxidation of **15** (1.38 g) with TTN in methanol according to the general procedure A gave, after recrystallization of the crude product from petroleum ether (bp 35–40°), 0.75 g (45%) of pure product: mp 56–57°; ir (KBr) 1680 (C=O), 1650 (C=C), and 1610 cm^{-1} (C=C); NMR ($CDCl_3$) δ 3.46 (s, 3, 4-OCH_3), 5.62 (d, 1, ^4J = 2 Hz), 5.70 (d, 2, $-OCH_2O-$) 6.40 (q, 1, ^3J = 10, ^4J = 2 Hz, 6-H), 6.95 (*d*, 1, ^3J = 10 Hz, 5-H).

Anal. Calcd for $C_8H_8O_4$: C, 58.55, H. 2.46. Found: C, 58.62; H, 2.38

4-Ethoxy-3,4-methylenedioxycyclohexa-2,5-dienone (16b). Oxidation of **15** with ethanol according to the general procedure A gave, after recrystallization of the crude product from petroleum ether (bp 35–40°), a 59% yield of **16b** as colorless needles: mp 57–59°; NMR ($CDCl_3$) δ 1.20 (t, 3, J = 7 Hz, OCH_2CH_3), 3.40–4.10 (ABX_3 m, 2, OCH_2CH_3); the other signals were similar to those of **16a**.

Anal. Calcd for $C_9H_{10}O_4$: C, 59.34; H, 5.53. Found: C, 59.53; H, 5.41.

4-Acetoxy-3,4,5-trimethoxycyclohexa-2,5-dienone (17). TTN (500 mg) was added to a solution of **5e** (184 mg, 1 mmol) in anhydrous ethyl acetate (10 ml) containing acetic acid (3 ml) and anhydrous sodium acetate (0.5 g) cooled to −20°. The reaction mixture was stirred for 30 min, the thallium(I) nitrate which had precipitated was removed by filtration, and the filtrate was poured into water. The resulting mixture was extracted with chloroform and the extracts were dried (Na_2SO_4) and evaporated under reduced pressure to give 45 mg (19%) of **17** as pale yellow prisms: mp 153–155°; ir (KBr) 1750 (CH_3CO), 1660 cm^{-1} (C=O); NMR ($CDCl_3$) δ 2.17 (s, 3, CH_3COO), 2.45 (s, 3, 4-OCH_3), 3.80 (s, 6, 3,5-OCH_3), 5.59 (s, 2, 2,6-H).

Anal. Calcd for $C_{11}H_{14}O_6$; c, 54.54; H, 5.83. Found: C, 54.32; H, 5.97.

4-Acetoxy-2,4,6-tri-*tert*-butylcyclohexa-2,5-dienone (18). Oxidation of **13** as described for **5e** above gave, after fractional crystallization of the crude product from methanol, 25% of **14** and 10% of **18**.[30] The latter compound was characterized spectroscopically: ir (KBr) 1735 (CH_3COO), 1665 cm^{-1} (C=O); NMR ($CDCl_3$) δ 0.99 (s, 9, 4-*t*-C_4H_9), 1.50 (s, 18, 2,6-*t*-C_4H_9), 2.08 (s, 3, CH_3COO), 6.50 (s, 2, 3,5-H).

5,6,6-Trimethoxycyclohexa-2,5-dienone (20). Oxidation of **19** (0.77 g) by the general procedure A gave, after chromatography of the crude product on silica gel, 0.22 g (25%) of **20** as pale yellow needles, mp 76–78°, after recrystallization from petroleum ether (bp 35–40°): ir (KBr) 1670 (C=O), 1630 and 1560 cm^{-1} (C=C); NMR ($CDCl_3$) δ 3.36 (s, 6, 6,6-OCH_3), 3.83 (s, 3, 5-OCH_3), 5.42 (d, 1, J_{BX} = 8 Hz, 2-H), 5.85 (d, 1, J_{AX} = 10 Hz, 4-H), 7.08 (q, 1, J_{BX} = 8, J_{AX} = 10 Hz, 5-H).

Anal. Calcd for $C_9H_{12}O_4$: C, 58.69; H, 6.57. Found: C, 58.79; H, 6.51.

Acknowledgment. One of us (D.H.P.) acknowledges the receipt of an I. C. I. Fellowship.

Registry No.—**5a,** 150-76-5; **5b,** 5307-05-1; **5c,** 2431-91-6; **5d,** 489-01-0; **5e,** 642-71-7; **5f,** 22248-14-2; **5g,** 18113-03-6; **5h,** 17332-11-5; **6a,** 935-50-2; **6b,** 57197-11-2; **6c,** 57197-12-3; **6d,** 33974-39-9; **6e,** 57197-13-4; **6f,** 57197-14-5; **6g,** 57197-15-6; **6h,** 57197-16-7; **7a,** 94-71-3; **7b,** 7495-77-4; **7c,** 122-94-1; **7d,** 13037-86-0; **7e,** 103-16-2; **7f,** 831-82-3; **8,** 52366-32-2; **9a,** 52250-33-6; **9b,** 57197-17-8; **9c,** 57197-18-9; **10,** 3877-67-6; **11,** 57197-19-0; **12a,** 57197-20-3; **12b,** 57197-21-4; **12c,** 57197-22-5; **13,** 732-26-3; **14,** 4971-61-3; **15,** 533-31-3; **16a,** 57197-23-6; **16b,** 57197-24-7; **17,** 57197-25-8; **18,** 20778-61-4; **19,** 5150-42-5; **20,** 57197-26-9; **21a,** 527-60-6; **21b,** 128-37-0; **22a,** 38876-36-7; **22b,** 2411-18-9; **22c,** 15910-49-3; TTN, 13746-98-0.

Supplementary Material Available. Full yield, melting point, analytical, and spectroscopic data (NMR, ir) for compounds **6a–h, 12a–c, 14,** and **22a–c** (3 pages) will appear following these pages in the microfilm edition of this volume of the journal.

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A Synthesis of the Pyrazomycins[15]

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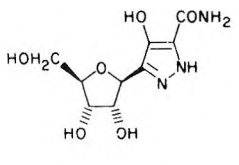
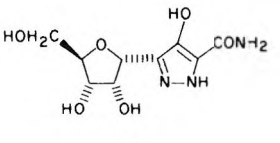
Pyrazomycin (**1**), an antiviral metabolite of *Streptomyces candidus*, and its congener pyrazomycin B (**2**) were synthesized. Reaction of 2,3-*O*-isopropylidene-5-*O*-*p*-nitrobenzoyl-β-D-ribosyl bromide (**6**) with diethyl 1,3-acetonedicarboxylate afforded 3-oxo-2-(2,3-*O*-isopropylidene-5-*O*-*p*-nitrobenzoyl-α-D-ribosyl)glutaric acid diethyl ester (**7**). Diazotization of **7** with *p*-toluenesulfonyl azide gave 5-(2,3-*O*-isopropylidene-5-*O*-*p*-nitrobenzoyl-α-D-ribosyl)-4-oxo-2-pyrazoline-3,5-dicarboxylic acid diethyl ester (**11**). Treatment of **11** with sodium ethoxide accomplished removal of the *p*-nitrobenzoyl group and of the quaternary ethoxycarbonyl function to produce 3-(2,3-*O*-isopropylidene-α-D-ribofuranosyl)-4-hydroxypyrazole-5-carboxylic acid ethyl ester (**12**). Ammonolysis of **12** afforded the corresponding amide **13,** and under slightly different conditions, the epimeric amide **14.** Removal of the isopropylidene group from **13** and **14** completed the synthesis of **1** and **2**, respectively.

In recent years considerable interest has been accorded to *C*-nucleoside antibiotics.[1] In this new class of natural products, pyrazomycin[2] deserves particular attention, owing to reports of its antitumor[3] and broad spectrum antiviral[4] activity. Pyrazomycin, 3-(1′-β-D-ribofuranosyl)-4-hydroxypyrazole 5-carboxamide (**1**), was first isolated from fermentations of a strain of *Streptomyces candidus*.[2,5] This organism has recently yielded a second factor, which was characterized as the 1′-α epimer, pyrazomycin B (**2**).[6] A synthesis of **1** has previously been reported.[7] We now wish to describe a new and shorter synthetic route which allowed the preparation of both **1** and **2**.

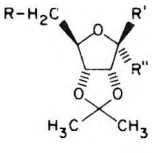


1



2

Our starting material was 2,3-*O*-isopropylidene-D-ribofuranose (**3**),[8] containing both anomers, α and β, in a ratio of 1:9. Reaction of **3** with *p*-nitrobenzoyl chloride in pyridine afforded the two di-*p*-nitrobenzoates **4** and **5** (8:1),

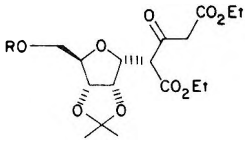


3: R = –OH; R′,R″ = –H,–OH
4: R = R′ = *p*-$NO_2C_6H_4CO_2$–; R″ = –H
5: R = R″ = *p*-$NO_2C_6H_4CO_2$–; R′ = –H
6: R = *p*-$NO_2C_6H_4CO_2$–; R′ = –Br; R″ = –H

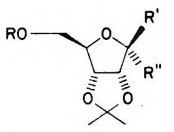
which could be separated by fractional crystallization. The configurations at the anomeric carbon atoms (C-1) in **4** and **5** were assigned with the help of NMR spectral data.

While the conformational motility of five-membered rings ordinarily does not permit configurational assignments to be made on the basis of coupling constants of vicinal protons,[9] it has recently been shown that in *O,O'*-isopropylidene derivatives of furanoses protons in a vicinal cis relationship consistently have coupling constants of 3–6.5 Hz, while those which are trans to each other are coupled by less than 1 Hz.[10] Accordingly, in the NMR spectrum of **4**, the anomeric proton (H-1) gives rise to a singlet at 6.02 ppm (in $CDCl_3$), while H-1 of **5** is seen as a doublet ($J_{1,2}$ = 4.5 Hz) at 6.53 ppm.

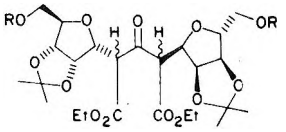
When the mixture of **4** and **5** was allowed to react at 0° with a saturated solution of hydrogen bromide in methylene chloride, a single crystalline ribosyl bromide **6** was obtained. In agreement with the β-anomeric structure, the NMR spectrum of **6** (in $CDCl_3$) contains a singlet at 6.49 ppm, assignable to H-1. Alkylation of the potassium salt of diethyl acetonedicarboxylate with **6** was effected in benzene in the presence of a solid–liquid phase transfer catalyst (18-crown-6). The reaction led to a mixture in which the desired C-alkylation product **7** was the major component (43% yield). Chromatographic separation afforded, in addition to **7**, the O-alkylation product **8**, a small amount of its β epimer **9**, and a dialkylated derivative **10**. The configu-



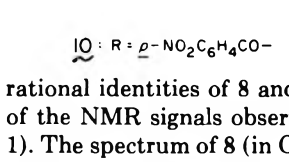
7: R = *p*-$NO_2C_6H_4CO$–



8: R = *p*-$NO_2C_6H_4CO$–
R' = –H
R'' = –O–C(CH_2CO_2Et)=$CHCO_2Et$



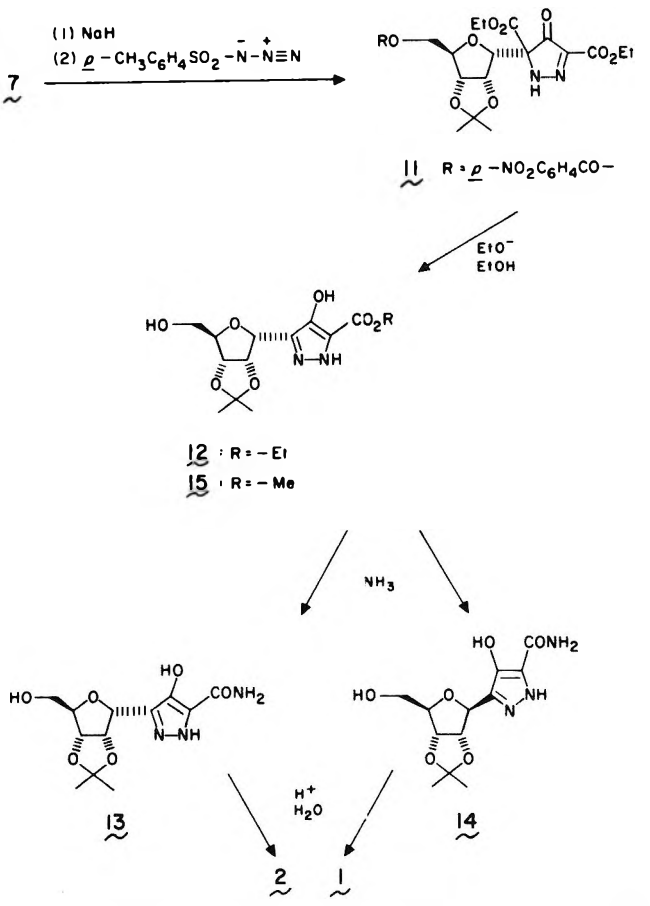
9: R = *p*-$NO_2C_6H_4CO$–
R' = –O–C(CH_2CO_2Et)=$CHCO_2Et$
R'' = –H



10: R = *p*-$NO_2C_6H_4CO$–

rational identities of **8** and **9** were established on the basis of the NMR signals observed for the anomeric proton (H-1). The spectrum of **8** (in $CDCl_3$) contains a doublet for H-1 at 5.55 ppm ($J_{1,2}$ = 4 Hz), while that of **9** possesses two singlets at 5.52 and 5.66 ppm, one of which belongs to H-1 and the other one to the vinylic proton. Lacking usable spectroscopic evidence for the C-1 configuration of **7**, it was assumed that the new carbon–carbon bond had formed with inversion and that it therefore was α, as shown. This contention was confirmed by the subsequent conversion of **7** to **11**. The sodium salt of **7** (prepared with sodium hydride in dimethoxyethane) was subjected to diazotization with *p*-toluenesulfonyl azide,[11] affording directly the cyclic derivative **11**. In agreement with the pyrazolinone structure, the ir spectrum of **11** shows strong N–H stretching at 3445 cm^{-1}. There is no absorption assignable to diazo stretching (ca. 2100–2200 cm^{-1}). The uv spectrum of **11** (in EtOH), arising from *p*-nitrobenzoyl and pyrazolinone absorption,[12] has a maximum at 245 nm (ϵ 16000), a shoulder at 260 nm (ϵ 14400), and a second maximum at 330 nm (ϵ 6800). The presence of a doublet for H-1 (at δ 4.93, $J_{1,2}$ = 3.8 Hz) in the NMR spectrum confirms the α-configuration at C-1 of the ribosyl moiety.

Treatment of **11** with sodium ethoxide in ethanol at room temperature accomplished solvolysis of the *p*-nitrobenzoyl ester function and selective removal of the quaternary ethoxycarbonyl group, resulting in aromatization of



the heterocycle and producing **12**. The uv spectrum of **12** reveals the typical 4-hydroxypyrazole chromophore[13] having absorption maxima at 227 (ϵ 7300) and 271 nm (5200), when measured in ethanol, and at 235 (5300) and 317 nm (7900) when taken in alkaline solution. The 1'-α configuration is evident from the NMR spectrum (in $CDCl_3$), in which the anomeric proton gives rise to a doublet at 5.26 ppm ($J_{1,2}$ = 2.6 Hz).

When **12** was heated for 3 hr at 100° in methanolic ammonia solution, the major part of the substance was converted to the amide **13**. In addition, the epimeric amide **14** was obtained as a minor by-product, and some material was recovered as the methyl ester **15**. Prolonged exposure of **12** to the above reaction conditions (12 hr) afforded **14** as the sole product. The apparent ease with which **13** epimerized to **14** suggests that intermediate (resonance stabilized) opening of the ribose ring was involved in this transformation. Other *C*-nucleosides are known to exhibit similar behavior.[14] The stereochemical relationship of **13** and **14** is reflected in the differences in their respective NMR spectra. While the spectrum of **13** (in CD_3OD) contains a doublet at 5.27 ppm ($J_{1',2'}$ = 3 Hz) arising from H-1', that of **14** has a singlet at 4.99 ppm.

Removal of the isopropylidene protecting group from **13** and **14**, respectively, with 90% trifluoroacetic acid completed the syntheses of the two antibiotics **2** and **1**. The physical properties of **2** agreed with those reported for pyrazomycin B.[6] Our synthetic **1** was found to be identical with an authentic sample of pyrazomycin.[2,5–7]

Experimental Section

General. Melting points were taken on a Kofler hot stage melting point apparatus (Reichert) and are uncorrected. Thermal analyses were carried out on a Du Pont 900 thermal analyzer. Infrared spectra were obtained on a Perkin-Elmer 621, a Beckman IR-9, or a Digilab FTS 14 spectrometer. Ultraviolet spectra were recorded on a Cary Model 16 spectrophotometer. Rotations were measured on a Perkin-Elmer 141 automatic polarimeter. Proton NMR spec-

tra were obtained on Varian HA-100 and XL-100 instruments and are reported in parts per million downfield from internal tetramethylsilane.

2,3-*O*-Isopropylidene-1,5-di-*O*-*p*-nitrobenzoyl-D-ribofuranoses (4 and 5). To a cold solution of 46.8 g (0.246 mol) of 2,3-*O*-isopropylidene-D-ribofuranose[8] in 650 ml of dry pyridine was added in portions, while vigorously stirring, 115 g (0.62 mol) of *p*-nitrobenzoyl chloride. The reaction mixture was kept stirring for another 1 hr in an ice bath and for 20 hr at room temperature. It was then cooled again and 500 ml of saturated aqueous $NaHCO_3$ was carefully added. Upon dilution with 5 l. of ice–water a precipitate formed, which was collected by filtration, washed with water, and dissolved in 1200 ml of CH_2Cl_2. The organic solution was washed with 600 ml of 0.2 *N* HCl and with water, dried over Na_2SO_4, and evaporated in vacuo. Crystallization of the residue from CH_2Cl_2–Et_2O afforded 97.5 g of 2,3-*O*-isopropylidene-1,5-di-*O*-*p*-nitrobenzoyl-β-D-ribose (**4**): mp 139–140°; $[\alpha]^{25}D$ 0.00° (c 1.673, $CHCl_3$); uv max (EtOH) 257 nm (ε 26000), infl 300 (4000); ir ($CHCl_3$) 1735, 1610, 1535, 1345, 1270 cm^{-1}; NMR ($CDCl_3$) δ 1.39 (s, CH_3), 1.57 (s, CH_3), 4.4–4.9 (3), 4.94 (d, CH_2O), 6.52 (s, H-1), 8.05–8.35 ppm (8, aromatic).

Anal. Calcd for $C_{22}H_{20}N_2O_{11}$: C, 54.10; H, 4.13; N, 5.74. Found: C, 54.10; H, 4.20; N, 5.77.

The mother liquor was evaporated and repeatedly recrystallized from MeOH and CH_2Cl_2–Et_2O. There were obtained 14.5 g of a crystalline mixture of the anomers **4** and **5** and finally 3.8 g of 2,3-*O*-isopropylidene-1,5-di-*O*-*p*-nitrobenzoyl-α-D-ribose (**5**). Pure **5** had mp 157–158°; $[\alpha]^{25}D$ +12.44° (c 1.6322, $CHCl_3$); uv (EtOH) max 258 nm (ε 27100), infl 300 (4200); ir ($CHCl_3$) 1725, 1601, 1535, 1345, 1270 cm^{-1}; NMR ($CDCl_3$) δ 1.37, 1.39 (2 s, CH_3), 4.5–5.1 (5), 6.53 (d, H-1, $J_{1,2}$ = 4.5 Hz), 8.1–8.45 ppm (8, aromatic).

Anal. Calcd for $C_{22}H_{20}N_2O_{11}$: C, 54.10; H, 4.13; N, 5.74. Found: C, 54.13; H, 4.27; N, 5.97.

The combined yield of all fractions was 96.4%.

2,3-*O*-Isopropylidene-5-*O*-*p*-nitrobenzoyl-β-D-ribosyl Bromide (6). 2,3-*O*-Isopropylidene-1,5-di-*O*-*p*-nitrobenzoyl-β-D-ribose (**4**, or the mixture of anomers) (8.5 g, 17.4 mmol) was added in one portion to 140 ml of dry CH_2Cl_2, previously saturated with anhydrous HBr at 0°. The flask was sealed with a rubber septum and the reaction mixture was stirred in an ice bath for 30 min. It was then allowed to warm to room temperature within 1 hr. The precipitated *p*-nitrobenzoic acid was removed by filtration under a blanket of dry argon. The filtrate was concentrated at 25° (bath temperature) to approximately ¼ of the original volume. The solution was repeatedly diluted with dry Et_2O and petroleum ether (bp 30–60°) and partially concentrated in vacuo until the bromide **6** crystallized spontaneously on the walls of the flask. After cooling, decanting, and washing with petroleum ether, the crystals were dried at room temperature (0.005 mmHg), affording 6.421 g (91.7%) of **6**.

An analytical sample was obtained by recrystallization from CH_2Cl_2–Et_2O–petroleum ether: mp 118.5–120.5°; $[\alpha]^{25}D$ −67.45° (c 1.478, $CHCl_3$); uv max (Et_2O) 255 nm (ε 13200); ir ($CHCl_3$) 1730, 1530, 1350, 1270 cm^{-1}; NMR ($CDCl_3$) δ 1.39 (s, CH_3), 1.46 (s, CH_3), 4.70 (3, $CHCH_2$), 4.97, 5.29 (2 d, H-2, H-3), 6.49 (s, H-1), 8.28 ppm (4, aromatic).

Anal. Calcd for $C_{15}H_{16}BrNO_7$: C, 44.79; H, 4.01; N, 3.48; Br, 19.86. Found: C, 44.85; H, 4.06; N, 3.40; Br, 19.97.

The bromide **6** was stable for several days when stored in a sealed container under argon at −10°.

Reaction of 2,3-*O*-Isopropylidene-5-*O*-*p*-nitrobenzoyl-β-D-ribosyl Bromide (6) with Diethyl 1,3-Acetonedicarboxylate. To a suspension of 805 mg (20.07 mmol) of KH in 40 ml of dry benzene (stirred under argon) was added dropwise 4 ml of diethyl 1,3-acetonedicarboxylate, followed by a solution of 3.750 g (14.2 mmol) of 18-crown-6 in 30 ml of benzene. After H_2 evolution had ceased, a larger excess (22 ml) of diethyl 1,3-acetonedicarboxylate was added in one portion. Then, a solution of 5.93 g (14.74 mmol) of **6** in 80 ml of dry benzene was added dropwise over 30 min. The reaction mixture was stirred at room temperature for 16 hr (under argon). It was then diluted with 1000 ml of Et_2O. The ether phase was washed with 3 × 300 ml of H_2O, diluted with 300 ml of benzene, and dried (Na_2SO_4). After evaporation of the solvents under reduced pressure, the excess diethyl 1,3-acetonedicarboxylate was distilled off in a Kugelrohr apparatus (bulb to bulb) at 80–85° (0.01 mmHg). The residue was dissolved in 15 ml of toluene–ethyl acetate (10:1) and chromatographed on a column containing 550 g of a mixture of 75% of silica gel 60 and 25% of silica gel PF-254 (both E. Merck). The column was developed with toluene–ethyl acetate, 10:1 (3600 ml, fractions 1–149), 10:1.5 (2300 ml, fractions 150–265), and 10:3 (1300 ml, fractions 266–300). The eluate was monitored by thin layer chromatography in toluene–ethyl acetate (10:1.75) and cyclohexane–ethyl acetate (3:1).

Fractions 80–114, after evaporation and drying in vacuo at 60° (0.01 mmHg), afforded 0.410 g (5.3%) of **3-(2,3-*O*-isopropylidene-5-*O*-*p*-nitrobenzoyl-β-D-ribosyl)oxy-2-pentenedioic acid diethyl ester (9)** as a colorless oil: $[\alpha]^{25}D$ −96.79° (c 1.1231, $CHCl_3$); uv (EtOH) max 233 nm (ε 18600), infl 255 nm (14200); ir ($CHCl_3$) 1730, 1705 (sh), 1640, 1605 (sh), 1530, 1270 cm^{-1}; NMR ($CDCl_3$, partial) δ 5.52 and 5.66 ppm (2 s, H-1 and =CH–).

Anal. Calcd for $C_{24}H_{29}NO_{12}$: C, 55.07; H, 5.58; N, 2.68. Found: C, 54.90; H, 5.69; N, 2.53.

Fractions 115–188, upon evaporation and drying, gave 2.850 g of **2-(2,3-*O*-isopropylidene-5-*O*-*p*-nitrobenzoyl-α-D-ribosyl)-3-oxoglutaric acid diethyl ester (7).** An additional 0.450 g of the desired **7** was obtained upon rechromatographing fractions 189–230, giving a total yield of 42.8%: colorless oil; $[\alpha]^{25}D$ +44.8° (c 0.9434, $CHCl_3$); uv max (EtOH) 258 nm (ε 11300); uv max (0.1 *N* KOH) 279 nm (ε 28000); ir ($CHCl_3$) 1735, 1605, 1530, 1270 cm^{-1}.

Anal. Calcd for $C_{24}H_{29}NO_{12}$: C, 55.07; H, 5.58; N, 2.68. Found: C, 55.17; H, 5.61; N, 2.62.

Fractions 231–310 (combined with the remainder from fractions 189–230) were rechromatographed on 450 g of silica gel mixture (vide supra). The column was eluted with ethyl acetate–cyclohexane, 25:75 (4200 ml) and 30:70 (3000 ml). From appropriate fractions there was obtained after evaporation 1.625 g (21.1%) of **3-(2,3-*O*-isopropylidene-5-*O*-*p*-nitrobenzoyl-α-D-ribosyl)oxy-2-pentenedioic acid diethyl ester (8):** $[\alpha]^{25}D$ +41.72° (c 1.1313, $CHCl_3$); uv (EtOH) max 234 nm (ε 16200), infl 260 (12000); ir 1710, 1685 (sh), 1620, 1590, 1515, 1270 cm^{-1}; NMR ($CDCl_3$, partial) δ 5.49 (s, –CH=), 5.55 ppm (d, H-1, $J_{1,2}$ = 4.0 Hz).

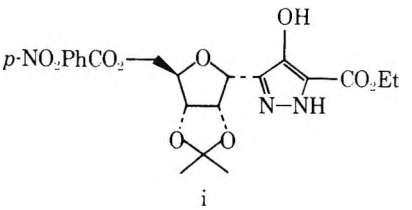
Anal. Calcd for $C_{24}H_{29}NO_{12}$: C, 55.07; H, 5.58; N, 2.68. Found: C, 54.78; H, 5.58; N, 2.59.

Later fractions afforded 1.488 (23.9%) of **2,4-bis(2,3-*O*-isopropylidene-5-*O*-*p*-nitrobenzoyl-α-D-ribosyl)-3-oxoglutaric acid diethyl ester (10):** $[\alpha]^{25}D$ +45.58° (c 1.1254, $CHCl_3$); uv max (EtOH) 258 nm (ε 25500); uv max (0.1 *N* KOH) 278 nm (ε 35500); ir ($CHCl_3$) 1730, 1605, 1525, 1270 cm^{-1}.

Anal. Calcd for $C_{39}H_{44}N_2O_{19}$: C, 55.46; H, 5.25; N, 3.32. Found: C, 55.51; H, 5.33; N, 3.25.

5-(2,3-*O*-Isopropylidene-5-*O*-*p*-nitrobenzoyl-α-D-ribosyl)-4-oxo-2-pyrazoline-3,5-dicarboxylic Acid Diethyl Ester (11). A solution of 4.067 g (7.77 mmol) of **7** in 80 ml of dry 1,2-dimethoxyethane (DME) was added during 5 min to a stirred suspension of 200 mg (8.33 mmol) of NaH in 40 ml of dry DME under argon. An excess of tosyl azide (4 ml) was then added dropwise with a syringe. After stirring for 3 hr the reaction mixture was distributed between 1000 ml of cold ethyl acetate and 500 ml of ice–water. The aqueous layer was acidified to pH 3 with 1 *N* HCl and extracted with a second portion of ethyl acetate. The extracts were washed with half-saturated aqueous NaCl, dried (Na_2SO_4), and evaporated in vacuo.

The residual oil was purified by column chromatography on 500 g of silica gel. The column was developed with ethyl acetate–cyclohexane, 40:60 (4000 ml), then 60:40 (1500 ml), and finally ethyl acetate (1000 ml). Excess tosyl azide and tosyl amide (mp 139°, from H_2O) were eluted first. Then fractions were collected, which yielded 3.085 g (84.3%) of **11**. Early fractions of **11** were almost pure, while later fractions contained small amounts of a new compound, which had formed during the chromatography, and which was identified as the deethoxycarbonylation product, **3-(2,3-*O*-isopropylidene-5-*O*-*p*-nitrobenzoyl-α-D-ribosyl)-4-hydroxypyrazole-5-carboxylic acid ethyl ester (i).** Analytical samples of **11**



i

and **i** were obtained by preparative thin layer chromatography on silica gel with ethyl acetate–cyclohexane, 60:40.

Pure **11** was obtained as a colorless glass: $[\alpha]^{25}D$ +132.1° (c 1.0220, $CHCl_3$); uv (EtOH) max 245 nm (ε 16000), sh 260 (14400), max 330 (6700); ir ($CHCl_3$) 3445, 1760, 1730, 1605, 1535, 1500, 1420, 1390, 1355, 1270 cm^{-1}; NMR ($CDCl_3$) δ 1.27 (t, CH_3CH_2–), 1.36 (t, CH_3CH_2), 1.36 (s, CH_3), 1.61 (s, CH_3), 4.24 (q, CH_3CH_2),

4.34 (q, CH_3CH_2), 4.37 (d, CH_2O), 4.45 (t, H-4), 4.76 (d, H-3, $J_{2,3}$ = 5.8 Hz), 4.93 (d, H-1, $J_{1,2}$ = 3.8 Hz), 5.18 (d of d, H-2), 8.17, 8.32 (aromatic AA'BB'), 8.66 ppm (NH).

Anal. Calcd for $C_{24}H_{27}N_3O_{12}$: C, 52.46; H, 4.95; N, 7.65. Found: C, 52.30; H, 4.98; N, 7.53.

Pure i had $[\alpha]^{25}D$ −31.01° (c 1.0595, $CHCl_3$); uv max (EtOH) 227 nm (ε 12600), 261 (16800); ir ($CHCl_3$) 3450, 1730, 1695, 1610, 1530, 1350, cm^{-1}; NMR ($CDCl_3$) δ 1.37 (s, CH_3), 1.39 (t, CH_3CH_2), 1.59 (s, CH_3), 4.3–4.7 (m, 5), 4.86 (d, H-3, $J_{2,3}$ = 5.7 Hz), 4.97 (d or d, H-2), 5.27 (d, H-1, $J_{1,2}$ = 3.2 Hz), 7.28 (NH), 8.1–8.4 (aromatic AA'BB'), 10.7 ppm (OH).

Anal. Calcd for $C_{21}H_{23}N_3O_{10}$: C, 52.83; H, 4.86; N, 8.80. Found: C, 52.97; H, 4.89; N, 8.41.

3-(2,3-*O*-Isopropylidene-α-D-ribofuranosyl)-4-hydroxypyrazole-5-carboxylie Acid Ethyl Ester (12). To a stirred solution of 5.28 g (9.5 mmol) of **11** in 100 ml of absolute EtOH was added 700 mg of sodium ethoxide. After 45 min at 20° the reaction mixture was neutralized with AG 50W-X4 ion exchange resin (H^+, prewashed with EtOH). The resin was removed by filtration and washed with EtOH. After evaporation of the filtrate in vacuo, the residue was purified by preparative thin layer chromatography on silica gel with ethyl acetate as developing solvent. Elution of the appropriate fractions with ethyl acetate afforded 2.25 g (72%) of **12** (colorless glass): $[\alpha]^{25}D$ −37.94° (c 1.0200, $CHCl_3$); uv max (EtOH) 227 nm (ε 7300), 271 (5200); uv max (0.01 *N* NaOH) 317 nm (ε 7900); ir ($CHCl_3$) 1700, 1540 cm^{-1}; NMR ($CDCl_3$) δ 1.33 (s, CH_3), 1.37 (t, CH_3CH_2), 1.52 (s, CH_3), 3.72 (d, CH_2OH), 4.22 (t, H-4) 4.38 (q, CH_3CH_2), 4.73–4.95 (m, H-2 and H-3), 5.26 ppm (d, H-1, $J_{1,2}$ = 2.6 Hz).

Anal. Calcd for $C_{14}H_{20}N_2O_7$: C, 51.22; H, 6.14; N, 8.53. Found: C, 50.76; H, 6.40; N, 8.25.

3-(2,3-*O*-Isopropylidene-α-D-ribofuranosyl)-4-hydroxypyrazole-5-carboxamide (13). A solution of 600 mg (1.83 mmol) of **12** in 20 ml of dry MeOH was saturated with anhydrous NH_3 at 20° and heated in a sealed tube for 3 hr at 95°. After evaporation to dryness in vacuo, the residue was chromatographed on 125 g of silica gel. The column was developed with AcOEt–Me_2CO–MeOH–H_2O, 70:10:5:2.5. Fractions containing the transesterification product **15** and some β epimer **14** were eluted first. These were saved and resubjected to ammonolysis and chromatography as above. Fractions from both reactions containing the desired α epimer **13** were combined, evaporated, and redissolved in H_2O. The aqueous solution was lyophilized to give 390 mg (69%) of **13** as a white powder: $[\alpha]^{25}D$ −46.22° (c 1.1100, EtOH); uv max (EtOH) 220 nm (ε 7600), 263 (5800); uv max (0.01 *N* KOH) 310 nm (8200); ir (KBr) 1670, 1620, 1590 (sh), 1540, 1380 cm^{-1}; NMR (CD_3OD) δ 1.32 (s, CH_3), 1.49 (s, CH_3), 3.67 (d, CH_2OH), 4.18 (t, H-4), 4.8–5.2 (H-2, H-3), 5.26 ppm (d, H-1, $J_{1,2}$ = 3 Hz).

Anal. Calcd for $C_{12}H_{17}N_3O_6 \cdot 0.5H_2O$: C, 46.75; H, 5.88; N, 13.63. Found: C, 46.95; H, 5.90; N, 13.43.

From the remaining fractions there was obtained 80 mg of **15**.

3-(2,3-*O*-Isopropylidene-β-D-ribofuranosyl)-4-hydroxypyrazole-5-carboxamide (14). A solution of 600 mg (1.83 mmol) of **12** in 20 ml of dry MeOH was saturated with anhydrous ammonia at 10–15° and heated in a sealed tube for 12 hr at 95–100°. After removal of the solvents under reduced pressure, the residue was purified by chromatography on 125 g of silica gel, with AcOEt–Me_2CO–MeOH–H_2O, 70:10:5:5, as the eluent. Fractions containing **14** were evaporated in vacuo. The residue was redissolved in H_2O. The aqueous solution was freeze-dried to afford 398 mg (71%) of **14** as a colorless powder: $[\alpha]^{25}D$ −78.45° (c 1.1153, EtOH); uv max (EtOH) 225 nm (ε 9100), 264 (7300); uv max (0.01 *N* KOH) 309 nm (ε 10500); ir (KBr) 1670, 1625, 1590 (sh), 1550, 1390 cm^{-1}; NMR (CD_3OD) δ 1.34 (s, CH_3), 1.55 (s, CH_3), 3.64 (d, CH_2OH), 4.12 (d of t, H-4), 4.7–4.95 (H-2, H-3), 4.99 ppm (s, H-1).

Anal. Calcd for $C_{12}H_{17}N_3O_6 \cdot 0.4H_2O$: C, 47.03; H, 5.85; N, 13.71. Found: C, 47.08; H, 5.86; N, 13.65.

3-(α-D-Ribofuranosyl)-4-hydroxypyrazole-5-carboxamide (Pyrazomycin B, 2). A solution of 335 mg (1.1 mmol) of **13** in 20 ml of 90% CF_3CO_2H was kept under argon at room temperature for 1 hr. Then the solvents were removed at 5° under reduced pressure, at last under high vacuum. The residue consisted mainly (>90% by TLC) of the desired pyrazomycin B (**2**). It was contaminated with ca. 5% of pyrazomycin (**1**) which had formed by epimerization during reaction. Purification was accomplished by chromatography on silica gel (125 g) with EtOAc–Me_2CO–MeOH–H_2O, 6:1:1:1. Fractions containing **2** were evaporated at low temperature. The residue was redissolved in H_2O. The aqueous solution was filtered through a millipore filter and freeze-dried. There was obtained 306 mg (90%) of pure **2** as a dihydrate (white powder).

A sample of **2** was recrystallized from H_2O. It had mp 76° (unsharp). Thermal analysis showed a transition from the crystalline form to an amorphous solid at 76°: $[\alpha]^{25}D$ −7.56° (c 0.7278, H_2O); uv max (EtOH) 225 nm (ε 8000), 276 (6700); uv max (0.1 *N* KOH) 304 nm (ε 8400); ir (KBr) 1658, 1622 cm^{-1}; NMR (D_2O) δ 4.35 (m, CH_2OH), 4.67 (m, H-4), 4.9–5.1 (H-2, H-3), 5.83 ppm (d, H-1, $J_{1,2}$ = 3 Hz).

Anal. Calcd for $C_9H_{13}N_3O_6 \cdot 1.5H_2O$: C, 37.77; H, 5.63; N, 14.68. Found: C, 37.91; H, 5.68; N, 14.88.

3-(β-D-Ribofuranosyl)-4-hydroxypyrazole-5-carboxamide (Pyrazomycin, 1). A solution of 406 mg (1.33 mmol) of **14** in 20 ml of 90% CF_3CO_2H was kept at room temperature for 45 min. Then the solvents were removed at 5° under reduced pressure, at last under high vacuum. The residue was chromatographed on silica gel with EtOAc–Me_2CO–MeOH–H_2O, 6:1:1:1. Fractions containing **1** were evaporated at <20°. The residue was redissolved in H_2O. The aqueous solution was filtered through a millipore filter and lyophylized. Recrystallization from water afforded 248 mg (72%) of pyrazomycin (**1**), mp 112–115°, mmp with an authentic sample 112–115°.

Both the authentic sample and synthetic material formed higher melting polymorphs when stored at room temperature. Thermal analysis of freshly recrystallized material showed a broad endothermic phase transition (melting) at 108°, partial recrystallization at 117° (exotherm), and a second melting range at ca. 170°. When these samples were heated at 135°, cooled, and reheated, they showed only one phase transition at 178°. Thermal analysis of stored samples (3 months) revealed one phase transition (melting point) at 182°: $[\alpha]^{25}D$ −49.6° (c 0.7984, H_2O); uv max (EtOH) 226 nm (ε 7600), 267 (6000); uv max (0.01 *N* KOH) 233 nm (ε 4800), 307 (8300); ir (KBr) 1665, 1610, 1545 cm^{-1}; NMR (D_2O) δ 4.35 (m, CH_2OH), 4.65 (q, H-4, $J_{4,5}$ = 3, $J_{4,5}$ = 5 Hz), 4.79 (t, H-3, $J_{3,2}$ = 5, $J_{3,4}$ = 4 Hz), 4.94 (m, H-2), 5.54 (d, H-1, $J_{1,2}$ = 7 Hz).

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Registry No.—i, 57274-16-5; **1**, 30868-30-5; **2**, 41897-20-5; **4**, 57274-17-6; **5**, 57274-18-7; **6**, 57274-19-8; **7**, 57274-20-1; **8**, 57304-90-2; **9**, 57274-21-2; **10**, 57274-22-3; **11**, 57274-23-4; **12**, 57274-24-5; **13**, 57274-25-6; **14**, 57274-26-7; D-ribose-2,3-isopropylidene, 13199-25-2; *p*-nitrobenzoyl chloride, 122-04-3; diethyl 1,3-acetonedicarboxylate, 105-50-0.

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Hemiaminal Derivatives of Neothiobinupharidine[1]

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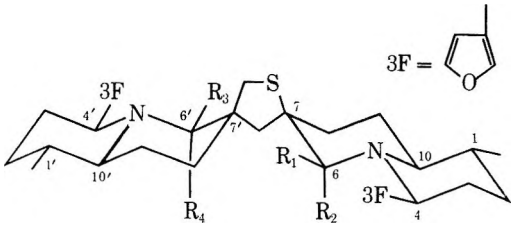
6- and 6′-hydroxyneothiobinupharidine were isolated from *Nuphar luteum* from Poland. The presence of infrared Bohlmann bands, hydroxyl groups reduced by sodium borodeuteride, and the appearance of the pairs of peaks at *m/e* 230 and 228 and 178 and 176 in the mass spectrum indicated the dual hemiaminal–amine nature of each of the two alkaloids. The ^{1}H NMR signals at δ 4.57 given by the one isomer and at δ 4.08 given by the other demonstrated that the hemiaminal hydroxyl was located at a C-6 or C-6′ position. On sodium borodeuteride reduction, singly labeled neothiobinupharidines were formed, that from the C-6 hemiaminal giving *m/e* 179 but that from the C-6′ hemiaminal giving *m/e* 178. The absence of the C-6 axial proton and the appearance of the C-6 equatorial proton as a singlet in the ^{1}H NMR indicated the presence of an axial deuterium at C-6 in neothiobinupharidine-6-d_1. Similar evidence indicated that the deuterium atom in neothiobinupharidine-6′-d_1 was axial also. The CD of both hemiaminals in acid gave negative bands, the one from the C-6 hemiaminal appearing at 295 nm, and the one from the C-6′ hemiaminal appearing at 279 nm.

6,6′-Dihydroxythiobinupharidine, one of the several hemiaminals recently isolated from *Nuphar*, possesses activity against human pathogenic fungi.[2] This finding, along with the discovery of the similar activity of synthetically derived deoxynupharidine α-thiohemiaminals,[3] has led us to extend our search for other *Nuphar* hemiaminals. The C_{30} thiaspiran hemiaminals previously studied belonged to the thiobinupharidine and thionuphlutine B stereochemical families.[4] This paper reports the detection, isolation, and structure determination of the hemiaminals of the neothiobinupharidine family.

Both 6- (**1**) and 6′-hydroxyneothiobinupharidine (**2**) were isolated from extracts of *Nuphar luteum* of Polish origin. A mixture of the two had been obtained and was the subject of an earlier report.[5] Since the separation of the components in the original mixture proved refractory, only the hemiaminal **1** was removed from this mixture and attention was focused on another fraction for the source of hemiaminal **2**. Noteworthy in regard to the purification of



1, $R_1 + R_2 = H + OH$; $R_3 = R_4 = H$

2, $R_1 = R_2 = H$; $R_3 + R_4 = H + OH$

3, $R_1 = R_3 = R_4 = H$; $R_2 = D$

4, $R_1 = R_2 = R_3 = H$; $R_4 = D$

the hemiaminals is the thin layer chromatographic appearance of **1**. When freshly chromatographed from a column of alumina, this hemiaminal appeared as a single spot but material which was aged but a few hours showed an additional somewhat more mobile second spot. The 6′ isomer, **2**, did not exhibit this behavior. Both freshly chromatographed and aged samples of **1** yielded neothiobinupharidine on reduction. Consequently we propose that the appearance of two spots results from epimeric hydroxyls at C-6.

Evidence adduced for establishing the dual hemiaminal–amine character within a C_{30} thiaspiran structure was similar to that offered previously in assigning structures of the monohemiaminals of thiobinupharidine and thionuphlutine B.[4d] Thus satisfactory values for the molecular weights corresponding to thiaspiran monohemiaminals were observed in the high-resolution mass spectra. Moreover, the pairs of mass spectral peaks *m/e* 230 and 228 and 178 and 176, in which the intensity of the peak of lower mass was equal to or greater than that of the higher mass peak of the pair, indicated[6] the presence of one fully reduced quinolizidine moiety and one C-6 hemiaminal quinolizidine moiety in each of the two alkaloids. The appearance of infrared Bohlmann bands and the facile borodeuteride reduction of the hemiaminal hydroxyl, coupled with the previous finding that bishemiaminal quinolizidines do not give Bohlmann bands,[4d] supported the monohemiaminal–amine character of the two new alkaloids.

6- and 6′-hydroxyneothiobinupharidine exhibited respectively ^{1}H NMR singlets at δ 4.57 and 4.08, the chemical shifts being consistent with those displayed by the C-6 and C-6′ monohemiaminals of thiobinupharidine and thionuphlutine B.[4d] Accordingly these resonances were assigned to the C-6 or C-6′ hemiaminal carbinyl protons. Hemiaminals located at C-4 or C-10 would show no carbinyl protons.

Each of the monohemiaminals was reduced with sodium borodeuteride to a singly deuterium labeled neothiobinupharidine identified by comparison to authentic unlabeled sample. These reductions not only established the stereochemical type of thiaspiran to which the hemiaminals belonged but also confirmed the monohemiaminal presence as well as its location. Earlier work[4d] demonstrated that deuterium located at C-6 in the AB quinolizidine system produced a shift of *m/e* 178 to 179 resulting from the fragmentation depicted in Figure 1. In contrast, when deuterium was located at C-6′, in the A′B′ quinolizidine system, *m/e* 178 was maintained. The mass spectrum of the deuterium labeled neothiobinupharidine (**3**), obtained from 6-hydroxyneothiobinupharidine, showed that *m/e* 178 was shifted to *m/e* 179 to the extent of 80% whereas the deuterium labeled counterpart, **4**, from the 6′ isomer exhibited only *m/e* 178.

In our studies of naturally occurring thiohemiaminals, two procedures have emerged for differentiating a C-6 hemiaminal (i.e., an α-thiohemiaminal) from a C-6′ hemiaminal (i.e., a β-thiohemiaminal).[4d] Employment of these procedures is especially advantageous in the examination of small amounts of *Nuphar* hemiaminals such as are the subjects of this report. One procedure consists in a sodium borodeuteride reduction followed by mass spectral analysis to locate the deuterium location. The examination of **1** and **2** by this procedure has just been described above.

The second procedure relies on the acidic solution ab-

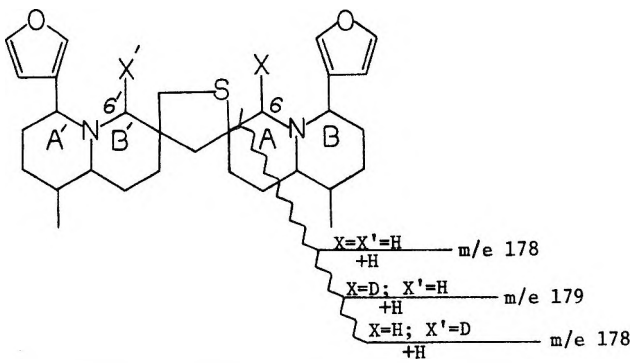
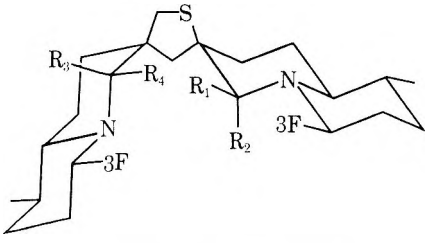


Figure 1. Mass spectral fragmentations of neothiobinupharidines labeled at C-6 and C-6′.

sorption of thiohemiaminals in the 270–310-nm region.[4a,4d,7] This procedure is more readily executed than the first and, when advantage is taken of the circular dichroism (CD), yields more information since not only are the C-6 and C-6′ hemiaminal positions differentiated but the stereochemical disposition of the thiohemiaminals can be ascertained as well.[7] α-Thiohemiaminals in acid solution absorb in the 290–300-nm region whereas β-thiohemiaminals absorb in a somewhat lower region, 270–280 nm. The α-thiohemiaminal **1** in acid produced an ultraviolet absorption maximum at 298 nm whereas the β-thiohemiaminal **2** gave a maximum at 275 nm. These observations support the positional assignments of the hemiaminal function.

The CD of 6-hydroxyneothiobinupharidine (**1**) in neutral solution exhibited a weak negative band at 255 nm and a weak positive band at 239 nm. In acid solution, a considerably stronger negative band is produced at 295 nm, as is depicted in Figure 2. These CD properties are virtually the same as those exhibited by 6-hydroxythionuphlutine B (**5**),



5. $R_1 + R_2 = H + OH$; $R_3 = R_4 = H$
9. $R_1 + R_2 = H + OH$; $R_3 + R_4 = H + OH$

which exhibits a negative band at 298 nm,[4d] and 7α-methylthiodeoxynupharidin-6-ol,[7] whose relative stereochemistry is secure and is derived from (−)-deoxynupharidine whose absolute configuration has been established. Contrasting with the CD properties of **1** and **5** are those of 6-hydroxythiobinupharidine (**6**), which gives a positive band at 296 nm (Figure 2),[7,4d] and 7β-methylthiodeoxynupharidin-6-ol, which, like the 7α isomer just mentioned, is also derived from (−)-deoxynupharidine. Therefore the acid solution CD properties of **1** are consistent with a 7*R* configuration, the same configuration being found in **5**.

The CD of 6′-hydroxyneothiobinupharidine (**2**) in neutral solution was much like that of the C-6 isomer, since **2** showed a weak negative band at 253 nm and a weak positive band at 239 nm. However, in acid solution, a negative band was produced at 279 nm. These acid-induced CD properties should be compared, as has been done in Figure 2, with those of 6′-hydroxythiobinupharidine (**7**), which, in acid solution, gives a positive CD band at 280 nm.[4d] The sign of the CD band given by **2** and position of the band, relative to that exhibited by **1**, is consistent with a β-thiohemiaminal possessing the 7′*S* configuration.

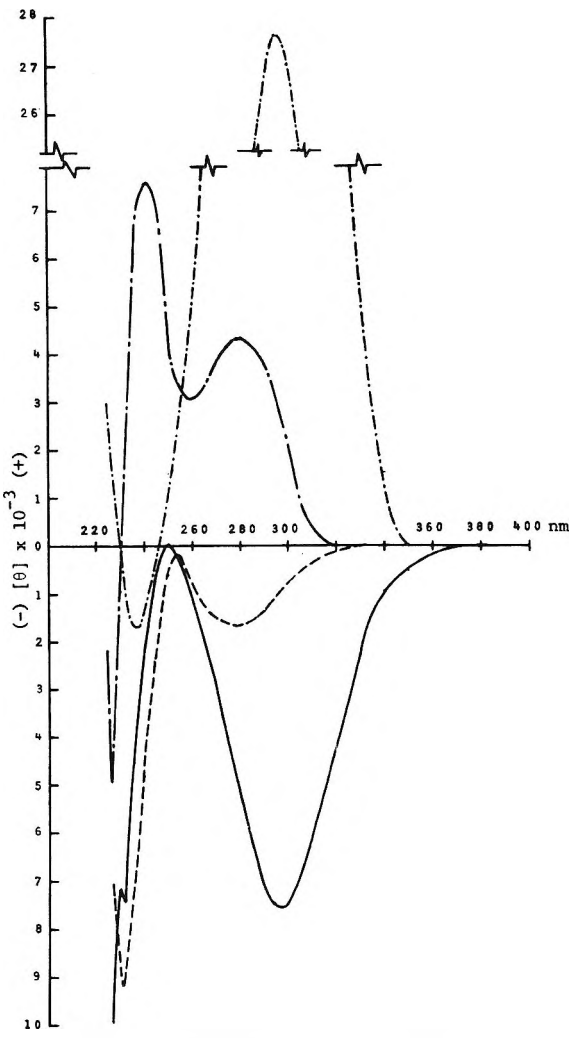
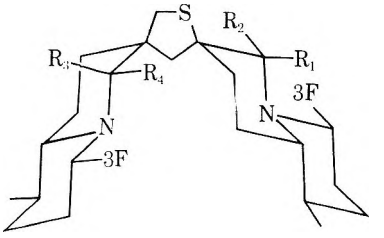


Figure 2. The circular dichroism in acid solution of 6-hydroxythiobinupharidine (**6**) (- · · · -); 6′-hydroxythiobinupharidine (**7**) (— · —); 6-hydroxyneothiobinupharidine (**1**) (——); 6′-hydroxyneothiobinupharidine (**2**) (- - - -).

The examination of the CD properties of 6′-hydroxyneothiobinupharidine (**2**) completes the series of 7*R*, 7*S*, 7′*R*, and 7′*S* α- and β-thiohemiaminals. In summary, the results of the present and preceding CD studies show that in acid solution the thiaspiran α-thiohemiaminals possessing 7*S* and 7*R* configurations give respectively positive and negative CD bands near 300 nm. The thiaspiran β-thiohemiaminals possessing 7′*R* and 7′*S* configurations give respectively positive and negative CD bands in the 275–285-nm region. Consistent with this generalization of the acid solution CD properties are those exhibited by the known bishemiaminals, 6,6′-dihydroxythiobinupharidine (**8**) and 6,6′-dihydroxythionuphlutine B (**9**).[7]

One other aspect of these results worthy of comment is the stereochemistry of the sodium borodeuteride reduction



6. $R_1 + R_2 = H + OH$; $R_3 = R_4 = H$
7. $R_1 = R_2 = H$; $R_3 + R_4 = H + OH$
8. $R_1 + R_2 = H + OH$; $R_3 + R_4 = H + OH$

of the α- and β-thiohemiaminals. Both 6-hydroxythiobinupharidine (6) and 6,6′-dihydroxythiobinupharidine (8) possess an equatorial sulfur atom at C-7 and undergo reduction with the incorporation of both axial and equatorial deuterium at C-6,[8] although in one study the incorporation was observed to be predominantly equatorial.[4b,9] However, 6,6′-dihydroxythionuphlutine B (9)[4b] and 6-hydroxyneothiobinupharidine (1) possess an axial sulfur atom at C-7 and undergo reduction with the incorporation of only axial deuterium at C-6. In the case of 1, the NMR of the labeled product (3) reveals no doublet at δ 1.71, which corresponds to the signal of the C-6 axial proton of unlabeled neothiobinupharidine. The C-6 equatorial proton at δ 3.20 appears as a broad singlet.

A number of model α-thiohemiaminals, derived from (−)-deoxynupharidine and possessing axial and equatorial C-7 sulfide groups, exhibit the same stereospecificity in reduction as the thiaspiran α-thiohemiaminals.[4b,3] Clearly the steric mode of sodium borodeuteride reduction is influenced by the stereochemistry of the C-7 sulfur atom, as previously discussed.[4b,9]

Contrasting with the steric course of α-thiohemiaminal reduction, the stereochemistry of β-thiohemiaminal reduction is independent of the configuration of C-7′ and the stereochemistry of the sulfur atom. β-Thiohemiaminal, 2, wherein the C-7′ thiomethylene is axial, undergoes axial incorporation of deuterium at C-6′ as evidenced by the ^{1}H NMR spectrum of the labeled compound 4, which shows no δ 1.55 doublet for the C-6′ axial proton as did the unlabeled neothiobinupharidine. However, both 6,6′-dihydroxythionuphlutine B (9) and 6,6′-dihydroxythiobinupharidine (8), wherein the C-7′ thiomethylenes are equatorial, also undergo reduction with incorporation of axial deuterium at C-6′.[4b]

The stereospecificity of α-thiohemiaminal reduction and the appearance of the 290–310-nm absorption bands of acidic α-thiohemiaminal solutions have been attributed[4b,7] to the interaction of sulfur with immonium ion. In the case of the β-thiohemiaminals, the thioimmonium absorption is observed but stereospecificity of reduction is not. This disparity of behavior suggests that the β-thioimmonium ion interaction, though sufficient to generate the absorption, is improperly disposed to direct the stereochemistry of sodium borodeuteride reduction.

Experimental Section

Spectra were determined as follows: proton nuclear magnetic resonance (^{1}H NMR) in solution specified, 2% Me_4Si (δ 0.00 ppm), on Varian XL-100-15 operating in the pulsed FT mode unless indicated otherwise, symbols br, s, d, q, and m refer to broad, singlet, doublet, quartet, and multiplet, respectively; infrared spectra (ir) on Perkin-Elmer 137 in solvents as indicated, symbols st, wk, and m refer to strong, weak, and moderate intensity, respectively; mass spectra (MS) on a Hitachi Perkin-Elmer RMU-6E using a direct inlet probe, 70 eV and 120°; high-resolution mass spectra were determined at the High Resolution Mass Spectrometry Laboratory, Battelle's Columbus Laboratories, Columbus, Ohio, on an AEI MS-9 using a direct inlet probe, 70 eV and 150 and 180°; circular dichroism (CD) on a Jasco Model 5 spectropolarimeter in solution at the concentrations indicated.

Optical rotations were determined in solution as indicated on a Perkin-Elmer 141 polarimeter. Thin layer chromatography was carried out on microscope slides uniformly coated with 0.25 mm of alumina GF_{254} and using the solvent systems specified. Elution chromatography employed neutral alumina in all cases. The sodium borodeuteride was purchased from Merck Sharp and Dohme and contained a minimum of 98% deuterium.

Isolation of 6-Hydroxyneothiobinupharidine (1). Chromatography of the combined mixture of two fractions, previously designated A-8 and A-9 and originating from *N. luteum* of Polish origin,[4d] was carried out on 20 g of alumina (4.5% water) using the eluting solvents in the volumes indicated and giving the fractions in amounts as follows: hexane, fraction A′1, 0 mg; hexane–Et_2O (9:1), 50 ml, fraction A′2, 2 mg; hexane–Et_2O (8:1), 50 ml, fraction A′3, 67 mg; hexane–Et_2O (8:2), 50 ml, fraction A′4, 59 mg; hexane–Et_2O (8:2), 50 ml, fraction A′5, 38.5 mg; hexane–Et_2O (8:2), 50 ml, fraction A′6, 21 mg; Et_2O, 100 ml, fraction A′7, 67 mg; MeOH, 100 ml, fraction A′8, 4 mg. Fraction A′7 was rechromatographed on 15 g of alumina (activity 3) using pyridine–Et_2O–hexane (3:10:37). After Dragendorf active eluate was first detected, five-drop fractions were taken and thereafter were collected several five-drop fractions totaling about 25 ml, the latter group of fractions and those preceding it being monitored by TLC [alumina, pyridine–Et_2O–hexane (3:10:37)]. Combination of fractions 1–8 gave combined fraction B′1 (46.8 mg); fractions 9–21 gave fraction B′2 (10 mg); and the last 25 ml of eluate gave fraction B′3 (18 mg) consisting of the previously described mixture of 6- and 6′-hydroxyneothiobinupharidine.[5] After standing at 5° for 5 months, B′3 became colored and therefore was chromatographed on 6 g of alumina which was eluted with two 30-ml portions of hexane, to obtain fractions B′4 (2 mg) and B′5 (11 mg), and 20 ml of Et_2O, to obtain fraction B′6 (0.5 mg). Fraction B′5 was chromatographed on 2 g of alumina (activity 2) with 75 ml of benzene to obtain fraction C′1 (9.4 mg) consisting of a mixture of 6- and 6′-hydroxyneothiobinupharidine: TLC (hexane–Et_2O, 9:1) R_f 0.26 and 0.36 (6-hydroxythiobinupharidine), 0.51 (6′-hydroxythiobinupharidine); high-resolution MS. obsd/calcd mass (formula) 510.2814/510.2915 ($C_{30}H_{42}N_2O_3S$), 509.2762/509.2838 ($C_{30}H_{41}N_2O_3S$), 508.2714/508.2759 ($C_{30}H_{40}N_2O_3S$). Fraction C′1 was chromatographed on 3 g of alumina (activity 3) eluting with hexane–Et_2O (9:1), the first 50 ml of which produced 8 mg of fraction D′1 [TLC (hexane–EtOAc, 9:1) R_f 0.26, 0.36, 0.51] and the second 30 ml of which yielded 1.4 mg of fraction D′2 consisting of 6-hydroxyneothiobinupharidine (1): TLC (hexane–EtOAc, 9:1) R_f 0.26 and on standing 0.26 and 0.36; CD (acidic 95% EtOH) $[\theta]_{298}$ −7500°.

To obtain a larger amount of 1, fraction D′1 was chromatographed on 10 g of alumina eluting first with CH_2Cl_2 in 16-ml and 12-ml portions to obtain fractions E′1 [1.6 mg, TLC (CH_2Cl_2) R_f 0.75] and E′2 [2 mg, TLC (CH_2Cl_2) R_f 0.45, 0.60, 0.75], respectively. Continued elution with 100 ml of CH_2Cl_2–MeOH (95:5) produced 5.8 mg of fraction E′3 consisting of 5.8 mg of 1: TLC (CH_2Cl_2) R_f 0.45 (major), 0.60 (minor), (hexane–EtOAc, 9:1) R_f 0.26 (major), 0.36 (minor), (hexane–EtOAc 8:2, twice developed) R_f 0.30 (major), 0.45 (minor), (CH_2Cl_2 and 1 drop MeOH) R_f 0.80; uv (acidic 95% EtOH) λ_{max} 298 nm (ε 2700); ir ($CDCl_3$) 3.1 (br, wk, OH), 2.65 (wk Bohlmann bands), 11.45 μ (st, 3-furyl); ^{1}H NMR (c 2.5 mg/0.3 ml $CDCl_3$) δ 8.32 (m, 4 H, 3-furyl β-H), 7.57 and 7.33 (br s, 2 H, 3-furyl β-H), 4.57 (s, 1 H, C-6 H), 3.96 (m, 1 H, C-4 H), 2.62 (br s, 2 H, CH_2S), 0.86 (d, 6 H, C-1 and C-1′ CH_3); high-resolution MS, obsd/calcd mass (formula) 510.2883/510.2916 ($C_{30}H_{42}N_2O_3S$), 509.2831/509.2838 ($C_{30}H_{41}N_2O_3S$), 508.2764/508.2766 ($C_{30}H_{40}N_2O_3S$), 492.2744/492.2810 ($C_{30}H_{40}N_2O_2S$), 230.1529/230.1545 ($C_{15}H_{20}NO$), 228.1380/228.1388 ($C_{15}H_{18}NO$), 178.1216/178.1232 ($C_{11}H_{16}NO$), 176.1057/176.1075 ($C_{11}H_{14}NO$); CD (c 0.7 mg/ml, neutral 95% EtOH) $[\theta]_{290}$ ±0°, $[\theta]_{255}$ −474°, $[\theta]_{248}$ ±0°, $[\theta]_{239}$ +1750°, $[\theta]_{233}$ ±0°, $[\theta]_{230}$ −1640°, $[\theta]_{229}$ −801°; CD (c 0.7 mg and 1 drop of 0.2 *M* $HClO_4$ in 1 ml of 95% EtOH) $[\theta]_{370}$ ±0°, $[\theta]_{295}$ −7500°, $[\theta]_{250}$ ±0°, $[\theta]_{236}$ −4520°, $[\theta]_{232}$ −7430°, $[\theta]_{230}$ −7210°, $[\theta]_{227}$ −9910°.

Conversion of 6-Hydroxyneothiobinupharidine to Neothiobinupharidine-6-d_1 (3). A solution of 1.8 mg of 6-hydroxyneothiobinupharidine in 10 drops of MeOH was treated with 10 mg of sodium borodeuteride at ambient temperature for 30 min and thereafter the solvent was removed by vacuum evaporation, giving a residue whose TLC showed R_f 0.3 (hexane–Et_2O, 8:2) and 0.2 (benzene–CH_2Cl_2, 9:1). Chromatography of the residue on 2 g of alumina (activity 2) using benzene gave fraction 1 (3 ml, 0 mg), fraction 2 (10 ml, 0.3 mg), and fraction 3 (20 ml, 1.3 mg). Fractions 2 and 3 were combined to give 1.6 mg of neothiobinupharidine-6-d_1 (3): $[\alpha]^{25}D$ −175° (*c* 1.3 mg/ml, 95% EtOH); ^{1}H NMR (deuteriobenzene) δ 3.20 (s, C-6 H eq), 1.71 (d, J = 11.5 Hz, C-6 H ax) observed in the spectrum of neothiobinupharidine was absent; MS *m/e* (rel intensity) 497 (3), 496 (9), 495 (24), (15% d_0, 84% d_1, 1% d_2), 494 (8), 360 (9), 231 (18), 230 (27), 170 (100), 178 (26), 136 (11), 107 (22), 94 (31), 81 (18), 79 (16).

Isolation of 6′-Hydroxyneothiobinupharidine (2). Chromatography of a 333-mg fraction, previously designated A 60[4a] and originating from *N. luteum* of Polish origin, was carried out on 15 g of alumina (activity 2) eluting with hexane–EtOAc (9:1) in 45 (fraction F′1, 113 mg), 45 (fraction F′2, 187 mg), and 100 ml (fraction F′3, 10 mg) and finally with 50 ml of MeOH (fraction F′4, 10 mg). Fraction F′1, giving a TLC (hexane–EtOAc, 9:1) R_f 0.24 and

0.33, was chromatographed on 15 g of alumina (activity 2) by eluting with hexane–EtOAc (95:5) in two 50-ml portions, fractions G'1 and G'2, respectively (0 and 98 mg), and thereafter one 100-ml portion, fraction G'3 (34 mg). Fraction G'3, giving a TLC (hexane–EtOAc, 9:1) R_f 0.24 and 0.33, was chromatographed on 15 g of alumina (activity 2) by eluting with hexane–EtOAc (9:1) in 7 (fraction H'1, 0 mg), 4 (fraction H'2), 2 (fraction H'3), and 24 ml (fraction H'4, 69 mg). Fractions H'2 and H'3 were combined to give, after evaporation of solvent, 3.4 mg of 6'-hydroxyneothiobinupharidine (2): TLC (hexane–EtOAc, 9:1) R_f 0.33; uv (acidic 95% EtOH) λ_{max} 275 nm (ϵ 470); ir (CCl_4) 2.85 (wk OH), 3.7 (m, Bohlmann bands), 11.45 μ (st, 3-furyl); ^{1}H NMR (3 mg/0.3 ml $CDCl_3$) δ 7.3 (m, 4 H, 3-furyl α-H), 6.53 and 6.24 (br singlets, 2 H, 3-furyl β-H), 4.34 (br s, ~1 H, OH), 4.08 (br s, 1 H, C-6' H), 3.54 (m, C-4' H), 0.86 (d, 6 H, C-1 CH_3); high-resolution MS, obsd/calcd mass (formula) 510.2935/510.2916 ($C_{30}H_{42}N_2O_3S$), 509.2868/509.2838 ($C_{30}H_{41}N_2O_3S$), 508.2774/508.2759 ($C_{30}H_{40}N_2O_3S$), 492.2755/492.2810 ($C_{30}H_{40}N_2O_2S$), 230.1513/230.1545 ($C_{15}H_{20}NO$), 228.1367/228.1388 ($C_{15}H_{18}NO$), 178.1198/178.1233 ($C_{11}H_{16}NO$), 176.1047/176.1075 ($C_{11}H_{14}NO$); CD (c 0.34 mg/ml, neutral 95% EtOH) $[\theta]_{270}$ ±0°, $[\theta]_{253}$ −750°, $[\theta]_{246}$ ±0°, $[\theta]_{239}$ +1690°, $[\theta]_{234}$ ±0°, $[\theta]_{228}$ −4050°, $[\theta]_{227}$ +2850°; CD (c 0.34 mg and 1 drop of 0.2 M $HClO_4$ in 1 ml of 95% EtOH) $[\theta]_{330}$ ±0°, $[\theta]_{285}$ −1500°, $[\theta]_{280}$ −1650; $[\theta]_{278}$ −1650°, $[\theta]_{270}$ −1500°, $[\theta]_{253}$ −375°, $[\theta]_{231}$ −9150°, $[\theta]_{228}$ −7430°.

Conversion of 6'-Hydroxyneothiobinupharidine to Neothiobinupharidine-6'-d_1 (4). A solution of 1.5 mg of 6'-hydroxyneothiobinupharidine in 5 drops of MeOH was treated with 10 mg of sodium borodeuteride for 1 hr at ambient temperature. Thereafter the solvent was evaporated under a stream of nitrogen and the residue was digested with 5 ml of CH_2Cl_2. The solvent was evaporated from the resulting extract and the residual oil was chromatographed on 2 g of alumina (activity 2) eluted with hexane–Et_2O (8:2), in 10- and 40-ml portions, fractions 1 and 2, and thereafter with 20 ml of benzene which gave fraction 3 comprised of 1.4 mg of neothiobinupharidine-6'-d_1 (4): $[\alpha]^{25}D$ −160° (c 1.3 mg/ml, 95% EtOH); ir (CCl_4) 3.60 (st, Bohlmann band), 4.90 (wk, C–D), 11.45 μ; ^{1}H NMR (deuteriobenzene) δ 3.21 (d of d, J = 2 and 11.5 Hz, C-6 H eq), 2.60–3.05 (overlapping multiplets, 5 H, C-6' H eq, C-4 and C-4' H, CH_2S), 1.71 (d, J = 11.5 Hz, C-6 H ax), and the 1.55 (d, J = 11.5 Hz, C-6' H ax) observed in the spectrum of neothiobinupharidine was absent; MS m/e (rel intensity) 497 (2), 496 (6), (25.6% d_0, 73% d_1, 1.4% d_2), 495 (16.5), 494 (7.5), 360 (7), 231 (14), 230 (26), 179 (17), 178 (100), 136 (8), 94 (22), 81 (11), 79 (10).

Registry No.—1, 55869-57-3; 2, 55869-58-4; 3, 55869-59-5; 4, 55869-60-8; 6, 50478-55-2; 7, 52002-85-4; neothiobinupharidine, 4850-09-3.

References and Notes

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Fluorescent Modification of Guanine. Reaction with Substituted Malondialdehydes

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Six representative tricyclic 1,N^2-(allylidene)guanine derivatives (**3a–f**), or 10-oxo-9,10-dihydropyrimido[1,2-a]purines, which bear a variety of substituents at position 7 (the second carbon of the allylidene bridge), have been prepared by reaction of the corresponding malondialdehydes (**1a–f**) with guanine (**2**) in aqueous 1 N HCl at 40°. The substituted malondialdehydes, by pK_a determination, show acidities similar to those of substituted acetic acids and, by their ultraviolet absorption spectra, show amphoteric behavior. The guanine products (**3**), structural analogues of the naturally occurring Y bases, are compared in terms of their NMR, ultraviolet, and fluorescence spectroscopic properties. The three ring protons of the tricyclic 1,N^2-(2-R-allylidene)guanine system show proton magnetic resonance signals at low field in trifluoroacetic acid indicative of aromatic ring current. The ultraviolet spectra of the products (**3**) exhibit long-wavelength absorption in aqueous acidic, neutral, and alkaline solution where guanine does not absorb, and their fluorescence spectra exhibit solvent dependence. In general, 1,N^2-[2-(*p*-methoxyphenyl)allylidene]guanine has the most favorable ultraviolet absorption and fluorescence emission properties, which suggests the potential utility of *p*-methoxyphenylmalondialdehyde in reactions with more complex guanine derivatives.

Recent investigations in our laboratory have been directed toward the preparation of modified tRNA bases[1] or tRNA base analogues[2–4] which are fluorescent. In considering reactions which involve modification of the existing tRNA bases, we have endeavored to devise or elaborate selective reactions which can be carried out under mild aqueous conditions compatible with the stability of nucleosides, nucleotides, coenzymes, and nucleic acids. Using these guidelines, we have turned our attention to the preparation of fluorescent guanine derivatives.

Structural elucidation of the "Y" bases (or "Wye" bases, imidazo[1,2-a]purines),[5–9] as naturally occurring tricyclic guanine derivatives found in $tRNA^{Phe}$ from yeast, wheat germ, and other sources, has stimulated the synthesis of nucleosides having related structures.[10,11] The naturally occurring Y bases and the recently prepared synthetic Y-base analogues are fluorescent. Consideration of these findings led us to conclude that reagents capable of cyclization reactions involving the 1-NH and the exocyclic 2-NH_2 substituent of guanine and providing three ring atoms and two double bonds would give convenient access to fluorescent guanine derivatives.[1] Earlier reports have indicated that

Table I
Electronic Absorption Data. Malondialdehydes (1)

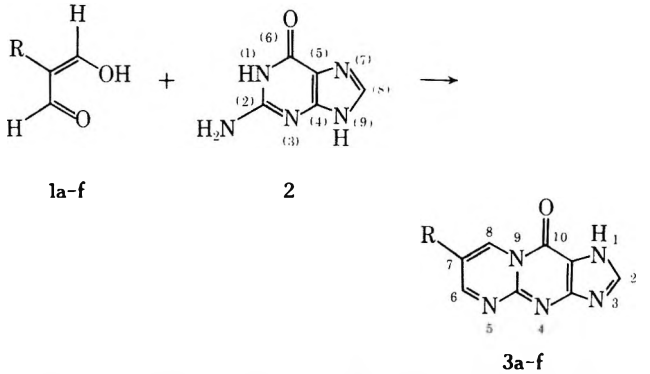
Compd	Acid 90% H_2SO_4 v/v		Acid 0.1 *N* HCl		Neutral[a] pH 6.8 ± 0.1		Alkaline 0.1 *N* NaOH		
	λ_{max}	$\epsilon \times 10^{-4}$	λ_{max}	$\epsilon \times 10^{-4}$	λ_{max}	$\epsilon \times 10^{-4}$	λ_{max}	$\epsilon \times 10^{-4}$	pK_a[b]
1a	270	1.35	250	1.02	275	1.48	275	1.49	4.7
1c	247	1.46	252	1.29	274	2.31	274	2.31	4.1
	305	0.490							
1d	247	2.32	234	1.75	275	2.12	275	2.17	4.3
	292	0.574	265 (sh)	0.895					
	315 (sh)	0.411							
1e	252	2.68	238	1.70	273	2.24	273	2.26	4.0
	300 (sh)	0.355							
1f	243	2.44	250	1.64	272	2.24	272	2.32	3.3
	249	2.48							5.7
	255	2.46							
	260 (sh)	2.05							
	280 (sh)	1.38							

[a] 0.08 *M* KH_2PO_4–Na_2HPO_4 buffer. [b] Solvent H_2O, 25°.

malondialdehyde reacts with DNA,[12] adenine, and guanine[13] to produce fluorescent products of unknown structure which emit at 460 nm upon excitation at 390 nm. In suitable control experiments,[14] it was observed that the highly unstable malondialdehyde alone produces products absorbing at 263 and 345 nm with fluorescence emission at 455 nm and exhibits the same new spots on cellulose TLC as one obtains in the presence of adenosine, cytidine, guanosine, uridine, and ammonium chloride. These results indicated that malondialdehyde offered little promise as a reagent for selective modification of nucleic acid components. In contrast, the substituted malondialdehydes are known to be considerably more stable than the unsubstituted parent molecule and to react with primary and secondary amines to produce a variety of nitrogen-containing heterocycles.[15–17]

Through the work of Arnold[18] and Reichardt[17] variously substituted malondialdehydes are now readily available. Our choice of which substituted malondialdehydes to employ for test reactions with guanine was governed by the requirements that the substituents present enhanced stability, that they be compatible with the display of fluorescence,[19] and that they permit reasonable solubility in aqueous media. We have examined the chemical and spectroscopic properties of six such aldehydes, **1a–f**, and those of their products, **3a–f**, of the respective reactions with guanine (**2**) in acidic aqueous solution.[20]

Scheme I



1a-f 2 3a-f

R: **a**, CH_3; **b**, CH_3O; **c**, C_6H_5; **d**, *p*-$CH_3OC_6H_4$; **e**, 3,4,5-$(CH_3O)_3C_6H_2$; **f**, *p*-$(CH_3)_2NC_6H_4$

Results and Discussion

Malondialdehydes. The substituted malondialdehydes **1a–e** (Scheme I) were prepared using published procedures.[15,21–23] *p*-Dimethylaminophenylmalondialdehyde (**1f**) had not been described previously. In general, the preparation of these materials involved Vilsmeier formylation of various substrates. Aldehydes **1a** and **1b**, for example, were prepared by formylation of propionaldehyde diethyl acetal[21,24] and methoxyacetaldehyde dimethyl acetal,[22] respectively, while the arylmalondialdehydes **1c–f** were synthesized by formylation of their corresponding arylacetic acids using the general method of Arnold[23] or the modified procedure of Coppola, Hardtmann, and Huegi.[15] Synthesis of **1f** was accomplished by causing *p*-dimethylaminophenylacetic acid[25] to react with a threefold molar excess of Vilsmeier reagent generated by reaction of phosphorus oxychloride with DMF, the formylation solvent. Treatment of the reaction solution with aqueous alkali provided α-(*p*-dimethylaminophenyl)-β-dimethylaminoacrolein as a solid which was easily hydrolyzed in alkaline ethanol–water solution to sodio-*p*-dimethylaminophenylmalondialdehyde. Neutralization of the conjugate base in aqueous acetic acid solution afforded **1f** in good yield.

All malondialdehydes employed in this investigation absorbed strongly in the ultraviolet. Eistert and Haupter[26] presented ultraviolet absorption data for ethoxy- and methoxymalondialdehyde (**1b**), and we include similar data for aldehydes **1a** and **1c–f** in Table I. Under mildly acidic conditions (0.1 *N* HCl), all aldehydes showed absorption maxima in the 230–270-nm region with extinction coefficients of 10000 or higher. In both neutral and alkaline aqueous solution the spectra of all the aldehydes were similar, showing shifts in their maximum absorption to near 275 nm accompanied by significant increases in the values of their extinction coefficients. The spectral changes in the pH range 1–7 are consistent with acidic dissociation of these dialdehydes to their respective anions within these pH extremes.

Osman[27] recently determined a pK_a of 4.46 ± 0.01 for malondialdehyde in water at 25° at an ionic strength of 0.1. A pK_a value of 3.7 for both ethoxy- and methoxymalondialdehyde (**1b**) has been presented by Eistert and Haupter.[26] For comparison, we include pK_a data for **1a** and **1c–f** in Table I as determined in aqueous solution at 25°. The pK_a values in Table I are closely related to the values for representative acetic acids. From the ionization constants presented by Kortüm, Vogel, and Andrussow,[28] the calculated pK_a's in water at 25° are as follows: acetic acid, 4.76; phenylacetic acid, 4.31; and *p*-methoxyphenylacetic acid, 4.36. Hoefnagel and Wepster[29] recently published a pK_a value of 3.75 for the dissociation of the carboxylic acid function in 4-trimethylammoniophenylacetic acid in water at 25°. Consideration of this value and comparison with the assigned dissociation values for the zwitterionic *p*-aminobenzoic acid (COOH, 2.38; NH_3, 4.89)[28] enabled us to assign

Table II
Electronic Absorption Data. 1,N^2-(2-R-allylidene)guanines (3)

Compd name and no.	Formula[a]	Mol wt[b]	Acid 0.1 N HCl λ_{max}	Acid 0.1 N HCl $\epsilon \times 10^{-4}$	Neutral[c] pH 6.8 ± 0.1 λ_{max}	Neutral[c] pH 6.8 ± 0.1 $\epsilon \times 10^{-4}$	Alkaline[d,e] pH 10.1 ± 0.1 λ_{max}	Alkaline[d,e] pH 10.1 ± 0.1 $\epsilon \times 10^{-4}$
1,N^2-(2-Methylallylidene)guanine (3a) or 7-Methyl-10-oxo-9,10-dihydropyrimido[1,2-*a*]purine	$C_9H_7N_5O$	201.19	218	2.26	218	2.97	228	3.90
			248	2.44	256	2.35	250 (sh)	1.59
			301 (sh)	0.490	309 (sh)	0.359	265	1.80
			312	0.558	319	0.395	315 (sh)	0.318
			342	0.490	355	0.414	372	0.340
1,N^2-(2-Methoxyallylidene)guanine (3b) or 7-Methoxy-10-oxo-9,10-dihydropyrimido[1,2-*a*]purine	$C_9H_7N_5O_2$	217.19	231	2.16	227	2.81	270	2.09
			259	2.09	265 (sh)	2.28	317	0.309
			267 (sh)	1.90	271	2.40	335	0.271
			287	0.428	300 (sh)	0.285	379	0.352
			300	0.404	365	0.381		
			312 (sh)	0.300				
			355	0.381				
1,N^2-(2-Phenylallylidene)guanine (3c) or 7-Phenyl-10-oxo-9,10-dihydropyrimido[1,2-*a*]purine	$C_{14}H_9N_5O$	263.25	248	2.26	244	2.66	245	3.18
			289	1.90	285	2.17	287	2.60
			315 (sh)	0.901	320 (sh)	0.591	323 (sh)	0.566
			360 (sh)	0.305	370	0.295	375	0.266
1,N^2-(2-*p*-methoxyphenylallylidene)-guanine (3d) or 7-*p*-Methoxyphenyl-10-oxo-9,10-dihydropyrimido[1,2-*a*]purine	$C_{15}H_{11}N_5O_2$	293.28	244	1.82	253	2.54	254	2.75
			258	1.84	256 (sh)	2.52	301	2.61
			306	2.53	304	2.59	335	0.614
			370 (sh)	0.260	370	0.307	380	0.260
1,N^2-[2-(3,4,5-trimethoxyphenyl)-allylidene]guanine (3e) or 7-(3,4,5-Trimethoxyphenyl)-10-oxo-9,10-dihydropyrimido[1,2-*a*]purine	$C_{17}H_{15}N_5O_4$	353.33	243	2.30	253	2.47	255	2.62
			307	2.14	256 (sh)	2.44	277	2.51
			370 (sh)	0.270	304	2.06	295	2.38
					370	0.285	380	0.285
1,N^2-(2-*p*-Dimethylaminophenyl-allylidene)guanine (3f) or 7-*p*-Dimethylaminophenyl-10-oxo-9,10-dihydropyrimido[1,2-*a*]purine	$C_{16}H_{14}N_6O$	306.32	245	2.26	222	2.26	231	2.65
			263 (sh)	2.08	257	1.98	270	2.01
			317	1.14	329	2.59	324	2.62
			360 (sh)	0.289				

[a] Satisfactory analytical data (± 0.3% for C, H, N) were reported for all compounds listed in the table. [b] Molecular ions were observed in the mass spectra for all compounds except 3e. [c] 0.08 *M* KH_2PO_4–Na_2HPO_4 buffer. [d] 0.1 *M* $NaHCO_3$–Na_2CO_3 buffer. [e] Spectra recorded within 10 min after preparation of alkaline solution.

the two pK_a values for **1f** in order of increasing value to the β-dialdehyde and *p*-dimethylammonium ionization, respectively.

While these data quantitatively substantiate the acidity of the substituted malondialdehydes, Table I also includes data demonstrating their weak basicity. Eistert and Haupter[26] provided spectroscopic evidence for protonation of ethoxy- and methoxymalondialdehyde (**1b**) in concentrated H_2SO_4. We have included similar data in Table I for aldehydes **1a** and **1c–f**. The ultraviolet spectra of all the aldehydes in 90% H_2SO_4 (v/v) differ significantly from their respective spectra in 0.1 *N* HCl. The spectrum of **1a** in 90% H_2SO_4 resembled that of its anion indicating that methylmalondialdehyde (**1a**) showed the same "amphoteric halochromism"[30] described for methoxymalondialdehyde (**1b**). Maxima for the arylmalondialdehydes in 90% H_2SO_4 were also shifted with respect to their values in 0.1 *N* HCl and, in addition, showed marked increases in absorption at longer wavelength. The results are consistent with O-protonation of the enolic β-dialdehyde moiety in strongly acidic solution. In the case of methylmalondialdehyde (**1a**) in particular, we found that this weak basicity could be used to advantage in its purification. Crude methylmalondialdehyde (**1a**) prepared from the sodium enolate salt by the original procedure of Arnold and Šorm,[21] required sublimation, crystallization, and additional sublimation for preparation of analytically pure product. The time required for purification can be shortened as a result of our observation that the neutral aldehyde can be precipitated from ether solution as a crude hydrochloride following addition of excess HCl in diethyl ether. The resulting hygroscopic crystalline solid loses HCl on standing in air. A 1% aqueous solution of this material is strongly acidic to pH paper and shows a positive test for chloride ion with 2% $AgNO_3$ solution. This acid-precipitable material is converted to free methylmalondialdehyde (75% yield) by storing at 1.5 mmHg over solid KOH at 25° for 12 hr.

Synthesis of Tricyclic Products (3). Products of type **3**, substituted 1,N^2-(allylidene)guanine derivatives or 10-oxo-9,10-dihydropyrimido[1,2-*a*]purines, 1*H* tautomeric form shown (see general formula for *Chemical Abstracts* numbering system)[31] were prepared by treating guanine (**2**) as the hydrochloride with a fivefold molar excess of substituted malondialdehyde (**1**) in 1 *N* HCl at 40° for 24 hr (Scheme I). These particular conditions proved most effective, although tricyclic products can be obtained under less acidic conditions. Crude hydrochlorides of **3a, 3c, 3d,** and **3e** were precipitated when their reaction solutions were chilled following the reaction incubation. The respective free bases (Table II) were obtained in 40–50% overall yield by acid–base crystallization. Crude product **3f** was recovered as a solid from the neutralized reaction solution and was obtained as a hemihydrate by crystallization from ethanol–water or as the anhydrous material following crystallization of the hemihydrate from absolute methanol. Preparation of the methoxy derivative **3b** required chromatographic purification as the hydrochloride followed by acid–base crystallization. Elemental analyses and mass spectra for the products were completely consistent with the molecular formulas, although the trimethoxyphenyl derivative **3e** failed to show a molecular ion. The molecular ion for all other derivatives appeared as the base peak in the respective spectra. In all cases, the mass spectra recorded at electron beam energies of either 10 or 70 eV were simple and

showed very few fragments, indicating substantial stability in the products—stability indicative of their polycyclic heteroaromatic nature.

The 100-MHz NMR spectra for compounds **3** in trifluoroacetic acid (therefore protonated) were also consistent with structures of a highly aromatic, polycyclic nature. All spectra for the protonated products **3** showed low-field resonances for three aromatic protons in addition to signals assignable to the substituents present in the aldehyde from which the products were derived. The spectrum of the methoxy-substituted compound (**3b**), for example, showed a three-proton singlet at δ 4.17 (downfield from Me_4Si) for the three *O*-methyl protons and coupled doublets at δ 9.10 and 9.30 (J = 3.2 Hz) for the 6 and 8 protons. A one-proton singlet for the 2-H appeared at δ 9.38. The coupling constant for the 6 and 8 protons was of the order of 2 Hz for compounds **3c–f.** In the spectrum of **3a,** a three-proton doublet (J = 1.1 Hz) at δ 2.68 for the 7-methyl group showed coupling with the one-proton quartet (J = 1.1 Hz) at δ 9.49 for the adjacent hydrogen at position 8. Similar splitting through a double bond has been observed for the Y bases synthesized by Kasai et al.[6] Protons 2 and 6 had identical chemical shifts in **3a** and appeared as a two-proton singlet at δ 9.33 in trifluoroacetic acid. The chemical shift for the singlet 2-H resonance appeared between δ 9.3 and 9.5 in the spectra for all products of type **3.** The corresponding 8 proton in the spectrum of protonated guanine (**2**) measured in trifluoroacetic acid appeared at δ 8.92. Clearly, the ring protons in the protonated products **3** are more extensively deshielded than the ring proton of guanine conjugate acid. They are also deshielded with respect to 2,6 and 7 protons observed for the linear tricyclic model, a substituted 10-oxo-9,10-dihydro-1,2,4-triazino[2,3-*a*]purine, in neutral $(CD_3)_2SO$ solution.[11] It would be instructive to inspect the NMR spectrum of the latter type in trifluoroacetic acid. In any case, the extended conjugation and ring current enhancement indicated by the substantial deshielding of all the ring protons coincides with the structure **3** that includes the additional six-membered ring attached linearly to the original guanine.

The linear tricyclic structure **3** is assured over the angular formulation of an N^2,3-(allylidene)guanine, which would have resulted from cyclization involving the exocyclic 2-NH_2 and the 3-NH (alternative, less contributing tautomeric form) of guanine, by analogy with the reaction between a guanine moiety and glyoxal, pyruvaldehyde, or α-keto-β-ethoxybutyraldehyde which leads to 1,N^2 cyclization and linear tricyclic products[32,33] and by the similarities in the ultraviolet spectral characteristics with those of the following linear tricyclic types: Y bases (imidazo[1,2-*a*]purines),[6,8] 1,2,4-triazino[2,3-*a*]purine derivatives,[11] and linear benzopurines (vs. their angular isomers).[2,3] The ultraviolet spectra for the compounds of type **3** (Table II) showed absorption at much longer wavelength, 300–450 nm, than guanine and maximum absorption in the 240–280-nm range at 5–7 times the absorption maxima at long wavelength. The neutral spectra for the aryl-substituted products **3c, 3d,** and **3e** exhibited an additional maximum in the 280–310-nm range, contributed by the benzenoid moiety, with extinction coefficients approaching or exceeding the values for their maxima at shorter wavelength (Figure 1). The neutral spectrum of the *p*-dimethylaminophenyl compound **3f** was exceptional in that its absorption maximum occurred at 329 nm and the spectrum lacked the well-defined maxima or shoulders at longer wavelength characteristic of the spectra for compounds **3a–e.** Ultraviolet spectra of products **3** in 0.1 *N* HCl were shifted with respect to the neutral spectra and exhibited changes consistent with protonation in acidic solution. The spectra in alkaline solution showed bathochromic shifts compared with the respective neutral spectra and general increases in overall absorbance throughout the 200–400-nm region attributable to the loss of a proton from the imidazole portion of the tricyclic system. The choice of pH 10.1 for recording the spectra in alkaline solution was governed by consideration of product stability. The alkaline spectrum of all products **3** changed with time at pH values higher than pH 10.1. The figures reported in Table II were recorded immediately following preparation of the solution and remained unchanged at pH 10.1 for at least 20 min.

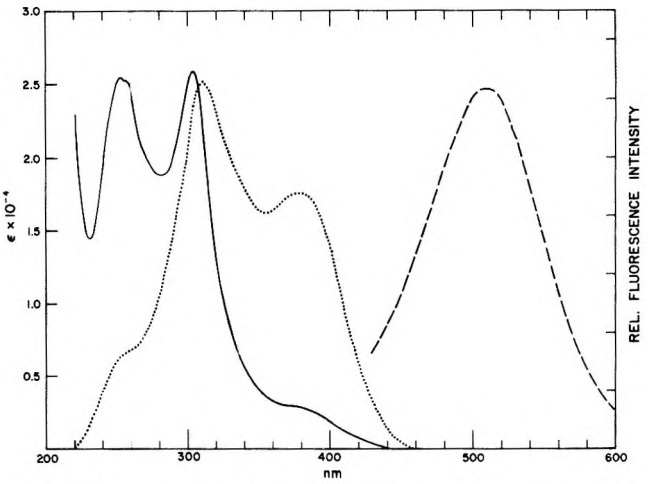


Figure 1. Ultraviolet absorption (—), fluorescence excitation (· · ·), and technical fluorescence emission (- - -) spectra for 1,N^2-[2-(*p*-methoxyphenyl)allylidene]guanine (**3d**) in water, pH 6.8.

Fluorescence Characteristics. Technical fluorescence emission and excitation data for compounds **3** at 25° in neutral aqueous solution and in various solvents at 25° have been summarized in Table III. The fluorescence characteristics of all compounds **3** were generally similar. Compounds **3a–d** exhibited detectable emission at 500 nm (excitation at their respective maxima) at concentrations of the order of 10^{-6}–10^{-5} *M* in water at pH 6.8. The trimethoxyphenyl and *p*-dimethylaminophenyl examples, **3d** and **3e,** however, were very weakly fluorescent in the protic solvents water and ethyl alcohol. Significantly, all compounds **3** showed substantial changes in their excitation and emission characteristics in nonprotic solvents of decreasing dielectric constant. Excitation maxima underwent shifts from 350 nm in water to 397 nm in less polar solvents in agreement with the position of their respective long wavelength ultraviolet absorption. While the wavelength of the emission maxima for compounds **3** did not change significantly with decreasing solvent polarity, the relative quantum yields and fluorescence lifetimes showed substantial increases. The relative quantum yield of **3d** (determined from uncorrected emission spectra), for example, showed an eightfold increase over the solvent series employed accompanied by a fivefold increase in fluorescence lifetime. These changes in emission characteristics were quite analogous to those recently observed in this laboratory for derivatives in the *lin*-benzoadenine series.[4]

After general consideration of all the properties of the six products prepared in this investigation, we concluded that guanine derivatives modified by *p*-methoxyphenylmalondialdehyde (**1d**) showed the greatest promise for future investigations involving fluorescent modification of guanine-containing materials. The long wavelength ultraviolet absorption of products **3d** should make it possible to monitor conveniently the extent of reactions involving **1d** and guanine derivatives using either ultraviolet or fluorescence spectroscopic techniques. Product **3d** can be excited in the

Table III
Fluorescence Emission and Excitation Data

Compd	Solvent	Emission[a] λ_{max}, nm	Excitation[b] λ, nm	τ, nsec	Φ relative[e]
3a	H_2O (pH 6.8)	500	360	0.8[c]	0.004
	EtOH	505	380	1.4[c]	0.010
	DMF	500	397	2.4[d]	0.027
	EtOAc	495	397	2.9[d]	0.038
	Dioxane	500	397	2.5[d]	0.030
3b	H_2O (pH 6.8)	510	375	0.8[c]	0.003
	EtOH	515	397	1.6[c]	0.008
	DMF	515	397	2.5[d]	0.017
	EtOAc	510	397	2.7[c]	0.030
	Dioxane	515	397	2.6[d]	0.026
3c	H_2O (pH 6.8)	505	290, 340, 370	0.7[c]	0.002
	EtOH	510	300, 345, 397	1.5[c]	0.005
	DMF	510	295, 345, 397	2.3[c]	0.008
	EtOAc	495	295, 345, 397	2.9[c]	0.025
	Dioxane	500	300, 345, 397	2.8[d]	0.021
3d	H_2O (pH 6.8)	510	310, 378	0.7[c]	0.004
	EtOH	510	335, 397	1.6[d]	0.006
	DMF	510	340, 397	3.1[d]	0.013
	EtOAc	500	318, 340, 397	3.6[d]	0.031
	Dioxane	500	320, 343, 397	3.7[d]	0.026
3e	H_2O (pH 6.8)	500	320		
	EtOH	500	322, 397	0.8[c]	0.003
	DMF	505	343, 397	1.5[c]	0.008
	EtOAc	498	320, 397	3.3[d]	0.027
	Dioxane	500	327, 397	2.9[d]	0.027
3f	H_2O (pH 6.8)				
	EtOH				
	DMF	535	340	0.8[c]	<0.001
	EtOAc	535	340	1.5[c]	0.001
	Dioxane	535	343	4.1[d]	0.004

[a] Fluorescence emission spectra were measured with excitation at the longest wavelength excitation maximum. [b] Excitation spectra were measured by holding fluorescence emission at 500 nm. [c] Fluorescence lifetime measured by phase only (see ref 38, 39). [d] Fluorescence lifetimes measured by phase and modulation and were identical to within 0.2 nsec (see ref 38, 39). [e] Determined using uncorrected emission spectra by comparison with quinine sulfate (in 0.1 *N* H_2SO_4) which has a quantum yield of 0.7 (see ref 40).

350–400-nm region, far beyond the usual protein and nucleic acid absorption range. Unlike compounds **3e** and **3f**, compound **3d** fluoresces at 500 nm with readily measurable emission in both protic and nonprotic solvents, thus ensuring the possibility that fluorescence parameters could be measured in aqueous media. Furthermore, of the products **3a–d**, the greatest increase in fluorescence lifetime with changing solvent polarity is observed for **3d**.

The influence of the molecular environment on the fluorescence of **3d** might prove to be very useful if the **3d** fluorophore were incorporated into guanine-containing nucleosides, nucleotides, or nucleic acids. If, for example, a modified and active guanine-containing coenzyme exhibited fluorescence enhancement in the presence of an enzyme specific for the unmodified coenzyme, it should be possible to obtain useful information about the nature of the site at which the enzyme and modified coenzyme interact. Similarly, the **3d** fluorophore in nucleic acids might be capable of monitoring conformational changes in the polymer since the properties of the environment surrounding the modified guanine residue might change as a result of conformational alteration in the larger polymer.[34] In sequels, we will describe the results of our investigations dealing with the preparation, properties, and interactions with enzymes of modified guanine nucleosides and nucleotides.

Finally, in any work employing new reagents for nucleic acid bases, it is advisable to determine whether facile chemical alteration of structure is accompanied by mutagenicity in living organisms. We are indebted to Dr. Graham C. Walker of the University of California, Berkeley, who carefully checked findings that all of the substituted malondialdehydes described here (**1a–f**) were nonmutagenic in Ames' tester strains TA 100 and TA 98 when incorporated into the top agar at a level of 2 mg/plate.[35,36] It may be that metabolic processes compete successfully in faster rates of conversion than the rate of chemical attack on the nucleic acid bases. Or it may be a function of the pH of the medium, since the reaction of the substituted malondialdehydes with guanine derivatives proceeds favorably only below pH 4.5. Chloroacetaldehyde, which has been used for fluorescence labeling of adenine- and cytosine-containing compounds,[1] reverts the *Salmonella* bacterial tester strain TA 100 and thus is mutagenic.[37] Since, in the opinion of Ames and his co-workers,[35–37] there is a high probability that chemicals found to be mutagens in the *Salmonella* test will turn out to be carcinogens, special care should be exercised by those working with reagents that readily (and specifically) alter the nucleic acid bases.

Experimental Section

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are corrected. Nuclear magnetic resonance spectra were recorded on either a Varian A-60 or HA-100 spectrometer using either trifluoroacetic acid or deuteriochloroform as solvent. Tetramethylsilane was used as an internal standard in both solvents. Mass spectra were run on a Varian MAT CH-5 spectrometer coupled with a 620i computer and STATOS recorder. Ultraviolet absorption spectra were obtained on a Beckman ACTA M VI spectrophotometer. For quantitative electronic absorption measurements a specific amount of material was weighed in a volumetric flask and dissolved in 0.01 *N* HCl. Aliquots of these stock solutions were diluted 1:5 with an appropriate aqueous buffer to arrive at solutions with concentrations of the order of $2–5 \times 10^{-5}$ *M* in compounds **3** at either pH 6.8 or pH 10.1, or in 0.1 *N* HCl. The spectra of these solutions were measured against an appropriate solvent blank. Fluorescence emission and excitation spectra were measured on a Hitachi Perkin-Elmer MPF-2A fluorescence spectrophotometer. Fluorescence lifetimes

were determined by phase and modulation as indicated (Table III) using the cross-correlation fluorometer described by Spencer and Weber.[38,39] The exciting light was selected with a monochromator and filtered through a Corning CS-7-54 filter. Emitted light was filtered through a Corning 3-71 filter. Relative quantum yields (Table III) were determined by comparing the area under the uncorrected emission spectra for products **3** with the area beneath the emission spectrum of quinine sulfate (in 0.1 *N* H_2SO_4), which has a quantum yield of 0.70.[40] All solvents used in fluorescence studies were freshly distilled and checked to ensure absence of emission in the 400–600-nm region when excited at 350 nm. Microanalyses were performed by Mr. Josef Nemeth and staff, who weighed samples for quantitative electronic absorption studies. The pK_a values for the aldehydes were determined potentiometrically for us at the Lilly Research Laboratories, Eli Lilly and Co., Indianapolis, Ind., and we are grateful to Ms. Mary Ann Bogan and Mr. George Maciak for their assistance.

Guanine (ICN Grade) was obtained from ICN Pharmaceuticals, City of Industry, Calif. The hydrochloride was prepared by crystallization from 1 *N* HCl. **Methylmalondialdehyde (1a)** was prepared through Vilsmeier formylation of propionaldehyde diethyl acetal[24] by the method of Arnold and Šorm[21] and was purified by conversion through its hydrochloride salt. To a vigorously stirred suspension of 5.0 g (0.046 mol) of the sodium salt of methylmalondialdehyde in 100 ml of ether was added 15 ml of 3 *N* HCl in ether and the suspension was stirred for 10 min. The solution was diluted to 200 ml with ether, stirred for an additional 5 min, and filtered to remove precipitated sodium chloride. The filtrate was acidified by the addition of 45 ml of 3 *N* HCl in ether and the precipitate was filtered and washed with ether to afford 3.4 g (61%) of presumed methylmalondialdehyde hydrochloride, mp (open tube, uncorrected) partial dec 90°, final dec 100–105°.

A 1% solution of this material in water is acid (pH < 2) to pH paper and shows a positive test for chloride ion when mixed with an equal volume of 2% $AgNO_3$ solution. The acid-precipitable material is converted to free methylmalondialdehyde by storing at 1.5 mmHg, 25° over KOH for 12 hr: yield 1.8 g (75% based on hydrochloride; 45% based on sodium salt); mp 89–89.5° (lit.[21] 88–89.5°); mass spectrum at 10 eV showed peaks at *m/e* 86 $(M)^+$, 85 $(M - H)^+$, 68 $(M - H_2O)^+$, 57 $(M - CHO)^+$; NMR ($CDCl_3$–Me_4Si) δ 1.74 (s, 3, CH_3), 8.30 (s, 2, CHO), 10.38 (broad, 1, OH). A 1% aqueous solution of this solid is slightly acidic to pH paper (pH 4–5) and shows no turbidity on mixing with an equal volume of 2% $AgNO_3$ solution.

Phenylmalondialdehyde (1c), *p*-methoxyphenylmalondialdehyde (1d),[15] and **3,4,5-trimethoxyphenylmalondialdehyde (1e)**[15] were prepared from the corresponding arylacetic acids using the general procedure of Arnold.[23] **Methoxymalondialdehyde (1b)**[26] was obtained through alkaline hydrolysis of 1,3-bis(dimethylamino)-2-methoxytrimethinium perchlorate prepared by Arnold.[22] The hydrolysis procedure employed was that described by Arnold and Šorm[21] for the conversion of α-methyl-β-dimethylaminoacrolein to the sodium salt of methylmalondialdehyde. The recovered sodium salt of methoxymalondialdehyde was neutralized with 1 equiv of HCl in ether, and following filtration of the precipitated sodium chloride, the ether was removed under reduced pressure to afford solid methoxymalondialdehyde (**1b**) which was thoroughly dried and used without further purification. ***p*-Dimethylaminophenylmalondialdehyde (1f)** was prepared by formylation of *p*-dimethylaminophenylacetic acid.[25]

***α*-(*p*-Dimethylaminophenyl)-β-dimethylaminoacrolein.** To 100 ml of chilled dimethylformamide was added 46 g (0.3 mol) of phosphorus oxychloride. The warm solution was allowed to stand for 5 min and 18 g (0.1 mol) of *p*-dimethylaminophenylacetic acid was added as a solid. The resulting solution was stirred at 75° for 4 hr, cooled to room temperature, and poured over 300 g of ice. Solid sodium hydroxide (36 g, 0.9 mol) was added and the suspension was stirred on ice until all solid had dissolved. The solution was made strongly alkaline by the addition of 200 ml of 10 *N* NaOH and was chilled to ensure that the temperature did not exceed 40°. After standing for 2 hr, the voluminous solid which precipitated was filtered and resuspended in 500 ml of water with vigorous stirring. The brown, undissolved solid was filtered, washed with water, and dried to afford 11 g (50%) of α-(*p*-dimethylaminophenyl)-β-dimethylaminoacrolein: mp 155° dec; mass spectrum *m/e* 218 (M^+); NMR ($CDCl_3$–Me_4Si) δ 2.80 [s, 6, $(CH_3)_2N$–], 2.90 [s, 6, $(CH_3)_2NAr$], 6.80 [s, 1, $(CH_3)_2NCH{=}C<$], 6.85 (m, 4, –Ar–), 9.07 (s, 1, –CHO).

Anal. Calcd for $C_{13}H_{18}N_2O$: C, 71.53; H, 8.31; N, 12.83. Found: C, 71.45; H, 8.16; N, 12.92.

***p*-Dimethylaminophenylmalondialdehyde (1f).** To a solution of 2 g (0.05 mol) of NaOH in 50 ml of 50% aqueous ethanol was added 2.5 g (0.01 mol) of α-(*p*-dimethylaminophenyl)-β-dimethylaminoacrolein, and the mixture was heated at reflux for 2 hr. The ethanol was removed under reduced pressure and the remaining solution was acidified by the addition of 5 ml of glacial acetic acid. A dark semisolid separated immediately. After brief standing the orange supernatant was decanted and chilled on ice to afford 1.1 g (50%) of *p*-dimethylaminophenylmalondialdehyde (**1f**): mp 144°; mass spectrum *m/e* 191 (M^+); NMR ($CDCl_3$–Me_4Si) δ 2.95 [s, 6, $(CH_3)_2N$–], 6.95 (m, 4, –Ar–), 8.53 (s, 2, =CHOH), 11.42 (broad, 1, =CHOH).

Anal. Calcd for $C_{11}H_{13}NO_2$: C, 69.09; H, 6.85; N, 7.32. Found: C, 68.90; H, 6.87; N, 7.04.

Reaction of Aldehydes 1a–f with Guanine Hydrochloride. General Procedure. To a solution of 0.18 g (1 mmol) of guanine hydrochloride in 7–10 ml of 1 *N* HCl was added 5 mmol of aldehyde, and the resulting homogeneous solutions (for reactions involving **1a**, **1b**, or **1f**) or suspensions (for reactions with **1c**, **1d**, or **1e**) were stirred at 40–45° for 24 hr. The products **3a**, **3c**, **3d**, and **3e** could be recovered as crude hydrochlorides in 50–60% yield when their respective reaction solutions were chilled to 10° for 1–2 hr following the reaction incubation. After water and ethanol washes of the acid precipitates, the free bases (Table I) were recovered in 40–50% overall yield by cautious neutralization of hot acid solutions of the hydrochlorides. Preparation of **3f** required neutralization of the reaction solution and liberal washing of the crude precipitate by suspension in absolute ethanol and filtration. Following acid–base precipitation from water, the recovered solid was crystallized from 80% aqueous ethanol. Drying under vacuum at room temperature over P_2O_5 for 24 hr afforded an analytical sample of **3f** as the hemihydrate. Recrystallization of the hemihydrate from absolute methanol followed by drying at 110° for 24 hr at 2 mmHg provided an analytical sample of anhydrous **3f** in 25% overall yield. Preparation of **3b** required chromatographic purification. Thus, following neutralization of the acidic reaction solution of **1b** with 2 (threefold scale up), the crude product (300 mg) was dissolved in 5 ml of 1 *N* HCl and layered on a 4.5 × 50 cm cellulose column. Elution was carried out with isopropyl alcohol–H_2O (7:3). The hydrochloride eluted as a yellow-green band. Following removal of the solvent under reduced pressure the solid residue was twice precipitated from hot acid solution by cautious neutralization to afford 60 mg (10%) of pure **3b**.

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Registry No.—**1a**, 57325-58-3; **1b**, 57325-59-4; **1c**, 4432-64-8; **1d**, 53868-40-9; **1e**, 53868-43-2; **1f**, 57325-60-7; **2** HCl, 635-39-2; **3a**, 57325-61-8; **3b**, 57325-62-9; **3c**, 57325-63-0; **3d**, 57325-64-1; **3e**, 57325-65-2; **3f**, 57325-66-3; α-(*p*-dimethylaminophenyl)-β-dimethylaminoacrolein, 57325-67-4; dimethylformamide, 68-12-2; *p*-dimethylaminophenylacetic acid, 17078-28-3.

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Self-Immolative Asymmetric Synthesis. I. Allylic Rearrangement of Optically Active Amine Oxide[1]

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Transfer of chirality from tetracoordinate nitrogen to trigonal carbon was achieved in the allylic rearrangement of (*R*)-(+)-*N*-*trans*-crotyl-*N*-methyl-*p*-toluidine oxide to (*S*)-(+)-*O*-methylvinylcarbinyl-*p*-tolylhydroxylamine with nearly complete conservation of chirality. The present thermally allowed [2,3]sigmatropic rearrangement proceeds via a transition state conformation such as to meet the orbital symmetry requirements in a doubly suprafacial fashion.

Extensive studies on [2,3]sigmatropic rearrangements have been made during the last few years and the accumulated knowledge[3] suggests that this process proceeds through a five-membered cyclic transition state of a doubly suprafacial migration. The transition state is of the Hückel type, and since six electrons participate, the reaction is expected to be thermally allowed in accordance with the Woodward–Hoffmann orbital symmetry rule.[4]

The [2,3] shifts are the anionic equivalent of the Cope rearrangement, and like the [3,3] changes, are not confined to carbon systems,[5] but also involve many hetero systems. The Wittig,[6] Stevens,[7] and Meisenheimer rearrangements of allylic systems,[8] the Sommelet rearrangement,[9] the rearrangements of allylic sulfonium ylides,[10] sulfenates,[11] phosphinates,[12] amidoammonium salts[13] and other hetero systems[14] can be categorized as [2,3]sigmatropic processes.

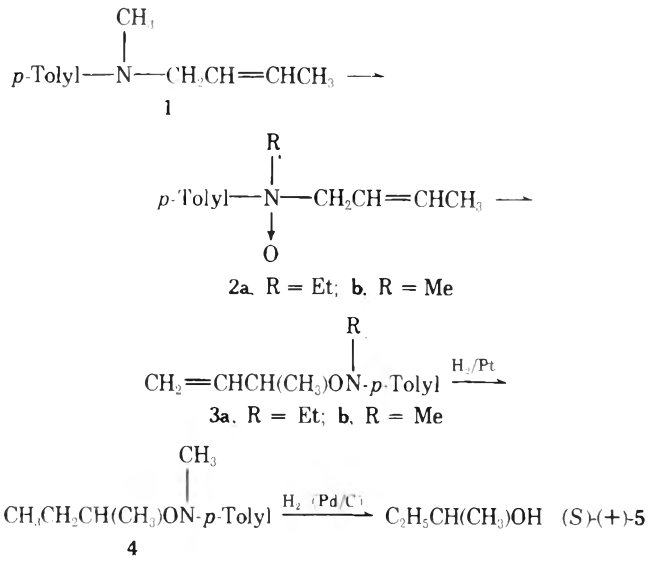
It is also known that this process is accompanied by a second pathway of higher activation energy, shown to be a radical-pair mechanism. The mechanistic difference depends on molecular environment and reaction conditions. In cases where the substrate has an allylic group, the concerted [2,3] shift competes favorably with the radical process. The former usually has the lower activation energy, as revealed by the fact that the proportion of the product which is formed by the concerted pathway increases at lower temperature. In contrast, the rearrangement of nonallylic compounds proceeds through a radical dissociation–recombination as demonstrated in the Wittig rearrangement of nonallylic ethers[15] and in the rearrangement of benzylamine oxide.[16]

In a preliminary report,[1] we described the first example of self-immolative asymmetric synthesis, in which the chirality on tetracoordinate nitrogen atom of (+)-*N*-*trans*-crotyl-*N*-ethyl-*p*-toluidine oxide (**2a**) was transferred, upon heating, completely to the trigonal carbon to give (+)-*O*-methylvinylcarbinyl-*N*-ethyl-*p*-tolylhydroxylamine (**3a**). However, since neither the absolute configuration nor the maximum rotation of **2a** was heretofore known, it was impossible to assess the degree of stereoselectivity and to formulate the transition state topology with certainty.

We now present unambiguous stereochemical evidence supporting the concerted nature of the [2,3]sigmatropic rearrangements of allylic amine oxide.

(*R*)-(+)-*N*-*trans*-Crotyl-*N*-methyl-*p*-toluidine oxide[17] (**2b**) was derived from the parent amine (**1**) by oxidation with *O,O*-dibenzoyl-L-pertartaric acid in chilled chloroform. Reflux of (+)-**2b** in 10% aqueous sodium hydroxide for 30 min gave (+)-*O*-methylvinylcarbinyl-*N*-methyl-*p*-tolylhydroxylamine (**3b**, $[\alpha]_D$ 2.42°) in 90% yield. This shows that a sigmatropic [2,3] allylic shift took place in the present system, as was the case with the *N*-ethyl homologue.[1] The absolute configuration of the newly created tetrahedral carbon was correlated by the sequential reduction to (*S*)-2-butanol (**5**) (Scheme I). Catalytic hydrogenation of (+)-**3b** over platinum oxide yielded (+)-*O*-2-butyl-*N*-methyl-*p*-tolylhydroxylamine (**4**, $[\alpha]_D$ 2.38°). Hydrogenol-

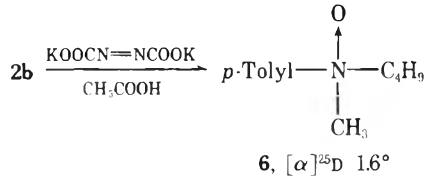
Scheme I



ysis of (+)-**4** over palladium on charcoal yielded 2-butanol (**5**, $[\alpha]$D 1.71°), together with *N*-methyl-*p*-toluidine. Since the *S* configuration of (+)-**5** has been unequivocally established,[18] the same configuration can be assigned to (+)-**3b** and (+)-**4**, and their optical purity was 13.6% based on the maximum rotation, 13°,[14] of the end product (**5**).

The absolute assignment of the nitrogen chirality as well as the enantiomeric purity of the starting amine oxide (+)-**2b**, crucial to the mechanistic picture for the present rearrangement, were obtained with success by the Pirkle method[20] of magnetic nonequivalence of chemical shifts in the ^{1}H NMR spectrum. To simplify the correlations based on Pirkle's chiral solute–chiral solvent interaction model, the double bond was first reduced so that the aromatic ring is the only remaining unsaturated substituent. Therefore, (+)-**2b** was reduced by the use of potassium diazocarbonate to (+)-**6**, $[\alpha]$D 1.65°, without disturbing the chiral nitrogen center (Scheme II). For more reliable determination of enantiomeric purity and sense of nonequivalence, we prepared (+)-**6** of a higher rotation, $[\alpha]$D 6.7°, according to the literature method.

Scheme II



With this optically active sample, the determination of absolute configuration and enantiomeric purity was undertaken. In optically active (*S*)-(+)-2,2,2-trifluoro(α-naphthyl)ethanol[21] (**7**), the *N*-methyl of (+)-enriched *N*-methyl-*N*-*n*-butyl-*p*-toluidine oxide shows a high field sense of nonequivalence (17 Hz), whereas in the enantiomeric (*R*)-(−) alcohol **7**, *N*-methyl shows a low field sense of nonequivalence (220 MHz at 29°) (Figures 1 and 2). Using Pirkle's solvation model,[20] one concludes that the methyl resonance should appear at higher field in the *R*–*S* solvate than in the *R*–*R*, while the opposite should be true for the *n*-butyl resonance. However, the latter resonance are coincident.

Based on the separation pattern and peak heights of the *N*-methyl resonances, it is concluded that (+)-amine oxide

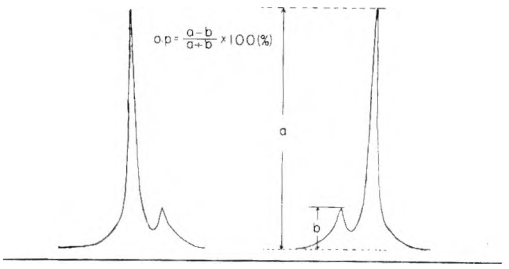


Figure 1. Enantiomeric nonequivalence exhibited by (+) enriched *N*-Methyl-*N*-*n*-butyl-*p*-toluidine oxide in optically active (*S*)-(+)- or (*R*)-(−)-2,2,2-trifluoro(α-naphthyl)ethanol at 220 MHz and 29°.

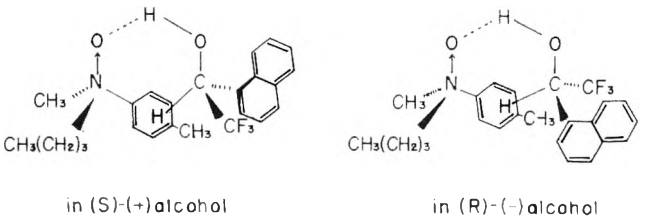


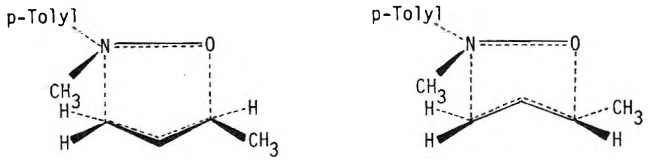
Figure 2. Conformations of the solvate between (*R*)-(+) *N*-oxide and (*S*)-(+) or (*R*)-(−) alcohol.

6 possesses the *R* configuration and the enantiomeric purity is 64.5%; therefore, the maximum rotation of the enantiomerically pure material is 10.4°. It then follows that the parent (+)-*N*-*trans*-crotyl-*N*-methyl-*p*-toluidine oxide (+)-(**2b**) has the same *R* configuration and an enantiomeric purity of 16%.

Independent confirmation of the enantiomeric purity was provided also by observation of the ^{1}H NMR spectrum of (+)-**6**, $[\alpha]$D 5.7°, in the presence of tris[3-(trifluoromethylhydroxymethylene)-*d*-camphorato]europium.[22] The separation of enantiotopic methyl singlets was 22 Hz. The peak height determination shows the enantiomeric excess to be 57.3% and then the maximum rotation to be 10°, in good agreement with that by the Pirkle method.

Consequently, the conservation of enantiomeric purity during the rearrangement was as high as 83% and may well be looked upon as being nearly complete when one takes into consideration the subsequent chemical transformations to 2-butanol **5**. Thus, the chirality of the tetracoordinate nitrogen atom in (+)-**2b** was transferred to the originally nondissymmetric trigonal carbon, giving rise to a newly created asymmetric carbon at the expense of nitrogen chirality.

With the knowledge of the *R* configuration of the starting amine oxide (+)-**2b** and the *S* configuration of the rearrangement product (+)-**4**, combined with the nearly complete conservation of chirality during the process, it can be concluded that the present rearrangement proceeds through a five-membered cyclic transition state by a concerted mechanism and the radical dissociation–recombination mechanism can be excluded. Concerning the potential generality to the stereochemistry of [2,3]sigmatropic rearrangement, Baldwin[3] stated that a doubly suprafacial transition state is more favored than a doubly antarafacial mode because of the geometrical and therefore energetic stringency of the latter. Application of the concept enables us to formulate the transition state topology for the present system. Figure 3 depicts such two rotational fashions of suprafacial modes **8** and **9**. The stereochemical evidence presented above cogently supports the mode **8** as the preferred one. Consistently, the nonbonded interaction between methyl and *N*-*p*-tolyl groups is minimized in **8**, which is therefore thermodynamically more favored.



8 9

Figure 3.

By analogy, the discussion may hold also for the thermal rearrangement of the *N*-ethyl homologue reported in the preliminary communication.[1]

Experimental Section

Melting and boiling points are uncorrected. Ir spectra were recorded on a Hitachi EPS-2 and ^{1}H NMR spectra on a Varian A-60 spectrometer. Optical rotations were observed with a Yanagimoto ORD-185A recording spectrophotometer.

***N*-*trans*-Crotyl-*N*-methyl-*p*-toluidine (1).** Crotyl bromide (15 g, 0.11 mol) in benzene (30 ml) was slowly added with stirring to *N*-methyl-*p*-toluidine[23] (10 g, 0.083 mol) in benzene (30 ml). The reaction mixture was heated for 30 min with stirring. After adding 10% aqueous sodium hydroxide (50 ml), the product was extracted with ether (200 ml), washed successively with dilute hydrochloric acid, dilute aqueous sodium hydroxide, and water, and dried over sodium sulfate. *N*-*trans*-Crotyl-*N*-methyl-*p*-toluidine distilled at 107–110° (8 mm); n^{28}D 1.5343; 11.5 g (79.3%); ir (liquid) $\nu_{C=C}$ (trans) 1670, δ_{CH} (trans) 970 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.68 (m, 3 H, crotyl CH_3), 2.25 (s, 3 H, ring CH_3), 2.84 (s, 3 H, NCH_3), 3.70 (m, 2 H, NCH_2), 5.68–5.18 (m, 2 H, CH=CH), 7.18–6.50 (m, 4 H, phenyl protons).

***N*-Methyl-*N*-*n*-butyl-*p*-toluidine.** *n*-Butyl bromide (30 g, 0.22 mol) was added to *N*-methyl-*p*-toluidine (24 g, 0.2 mol) in benzene (50 ml). The mixture was refluxed for 3 days. After adding 15% aqueous sodium hydroxide (70 ml), the product was extracted with ether, washed with dilute hydrochloric acid, dilute aqueous sodium hydroxide, and water, and dried over sodium carbonate. Distillation gave *N*-methyl-*N*-*n*-butyl-*p*-toluidine: bp 105–107° (8 mm); n^{25}D 1.5210; 25.1 g (95.1%); ^{1}H NMR ($CDCl_3$) δ 0.90 (t, 3 H, butyl CH_3), 1.41 (m, 4 H, $NCH_2CH_2CH_2$), 2.20 (s, 3 H, ring CH_3), 2.84 (s, 3 H, NCH_3), 3.22 (m, 2 H, NCH_2), 7.17–6.45 (m, 4 H, phenyl protons).

(*R*)-(+)-*N*-Methyl-*N*-*n*-butyl-*p*-toluidine Oxide (6). *N*-Methyl-*N*-*n*-butyl-*p*-toluidine (10 g, 0.057 mol) was allowed to react with 1 equiv of 40% peracetic acid in chilled chloroform with stirring and the reaction mixture was stirred for a further 5 days at room temperature. After adding 10% aqueous sodium hydroxide under cooling, *N*-methyl-*N*-*n*-butyl-*p*-toluidine oxide was extracted with three 40-ml portions of chloroform. The combined chloroform extracts were washed with 10% aqueous sodium hydroxide, dried over potassium carbonate, and evaporated under reduced pressure to give crude *N*-methyl-*N*-*n*-butyl-*p*-toluidine oxide (10.2 g, 91.7%).

(−)-*O*,*O*-Dibenzoyltartaric acid[24] (18 g, 0.057 mol) in ethanol (20 ml) was added with stirring to the crude amine oxide (10 g) in ethanol (30 ml). After standing still in the refrigerator overnight, crude precipitate [$[\alpha]^{25}$D −67.7° (*c* 0.3), 15 g, 50%] was collected. Several recrystallizations from ethanol (99.5%) gave the tartrate salt with constant physical properties: mp 158°; $[\alpha]^{25}$D −76.3° (*c* 0.82, MeOH); 4.2 g (13.4%); ir (KBr) ν_{OH} 3500, $\nu_{C=O}$ 1725 cm^{-1}.

Anal. Calcd for $C_{30}H_{33}NO_9$: C, 65.32; H, 6.03; N, 2.54. Found: C, 65.28; H, 6.18; N, 2.54.

The optically active amine oxide liberated from the salt was identified by comparison of ir and ^{1}H NMR spectra with those of an authentic sample: $[\alpha]^{25}$D +6.7° (*c* 3.57, chloroform); ^{1}H NMR ($CDCl_3$) δ 0.88 (t, 3 H, butyl CH_3), 1.70–0.95 (m, 4 H, $NCH_2CH_2CH_2$), 2.40 (s, 3 H, ring CH_3), 3.50 (s, 3 H, NCH_3), 3.60 (m, 2 H, NCH_2), 7.83–7.12 (m, 4 H, phenyl protons).

(+)-*N*-*trans*-Crotyl-*N*-methyl-*p*-toluidine Oxide (2b). *N*-*trans*-Crotyl-*N*-methyl-*p*-toluidine (**1**, 15 g, 0.078 mol) was oxidized at −70 to −75° with an equivalent amount of (*R*,*R*)-*O*,*O*-dibenzoylpertartaric acid in chloroform for 1 hr. The reaction mixture was kept at −20° overnight and then the solvent was evaporated at −10° under reduced pressure. Absolute ethanol (40 ml) was added to the residue and the solution was allowed to stand still in a refrigerator. The crystalline deposite (9.3 g) was recrystallized two times from warm ethanol. *N*-*trans*-Crotyl-*N*-methyl-*p*-toluidine oxide dibenzoyltartrate had mp 137–140.5° dec; $[\alpha]^{25}$D −78.4° (*c* 1.20, MeOH).

Anal. Calcd for $C_{30}H_{31}NO_9$: C, 65.56; H, 5.69; N, 2.55. Found: C, 65.26; H, 5.70; N, 2.53.

Picrate. The dibenzoyltartrate salt ($[\alpha]^{20}$D −75°) was decomposed with 10% aqueous sodium hydroxide below −10°. The aqueous mixture was extracted with cold chloroform and the chloroform layer was washed with dilute aqueous sodium hydroxide and dried over potassium carbonate. After removal of solvent under reduced pressure below −15°, an alcohol solution of picric acid was added slowly to the oily residue and the solution was kept cold in a refrigerator for at least 3 days: yellow needles, mp 118–120° dec, $[\alpha]^{18}$D 0°; $[\alpha]^{18}_{546}$ ±1°; $[\alpha]^{18}_{436}$ 19° (*c* 1.43, MeOH).

Anal. Calcd for $C_{18}H_{20}N_4O_8$: C, 51.15; H, 5.01; N, 13.23. Found: C, 51.42; H, 4.80; N, 13.33.

Reduction of *N*-*trans*-Crotyl-*N*-methyl-*p*-toluidine Oxide Dibenzoyltartrate with Potassium Diazocarbonate. Potassium diazocarbonate (900 mg) in methanol was added to the (−)-dibenzoyltartrate salt (500 mg) in methanol (6 ml), and acetic acid (500 mg) in methanol (3 ml) was slowly added to the mixture at 4° in a nitrogen atmosphere. The reaction mixture was stirred at 4° for 24 hr and was filtered, made alkaline, and extracted with three 10-ml portions of chloroform. The combined extracts were washed with 10% aqueous sodium hydroxide, dried over potassium carbonate, and evaporated under reduced pressure. The residue was separated on an alumina column. Elution with chloroform afforded first the rearrangement product (**3b**), and then with chloroform–methanol (3:1), the reduction product, *N*-methyl-*N*-*n*-butyl-*p*-toluidine oxide (**6**). The ir and ^{1}H NMR spectra were identical in every respect with those of the authentic sample: 32 mg (17.8%); $[\alpha]^{25}$D 1.6° (*c* 6.50, chloroform).

Rearrangement of Optically Active *N*-*trans*-Crotyl-*N*-methyl-*p*-toluidine Oxide (2b). The benzoyltartrate salt of *N*-*trans*-crotyl-*N*-methyl-*p*-toluidine oxide ($[\alpha]^{25}$D −78.4°, mp 137–140.5°, 8 g) was decomposed in 10% aqueous sodium hydroxide, and the liberated amine oxide was extracted with two 50-ml portions of chloroform. The combined chloroform extracts were evaporated, and the residue was heated in an alkaline solution for 1 hr. After cooling, the product was extracted with ether (200 ml), washed with dilute hydrochloric acid, dilute sodium hydroxide, and water, and then dried over sodium sulfate. Distillation gave (+)-*O*-2-butenyl-*N*-methyl-*p*-tolylhydroxylamine (**3b**): 2.5 g (89.3%); bp 95–98° (4 mm); n^{22}D 1.5180; $[\alpha]^{20}$D 2.42° (*c* 1.25, chloroform); ir (liquid) $\nu_{C=CH_2}$ 1640 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.30 (d, 3 H, $CHCH_3$), 2.30 (s, 3 H, ring CH_3), 3.00 (s, 3 H, NCH_3), 4.32 (m, 1 H, $CHCH_3$), 6.40–4.90 (m, 3 H, $CH=CH_2$), 7.10–6.80 (s, 4 H, phenyl protons).

Hydrogenation of (+)-*O*-2-Butenyl-*N*-methyl-*p*-tolylhydroxylamine (3b). (+)-*O*-2-Butenyl-*N*-methyl-*p*-tolylhydroxylamine (**3b**, 2.5 g, 0.013 mol, $[\alpha]^{20}$D 2.42°) was hydrogenated over a catalytic amount of platinum oxide in ether (150 ml). An equivalent amount of hydrogen was absorbed (250 ml) at room temperature. The catalyst was filtered off and the filtrate was washed with dilute hydrochloric acid, dilute aqueous sodium hydroxide, and water and dried over sodium sulfate. (+)-*O*-2-Butyl-*N*-methyl-*p*-tolylhydroxylamine (**4**) distilled at 80–82° (3 mm): n^{22}D 1.4997; $[\alpha]^{20}$D 2.38° (*c* 1.82, chloroform); 2.4 g (96%); ^{1}H NMR ($CDCl_3$) δ 0.92 (t, 3 H, CH_2CH_3), 1.20 (d, 3 H, $CHCH_3$), 2.00 (m, 2 H, CH_2CH_3), 2.30 (s, 3 H, ring CH_3), 3.00 (s, 3 H, NCH_3), 3.74 (m, 1 H, $CHCH_3$), 7.10–6.80 (s, 4 H, phenyl protons).

Hydrogenolysis of (+)-*O*-2-Butyl-*N*-methyl-*p*-tolylhydroxylamine (4). The hydroxylamine (+)-4 ($[\alpha]^{23}$D 2.38°, 2.1 g, 0.011 mol) was hydrogenolized in ether (30 ml) containing 500 mg of palladinized carbon. Hydrogenolysis proceeded very slowly at room temperature until 60% of the theoretical amount of hydrogen was absorbed, and did not proceed any further. After filtration, the solvent was removed below 50° and the residue was carefully distilled to give (*S*)-(+)-2-butanol boiling at 100–102°, n^{18}D 1.3985, $[\alpha]^{20}$D 1.71° (*c* 1.46, EtOH), optical purity 13.2% based on the reported maximum rotation ±13°. The ir and ^{1}H NMR spectra and other physical properties except optical rotation were identical with those of the authentic sample.

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Registry No.—**1**, 57049-22-6; **2b**, 57049-23-7; **2b** dibenzoyltartrate salt, 57049-24-8; **2b** picrate, 57049-25-9; **3b**, 57049-26-0; **4**, 57049-27-1; **6**, 57049-28-2; **6** dibenzoyltartrate salt, 57049-29-3;

crotyl bromide, 4784-77-4; *N*-methyl-*p*-toluidine, 623-08-5; *N*-methyl-*N*-*n*-butyl-*p*-toluidine, 57049-30-6; *n*-butyl bromide, 109-65-9; peracetic acid, 79-21-0; (−)-*O*,*O*-dibenzoyltartaric acid, 2743-38-6; (*R*,*R*)-*O*,*O*-dibenzoylpertartaric acid, 57049-31-7; potassium diazocarbonate, 4910-62-7; (*S*)-(+)-2-butanol, 4221-99-2.

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Self-Immolative Asymmetric Synthesis. II. Transfer of Chirality from Tetrahedral Carbon to Trigonal Carbon in Chiral Amine Oxide Rearrangement[1]

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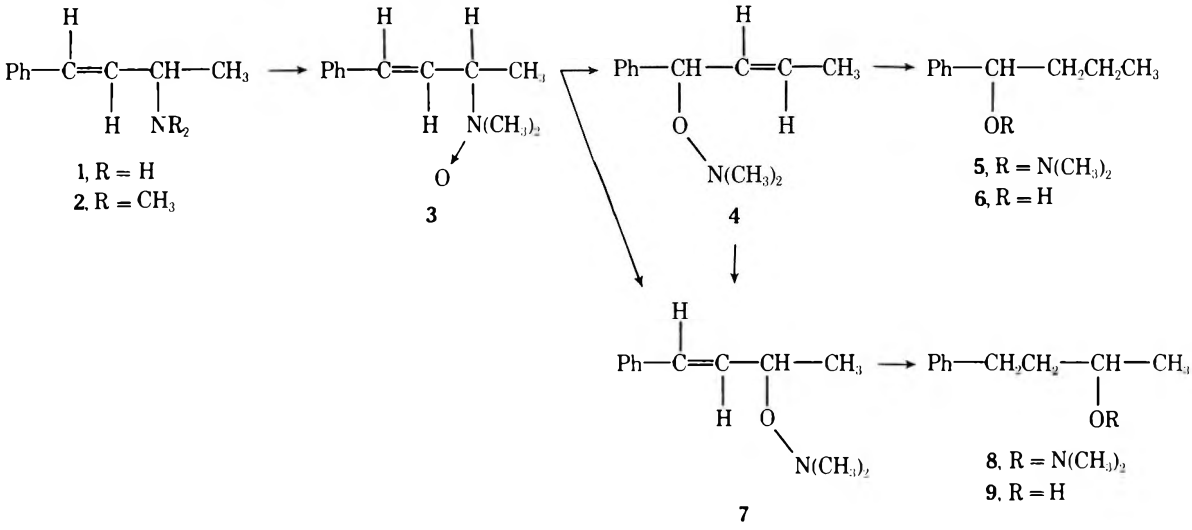
The [2,3]sigmatropic rearrangement of (*S*)-*N*,*N*-dimethyl-3-(*trans*-1-phenyl-1-butenyl)amine oxide to give (*S*)-*O*-*trans*-1-phenyl-2-butenyl-*N*,*N*-dimethylhydroxylamine was effected at −20° with nearly complete transfer of chirality from tetrahedral carbon to trigonal carbon. At higher temperature, the radical path prevailed to yield exclusively the [1,2] shift product, *O*-*trans*-1-methyl-3-phenyl-2-propenyl-*N*,*N*-dimethylhydroxylamine, with conservation of chirality to the extent of 20%.

In the preceding paper, we described the thermal [2,3]sigmatropic rearrangement of chiral amine oxide in which the chirality of nitrogen atom was nearly completely transferred to trigonal carbon at the expense of the former. We now wish to report another example of the same reaction in which the chirality of tetrahedral carbon was transferred to trigonal carbon.

The substrate used in the present study was the chiral amine oxide, (*S*)-*N*,*N*-dimethyl-3-(*trans*-1-phenyl-1-butenyl)amine oxide (**3**), prepared from (−)-*trans*-1-phenyl-3-amino-1-butene [(−)-**1**], $[\alpha]^{20}D$ −7.8°. The Eschweiler–Clarke methylation of (−)-**1**, followed by peracetic acid oxidation of the N-methylated amine (−)-**2**, $[\alpha]^{20}D$ −34.0°, afforded **3**, which was characterized by the picrate, $[\alpha]^{21}D$ −54.4°, in a parallel run starting from (−)-**2** having a rotation $[\alpha]^{18}D$ −36.4°. The *S* configuration[2] of (−)-**1** was established by chemical correlation of the enantiomeric (+)-**1** to (−)-benzoylalanine methyl ester of the well-defined *R* configuration,[3] through the consecutive N-benzoylation, barium permanganate cleavage, and esterification with diazomethane. The optical purity of (−)-**1** was determined to be 81% on the basis of the maximum rotation found by the optical resolution via (−)-malic acid salt.

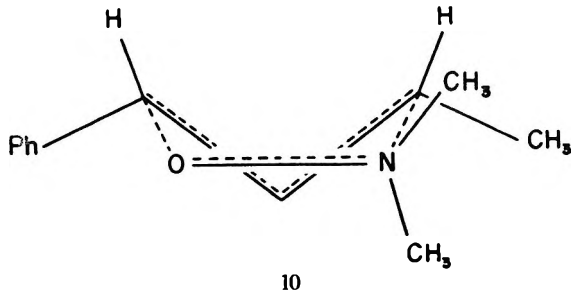
The amine oxide (**3**) thus obtained was allowed to stand at −20° for 24 days, during which **3** rearranged to *O*-*trans*-1-phenyl-2-butenyl-*N*,*N*-dimethylhydroxylamine (**4**) in 44% yield based on (−)-**2**. The trans geometry of the double bond in **4** was established by ir and ^1H NMR spectra in comparison with *trans*-1-phenyl-2-buten-1-ol. Since the rearrangement product **4** was not so stable as to permit one to observe constant rotation at room temperature, it was at once hydrogenated over platinum oxide to give (−)-*O*-1-phenylbutyl-*N*,*N*-dimethylhydroxylamine [(−)-**5**], $[\alpha]^{26}D$ −83.4°. Reductive N–O bond fission of (−)-**5** with zinc in



acetic acid afforded (−)-1-phenyl-1-butanol [(−)-**6**], $[\alpha]^{22}D$ −31.6°.

Successful transfer of the chirality originally residing on the tetrahedral carbon to the trigonal carbon was thus achieved in the present system. Since the *S* configuration of the end product (−)-**6** has been unambiguously established,[4] the same configuration can be assigned to the parent (−)-**5** and **4**. Consequently, the *S* configuration of the rearrangement product **4** was newly created at the expense of the *S* configuration of the substrate amine oxide (**3**). The optical purity of (−)-**6** proved to be 69% based on the reported maximum rotation $[\alpha]D$ −45.9°,[5] so that 85% optical activity was retained during the present process. It was reported that ca. 16% racemization occurred when the hydroxylamine derivative of (−)-benzyl alcohol-α-*d* was treated with zinc dust in acetic acid.[6] To assess the extent of racemization inherent to the method for N–O bond cleavage, (−)-1-phenyl-1-butanol[7] having a rotation $[\alpha]^{19}D$ −41.2° was subjected to exactly the same treatment and the recovered alcohol had a rotation of $[\alpha]^{20}D$ −35.4°, which corresponded to ca. 86% retention of optical activity. It then follows that the optical yield in the present self-immolative asymmetric synthesis can be looked upon as being nearly quantitative.

The complete transfer of chirality during the [2,3] shift supports the concerted mechanism and excludes the radical dissociation–recombination. There are two conceivable transition states expected for thermally allowed [2,3]sigmatropic rearrangement from the viewpoint of the conservation of orbital symmetry: doubly suprafacial and doubly antarafacial.[8] The finding that the (*S*)-*trans*-amine oxide (**3**) rearranged to give (*S*)-*trans*-hydroxylamine (**4**) cogently supports the fashion **10**. In this fashion, both fragments



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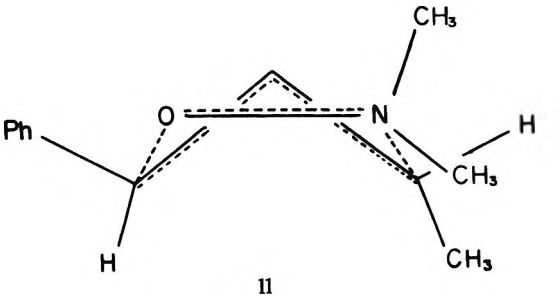
orient doubly suprafacial, which is geometrically preferred to the antarafacial modes. The preference of the mode **10** to an alternative suprafacial **11** could be rationalized by the unfavorable nonbonded interaction between methyl group and hydrogen atom which orient syn-quasi-axial in an envelope form of the latter.



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When the amine oxide (**3**) derived from (*R*)-(+)-**2**, $[\alpha]^{25}D$ 36.6° (87% optical purity), was heated in chloroform under reflux for 1 hr, the [1,2] shift product, (+)-*O*-*trans*-1-methyl-3-phenyl-2-propenyl-*N*,*N*-dimethylhydroxylamine [(+)-**7**], $[\alpha]^{25}D$ 6.9°, was obtained in an overall yield of 56% from **2** through **7**. There was no detectable contamination of the [2,3] shift product **4**.

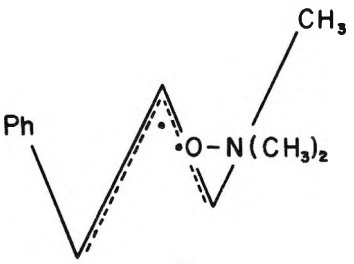
Hydrogenation of (+)-**7** over platinum oxide gave (−)-*O*-1-methyl-3-phenylpropyl-*N*,*N*-dimethylhydroxylamine (**8**), $[\alpha]^{25}D$ −6.6°. Subsequent treatment of (−)-**8** with zinc dust in acetic acid afforded (−)-1-phenyl-3-butanol (**9**), $[\alpha]^{26}D$ −3.2°. The *R* configuration can be safely assigned to (−)-**8** and (+)-**7**, and the optical purity was assessed to be 17% by transformation to (−)-**9** whose *R* configuration[9] and maximum rotation, $[\alpha]^{20}D$ −19.41°,[10] have been known.

The chirality at the carbon atom originally bonded to the nitrogen atom was conserved to the extent of 20% (corrected for the optical purity of the amine oxide used) at the same chiral center during the present thermal process.

An aliquot of the chloroform solution of the chiral amine oxide (**3**) was subjected to [2,3] rearrangement under the same condition described above and the resultant product **4** was then heated in chloroform under reflux for 1 hr. Along with a small amount of **4**, the compound (+)-**7** was obtained, which upon hydrogenation was converted into (−)-**8** having a rotation $[\alpha]^{27}D$ −6.5°. Consequently, the conservation of chirality in the course of the present consecutive [2,3] and [1,3] rearrangements compared well with that of the direct thermal [1,2] shift.

These facts show that the higher the temperature, the more the radical path prevails in competition with the [2,3] concerted process.[8] The [1,2] shift upon heating seems to take place via the classical Meisenheimer mechanism.[11] The radical dissociation–recombination is supported by the fact that the conservation of chirality at the carbon atom

was of the extent of 20%. The value is in accordance with the observation that the rearrangement of (+)-*N,N*-dimethylbenzyl-α-*d* amine oxide proceeded with 22–39% retention of configuration.[12] The radical pair intermediate can be formulated as explicit in **12**. *N,N*-Dimethylnitroxide



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radical is in juxtaposition to the allylic radical. The orientation seems to permit access of no less than 20% of retention at the chiral center concerned during the thermal process which has inevitable randomness.

It seems likely that the [1,3] shift from **4** to **7** involves a process of dissociation into two halves, since the magnitude of racemization is comparable with that of the direct [1,2] shift. The same solvent-caged radical pair was assumed in the [1,3] rearrangement of *O*-linalyl-*N,N*-dimethylhydroxylamine.[13] It can be explained by product stability that the [1,2] shift product was finally obtained on heating. The higher stability of **7** than **4** is rationalized by the conjugation of double bond with phenyl.

Experimental Section

(−)-*trans*-1-Phenyl-3-amino-1-butene [(−)-1]. The racemic amine[14] (30 g, 0.2 mol) was added to (+)-tartaric acid (30.6 g, 0.2 mol) in ethanol (1200 ml) and the salt formed was recrystallized twice from ethanol to yield colorless plates (11.4 g), mp 165–166°, $[\alpha]^{21}$D 0.0° (c 0.20, ethanol). The amine liberated from the salt had bp 120–122° (20 mm), n^{21}D 1.5614, $[\alpha]^{20}$D −7.8° (*c* 10.0, benzene).

The optically pure (+) enantiomer was obtained via the (−)-malate salt, mp 157–158°, $[\alpha]^{26}$D 35.1° (*c* 1.0, ethanol), $[\alpha]^{27}$D 9.6° (*c* 9.8 benzene).

Configurational Correlation of (+)-1. The N-benzoylation of (+)-1 (4.0 g, 0.027 mol, $[\alpha]^{20}$D 7.2°) was effected in the usual manner to give (+)-*trans*-1-phenyl-3-benzoylamino-1-butene (6.5 g, 95.2%), mp 132° (136–137° reported for the racemate[14]), $[\alpha]^{20}$D 34.2° (c 1.0, methanol). The benzoylamine (2.5 g, 0.01 mol) was treated with barium permanganate in the reported manner[15] and the crude product was esterified by the standard method with diazomethane. Purification on a silica gel column with benzene–ethyl acetate (8:1) used as eluent and crystallization from ligroin yielded (−)-benzoylalanine methyl ester: mp 53–54° (lit.[3] 58°); $[\alpha]^{19}$D −29° (*c* 2.0, acetylene tetrachloride); ir (KBr) ν_{NH} 3300, $\nu_{OC=O}$ 1745, $\nu_{NC=O}$ 1630 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.52 (d, 3 H, CH_3), 3.82 (s, 3 H, OCH_3), 4.62–5.13 (m, 1 H, CH), 6.65–7.08 (broad, 1 H, NH), 7.40–8.08 (m, 5 H, phenyl).

Anal. Calcd for $C_{11}H_{13}NO_3$: C, 63.75; H, 6.32; N, 6.76. Found: C, 63.75; H, 6.49; N, 6.94.

The ir and ^{1}H NMR spectra were identical in every respect with those of the authentic (*S*)-(+)-benzoylalanine methyl ester, which was derived from (*S*)-alanine, $[\alpha]^{19}$D 33°.

(−)-*trans*-1-Phenyl-3-*N,N*-dimethylamino-1-butene [(−)-2]. The Eschweiler–Clarke methylation[16] of (−)-1 (4.0 g, 0.027 mol, $[\alpha]^{20}$D −7.8°) with formic acid and formaldehyde gave (−)-**2** (2.3 g, 47.4%): bp 133–134° (21 mm); n^{22}D 1.5351 [lit.[17] bp 139–140° (25 mm), n^{25}D 1.5350 for the racemate]; $[\alpha]^{20}$D −34.0° (c 10.0, benzene).

Picrate of *N,N*-Dimethyl-3-(*trans*-1-phenyl-1-butenyl)amine Oxide (3). Peracetic acid (40%, 1.3 g, 0.007 mol) was added dropwise at −40° to (−)-2 (0.81 g, 0.0047 mol, $[\alpha]^{18}$D −36.4°) in chloroform (20 ml). The reaction mixture was allowed to stand at −20° overnight and then made alkaline with 10% aqueous sodium hydroxide and the aqueous layer was extracted with chloroform (15 ml × 3). The combined extract was dried over anhydrous potassium carbonate and filtered. Picric acid (0.85 g, 0.0037 mol) in ethanol (20 ml) was added to the filtrate, and the mixture was stored in a refrigerator. The picrate salt deposited (0.75 g, 38.4%): mp 144–145°, $[\alpha]^{21}$D −54.4° (c 0.50, methanol); ir (KBr) ν_{N-O}, $\delta_{=CH}$ (trans) 968, 962 cm^{-1}; ^{1}H NMR (Me_2SO-d_6) δ 1.57 (d, 3 H, CH_3), 3.30 (broad, 1 H, OH), 3.39 and 3.42 [s, 6 H, $N(CH_3)_2$], 4.50 (m, 1 H, CH), 6.15–7.08 (m, 2 H, CH=CH), 7.22–7.68 (m, 5 H, phenyl), 8.58 (s, 2 H, picrate).

Anal. Calcd for $C_{18}H_{20}N_4O_8$: C, 51.43; H, 4.80; N, 13.33. Found: C, 51.14; H, 4.98; N, 13.10.

[2,3] Rearrangement of 3. The amine oxide (**3**) was obtained by the oxidation of (−)-**2** (2.3 g, 0.013 mol, $[\alpha]^{20}$D −34.0°) with 40% peracetic acid (3.8 g, 0.02 mol) in chloroform (60 ml) in exactly the same way as described above. The amine oxide extracted was allowed to stand still at −20° for 24 days. The chloroform solution was filtered through 50 g of activated alumina and evaporated in vacuo at 0°. *O-trans*-1-Phenyl-2-butenyl-*N,N*-dimethylhydroxylamine (**4**) was obtained in an overall yield of 44% from (−)-**2**: 1.1 g; ir (liquid) $\delta_{=CH}$ (trans) 962 cm^{-1}; ^{1}H NMR (CCl_4) δ 1.70 (m, 3 H, CH_3), 2.47 [s, 6 H, $N(CH_3)_2$], 4.74–5.72 (m, 3 H, CH and CH=CH), 7.27 (m, 5 H, phenyl).

(−)-*O*-1-Phenylbutyl-*N,N*-dimethylhydroxylamine [(−)-5]. The hydrogenation of **4** (1.1 g) over platinum oxide in ethanol at 0° gave (−)-**5** (1.0 g, 90.1%). The analytical sample was obtained by preparative VPC (5% DEGS on Neosorb, 150°, He 80 ml/min): n^{25}D 1.4842; $[\alpha]^{26}$D −83.4° (*c* 6.0, benzene); ^{1}H NMR (CCl_4) δ 0.93 (m, 3 H, CH_3), 1.15–1.85 (m, 4 H, CH_2CH_2), 2.37 [s, 6 H, $N(CH_3)_2$], 4.43 (t, 1 H, CH), 7.19 (m, 5 H, phenyl).

(−)-1-Phenyl-1-butanol [(−)-6]. Zinc dust (2.0 g, 0.026 g-atom) and 30% acetic acid (20 ml) were added to (−)-**5** (1.0 g, 0.0052 mol, $[\alpha]^{26}$D −83.4°). The mixture was heated under reflux for 5 hr and extracted with ether. The ether extract was washed with saturated sodium carbonate solution and water, dried over sodium sulfate, and evaporated. (−)-1-Phenyl-1-butanol [(−)-**6**] was obtained (0.58 g, 74.6%). The analytical sample was obtained by preparative VPC (5% PEG 20M on Neosorb, 200°, He 70 ml/min): mp 36–37° (lit.[5] 49–50° for pure enantiomer), $[\alpha]^{22}$D −31.6° (c 10.0, benzene); ^{1}H NMR ($CDCl_3$) δ 0.98 (m, 3 H, CH_3), 1.14–1.95 (m, 4 H, CH_2CH_2), 2.03 (s, 1 H, OH), 4.73 (t, 1 H, CH), 7.42 (m, 5 H, phenyl).

Anal. Calcd for $C_{10}H_{14}O$: C, 79.95; H, 9.39. Found: C, 79.77; H, 9.53.

Zinc dust (4.0 g) and 30% acetic acid (40 ml) were added to (−)-**6** (1.55 g, $[\alpha]^{19}$D −41.2°) and the mixture was treated in exactly the same way as described above. The recovered alcohol (−)-**6** (1.3 g) had $[\alpha]^{20}$D −35.4°.

[1,2] Rearrangement of 3 to Give (+)-*O-trans*-1-Methyl-3-phenyl-2-propenyl-*N,N*-dimethylhydroxylamine [(+)-7]. The amine oxide **3**, obtained from (+)-**2** (5.0 g, $[\alpha]^{25}$D 36.6°) and 40% peracetic acid (8.2 g) in chloroform (120 ml), was divided into two portions, (1) 200 ml and (2) 160 ml.

The portion 1 was heated under reflux for 1 hr and the product was purified on an alumina column with *n*-hexane used as eluent. (+)-**7** (1.7 g, 56.2%): n^{26}D 1.5178; $[\alpha]^{25}$D 6.9° (c 5.8, benzene); ir (liquid) $\delta_{=CH}$ (trans) 955 cm^{-1}; ^{1}H NMR (CCl_4) δ 1.27 (d, 3 H, CH_3), 2.55 [s, 6 H, $N(CH_3)_2$], 4.35 (m, 1 H, CH), 6.00–6.78 (m, 2 H, CH=CH), 7.20–7.62 (m, 5 H, phenyl).

(−)-*O*-1-Methyl-3-phenylpropyl-*N,N*-dimethylhydroxylamine [(−)-8]. The hydrogenation of (+)-**7** (1.7 g, $[\alpha]^{25}$D 6.9°) over platinum oxide in ethanol gave (−)-**8** (1.3 g, 75.8%). The analytical sample was obtained by preparative VPC (5% PEG 20M on Neosorb, 180°, He 80 ml/min): n^{26}D 1.4823; $[\alpha]^{25}$D −6.6° (*c* 10.3, benzene); ^{1}H NMR (CCl_4) δ 1.15 (d, 3 H, CH_3), 1.34–2.17 and 2.58–2.99 (m, 4 H, CH_2CH_2), 2.53 [s, 6 H, $N(CH_3)_2$], 3.71 (m, 1 H, CH), 7.27 (m, 5 H, phenyl).

(−)-1-Phenyl-3-butanol [(−)-9]. The zinc dust–acetic acid treatment of (−)-**8** (0.8 g, $[\alpha]^{25}$D −6.6°) and the subsequent work-up in exactly the same manner as described for (−)-**6** yielded (−)-**9** (0.64 g, 96.4%): n^{28}D 1.5090; $[\alpha]^{26}$D −3.2° (c 6.2, benzene); ^{1}H NMR (CCl_4) δ 1.17 (d, 3 H, CH_3), 1.49–1.92 and 2.53–2.90 (m, 4 H, CH_2CH_2), 2.13 (s, 1 H, OH), 3.75 (m, 1 H, CH), 7.19 (m, 5 H, phenyl); phenylurethane, mp 113–114° (lit.[18] mp 113° for the racemate).

Anal. Calcd for $C_{17}H_{19}NO_2$: C, 75.81; H, 7.11; N, 5.20. Found: C, 76.03; H, 7.27; N, 5.25.

Consecutive [2,3] and [1,3] Rearrangements of 3. The portion 2 containing the amine oxide **3** was first allowed to stand at −20° and worked up in the same way as described for **4** to afford the same product **4** (1.2 g, 48%), which was then heated in chloroform under reflux for 1 hr to yield crude (+)-**7** (1.1 g, 91.6%). The contamination by **4** was detected to an extent of ca. 17% as estimated by ^{1}H NMR spectroscopy. The product **7** was hydrogenated

to give (−)-8, which on purification by preparative VPC afforded the analytical sample, $[\alpha]^{27}D$ −6.5°.

trans-1-Phenyl-2-buten-1-ol:[19] ir (liquid) $\delta_{=CH}$ (trans) 958 cm^{-1}; ^1H NMR (CCl_4) δ 1.72 (m, 3 H, CH_3), 2.56 (s, 1 H, OH), 4.94–5.84 (m, 3 H, CH and CH=CH), 7.34 (m, 5 H, phenyl).

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Registry No.—(−)-1, 57128-66-2; (−)-1 tartrate, 57128-67-3; (+)-1, 51773-65-0; (+)-1 malate, 57066-04-3; (±)-1, 57128-68-4; (−)-2, 57066-05-4; 3 picrate, 57066-07-6; 4, 51729-87-4; (−)-5, 51729-88-5; (−)-6, 22135-49-5; (+)-7, 57066-08-7; (−)-8, 57066-09-8; (−)-9, 39516-03-5; (−)-9 phenylurethane, 57066-10-1; (+)-*trans*-1-phenyl-3-benzoylamino-1-butene, 57066-11-2; (−)-benzoylalanine methyl ester, 7260-27-7; *trans*-1-phenyl-2-buten-1-ol, 52755-39-2.

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(2) In the preliminary communication,[1] we erroneously deduced the *R* configuration to (−)-1 based on the catalytic hydrogenation of (−)-1 to give (+)-1-phenyl-3-aminobutane, to which the *R* configuration was inferred by Červinka.[9] In contrast, the opposite *S* configuration was claimed for the same (+) enantiomer by Terent'ev [*Zh. Obshch. Khim.*, **35**, 1538 (1965); *Chem. Abstr.*, **63**, 17854*h* (1965)]. We were inextricably confused by this situation and so we worked out the absolute assignment of configuration by independent and unambiguous means in the present study.
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Adenine Nucleosides Derived from 6-Deoxyhexofuranoses[1]

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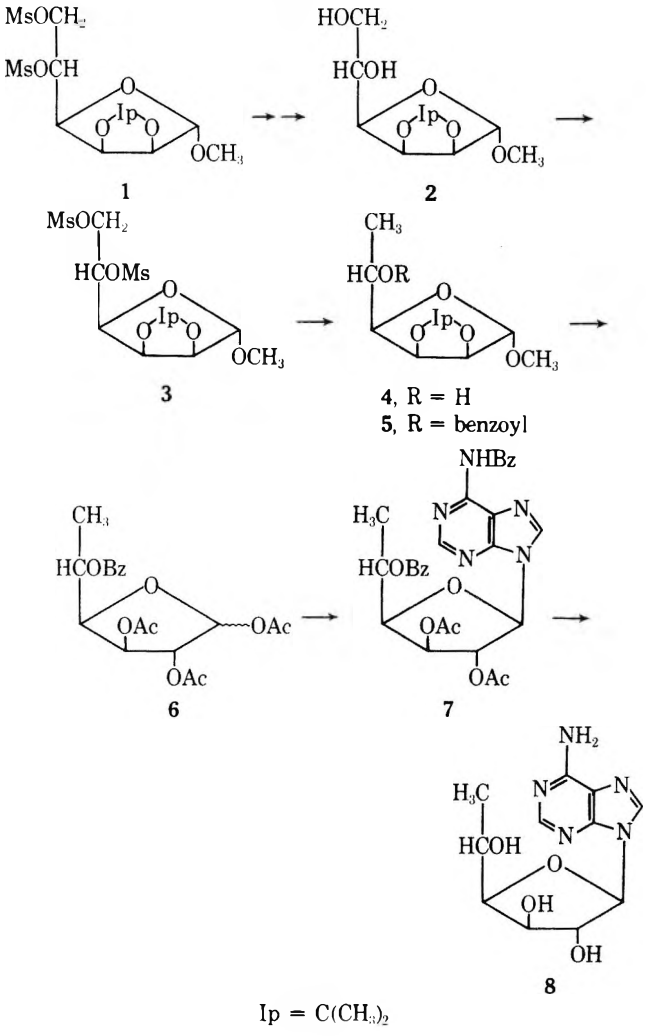
Methyl 2,3-*O*-isopropylidene-β-L-gulofuranoside (**2**) was converted into methyl 2,3-*O*-isopropylidene-5,6-di-*O*-methanesulfonyl-β-L-gulofuranoside (**3**) and treatment of this with lithium aluminum hydride afforded methyl 6-deoxy-2,3-*O*-isopropylidene-β-L-gulofuranoside (**4**). The 5-*O*-benzoate (**5**) was prepared and subjected to acetolysis under conditions known to result in epimerization at C-2. The acetolysis product was condensed with 6-benzamidochloromercuripurine by the titanium tetrachloride method. Removal of blocking groups afforded 9-(6-deoxy-α-L-idofuranosyl)adenine (**8**). Methyl 5-*O*-benzoyl-6-deoxy-2,3-*O*-isopropylidene-β-D-gulofuranoside (**9**) was used to prepare 9-(6-deoxy-β-D-gulofuranosyl)adenine (**14**). First, the isopropylidene group was removed and replaced with benzoates. Then the methoxyl group was exchanged for an acetoxyl group and **14** was prepared by the titanium tetrachloride coupling method. 9-(6-Deoxy-β-L-gulofuranosyl)adenine (**15**) was prepared starting from **5** by a series of reactions which were identical with the preparation of **14**. 9-(6-Deoxy-α-D-idofuranosyl)adenine (**16**) was prepared by acetolysis of **9** and coupling to the base as described for **8**. Nucleoside **8** was a substrate for adenosine deaminase from calf intestinal mucosa.

Nucleosides derived from 6-deoxyhexofuranoses are of potential use in this laboratory as precursors for the synthesis of other compounds of biological interest. However, some of these nucleosides may be of biological value in their own right. For instance, it has been demonstrated that 9-(6-deoxy-β-D-allofuranosyl)adenine is an inhibitor of adenine phosphoribosyl transferase (EC 2.4.2.7),[2] an important enzyme in nucleic acid metabolism. Furthermore, this compound is capable of acting as a substrate for adenosine deaminase (adenosine aminohydrolase, EC 3.5.4.4) and this is also the case for the 5′ epimer, 9-(6-deoxy-α-L-talofuranosyl)adenine.[3] These findings indicate that such compounds do have the ability to bind to enzymes of nucleic acid metabolism and may be useful antimetabolites.

A series of 6-deoxyhexofuranosyl nucleosides was originally prepared by Baker and co-workers. They reported the synthesis of adenine nucleosides derived from 6 deoxy-L-mannose,[4a] 6-deoxy-D-allose,[4b] 6-deoxy-D-glucose,[4c] 6-deoxy-L-idose,[4d] and 6-deoxy-L-talose.[4e] It has recently been shown that the compound reported in ref 4a as 9-(6-deoxy-α-L-mannofuranosyl)adenine was incorrect and the real nucleoside bearing this name was prepared and completely structure proofed.[5] It was also shown by Ryan et al.[6] that the nucleoside reported to be 9-(6-deoxy-α-L-idofuranosyl)adenine was really 9-(5-deoxy-β-D-*xylo*-hexofuranosyl)adenine on the basis of the NMR spectrum which lacked a peak for a terminal methyl group. Later work[7] verified that treatment of 6-*O*-benzoyl-2,3-*O*-isopropylidene-5-*O*-*p*-toluenesulfonyl-α-D-glucofuranose with lithium aluminum hydride yielded 5-deoxy-1,2-*O*-isopropylidene-β-D-*xylo*-hexofuranose rather than 6-deoxy-1,2-*O*-isopropylidene-α-L-idofuranose as assumed by Baker and co-workers[4d] when they prepared it as a starting material. Since there appears to be no report in the literature dealing with the synthesis of 9-(6-deoxy-α-L-idofuranosyl)adenine, it is probable that biological data reported[8] under this name are actually for the 5′-deoxy analogue instead. The original intent of the present work was the preparation of 9-(6-deoxy-β-D-gulofuranosyl)adenine, a heretofore unknown nucleoside analogue. Owing to the recent development of some rather convenient synthetic procedures, this work has been extended to include the preparation of both enantiomers of adenine nucleosides derived from 6-deoxygulose and 6-deoxyidose.

Scheme I

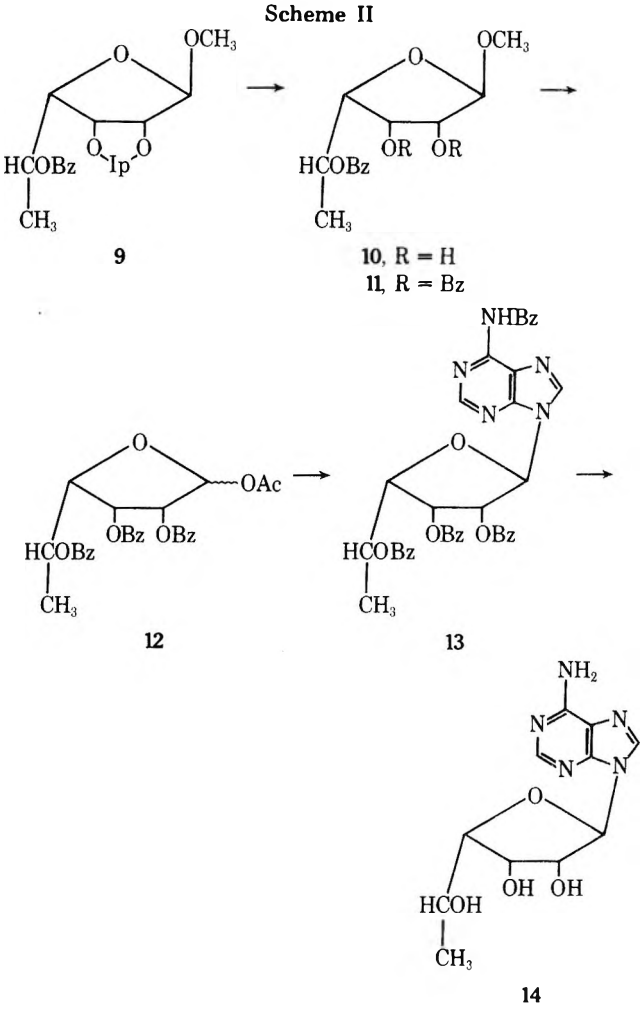


Ip = $C(CH_3)_2$

Synthetic Chemistry. The conversion of methyl 2,3-*O*-isopropylidene-5,6-di-*O*-methanesulfonyl-α-D-mannofuranoside (**1**) into methyl 2,3-*O*-isopropylidene-β-L-gulofuranoside (**2**) was recently reported by treatment of **1** with sodium acetate in hot *N,N*-dimethylformamide.[9] The preparation of **2** from **1** in large quantity in an identical yield enabled the preparation of methyl 5-*O*-benzoyl-6-deoxy-2,3-*O*-isopropylidene-β-L-gulofuranoside (**5**) (Scheme I), an important starting material for the synthesis of 9-(6-deoxy-α-L-idofuranosyl)adenine (**8**). The procedure followed for the preparation of **5** was similar to the one already reported[10] for the preparation of the D enantiomer **9**. Compound **2** was treated with methanesulfonyl chloride in pyridine to give **3** as an impure syrup. Treatment of this bis(methanesulfonate) with lithium aluminum hydride in an ether–benzene mixture afforded a good yield of 6-deoxy-2,3-*O*-isopropylidene-β-L-gulofuranoside (**4**) which was converted into the 5-*O*-benzoate **5**. The latter compound was subjected to acetolysis conditions which are known not only to result in acetyl substitution for the isopropylidene and glycoside groups, but which cause, in addition, an epimerization at C-2. This reaction is well documented in the literature[11] and has been utilized in this laboratory for synthetic purposes.[12] The carbohydrate derivative **6** was condensed with 6-benzamidochloromercuripurine by the titanium tetrachloride method in hot 1,2-dichloromethane.[13] Removal of the blocking groups with sodium methoxide in methanol afforded the desired product, 9-(6-deoxy-α-L-idofuranosyl)adenine (**8**).

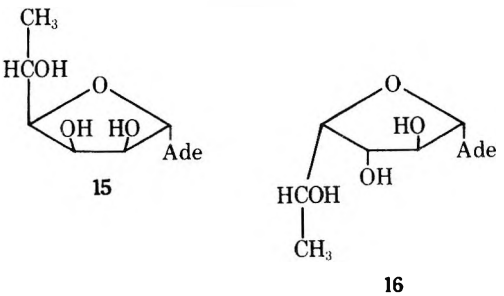
The preparation of 9-(6-deoxy-β-D-gulofuranosyl)adenine (**14**) is shown in Scheme II. Methyl 5-*O*-benzoyl-6-deoxy-2,3-*O*-isopropylidene-β-D-gulofuranoside[10] (**9**) was treated with 9:1 trifluoroacetic acid–water to remove the isopropylidene group.[14] The free hydroxyl groups were blocked as the benzoate esters and the methoxyl group at C-1 was exchanged for an acetoxyl group by acetolysis. The configuration at C-2 is unaffected when the blocking groups are benzoates rather than acetates.[15] The nucleoside **14** was then prepared by the titanium tetrachloride procedure followed by removal of the blocking groups.

Scheme II



In a manner quite similar to the preparation of **14**, 9-(6-deoxy-β-L-gulofuranosyl)adenine (**15**) was prepared from **5**. 9-(6-Deoxy-α-D-idofuranosyl)adenine (**16**) was prepared from **9** by acetolysis and coupling as described for the L form **8**.

Chart I



Ade = adenine

Proof of Structure. The elemental analyses of **8**, **14**, **15**, and **16** agreed with theoretical values. The ir and uv spec-

Table I
Optical Rotations of Hexofuranosyl Nucleosides

Hexofuranose confign	$[\alpha]_D$, deg 6'-CH_2OH	6'-CH_3
β-D-gluco	−58[a]	−60[b]
α-L-talo	−32[c,d]	−35[e]
α-L-manno	−75[f]	−72[g]
β-D-allo	−57[c]	−74[h]
β-D-gulo (14)	−56[c]	−62
α-D-ido (16)	+38[i]	+24

[a] E. J. Reist, R. R. Spencer, and B. R. Baker, *J. Org. Chem.*, 23, 1958 (1958). [b] Reference 4c. [c] P. Kohn, R. H. Samaritano, and L. M. Lerner, *J. Org. Chem.*, 31, 1503 (1966). [d] The number reported is the absolute value, with a change of sign to conform to the expected value for the unknown enantiomer. [e] Reference 4e. [f] L. M. Lerner and P. Kohn, *J. Org. Chem.*, 31, 339 (1966). [g] Reference 5. [h] Reference 4b. [i] Reference 16.

tra supported the structures as being nucleosides. The peak near 260 nm, which did not change significantly with change in pH, indicated that the glycosyl bond was linked at N-9 of the adenine ring. The enantiomeric pairs had identical physical properties except for the sign of the optical rotation.

The identity of the sugar moiety was demonstrated by the rate of periodate consumption. These studies were performed on nucleosides **14** and **16.** The D-gulo nucleoside **14** consumed 0.93 molar equiv of periodate in less than 0.5 hr, whereas it took the D-ido compound nearly 1 week to consume this amount. The uptake of only 1 molar equiv of periodate demonstrated that the sugar ring structure of the nucleosides was in the furanose form, since the pyranose form would be expected to consume 2 molar equiv of periodate. The rapid uptake of periodate by **14** indicated that the vicinal hydroxyl groups were oriented in a cis relationship. Furthermore, the identity of the sugar as 6-deoxy-D-gulose was shown in a separate experiment.[10] The very slow uptake of periodate by **16** was typical for a nucleoside in the furanose form having the vicinal hydroxyls in a trans relationship. That the sugar moiety had the D-ido configuration was expected from the synthetic procedure used. The acetolysis step is known to yield a product with the configuration at C-2 inverted,[11,12] and in a previous publication[16] the preparation of 9-α-D-idofuranosyladenine was achieved from methyl 2,3-*O*-isopropylidene-β-D-gulofuranoside using the same techniques.

The assignment of the anomeric configurations was based upon the accumulation of the following evidence. It was expected that the anomeric configuration obtained in each case would be trans to the hydroxyl group at C-2′ owing to the directive effect of the acyloxy group during the condensation step.[17] A comparison of the optical rotations of the corresponding 6′-hydroxymethyl hexofuranosyl nucleosides of known anomeric configuration with the optical rotations of the 6′-methyl analogues showed a good correlation (Table I).

NMR studies with **8** revealed a one-proton singlet at δ 5.95 for the anomeric proton. Numerous studies have demonstrated that the trans relationship of the protons at C-1′ and C-2′ of furanose nucleosides can only be determined with confidence when the coupling constant is below 1 Hz.[18] Therefore, the singlet obtained was interpreted as demonstrating that the configuration of **8** was indeed α-L. Further proof was obtained by utilization of **8** as an enzyme substrate. Adenosine deaminase from calf intestinal mucosa has been shown to have very specific requirements concerning the structure of any potential substrate.[19] In addition to the adenine ring, the sugar must be in the β-D or α-L configuration and there must be a hydroxyl group for binding either at C-3′ in the "up" position, and/or an hydroxyl group at C-5′, likewise in the "up" position. For example, it was mentioned earlier that the β-D-allo and α-L-talo diastereomers of **8** were substrates for the enzyme. Since **8** is the only nucleoside of the present group to have the necessary structural features, it was treated with adenosine deaminase in a phosphate buffer and the reaction was followed spectrophotometrically. The nucleoside was found to be a substrate and the uv absorption spectrum of the product, in comparison to inosine, indicated that the product was most probably 9-(6-deoxy-α-L-idofuranosyl)hypoxanthine.

Table II
Optical Rotations of Alcohols Derived from Nucleosides

9-(6′-Deoxyhexofuranosyl)adenine	$[\alpha]_D$ of alcohol, deg[a]
β-D-gulo (14)	+37
α-D-ido (16)	−64
β-L-gluco	−69
α-L-manno	+65

[a] Based upon the calculated dry weight of the alcohol product.

Unfortunately, nature was not as kind with the NMR spectrum of **14.** The anomeric proton appeared centered at δ 5.97 as a doublet with $J_{1',2'}$ = 6 Hz. The expected coupling constant for a β-D configuration with a trans relationship for the protons at C-1′ and C-2′ is 0–8 Hz, whereas for the cis relationship the expected values are 3.5–8 Hz.[20] Therefore, no decision could be made regarding the anomeric configuration from the NMR spectrum. The preparation of the 2′,3′-*O*-isopropylidene derivative of **14** would enable two other NMR interpretations to be brought to bear on this problem,[18,21] but as yet a pure crystalline derivative has not been obtained.

There is, however, another argument that can be applied in support of the β-D configuration of **14.** For a good number of years the anomeric configurations of glycosides and nucleosides have been demonstrated by first cleaving the sugar ring with periodate and then reduction of the aldehydes to trialcohols. Since the trialcohols had only one asymmetric center, which was originally the anomeric position of the nucleoside, it was only necessary to determine the optical rotations of the unknowns and compare them to a standard of known anomeric configuration.[22] When the original configuration of the nucleoside was β-D or α-L, the optical rotation was a positive value, and when α-D or β-L, the value was negative but of equal value as expected of the enantiomer. Originally, the standards used had an aglycone that was identical with that of the unknowns, but in recent years comparisons have been made using dissimilar aglycones and arguments have been presented to support the assignment of the anomeric configuration on this basis.[23] In recent work involving the preparation of alcohols from nucleosides, some of the alcohols had two centers of asymmetry and still gave optical rotations corresponding to the same configuration designations as presented above.[24] It appeared to be a good idea to apply this procedure to 6′-deoxyhexofuranosyl nucleosides available in this laboratory even though the products would have three asymmetric centers. Each of the nucleosides was treated with sodium periodate and the products reduced with sodium borohydride. The optical rotations are shown in Table II. Two previously reported nucleosides, 9-(6-deoxy-β-L-glucofuranosyl)adenine and 9-(6-deoxy-α-L-mannofuranosyl)adenine, were of known anomeric configuration, as was **16** since the latter was the enantiomer of **8.** Although the alcohols obtained were all diastereomers, it can be seen that the

β-D and α-L nucleosides had a positive rotation and the α-D and β-L nucleosides had a negative rotation. The data argue for the assignment of 14 as the β-D configuration but should not be construed as a definitive proof, especially since the number of test samples was so small. Further work is required to determine if this correlation is a reasonably good one in those cases where it can be applied. Quite obviously this technique is not applicable to nucleosides derived from ketoses, since most of these would yield products with no asymmetric center. Another exception may be the 2′-deoxypyranosyl nucleosides. The enantiomeric dialcohols derived from the anomeric 9-(2′-deoxyribopyranosyl)adenines had optical rotations whose signs were opposite to those expected.[24]

Experimental Section[25]

Methyl 2,3-*O*-isopropylidene-β-L-gulofuranoside (2). This compound was prepared in large scale from D-mannose according to the procedure of Evans and Parrish.[9] The yield (64.5%) was identical with that reported: long, prismatic needles, mp 78.5–80°, $[\alpha]^{22}D$ +82.5° (*c* 1.10, methanol) [lit.[9] mp 76.5–77°, $[\alpha]D$ +82.3° (c 1.17, methanol)].

Methyl 6-Deoxy-2,3-*O*-isopropylidene-β-L-gulofuranoside (4). A mixture containing 18 g of 2 in 125 ml of dry pyridine was chilled in an ice bath. To this stirred solution was slowly added, dropwise, 35 ml of methanesulfonyl chloride. Stirring was continued at room temperature for 2 hr, then the mixture was chilled again and treated slowly with 60 ml of cold water. After 45 min, the contents were poured into 500 ml of water and extracted with chloroform (3 × 80 ml). The chloroform solution was washed with saturated sodium bicarbonate (200 ml) and water (200 ml), and dried. Evaporation and coevaporation with toluene gave 30.1 g of brown syrup (3).

The entire sample was dissolved in a mixture of ethyl ether (400 ml) and benzene (200 ml) and treated with 20 g of lithium aluminum hydride under reflux for 6 days. The stirring mixture was chilled in an ice bath and 20 ml of water was added very slowly, followed by 60 ml of 15% sodium hydroxide solution and an additional 20 ml of water. The white, granular precipitate was removed by suction filtration and washed well with ethyl ether. Evaporation gave a clear syrup which began to crystallize almost immediately. Recrystallization from *n*-hexane afforded 9.44 g (56%) of 4 in three crops, mp 79–79.5°, $[\alpha]^{23}D$ +88.9° (*c* 1.26, methanol). The ir spectrum was identical with that of the D form for which the following data were recorded:[10] mp 78.5–79.5°; $[\alpha]^{25}D$ −90.7° (c 1.26, methanol).

Anal. Calcd for $C_{10}H_{18}O_5$: C, 55.03; H, 8.31. Found: C, 55.07; H, 8.26.

Methyl 5-*O*-Benzoyl-6-deoxy-2,3-*O*-isopropylidene-β-L-gulofuranoside (5). A solution containing 6.1 g of 4 in 50 ml of dry pyridine was treated with 5.2 ml of benzoyl chloride as previously described for the D enantiomer.[10] The yield was 8.65 g (96%). A small sample was recrystallized from methanol–water for analytical purposes, mp 79.5–80°, $[\alpha]^{23}D$ +119.5° (*c* 1.23, methanol). The ir spectrum was identical with that of the D enantiomer, which had mp 78.5–79°, $[\alpha]^{22}D$ −118° (c 1.30, methanol).

Anal. Calcd for $C_{17}H_{22}O_6$: C, 63.33; H, 6.88. Found: C, 63.44; H, 6.92.

9-(6-Deoxy-α-L-idofuranosyl)adenine (8). A mixture containing 4.2 g of 5, 114 ml of glacial acetic acid, 11.4 ml of acetic anhydride, and 6 ml of concentrated sulfuric acid was kept at room temperature for 65 hr. The mixture was poured into 350 ml of ice and stirred until the ice melted. The product was extracted with chloroform (3 × 50 ml) and the chloroform solution was washed with water (2 × 200 ml), saturated sodium bicarbonate (200 ml), and again with water, and dried. Evaporation and coevaporation with benzene (3 × 10 ml) afforded 3.62 g of a clear, colorless gum (6).

The gum was dissolved in 300 ml of 1,2-dichloroethane and 5.21 g of 6-benzamidochloromercuripurine and 5.21 g of Celite-545 were added. Distillation of 50 ml of solvent removed traces of water. Titanium tetrachloride (1.3 ml) in 50 ml of fresh, dry 1,2-dichloroethane was added and the mixture was heated under reflux for 22 hr. After cooling at room temperature, 185 ml of saturated sodium bicarbonate was added, and the mixture was stirred for 1.5 hr and then filtered through a pad of Celite. The filter cake was washed with 150 ml of hot 1,2-dichloroethane and the organic layer was separated. Evaporation gave a residue which was dissolved in 100 ml of chloroform, washed with 30% aqueous potassium iodide (2 × 100 ml) and water (100 ml), and dried. Evaporation of the solvent afforded a yellow foam weighing 5.27 g. This was dissolved in 100 ml of methanol and treated with 7 ml of 1 *N* methanolic sodium methoxide under reflux for 1.5 hr. The solution was neutralized with Amberlite CG-120 (H^+) ion-exchange resin and the resin was removed by filtration. The methanol was evaporated and the residue was coevaporated with water to remove methyl benzoate as the azeotrope. The residue was crystallized from ethanol, then recrystallized from ethanol–water to afford 0.794 g (22%) in two crops. The product (8) softened upon heating above 210° with small droplets forming on the cover slip until the sample melted at 239–244°, $[\alpha]^{24}D$ −22.2° (c 1.14, 1 *N* HCl).

Anal. Calcd for $C_{11}H_{15}N_5O_4$: C, 46.96; H, 5.41; N, 24.90. Found: C, 47.00; H, 5.31; N, 24.91.

9-(6-Deoxy-β-D-gulofuranosyl)adenine (14). Methyl 5-*O*-benzoyl-6-deoxy-2,3-*O*-isopropylidene-β-D-gulofuranoside (9)[10] (5.13 g) was treated at room temperature with 52 ml of 9:1 (v/v) trifluoroacetic acid–water for 0.5 hr. The solvents were removed by evaporation (35°). The residue was dissolved in 100 ml of 1:1 (v/v) ethyl acetate–benzene, washed with saturated sodium bicarbonate (2 × 50 ml) and water (50 ml), and dried. Evaporation gave a white foam containing 10, 4.49 g. This was treated with 5 ml of benzoyl chloride in 30 ml of dry pyridine at room temperature for 21 hr. The mixture was poured into 200 ml of ice-saturated sodium bicarbonate and stirred until the ice melted. The product was extracted with chloroform three times (total volume 100 ml) and this solution was washed with saturated sodium bicarbonate (100 ml) and water (100 ml) and dried. The chloroform was evaporated and coevaporation with toluene gave an amber syrup (11), 8.17 g. The NMR spectrum confirmed the presence of the methoxyl group. The syrup (8.05 g) was treated with a mixture containing 60 ml of acetic acid, 6.8 ml of acetic anhydride, and 3.6 ml of sulfuric acid for 16 hr at room temperature. The reaction mixture was worked up as described for 6 above, except that the formation of emulsions during the washing steps required the use of sodium chloride solutions. After evaporation, a thick syrup (12) was obtained, 5.4 g.

The syrup was condensed with 6-benzamidochloromercuripurine (5.9 g) in a mixture also containing 5.9 g of Celite-545, 1.8 ml of titanium tetrachloride, and 310 ml of 1,2-dichloroethane. The reaction and work-up were carried out as described for the preparation of 8. The blocking groups were removed in boiling methanolic sodium methoxide and immediately upon evaporation of methyl benzoate as the water azeotrope, crystallization of 14 occurred. Recrystallization from ethanol–water afforded 0.555 g (12.4%): mp 255–258° dec; $[\alpha]^{24}D$ −62.5° (*c* 1.05, 1 *N* HCl); uv λ_{max} (pH 1) 257 nm (ε 13820), λ_{max} (H_2O) 259 (14100), λ_{max} (pH 13) 259 (14460); NMR (Me_2SO-d_6) δ 8.40, 8.22 (both s, 1 proton each, H-8, H-2), 5.97 (d, 1, $J_{1',2'}$ = 6 Hz, H-1′), 1.13 (d, 3, C-6′ CH_3).

Anal. Calcd for $C_{11}H_{15}N_5O_4$: C, 46.96; H, 5.41; N, 24.90. Found: C, 46.92; H, 5.42; N, 24.88.

9-(6-Deoxy-β-L-gulofuranosyl)adenine (15). This nucleoside was prepared starting from 5 (4.14 g) by the same sequence of reactions used for the preparation of 14. In the final step, the nucleoside did not crystallize easily, so the entire product was chromatographed on a column (28 × 2.2 cm) of Bio-Rad AG1-X2 (OH^-, 200–400 mesh) using 30% aqueous methanol as eluent.[26] Fractions of 15 ml were collected. The major uv (254 nm) absorbing peak was in tubes 6–18. The contents were combined, the solvents evaporated, and crystallization achieved from ethanol–water. Recrystallization afforded 0.339 g, mp 255–258° dec, $[\alpha]^{22}D$ +64.5° (c 1.05, 1 *N* HCl). The ir spectrum was identical with that of the D enantiomer.

Anal. Calcd for $C_{11}H_{15}N_5O_4$: C, 46.96; H, 5.41; N, 24.90. Found: C, 46.69; H, 5.23; N, 24.71.

9-(6-Deoxy-α-D-idofuranosyl)adenine (16). Acetolysis of 9 (3.5 g) as described for 5 yielded a gum weighing 2.95 g. This was condensed with 4.25 g of 6-benzamidochloromercuripurine in a mixture also containing 4.25 g of Celite-545, 1.0 ml of titanium tetrachloride, and 250 ml of 1,2-dichloroethane. The reaction and work-up were performed as described for the preparation of 8. After removal of blocking groups with sodium methoxide the product 16 was crystallized from ethanol. Recrystallization from ethanol–water afforded 0.425 g (13.9%). The crystals became soft above 210°, melting at 238–244°: $[\alpha]^{23}D$ +24.4° (c 1.07, 1 *N* HCl); uv λ_{max} (pH 1) nm (ε 13830), λ_{max} (H_2O) 259 (14090), λ_{max} (pH 13) 260 (14230); NMR (Me_2SO-d_6) δ 8.37, 8.23 (both s, 1 proton each, H-8, H-2), 5.95 (s, 1 H-1′), and 1.19 (d, 3, C-6′ CH_3). The ir spectrum was identical with that of the L form 8.

Anal. Calcd for $C_{11}H_{15}N_5O_4$: C, 46.96; H, 5.41; N, 24.90. Found: C, 47.11; H, 5.65; N, 24.59.

Periodate Uptake. The spectrophotometric procedure of Rammler and Rabinowitz[27] was used to determine the consumption of periodate. 9-(6-Deoxy-β-D-gulofuranosyl)adenine (**14**) consumed a total of 0.93 molar equiv of periodate in under 0.5 hr, whereas it took 9-(6-deoxy-α-D-idofuranosyl)adenine (**16**) 160 hr to consume 0.90 molar equiv.

Polarimetric Studies. Between 10 and 13 mg of each nucleoside was dissolved in 0.75 ml of hot water in a 2-ml volumetric flask and then cooled to room temperature. To the solution was added 0.5 ml of 0.25 *M* sodium periodate. The reaction mixture was kept in the dark at room temperature, the time of reaction being 1 day for **14** and 5 days for **16.** At the end of the reaction time, 60 mg of sodium borohydride was added and after 1 hr, the excess hydride was destroyed by slow addition of 0.4 ml of 20% acetic acid solution. When effervescence stopped (1–2 hr) the volume was adjusted with water to 2 ml and the optical rotation was measured. The results are shown in Table II.

Deamination of 8 with Adenosine Deaminase. The enzyme reaction was followed spectrophotometrically[28] at 265 nm at 25° in 0.5 *M* phosphate buffer (pH 7.6). The concentration of 8 was 6×10^{-6} *M* and 3 ml of this solution was added to a cuvette. A solution of buffer containing the enzyme (0.1 ml, 2.1 units) (Sigma Chemical Co.) was added to start the reaction and this was mixed thoroughly. The uv absorption leveled off at a constant value after 5 min. The uv absorption spectrum had a maximum at 249 nm. An identical reaction using adenosine gave an almost instantaneous leveling off of the optical density and a shift in the uv to λ_{max} 248 nm.

Registry No.—**1,** 50692-25-6; **2,** 50692-26-7; **4,** 57207-09-7; **5,** 57207-10-0; **8,** 57237-22-6; **9,** 57207-11-1; **14,** 57237-23-7; **15,** 57237-24-8; **16,** 57237-25-9; benzoyl chloride, 98-88-4; 6-benzamidochloromercuripurine, 17187-65-4.

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Reaction of 4,5-Diamino-1,3-dimethyluracil with Diketones

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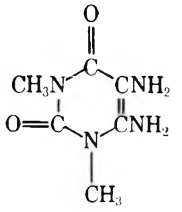
4,5-Diamino-1,3-dimethyluracil when treated with acetylacetone and with dibenzoylmethane formed 4-(4-amino-1,3-dimethyluracil-5-amino)-3-buten-2-one and β-(4-amino-1,3-dimethyluracil-5-amino)chalcone, respectively. The reaction of the diamine with *trans*-1,2-di-*p*-toluylethylene in ethanol gave 3-*p*-tolyl-5,7-dimethyl-6,8-dioxo-5,6,7,8-tetrahydropteridine and 1,3-dimethyl-8-*p*-tolylxanthine. The same reaction in acetic acid gave the isomeric pteridines and a diazepine. Condensation of the diamine with 1,2-di-*p*-toluylethane in ethanol formed a pyrrole.

The reaction of 4,5-diamino-1,3-dimethyluracil (**1**) with acetylacetone, dibenzoylmethane, *trans*-di-*p*-toluylethylene, and 1,2-ditoluylethane has been studied to determine whether this diamine **1** would behave in a similar manner to that found for *o*-phenylenediamine with similar compounds.

4,5-Diamino-1,3-dimethyluracil (**1**) gave with acetylacetone and dibenzoylmethane in ethanol containing a trace of acetic acid the corresponding substituted unsaturated ketones (**2,** R = CH_3 or C_6H_5). Evidence for these structures was the elemental analysis and spectral data; the NMR spectra showed three exchangeable protons in the presence of deuterium oxide.

Attempts to convert **2** (R = CH_3) to the diazepine were



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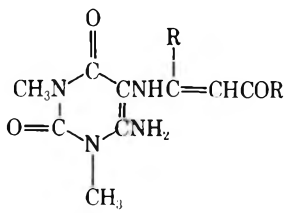

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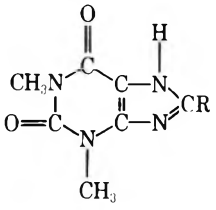
not successful; thermolysis at its decomposition point proceeded with the elimination of acetone and formation of the xanthine **3** (R = CH_3). Heating **2** (R = CH_3) with acetic anhydride gave a mixture of 5-acetylamino-4-amino-1,3-dimethyluracil and the xanthine **3** (R = CH_3). Using acetic



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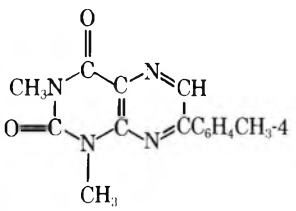

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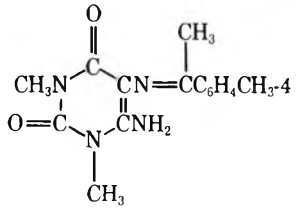
acid as a solvent for the condensation of **1** and acetylacetone gave a similar mixture of compounds. These conditions when applied to *o*-phenylenediamine are reported to form the diazepine.[1] Compound **2** (R = C_6H_5) upon heating behaved in a similar fashion to the methyl derivative **2** (R = CH_3); softening occurred at 370° with a final melting at 389–395°, which is the melting point of the xanthine **3** (R = C_6H_5). This xanthine **3** (R = C_6H_5) was also isolated in a small amount in the condensation of **1** with dibenzoylmethane.

Condensation of the diamine **1** with *trans*-di-*p*-tolylethylene in absolute ethanol under nitrogen gave the pteridine **4**, small amounts of the xanthine **3** (R = 4-$CH_3C_6H_4$), and 1,2-di-*p*-toluylethane. This reaction parallels that reported between *o*-phenylenediamine and *trans*-dibenzoylethylene[2] except that the by-product from the formation of the pteridine **4**, *p*-methylacetophenone, was not isolated. This ketone may be the precursor of the xanthine **3** (R = 4-$CH_3C_6H_4$), since the condensation product **5**



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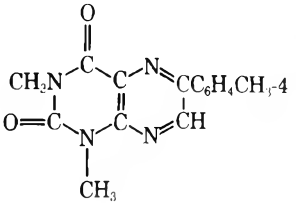

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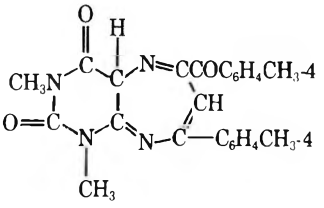
from the diamine **1** and *p*-methylacetophenone upon melting forms **3** (R = $C_6H_4CH_3$-4). This behavior resembles that reported for the thermolysis of ketone derivatives of *o*-phenylenediamine.[3]

The reaction between the diamine **1** and *trans*-di-*p*-tolylethylene in acetic acid gave a mixture of products from which the following were isolated and characterized: the pteridine **4**, the isomeric pteridine **6**, diazepine **7**, *p*-methylacetophenone, 2,5-di-*p*-tolylfuran, *trans*-di-*p*-toluylethylene, 1,2-di-*p*-toluylethane, and 5-acetylamino-4-amino-1,3-dimethyluracil. In contrast to the reaction of *o*-phenylenediamine with *trans*-dibenzoylethylene under similar conditions,[2] none of the pyrrole **8** was isolated. This compound (**8**) was prepared, however, by the condensation of the diamine **1** with 1,2-di-*p*-toluylethane in absolute ethanol under nitrogen. The equivalency of the vinyl hydrogens and the *p*-tolyl groups in the NMR spectrum eliminated a dihydrodiazocine structure as a possibility for this compound.



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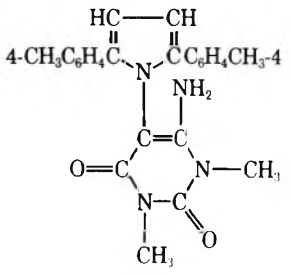
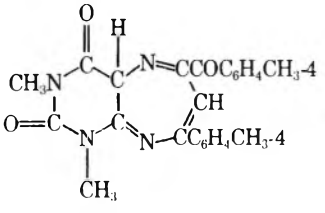
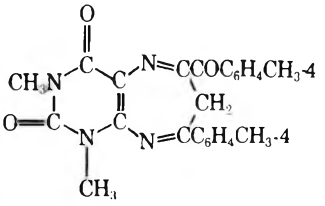


8

The structure of the isomeric pteridine **6** was indicated by elemental analysis and spectral data. The NMR spectrum was similar to that for the pteridine **4** with slight variations in the chemical shifts; the largest differences occurred for the ortho hydrogens in the *p*-tolyl group and the 3 hydrogen. Similarities occurred in the infrared spectrum with the exception of the 12–12.5-μ region. The pteridine **4** showed two absorptions at 12 and 12.4 μ whereas the isomer **6** showed only one at 12.1 μ. The mass spectra showed similar fragmentations but the intensities of some of the peaks varied.

The formulation of the diazepine **7** was based on the infrared and NMR spectra. The former showed no absorption for a NH group. The NMR spectra in trifluoroacetic acid and deuterionitrobenzene showed two singlets for the vinyl hydrogen and the bridgehead hydrogen. Both of these singlets disappeared in deuterated trifluoroacetic acid. Exchange would occur through an equilibrium between the following tautomeric forms.





Such an equilibrium may also account for the unequal heights observed for the methyl peaks in the NMR spectrum in trifluoroacetic acid. These heights were likewise temperature dependent.

Solutions of diazepine **7** in trifluoroacetic acid were dark red in color; a similar color is reported for the diazepines from *o*-phenylenediamine.[1] In contrast to the latter, addition of water caused precipitation of the diazepine **7**; no contraction in the diazepine ring occurred comparable to that observed with *o*-phenylenediamine derivatives.[4] This compound **7** was also thermally stable in contrast to 1-phenyl-2-(3-phenyl-1,2-dihydroquinoxaline-2-ylidene)ethan-

one isolated from *o*-phenylenediamine and *trans*-dibenzoylethylene,[2] which had been formulated previously as a diazepine.[5]

Experimental Section

Melting points are not corrected. Infrared spectra were recorded on a Model 185 Perkin-Elmer spectrometer and a Beckman Model 1R-20A spectrometer and the NMR spectra were obtained with a Varian A-60 spectrometer. Mass spectra were obtained with a Hitachi RMUGE spectrometer.

4,5-Diamino-1,3-dimethyluracil (1). A suspension of 5-nitroso-4-amino-1,3-dimethyluracil (18.4 g) in absolute ethanol (150 ml) was reduced with hydrogen (45 psi) in the presence of platinum oxide (0.1 g). The reduction was terminated when the red-colored suspension became a pale tan precipitate. The liquid was decanted and the solid was recrystallized from ethanol, yield 9.0 g, mp 211–214° (lit.[6] 209°). Concentration of the filtrate gave an additional 1.57 g which melted at 190–211°.

4-Methyl-4-(4-amino-1,3-dimethyluracil-5-amino)-3-buten-2-one (2, R = CH_3). A solution of the diamine 1 (1.7 g) and acetylacetone (1.0 g) in absolute ethanol (30 ml) containing 1 drop of glacial acetic acid was heated at reflux for 7 hr. The resulting solid (2.26 g) upon heating darkened and softened between 209 and 219° and then melted at 327–330°. Recrystallization from ethanol did not change this behavior: ir (Nujol) 3333, 3125 (NH), 1695, 1623 cm^{-1} (CO); NMR (Me_2SO-d_6, 135°) δ 1.7 (s, 3, CH_3CO), 1.93 (s, 3, CH_3C=C), 3.13 (s, 3, CH_3N), 3.33 (s, 3, CH_3N), 5.17 (s, 1, CH), 6.40 (broad s, 2, NH_2), 10.7 (broad s, 1, NH).

Anal. Calcd for $C_{11}H_{16}O_3N_4$: C, 52.38; H, 6.35; N, 22.22. Found: C, 52.35; H, 6.38; N, 22.43.

Thermolysis of 2 (R = CH_3). Compound 2 (R = CH_3) (0.6 g) was heated at 225–235° for 30 min and the resulting solid was extracted with hot water (12 ml) and filtered. The solution on cooling gave 1,3,8-trimethylxanthine 3 (R = CH_3) (0.10 g), mp 330–335° (lit.[7] 325°).

Reaction of 2 (R = CH_3) with Acetic Anhydride. Compound 2 (R = CH_3) (1.26 g) was dissolved in a mixture of acetic anhydride (1 ml) and acetic acid (10 ml) by heating at 90° and the resulting solution was allowed to stand for 22 hr at room temperature. Addition of water followed by removal of the solvent under reduced pressure gave a solid which upon fraction crystallization from methanol gave 1,3,8-trimethylxanthine 3 (R = CH_3) (0.02 g) and 5-acetylamino-4-amino-1,3-dimethyluracil (0.67 g): mp 272–282°, solidified and remelts at 330° (lit.[8] 275–276°); NMR (D_2O) δ 2.62 (s, 3, CH_3CO), 3.68 (s, 3, CH_3N) 3.85 (s, 3, CH_3N).

Reaction of 1 with Acetylacetone in Acetic Acid. The diamine 1 (1.7 g) and acetylacetone (1.0 g) were heated at reflux in acetic acid (25 ml) for 7.5 hr. Addition of water followed by evaporation to dryness under reduced pressure gave a solid which upon fractionation from methanol gave 1,3,8-trimethylxanthine 3 (R = CH_3) (1.28 g) and 5-acetylamino-4-amino-1,3-dimethyluracil (0.3 g).

β-(4-Amino-1,3-dimethyluracil-5-amino)chalcone (2, R = C_6H_5). A solution of the diamine 1 (1.70 g) and dibenzoylmethane (2.24 g) in absolute ethanol (75 ml) containing 3 drops of acetic acid was heated at reflux for 17 hr. The solution upon cooling gave a yellow solid (1.67 g). Recrystallization from ethanol gave 8-phenyl-1,3-dimethylxanthine (3, R = C_6H_5) (0.11 g): mp 388–394° (lit.[9] >300°); NMR (CF_3COOH) δ 3.63 (s, 3, NCH_3), 3.88 (s, 3, NCH_3), 7.5–7.9 (m, 3, meta and para aromatic H), 7.9–8.2 (m, 2, ortho aromatic H), 10.97 (broad s, 1, NH).

Concentration of the alcohol filtrate gave 2 (R = C_6H_5) (1.38 g) which upon recrystallization from ethanol gave yellow needles (1.05 g) that softened at 370° and melted at 389–395°; ir (Nujol) 3333, 3150 (NH), 1705 (CO), 1665 (CO), 1580 cm^{-1} (broad) (C=N, C=C); NMR (Me_2SO-d_6) δ 2.93 (s, 3, CH_3N), 3.17 (s, 3, CH_3N), 6.03 (s, 1, C=CH), 7.28–7.65 (m, 6, C_6H_5, meta and para aromatic H), 7.65–8.1 (m, 4, ortho aromatic H), 7.20 (broad s, 2, NH_2), 11.37 (s, 1, NH). Treatment with D_2O caused the singlets at δ 7.20 and 11.37 to disappear.

Anal. Calcd for $C_{21}H_{20}N_4O_3$: C, 67.02; H, 5.32; N, 14.89. Found: C, 67.20; H, 5.15; N, 14.90.

3-*p*-Tolyl-5,7-dimethyl-6,8-dioxo-5,6,7,8-tetrahydropteridine (4). The diamine 1 (1.70 g) and *trans*-di-*p*-toluylethylene (2.64 g) in absolute ethanol (100 ml) were heated at reflux under nitrogen for 24 hr. The solid (0.66 g) obtained upon cooling was treated with chloroform and the soluble portion after removal of the chloroform and recrystallization from ethyl acetate melted at 250–252°, yield 0.33 g. Successive crystallizations from ethanol and methanol gave the pteridine 4 melting at 255–258° (lit.[10] 257°); NMR ($CDCl_3$) δ 2.44 (s, 3, CH_3), 3.50 (s, 3, CH_3N), 3.76 (s, 3, CH_3N), 7.33 (d, 2, meta H, J = 8 Hz), 8.03 (d, 2, ortho H, J = 8 Hz), 8.95 (s, 1, CH).

The insoluble portion (0.03 g) from the chloroform extract was 8-*p*-tolyl-1,3-dimethylxanthine (3, R = *p*-$CH_3C_6H_4$): mp 375–380°; ir (Nujol) 3125 (NH), 1689, 1639 cm^{-1} (CO); NMR (CF_3COOH) δ 2.52 (s, 3, CH_3), 3.62 (s, 3, NCH_3), 3.85 (s, 3, NCH_3), 7.52 (d, 2, meta ArH, J = 8 Hz), 7.97 (d, 2, ortho ArH, J = 8 Hz).

Anal. Calcd for $C_{14}H_{14}N_4O_2$: C, 62.22; H, 5.19; N, 20.74. Found: C, 62.08; H, 5.22; N, 20.37.

The filtrate from the reaction was evaporated to dryness and the resulting highly colored residue was extracted with hexane; no *p*-methylacetophenone was found by GLC analysis. The residue was taken up in benzene and chromatographed on silica gel. Elution with benzene gave 1,2-di-*p*-toluylethane (0.34 g). Identification was made by comparison with an authentic sample.[11] Further elution with chloroform and with ethyl acetate gave glassy materials which were not investigated.

Reaction of Diamine 1 with *trans*-Di-*p*-toluylethylene in Acetic Acid. A solution of the diamine 1 (3.18 g) and *trans*-di-*p*-toluylethylene (4.94 g) in acetic acid (70 ml) was heated at reflux for 21 hr. Addition of water followed by removal of the solvent under reduced pressure gave a solid which was heated with methanol (100 ml) and the resulting mixture was cooled. The solid present was filtered and washed with methanol (50 ml), yield 1.53 g. Extraction with hot ethyl acetate gave the insoluble diazepine 7, yield 1.04 g, mp 245–250°. Recrystallization from chloroform gave a sample (0.92 g) melting at 253–255°; ir (Nujol) 1709 (CON), 1667 (COAr), 1604 cm^{-1} (C=C); NMR ($C_6D_5NO_2$, 150°) δ 2.28 (s, 2.35, CH_3), 2.38 (s, 3.65, CH_3), 3.53, 3.55 (two singlets, 4.3, NCH_3), 3.68 (s, 1.7, NCH_3), 4.78 (s, 1, COCH), 6.55 (s, 1, =CH), 7.0–8.12 (m, aromatic H); NMR (CF_3COOH) δ 2.42 (s, 4.6, CH_3), 2.56 (s, 1.4, CH_3), 3.56, 3.63 (two s, 3, CH_3N), 3.80, 3.88 (two s, unequal height with a ratio of 3:4, 3, CH_3N), 4.92 (s, 1, COCH), 6.75 (s, 1, =CH), 7.28 (d, 2, meta ArH, J = 8 Hz), 7.35 (s, 2, meta ArH), 7.58 (s, 2, ortho ArH), 7.80 (d, 2, ortho ArH, J = 8 Hz); NMR (CF_3COOD, room temperature) same spectrum except that the peaks at δ 4.92 and 6.75 were absent. At 70° the peak at δ 2.42 increased at the expense of the peak at δ 2.57; the two peaks at δ 3.56 and 3.63 coalesced into one at δ 3.63 and the two singlets at δ 3.80 and 3.88 appeared at δ 3.80 and 3.92 in a ratio of 2.4:1. The aromatic region showed very little change, *m/e* 414.

Anal. Calcd for $C_{24}H_{22}N_4O_3$: C, 69.60; H, 5.31; N, 13.52. Found: 69.30; H, 5.20; N, 13.30.

The ethyl acetate extract upon concentration gave 0.24 g of a solid which after crystallization from benzene gave 0.13 g of the pteridine 4, mp 253–255°. Further concentration of the ethyl acetate gave 0.1 g of a solid which after two crystallizations from benzene gave the isomeric pteridine 6 melting at 235–237°; ir (Nujol) 1739, 1661 cm^{-1} (CO); NMR (CF_3COOH) δ 2.45 (s, 3, CH_3), 3.65 (s, 3, NCH_3), 3.87 (s, 3, NCH_3), 7.35 (d, 2, meta ArH, J = 8 Hz), 7.83 (d, 2, ortho ArH, J = 8 Hz), 8.65 (s, 1, =CH); *m/e* 282.

Anal. Calcd for $C_{15}H_{14}N_4O_2$: C, 63.83; H, 4.96; N, 19.86. Found: C, 63.89; H, 5.12; N, 19.72.

The methanol extracts were evaporated to dryness under reduced pressure and the solid obtained was treated with benzene. The insoluble portion (0.99 g) when recrystallized from ethanol gave 0.50 g of 5-acetylamino-4-amino-1,3-dimethyluracil melting at 278° with decomposition.

The benzene filtrate was chromatographed on silica gel. Elution with benzene gave 2,5-di-*p*-tolylfuran which after crystallization from methanol melted at 162–165°, yield 0.12 g. Identification was made by comparison with an authentic sample.[12] Further elution with benzene gave 0.56 g of a mixture of *trans*-1,2-*p*-toluylethylene and 1,2-toluylethylene melting at 124–137°. Analysis by NMR indicated that the ratio of unsaturated diketone to the saturated diketone was 65:35.

Elution further with benzene and then with chloroform gave a mixture of the isomeric pteridines (4, 6) (0.16 g) (by ir spectral analysis) and the pteridine 4 (0.11 g).

In a separate run the solid obtained by evaporating the methanol extract was extracted with hexane and gave 0.16 g of *p*-methylacetophenone. Identification and quantification were made by gas–liquid chromatography using a 5% SE-30 on 100–120 mesh Chromosorb P column at 119°.

5-(1-Methyl-*p*-tolylidene)amino-4-amino-1,3-dimethyluracil (5). The diamine 1 (0.85 g) was heated with *p*-methylacetophenone (2 ml) under nitrogen at 100° for 17 hr. Addition of chloroform to the product gave a solid (1.1 g) which after two crystalliza-

tions from ethanol when heated softened at 217° and melted with gas evolution at 221°: ir (Nujol) 3266 (NH_2), 1681 (CO), 1600 cm^{-1} (C=N).

Anal. Calcd for $C_{15}H_{18}N_4O_2$: C, 62.94; H, 6.29; N, 19.58. Found: C, 63.03; H, 6.04; N, 19.81.

Thermolysis of 5. Compound **5** (1.09 g) was heated at 220–230° for 15 min and the resulting solid was treated with water. Filtration gave 0.47 g of a solid which was extracted with chloroform and recrystallized twice from ethanol, mp 372–384°. The ir spectrum was similar to that of the compound isolated in the reaction of the diamine **1** with *trans*-di-*p*-toluylethylene in ethanol.

Condensation of Diamine 1 with 1,2-Di-*p*-toluylethane. The diamine **1** (0.85 g) was heated at reflux with 1,2-di-*p*-toluylethane (1.33 g) in absolute ethanol (50 ml) under nitrogen for 31 hr. The solution upon filtration gave 1.50 g of the pyrrol **8** which after recrystallization successively from ethyl acetate and methanol melted at 303–309° dec; ir (Nujol) 3333 (NH), 1701 (CO), 1600 cm^{-1} (C=C); NMR (Me_2SO-d_6) δ 2.23 [s, 6, $(CH_3)_2$], 3.13 (s, 3, NCH_3), 3.18 (s, 3, NCH_3), 6.26 (broad s, 2, NH_2), 6.39 (s, 2, =CH), 7.03 (d, 4, meta ArH, J = 8 Hz), 7.30 (d, 4, ortho ArH, J = 8 Hz). Upon the addition of D_2O the peak at δ 6.26 disappeared, *m/e* 400.

Anal. Calcd for $C_{24}H_{24}N_4O_2$: C, 72.0; H, 6.0; N, 14.0. Found: C, 71.86; H, 6.00; N, 13.82.

Registry No.—**1**, 5440-00-6; **2** (R = CH_3), 57196-68-6; **2** (R = C_6H_5), 57196-69-7; **3** (R = CH_3), 830-65-9; **3** (R = C_6H_5), 961-45-5; **3** (R = *p*-$CH_3C_6H_4$), 57196-70-0; **4**, 51445-58-0; **5**, 57196-71-1; **6**, 57196-72-2; **7**, 57196-73-3; **8**, 57196-74-4; 5-nitroso-4-amino-1,3-dimethyluracil, 6632-68-4; acetylacetone, 123-54-6; 5-acetylamino-4-amino-1,3-dimethyluracil, 10184-41-5; dibenzoylmethane, 120-46-7; *trans*-di-*p*-toluylethylene, 17342-09-5; 2,5-di-*p*-tolylfuran, 57196-75-5; *p*-methylacetophenone, 122-00-9; 1,2-di-*p*-toluylethane, 13145-56-7.

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Synthesis of β,γ-Acetylenic 3-Oxo Steroids of the 5,10-Seco Series[1]

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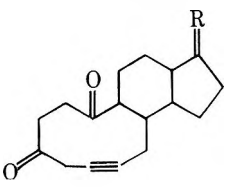
The synthesis is reported of 5,10-seco-19-norcholest-5-yne-3,10-dione (**1a**) and its estryne and 19-norpregnyne analogues (**1b** and **1c**, respectively). The key $\Delta^{5(10)}$-6-oxo intermediates (**3a–c**), prepared by direct chromium trioxide–pyridine oxidation of the corresponding Δ^5-19-hydroxy steroids (**2a–c**), were converted to the 5β,10β-oxido-6-oxo steroids (**4a–c**) using alkaline hydrogen peroxide or *m*-chloroperbenzoic acid. Compounds **4a–c** gave, after Tanabe–Eschenmoser fragmentation, the 3β-acetoxy-5,10-seco-5-yne derivatives (**5a–c**), which in turn yielded **1a–c**, after hydrolysis of the acetoxy groups followed by Jones oxidation. The 5β,10β configuration in the 5,10-oxido-6-oxo steroids was assigned on the basis of CD and of chemical evidence. Another route to the 5β,10β-oxido-6-ketone grouping was found in treatment of the $\Delta^{5(10)}$-6β-acetoxy compound **10** with Jones reagent to give directly the 5β,10β-oxido-6-ketone **4b**.

Studies concerned with the design and synthesis of specific enzyme-generated inhibitors of the Δ^5-3-keto steroid isomerase of *P. testosteroni* required the synthesis of 5,10-seco acetylenic steroids with the structures **1a–c**.



1a, R = β-C_8H_{17}, α-H
b, R = O
c, R = β-CH_3CO, α-H

These compounds were designed as substrates for Δ^5-3-keto steroid isomerase[2] with the hope that the enzyme, through its normal mode of action,[2,3] would convert the β,γ-acetylenic ketone system to the conjugated allenic ketone grouping. Thus, the enzyme converts Δ^5-3-oxo steroids to the corresponding Δ^4-3-oxo steroids by removing the 4β proton which is transferred intramolecularly to the 6β position, most plausibly via an enol intermediate. If compounds such as **1** proved to be substrates for the enzyme, the same process should generate the reactive $\Delta^{4,5}$-dien-3-one system. It was hoped that the latter would then react with a nucleophilic amino acid residue at or near the active site.

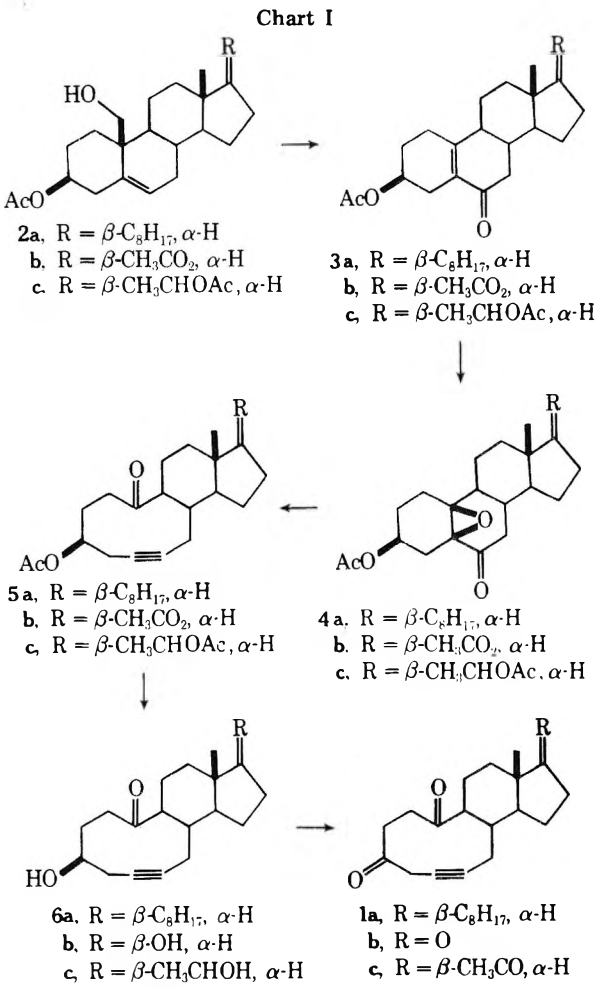
Examination of models suggested that these 5,10-seco steroids, with the ten-membered ring partly rigidified by the constraints of the acetylenic and carbonyl groupings, as well as by the ring junction at C-8 and C-9, might approximate conformationally to the natural tetracyclic Δ^5-3-oxo steroid system. In the event, seco steroids **1b** and **1c** indeed proved[4] to be excellent substrates for, and potent irreversible inhibitors of, the enzyme.

We report here the synthetic routes leading to compounds **1a–c**, as illustrated in Chart I, initially carried out in the cholestane series for calibration purposes.

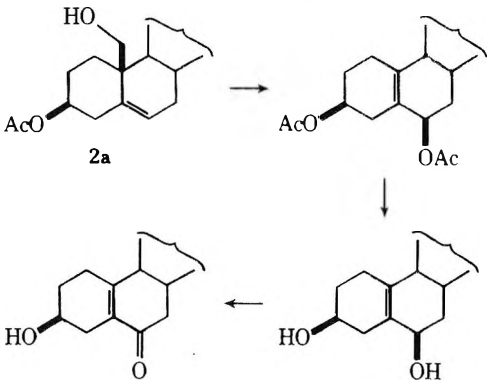
The critical part of the route involved generation of the key $\Delta^{5(10)}$-6-oxo intermediate (**3a**) with subsequent fragmentation of the derived 5β,10β-oxido-6-ketone (**4a**) to **5a** by the Tanabe–Eschenmoser[5,6] procedure. It was necessary to accumulate large quantities of the $\Delta^{5(10)}$-6-ketone (**3a**) and we first tried the known procedure[7] shown below.

This involved lead tetraacetate induced fragmentation of 3β-acetoxy-19-hydroxycholest-5-ene (**2a**) followed by cleavage of the acetoxy groups (lithium aluminum hydride) and selective oxidation at C-6 with manganese dioxide. In

Chart I



our hands this was not an entirely satisfactory process on the large scale, primarily owing to separation problems after the lithium aluminum hydride reaction.

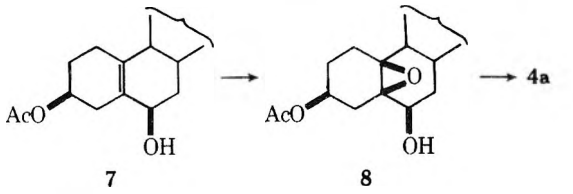


During our search for other ways to prepare the $\Delta^{5(10)}$-6-ketone **3a**, we were fortunate to have our attention directed[8] to an interesting and practical method described[9] in the patent literature. The method involves direct conversion of Δ^{5}-19-hydroxy steroids to $\Delta^{5(10)}$-6-ketones using chromium trioxide–pyridine at 25°.

Indeed, the $\Delta^{5(10)}$-6-ketone **3a** could be prepared conveniently in 40% yield on the large scale by this procedure (4 days at ambient temperature followed by chromatography on silica gel). Epoxidation of **3a** to give the oxido ketone **4a** was carried out using alkaline hydrogen peroxide, followed by reacetylation at C-3 for easier isolation and characterization.

The 5β,10β configuration for **4a** was inferred from the negative CD curve,[10] as well as from the following evidence.

The known 3β-acetoxy-$\Delta^{5(10)}$-6β-ol (**7**) of established[11] stereochemistry was converted quantitatively by *m*-chloroperbenzoic acid to the 5,10-oxido compound (**8**). The well-established[12] directive effect of the hydroxyl group in the peracid epoxidation of allylic alcohols argues most strongly for the 5β,10β configuration of the epoxide grouping in **8**. Oxidation of **8** with Jones reagent then gave in quantitative yield the oxido ketone **4a**, identical in all respects with **4a** which had been prepared by H_2O_2–NaOH epoxidation of the conjugated ketone **3a** followed by reacetylation at C-3.



The 5β,10β-oxido-6-ketone **4a** was then fragmented to give **5a** by the Tanabe–Eschenmoser reaction[5,6] (*p*-toluenesulfonyl hydrazide in acetic acid–chloroform at room temperature). Spectroscopic and analytical data were consistent with structure **5a** while positive evidence for the acetylenic grouping came from the Raman spectrum,[13] which showed absorption at 2230 cm^{-1}. In addition, catalytic hydrogenation of **5a** using Adams catalyst gave the tetrahydro derivative.

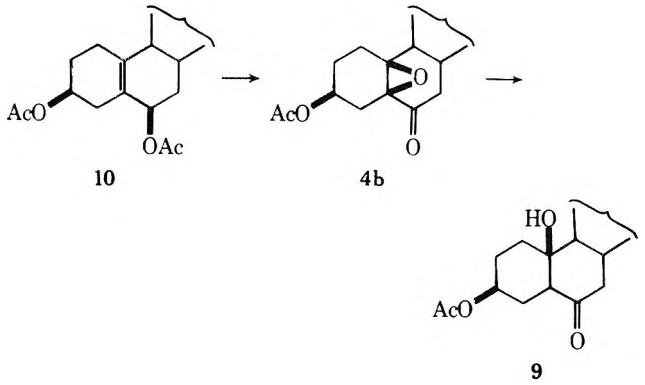
The 3β-acetoxy-5,10-seco steroid **5a** was now hydrolyzed to the 3β-ol **6a**, and oxidation with Jones reagent then afforded, in ca. 50% yield, the final product **1a**, which gave appropriate spectroscopic and analytical data.

The marked lack of reactivity of the C-10 carbonyl group in **5a** is noteworthy. Attempts to prepare the *p*-toluenesulfonylhydrazone failed, even under forcing conditions (e.g., *p*-toluenesulfonyl hydrazide and *p*-toluenesulfonic acid in sulfolane–dimethylformamide at 100°). Attempts to generate the oxime, using conditions (hydroxylamine–pyridine, reflux) suitable[14] for hindered 11-oxo steroids also failed. Furthermore, no reduction of the 10-ketone was observed under forcing Wolff–Kishner conditions, or by the use of sodium borohydride or lithium aluminum hydride. This lack of reactivity might be due in part to electronic interaction between the acetylene and 10-carbonyl functions. However, this is unlikely to be a major factor, as the tetrahydro compound obtained by catalytic hydrogenation of the acetylenic compound **5a** also proved to be inert to hydrazone-forming reagents. The formation of an intermediate complex would result in severe transannular interactions in the ten-membered ring, and this effect may play a critical role.

Turning now to the 5,10-secoestryne **1b** and 5,10-seco-19-norpregnyne (**1c**), we applied the synthetic sequence of Chart I as outlined above for the cholestane series. During these studies we observed that the 5β,10β-oxido ketone system (e.g., **4b**) can be conveniently prepared by treatment of the corresponding $\Delta^{5(10)}$-6-ketone with *m*-chloroperbenzoic acid in benzene under reflux. The undesired Baeyer–Villiger reaction did not compete to a major extent, and this procedure gave the crystalline oxido ketone **4b** directly in 67% yield without the reacetylation required after the H_2O_2–NaOH procedure.

The 5β,10β configuration for the oxido compounds **4b** and **4c** was inferred from their negative CD curves, as well as from analogy with the cholestane series. In addition, chromous acetate[15] reduction of **4b** gave the 10β-hydroxy-6-ketone **9**, which showed a negative CD spectrum as expected for a 6-oxo steroid of the 5α,10β series.

During a search for other paths to the 5β,10β-oxido ketone system, the interesting observation was made that Jones oxidation of the $\Delta^{5(10)}$-3β,6β,17β-triacetate[7] **10** led



directly within 10 min at 25° to the 5β,10β-oxido-6-ketone **4b**. Compound **4b** was identified by comparison with authentic samples prepared by the methods outlined above. The yield was only 20%, however, and the other reaction products have not yet been identified. The conjugated ketone **3b** is stable to these oxidation conditions, and further study of this reaction is planned.

Returning now to the synthesis of **1b** and **1c**, the final products **1b** and **1c** were obtained by fragmentation of oxido ketones **4b** and **4c**, followed by hydrolysis of the acetate groupings and oxidation with Jones reagent, as for the cholestane series.

We note, also, that hydrolysis of the acetoxy groups in **5a–c** with base does not cause epimerization at C-9. Thus, reacetylation of the hydrolyzed products **6a–c** generates, in quantitative yield, unchanged **5a–c** as evidenced by spectroscopic, chromatographic, and CD measurements.

Experimental Section

Melting points were determined on a Kofler hot stage and are uncorrected. NMR spectra were determined on Varian HA-100 or Perkin-Elmer R-12B spectrometers for $CDCl_3$ solutions, unless otherwise stated, with Me_4Si as internal standard. Chemical shifts are expressed as δ values (Me_4Si 0) with signal multiplicities shown as s, singlet; d, doublet; t, triplet; m, multiplet. Infrared spectra were obtained on Perkin-Elmer 137 or 521 spectrometers (in $CHCl_3$ solution unless otherwise stated). Ultraviolet spectra were measured on a Cary 15 spectrophotometer. Mass spectra were determined on CEC-21-110 or Du Pont 21-491 spectrometers. Circular dichroism measurements were made using a Cary 60 instrument and are expressed as molar ellipticities. Elemental analyses were performed by Microanalysis Inc., Wilmington, Del. All chromatographic separations were performed on Woelm dry column silica gel or alumina. Analytical thin layer plates (0.25 mm) were obtained from Analtech, Inc., Newark, Del. High-pressure liquid chromatographic separations were performed on a Waters Associates Model 6000 instrument equipped with a Model 660 solvent programmer.

3β-Acetoxy-19-norcholest-5(10)-en-6-one (3a). 3β-Acetoxy-19-hydroxycholest-5-ene (15.8 g, 0.036 mol) was dissolved in pyridine (100 ml) and stirred with chromium trioxide–pyridine complex (0.30 mol) at ambient temperature for 4 days. The mixture was diluted with EtOEt (1.5 l.) and filtered. The ethereal phase was washed successively with 5% NaOH and H_2O. The residue obtained by concentration in vacuo was chromatographed on silica gel by elution with 6% EtOAc–$CHCl_3$. Early fractions contained several nonpolar compounds followed by **3a** (5.7 g, 0.0133 mol, 36%): mp 122–123° (from MeOH) (reported[8] mp 124–125°); mass spectrum *m/e* 428 (M^+), 400, 382, 368; λ_{max} (MeOH) 246 nm (ε 11430); [θ] (MeOH) +2530° (329 nm); ν_{max} (KBr) 1725 (ester C=O), 1660 (C=O), 1625 cm^{-1} (C=C); NMR (C_6D_6) 4.50 (m, 1, CHOAc), 2.46 (m, 2, $COCH_2$), 2.00 (s, 3, CH_3CO), 0.85 ppm (s, 3, 18-CH_3).

Anal. Calcd for $C_{28}H_{44}O_3$: C, 78.45; H, 10.35. Found: C, 78.43; H, 10.15

3β-Acetoxy-5β,10β-oxido-19-norcholestan-6-one (4a). 3β-Acetoxy-19-norcholest-5(10)-en-6-one (**3a**, 235 mg, 0.00055 mol) was dissolved in MeOH–$CHCl_3$ (15 ml:3 ml). At ambient temperature a mixture of 30% H_2O_2 (1 ml) and 5 *N* NaOH (1 ml) was added. After stirring for 5 hr the reaction mixture was diluted with aqueous NaCl (saturated) and extracted with $CHCl_3$. Drying (Na_2SO_4) and removal of solvent in vacuo left a solid which was acetylated with acetic anhydride–pyridine (18 hr, room temperature). After work-up in the usual manner the residue was crystallized from MeOH to give **4a** as needles (150 mg, 0.00033 mol, 58%): mp 173–174°; mass spectrum *m/e* 444 (M^+), 384, 368, 356, 340; ν_{max} 1735 (ester C=O), 1705 cm^{-1} (C=O); [θ] (CH_3OH) −8894° (307.5 nm); NMR 4.62 (m, 1, CHOAc), 2.02 (s, 3, CH_3CO), 0.70 ppm (s, 3, 18-CH_3)

Anal. Calcd for $C_{28}H_{44}O_4$: C, 75.63; H, 9.97. Found: C, 75.48; H, 9.79.

3β-Acetoxy-5β,10β-oxido-19-norcholestan-6-one (4a) from 3β-Acetoxy-6β-hydroxy-19-norcholest-5(10)-ene (7). A solution of the $\Delta^{5(10)}$-6β-ol[11] **7** (54 mg, 0.00013 mol) and 85% *m*-chloroperbenzoic acid (54 mg, 0.00027 mol) in $CHCl_3$ (8 ml) was left at ambient temperature for 18 hr. Water was then added, and the $CHCl_3$ phase was washed successively with 10% aqueous Na_2SO_3 solution, 10% $NaHCO_3$ solution, and water, and then was dried (Na_2SO_4) and evaporated. The residue was crystallized from acetone to give 8, mp 140–141°, mass spectrum *m/e* 428 (M − 18), 386, 368.

Oxidation of the above product with Jones reagent in acetone at 5° for 15 min gave crude **4a** as a crystalline product. This material was homogenous by TLC, had mp 173–174°, and was identical in all respects (ir, NMR, CD, MS) with a sample of **4a**, prepared by H_2O_2–NaOH epoxidation of the conjugated ketone **3a** followed by reacetylation at C-3.

3β-Acetoxy-5,10-seco-19-norcholest-5-yn-10-one (5a). 3β-Acetoxy-5,10-oxidocholestan-6-one (**4a**, 666 mg, 0.0015 mol) and *p*-toluenesulfonyl hydrazide (333 mg, 0.0018 mol) were dissolved in 1:1 $CHCl_3$–AcOH (50 ml). After stirring for 5 hr at ambient temperature the reaction mixture was diluted with water and $CHCl_3$. The organic phase was washed with water and 5% $NaHCO_3$. Removal of the dried (Na_2SO_4) solvent in vacuo gave an oil which crystallized from MeOH, giving **5a** as plates (471 mg, 0.0011 mol, 73%): mp 105–106°; mass spectrum *m/e* 428 (M^+), 386, 368, 350; ν_{max} 1730 (ester C=O), 1705 cm^{-1} (C=O); [θ] (CH_3OH) −2805° (283 nm); NMR 4.80 (m, 1, CHOAc), 2.02 (s, 3, CH_3CO), 0.76 ppm (s, 3, 18-CH_3).

Anal. Calcd for $C_{28}H_{44}O_3$: C, 78.45; H, 10.35; 0, 11.20. Found: C, 78.27; H, 10.35; 0, 11.20

3β-Hydroxy-5,10-seco-19-norcholest-5-yn-10-one (6a). The acetate **5a** (35 mg, 0.00008 mol) was dissolved in MeOH (7 ml) and stirred with anhydrous K_2CO_3 (150 mg) for 2 hr. Filtration and evaporation of the solvent left a solid which was crystallized from hexane to give **6a** as needles (30 mg, 0.000078 mol, 97%): mp 153–154°; mass spectrum *m/e* 386 (M^+), 368, 340; ν_{max} (KBr) 3400 (OH), 1705 cm^{-1} (C=O); [θ] (CH_3OH) −2556° (283 nm); NMR 3.84 (m, 1, CHOH), 0.75 ppm (s, 3, 18-CH_3).

Anal. Calcd for $C_{26}H_{42}O_2$: C, 80.83; H, 10.88. Found: C, 80.66; H, 10.79

5,10-Seco-19-norcholest-5-yne-3,10-dione (1a). 3β-Hydroxy-5,10-seco-19-norcholest-5-yn-10-one (**6a**, 163 mg, 0.00042 mol) was dissolved in acetone (50 ml) and oxidized with excess Jones reagent for 10 min at ambient temperature. The mixture was diluted with H_2O and extracted with $CHCl_3$. Drying (Na_2SO_4) and removal of the solvent in vacuo gave an oil which was crystallized from MeOH–EtOEt to give **1a** (77 mg, 0.0002 mol): mp 94–96°; mass spectrum *m/e* 384 (M^+), 269, 256, 299; [θ] (dioxane) −6696° (287 nm); ν_{max} (KBr) 1705 cm^{-1}; NMR 0.75 ppm (s, 3, 18-CH_3).

Anal. Calcd for $C_{26}H_{40}O_2$: C, 81.25; H, 10.42. Found: C, 81.49; H, 10.53

3β,17β-Diacetoxyestr-5(10)-en-6-one (3b). Compound **3b** was prepared in a manner identical with that for **3a** as described above: mp 116–118°; mass spectrum *m/e* 374 (M^+), 332, 314, 286; λ_{max} (MeOH) 245 nm (ε 11078); [θ] (CH_3OH) +2372° (330 nm); ν_{max} (KBr) 1730 (ester C=O), 1660 (C=O), 1620 cm^{-1} (C=C); NMR 5.11 (m, 1, CHOAc), 4.66 (m, 1, CHOAc), 2.02 (s, 3, CH_3CO), 2.00 (s, 3, CH_3CO), 0.86 ppm (s, 3, 18-CH_3).

Anal. Calcd for $C_{22}H_{30}O_5$: C, 70.58; H, 8.02. Found: C, 70.31; H, 8.14.

3β,17β-Diacetoxy-5β,10β-oxidoestran-6-one (4b). A mixture of 3β,17β-diacetoxyestr-5(10)-en-6-one (**3b**, 3.74 g, 0.01 mol) and 85% *m*-chloroperbenzoic acid (5.74 g, 0.028 mol) was refluxed in benzene (300 ml) for 1 hr. The cooled solution was washed successively with water, 5% $NaHCO_3$, and water and dried (Na_2SO_4). The residue crystallized from MeOH, after removal of the solvent in vacuo, to give pure epoxide **4b**. Chromatography of the mother liquor on silica gel (elution with 8% EtOAc–$CHCl_3$) gave additional **4b**, total yield 2.7 g (0.0067 mol, 67%): mp 245–247°; mass spec-

trum *m/e* 390 (M^+), 330, 314, 302, 286; ν_{max} 1725 (ester C=O), 1705 (C=O), 1250 cm^{-1} (ester); [θ] (CH_3OH) −8506° (306 nm); NMR (C_6D_6) 4.60 (m, 2, CHOAc), 2.06 (s, 3, CH_3CO) 2.01 (s, 3, CH_3CO), 0.84 ppm (s, 3, 18-CH_3).

Anal. Calcd for $C_{22}H_{30}O_6$: C, 67.67; H, 7.74. Found: C, 67.65; H, 7.66.

3β,17β-Diacetoxy-5β,10β-oxidoestran-6-one (4b) from 3β,6β,17β-Triacetoxyestr-5(10)-ene (10). To a solution of the triacetate **10** (1.0 g, 0.0026 mol) in acetone (40 ml) at 25° was added Jones reagent (1.2 ml) with swirling. After 10 min, excess reagent was destroyed by dropwise addition of MeOH, and the reaction mixture was diluted with water and extracted with $CHCl_3$. The $CHCl_3$ extract was washed with water, dried (Na_2SO_4), and evaporated in vacuo to give a solid residue which was chromatographed on silica gel (elution with $CHCl_3$–EtOAc, 9:1). The first fractions contained starting material (**10**, 119 mg), and later fractions contained the oxido ketone **4b** (200 mg), mp 247° (from MeOH), identical in all respects (ir, NMR, TLC, MS) with an authentic sample of **4b**.

3β,17β-Diacetoxy-5,10-secoestr-5-yn-10-one (5b). A mixture of 3β,17β-diacetoxy-5β,10β-oxidoestran-6-one (**4b**, 2.0 g, 0.005 mol) and *p*-toluenesulfonyl hydrazide (1.24 g, 0.0067 mol) was stirred for 6 hr in 1:1 $CHCl_3$–AcOH (150 ml) at ambient temperature. The $CHCl_3$ extract, after dilution with water, was washed with 5% $NaHCO_3$ and water and dried (Na_2SO_4). Removal of the solvent in vacuo and crystallization of the residue (MeOH) gave **5b** as plates (1.7 g, 0.0045 mol, 90%): mp 204–206°; mass spectrum *m/e* 374 (M^+), 332, 316, 304, 286; ν_{max} 1724 (C=O), 1250 cm^{-1} (ester); [θ] (CH_3OH) −2710° (284 nm); NMR 4.62 (m, 2, CHOAc), 2.01 (s, 6, CH_3CO at C-3 and C-17), 0.88 ppm (s, 3, 18-CH_3).

Anal. Calcd for $C_{22}H_{30}O_5$: C, 70.56; H, 8.08. Found: C, 70.70; H, 7.94.

3β,17β-Dihydroxy-5,10-secoestr-5-yn-10-one (6b). The diacetate **5b** (374 mg, 0.001 mol) was stirred at ambient temperature for 3 hr in 3% methanolic KOH (75 ml). Concentration in vacuo after the addition of saturated NaCl (40 ml), extraction with $CHCl_3$, drying (Na_2SO_4), and removal of the solvent gave the pure diol **6b**. Crystallization from hexane–EtOH gave **6b** as needles (280 mg, 0.0096 mol, 96%): mp 205–207°; mass spectrum *m/e* 290 (M^+), 272, 262, 254, 244; ν_{max} (KBr) 3440 (OH), 1725 cm^{-1} (C=O); [θ] (CH_3OH) −2744° (283 nm); NMR (Me_2SO-d_6) 4.85 (m, 1, CHOH), 4.57 (m, 1, CHOH), 0.78 ppm (s, 3, 18-CH_3).

Anal. Calcd for $C_{18}H_{26}O_3$: C, 74.44; H, 9.03. Found: C, 74.21; H, 8.99.

5,10-Secoestr-5-yne-3,10,17-trione (1b). The 3β,17β-diol **6b** (186 mg, 0.0006 mol) was dissolved in acetone (40 ml) and oxidized with excess Jones reagent for 5 min at ambient temperature. The reaction mixture was diluted with water and extracted with $CHCl_3$. The residue obtained after removal of solvent was crystallized from petroleum ether–$CHCl_3$ to give **1b** as plates (98 mg, 0.00034 mol, 53%): mp 163–166°; mass spectrum *m/e* 286 (M^+), 271, 258, 243, 230, 215; ν_{max} 1730 cm^{-1} (C=O); [θ] (MeOH) +4607° (305 nm), −3016° (277 nm), +1426° (248 nm); NMR 0.93 ppm (s, 3, 18-CH_3).

Anal. Calcd for $C_{18}H_{22}O_3$: C, 75.49; H, 7.74; 0, 16.77. Found: C, 75.25; H, 7.61; 0, 16.67.

3β,10β,17β-Trihydroxy-5α-estran-6-one 3β,17β-Diacetate (9). A mixture of 3β,17β-diacetoxy-5β,10β-oxidoestran-6-one (**4b**, 800 mg, 0.0021 mol) and chromous acetate[15] (3.4 g, ca. 0.2 mol) was stirred at ambient temperature for 24 hr in 90% aqueous acetone (150 ml) under an atmosphere of argon. The reaction mixture was diluted with water and extracted with $CHCl_3$. The extract was washed with H_2O, dried (Na_2SO_4), and evaporated in vacuo. The residue was chromatographed on silica gel (elution with 11% EtOAc in $CHCl_3$). Early fractions gave unchanged oxido ketone **4b** followed by enone **3b**. The most polar fractions gave the desired β-hydroxy ketone **9** (75 mg, 0.00019 mol, 9%): mp 196–199°; mass spectrum *m/e* 392 (M^+), 376, 349, 314, 304, 272; ν_{max} (KBr) 3480 (OH), 1735 cm^{-1} (C=O); [θ] (CH_3OH) −5078° (288 nm). Calcd for $C_{22}H_{32}O_6$: *m/e* 392.21900. Found: *m/e* 392.22510.

3β,20β-Diacetoxy-19-norpregn-5(10)-en-6-one (3c). Compound **3c** was prepared in a manner identical with that for **3a** as described above: mp 126–127° (from acetone–light petroleum); mass spectrum *m/e* 402 (M^+), 342, 300, 254; λ_{max} (MeOH) 247 nm (ε 10435); [θ] (MeOH) +2747° (330 nm); ν_{max} ($CHCl_3$) 1725 (ester C=O), 1660 (C=O), 1625 cm^{-1} (C=C); NMR 4.82 (m, 2, CHOAc), 2.0 (s, 6, CH_3CO), 0.65 ppm (s, 3, 18-CH_3).

Anal. Calcd for $C_{24}H_{34}O_5$: C, 71.61; H, 8.51. Found: C, 71.60; H, 8.26.

3β,20β-Diacetoxy-5β,10β-oxidopregnan-6-one (4c). 3β,20β-Diacetoxy-19-norpregn-5(10)-en-6-one (**3c**, 250 mg, 0.00062 mol) was dissolved in MeOH (18 ml) containing 30% H_2O_2 (1.25 ml) and 5 *N* NaOH (1.25 ml). After stirring for 3 hr at ambient temperature the reaction mixture was diluted with brine and extracted with $CHCl_3$. The extract was washed with 5% $NaHSO_3$, dried with Na_2SO_4, and removed in vacuo. The residue was acetylated pyridine–acetic anhydride) and worked up in the usual manner. Crystallization from hexane–EtOH afforded the pure oxide **4c** (186 mg, 0.00045 mol, 72%): mp 143–145°; mass spectrum *m/e* 418 (M^+), 360, 358, 342, 340, 330, 298, 270; ν_{max} 1740 (ester C=O), 1700 cm^{-1} (C=O); [θ] (CH_3OH) −9000° (307 nm); NMR 4.68 (m, 2, CHOAc), 2.00 (s, 6, CH_3CO), 1.14 (d, 3, J = 6 Hz, 21-CH_3), 0.68 ppm (s, 3, 18-CH_3).

Anal. Calcd for $C_{24}H_{34}O_6$: C, 68.87; H, 8.19. Found: C, 68.71; H, 8.11.

3β,20β-Diacetoxy-5,10-seco-19-norpregn-5-yn-10-one (5c). A mixture of 3β,20β-diacetoxy-5β,10β-oxidopregnan-6-one (**4c**, 150 mg, 0.00036 mol) and *p*-toluenesulfonyl hydrazide (78 mg, 0.0043 mol) was stirred for 6 hr at ambient temperature in 1:1 $CHCl_3$–AcOH (15 ml). The reaction mixture was diluted and extracted with $CHCl_3$. The extract was washed successively with H_2O, 5% $NaHCO_3$, and H_2O. The residue obtained after drying (Na_2SO_4) and removal of solvent was crystallized from hexane–acetone to give **5c** as plates (105 mg, 0.00026 mol, 72%): mp 119–120°; mass spectrum *m/e* 402 (M^+), 360, 358, 342, 340, 330, 298, 270; ν_{max} 1735 cm^{-1} (C=O); [θ] (CH_3OH) −2098° (283 nm); NMR 4.80 (m, 2, CHOAc), 2.05 (s, 3, CH_3CO), 2.00 (s, 3, CH_3CO), 1.15 (d, 3, J = 6 Hz, 21-CH_3), 0.80 ppm (s, 3, 18-CH_3).

Anal. Calcd for $C_{24}H_{34}O_5$: C, 71.61; H, 8.51. Found: C, 71.53; H, 8.64.

3β,20β-Dihydroxy-5,10-seco-19-norpregn-5-yn-10-one (6c). The diacetate **5c** (30 mg, 0.000075 mol) was refluxed in 3% methanolic KOH (7 ml) for 2 hr. The reaction mixture was diluted with brine, extracted with $CHCl_3$, dried (Na_2SO_4), and concentrated in vacuo to give **6c** (23 mg, 0.00072 mol, 96%): mp 180–182° (from hexane–EtOH); mass spectrum m/e 318 (M^+), 300, 285, 282, 272; ν_{max} (KBr) 3500 (OH), 1720 cm^{-1} (C=O); [θ] (MeOH) −3067° (283 nm); NMR 3.74 (m, 2, CHOH), 1.09 (d, 3, J = 6 Hz, 21-CH_3), 0.83 ppm (s, 3, 18-CH_3).

Anal. Calcd for $C_{20}H_{30}O_3$: C, 75.43; H, 9.50. Found: C, 75.38; H, 9.50.

5,10-Seco-19-norpregn-5-yne-3,10,20-trione (1c). 3β,20β-Dihydroxy-5,10-seco-19-norpregn-5-yn-10-one (**6c**, 140 mg, 0.00044 mol) was dissolved in acetone (50 ml). Excess Jones reagent was added and the mixture was stirred for 5 min at ambient temperature. The residue obtained after dilution with water and extraction with $CHCl_3$ was crystallized from hexane–EtOH to give **1c** (75 mg, 0.00024, 54%): mp 156–159°; mass spectrum *m/e* 314 (M^+), 286, 271; ν_{max} (KBr) 1705 cm^{-1}; [θ] (dioxane) +4737° (301 nm); NMR 2.14 (s, 3, 21-CH_3CO), 0.75 ppm (s, 3, 18-CH_3).

Anal. Calcd for $C_{20}H_{26}O_3$: C, 76.40; H, 8.34; 0, 15.66. Found: C, 76.22; H, 8.21; 0, 15.97.

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Registry No.—**1a**, 57237-48-6; **1b**, 26012-92-0; **1c**, 55512-68-0; **2a**, 750-59-4; **2b**, 1249-36-1; **2c**, 6764-88-1; **3a**, 50888-45-4; **3b**, 15335-35-0; **3c**, 57214-99-0; **4a**, 57215-00-6; **4b**, 57215-01-7; **4c**, 57215-02-8; **5a**, 57237-49-7; **5b**, 57215-03-9; **5c**, 57215-04-0; **6a**, 57215-05-1; **6b**, 57215-06-2; **6c**, 57215-07-3; **7**, 33487-93-3; **8**, 57215-08-4; **9**, 57215-09-5; **10**, 57215-10-8; chromium trioxide–pyridine complex, 55960-78-6; H_2O_2, 7722-84-1; *m*-chloroperbenzoic acid, 937-14-4; *p*-toluenesulfonyl hydrazide, 1576-35-8; chromous acetate, 628-52-4.

References and Notes

(1) This work was supported in part by U.S. Public Health Service Grant AM 15918.
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Krukovine, a New Bisbenzylisoquinoline Alkaloid from *Abuta splendida* Krukoff and Moldenke

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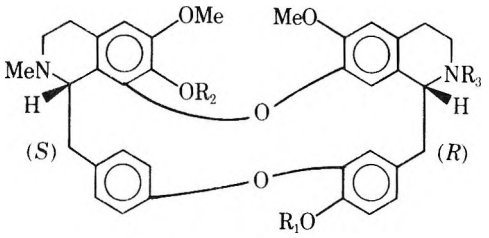
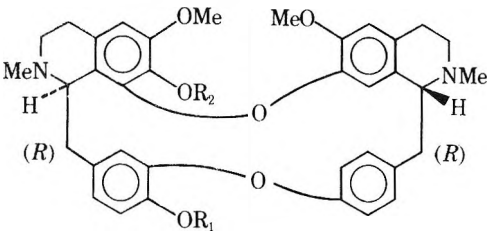
The bisbenzylisoquinoline alkaloids aromoline, homoaromoline, and krukovine have been found to be the major components of *Abuta splendida* Krukoff and Moldenke. Krukovine has been assigned structure **4** on the basis of both spectroscopic evidence and chemical degradation.

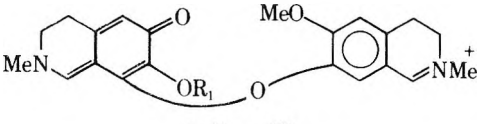
In a continuing search for natural anticancer agents, we have been studying some hitherto unexamined sources of bisbenzylisoquinoline alkaloids, in particular, plants of the genus *Abuta* (*Menispermaceae*).[1] We now wish to report the isolation of the major alkaloidal constituents of the Amazonian species, *Abuta splendida*.[2,3] These include the known bisbenzylisoquinolines aromoline (**1**) and homoaromoline (**2**) as well as the new alkalodd krukovine, which has been shown to have structure **4**.



1, $R_1 = R_2 = H$; $R_3 = Me$
2, $R_1 = Me$; $R_2 = H$; $R_3 = Me$
3, $R_1 = R_2 = R_3 = H$



4, $R_1 = R_2 = H$
5, $R_1 = R_2 = Me$
6, $R_1 = R_2 = CD_3$



7, $R_1 = CD_3$

Aromoline (**1**)[4] was obtained as tiny, colorless prisms, mp 182–183°. Positive identification of this alkaloid was made by direct comparison (ir, mixture melting point, TLC) with an authentic sample obtained by the N-methylation of natural daphnoline (**3**).

Homoaromoline (**2**)[5] was obtained as tiny, white needles, mp 236–237°. It was found to be identical (TLC, mixture melting point) with an authentic sample.

Krukovine (**4**) crystallized from chloroform as colorless prisms of the chloroform solvate, mp 182–183°. The composition $C_{36}H_{38}O_6N_2$ was determined by high-resolution mass spectrometry.

The infrared spectrum of krukovine showed a band at 3400 cm^{-1}, attributable to a nonassociated phenolic group. The NMR spectrum of krukovine showed the presence of two aromatic methoxyls at δ 3.30 and 3.73, as well as two methylimino groups at δ 2.28 and 2.58. Of the ten aromatic protons present five were clearly discernible, one as a singlet at δ 5.97 and four as a pair of doublets at δ 7.11 (d, J = 8 Hz, 2 H) and 7.32 (d, J = 8 Hz, 2 H).

Treatment of krukovine with excess diazomethane, followed by crystallization from acetone, afforded *O,O*-dimethylkrukovine (**5**), mp 125°, confirming the presence of two phenolic functions in the parent molecule. The composition $C_{38}H_{42}O_6N_2$ was determined by high-resolution mass spectroscopy. The corresponding reaction of krukovine with deuteriodiazomethane in dioxane–deuterium oxide[6] yielded the corresponding *O,O*-bistrideuteriomethyl derivative (**6**). A comparison of the NMR spectra of **5** and **6** showed that the new methyl groups of the dimethyl ether **5** are represented by signals at δ 3.18 and 3.93. These values can be assigned to the C-7 and C-12 aromatic methoxyls of a normal head-to-head dimer, since it has been pointed out that a methoxyl at C-7 is highly shielded, while a methoxyl at C-12 (or C-12′) appears in the usual range.[7]

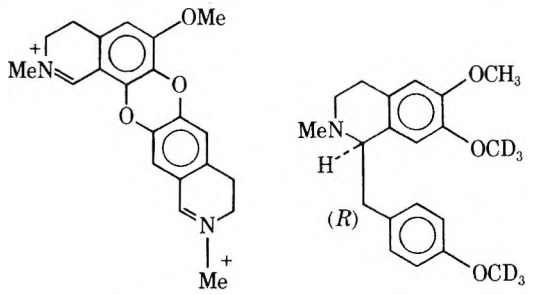
The mass spectrum of krukovine is typical of that of a bisbenzylisoquinoline alkaloid containing both head-to-head and tail-to-tail ether bridges.[8] Thus, a weak peak at M − 107 occurs in the spectra of krukovine (**4**), its dimethyl ether **5**, and the deuterated dimethyl ether **6**. Furthermore, a weak peak at M − 137 is observed in the spectrum of the dimethyl ether **5**, which is shifted to M − 140 in the spectrum of the corresponding deuterated derivative **6**, whereas this feature is absent in the spectrum of krukovine itself. These latter peaks are characteristic of a tail-to-tail diphenyl ether system containing one methoxyl substituent. This requires that one of the phenolic groups of **4** be located on the tail-to-tail diphenyl ether system, and that the second phenolic group of **4** be located on one of the isoquinoline units. In accord with this general formulation, the very strong peak of krukovine representing the linked isoquino-

line units is seen at *m/e* 381, a value which is shifted to *m/e* 395 in the spectrum of dimethyl ether **5**, and to *m/e* 398 in the spectrum of the deuterated dimethyl ether **6**.

The mass spectrum of the *O,O*-bistrideuteriomethyl ether (**6**) further defines the environment of the original phenolic hydroxyl of **4** located on the linked isoquinoline units. Loss of CH_3 from the head-to-head fragment of the molecule gives rise to an ion **7** at *m/e* 384, consistent with the loss of this group from a C-6 (or C-6′) position to give a stabilized *p*-quinonoid species. Furthermore, the same doubly charged dioxane fragment at *m/e* 175 (**8**) appears in the mass spectra of both the dimethyl ether **5** and the bistrideuteriomethyl analogue (**6**), indicative of the presence of an *o*-hydroxy-*o*′-methoxydiphenyl ether system in the top portion of krukovine itself.

The above data, as well as the negative rotation of dimethylkrukovine (**5**), suggested that the latter might be identical with phaeanthine,[9] despite the far higher melting point (216–217°, ether) reported for the latter. Indeed, crystallization of authentic high-melting phaeanthine from acetone afforded the low-melting form, identical with *O,O*-dimethylkrukovine.

Treatment of *O,O*-bis(trideuteriomethyl)krukovine (**6**) with sodium in liquid ammonia cleanly cleaved the molecule into nonphenolic and phenolic portions.[10] The nonphenolic product was identical with an authentic sample of (*R*)-*O,O*-bis(trideuteriomethyl)-*N*-methylcoclaurine (**9**). The phenolic product was identified as (*R*)-*N*-methylcoclaurine (**10**) by comparison with an authentic sample of its enantiomer and by conversion to the known crystalline oxalate[11] of its *O,O*-diethyl ether (**11**). These observations are



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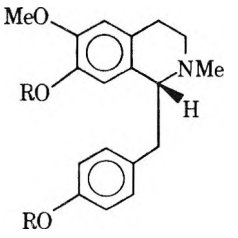

10, R = H
11, R = Et

entirely consistent with structure **4** for krukovine as the enantiomer of atherospermoline[12] (**4**, *SS*).

Experimental Section

Melting points are uncorrected. NMR spectra were determined in $CDCl_3$ solution (unless otherwise indicated) with tetramethylsilane as internal standard using Varian A-60, HR-100, and Jeol instruments. Infrared (KBr), ultraviolet (ethanol solution), mass spectra, and optical rotations (chloroform solutions at room temperature) were determined using Perkin-Elmer Models 137, 202, 270, and 141 instruments, respectively. All preparative chromatography (PLC) was carried out on silica plates using 20:1 $CHCl_3$–MeOH. *Abuta splendida* (Schunke 1971/38) was collected by J. Schunke in Mariscal Caceres, Tocache Nuevo, Department of San Martin, Peru, and identified by B. A. Krukoff. A voucher specimen has been deposited at the New York Botanical Garden and other institutions.

Isolation of Aromoline (1), Homoaromoline (2), and Krukovine (4) from *Abuta splendida* Krukoff and Moldenke. Stems of liana (4.86 kg) were exhaustively extracted first with aqueous ammonia–ether and then with 2 *N* HCl. The combined ether extracts yielded 43.5 g of crude residue consisting of neutral and basic material. This material was subjected to gradient pH countercurrent distribution (200 transfers) between chloroform and aqueous acid, starting with pH 6.5 citrate–phosphate buffer and ending with 3 *M* phosphoric acid. The acidic aqueous layers were basified, reextracted with chloroform, and divided into several fractions: A (tubes 1–16), B (tubes 17–25), C (tubes 26–36), D (tubes 37–42), E (tubes 43–55), F (tubes 56–66), G (tubes 67–104), H (tubes 105–122).

Fraction B (4.64 g) crystallized from chloroform to give colorless prisms (1.84 g) of krukovine (**4**): mp 182–183°; $[\alpha]_D$ −180° (*c* 0.06); ir (KBr) 3400 cm^{-1} (OH); uv λ_{max} (ε) 285 (6600); λ_{min} 260 (2850); λ_{max} (NaOH) 291 (9430); λ_{min} (NaOH) 272 (7540); NMR ($CDCl_3$ + Me_2SO-d_6) δ 2.28, 2.58 (s, 3 H each, 2 NMe), 3.30, 3.73 (s, 3 H each, 2 OMe), 5.97 (s, 1 H), 7.11 (d, *J* = 8 Hz, 2 H), 7.32 (d, *J* = 8 Hz, 2 H) (m, 6.28–6.75); mass spectrum *m/e* (rel intensity) 594 (M^+, 69), 593 (44), 487 (<1), 403 (14), 381 (100), 192 (75), 191 (95), 190 (24), 174 (32), 168 (25); high-resolution mass spectrum *m/e* 594.27492 (calcd for $C_{36}H_{38}O_6N_2$, 594.27298). Solvent-free **4** showed $[\alpha]_D$ −201°, indicating a $CHCl_3$ content of ca. 10% (0.5 molar equiv) for the crystalline solvate.

Crystallization ($CHCl_3$) of the mother liquors of fraction B yielded aromoline (**1**, 2.1 g) as colorless prisms, mp 182–183°, $[\alpha]_D$ +235°. Two further recrystallizations from $CHCl_3$ gave crystals: mp 182–183; $[\alpha]_D$ +320° (c 0.05) (lit.[4] mp 175°, $[\alpha]_D$ + 327°); NMR δ 2.48, 2.55 (s, 3 H each, 2 NMe), 3.57, 3.79 (s, 3 H each, 2 OMe), 5.63 (s, 1 H) (m, 6.39–7.69); mass spectrum *m/e* (rel intensity) 594 (M^+, 41), 593 (34), 487 (4), 403 (6), 381 (90), 192 (30), 191 (100), 190 (18), 175 (18), 174 (35), 168 (40).

Fraction C (6.56 g) crystallized from $CHCl_3$ to give aromoline (5.15 g).

Fraction F (0.18 g) crystallized from acetone to give white needles of homoaromoline (**2**, 0.10 g): mp 236–237°; $[\alpha]_D$ +371° (c 0.1) [lit.[5] mp 238–240°, $[\alpha]_D$ +416° ($CHCl_3$)]; ir (KBr) 3400 cm^{-1} (OH); NMR δ 2.47, 2.53 (s, 3 H each, 2 NMe), 3.57, 3.75, 3.87 (s, 3 H each, 3 OMe), 5.61 (s, 1 H) (m, 6.21–7.15); mass spectrum *m/e* (rel intensity) 608 (M^+, 38), 607 (24), 501 (6), 471 (1), 417 (4), 381 (59), 192 (100), 191 (78), 176 (10), 175 (15), 168 (19).

***O,O*-Dimethylkrukovine (5).** To a solution of **4** in methanol–ether was added ethereal diazomethane in two portions during 24 hr. The mixture was set aside in the dark. The usual work-up gave **5** as an oil which crystallized from acetone as tiny needles: mp 125°; $[\alpha]_D$ −260° (c 0.1); NMR δ 2.33, 2.62 (s, 3 H each, 2 NMe), 3.18, 3.37, 3.74, 3.93 (s, 3 H each, 4 OMe), 6.00 (s, 1 H) (m, 6.30–7.26); mass spectrum *m/e* (rel intensity) 622 (M^+, 100), 621 (40), 515 (<1), 485 (2), 430 (7), 431 (6), 395 (52), 198 (28), 192 (10), 190 (5), 175 (13), 174 (18); high-resolution mass spectrum *m/e* 622.30181 (calcd for $C_{38}H_{42}N_2O_6$, 622.30428).

An authentic sample of phaeanthine, mp 216–217°, was crystallized from acetone to give colorless needles, mp 124–125°, identical in all respects (ir, mixture melting point, TLC) with *O,O*-dimethylkrukovine (**5**).

***O,O*-Bis(trideuteriomethyl)krukovine (6).** To a cooled solution of excess diazomethane in dry dioxane (10 ml) and D_2O (1 ml) was added a solution of **4** (50 mg) in dry dioxane (2 ml) and D_2O (1 ml). After standing for 24 hr in the dark, the usual work-up afforded **6** as an amorphous solid: NMR δ 2.33, 2.61 (s, 3 H each, 2 NMe), 3.37, 3.75 (s, 3 H each, 2 OMe), 6.00 (s, 1 H) (m, 6.29–7.25); mass spectrum *m/e* (rel intensity) 628 (M^+, 100), 627 (77), 626 (35), 521 (<1), 488 (3), 437 (8), 436 (11), 398 (95), 199.5 (68), 192 (22), 190 (6), 175 (35), 174 (37).

Sodium–Ammonia Cleavage of 6. To liquid ammonia (400 ml) at −78° was added alternately, with stirring, small pieces of sodium (total of 1 g) and portions of a solution of **6** (230 mg) in dry tetrahydrofuran, making sure that the color remained blue, prior to each addition of the alkaloid solution. Finally some extra pieces of sodium were added until the blue color persisted for 15 min. The ammonia was then alowed to evaporate overnight. The residue was extracted into methanol. The residue from the methanol was dissolved in water and extracted with ether to separate the nonphenolic fraction (100 mg). From the aqueous fraction after saturation with ammonium chloride (pH 8–9) and extraction with ether (addition of a little $NaBH_4$ retarded air oxidation) was obtained the phenolic fraction (70 mg).

From the nonphenolic fraction, **9** was isolated by PLC as an oil: NMR δ 2.53 (s, 3 H, 1 NMe), 3.83 (s, 3 H, 1 OMe), 6.10 (s, 1 H),

6.60 (s, 1 H), 6.81 (d, J = 8 Hz, 2 H), 7.06 (d, J = 8 Hz, 2 H); mass spectrum m/e (rel intensity) 333 (M^+ <1), 332 (1), 209 (100), 124 (13).

The oxalate of 9 crystallized from ethanol–ether as colorless needles, mp 127–129°, $[\alpha]_D$ −93° (c 0.14). An authentic sample of (*S*)-*O*,*O*-bis(deuteriomethyl)-*N*-methylcoclaurine was prepared by deuteriomethylation of (*S*)-*N*-methylcoclaurine. Its oxalate crystallized from ethanol–ether as needles, mp 128–129°, $[\alpha]_D$ +101° (c 0.1), and it was found to be identical (ir, mixture melting point, TLC) with the oxalate of **9**.

From the phenolic fraction, **10** was isolated by PLC as an oil: $[\alpha]_D$ −36° (c 0.05); NMR δ 2.42 (s, 3 H, 1 NMe), 3.77 (s, 3 H, 1 OMe), 5.90 (br, 2 H, 2 OH), 6.52 (s, 1 H), 6.29 (s, 1 H), 6.60 (d, J = 8 Hz, 2 H), 6.90 (d, J = 8 Hz, 2 H); mass spectrum m/e (rel intensity) 299 (M^+, 1), 192 (100), 107 (9). The ir ($CHCl_3$) and NMR spectra of **10** were identical with those of an authentic sample of its enantiomer.

A portion of the phenolic fraction (20 mg) was treated with ethereal diazoethane. Work-up in the usual manner after 2 days yielded *O*,*O*′-diethyl-*N*-methylcoclaurine (**11**, 17 mg) as a pale yellow oil. It was converted to the oxalate which crystallized from ethanol–ether as needles: mp 172–174°; $[\alpha]_D$ −114° (c 0.05) (lit.[11] mp 173–174°, $[\alpha]_D$ −123°); mass spectrum m/e (rel intensity) 355 (M^+, 1), 220 (100), 135 (11). The ir spectrum, mixture melting point, optical rotation, and R_f of this compound were identical with those of an authentic sample.

N-Methylation of Daphnoline (3). To a methanol–chloroform solution of daphnoline (**3**, 13 mg), excess of 40% formaldehyde solution was added, and the mixture was stirred at room temperature for 2 hr.

The solution was then cooled in an ice bath and $NaBH_4$ was added in small portions. The solution was further stirred for 1 hr. Work-up as usual gave 13 mg of a transparent oil which crystallized from chloroform as colorless prisms, mp 182–183°, identical (ir, mixture melting point, TLC) with aromoline (**1**).

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Registry No. —**1**, 519-53-9; **2**, 17132-74-0; **3**, 479-36-7; **4**, 57377-42-1; **5**, 1263-79-2; **6**, 57288-11-6; **9**, 57256-00-5; **9** oxalate, 57256-01-6; **10**, 5096-70-8; **11**, 6681-71-6.

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β-Phenethylamine and Tetrahydroisoquinoline Alkaloids from the Mexican Cactus *Dolichothele longimamma*[1]

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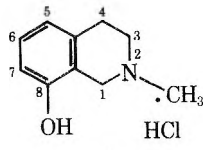
Seven crystalline alkaloids have been isolated and identified from extracts of a Mexican "peyote" cactus, *Dolichothele longimamma* (DC.) Br. and R. Five of these are new alkaloids: *N*-methyl-β-hydroxy-4-methoxy-β-phenethylamine (longimammine or 4-*O*-methylsynephrine), 6-hydroxy-2-methyl-1,2,3,4-tetrahydroisoquinoline (longimammosine), 8-hydroxy-2-methyl-1,2,3,4-tetrahydroisoquinoline (longimammidine), 6-methoxy-1,2,3,4-tetrahydroisoquinoline (longimammatine), and 4,8-dihydroxy-2-methyl-1,2,3,4-tetrahydroisoquinoline (longimammamine). Although these compounds have all previously been synthesized, a new and convenient route is described for the syntheses of longimammidine and longimammosine. The known cactus alkaloids, (−)-normacromerine and (±)-synephrine, were also found in this species.

The peyote cactus, *Lophophora williamsii* (Lem.) Coult., has a well-documented history as a folkloric medicine and is known to contain many β-phenethylamine and tetrahydroisoquinoline alkaloids including the hallucinogen, mescaline.[2] Several ethnobotanical reports by Schultes suggest that *Dolichothele longimamma* (DC.) Br. and R., another Mexican "peyote" cactus, may cause similar psychoactive effects.[3] Early reports state that this genus contains unknown poisonous alkaloids,[4] and in a recent TLC screen of some *Dolichothele* species several new unidentified cactus alkaloids were detected in *D. longimamma*.[5] In the present communication we report the isolation and structure determination of seven alkaloids from this cactus.

TLC visualization[1a,6] of alkaloid-bearing fractions[5] from freeze-dried and pulverized *D. longimamma* confirmed the presence of several compounds that were distinct from previously known cactus alkaloids.[6,7] Large-scale extraction, involving basification of the plant material, chloroform ma-

cerations, acid–base partitioning, and anion-exchange chromatography, yielded three fractions consisting of the water-soluble, the nonphenolic, and the phenolic alkaloids. Separation of the alkaloids in these fractions was achieved by preparative TLC using silica gel as the adsorbent.

Three new tetrahydroisoquinolines (**1–3**) and a known β-phenethylamine, synephrine (**4**), were crystallized from the phenolic fraction. The structure determinations of compounds **1–3** were based primarily on their ^{1}H NMR and mass spectra; synephrine was identified by TLC.



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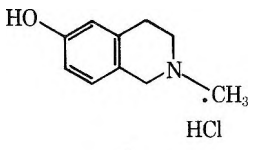

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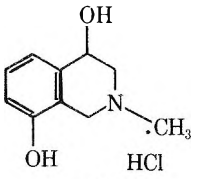

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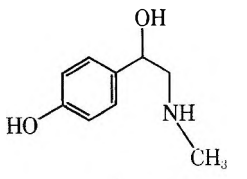

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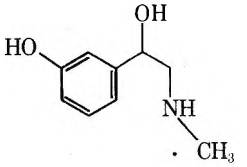
The mass spectrum of compound **1** exhibited a high-intensity molecular ion peak corresponding to $C_{10}H_{13}NO$ (*m/e* 163). An intense peak at *m/e* 120 (M − 43), due to a retro-Diels–Alder reaction[8] of the molecular ion, strongly suggested a tetrahydroisoquinoline structure. The ^{1}H NMR spectrum displayed a three-proton singlet at δ 3.08 attributable to the *N*-methyl protons and a four-proton multiplet centered at δ 3.45 corresponding to the C-3,4 ethylene protons. A two-proton AB pattern centered at δ 4.29 (J = 16 Hz) was assigned to the C-1 protons.[9] The aromatic region showed a one-proton triplet centered at δ 7.25 (J_o = 8 Hz) and a two-proton doublet (two overlapping doublets) centered at δ 6.85 (J_o = 8 Hz); similar ^{1}H NMR patterns have been observed for other tetrahydroisoquinoline hydrochlorides that are monosubstituted on the aromatic ring.[10] An aromatic pattern of a triplet and doublets, as observed for compound **1**, is characteristic of C-5 and C-8 oxygenated tetrahydroisoquinoline hydrochlorides and serves to distinguish these compounds from their C-6 and C-7 oxygenated isomers, which exhibit an aromatic pattern of two doublets and a doublet of doublets.[10] A C-8 hydroxyl explains the relatively large difference in chemical shifts (53 Hz) between the A and B protons of C-1.[9]

The essentially identical mass spectra of compounds **1** and **2** (longimammosine hydrochloride) indicated an isomeric relationship between these two alkaloids involving, perhaps, an alternative positioning of the hydroxyl at C-5, C-6, or C-7. The ^{1}H NMR spectra of **1** and **2** were quite similar except for the aromatic absorption patterns. In the aromatic region **2** exhibited a one-proton doublet centered at δ 7.10 (J_o = 8 Hz), a doublet of doublets (J_o = 8, J_m = 2.5 Hz), partially resolved and centered at δ 6.82, and an unresolved doublet (meta coupling) centered at δ 6.77. This pattern is indicative of a C-6 or C-7 hydroxyl,[10] but the exact positioning was not proven to be at C-6 until **2** was synthesized.

Compound **3** (longimammamine hydrochloride) was optically active ($[\alpha]^{25}$D −60°) indicating asymmetry. The mass spectrum exhibited a molecular ion corresponding to $C_{10}H_{13}NO_2$ (*m/e* 179). An intense peak at *m/e* 136 (*M* − 43) indicated a retro-Diels–Alder reaction, again implicating a tetrahydroisoquinoline.[8] A peak attributable to a loss of hydrogen and water was observed at *m/e* 160 (*M* − 19) and hinted that a C-4 hydroxyl might be present. Such 4-hydroxytetrahydroisoquinolines would not be unexpected in nature; biosynthetically they could arise from cyclization of β-hydroxy-β-phenethylamines, such as synephrine and normacromerine, which are not uncommon in cacti.[5,7,11]

The ^{1}H NMR spectrum of **3** exhibited a one-proton triplet at δ 5.07 (J = 3 Hz) due to the C-4 proton and a broad two-proton singlet at δ 3.60 attributable to the C-3 protons. Previous reports[12] describing the ^{1}H NMR spectra of simple 4-hydroxytetrahydroisoquinolines containing oxygenated substituents on the aromatic ring describe similar absorption values for the C-3 and C-4 protons. A singlet at δ 3.12 corresponded to the three *N*-methyl protons. An aromatic pattern of two doublets of one proton each centered at δ 7.04 and 6.92 (J_o = 8 Hz) and a one-proton triplet at δ 7.32 (J_o = 8 Hz) implicated a C-5 or C-8 hydroxyl on the benzene ring. A two-proton AB pattern, due to the C-1 protons, centered at δ 4.34 (J = 16 Hz), in which the chemical shift difference between the A and B protons is of the same order of magnitude (41 Hz) as the C-1 protons in compound **1**, indicated that **3** also possessed an 8-hydroxy function.

Recently, the Pictet–Spengler synthesis of tetrahydroisoquinolines has been applied to the reaction of phenylephrine (**5**) with formaldehyde; this reaction has yielded two isomeric compounds, **6** and **3**, the respective products of para and ortho ring closure of **5**.[13] We employed this reaction starting with L-phenylephrine, to obtain **6** and **3**. The synthesized **3** exhibited $[\alpha]^{25}$D −40°, indicating some racemization when compared with the natural compound ($[\alpha]^{25}$D −60°). Bobbitt et al.[12a,14] have hydrogenolyzed a series of 4-hydroxytetrahydroisoquinoline hydrochlorides to the corresponding tetrahydroisoquinoline hydrochlorides. We used this reaction to obtain **1** and **2** from **3** and **6**, respectively. The combination of these two reactions represents a new and convenient route to **1** and **2**. The synthetic **1**, **2**, and **3** exhibited physical and spectral properties indistinguishable from those of the compounds isolated from the phenolic fraction of *D. longimamma* and served to verify the correctness of the proposed structures.



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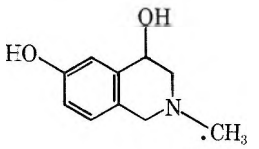

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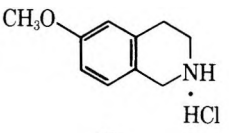
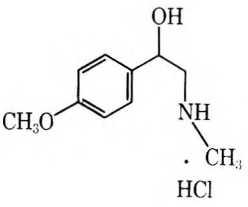
Compound **4** (synephrine) was identified initially by chromatographic comparisons with reference (±)-synephrine. The isolated alkaloid exhibited no optical rotation at the sodium D line. Spectral, physical, and TLC comparisons of the isolate with reference (±)-synephrine verified the identification. A larger quantity (1.5 g) of (±)-synephrine was isolated from the water-soluble fraction of the alkaloid extracts and was the only isolate obtained from this fraction. Synephrine represented the major alkaloid of this cactus species.

Three crystalline alkaloid hydrochlorides, compounds **7–9**, were isolated and identified from the nonphenolic alkaloid fraction.

Compound **7** (longimammatine hydrochloride) exhibited a high-intensity molecular ion in the mass spectrum corresponding to $C_{10}H_{13}NO$ (*m/e* 163). A high-intensity peak in the mass spectrum at *m/e* 134 (M − 29) again indicated a retro-Diels–Alder reaction and suggested that **7** was another tetrahydroisoquinoline. The ^{1}H NMR spectrum showed a two-proton singlet at δ 4.30 attributable to the C-1 protons. A three-proton singlet at δ 3.81 indicated a methoxy



7



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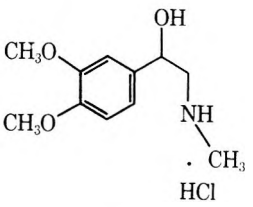

9

substituent on the benzene ring. An A_2X_2 pattern of two triplets of two protons each was observed at δ 3.50 and 3.09 (J = 6 Hz) and was assigned to the C-3 and C-4 protons, respectively. A three-proton aromatic pattern similar to that observed for compound **2** indicated that the methoxy substituent was likely at C-6. A Pictet–Spengler synthesis of **7** from *m*-methoxy-β-phenethylamine was performed by a method analogous to one used by Helfer.[15] The physical and spectral properties of the synthetic compound and the isolated **7** were essentially identical.

Compound **8** (longimammine hydrochloride or 4-*O*-methylsynephrine) was optically active ($[\alpha]^{25}D$ −36°) indicating asymmetry. A low-intensity molecular ion peak corresponding to $C_{10}H_{15}NO_2$ (*m/e* 181) was present in the mass spectrum and a base peak at *m/e* 44 and an intense peak at *m/e* 137 (M − 44) indicated an *N*-methyl-β-phenethylamine. In the ^1H NMR spectrum a three-proton singlet at δ 2.77 confirmed the presence of an *N*-methyl group. An A_2X pattern of a two-proton doublet (J = 7 Hz) centered at δ 3.29 and a one-proton triplet (J = 7 Hz) centered at δ 5.01 indicated a β-hydroxy substituent. A four-proton A_2B_2 aromatic pattern centered at δ 7.21 suggested para substitution on the benzene ring, and a three-proton singlet at δ 3.83 indicated that this para substituent was a methoxy group. Racemic **8** was synthesized via a Houben–Hoesch condensation followed by sodium borohydride reduction.[16] ^1H NMR and mass spectra of the synthetic and isolated **8** were essentially identical. In addition, the synthetic and isolated compounds consistently cochromatographed in TLC.

Compound **9** was also optically active ($[\alpha]^{25}D$ −60.6°). The ^1H NMR and mass spectral data indicated that this compound was (−)-*N*-methyl-3,4-dimethoxy-β-hydroxy-β-phenethylamine (normacromerine). This identification was confirmed by mixture melting point comparisons, cochromatography, and essentially identical ir spectra of the isolated compound **9** and reference (−)-normacromerine hydrochloride.[16a]

Compounds **1** (longimammidine hydrochloride), **2** (longimammosine hydrochloride), **3** (longimammamine hydrochloride), **7** (longimammatine hydrochloride), and **8** (longimammine) have never before been isolated from nature and represent new cactus alkaloids; their syntheses have been previously reported.[10,13a,15,16] Synephrine and normacromerine are previously known as cactus alkaloids.[11] A single oxygenated substituent at C-6 or C-8 in compounds **1–3** and **7** are unusual for plant tetrahydroisoquinolines since tyrosine, the usual precursor, would only give rise to C-7 oxygenated derivatives.[9,17] These tetrahydroisoquinolines may be biosynthetically cyclized from meta tyramines; the aromatic substituents may be added by oxidations after cyclization of the phenethylamine has occurred; or the aromatic ring could represent Dopa which has been reduced at the para position. The origin of the 4-hydroxyl of compound **3** gives rise to additional biogenetic speculations. The biosynthesis of these new compounds as well as their possible psychoactive effect remains to be determined. Synephrine is a well-known sympathomimetic;[18] normacromerine produced no effects on the conditioned avoidance response in rats and is probably not psychoactive;[19] and (±)-*N*-methyl-4-methoxy-β-hydroxy-β-phenethylamine (**3**, longimammine) has recently been reported to have monoamine oxidase (MAO) inhibiting activity.[20] The co-occurrence of longimammine and synephrine could block the activity of MAO, potentiate the stimulant effects of synephrine, and possibly help to explain the folkloric uses of *D. longimamma* as a psychoactive "peyote" cactus.

Experimental Section

General Experimental. Melting points were determined on a Laboratory Apparatus Mel-Temp melting point apparatus and are uncorrected. Ultraviolet spectra were determined in 95% ethanol on a Cary Model 17 recording spectrophotometer. Infrared spectra were determined on a Beckman Model IR-33 recording spectrophotometer using KBr pellets. Proton magnetic resonance spectra were determined on a Jeol PFT-100 spectrometer or a Varian A-60 spectrometer using Me_4Si or DSS as internal standards. Mass spectra were determined on a Hitachi RMU-6 spectrometer with the sample being introduced by the direct insertion probe. Values of $[\alpha]D$ were determined on a Cary 60 recording spectropolarimeter. All hydrogenations were carried out on a Parr hydrogenation apparatus.

Analytical TLC plates were purchased from Baker (Baker-flex silica gel 1B or 1B2-F). Preparative TLC plates (20 × 20 cm) were prepared with a 1 mm layer of silica gel PF-254 (Brinkmann). Analytical separations and cochromatography were achieved by use of the following solvent systems:[11a] solvent A, ethyl acetate–methanol–58% ammonium hydroxide (17:2:1); solvent B, chloroform–ethanol–58% ammonium hydroxide (15:20:1); solvent E, diethyl ether–acetone–methanol–58% ammonium hydroxide (9:8:2:1); solvent F, diethyl ether–methanol–58% ammonium hydroxide (17:2:1); solvent G, chloroform–acetone–58% ammonium hydroxide (10:17:1). Fluorescamine,[1a] dansyl chloride,[6] iodoplatinate,[1a] and tetrazotized benzidine (TZB)[6] were used as the visualization reagents. Preparative scale isolations were achieved using solvent F with repeated developments. The degree of separation of the various bands on the TLC plates was monitored under short-wave uv light and by spraying the edge of each plate, when necessary, with dansyl chloride, followed by overspraying with TZB. The appropriate bands were scrapped from the plates, combined, and eluted with 5% ammonium hydroxide in ethanol.

***Dolichothele longimamma*. Extraction and Fractionation into Phenolic, Nonphenolic, and Water-Soluble Portions.** Freeze-dried, pulverized *D. longimamma* (354 g)[21] was placed in a Soxhlet extractor and continuously extracted with petroleum ether (bp 30–60°) for 24 hr to remove lipids (37 g, 10.5%). The defatted marc was basified with chloroform–methanol–58% ammonium hydroxide, 2:2:1, and extracted with a 1-l. solution of chloroform–methanol–ammonium hydroxide, 9:9:1, and by maceration with ten 1-l. portions of chloroform. The combined extracts were condensed under vacuum evaporation to give 50 ml of a thick black-brown syrup. This material was processed, essentially as previously described,[11c] to yield fractions A (alkaloids), B (nonalkaloidal materials), and C (water-soluble alkaloids). Fraction A was separated into phenolic and nonphenolic fractions using 70 g of the strongly basic ion-exchange resin, Amberlite IRA-401S in the hydroxide form, packed in a glass column (2 × 34.5 cm).[6]

Resolution and Identification of Phenolic Alkaloids. Spraying of an analytical TLC plate spotted with portions of the phenolic fraction and developed in solvent F showed six spots with the following R_f values 0.76, 0.67, 0.53, 0.41, 0.31, and 0.18. Preparative TLC (eight plates) was employed to give four crystalline compounds.

Compound **1**, longimammidine hydrochloride, was isolated as the free base and had an R_f of 0.76. This compound, when chromatographed on a TLC plate, showed no visualization reaction with fluorescamine. Overspraying with dansyl chloride showed a yellow fluorescent spot, while a third spraying with iodoplatinate produced a purple spot. A second plate sprayed with TZB showed an orange spot. Recrystallization from ethanol gave 68 mg of brown crystals (mp 171–174°, lit.[10] mp 175.5–176°).

The hydrochloride 1 was prepared by the addition of 5% hydrochloric acid in ethanol to give 67 mg (0.0019% yield) of colorless crystals. Recrystallization from ethanol–ether gave 57 mg of crystals (mp 246–247°, lit.[10] mp 243–244°): uv max λ (ε) 279 (2100), 217 (6400); ^{1}H NMR (100 MHz, D_2O) δ 3.08 (3 H, s, NCH_3), 3.45 (4 H, m, 3-CH_2, 4-CH_2), 4.29 (2 H, 2d, J = 16 Hz, $\Delta\nu$ = 53 hz, 1-CH_2), 6.85 (2 H, d, J_o = 8 Hz, 5-CH, 7-CH), 7.25 (1 H, t, J_o = 8 Hz, 6-CH); low-resolution mass spectrum m/e (percent) 163 (M^+, 68), 162 (base peak), 120 (58), 91 (28), 44 (41); ir 3100, 1590, 1460, 1270, 990 cm^{-1}. A mixture melting point determination with the synthetic compound showed no depression. Cochromatography of the isolate with synthetic material showed identical mobilities in solvents A, B, E, F, and G. The ir spectra of the isolate and synthetic material were indistinguishable.

Longimammosine hydrochloride (2) was isolated as the free base (R_f 0.67, solvent F). This compound gave the same TLC visualization reactions with fluorescamine and dansyl chloride as did compound 1. A blue spot was observed on overspraying with iodoplatinate, and a yellow-brown spot formed with TZB. Recrystallization from ethanol gave 62 mg of the free base (mp 180–182°). Conversion to the hydrochloride gave 68 mg (0.0019% yield) of colorless crystals (mp 234–235°, lit.[22] mp 236°): uv max λ (ε) 286 (1700), 228 (6200), and 221 (6600); ^{1}H NMR (100 MHz, D_2O) δ 3.05 (3 H, s, NCH_3), 3.47 (4 H, m, 3-CH_2, 4-CH_2), 4.33 (2 H, 2 d, J = 16 Hz, $\Delta\nu$ = 27 Hz, 1-CH_2), 6.77 (1 H, s, 5-CH), 6.82 (1 H, dd, 1 d unresolved, J_m = 2.5, J_o = 8 Hz, 7-CH), 7.10 (1 H, d, J_o = 8 Hz, 8-CH); low-resolution mass spectrum m/e (percent) 163 (M^+, 52), 162 (base peak), 120 (78), 91 (18), 44 (28); ir 3220, 2920, 2680, 2600, 1430, 1200 cm^{-1}. A mixture melting point determination of 2 with the synthetic compound showed no depression. Cochromatography of the isolate with synthetic material showed one spot in solvents A, B, E, F, and G. The isolate and synthetic material exhibited indistinguishable ir spectra.

The free base of compound 3, longimammamine, was converted to the hydrochloride (R_f 0.53, solvent F). Recrystallization from ethanol–ether afforded 3 mg (0.0008% yield) of colorless crystals, mp 224–228°. This compound gave no TLC visualization reaction with fluorescamine, a fluorescent yellow color with dansyl chloride, and a blue-green spot after overspraying with iodoplatinate. A brown spot was observed after spraying 3 with TZB: $[\alpha]^{25}$D −60°; uv max λ (ε) 279 (1700), 216 (4100); ^{1}H NMR (100 MHz, D_2O as solvent and internal standard) δ 3.12 (3 H, s, NCH_3), 3.60 (2 H, broad, 3-CH_2), 4.34 (2 H, 2d, J = 16 Hz, $\Delta\nu$ = 41 Hz, 1-CH_2), 5.07 (1 H, t, J = 3 Hz, 4-CH), 6.92 (1 H, d, J_o = 8 Hz, 7-CH), 7.04 (1 H, d, J_o = 8 Hz, 5-CH), 7.32 (1 H, t, J_o = 8 Hz, 6-CH); low-resolution mass spectrum m/e (percent) 179 (M^+, 16), 136 (21), 135 (18), 107 (10), 77 (11), 44 (base peak); ir 3220, 3170, 3070, 2960, 1460, 1270 cm^{-1}. Cochromatography of the isolate with synthetic material showed one spot in solvent F, as well as identical iodoplatinate and TZB visualization reactions. The ir spectra of the isolated longimammamine hydrochloride and the synthetic material were essentially identical.

Synephrine, compound 4, having R_f 0.18 in solvent F, was crystallized from ethanol and recrystallized to give 25 mg of the colorless free base (mp 183–185°). The ir spectra of synthetic (±)-synephrine (Sigma Chemical Co.) and the isolate were indistinguishable. The isolate exhibited no optical rotation at the sodium D line, and a mixture melting point determination with synthetic (±)-synephrine and the isolate showed no depression (183–186°). Cochromatography of the isolate with the reference in five TLC solvent systems (A, B, E, F, G) showed only one spot, further substantiating the identification.

Extract C, the water-soluble alkaloid fraction, showed two spots (R_f values 0.18 and 0.31, solvent F) with TLC analysis. Upon concentrating this extract to a small volume in ethanol, crystals of synephrine precipitated. Filtration and recrystallization yielded an additional 1.5 g (0.43% yield) of (±)-synephrine. The compound having R_f 0.31 failed to yield crystals, even after preparative TLC.

Resolution and Identification of Nonphenolic Alkaloids. Analytical TLC of this fraction indicated the presence of seven alkaloids that formed yellow fluorophors after being sprayed with dansyl chloride and viewed under uv light, as well as visible chromophores on spraying with TZB. The following R_f values in solvent F were obtained: 0.27, 0.42, 0.47, 0.60, 0.74, 0.79, and 0.85. Preparative TLC (20 plates) was employed to give three crystalline alkaloids, these being the major components of this fraction.

Longimammatine (7) had R_f 0.60 and was isolated as the hydrochloride salt. Recrystallization from ethanol–ether yielded 10 mg (0.0028% yield) of colorless, platelike crystals (mp 244–245.5°, lit.[10] mp 238–239°). Spraying a developed TLC plate with fluorescamine followed by dansyl chloride gave the characteristic fluorophor of a secondary amine. A white spot appeared after overspraying with TZB: uv max λ (ε) 285 (1600), 277 (1700), 226 (7100), 220 (sh, 6500); ^{1}H NMR (100 MHz, D_2O as solvent and internal standard) δ 3.09 (2 H, t, J = 6 Hz, 4-CH_2), 3.50 (2 H, t, J = 6 Hz, 3-CH_2), 3.81 (3 H, s, OCH_3), 4.30 (2 H, s, 1-CH_2), 6.87 (1 H, unresolved d, 5-CH), 6.90 (1 H, d, J_o = 8 Hz, 7-CH), 7.17 (1 H, d, J_o = 8 Hz, 8-CH); low-resolution mass spectrum m/e (percent) 163 (M^+, 53), 162 (base peak), 134 (77), 118 (21), 91 (48), 44 (27); ir 2920, 2830, 2780, 1240, 1215, 1160 cm^{-1}. A mixture melting point determination with the synthetic material showed no depression. This isolate and synthetic reference material showed identical chromatographic mobilities in solvent F, as well as identical TLC color reactions and indistinguishable ir spectra.

Longimammine (8) (R_f 0.42, solvent F) was isolated and converted to the hydrochloride (1.3 mg, 0.00037% yield) with mp 144–146°. Spraying a developed TLC plate with fluorescamine followed by dansyl chloride verified a secondary amine function. A white spot appeared after overspraying with TZB: $[\alpha]^{25}$D −36°; uv max λ (ε) 281 (174), 274 (220), 225 (2100); ^{1}H NMR (100 MHz, D_2O) δ 2.77 (3 H, s, NCH_3), 3.29 (2 H, d, J = 7 Hz, α-CH_2), 3.83 (3 H, s, OCH_3), 5.01 (1 H, t, J = 7 Hz, β-CH), 7.21 (4 H, 2 d, J = 9 Hz, o- and m-H's); low-resolution mass spectrum m/e (percent) 181 (M^+, 3), 137 (15), 44 (base peak). Synthetic (±)-longimammine hydrochloride exhibited mass and ^{1}H NMR spectra indistinguishable from those of the isolate. Cochromatography of the isolate with the reference compound showed one spot in solvents A, B, E, F, and G, as well as identical TLC color reactions.

Normacromerine hydrochloride (9) (R_f 0.27) yielded brown, needle-shaped crystals which were recrystallized from ethanol–ether to give 42 mg (0.012% yield) of the hydrochloride (mp 130–131°, lit.[16a] mp 132–133°). The isolate exhibited $[\alpha]^{25}$D −60.6°; and spectral data (ir, MS, uv, and ^{1}H NMR) obtained with reference (−)-normacromerine hydrochloride[23] and the isolate were essentially identical. A mixture melting point determination showed no depression. Cochromatography of the isolate with the reference in five TLC systems (solvents A, B, E, F, and G) showed one spot, plus identical TLC visualization reactions.

Synthesis of *N*-Methyl-4,6-dihydroxy-1,2,3,4-tetrahydroisoquinoline Hydrochloride (6) and Longimammamine Hydrochloride (3). To 20 g (98 mmol) of L-phenylephrine hydrochloride (Sigma Chemical Co.) dissolved in 45 ml of water was added 8 g (99 mmol) of 37% aqueous formaldehyde solution. After 3 days 1.2 g of colorless crystals of 3 was obtained by filtration (TLC showed one spot). The filtrate was reduced to 30 ml with the precipitation of a second crop of crystalline 3, which was recrystallized from water to give 1.7 g. Total yield of 3 was 2.9 g (14 mmol), 14%: mp 235–236.5°; $[\alpha]^{25}$D −40°.

The remaining filtrate was reduced to 20 ml and 70 ml of ethanol was added with the subsequent gradual formation of colorless crystals of 6. This material was recrystallized from methanol–ethanol to give 5.4 g of 6. The filtrate was reduced to 10 ml, and 24 ml of ethanol was added resulting in the formation of an additional 1.5 g of 6. Total yield of 6 was 6.9 g (32 mmol), 33%, mp 193–194°.

Synthesis of Longimmamidine Hydrochloride (1) and Longimammosine Hydrochloride (2). Catalytic hydrogenations of 3 and 6 employing a procedure similar to that described by Bobbitt and Sih[12a] gave 1 and 2, respectively. Thus, 1.9 g (8.8 mmol) of 3 was dissolved in 60 ml of 6 *N* HCl, and 1.9 g of 5% palladium on carbon was added. Hydrogenation was carried out in a Parr bottle for 44 hr at room temperature and 18 psi. The catalyst was removed by filtration, and the filtrate was condensed to near dryness. Methanol was added and the solution was condensed to near dryness; this procedure was repeated several times. Recrystallization from methanol afforded 0.52 g of 1. TLC of the filtrate (solvent F) showed the presence of some starting material. Preparative TLC (15 plates) was employed to obtain an additional 0.58 g of 1, total yield 1.1 g (5.5 mmol), 63%, mp 247–248.5°, ir indistinguishable from literature ir.[10]

A Parr bottle was charged with 3.1 g (14.4 mmol) of 6, dissolved in 20 ml of 6 *N* HCl and 3.1 g of 5% palladium on carbon. Hydrogenation was carried out for 7 days at room temperature and 20 psi, after which time hydrogen consumption stopped. TLC of the reaction mixture indicated a 1:1 ratio of starting material to product. The reaction mixture was filtered, a fresh portion (2 g) of 5% palladium on carbon was added, and hydrogenation was continued for 5 days (20 psi), after which time hydrogen consumption ceased. The reaction mixture was filtered, and the filtrate was reduced in volume to near dryness. Methanol was added and the solution was condensed to near dryness; this procedure was repeated several

times. Recrystallization from methanol afforded 0.53 g of colorless crystals of **2**. TLC of the mother liquor indicated some starting material. Preparative TLC (six plates) was employed to obtain an additional 0.69 g of **2**, total yield 1.2 g (6.12 mmol), 43%, mp 234–235.5°.

Synthesis of Longimammine Hydrochloride (8). A Houben–Hoesch condensation of anisole with *N*-methylaminoacetonitrile hydrochloride afforded a 29% yield of 4-methoxy-ω-methylaminoacetophenone hydrochloride, mp 229–230.5°, lit.[24] mp 229–231°. This compound was reduced with sodium borohydride to give optically inactive **8** which was converted to the hydrochloride (mp 116–117°, lit.[20] mp 117–118°).

Synthesis of Longimammatine Hydrochloride (7). The condensation of *m*-methoxybenzaldehyde with nitromethane afforded *m*-methoxy-ω-nitrostyrene (mp 90–91°, lit.[25] mp 91–92°). A lithium aluminum hydride reduction of *m*-methoxy-ω-nitrostyrene afforded *m*-methoxy-β-phenethylamine which was converted to the hydrochloride, mp 129–130.5°. Following slight modification of the procedure described by Helfer,[15] the *m*-methoxy-β-phenethylamine hydrochloride cyclized with formaldehyde to yield **7** (mp 244–245.5°, lit[10] mp 238–239°).

Registry No.—**1**, 34222-77-0; 1 free base, 14788-32-0; **2**, 57196-60-8; **2** free base, 14097-39-3; **3**, 57286-92-7; **3** free base, 57236-57-4; **4**, 582-84-3; **6**, 57196-61-9; **7**, 57196-62-0 **8**, 57286-93-8; 8 HCl, 57236-58-5; **9**, 41136-36-1; L-phenylephrine hydrochloride, 61-76-7; anisole, 100-66-3; *N*-methylaminoacetonitrile, 5616-32-0; *m*-hydroxybenzaldehyde, 100-83-4; nitromethane, 75-52-5.

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(1) (a) Part XXVIII in the series "Cactus Alkaloids". For Part XXVII, see R. L. Ranieri and J. L. McLaughlin, *J. Chromatogr.*, **111**, 234 (1975). (b) This work was supported by U.S. Public Health Service Research Grant GM-21,211 from the National Institute of General Medical Sciences, and by a grant from the Cactus and Succulent Society of America. (c) The authors acknowledge the valuable advice and assistance of C. Glass, W. C. Bogard, Jr., J. W. Clevenger, R. G. Cooks, C. J. Chang, D. E. Nichols, and S. Teitel.

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Protonated Cyclopropane Intermediates from the Deamination of 3-Methyl-2-aminobutane

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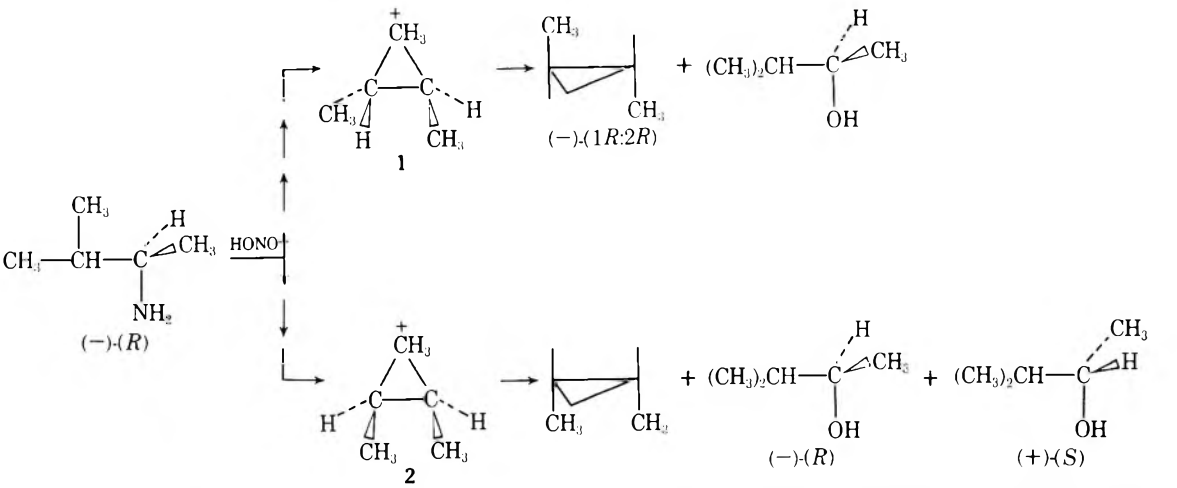
The formation of 1,2-dimethylcyclopropanes in the aqueous deamination of 3-methyl-2-aminobutane suggests that the 3-methyl group of the amine plays a role in the reaction. The extent of this role has now been established. Deamination of optically active amine provides *trans*-1,2-dimethylcyclopropane with 57 ± 2% net inversion and 3-methyl-2-butanol with a remarkable 37 ± 3% net *retention* of configuration. Study of the products obtained by deamination of 3-methyl-2-aminobutane-*1,1,1,3-d*$_4$ proves that 37 ± 4% of the 3-methyl-2-butanol formed but essentially none of the 2-methyl-2-butanol has undergone 1,2-methyl rearrangement. A scheme postulating the intervention in the deamination reactions of corner-protonated (methylene carbon) *cis*- and *trans*-1,2-dimethylcyclopropane intermediates adequately rationalizes all the observations. This mechanism cannot be distinguished from one implicating rapidly equilibrating edge-protonated cyclopropane intermediates.

Several carbonium ion reactions apparently generate[1,2] the protonated cyclopropane cation, c-$C_3H_7^+$. For example, postulation that deamination of 1-aminopropane-*1*-^{14}C produces a trace of c-$C_3H_7^+$ provides a simple explanation for the fact that the C_3H_6 fraction obtained contains 10% cyclopropane and that positions 2 and 3 of the 1-propanol formed each contain 2% of the ^{14}C label. Whether c-$C_3H_7^+$ is best represented as edge- or corner-protonated remains undecided.[1,3]

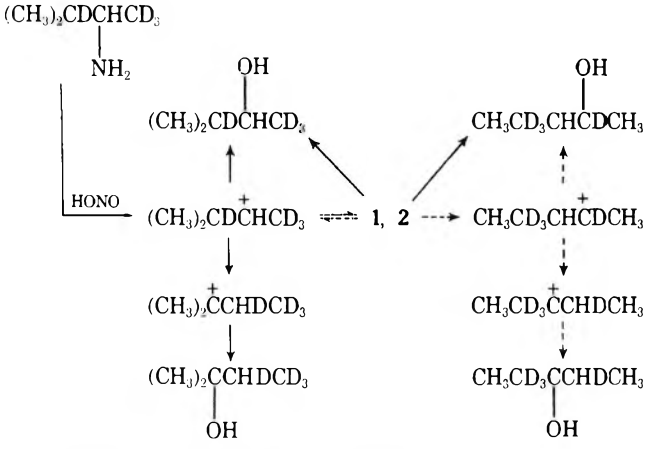
Protonated cyclopropane intermediates seemingly are less important in the deamination of higher alkylamines. The hydrocarbon fraction obtained from deamination of *n*-, *sec*-, or isobutylamine, 1-aminopentane, 2-aminopentane, isopentylamine, or 2-methyl-1-aminobutane contained only 1–5% of the pertinent alkylcyclopropane derivatives.[4,5] Likewise deamination of suitably deuterium-labeled *n*-, *sec*-, or isobutylamine afforded butanols and methylcyclopropane which revealed almost none of the

Scheme I[a]



[a] Illustration of how the intervention of protonated cyclopropanes 1 and 2 in the deamination of optically active 3-methyl-2-aminobutane could result in the formation of *trans*-1,2-dimethylcyclopropane with net inversion and 3-methyl-2-butanol with net retention of configuration.

Scheme II[a]



[a] Simplified representation of the deamination of 3-methyl-2-aminobutane-*1,1,1,3-d*$_4$. The appearance of CH_3 protons at the 1 position of 3-methyl-2-butanol and the 4 position of 2-methyl-2-butanol reveal the extent of participation by 1 and 2. The dotted arrows describe potential reaction paths which we were unable to detect.

deuterium rearrangement expected if protonated cyclopropanes had been formed.[6-8] This diminished contribution of alkyl-substituted protonated cyclopropane intermediates has been attributed to the destabilizing influence of alkyl–hydrogen eclipsing interactions.[6,7,9]

The deamination of 3-methyl-2-aminobutane (hereafter RNH_2) significantly differs from the deaminations just cited, for it yields a C_5H_{10} fraction of which 13–18% are 1,2-dimethylcyclopropanes.[4,10a] Protonated cyclopropane intermediates approximating **1** and **2** (Scheme I) may therefore be of significance in the deamination of RNH_2. If so, they could reveal their presence in three other ways: (1) optically active RNH_2 should yield *trans*-1,2-dimethylcyclopropane with inversion of configuration (Scheme I);[10b] (2) optically active RNH_2 might provide 3-methyl-2-butanol with net retention of configuration (Scheme I); and (3) 3-methyl-2-aminobutane-*1,1,1,3-d*$_4$ could afford 3-methyl-2-butanol and/or 2-methyl-2-butanol in which the CD_3 group had undergone a 1,2 shift (Scheme II). Results for all three experiments, presented below, establish that protonated cyclopropanes **1** and **2** are major intermediates in the deamination of 3-methyl-2-aminobutane.[11]

Experimental Section

Instrumental Methods. Most of the polarimetric data were obtained with a Perkin-Elmer 141 polarimeter; a few were obtained with a Zeiss 0.01° circular scale instrument. NMR spectra were run on a Varian A-60 instrument at room temperature; integrations of spectra employed either the device incorporated into the spectrometer or a Keuffel and Esser Compensating Polar planimeter. Eu(dpm) [tris(2,2,6,6-tetramethylheptanedionato)europium(III)] was an Alfa-Ventron product. Both Aerograph 90-P and 1520 gas–liquid chromatographs were used; peak areas were determined with either the planimeter or a Vidar 6300 digital integrator. Studies with solutions of known composition established that peak areas accurately reflected percent composition in determining both the amount of *trans*-1,2-dimethylcyclopropane in the C_5H_{10} mixture and the amount of 3-methyl-2-butanol in the $C_5H_{12}O$ mixture. VPC analysis of alcohol or alcohol-acetate fractions typically employed a 5 ft × 0.25 in. column packed with 10% Carbowax on 80–100 Chromosorb W operated at 75°. For the hydrocarbons, we used a 8 ft × 0.25 in. silver nitrate–ethylene glycol column in series with a nonylphenoxypolyoxyethyleneethanol on Firebrick column of the same size, both operated at room temperature. Under these conditions, *trans*-1,2-dimethylcyclopropane had the lowest retention time of the hydrocarbons present. Infrared spectroscopy (Perkin-Elmer 137 Infracord) confirmed the VPC-determined composition of several alcohol reaction mixtures.

Aqueous Deamination Reactions. The reaction apparatus consisted of a 2-l. three-necked round-bottomed flask immersed in a 55° bath and equipped with magnetic stirrer, combination pH electrode, pressure-equalizing dropping funnel, and a gas outlet tube attached to a trap filled with KOH pellets (cooled in ice) which in turn was attached to two empty dry ice cooled traps. Combination of a solution of sodium nitrite (41.5 g, 0.60 mol) in 370 ml of water with a solution of 3-methyl-2-aminobutane [21.9 g, 0.25 mol, $[\alpha]^{23}D$ +2.90° (neat)][12] in aqueous perchloric acid (22 ml of 70% $HClO_4$ plus 200 ml of water) produced the initial reaction mixture, pH 4.6. Addition of 70% $HClO_4$ from the dropping funnel adjusted the pH to 4.0; periodic further additions of acid maintained the pH at 4.0 ± 0.1 until reaction had ceased (~70 min). When the apparatus was disassembled, the first dry ice trap contained the bulk of the hydrocarbon. This material was dried over KOH and transferred to a precooled 25-ml distilling flask. The flask was immersed in an oil bath at room temperature and the hydrocarbon distilled into ice-cold 3-in. test tubes as the temperature of the oil bath was gradually increased. Normally we collected a single fraction. In the run described here four fractions of ~0.3 ml each were obtained, at the following bath temperatures: ≤27°, 28–34°, 34–41°, and 41–47°. Determination of the *trans*-1,2-dimethylcyclopropane content (6.1–6.6%) and optical rotation of each fraction provided the specific rotations entered in lines 5–8 of columns 4–6 of Table II. The higher "% net inversion" found for the highest boiling fraction must be caused by a trace impurity (contaminating nitrite?) whose nature was revealed by neither VPC nor infrared.

Table I
Stereochemistry of 3-Methyl-2-butanol from the Deamination of Optically Active 3-Methyl-2-aminobutane at 55°

	3-Methyl-2-aminobutane[a]		$(CH_3)_2CHCHOHCH_3$[b]		
Reaction conditions	$[\alpha]^{23}D$, deg	% optical purity	$[\alpha]^{27}D$, deg	% optical purity	% net retention[c]
H_3O^+–$NaNO_2$[d]	+2.69	77	+1.39	28	36
	−1.34	39	−0.84	17	44
	−2.09	60	−1.25	25	42[e]
	+3.14	90	+1.31	26	29
	+2.09	60	+1.12	21[f-h]	35
			+1.08	20[f]	34
	+2.90	83	+1.54	31[g,i]	37
			+1.66	33	40
			+1.60	32	39
HOAc–$NaNO_2$	−0.94	27	−0.26	4.8[f]	18
	−2.37	68	−0.48	9.6[g,j]	14
			−0.57	11.5	17
			−0.58	11.7	17

[a] Rotations are for neat amine, which when optically pure has $[\alpha]^{24}D \pm 3.5°$ (ref 13, 16). Experiments for each set of reaction conditions are listed in order of performance. [b] For deamination in acetic acid, the rotation is for the alcohol obtained from saponification of an alcohol–acetate mixture, primarily derived from the acetate portion. Data are for a neat mixture of 3-methyl-2-butanol and 2-methyl-2-butanol containing 30–70% of the former. Neat optically pure 3-methyl-2-butanol has $[\alpha]^{27}D \pm 5.0°$ (ref 16). [c] See text for references to absolute configurations. [d] Aqueous perchloric acid, pH 4.0. [e] Data for this run unaffected by redistillation of the alcohol mixture. [f] Rotations measured on a 20–40% solution of the C_5 alcohol mixture in ethanol. Optically pure 3-methyl-2-butanol has $[\alpha]D \pm 5.34°$ (c 5, EtOH) (ref 17). [g] Collected fractions were of approximately equal size; they are listed in order of increasing boiling point. [h] Two fractions. [i] Three fractions with bp 104–107, 107–108, and 108–109°, respectively. [j] Three fractions with bp 88–100, 100–107.5, and 107.5–108°, respectively.

Table II
Stereochemistry of *trans*-1,2-Dimethylcyclopropane from the Deamination of Optically Active 3-Methyl-2-aminobutane at 55°

	3-Methyl-2-aminobutane[a]		*trans*-1,2-Dimethylcyclopropane[b]		
Reaction conditions	$[\alpha]^{23}D$, deg	% optical purity	$[\alpha]^{15}D$, deg	% optical purity	% net inversion
H_3O^+–$NaNO_2$[c]	−2.09	60	−15.9	35	58
	+3.24	90	+21.3	46	52
	+2.09	60	+15.8	34	57[d,e]
			+19.6	43	71
	+2.90	83	+20.7	45	54[d,f]
			+20.1	44	53
			+23.7	52	62
			+28.2	61	73
HOAc–$NaNO_2$	−1.94	55	−15.2	33[g]	59
	+2.53	72	+18.2	40[g]	55
	+2.53	72	+18.9	41[g]	57
	−2.37	68	−18.4	40	59[d,f]
			−17.4	38	56
			−17.9	39	57
			−17.6	38	56

[a] See footnote *a*, Table I. [b] Rotations measured on a diglyme solution containing 5–20% of a mixture of C_5H_{10} hydrocarbons of which 6–12% was *trans*-1,2-dimethylcyclopropane. Observed rotations were 0.04–0.66°. Optically pure material has $[\alpha]^{20}D \pm 46°$ and the absolute configuration is known (ref 22). [c] Aqueous perchloric acid, pH 4.0. [d] Collected fractions were of approximately equal size; they are listed in order of increasing boiling point. [e] Two fractions. [f] Four fractions. [g] Rotations measured at 5°.

Steam distillation of the deamination mixture in the reaction vessel gave a two-phase distillate to which several grams of KOH pellets were added. The separated organic layer was washed with water, dilute HCl, and water and dried over sodium sulfate. The decanted alcohol mixture was distilled through a small distillation apparatus. Normally a single fraction was collected; it was suitable for either optical rotation determination or NMR analysis. In the run described here, four fractions were collected, bp 91–104° (1.2 ml, 41.6%), 104–107° (2.2 ml, 46.8%), 107–108° (2.5 ml, 54.0%), and 108–109° (1.7 ml, 70.0%), where the percentage of 3-methyl-2-butanol in each fraction is specified. The calculated $[\alpha]^{27}D$'s for 3-methyl-2-butanol in the last three fractions were identical [+1.60 ± 0.04° (neat); lines 7–9, columns 4–6, Table I] but in the fraction of lowest boiling point it had $[\alpha]^{27}D$ +1.19°, corresponding to 29% net retention. Both the infrared spectrum and VPC indicated that fraction 1 contained small amounts of nitrites.

Deaminations in Acetic Acid. The reaction was carried out in a thermostated 2-l. three-necked round-bottomed flask equipped with magnetic stirrer, cork, gas outlet tube connected as described above, and a piece of rubber tubing to which was attached a flask containing 35 g (0.51 mol) of $NaNO_2$. The reaction vessel held 22 g [0.25 mol, $[\alpha]^{23}D$ −2.37° (neat)] of amine dissolved in 200 ml of acetic acid. Cautious addition of the $NaNO_2$ required ~60 min. Soon thereafter the apparatus was disassembled. The dry ice traps held a plentiful amount of hydrocarbon which, when treated as usual, gave four fractions with identical calculated $[\alpha]^{15}D$'s (lines 12–15, columns 4–6, Table II): bp 38° (1.5 ml); 38–42° (1.5 ml); 42–43° (1.0 ml); 43–44° (1.5 ml) (each contained 9.9–10.2% *trans*-1,2-dimethylcyclopropane). Addition of 20% NaOH raised the pH of the mixture in the reaction flask to 6.

In polarimetric experiments, the pH 6 material was steam distilled. The separated top layer (~15 ml) consisted of 19% 2-methyl-2-butyl acetate, 60% 3-methyl-2-butyl acetate, 5.5% 2-methyl-2-butanol, and 15.5% 3-methyl-2-butanol. Saponification of 7 ml of the mixture by heating it for 60 min under reflux with a solution of 6.5 g of KOH in 5 ml of water plus 25 ml of triethylene glycol was followed by steam distillation. The alcohol layer was separated, dried, and analyzed by VPC. It was then distilled and the three fractions obtained (usually only one) showed nearly identical values of $[\alpha]^{27}D$ for 3-methyl-2-butanol (last three entries, columns 4–6, Table I): bp 88–100° (1.2 ml, 60.0%); 100–107.5° (2.0 ml, 70.0%); 107.5–108° (1.5 ml, 78.2%). These calculated specific rotations primarily reflect the stereochemistry characterizing formation of 3-methyl-2-butyl acetate.

Experiments with deuterioamine were performed on a much smaller scale. The pH 6 material was extracted with CCl_4 and the CCl_4 solution was washed with dilute HCl and water, dried over Na_2SO_4, filtered, and concentrated to a small volume, suitable for NMR analysis. Such a sample was primarily a mixture of 3-methyl-2-butyl and 2-methyl-2-butyl acetate, and contained a little CCl_4 and only traces of 3-methyl-2-butanol plus 2-methyl-2-butanol. NMR analysis established the deuterium distribution in only the secondary acetate.

Synthesis and Deamination of 3-Methyl-2-aminobutane-*1,1,1,3-d*$_4$. Repeated base-catalyzed exchanges[14] of 3-methyl-2-butanone with D_2O provided 3-methyl-2-butanone-*1,1,1,3-d*$_4$. Reduction of the corresponding ketoxime with sodium in ethanol supplied the desired amine. NMR analysis established that the ketone, oxime, and amine held >98% deuterium in the 3 position and that the first two held >95%, but the amine seemingly only 85 ± 3% deuterium in the 1 position [analysis of the deuterium content of RNH_2 required the use of $Eu(dpm)_3$, 0.171 mol/mol RNH_2]. Deuterium may have been lost during the sodium reduction or a trace impurity may have fortuitously caused the amine to show a spuriously large CH_3CHNH_2 peak. The data presented at the end of this section for the deuterium distribution in the 2-methyl-2-butanol isolated from aqueous deamination suggest that the second explanation is probably correct.

Studies with synthetic mixtures established that addition of $Eu(dpm)_3$ to a solution of 20–25 mg of a mixture of 3-methyl-2-butanol and 2-methyl-2-butanol in 0.5 ml of $CDCl_3$ (containing 1% Me_4Si) make it possible to integrate accurately the *gem*-dimethyl and single methyl resonances of each alcohol. The $Eu(dpm)_3$ to alcohol mole ratio was 0.3–0.5:1 and filtration of the NMR sample through glass wool removed insoluble matter and greatly improved the quality of the NMR spectra. In a typical experiment a ratio of 0.46:1 caused the $(CH_3)_2C$ resonance of secondary alcohol to ap-

Table III
Extent of Methyl Rearrangement in the 3-Methyl-2-butyl Product Formed by Deamination of $(CH_3)_2CDCHNH_2CD_3$ at 55°

Reaction conditions[a]	No. of samples[b]	% shift[c] Minimum[d]	% shift[c] Maximum[e]
H_3O^+–$NaNO_2$	2	33	40
	1	34	40
HOAc–$NaNO_2$	4	23	30
	2	23	32

[a] Two runs were performed in each solvent. Aqueous deamination (perchloric acid, pH 4.0) provided 3-methyl-2-butanol; acetic acid yielded 3-methyl-2-butyl acetate. [b] Multiple integrations were performed on each sample. [c] The error for each value is ±3%. [d] Based on the assumption that starting amine contained 85% deuterium in the CD_3 group. [e] Based on the assumption that starting amine contained 95% deuterium in the CD_3 group.

pear at τ 5.61 and the single CH_3 peak at τ 3.62. For tertiary alcohol, the corresponding peaks appeared at τ 4.83 and 6.80. The remaining proton resonances of the two alcohols did not interfere with any of the four peaks of interest. Analysis of the mixture of 3-methyl-2-butyl and 2-methyl-2-butyl acetates from deamination in acetic acid employed a similar technique but an accurate integration was only possible for the former.

$$\% \text{ shift} = 100(6.0 - 0.45R)/2.55(1 + R) \quad (1)$$

Table III records the data obtained in the deuterioamine studies. If it is assumed that d_4 amine contained 85% deuterium in the 1 position (0.45 protons/molecule) and if R = (dimethyl intensity)/(single methyl intensity), eq 1 defines the "minimum" percent methyl shift accompanying formation of 3-methyl-2-butyl product. A similar calculation which assumes 95% deuterium content in the 1 position provides the "maximum" values of Table III. These two estimates undoubtedly bracket the true value for percent methyl shift. The calculations make the valid assumption[11,15] that no loss of deuterium accompanied protic deamination of RNH_2-d_4.

Evaluation of the amount of methyl migration characterizing formation of 2-methyl-2-butanol proved difficult with the available NMR equipment. In theory the mixture of deuterated alcohols should exhibit weak adsorption at the CH_3CH_2 resonance in the absence of any methyl rearrangement because of incomplete deuteration in starting amine; an increase in this peak signifies methyl-shifted tertiary alcohol. Experimentally the CH_3CH_2 resonance, relative to the $(CH_3)_2C$ peak for tertiary alcohol, was smaller than expected if the starting amine contained 85% deuterium at the 1 position and *no* rearrangement had occurred. The best estimate for the area of the CH_3CH_2 peak derived from a comparison of the size of this peak relative to that of the *gem*-dimethyl peak for a weighed sample of deuterioalcohols [with $Eu(dpm)_3$] before and after the addition of a weighed amount of 3-methyl-2-butanol. This experiment suggested that the *tert*-pentyl alcohol from the deamination reaction contained ≥95% deuterium in the CH_3CH_2 position. It therefore appears that the RNH_2-d_4 held ≥95% deuterium in its CH_3CHNH_2 position and that essentially no methyl-rearranged 2-methyl-2-butanol is present. Our data are insufficiently accurate to prove the absence of methyl-rearranged tertiary alcohol, but we can confidently assert that ≤5% of the tertiary alcohol formed had undergone methyl rearrangement, far less than the corresponding figure for secondary alcohol (Table IV) (see also ref 11).

Miscellaneous Details. The experimental procedures described above were dictated by our concern to obtain the purest material possible. No effort was made to maximize yields.

We sought to determine if 2-methyl-1-butanol, 2-pentanol, or 3-pentanol were present in the alcohol mixtures. No satisfactory separation of 3-pentanol from 3-methyl-2-butanol was achieved. No 2-pentanol could be detected so <0.5% was present. A small VPC peak indicated that a trace of 2-methyl-1-butanol (≲1%) may have been produced in aqueous deamination only. The maximum effect of the presence of 0.5% 2-pentanol plus 1% 2-methyl-1-butanol would be to cause the "% net retention" data of Table I to be 3% too high or low.

The percentage of 2-methyl-2-butanol in the alcohol mixtures was as follows: H_2O, 54 ± 3% ($C_5H_{13}N$) vs. 47 ± 1% ($C_5H_9D_4N$), k_H/k_D = 1.3 ± 0.1; HOAc, 25 ± 1% ($C_5H_{13}N$) vs. 15.5 ± 1% ($C_5H_9D_4N$), k_H/k_D = 1.8 ± 0.2. Calculation of k_H/k_D for the 3,2-hydride shift assumes that the four deuterium atoms present have altered the composition of the alcohol fraction solely by reducing the rate of this shift, which is probably nearly true.

It seemed possible that methyl-shifted 3-methyl-2-butanol could derive from solvolysis of 1,2-dimethylcyclopropane. If so, 1,1-dimethylcyclopropane should undergo solvolysis still more rapidly, since it directly yields the *tert*-pentyl cation. We were unable to detect any *tert*-pentyl alcohol among the reaction products from the aqueous deamination of *tert*-butylamine in the presence of 1,1-dimethylcyclopropane.

The ratio of *trans*- to *cis*-1,2-dimethylcyclopropane was 3.5:1 in water and 2.5:1 in acetic acid.

Results[5]

The reaction products from aqueous deamination of 3-methyl-2-aminobutane are readily separated into a high- and low-boiling fraction. The former is a mixture of 3-methyl-2-butanol and 2-methyl-2-butanol. Since only 3-methyl-2-butanol is chiral and since the absolute configuration and specific rotation of optically pure 3-methyl-2-aminobutane and 3-methyl-2-butanol are known,[13,16–21] determination of the composition and rotation of the alcohol mixture obtained from deamination of optically active amine defines the stereochemistry governing 3-methyl-2-butanol formation (Scheme I and Table I). Because the lower boiling fraction also contains only one chiral component, *trans*-1,2-dimethylcyclopropane, of known absolute configuration and maximum specific rotation,[22] the same technique permitted ready evaluation of the stereochemistry characterizing *trans*-1,2-dimethylcyclopropane formation (Scheme I and Table II).

We believe that the quantitative stereochemical data of Tables I and II, based on the measured optical rotations of purified mixtures of alcohols or hydrocarbons, are reliable. The products formed by deamination of RNH_2 have been extensively characterized (ref 10a). The tabulated data exhibit good reproducibility and are identical, within experimental error, whether based on the measured rotation for an unfractionated or fractionated reaction mixture. Only in the case of *trans*-1,2-dimethylcyclopropane from aqueous deamination did the fractionation procedure cause the stereochemical result to show a trend. In this instance we decided that refinement of the data of Table II did not justify the effort required if we were to determine accurately the specific rotation of isolated pure *trans*-1,2-dimethylcyclopropane from aqueous deamination of optically active amine. The yield of the hydrocarbon in the reaction is only ~0.25%.

In another series of experiments we employed NMR to measure the deuterium distribution in the alcohols isolated from deamination of 3-methyl-2-aminobutane-*1,1,1,3*-d_4 and thus to determine the amount of methyl rearrangement accompanying production of 3-methyl-2-butanol and 2-methyl-2-butanol. As Scheme II illustrates, such rearrangement causes, for each alcohol, the growth of the single methyl resonance at the expense of the *gem*-dimethyl peak. Table III shows that the secondary alcohol is extensively rearranged; in marked contrast, less than 5% of the tertiary alcohol from aqueous deamination had undergone methyl rearrangement.

Discussion

The four paragraphs which follow assess the significance of our experimental findings, as summarized in Table IV, and establish that the 3-methyl group participates to an extraordinary extent in the deamination of 3-methyl-2-aminobutane.

(1) Formation of *trans*-1,2-dimethylcyclopropane with 57% net inversion shows that methyl rearrangement in the deamination of RNH_2 closely follows loss of nitrogen from

Table IV
Description of the Reaction Products from the Protic Deamination of 3-Methyl-2-aminobutane at 55°

Property	H_2O[a]	HOAc[b]
trans-/*cis*-1,2-Dimethylcyclopropane	3.5	2.5
$(CH_3)_2CHCHXCH_3$/$(CH_3)_2CXCH_2CH_3$	0.85	3.0
Percent net inversion in *trans*-1,2-dimethylcyclopropane	57 ± 2	57 ± 2
Percent net retention in $(CH_3)_2CHCHXCH_3$	37 ± 3	17 ± 3
Percent methyl migration in $(CH_3)_2CHCHXCH_3$	33–40	23–32
Percent methyl migration in $(CH_3)_2CXCH_2CH_3$	<5	Not determined

[a] X = OH. [b] X = OAc.

Table V
Predicted Stereochemistry of $(CH_3)_2CHCHXCH_3$ Formed by the Deamination of 3-Methyl-2-aminobutane If Scheme I Is Correct[a]

Step of calculation[b]	H_2O	HOAc
1. % of RX derived from 1 + 2	73 (2 × 36.5)	55 (2 × 27.5)
2. % of RX derived from 1	57 (73 × 3.5/4.5)	39 (55 × 2.5/3.5)
3. % net retention in RX because of 1 pathway	32 (57 × 0.57)	22 (39 × 0.57)
4. % net inversion in RX because of non-1, 2 pathway	6 (27 × 0.23)	13 (45 × 0.28)
5. Predicted % retention in RX[c]	26	9
6. Observed % retention in RX	37 ± 3	17 ± 3

[a] X = OH (H_2O) or OAc (HOAc). [b] The numbers refer to statements in the text where the calculation is explained. The data employed may be found in Table IV or the text. [c] Line 3 minus line 4.

the alkyldiazonium ion (see Scheme I). Methyl rearrangement in the deamination of optically active neopentylamine-*1-d*, which resembles the methyl migration of Scheme I, causes at least 85% net inversion at the migration terminus.[23]

(2) The process just described can also explain the observed net *retention* of configuration in 3-methyl-2-butanol, particularly if ion **1** is the intermediate from which much of the alcohol derives. This unexpected retention of configuration cannot be attributed to micelle phenomena, given the molecular weight of RNH_2 and the reaction conditions employed.[24,25] By contrast deamination of a secondary alkylamine generally yields *inverted* substitution product; for example, 2-aminobutane affords 2-butyl alcohol (or acetate) with 23 (H_2O)–28% (HOAc) net inversion.[24,26]

(3) The stereochemical experiment of 2 only reveals 3-methyl-2-butanol originating from **1**, but the deuterioamine experiment counts rearrangements occurring via both **1** and **2**. If **1** and **2** are intermediates, they are the source of a remarkable 66–80% of the 3-methyl-2-butanol formed by the aqueous deamination of RNH_2. While <1% of the 3-methyl-2-butyl acetate obtained from acetolysis of 3-methyl-2-butyl tosylate has undergone methyl rearrangement (hydrogen participation dominates),[27,28] the corresponding figure is >23% for acetic acid deamination of RNH_2.

(4) The absence of an appreciable amount of methyl-shifted 2-methyl-2-butanol, $CH_3CD_3COHCHDCH_3$, from among the products of aqueous deamination of deuterioamine eliminates $CH_3CD_3C^+CHDCH_3$ as an important intermediate in the reaction (Scheme II). Deaminative ions **1** and **2**, like their relatives in strongly acidic media,[3,29] therefore cannot open directly to the *tert*-pentyl cation. Moreover, the absence of $CH_3CD_3C^+CHDCH_3$ renders highly unlikely the intervention of $CH_3CD_3CHC^+DCH_3$ in the deamination of deuterioamine, for there is no reason to suspect that the pedigree of this 3-methyl-2-butyl cation would render it, once formed, incapable of undergoing extensive favorable hydride shift to $CH_3CD_3C^+CHDCH_3$. Certainly in other deaminations a cation formed by prior rearrangement exhibits no impaired ability to undergo still further rearrangement. The 3-methyl-2-butyl cation generated by a 1,2-hydride shift in the deamination of 3-methyl-1-aminobutane gives a higher ratio of *tert*-pentyl to 3-methyl-2-butyl product than does that obtained directly from 3-methyl-2-aminobutane.[10,30] Similarly the extent of isoenergetic 1,2-hydride shift by the 2-butyl cation is approximately the same when the cation is formed by deamination of 2-aminobutane, 1-aminobutane (prior 1,2-hydride shift), or 2-methyl-1-aminopropane (prior 1,2-methide shift).[6,7]

Scheme I qualitatively accommodates the above observations on the deamination of 3-methyl-2-aminobutane. It postulates that cations **1** and **2** are intermediates which undergo either deprotonation to form 1,2-dimethylcyclopropane or nucleophilic attack with inversion by solvent[31] to yield 3-methyl-2-butanol of retained configuration, but which do not open to either the 3-methyl-2-butyl or 2-methyl-2-butyl cation. Since the scheme posits an intimate relationship between cyclopropane formation and the methyl rearrangement and stereochemistry characterizing formation of 3-methyl-2-butanol, it can be quantitatively tested for internal consistency. If it is assumed that secondary product derives only from Scheme I or a competitive, "normal" substitution process which affords material of net inverted configuration (4 below), the available data permit us to calculate the stereochemistry expected for 3-methyl-2-butanol without reference to the measured value for the quantity. The calculation, outlined in Table V, requires five steps: (1) the percent of $(CH_3)_2CHCHXCH_3$ derived from (1 + 2) is set at twice the percent methyl migration in $(CH_3)_2CHCHXCH_3$; (2) ions **1** and **2** are assumed to give the same $(CH_3)_2CHCHXCH_3$/1,2-dimethylcyclopropane ratio, so that the amount of $(CH_3)_2CHCHXCH_3$ obtained from **1** relative to that obtained from **2** is taken as identical with the ratio of *trans*- to *cis*-1,2-dimethylcyclopropane; (3) the net retention in that $(CH_3)_2CHCHXCH_3$ derived from **1** is set equal to the net inversion in *trans*-1,2-dimethylcyclopropane, while **2** affords only racemic alcohol or ester; (4) the stereochemistry of $(CH_3)_2CHCHXCH_3$ not originating from **1** and **2** is assumed to be the same[32] as that of $CH_3CH_2CHXCH_3$ produced by deamination of 2-aminobutane (see above); (5) the result is that, in water, deamination of RNH_2 is predicted to afford 3-methyl-2-butanol with 26% net retention of configuration (37 ± 3% observed) while in acetic acid it should yield 3-methyl-2-butyl acetate with 9% net retention (17 ± 3% observed).

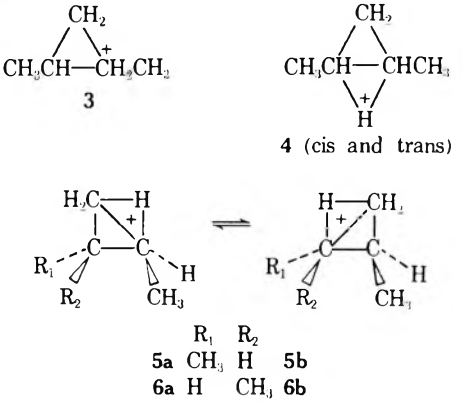
Given the simplicity of Scheme I, the approximations made in the calculation, and the experimental uncertainty in the numerical data employed, the agreement between expectation and observation is quite reasonable.

Mechanistic alternatives to Scheme I which assume that **1** and **2** represent transition states seem far more ad hoc.

Such mechanisms must introduce an additional reaction sequence to explain 1,2-dimethylcyclopropane formation. The rearranged 3-methyl-2-butyl cation, $CH_3CD_3CHC^+DCH_3$, might react with solvent to provide $(CH_3)_2CHCHXCH_3$ of some net retained configuration;[33] the failure of this cation to undergo 1,2-hydride shift would have to be attributed to conformational factors. While our data offer no evidence for this open, rearranged 3-methyl-2-butyl cation, such a species might be the source of the 3-methyl-1-butene-2-*d* obtained[11] by deamination of 3-methyl-2-aminobutane-*3-d*. To explain formation of this olefin in the context of Scheme I, we must allow **1** and **2** to undergo deprotonation directly to 3-methyl-1-butene.

Edge- or Corner-Protonated? Neither edge- nor corner-protonated cyclopropanes appear capable of rationalizing all the reactions in which such intermediates have been implicated. With regard to the parent ion, c-$C_3H_7^+$, the edge-protonated species best explains[1] the isotopic distribution in (a) 1-propanol obtained from solvolysis of cyclopropane in deuteriosulfuric acid; (b) 1-propyl formate produced by formolysis of 1-propyl-*1*-^{14}C tosylate; and (c) unreacted 1-bromopropane recovered after treating 1-bromopropane-*1*-^{13}C with aluminum bromide. However, corner-protonated c-$C_3H_7^+$ seemingly is the essential intermediate[3] in rearrangements of the isopropyl cation in SbF_5–SO_2ClF. We wish to inquire whether edge- or corner-protonated dimethylcyclopropane intermediates better account for the data in Table IV.

Let us assume that **1**–**6** represent the complete set of protonated 1,2-dimethylcyclopropanes. Kramer's report[29] that protonated cyclopropanes in SbF_5–HSO_3F generally possess a single exchangeable hydrogen is compatible with either the edge- or a somewhat unsymmetrical[31] corner-protonated formulation. For the case at hand complete equilibration of **5a** with **5b** and **6a** with **6b** before product formation is indistinguishable from Scheme I, but a mechanism postulating partial equilibration is worth exploring.[34,35]



In this mechanism only **5a** and **6a** are initially formed by deamination of RNH_2. Each could be the source of the trace of 2-methyl-1-butanol detected. Each, prior to equilibration with its tautomer, would afford 3-methyl-2-butanol of *retained configuration* but *unrearranged* methyl groups. Since the calculation of Table V recognizes as retention events only those reactions passing through **1** (or equilibrations of **5a** with **5b**), it should underestimate (as may well be the case) the extent of net retention attending formation of 3-methyl-2-butanol if the edge-protonated mechanism is correct. Can the same edge-protonated intermediates explain certain aspects of the deamination of 2-methyl-1-aminobutane?[33]

This deamination produces 9.5% 2-pentanol and 0.5% 3-methyl-2-butanol. An attractive edge-protonated mechanism to explain these observations[36] is $CH_3CH_2CH(CH_3)CH_2N_2^+ \rightarrow$ **5a, 6a** $\rightarrow [3]^\ddagger \rightarrow$ **4** $\rightarrow$ 2-pentanol, with **5a, 6a** $\rightarrow$ 3-methyl-2-butanol. Thus both the small yield of 3-methyl-2-butanol from 2-methyl-1-aminobutane and the failure of RNH_2 to afford any 2-pentanol are incompatible with **5a, 6a** as the sole initial protonated cyclopropane intermediates common to the deamination of the two amines. If the edge-protonated mechanism for deamination of RNH_2 is preferred, we must postulate that deamination of 2-methyl-1-aminobutane forms **5a, 6a** and $[3]^\ddagger$ in competitive reactions: $(CH_3)_2CHCHOHCH_3 \leftarrow$ **5a, 6a** $\leftarrow CH_3CH_2CH(CH_3)CH_2N_2^+ \rightarrow [3]^\ddagger \rightarrow CH_3C^+HCH_2CH_2CH_3 \rightarrow$ 2-pentanol.

The corner-protonated intermediates explain all but one of the cited observations, if it is assumed that **1** and **2** are more stable than **3**.[3] Deamination of 2-methyl-1-aminobutane initially provides **3**, which primarily affords 2-pentanol but to a small extent isomerizes to **1, 2**, ultimately yielding 3-methyl-2-butanol. Deamination of 3-methyl-2-aminobutane proceeds according to Scheme I. The failure of the isomerization **1, 2** $\rightarrow$ **3** to occur explains the lack of 2-pentanol, but the origin of the trace of 2-methyl-1-butanol remains obscure.

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Registry No.—(−)-(*R*)-3-Methyl-2-aminobutane, 34701-33-2; (−)-(*R*)-3-methyl-2-butanol, 1572-93-6; (+)-(*S*)-3-methyl-2-butanol, 1517-66-4; (−)-(1*R*:2*R*)-1,2-dimethylcyclopropane, 20520-64-3; *cis*-1,2-dimethylcyclopropane, 930-18-7; (−)-(*R*)-3-methyl-2-butanol acetate, 57274-06-3; (+)-(*S*)-3-methyl-2-butanol acetate, 56640-64-3; 3-methyl-2-aminobutane-*1,1,1,3-d*$_4$, 57274-07-4; 3-methyl-2-butanone, 563-80-4; D_2O, 7789-20-0.

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(35) No attempt will be made to distinguish between partial equilibration of **5a** with **5b** and **6a** with **6b** and initial formation of **5a**, **6a** with subsequent isomerization to **1,2**.
(36) Other protonated cyclopropane intermediates are responsible for the partial racemization of the isolated 2-methyl-1-butanol (ref 33).

Thermal Fragmentation of β-Halo Esters via Chain Halogenolysis–Decarboxylation–Elimination[1]

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Solution pyrolysis (240°) of dimethyl 1,2-dibromocyclobutane-1,2-dicarboxylate gives CO_2 and methyl bromide (2 mol) in good yield in lieu of cracking or geometrical isomerization. According to their behavior under pyrolysis conditions, methyl 3-bromocyclobutene-2-carboxylate and methyl 3-bromobutadiene-2-carboxylate are permissible intermediates in the cyclobutane decomposition. Elimination–debromocarbomethoxylation of β-halo esters appears to be quite general since derivatives of the methyl 3-halopropenoates and methyl 3-bromopropanoate also decompose to CO_2 and methyl halide at elevated temperatures. Elimination products, unstable under high temperature pyrolysis conditions, are not obtained in significant yield. The kinetics for these fragmentations appear complex, exhibiting in some cases autocatalytic behavior. Substituent and solvent effect data and the results of gas phase decomposition rule out pericyclic or ion pair mechanistic possibilities. The effects of additives on the course of pyrolysis reveal that a chain decomposition is important, more likely involving halide ion displacement on the ester group followed by decarboxylation–elimination than a similar free-radical chain mechanism. Catalysis of halo ester fragmentation by halide ion is quite effective, and in some cases moderate yields of elimination product are obtained. The use of halogenolysis–decarboxylation–elimination in synthetic and degradative schemes is discussed.

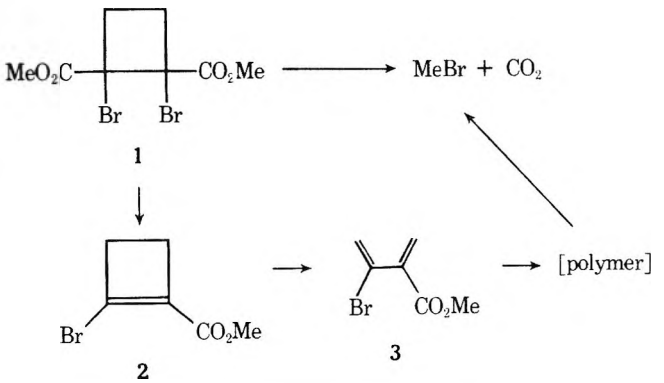
In search for heavy-atom effects in thermal reactions which in principle involve diradicals, we have examined the pyrolysis of halogen substituted cyclobutanes. In one series a surprising fragmentation took place in lieu of expected ring opening. We report now the generality of this halogenolytic degradation of β-halo esters along with data that suggest a mechanism.

Results and Discussion

Neither cracking to methyl 2-bromopropenoate nor geometrical isomerization[2] were observed on static pyrolysis of the stereoisomeric dimethyl 1,2-dibromo-1,2-cyclobutanedicarboxylates (**1**)[3] in diphenyl ether (DPE), diphenylmethane (DPM), or nitrobenzene (NB). Decomposition at 240° produced in nearly quantitative yield methyl bromide (2 mol), identified by GLC and NMR comparison with authentic material. No other volatile organic material was obtained in significant amount, but CO_2 (60% of the theoretical 2 mol) was trapped from pyrolysis solutions using Ascarite.

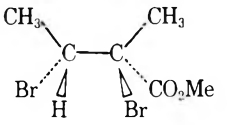
Cyclobutene **2**, the product of a suspected eliminative debromocarbomethoxylation of **1**, was prepared independently and pyrolyzed. At 160° smooth first-order ring opening to **3** ($k = 5.1 \times 10^{-4}$ sec^{-1}) occurred, followed by slow decomposition to nonvolatile, presumably polymeric material. Butadiene **3** from preparative GLC of a pyrolysate of **2** polymerized as a neat sample at room temperature. Characterization involved ir, NMR, and tandem VPC–mass spectral analysis of a CCl_4 solution of **3** obtained by collection of a GLC injector port pyrolysis of **2**. Remarkably, heating a sample of **2**, after ring opening at 160°, briefly at 240° gave methyl bromide and CO_2.

With the novel eliminative degradation of **1** a strong possibility, we examined other halo esters expecting that the fragmentation might be general. Indeed, solution pyrolysis of **4–7** gave methyl bromide and CO_2 (about 60% each). The halomaleates, obtained from commercially available bromo- and chloromaleic anhydride, were the starting materials for **4–6**. Preequilibrium of maleates and fumarates (about 40:60), which was rapidly established at the onset temperatures for fragmentation to methyl bromide (300, 290, and 250°, respectively), was indicated by GLC and the appearance in the NMR of new signals assignable to olefinic (lower field for the fumarates) and OMe resonances. Dimethyl bromofumarate (**5**),[4] obtained by preparative GLC of a partial pyrolysate, was identified from spectral data and pyrolyzed separately. Brief pyrolysis of the *Z* and *E* diastereomers of **7**, obtained separately from the HBr addition products of methyl phenylpropiolate,[5] allowed the approach to preequilibrium (63 ± 4% *Z*, 290°, DPE) from both sides. The nature of the pyrolytic isomerization for **4–7** which accompanied fragmentation to methyl bromide was not established, and heterogeneous as well as molecular mechanisms are possible.[6]



$$R(X)C{=}CHCO_2Me \longrightarrow MeX + CO_2$$

4. R = CO_2Me; X = Cl
5. R = CO_2Me; X = Br
6. R = CO_2Me; X = I
7. R = Ph; X = Br



9

The "parent" system, methyl 3-bromopropionate (8), and 9 were also pyrolyzed. The conditions for production of methyl halide for these esters as well as for 1 and 4–7 are compiled in Table I. First-order rate constants, readily obtained from the spectral appearance of methyl halide vs. an internal standard on pyrolysis in sealed NMR tubes, represent rates of decomposition at low conversion only. The kinetics were generally complex with first-order plots showing upward curvature (autocatalysis, vide infra). The low conversion rate data showed some scatter, but were considered valuable in revealing major structure–reactivity relationships. (1) An "element" effect (X = Cl vs. Br vs. I) results in relative rates of approximately 1:10:50 for decomposition of 4–6, respectively (DPE, 290°). (2) Stereoisomers 1, which do not interconvert under the pyrolysis conditions, show similar reactivities. (3) An increase in pyrolysis solvent polarity (DPE, ϵ_{20} = 3.7 vs. NB ϵ_{25} = 34.8) results in only a slight increase in initial rate (~ten times). A large rate acceleration is observed in dimethylformamide (DMF) (ϵ_{25} = 36.7), but this solvent effect may very well be specific (vide infra) rather than general (polar). (4) Comparison of 5 and 7 reveals little substituent effect, Ph vs. CO_2Me.

Radical scavengers, hydroquinone, stilbene, or oxygen (as well as DPM, Table I), inhibited the decomposition to methyl halide slightly at most and acetic acid or an increase in surface to volume ratio with the introduction of glass wool did not appreciably affect the rate. (See paragraph at end of paper regarding supplementary material.) Methyl propiolate, phenylacetylene, and 2-bromo-2-butene, expected products of debromocarbomethoxylative elimination of 4–7 and 9, were found in no more than trace amounts in pyrolysis mixtures. Although these olefins were relatively stable at elevated temperatures, they were destroyed during copyrolysis with the halo esters.

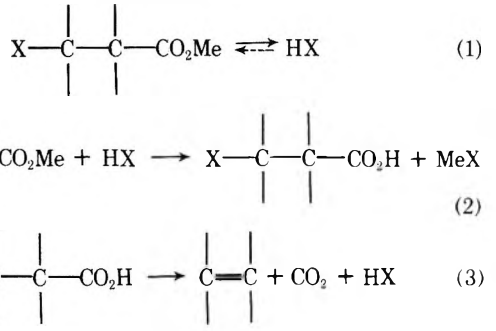
Several mechanisms for formation of MeX and putative elimination product from the halo esters have been considered. A pericyclic decomposition reminiscent of that proposed for halogenolytic rearrangement of bromoketals[7-9] is discounted since 5 or 6 did not give MeX in the gas phase (flow system, 5–10 sec contact time). Decomposition (500°) and geometrical isomerization (420°) were observed in these experiments, and MeX and methyl propiolate were shown to survive the pyrolysis conditions. An ion-pair mechanism for fragmentation is possible, but large solvent[10] and substituent effects[11] on the rate are expected but not observed. We find the mechanism of Scheme I more in accord with the experimental findings. It involves the production of HX in an initiation step, either via molecular (but less likely radical[12]) 1,2 elimination or perhaps by some more complicated route,[13] followed by halogenolytic displacement on starting ester (step 2).[14] The products of such 1,2 HX elimination were not generally detected, but consistent low yields of methyl acrylate were obtained on pyrolysis of 8. Propagation of a chain elimination sequence results from debromocarboxylation of derived β-halo acid (step 3).[15]

Table I
Methyl Halide Formation in the Pyrolysis of β-Halo Esters

Starting halo ester	Concn, M	Solvent	Pyrolysis temp, °C	k, sec^{-1} [a]
1 (cis)	0.8	DPM	240	1.3×10^{-4}
	0.5	NB	240	6.8×10^{-4}
	0.6	DPE	240	4.6×10^{-5}
	0.3	DPE	240	7.6×10^{-5}
1 (trans)	0.3	DPE	240	1.1×10^{-4}
4 (E)	1.2	DPE	290	1.6×10^{-6}
5 (E)	1.4	DPE	290	1.3×10^{-5}
	1.4	NB	290	1.8×10^{-4}
5 (Z)	0.7	DPE	290	1.2×10^{-5}
6 (E)	0.8	DPE	250	5.7×10^{-6}
	1.4	DPE	290	7.3×10^{-5}
	0.8	NB	250	1.9×10^{-5}
	1.4	DMF-d_7	160	7.3×10^{-6}
7 (E + Z)	1.1	DPE	290	5.2×10^{-5}
7 (E)	0.3	DPE	290	2.5×10^{-5}
	0.7	NB	290	4.4×10^{-4}
8	0.8	DPE	290	2.6×10^{-4}
	0.8	DMF-d_7	160	1.1×10^{-4}
9	0.8	DPE	210	9.4×10^{-5}
	1.0	NB	190	2.2×10^{-4}

[a] Pseudo-first-order appearance of methyl halide; generally three to six points at 10–30% conversion, ±30%.

Scheme I



An examination of rates reported for HX elimination[12] (possible step 1), halogenolysis[14] (step 2), and decarboxylative elimination[15] (step 3) suggests that the first of these processes should be initially rate determining (and should not display large polar substituent and solvent effects) followed by relatively rapid consumption (and regeneration) of HX. Application of the steady state assumption for the formation and destruction of HX and assuming the poor competitive position of k_{-1} leads to eq 4, which relates the rate of production of methyl halide to steps in Scheme I.

$$\frac{d(MeX)}{dt} = k_1 (\text{halo ester}) + k_3 (\text{halo acid}) \qquad (4)$$

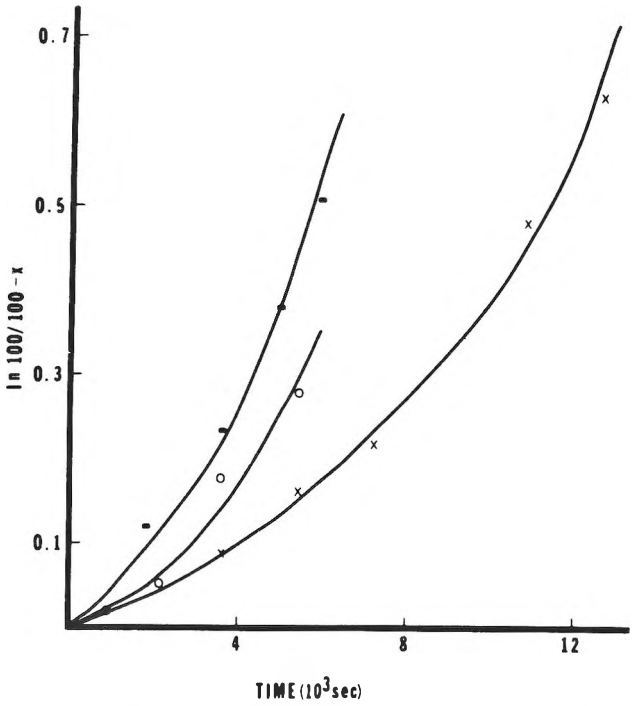


Figure 1. First-order plots for the appearance of methyl halide in the uncatalyzed pyrolysis of **1** (cis isomer, 0.6 *M* in DPE, 240°) (×), **5** (*E* isomer, 1.8 *M* in DPE, 290°) (○), and **6** (*E* isomer, 1.4 *M* in DPE, 290°) (■). X = % appearance of MeX.

Representative rate data, potentially testing the mechanism of Scheme I and eq 4, are shown graphically in Figure 1. The deviation from first-order behavior (autocatalysis) is apparent for halo esters **1**, **5**, and **6** (**4** and **7** behave similarly) and is consistent with early rate-determining HX elimination (initiation) (step 1, k_1) with rapidly increasing dependence on the rate of halo acid decomposition (propagation) (step 3, k_3) where $k_3 > k_1$.[16]

GLC identification of elimination and HX trapping product in variable low yield for one substrate provided direct evidence for the involvement of decarboxylative elimination in halo ester decomposition. Thus, in several experiments, pyrolysis of **7** (*Z* or *E*), 0.7 *M* in NB, at 290° gave phenylacetylene and α-bromostyrene in 9–17 and 4–27% yield, respectively. Elimination product instability, presumably owing to myriad destructive (polymerization) paths under the conditions employed, mitigated the reproducibility of such experiments as well as extension to the other substrates.

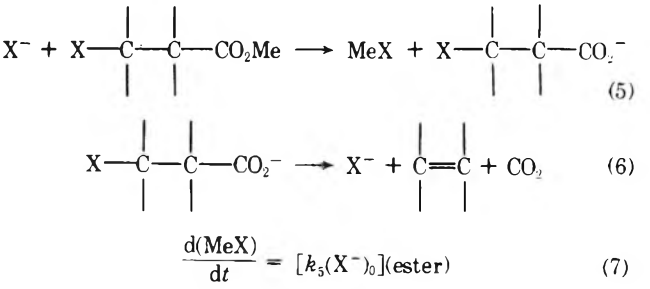
Other chain mechanisms for halo ester decomposition involving free radicals are possible but appear less likely. Halogen atoms produced from halo ester in an initiation step could bring about homolytic halogenolysis followed by radical decarboxylative elimination (regenerating halogen atom) equivalent to the mechanism of Scheme I. Objectionably, this path involves a free radical displacement on carbon (S_H2 reaction) which has been rarely observed, only where displacement is accompanied by the opening of a small ring.[17] Moreover, the aromatic solvents employed would have readily diverted halogen atoms for aromatic substitution.[18] Also, NB is an effective inhibitor of halogen atom chain reactions.[18b] A second possibility involving methyl radical as a chain carrier is similarly improbable.

Certain additives dramatically catalyzed the pyrolytic formation of methyl halide. For example, **1** (cis), **4** (*E*), **6** (*E*), and **9** with 10 mol % NaBr in DMF-d_7 or CD_3CN fragmented at a moderate rate at 160°. Decomposition was also brought about well below the normal pyrolysis temperatures with the introduction of LiBr, NaI, or HBr in DPE, NB, or CD_3CN. Pyridine and X_2 (with peroxide) were also catalysts, presumably by providing the effective ingredient, nucleophilic halogen, through base-catalyzed 1,2 elimination and radical hydrogen abstraction, respectively.[19]

That catalyzed halogenolysis was accompanied by decarboxylative elimination was confirmed in "crossover" and preparative (vide infra) experiments. For example, both MeBr and MeCl were obtained from **4** and 25 mol % HBr in DPE (165°) with MeBr predominating at low conversion. Similarly, **5** gave predominantly MeBr on pyrolysis in DPE at 165° with the addition of small amounts of iodine and benzoyl peroxide. MeBr and MeI were produced in roughly equal amounts when **6** was pyrolyzed at 250° with 100 mol % aqueous HBr in DPE. The time dependence of the methyl halide ratio was uncertain since the methyl halides in control experiments scrambled moderately. In DMF both starting halo esters and methyl halides[20] underwent exchange under "crossover" catalysis conditions. However, the halo esters were shown to be stable in DPE so that the observed crossovers remain significant, implicating the ionic chain eliminative decomposition. Finally, in view of the nature of the catalysis, the specific accelerating effect of DMF solvent (Table I) may be understood in terms of its known reaction with organic halides to give nucleophilic halogen.[21,22]

The probable course of catalyzed halogenolysis–elimination is shown in Scheme II. Halogenolysis of esters[14,23]

Scheme II



(even with decarboxylation)[24] is well known, and several examples of decarboxylative elimination of β-halocarboxylates[25] (including important relatives of **4**–**7**[15]) have appeared. If step 5 be rate limiting in the chain sequence or if halogenolysis and elimination be concerted (steps 5 and 6 combined), then (X^-) will remain unchanged, over the course of decomposition, justifying simplification to first order of the rate law for the formation of methyl halide (eq 7). A first-order plot (see supplementary material) for methyl halide appearance from **1** (catalyzed by NaBr in CD_3CN, 135°) is nonlinear. The steady state assumption concerning X^- in this case appears invalid; i.e., eliminative replenishment of X^- (step 6) lags consumptive halogenolysis (step 5). The production of MeX deviates from first order if second-order halogenolysis (presumably through the $B_{A1}2$ mechanism[23a]) is initially rate determining until *added* halogen is virtually consumed and the (slower) rate of decarboxylative elimination becomes important. That the overall decomposition is nonconcerted is supported by direct evidence. Aqueous extraction followed by acidification and work-up of a solution of **7** and 100 mol % NaBr in DMF-d_7 partially pyrolyzed at 145° yields an acidic fraction, whose ir spectrum is identical with that of a mixture of isomers of the parent acid of **7** and which can be esterified (CH_2N_2) for GLC comparison (38% yield), and an organic fraction containing CH_3Br, phenylacetylene (trace), and recovered **7** (48%).

Table II
Elimination Products from Catalyzed Dehalocarbomethoxylation of β-Halo Esters

Halo ester (concn, M)	Catalyst (10 mol %)[a]	Solvent	Pyrolysis temp, °C	Elimination product (% yield)[b]
1 (cis) (1.4)	NaBr	DMF	160	3 (25)
1 (trans) (1.0)	NaBr	CD_3CN	135	3 (30)
	18-Crown-6			
4 (*E*) (1.2)	NaI	DMF-d_7	160	Methyl propiolate (10)
5 (*E*) (1.2)	NaBr	DMF-d_7	160	Methyl propiolate (43)
6 (*E*) (1.4)	NaBr	DMF-d_7	160	Methyl propiolate (23)
	NaBr	CD_3CN	145	Methyl propiolate (52)
	18-Crown-6			
7 (*E*) (1.0)	NaBr	CD_3CN	155	Phenylacetylene (47)
	18-Crown-6			

[a] Mol % halo ester. [b] NMR and/or GLC analysis.

In summary, the evidence concerning pyrolytic fragmentation of β-halo esters (shown to be general with a variety of substrates) is consistent with a mechanism involving production in an initiation step of catalytic amounts of HX which subsequently leads to propagative halogenolysis–decarboxylation–elimination (Scheme I). This type of ionic chain elimination involving nucleophilic displacement by halogen appears to be without precedent, although a non-chain displacement-induced elimination has been reported.[26] These reactions are further examples of "fragmentation", the considerable generality of which has been demonstrated by Grob.[25a]

It is unlikely that *uncatalyzed* dehalocarbomethoxylation of β-halo esters will be of synthetic utility owing to the high temperatures involved. On the other hand, *catalyzed* fragmentation appears somewhat more promising. A limited survey of elimination yields is shown in Table II.[19] Catalysis in the presence of a crown ether, known to effectively promote displacement[27] and decarboxylation,[28] gave the best results. The latter conditions might well produce good yields where elimination products are not so readily polymerized. The utility of fragmentation may be confined to methyl esters owing to their ready displacement relative to other groups.[23a,24] In point of fact, ethyl 3-bromopropionate (in contrast to 8) gave ethyl acrylate in good yield at 290° in DPM but no ethyl bromide.

Experimental Section[19]

Melting points were taken on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 180 spectrophotometer using chloroform as the solvent except as indicated. The NMR spectra were run using a JEOL (Japan Electronic Optical Laboratory Co. Ltd.) C-60 HL high-resolution spectrometer and carbon tetrachloride as the solvent except as indicated.

All preparative gas chromatography was performed using a Varian Aerograph 90-P instrument equipped with a thermal conductivity detector and helium as the carrier gas. Analytical VPC was performed either on a Varian Aerograph 90-P, 920 (thermal conductivity detector), or 1400 (flame ionization detector). Columns and conditions used for specific analyses are listed in Table III. Carrier gas flow rates were 60–80 ml/min.

Dimethyl 1,2-dibromo-1,2-cyclobutanedicarboxylate (1) (cis and trans),[3] methyl β-bromocinnamate (7) (*E* and *Z*),[5] and methyl 2,3-dibromo-2-methylbutanoate (9) (threo)[29] were prepared as reported and ethyl and methyl 3-bromopropanoate (8) were obtained commercially. Pyrolysis solvents diphenylmethane (DPM), diphenyl ether (DPE), nitrobenzene (NB), and dimethylformamide (DMF) were distilled from sodium carbonate. Sodium bromide and iodide and lithium bromide were commercial samples used as received.

Methyl 2-Bromo-1-cyclobutene-1-carboxylate (2). Titration of an ether solution of 2-bromocyclobutene-1-carboxylic acid (mp 121–122°, lit.[15b] mp 121–122°), prepared from 1,2-dibromo-1,2-cyclobutanedicarboxylic acid,[15b] with a solution of diazomethane prepared from *N*-methyl-*N*-nitrosourea[30] gave after routine workup methyl 2-bromo-1-cyclobutene-1-carboxylate (2) as an oil which could be purified by GLC (column D). The spectral data follow: ir 5.75 μ; NMR δ 2.75 (s, 4 H, $-CH_2-$), 3.80 (s, 3 H, $-CO_2CH_3$).

Anal. Calcd for $C_6H_7BrO_2$: C, 37.85; H, 3.69; Br, 41.70. Found: C, 37.89; H, 3.88; Br, 41.80.

Table III

Column[a]	Substrate	Oven temp, °C
A, 10 ft × 0.25 in. 20% GE SF-96	1	160–200
	4–6	100–160
	7	180
	9	90–95
B, 10 ft × 0.375 in. 20% GE SF-96	1	160
C, 10 ft × 0.25 in. 20% Carbowax	1, 3	135–170
D, 10 ft × 0.375 in. 20% FFAP	2, 4–6	100–160

[a] Stationary support, 60/80 mesh Chromosorb W.

Methyl 3-Bromo-1,3-butadiene-2-carboxylate (3). GLC injector port (250°) pyrolysis of methyl 2-bromo-1-cyclobutene-1-carboxylate (2) (column D, 170°) gave (separate from recovered cyclobutene) an oil which polymerized on standing as a neat sample. The material was stable, however, when collected as a solution in carbon tetrachloride, and was assigned the structure 3 on the basis of the spectral data: ir (CCl_4) 5.75 μ; NMR δ 3.80 (s, 3 H, $-CO_2CH_3$), 6.18 (m, 4 H, $-CH_2$). Tandem GLC–mass spectrometry revealed a parent ion at *m/e* 191 consistent with the formula $C_6H_7BrO_2$.

Dimethyl Chloromaleate (4). A solution containing chloromaleic anhydride (10.0 g, 0.076 mol), concentrated sulfuric acid (2 ml), and methanol (50 ml) was refluxed for 40 hr. The methanol was removed at reduced pressure and the residue neutralized with 10% sodium bicarbonate solution (20 ml) and extracted with two 20-ml portions of anhydrous ether. After drying ($MgSO_4$) the ether was removed in vacuo. The crude yellow oil which remained was distilled, giving 12.0 g (89%) of dimethyl chloromaleate, bp 52–53° (0.25 mm), lit.[4] bp 100° (17.0 mm). The product was further purified by preparative GLC (column D): NMR δ 3.48 (s, 3 H, $-CO_2CH_3$), 3.55 (s, 3 H, $-CO_2CH_3$), 6.40 (s, 1 H, –CH).

Dimethyl Bromomaleate (5).[4] A solution containing bromomaleic anhydride (10.0 g, 0.057 mol), concentrated sulfuric acid (2 ml), and methanol (50 ml) was refluxed for 40 hr. The methanol was removed at reduced pressure and the residue neutralized with 10% sodium bicarbonate solution (20 ml) and extracted with two 20-ml portions of anhydrous ether; the ether was then removed at reduced pressure, giving 11.18 g of crude dimethyl bromomaleate, which was purified by preparative GLC (column D). The NMR spectrum displayed signals at δ 3.72 (s, 3 H, $-CO_2CH_3$), 3.85 (s, 3 H, $-CO_2CH_3$), 6.45 (s, 1 H, –CH).

Dimethyl Iodomaleate (6). A solution containing bromomaleic anhydride (5.0 g, 0.028 mol), sodium iodide (4.2 g, 0.028 mol), and acetone (20 ml)[31] was refluxed for 13 hr. This solution was filtered while still hot and the acetone removed at reduced pressure, giving 5.1 g (81%) of iodomaleic anhydride. A solution of the crude anhydride, sulfuric acid (1 ml), and methanol (30 ml) was refluxed for 40 hr. The methanol was removed at reduced pressure and the residue neutralized with 10% sodium carbonate solution (20 ml) and extracted with two 20-ml portions of anhydrous ether. The crude

product from the ether layer was recrystallized from ethanol giving 4.2 g (71%) of dimethyl iodomaleate, mp 59–60°. The spectral data follow: NMR δ 3.75 (s, 3 H, CO_2CH_3), 3.82 (s, 3 H, CO_2CH_3), 6.6 (s, 1 H, –CH); ir 5.80 and 6.20 μ.

Anal. Calcd for $C_6H_7IO_4$: C, 26.7; H, 2.59. Found: C, 27.42; H, 2.99.

Pyrolysis Apparatus and Procedures. Static pyrolysis was carried out in evacuated sealed medium wall NMR tubes. The procedure for preparation of the pyrolysis tubes included the following: washing with chromic acid cleaning solution; rinsing with distilled water, ammonium hydroxide, distilled water, and acetone; drying at 100° for 1 hr. The tubes were filled by syringe from stock solutions, evacuated through one freeze–thaw cycle, and sealed.

The apparatus for static pyrolysis at temperatures less than 160° consisted of a 6-l. stainless steel beaker equipped with a 3-ft coiled 500-W immersion heater. Power to the heater was provided by line voltage regulated with a powerstat transformer and an I^2R L7/600 Therm-O-Watch. The bath fluid was General Electric SF-96. Stirring was effected by a Lightnin' constant speed heavy duty stirrer regulated by a powerstat transformer for variable speed, and temperature was maintained within ±1.0°. For temperatures of 160° or greater a 6-l. stainless steel beaker equipped with a 3-ft coiled 500-W immersion heater and a 500-W knife blade heater was used. The immersion heater was powered as above; the knife blade was powered by an I^2R L7/600 Therm-O-Watch. The bath fluid was a molten mixture of potassium nitrate and sodium nitrite (1:1 w/w). Efficient stirring was provided by a transformer for variable speed. Insulation for the system was provided by a layer (2–4 in.) of vermiculite surrounding the beaker. The apparatus was contained in a 5-gal metal cylinder. The temperature fluctuation was maintained at ±0.5°. Mixtures to be pyrolyzed contained in NMR tubes prepared as described above were held in the bath by a stainless steel cylindrical tube holder and on removal from the pyrolysis bath were quenched in a beaker of water maintained at room temperature.

Product Analysis. Kinetics. Pyrolyses were interrupted intermittently and tubes analyzed directly by NMR for the appearance of methyl halide in the δ 2–3 region vs. an internal standard, *tert*-butylbenzene or DPM (methylene protons). Use of the integrated first-order rate equation gave rate constants for methyl halide appearance at low conversion (10–30%). The fragmentation to methyl halide for 4–7 was accompanied by the appearance of new olefinic and –OMe signals assignable to the geometric isomers of starting halo esters. Thus, for example, to the pattern of resonances in NB for dimethyl bromomaleate (**5**) at δ 3.40, 3.55, and 6.10 were added absorptions at δ 3.48, 3.55, and 7.03, which were associated with dimethyl bromofumarate[4] isolated from a partial pyrolysate (ir 5.8 μ). Pyrolysates were further examined by GLC for the appearance of methyl propiolate, phenylacetylene, and 2-bromo-2-butene (cis and trans) with authentic samples for comparison using coinjective techniques.

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Registry No.—*cis*-**1**, 10359-27-0; *trans*-**1**, 10358-76-6; **2**, 57325-23-2; **3**, 57325-24-3; **4**, 19393-45-4; (*E*)-**5**, 20688-29-3; (*Z*)-**5**, 2509-16-2; **6**, 57325-25-4; (*E*)-**7**, 1884-33-9; (*Z*)-**7**, 1884-32-8; **8**, 3395-91-3; **9**, 28127-71-1; 2-bromocyclobutene-1-carboxylic acid, 57325-26-5; diazomethane, 334-88-3; chloromaleic anhydride, 96-02-6; methanol, 67-56-1; bromomaleic anhydride, 5926-51-2; sodium iodide, 7681-82-5.

Supplementary Material Available. Tables of rate data for pyrolyses in the presence of additives (catalysts) along with kinetics plots for catalyzed and uncatalyzed fragmentation (4 pages) will appear following these pages in the microfilm edition of this volume of the journal.

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Studies on the Ionic Addition of Chlorine to Conjugated Dienes

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The compositions of dichloride mixtures obtained from reaction of chlorine under ionic conditions with cyclopentadiene (1), 1,3-cyclohexadiene (2), the 2,4-hexadienes, *cis,cis*-(**3a**), *trans,trans*-(**3b**), *cis,trans*-(**3c**), and the 1,3-pentadienes, *cis*-(**4a**) and *trans*-(**4b**) is reported for several solvents. The stereochemistry of 1,4 addition of chlorine to these dienes is predominantly syn but is generally less stereoselective than is bromine addition. The 1,2 addition of chlorine is generally nonstereospecific except for addition to the 3,4 bond of **4a,b** where attack is 89–95% anti. Appreciable cis 1,2-dichloride is obtained from chlorination of 1 and 2. The dienes **3a–c** show a preference for anti 1,2 addition only in the less polar solvents, carbon tetrachloride and pentane.

Recently we have reported investigations into the reactions of bromine with conjugated dienes, with our purpose being to determine the stereochemistry of 1,2 and 1,4 additions in such systems.[1a,b] We now wish to report results on the chlorination of these same dienes which will allow comparisons to be made between the mechanisms of reactions of these halogens.[2] The dienes which were chlorinated are cyclopentadiene (1), 1,3-cyclohexadiene (2), the 2,4-hexadienes, *cis,cis*-(**3a**), *trans,trans*-(**3b**), and *cis,trans*-(**3c**), the 1,3-pentadienes, *cis*-(**4a**) and *trans*-(**4b**).

Results and Discussion

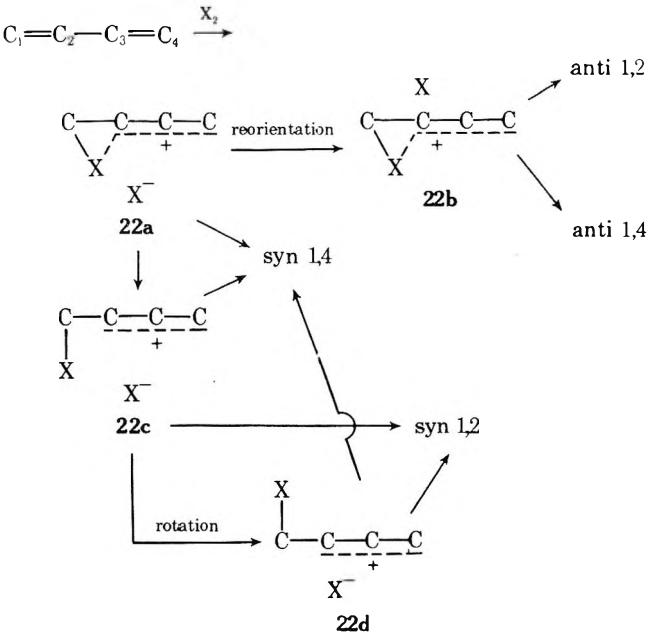
The dichlorides which were obtained from the dienes are identified as follows: from **1**, *cis*-3,4-dichlorocyclopentene (**5**), *trans*-3,4-dichlorocyclopentene (**6**), *cis*-3,5-dichlorocyclopentene (**7**), and *trans*-3,5-dichlorocyclopentene (**8**); from **2**, *cis*-3,4-dichlorocyclohexene (**9**), *trans*-3,4-dichlorocyclohexene (**10**), *cis*-3,6-dichlorocyclohexene (**11**), and *trans*-3,6-dichlorocyclohexene (**12**); from **3a–c**, *erythro*-4,5-dichloro-*cis*-2-hexene (**13**), *threo*-4,5-dichloro-*cis*-2-hexene (**14**), *dl*-2,5-dichloro-*trans*-3-hexene (**15**), *meso*-2,5-dichloro-*trans*-3-hexene (**16**), *threo*-4,5-dichloro-*trans*-2-hexene (**17**), and *erythro*-4,5-dichloro-*trans*-2-hexene (**18**); from **4a,b**, *threo*-3,4-dichloropentene (**19a**), *erythro*-3,4-dichloropentene (**19b**), *cis*-4,5-dichloro-2-pentene (**20a**), *trans*-4,5-dichloro-2-pentene (**20b**), and *trans*-1,4-dichloro-2-pentene (**21**).

Table I shows the composition of mixtures of dichlorides obtained by chlorinating each of the dienes in solvents of differing polarity. Reaction conditions were chosen so as to assure a polar mechanism.[3] Mixtures were analyzed by VPC under conditions which did not permit rearrangement of isomers. In most cases the dichlorides reported were isolated pure and their structures established by NMR or chemical methods.

Table II presents the data of Table I in terms of stereoselectivity in 1,2 and 1,4 addition. Stereochemical results for bromination are included for comparison.

Scheme I presents a mechanism which we believe accounts for results obtained in bromination and chlorination of dienes. According to this mechanism the products from diene addition result from ion pair **22a**. Because of dispersal of charge in the allylic system, the bond between halogen and C_2 is weakened so that an open carbonium ion, **22c**, readily forms allowing for the possibility of front-side attack by the anion with the resultant formation of syn 1,2 product. Syn 1,2-dichloride can also result from the linear dienes by rotation about the C_1–C_2 bond in **22c** to produce **22d**, followed by backside attack by anion.[4] Syn 1,4-dichloride can result by attack of anion on C_4 in either **22a**, **22c**, or **22d**. Formation of anti dichlorides (1,2 or 1,4) can only occur when there is appreciable reorientation in the ion pair **22a** to give **22b**. Attack by anion on C_2 in **22b** yields anti 1,2-dichloride and attack at C_4 yields anti 1,4-dichloride.

Scheme I

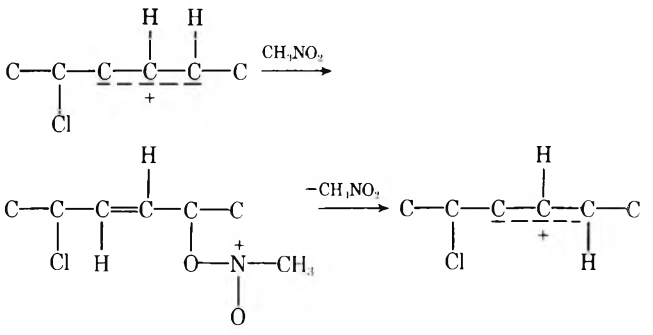


In comparing the results of chlorination with bromination one of the most striking differences is observed with the cyclic dienes, **1** and **2**. Each of these dienes gives appreciable syn 1,2 addition with chlorine. As we have previously stated,[2d] this is evidently explained by the fact that stable allylic carbonium ions are formed from dienes **1** and **2** allowing for ready formation of the open carbonium ion, **22c**. The fact that bromine did not yield detectable syn 1,2-dibromide from dienes **1** and **2** does not necessarily suggest significant differences in the intermediates obtained with bromine and chlorine.[5] Considering the fact that 1,2 bromine addition to the 2,4-hexadienes is nonstereospecific (suggesting weak bridging by bromine), we would anticipate that the intermediate obtained from **1** and **2** with bromine would also be, to a considerable extent, an open carbonium ion. Therefore, absence of syn 1,2 addition with bromine is likely due to the greater steric interaction which would result from syn 1,2 collapse of the ion pair from bromine.[6]

In the less polar solvents (pentane, carbon tetrachloride), the 2,4-hexadienes (**3a–c**) give a 1,2-dichloride adduct which is more than 60% anti[7] suggesting that intermediate **22a** is sufficiently bridged in these systems so that reaction occurs primarily via **22b**. In the more polar solvents (methylene chloride, nitromethane) anti addition occurs less than 50% for **3a** and **3c** and slightly above 50% for **3b**. Bromination of these dienes also produces nonstereospecific 1,2 adduct but the preference for anti addition is substantially higher. One reason for this is that syn addition of bromine probably occurs only via rotation about the C_1–C_2 bond (**22a** to **22d**) rather than by direct syn collapse of open ion **22c**, a route which is possible for the ion pair from chlorine.

An additional comparison between bromine and chlorine relates to addition to the 3,4 bond in the 1,3-pentadienes (**4a,b**) (producing 3,4-dihalides). We have previously observed that bromine addition to the 3,4 bond in **4a,b** occurred 100% anti in contrast to 1,2 addition to the 2,4-hexadienes (**3a–c**), which was not stereospecific.[1] This was explained by noting that the cation from **3a–c** should be more stable (assuming charge dispersal via resonance) than the ion from the 1,3-pentadienes. Chlorine addition to the 3,4 bond in dienes **4a,b** followed the same trend (in comparison to addition to **3a–c**) as bromine addition, although with chlorine a small amount of syn addition was detected (5 and 11% syn addition to **4a** in carbon tetrachloride and methylene chloride, respectively; 5% to **4b** in pentane).

An additional observation concerning the stereochemistry of 1,2 addition which should be mentioned is that chlorination of the cis,cis diene, **3a**, in nitromethane yields significant amounts of 4,5-dichloro-*trans*-2-hexene. In the other solvents isomerization of the cis to the trans bond does not occur. Isomerization of the double bond in nitromethane may be due to the higher polarity of that solvent or perhaps to some specific interaction with nitromethane which would allow for rotation about the 4,5 bond, as shown in the following structures.



A further general observation which can be made is that the amount of 1,4 addition, compared to 1,2 addition, is usually appreciably less for chlorination than bromination.[8] For all runs in Table II the 1,4-dibromide adduct exceeds the 1,2-dibromo adduct. In about one-third of the chlorination runs the main product is the 1,2 adduct, but there are several cases where 1,4 addition is greater for chlorination than bromination. Cyclohexadiene (**2**) shows an especially great contrast between chlorination and bromination, 1,4 addition being highly favored in bromination and 1,2 addition generally favored in chlorination.

A principal interest of our study concerns the stereochemistry of the 1,4 addition. The data in Table II demonstrate that 1,4 chlorine addition occurs primarily by a syn process but that like bromine addition it varies greatly in the degree of stereoselectivity. All of the chlorination runs in Table II with the exception of chlorination of **3b** in methylene chloride show that more than 50% of the 1,4

Table I
Chlorination of the Dienes

Diene	Solvent	Dichlorides,[a] % 5	6	7	8
1	C_5H_{12}	13	29	29	28
1	CCl_4	27	23	39	11
1	CH_2Cl_2	38	35	18	9
		9	**10**	**11**	**12**
2	C_5H_{12}	15	49	33	3
2	CCl_4	8	22	69	1
2	CH_2Cl_2	14	58	21	7
2	CH_3NO_2	4	59	22	15
		13	**14**	**15**	**16**
3a	C_5H_{12}	15	57	19	9
3a	CCl_4	13	32	49	6
3a	CH_2Cl_2	24	21	31	24
3a	CH_3NO_2	*b*	*b*	36	33
		17	**18**	**15**	**16**
3b	C_5H_{12}	14	28	36	22
3b	CCl_4	13	22	52	13
3b	CH_2Cl_2	21	27	24	28
3b	CH_3NO_2	21	26	29	24
		18	**17**	**16**	**15**
3c[c]	C_5H_{12}	7	27	43	18
3c[c]	CCl_4	9	19	59	11
3c[c]	CH_2Cl_2	23	23	31	22
3c[c]	CH_3NO_2	29	16	31	24
		19	**20**	**21**	
4a	C_5H_{12}	29	20	46	
4a	CCl_4	29	31	40	
4a	CH_2Cl_2	10	47	43	
4a	CH_3NO_2	16	40	44	
4b	C_5H_{12}	10	42	48	
4b	CCl_4	4	47	49	
4b	CH_2Cl_2	2	66	32	
4b	CH_3NO_2	1	67	32	

[a] For dienes 1, 2, 3a–c, the columns of dichlorides (from left to right) represent syn-1,2, anti-1,2, syn-1,4, and anti-1,4 adducts. [b] 1,2 adducts follow (%): 13, 11; 18, 10; (14 + 17), 10. [c] Additional 1,2 adduct resulting from attack at the trans bond in 3c is as follows (%): pentane, 13, 3.1; 14, 1.7; CCl_4, 13, 1.4; 14, 0.9; CH_2Cl_2, (13 + 14), 1.4; CH_3NO_2, (13 + 14), 0.5.

product is syn. The average of all runs (Table II) is 68% syn 1,4 addition in chlorination compared to 75% in bromination. We have previously attributed the preference for syn 1,4 addition (over anti 1,4 addition) primarily to the specific geometry of the ion pair intermediate (**22a** or **22c**), rather than to some underlying orbital symmetry preference for syn attack.[9] Edmondson[2e] has suggested that if 1,4 addition occurs via a bridged ion (i.e., **22a** or **22b**) the SN2′ process should yield only syn product and that an increase in the amount of anti 1,4 product would be expected with an open carbonium ion (**22c**). Our findings in chlorination and bromination do not appear to be susceptible to such a simple interpretation. In the reactions where there is evidence for the most stable bridging by halogen, i.e., maximum anti stereochemistry in 1,2 addition, we do not necessarily find the highest percentage of syn 1,4 attack. In chlorination of cyclopentadiene the solvent (pentane) showing the highest preference for anti 1,2 addition (69%) shows the lowest preference for syn 1,4 addition (51%). The 2,4-hexadienes (**3a–c**) all show the highest stereospecificity of anti 1,2 addition in pentane (79, 67, and 79%, respectively) but the corresponding percentage of syn 1,4 addition is much lower in pentane than in carbon tetrachloride. Likewise, bromi-

Table II
Stereoselectivity in Chlorination and Bromination of the Dienes

Diene	Solvent	Chlorination			Bromination[c]		
		1,2 addn, % anti[a]	1,4 addn, % syn[b]	1,4/1,2 addn	1,2 addn % anti	1,4 addn % syn	1,4/1,2 addn
1	C_5H_{12}	69	51	1.4	100	54	1.1
1	CCl_4	46	78	1.0	100	52	1.6
1	CH_2Cl_2	48	67	0.37	100	72	2.8
1	CH_3NO_2				100	58	2.2
2	C_5H_{12}	77	92	0.56	100	83	3.0
2	CCl_4	73	99	2.3	100	96	4.6
2	CH_2Cl_2	81	75	0.39	100	98	4.3
2	CH_3NO_2	94	59	0.59			
3a	C_5H_{12}	79	68	0.39	92	73	1.1
3a	CCl_4	71	89	1.2	79	89	1.9
3a	CH_2Cl_2	47	56	1.2	79	93	4.3
3a	CH_3NO_2	*d*	52	2.2	89	70	1.3
3b	C_5H_{12}	67	62	1.4	88	71	1.4
3b	CCl_4	63	80	1.9	79	79	2.4
3b	CH_2Cl_2	56	46	1.1	85	79	2.7
3b	CH_3NO_2	55	55	1.1	71	62	1.9
3c	C_5H_{12}	79	70	1.6	89	72	1.2
3c	CCl_4	68	84	2.3	77	78	2.2
3c	CH_2Cl_2	50	58	1.1	85	78	2.8
3c	CH_3NO_2	36	56	1.2	78	66	1.4
4a	CCl_4	95		0.67	100		1.3
4a	CH_2Cl_2	89		0.75	100		2.7
4b	C_5H_{12}	95		0.92			

[a] Computed as follows: anti-1,2 adduct/total 1,2 adduct × 100. Anti-1,2 adduct = **6, 10, 14, 18, 17, 19a, 19b** from **1, 2, 3a, 3b, 3c, 4a, 4b**, respectively. For **3c** total 1,2 adduct is for attack at the cis bond only (see footnote c, Table I). [b] Computed as follows: syn-1,4 adduct/total 1,4 adduct × 100. Syn-1,4 adduct = **7, 11, 15, 15, 16** from **1, 2, 3a, 3b, 3c**, respectively. [c] See ref 1a, b. [d] See footnote *b*, Table I.

nation of **3a–c** shows the maximum stereospecificity (anti) in 1,2 addition in pentane with a somewhat lower percentage of syn 1,4 addition than in other solvents.

On the other hand, a large preference for syn (over anti) 1,4 attack often accompanies a low stereochemical preference for anti 1,2 attack. For example, in chlorination of cyclopentadiene (**1**) in carbon tetrachloride, 54% of the 1,2-dichloride is syn (formed evidently via an open carbonium ion) but the 1,4 attack is 78% syn. Likewise in chlorination of cyclohexadiene (**2**) in carbon tetrachloride where the maximum syn 1,2 product is obtained, the 1,4-dichloride is 99% syn. We interpret the above results to mean that the bridged ion in these systems can undergo either syn or anti 1,4 attack, and that the reorientation (**22a** → **22b**) necessary for anti 1,2 attack can also lead to anti 1,4 attack. This accounts for the increase in anti 1,4 product which tends to accompany an increase in anti 1,2 product. The preference for syn 1,4 attack is explained by the fact that 1,4 addition results from an intimate ion pair such as **22a** or **22c** and that the anion in such intermediates is present in a geometrical location which favors direct collapse to syn 1,4 product. Therefore, even in the cases where there is evidently an open carbonium ion (e.g., chlorination of **1** in carbon tetrachloride), the 1,4 addition is still largely syn because collapse of the ion pair is faster than reorientation.

The data on halogenation of these dienes reveal that solvents have a striking effect on product ratios. These changes in product ratios which accompany solvent changes for the most part do not seem to be readily explainable from a mechanistic standpoint but some definite trends may be noted. Bromination of dienes **1, 2,** and **3a–c** gave in every case the largest amount of 1,4 addition in methylene chloride. Also, the preference for syn 1,4 product tends to be highest in methylene chloride. Chlorination of these dienes in methylene chloride tends to give opposite results from bromination, i.e., the 1,4:1.2 ratio is lowest in that solvent. The decrease in 1,4 addition is accompanied by a decreased selectivity for syn addition. Chlorination in carbon tetrachloride gives more syn 1,4 addition than any other solvent for each of the dienes studied. The chlorination of cyclohexadiene (**2**) illustrates particularly well the significant differences observed with various solvents. In carbon tetrachloride 69% of the dichloride product is **11** but in methylene chloride, 58% of the product is **10**. Apparently solvents have subtle effects in stabilizing anions or in allowing solvent separation of ion pairs such as **22a**.

Experimental Section

General. Dienes and solvents were obtained commercially in high purity except for cyclopentadiene, which was prepared from its dimer just prior to use. Infrared spectra were obtained on a Beckman IR-10 spectrophotometer. Nuclear magnetic resonance spectra were obtained with Varian A-60, T-60A, and XL-100 instruments. Vapor phase chromatography was done with a Hewlett-Packard 7620A or F & M 1609 flame ionization instruments.

Chlorination Procedure. Chlorinations were done in the dark at −10 ± 2°C. The diene concentrations were 0.02 mole fraction with respect to the solvent. The amount of chlorine was 20–25% of the amount of diene. For example, a typical chlorination to obtain product ratios was done as follows: to 0.10 g (0.0012 mol) of **3c** dissolved in 5.7 ml of CCl_4 (saturated with oxygen gas) was added 0.36 ml of 0.86 *M* chlorine in carbon tetrachloride (0.00031 mol). In another procedure samples of liquid chlorine were vaporized with an oxygen stream into diene solutions. Dichloride product ratios did not differ significantly for the two methods of chlorine addition. Under the chlorination conditions described above cyclohexane was not chlorinated when it was the solvent. At high diene mole fraction (0.5) under nitrogen, detectible amounts of chlorocyclohexane were formed from cyclohexane. We conclude that the chlorination procedure used did not contain a radical component.[3]

Analysis Procedure. Mixtures resulting from chlorination were sampled directly by VPC, using one of the following columns: column A, 2.5% SE-30 on 60–80 Chromosorb W (AW-DMCS), 18 ft × 0.25 in. SS; column B, 2.5% β,β-oxydipropionitrile on 80–100 Chromosorb W (AW-DMCS), 6–14 ft × 0.125 in. SS. VPC analysis of dichloride mixtures is based on corrected peak areas which were established by means of VPC response factors. Response factors were obtained by analysis of known mixtures prepared from pure compounds and the internal standard which was used to obtain yields. The average yields[10] for chlorination in the solvents shown

in Table I for each of the dienes is as follows (%): 1, 60; 2, 37; **3a**, 70; **3b**, 71; **3c**, 79; **4a**, 60; **4b**, 56.

Dichlorocyclopentenes (5, 6, 7, 8). VPC analysis on column B (7 ft, 51°) gave retention times (min) of 4.4, 7.4, 20.6, and 22.6 for 6, 8, 5, and 7, respectively. Retention times on column A have been reported.[2d] *p*-Chlorobromobenzene was used as an internal standard. Data for the identification of **5, 6, 7,** and **8** have been reported previously.[2d]

Dichlorocyclohexenes (9, 10, 11, 12). VPC (70°) analysis on column A of chlorination mixtures of **2** gave four peaks with retention times of 12.8, 15.0, 16.2, and 18.8 min, assigned to **10, 12, 11,** and **9**, respectively. Bromobenzene was used as an internal standard. Pure samples of **10** and **11** were obtained by spinning-band distillation of chlorination mixtures. Compound **9** was obtained in about 85% purity by spinning-band distillation followed by preparative VPC. Identification of **12** is based on the fact that peak 2 in the chlorination mixtures had a VPC retention time identical with that of **12** prepared independently (below).

Structural assignments for **11** and **12** were made on the basis of preparation from the corresponding 3,6-dibromocyclohexenes by treatment with lithium chloride as reported previously[2d] for **7** and **8**. For example: 0.35 g of *trans*-3,6-dibromocyclohexene[1b] was added to a mixture of 0.62 g of LiCl in 20 ml of Me_2SO. The mixture was stirred at 15° for 15 min, then poured into ice–water and extracted with pentane. Evaporation of the pentane afforded **12**, a solid which melted at 62–63.5° after three recrystallizations from pentane. Compound **11** was obtained by an identical reaction from *cis*-3,6-dibromocyclohexene.[1b] After recrystallization from pentane, **11** had mp 31.5–32.5°.

Structures of **9** and **10** were established by diimide reduction to the dichlorocyclohexanes. For example, 0.25 g of pure **10** was treated with potassium azodicarboxylate in pyridine according to the procedure of Snyder.[11] Unreacted **10** was removed by addition of excess 0.1 *M* potassium permanganate and the product was extracted into pentane and purified by VPC. The product had an identical VPC retention time and ir and NMR spectra with authentic *trans*-1,2-dichlorocyclohexane.[12] By an identical procedure the compound of VPC peak 4 (above) was converted to a product having identical VPC retention time and NMR and ir spectra with authentic *cis*-1,2-dichlorocyclohexane.[13]

NMR analyses also confirmed the structures assigned to the cyclohexadiene dichlorides. All showed three regions of absorptions assignable to vinyl, methine, and methylene hydrogens with integrated intensities of 1:1:2, respectively. Spectra assigned to **11** and **12** showed striking resemblances to the respective isomeric dibromides.[1b] Spectra of **9** and **10** each showed two distinct methine protons and greater multiplicity for the vinyl hydrogen absorptions owing to the lesser degree of symmetry in the structures of **9** and **10**. Summary of NMR data (CCl_4, parts per million downfield from Me_4Si, **10, 11, 12,** 100 MHz; **9,** 60 MHz): **9**, 1.82–2.42 (m, 4, CH_2), 4.08–4.40 (m, 1, CHCl), 4.42–4.70 (m, 1, CHCl), 5.70–5.93 (m, 2, CH=CH); **10**, 1.84–2.56 (m, 4, CH_2), 4.26–4.42 (m, 1, CHCl), 4.42–4.54 (m, 1, CHCl), 5.60–6.02 (m, 2, CH=CH); **11**, 2.08–2.26 (m, 4, CH_2), 4.38–4.60 (m, 2, CHCl), 5.80–5.94 (m, 2, CH=CH); **12**, 1.88–2.57 (m, 4, CH_2), 4.48–4.66 (m, 2, CHCl), 5.86–6.02 (m, 2, CH=CH).

Summary of ir absorptions (cm^{-1}, CCl_4): **9**, 3040, 2960, 2920, 2840, 1640, 1420, 1231, 1205, 1092, 970, 945, 893, 853, 690, 672, 629; **10**, 3040, 2960, 2920, 2900, 2840, 1655, 1442, 1430, 1330, 1240, 1200, 1020, 685, 640, 555; **11**, 3040, 2960, 2900, 1455, 1440, 1390, 1215, 1235, 1190, 980, 885, 700, 620, 483; **12**, 3040, 2960, 1440, 1355, 1260, 1215, 1012, 946, 918, 675, 567.

Dichlorohexenes (13–18). Mixtures of dichlorides produced by chlorination of **3a–c** were analyzed by VPC using columns A and B. Retention times on these columns follow: column A (30°), 31.8, 35.0, 37.8, 37.8, 42.0, and 45.7 min for **13, 18, 17, 14, 16,** and **15**, respectively; column B (14 ft, 50°), 15.6, 16.0, 16.0, 17.6, 24.0, and 28.2 min for **13, 17, 18, 14, 16,** and **15**, respectively. Bromobenzene was used as internal standard.

Pure samples of **15** and **16** were obtained by recrystallization from chlorination mixtures. For example, for preparation of **16**, 2.0 g (0.024 mol) of **3c** in 230 ml of carbon tetrachloride was treated with 34 ml (0.019 mol) of 0.58 *M* chlorine solution (CCl_4). The solvent was removed in vacuo, pentane was added, and the mixture was caused to crystallize by cooling in a dry ice bath. After washing the crystals three times with cold pentane, the solvent was removed and the residue was distilled [bp 80° (35 mm)] to yield 0.64 g of **16** (97% by VPC). By a similar procedure **15** was obtained by starting with chlorination of **3b**.

Structures of **15** and **16** were established[14] by conversion to diepoxyhexanes by a procedure described previously for the corresponding dibromohexenes.[1b] Thus, **16**, obtained as described above, yielded a single diepoxide identical in ir spectrum and VPC retention time with *cis,trans-rac*-(2*R*,3*R*,4*R*,5*S*)-2,3,4,5-diepoxyhexane.[15] Dichloride **15** yielded by the same treatment two compounds having VPC retention times identical with those of *cis,cis-rac*-(2*R*,3*R*,4*R*,5*R*)-diepoxyhexane[15] and *trans,trans-rac*-(2*S*,3*R*,4*R*,5*S*)-2,3,4,5-diepoxyhexane.[15]

The 1,2-dichlorides resulting from chlorination of **3a–c** in CCl_4 were isolated by distillation and VPC collection. The 1,2 adduct isolated from each diene was a mixture of diastereomers having compositions as follows (%): from **3a, 14,** 65, **13,** 35; from **3b, 18,** 66, **17,** 34; from **3c, 17,** 56, **18,** 33, **13,** 7, **14,** 4. The NMR and ir data as well as the crotonaldehyde dichloride derivatives reported below were obtained on the above mixtures of diastereomers.

Assignment of structures to the 1,2 adducts is based on their NMR and ir spectra and on conversion to crotonaldehyde dichlorides by a procedure reported previously for the corresponding 4,5-dibromo-2-hexenes.[1b] Authentic crotonaldehyde dichloride [bp 60–70° (36 mm); reported[16] 58–60° (20 mm)] prepared by chlorination of crotonaldehyde showed two VPC peaks (column A, 38°), peak 1, 13.4 min, 87%, and peak 2, 16.4 min, 13%. The crotonaldehyde dichloride obtained from the 4,5-dichloro-2-hexenes showed identical VPC peaks in ratios as follows:[17] from dichloride of **3a**, peak 1, 48%, peak 2, 52%; from dichloride of **3b**, peak 1, 81%, peak 2, 19%; from dichloride of **3c**, peak 1, 50%, peak 2, 50%. The crotonaldehyde dichloride obtained from the 1,2-dichloride adduct of **3b** was isolated by VPC collection and found to have an ir spectrum identical with that of authentic crotonaldehyde dichloride, ir (CCl_4) O=CH, 2830, 2720; C=O, 1735 cm^{-1}.

The NMR spectra of **13–18** are consistent with the structures assigned. The 1,4 adducts **15** and **16** exhibited one absorption for methyl and one absorption for methine hydrogens whereas 1,2 adducts **13, 14, 17,** and **18** showed two different absorptions for methyl hydrogens. In **13** and **14** the methine hydrogens exhibit different chemical shifts. Spectra (60 MHz, CCl_4) are summarized as follows: (**13, 14**), 1.54 (d, CH_3CHCl of **14**, J = 7.0 Hz), 1.60 (d, CH_3CHCl of **13**, J = 7.0 Hz), 1.76 (d, 3, CH_3CH=CH, J = 5.5 Hz), 4.14 (m, 1, CH_3CHCl), 4.77 (m, 1, CH=CHCHCl), 5.45 (m, 2, CH=CH); **15**, 1.60 (d, 3, CH_3, J = 6.5 Hz), 4.48 (m, 2, CHCl), 5.78 (m, 2, CH=CH); **16**, 1.55 (d, 3, CH_3, J = 6.5 Hz), 4.46 (m, 2, CHCl), 5.68 (m, 2, CH=CH); (**17, 18**), 1.55 (d, CH_3CHCl of **18**, J = 6.5 Hz), 1.51 (d, CH_3CHCl of **17**, J = 6.8 Hz), 1.76 (d, 3, CH_3CH=CH, J = 5.2 Hz), 4.14 (m, 2, CHClCHCl), 5.54 (m, 2, CH=CH).

Summary of ir spectra (cm^{-1}, CCl_4): (**13, 14**), 3020 (C=CH), 1655 (C=C), 780 (cis CH=CH, CS_2), 1445, 1380, 1245, 1200, 850, 650; **15**, 956 (trans CH=CH), 1445, 1375, 1220, 1009, 640; **16**, 953 (trans CH=CH), 1443, 1370, 1200, 1003, 640; (**17, 18**), 3015 (C=CH), 1670 (C=C), 957 (trans CH=CH), 1447, 1380, 1245, 1200, 1181, 1000, 910, 855, 650.

Dichloropentenes (19a–21). Mixtures of dichlorides obtained from **4a,b** were analyzed by VPC using column B (12 ft, 50°). Retention times are 4.8, 5.2, 7.4, 7.4, and 16.4 min for **19a, 19b, 20a, 20b,** and **21**, respectively. Comparative amounts of erythro and threo (**19a, 19b**) isomers produced in reactions were determined by VPC collection and integration of the methyl absorption in the NMR. The fact that the 1,2-dichloride (**20a, 20b**) formed from **4a** or **4b**, respectively, without rearrangement of the double bond was shown by direct NMR measurement of the methylene region (~3.65) for **20a** or **20b** in chlorination mixtures. In VPC analysis of the above mixtures *o*-bromotoluene was used as internal standard.

All of the reported dichloride isomers were isolated by spinning band distillation or VPC collection. Structural assignments are based on NMR and ir spectra. Summary of NMR spectral data (CCl_4, 60 MHz): **19a**, 1.55 (d, 3, CH_3, J_{45} = 6.1 Hz), 4.18 (d of q, 1, $CHClCH_3$, J_{45} = 6.1, J_{34} = 3.8 Hz), 4.50 (dd, 1, CHCH=CH, J_{34} = 3.8, J_{23} = 6.6 Hz), 5.6–5.2 (m, 2, CH=CH_2), 6.04 (ddd, 1, CH=CH_2, J_{23} = 6.6, J' = 8.2, J'' = 18.4 Hz); **19b**, 1.62 (d, 3, CH_3, J_{45} = 6.1 Hz), 3.8–4.5 (m, 2, $CHClCH_3$ and CHCH=CH), 5.15–5.54 (m, 2, CH=CH_2), 5.99 (ddd, 1, CH=CH_2, J = 7.0, J' = 8.0, J'' = 17.2 Hz); **20a**, 1.78 (d, 3, CH_3, J_{12} = 6.5, J_{13} = 1.2 Hz), 3.53 [dd, 1, CH(H), J_{45} = 8.2, $J_{55'}$ = 10.3 Hz], 3.78 [dd, 1, CH(H), $J_{45'}$ = 5.0, $J_{55'}$ = 10.3 Hz), 4.76 (ddd, 1, CHCl, $J_{45'}$ = 5.0, J_{45} = 8.2, J_{34} = 8.0 Hz), 5.43 (dd, 1, CH=CHCCl, J_{23} = 11.0, J_{34} = 8.0, J_{13} = 1.2 Hz), 5.80 (dq, 1, CH=CHCCl, J_{12} = 6.5, J_{23} = 11.0 Hz); **20b**, 1.78 (d, 3, CH_3, J_{12} = 5.4, J_{13} = 1.2 Hz), 3.53 [dd, 1, CH(H), J_{45} = 8.0, $J_{55'}$ = 10.2 Hz], 3.76 [dd, 1, CH(H), $J_{45'}$ = 5.2, $J_{55'}$ = 10.2 Hz], 4.40 (ddd, 1, CHCl, $J_{45'}$ = 5.2, J_{45} = 8.0, J_{34} = 8.0 Hz), 5.32 (dd, 1, CH=CHCHCl, J_{34} = 8.0, J_{23} = 14.4, J_{13} = 1.2 Hz), 5.86 (dq, 1,

CH=CHCHCl, J_{12} = 5.4, J_{23} = 14.4 Hz); **21**, 1.60 (d, 3, CH_3, J_{45} = 6.8 Hz), 4.00 (m, 2, CH_2), 4.42 (m, 1, CHCl), 5.74 (m, 2, CH=CH).

Summary of ir data (cm^{-1}, CCl_4): **19a**, 983 and 930 ($CH=CH_2$), 3090, 2980, 2920, 1445, 1360, 1200, 750, 650 cm^{-1}; **20a**, 720, (CS_2, cis CH=CH), 1665 (C=C), 3040, 2950, 2910, 2860, 1430, 1380, 1310, 1270, 1200, 1170, 960, 920, 680; **20b**, 956 (trans CH=CH), 1670 (C=C), 3040, 2970, 2950, 2910, 2890, 2860, 1425, 1370, 1195, 1170, 670; **21**, 957 (trans CH=CH), 1670 (C=C), 3040, 2970, 2910, 2860, 1440, 1380, 1250, 1215, 1010, 685, 645.

Acknowledgment. Support for this work was provided by the Research Corporation and the donors of the Petroleum Research Fund, administered by the American Chemical Society.

Registry No.—**1**, 542-92-7; **2**, 592-57-4; **3a**, 6108-61-8; **3b**, 5194-51-4; **3c**, 5194-50-3; **4a**, 1574-41-0; **4b**, 2004-70-8; **5**, 51502-28-4; **6**, 31572-43-7; **7**, 31572-45-9; **8**, 31572-44-8; **9**, 53921-00-9; **10**, 53920-98-2; **11**, 54112-34-4; **12**, 53920-99-3; **13**, 57256-15-2; **14**, 57256-16-3; **15**, 57256-17-4; **16**, 57273-83-3; **17**, 57256-18-5; **18**, 57256-19-6; **19a**, 57256-20-9; **19b**, 53920-93-7; **20a**, 53920-95-9; **20b**, 53920-94-8; **21**, 53920-96-0.

References and Notes

(1) (a) V. L. Heasley, G. E. Heasley, S. K. Taylor, and C. L. Frye, *J. Org. Chem.*, **35**, 2967 (1970); (b) G. E. Heasley, V. L. Heasley, S. L. Manatt, H. A. Day, R. V. Hodges, P. A. Kroon, D. A. Redfield, T. L. Rold, and D. E. Williamson, *ibid.*, **38**, 4109 (1973).

(2) Previous studies on the chlorination of conjugated dienes follow. Butadiene: (a) M. L. Poutsma, *J. Org. Chem.*, **31**, 4167 (1966); (b) V. L. Heasley, G. E. Heasley, R. A. Loghry, and M. R. McConnell, *ibid.*, **37**, 2228 (1972). Isoprene: (c) G. D. Jones, N. B. Tefertiller, C. F. Raley, and J. R. Runyon, *ibid.*, **33**, 2946 (1968). Cyclopentadiene: (d) V. L. Heasley, G. E. Heasley, P. D. Davis, D. M. Ingle, and K. D. Rold, *ibid.*, **39**, 736 (1974). *trans,trans*-2,4-Hexadiene: (e) M. S. Edmondson, *Diss. Abstr.*, 3914 (1971).

(3) For a discussion of competition between radical and ionic mechanisms in chlorination of alkenes, see (a) M. L. Poutsma, *J. Am. Chem. Soc.*, **87**, 2172 (1965); (b) *J. Org. Chem.*, **31**, 4167 (1966).

(4) The attack by chloride ion in **22d** is anti to the chlorine atom already bonded to carbon but the dichlorides formed (both 1,2 and 1,4) from **22d** are the same as those resulting from direct syn addition of both chlorine atoms to the same side of the diene, i.e., they are syn products. For previous discussions of this matter see ref 1b and studies on the bromination of the 1-phenylpropenes [J. H. Rolston and K. Yates, *J. Am. Chem. Soc.*, **91**, 1469 (1969); R. C. Fahey and H. J. Schneider, *ibid.*, **90**, 4429 (1968)].

(5) Although there is evidence (mainly under conditions other than those employed in electrophilic addition) that bromine is a better bridging atom than chlorine [see, e.g., F. Freeman, *Chem. Rev.*, **75**, 454 (1975)], the ability of chlorine to form stable bridged ions in electrophilic addition has been amply demonstrated. Stereospecific anti addition has been observed with a diversity of alkenes such as cyclopentene,[2d] *cis*-2-butene,[3a] and *cis*-di-*tert*-butylethylene: R. C. Fahey, *J. Am. Chem. Soc.*, **88**, 4681 (1966).

(6) For a further discussion see our recent paper on the addition of bromine chloride to **1**: V. L. Heasley, C. N. Griffith, and G. E. Heasley, *J. Org. Chem.*, **40**, 1358 (1975).

(7) Edmondson[2e] reports that essentially equal amounts of anti and syn 1,2-dichloride are obtained from chlorination of **3b** in several solvents. Since our syn:anti 1,4-dichloride ratios and 1,4:1,2 ratios are in good agreement with his, the discrepancy on the ratio of 1,2-dichlorides may be due to the fact that his mixtures of erythro and threo dichlorides were analyzed via diimide reduction to the 2,3-dichlorohexanes. We were able to achieve direct VPC separation of the 1,2-dichlorides and also observed that the NMR spectra of the mixture of 1,2-dichlorides confirmed our VPC analysis.

(8) This trend has been observed for chlorination and bromination of butadiene in several solvents [V. L. Heasley, G. E. Heasley, R. A. Loghry, and M. R. McConnell, *J. Org. Chem.*, 37, 2228 (1972)]. Chlorination of isoprene[2c] gives more 1,4 than 1,2 addition in most solvents; bromination of isoprene also occurs predominantly 1,4 [V. L. Heasley, C. L. Frye, R. T. Gore, and P. S. Wilday, *ibid.*, **33**, 2342 (1968)].

(9) We assume that attack on a bridged bromonium ion (covalently bonded to both carbon atoms) is essentially a nucleophilic displacement and that opening by attack on the double bond would be an example of the S_N2' mechanism. Although a syn stereochemistry is generally accepted for S_N2', the evidence for this has been questioned [F. G. Bordwell, *Acc. Chem. Res.*, **3**, 281 (1970)]. Liotta [C. L. Liotta, *Tetrahedron Lett.*, 523 (1975)] and Fukui [K. Fukui, *ibid.*, 2427 (1965)] have predicted on theoretical grounds that S_N2' attack should be syn to the leaving group.

(10) The relatively low yields of dichlorides obtained with some of the dienes (particularly with **2**) is probably due to competing substitution reactions. De La Mare and Wong [*Recl. Trav. Chim. Pays-Bas*, **87**, 824 (1968)] have investigated the ionic chlorine substitution reaction which occurs with **4a,b**. We observed that chlorination of **2** in carbon tetrachloride produced benzene (identified by the NMR singlet at δ 7.26) in a mole ratio equal to the dichlorocyclohexenes. Benzene would be obtained by HCl elimination from the allylic substitution product of cyclohexadiene (**2**), 5-chloro-1,3-cyclohexadiene (benzene hydrochloride).

(11) J. W. Hamersma and E. I. Snyder, *J. Org. Chem.*, **30**, 3985 (1965).

(12) M. L. Poutsma, *J. Am. Chem. Soc.*, **87**, 2162 (1965).

(13) N. Isaacs and D. Kirkpatrick, *Tetrahedron Lett.*, 3869 (1972).

(14) Edmondson[2e] proved the structure of the principal 1,4-dichloride of **3b** (**15**) by diimide reduction to *dl*-2,5-dichlorohexane.

(15) G. E. Heasley, R. V. Hodges, and V. L. Heasley, *J. Org. Chem.*, **39**, 1769 (1974).

(16) C. Moureu, M. Murat, and L. Tampier, *Bull. Soc. Chim. Fr.*, **29**, 29 (1921).

(17) Since the major crotonaldehyde dichloride isomer is the same from chlorination of crotonaldehyde and when derived from the chlorination product of **3b** (in CCl_4), the major dichloride from **3b**, **18**, can be assigned the erythro structure on the assumption that chlorine addition to the largely *trans*-crotonaldehyde would be predominantly anti. The chlorination product (in CCl_4) from **3a** yielded a crotonaldehyde dichloride mixture in which the major dichloride was the opposite to that obtained from **3b**, so it follows that the major dichloride (**14**) of **3a** (CCl_4) is threo. Additional evidence for assignment of erythro and threo structures was obtained by converting the chlorination product of **4a** to crotonaldehyde dichlorides. The crotonaldehyde dichloride obtained in major amount (>95%) had a VPC retention time identical with that of the major crotonaldehyde dichloride derived from **3a**. Thus the assignment of the threo structure to **14** follows if the nearly stereospecific addition to the 3,4 bond in **4a** (and **4b**) is assumed to be anti.

New Precursors for Arylcarbenes. Photocycloelimination Reactions of Cyclic Carbonates[1,2]

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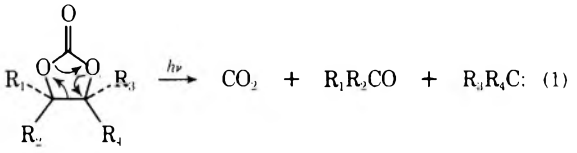
Cyclic arylpinacol carbonates undergo photoinduced [5 → 2 + 2 + 1] cycloeliminations to give arylcarbenes. The carbonates studied include benzopinacol carbonate, *meso*- and *dl*-hydrobenzoin carbonates, and the *dl*- and *meso*-α,α'-dimethylhydrobenzoin carbonates. Arylcarbenes formed by photolysis of these substrates react in methanol to give methyl ethers and the properties of phenylcarbene obtained from the *meso*- and *dl*-hydrobenzoin carbonates are found to be virtually identical with those obtained from conventional precursors such as *trans*-2,3-diphenyloxiranes and phenyldiazomethane; i.e., the secondary to primary insertion selectivity in pentane and the stereospecificity in the addition to *cis*-2-butene are the same.

It has become increasingly apparent that both thermal and photocycloelimination reactions, like the reverse reactions of cycloaddition, have broad synthetic utility.[4,5,6] We have recently described the [5 → 2 + 2 + 1] photocycloelimination of pinacol sulfites[4] and as part of our continuing research program in this area have investigated the chemi-

cal response of a series of cyclic pinacol carbonates of the type 1 to ultraviolet radiation. It has previously been established that a variety of polyaryl substituted heterocyclic substrates undergo photocycloelimination reactions to give arylcarbenes.[5] In view of our experience with related sulfites[4] and phospholanes[7] which photolyze to arylcarbenes it appeared probable that carbonates of the type 1 also would undergo facile photocycloelimination in a [5 → 2 + 2 + 1] manner to give carbenes (eq 1).[8-10]



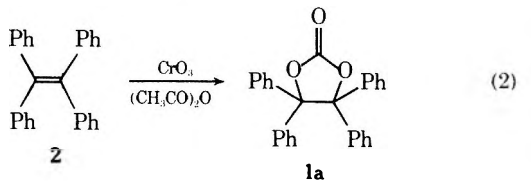
(1)

1a, $R_1 = R_2 = R_3 = R_4 = Ph$
b, $R_1 = R_3 = Ph$; $R_2 = R_4 = H$
c, $R_1 = R_4 = Ph$; $R_2 = R_3 = H$
d, $R_1 = R_3 = Ph$; $R_2 = R_4 = CH_3$
e, $R_1 = R_4 = Ph$; $R_2 = R_3 = CH_3$

Results and Discussion

Benzopinacol carbonate (**1a**), a cyclic carbonate incorporating structural features designed to facilitate photocycloelimination, was selected as a substrate for preliminary photocycloelimination studies. The anticipated carbene, diphenylmethylene, has been studied extensively both chemically[11a] and spectroscopically by optical[12] and EPR[13] techniques. Kirmse, Hörner, and Hoffmann[11a] have established that diphenylcarbene obtained photolytically from diphenyldiazomethane reacts with alcohols to give ethers. They proposed that the carbene is nucleophilic in character and is readily protonated in alcohols to give the benzhydryl carbonium ion which subsequently solvolyzes to benzhydryl ethers; however, this mechanism has been challenged recently.[11b] Diphenylcarbene, a triplet ground state species, reacts with alkanes and alkenes by hydrogen abstraction to give benzhydryl radicals which subsequently dimerize or react in other ways.[5b] These free-radical processes complicate investigations involving addition and insertion reactions of this divalent species and consequently methanol was selected as the most convenient solvent trapping agent for screening potential carbonate precursors for arylcarbene formation.

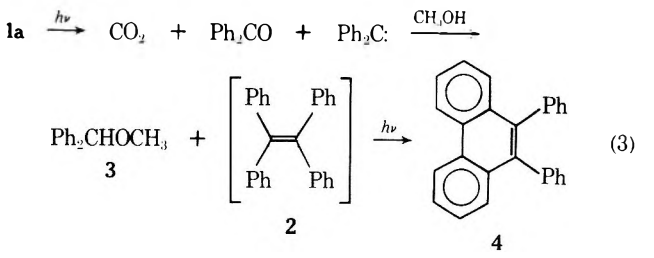
Two general methods for the preparation of cyclic carbonates, namely treatment of the requisite 1,2-diol with phosgene[14] or diethyl carbonate,[15] failed to give **1a** when applied to benzopinacol. The desired benzopinacol carbonate (**1a**) was finally obtained, albeit in low yield (17%), by oxidation of tetraphenylethylene (**2**) with chromium trioxide in acetic anhydride (eq 2). This method is described by



(2)

Mosher and co-workers,[16] who allude to the difficulties encountered in preparing **1a** from the diol by conventional methods.

Photolysis (254 nm) of benzopinacol carbonate (**1a**) in methanol induces a [5 → 2 + 2 + 1] cycloelimination reaction of the type anticipated to give diphenylcarbene as evidenced by formation of benzhydryl methyl ether (**3**, 60%) (eq 3).[2a]

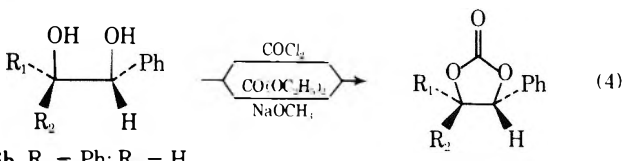


(3)

Other compounds identified among the photolysis products of **1a** include benzophenone (15%) and 9,10-diphenylphenanthrene (**4**, 10%). It was shown independently that tetraphenylethylene (**2**) undergoes dehydrophotocyclization under the reaction conditions and thus **4** is probably a secondary photoproduct arising from **2** as indicated in eq 3.[17] Similar results were obtained upon photolysis of benzopinacol sulfite and it was concluded that the alkene **2** in that case was formed as a result of a [5 → 3 + 2] cycloelimination reaction involving extrusion of sulfur trioxide.[4] A concerted [5 → 3 + 2] cycloelimination reaction leading to **2** is more difficult to formulate in the case of the carbonate **1a** and the origin of the tetraphenylethylene (**2**) remains to be established in this case; however, diphenylcarbene dimerization is an improbable reaction at ambient temperature in fluid solutions and is excluded as a significant source of **2**.[18] The presence of carbon dioxide among the photoproducts of **1a** was confirmed by means of mass spectrometry.

A sequential mechanism involving initial formation of tetraphenyloxirane (**5**) might be invoked to explain the photolysis of **1a** and would appear to be a reasonable proposal in light of the previously reported thermolytic conversions of carbonates to oxiranes[19,20] and the known photolability of the latter, which are excellent carbene precursors.[10] No tetraphenyloxirane (**5**) could be detected by TLC among the photoproducts obtained from **1a** in methanol even under conditions where conversion levels were minimal (10–15%). It is clear from calculations based upon the relative extinction coefficients and comparative fragmentation rates that shielding of the oxirane **5** by **1a** should be efficient enough to ensure buildup of detectable levels of **5**. For this reason a concerted cycloelimination mechanism is preferred for **1a** although a stepwise homolytic or ionic fragmentation process which circumvents formation of the oxirane **5** cannot be excluded at this time. Benzopinacol carbonate, like tetraphenyloxirane (**5**) and benzopinacol sulfite, proved photostable when irradiated in a Pyrex vessel at a longer wavelength (350 nm).

In order to evaluate the generality of the carbonate cycloelimination reaction the photochemistry of *meso*- and *dl*-hydrobenzoin carbonates (**1b** and **1c**, respectively) was also studied. The synthesis of the phenylcarbene precursors **1b** and **1c** (48 and 54%, respectively) was realized by treatment of *meso*- and *dl*-hydrobenzoin (**6b** and **6c**, respectively), with either phosgene or diethyl carbonate[14,15] (eq 4).



(4)

6b, $R_1 = Ph$; $R_2 = H$
c, $R_1 = H$; $R_2 = Ph$

1b, $R_1 = Ph$; $R_2 = H$
c, $R_1 = H$; $R_2 = Ph$

Phenylcarbene, the anticipated transient from **1b** and **1c**, has previously been characterized extensively and the ground state, like that of diphenylcarbene, has been desig-

nated as triplet on the basis of EPR and optical emission studies.[10,13] The EPR spectrum, which should be very sensitive to the geometry of phenylcarbene, has been shown to be independent of the structure of the precursor in several cases including the diazo compound, a geminal diazide, and benzaldehyde *p*-toluenesulfonylhydrazone in a variety of environments indicating that the observed structure is an intrinsic property of the carbene.[21,22] The emission spectrum of phenylcarbene also has been observed in a hydrocarbon matrix at −196°.[10] Extended Hückel calculations by Hoffmann and co-workers[23] are also interpreted as supporting a ground state triplet structure for phenylcarbene.

Extensive effort has been devoted to characterization of the reactive state(s) of phenylcarbene. The chemical behavior of phenylcarbene generated photochemically from phenyldiazomethane,[24-26] phenyloxiranes and cyclopropanes,[27] and cyclic pinacol sulfites[2,4] appears to be that of a singlet and is independent of precursor in both C–H insertion and alkene addition reactions. It has been found that the stereospecificity of cyclopropanation is reduced and an increase in alkene formation occurs when the photolysis is conducted in frozen *cis*-2-butene matrices (−196°). Triplet phenylcarbene in rapid thermal equilibrium or formed by decay from the singlet has been advanced as the key intermediate in the low-temperature matrix experiments; i.e., the degree of stereospecificity of cyclopropanation decreases with a concomitant increase in abstraction recombination processes leading to alkenes as triplet phenylcarbene chemistry intervenes.[26a] Comparative studies of 2-*n*-butylphenylcarbene generated by triplet photosensitized and thermal decomposition of the corresponding diazo compound have also been conducted and no significant difference in behavior was discerned between the carbenes generated from the two sources.[25c] To explain this observation it was proposed that singlet and triplet phenylcarbene equilibrate with each other more rapidly than they undergo C–H insertion or C=C addition reactions. In fact there appears to be a growing conviction that a facile equilibrium exists between triplet and singlet phenylcarbene.[26b]

Upon photolysis (254 nm) both *meso*- and *dl*-hydrobenzoin carbonates (**1b** and **1c**, respectively) give a species which exhibits the reactions anticipated for phenylcarbene, namely, insertion into saturated carbon–hydrogen bonds such as those of cyclohexane to give benzylcyclohexane (**7**) (eq 5),[25] addition to *cis*-2-butene to give the syn and anti cyclopropanes 8a and **8b**, respectively (eq 6),[24,28] and reaction with methanol to yield benzyl methyl ether (**9**) (eq 7).[11] Other products resulting from the fragmentation of **1b** and **1c** include benzaldehyde and carbon dioxide. The substrates **1b** and **1c** like **1a** were found to be photostable when irradiated with a lower energy source (>300 nm) in a Pyrex vessel and complete recovery of the starting material was achieved in both cases.

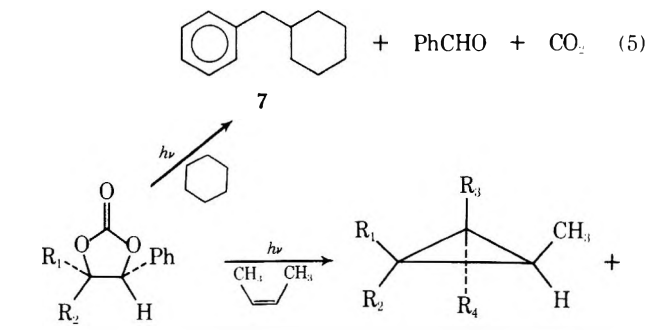
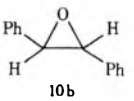
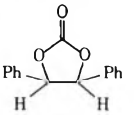
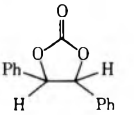
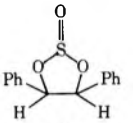
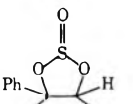


Table I
Insertion Selectivity of Phenylcarbene Generated from Diverse Sources

Phenylcarbene precursor	Yield, % (25 min, 8 lamps) 254 nm	Insertion ratio (11 + 12)/13	Insertion ratio[a] 11/12
 10b	45.4	8.33 ± 0.14[b]	1.35 ± 0.04
 1b	3.8	8.47 ± 0.20	1.42 ± 0.03
 1c	5.2	8.27 ± 0.23	1.42 ± 0.03
 14	5.5	8.48 ± 0.24	1.41 ± 0.05
 15	6.6	8.00 ± 0.18	1.45 ± 0.02
PhCHN2	18.3[c]	8.38 ± 0.19	1.33 ± 0.09

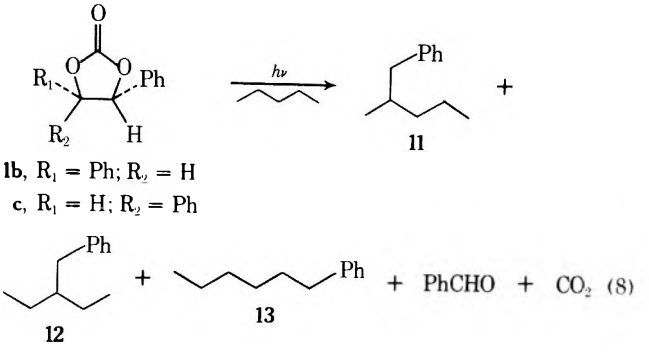
[a] Statistically corrected for the number of hydrogen atoms of each type. [b] Limits of error in each case represent standard deviations obtained by multiple integration of several chromatograms. [c] 350 nm, 16 lamps, 4 hr.

While irradiation (254 nm) of **1b** or **1c** in cyclohexane affords benzylcyclohexane (**7**) as well as benzaldehyde and carbon dioxide, it is significant that under the conditions employed for the photolysis no detectable amounts of the corresponding oxiranes, i.e., *cis*-2,3-diphenyloxirane (**10a**) and/or *trans*-2,3-diphenyloxirane (**10b**) in the case of **1b** and **1c**, were observed by TLC or ^{1}H NMR techniques. Competitive rate studies of the photofragmentation of **1c** and *trans*-2,3-diphenyloxirane (**10b**) in cyclohexane confirm that the initial oxirane cycloelimination rate exceeds that of **1c**. The faster rate observed for oxirane photolysis may be attributed in large measure to the differences in strain and extinction coefficients for the two substrates at 254 nm; however, the latter is not sufficiently great to allow **10b**, if formed as an intermediate, to escape detection.

Although it is apparent from the chemical data that both **1b** and **1c** undergo [5 → 2 + 2 + 1] cycloelimination reactions to produce "free" carbene, the characteristic phenylcarbene EPR signal could not be observed upon photolysis of these substrates for reasons yet undetermined.[29] Similar results were observed for *trans*-2,3-diphenyloxirane (**10b**) and triphenyloxirane where no EPR signal was detected for phenylcarbene despite convincing chemical evidence for its formation.[27] In the absence of direct EPR and/or optical spectroscopic data, it was necessary to obtain further chemical proof for the contention that **1b** and **1c** are indeed phenylcarbene precursors.

Competitive insertion experiments prove particularly useful as a method for comparing divalent carbon species generated from different sources such as **1b** and **1c**. Gutsche and co-workers[25] have previously determined the insertion selectivity of phenylcarbene generated from the conventional precursor phenyldiazomethane. Additional data on the selectivity of this carbene formed from a variety of other precursors including the oxirane **10b** have been reported by Griffin and co-workers.[4,27] A similar study of the insertion selectivity of the species generated from the carbonates **1b** and **1c** was initiated in connection with present work.

Solutions of the carbonates **1b** and **1c** of equal concentration were made in *n*-pentane and photolyzed (254 nm) simultaneously under identical conditions using the "merry-go-round" technique to ensure uniform exposure. Insertion product ratios and absolute yields were determined gas chromatographically employing an internal standard and predetermined response factors. To ensure that the results obtained reflect initial insertion rates, relatively short irradiation times (25 min) were employed and the number of lamps in the light source was adjusted from 16 to 8 to reduce the light flux to the required level.



The results of the insertion studies conducted with the carbonates **1b** and **1c** are tabulated for comparison along with the corresponding data for the oxirane **10b**, the sulfites **14** and **15**, and phenyldiazomethane. In a typical experiment the three insertion products **11**, **12**, and **13** were obtained from *dl*-hydrobenzoin carbonate (**1c**) in the ratio of 6.12:2.16:1.00, respectively. The ratio of the combined amounts of 2- and 3-benzylpentanes **11** and **12**, respectively (formed by insertion into the six secondary C–H bonds) to 1-phenylhexane (**13**) (produced by attack at the six primary C–H bonds) was established as 8.27 ± 0.23 (see Table I). The ratio of 2- to 3-benzylpentane correspondingly is 2.84, which when statistically corrected gives a selectivity factor between secondary hydrogens of C_2H or C_4H over C_3H of 1.42.

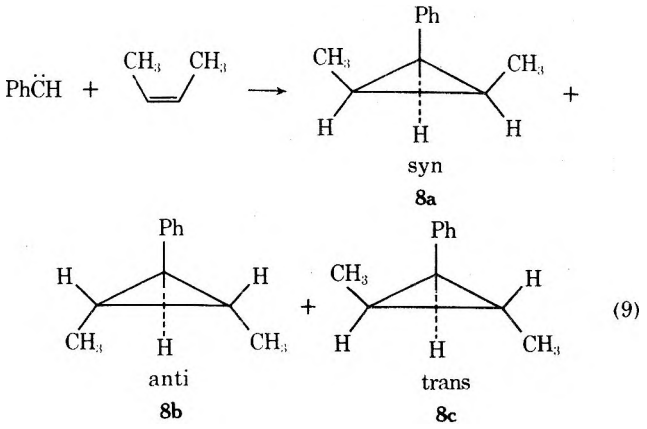
The results obtained in all cases substantiate the original proposal that the photolysis of cyclic carbonates does in fact give rise to species virtually indistinguishable chemically from those produced from conventional carbene precursors such as *trans*-2,3-diphenyloxirane (**10b**) and phenyldiazomethane. Higher yields are obtained with the oxirane **10b** and the diazo precursor (Table I), which indicates that their rate of fragmentation exceeds that of **1b** and **1c**. It remains to be determined if the quantum yield is higher for the former pair or if the difference in rate in only a reflection of their higher extinction coefficients. The carbonates presently under examination do afford significantly higher yields of insertion products upon prolonged irradiation and are of preparative value; however, determination of meaningful selectivity factors was, of course, of paramount importance in the present study, and photolyses were conducted at conversion levels only sufficient to permit reliable analyses to be conducted.

The stereochemistry of the cyclic carbonate precursors **1b** and **1c** exerts little or no influence upon the observed insertion selectivity factors, although the initial fragmentation rates for the *dl* isomer **1c** may be slightly higher. This is not unexpected in view of the higher extinction coefficient observed for this diastereomer at 254 nm.

Similar behavior was observed for the corresponding cyclic sulfites **14** and **15**. Analysis at low conversions (10%) where shielding of the alternate isomer if formed should be relatively effective shows that within the limits of detectability (^{1}H NMR and TLC) interconversion of the two diastereomers **1b** and **1c** does not occur. Furthermore, no fragmentation was observed when the carbonates **1b** and **1c** were irradiated in *n*-pentane at 350 nm for extended periods.

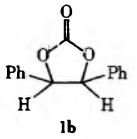
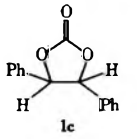
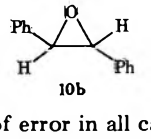
Whether a concerted or stepwise mechanism, perhaps involving the oxiranes, is operative remains to be established, although a stepwise mechanism circumventing the oxiranes is presently favored since neither *cis*- nor *trans*-2,3-diphenyloxirane (**10a** and **10b**, respectively) could be detected by TLC among the reaction products of either **1b** or **1c**.

Quantitative evaluation of the selectivity exhibited by phenylcarbene in the possible modes of addition to *cis*-2-butene has been widely employed as a sensitive method of comparing the properties of this species generated from different sources and for assessing the extent of triplet participation.[24,25,30] In order to complement our insertion studies we have conducted similar addition experiments with *cis*-2-butene using the cyclic carbonate precursors **1b** and **1c**. Solutions of known concentrations of **1b**, **1c**, and **10b** were irradiated in *cis*-2-butene at 254 nm. The photolysis mixtures were analyzed by GLC as described above for **11**, **12**, and **13**, and the isomeric cyclopropanes **8a–c** were identified by comparison of retention times with authentic samples obtained by preparative scale photolyses utilizing



trans-2,3-diphenyloxirane (**10b**) as the phenylcarbene source. The identities of the resulting isomeric cyclopropanes obtained from photolyses in *cis*- and *trans*-2-butene and separated by preparative GLC were readily established by comparison of ^{1}H NMR chemical shifts of the methyl protons which had previously been reported.[24] The addition studies using *cis*-2-butene were conducted using shorter irradiation times (9 min) than those employed in the C–H insertion reactions in order to preclude photoisomerization of the photolabile cyclopropanes and preserve product ratios which would in fact reflect the rates of the primary addition processes.[31,32,33] The reactions are highly stereospecific (>95%) in each case and from the results of the comparative studies delineated in Table II, it is clear

Table II
Stereoselectivity of Addition of Phenylcarbene from Diverse Sources to 2-Butene

Phenylcarbene precursor	Syn/anti ratio
 1b	1.18 ± 0.01[a]
 1c	1.19 ± 0.01
 10b	1.19 ± 0.01

[a] Limits of error in all cases are standard deviations based upon multiple integrations of several gas chromatograms.

that the stereochemistry of addition (syn/anti ratio) is essentially invariant regardless of source and agree with the results previously reported by Closs and Moss.[24]

The cycloaddition results coupled with the comparative C–H insertion data (vide supra) leave little doubt that a common intermediate is involved which we believe is "free" phenylcarbene on the basis of the insensitivity of chemical behavior on precursor structure. It is assumed that phenylcarbene is formed in the singlet state and adds to *cis*-2-butene faster than decay to the triplet ground state can occur. It appears, however, that a small amount of competitive intersystem crossing to triplet phenylcarbene must occur, since 2–5% of *trans*-2,3-dimethyl-1-phenylcyclopropane (**8c**) is produced in all cases studied. It is believed that this is a primary product of addition and not the result of isomerization since the major primary products, cyclopropanes **8a** and **8b**, were found to be stable to the reaction conditions provided that the irradiation times are not extended beyond the time employed (9 min).

While explanations may be advanced to account for the observed independence of C–H insertion and addition selectivity on the origin of the carbene, insufficient data are available to provide a definitive mechanistic interpretation for this behavior. It has been established in other systems (i.e., geminal diazide, diazo, and oxirane precursors) that there is sufficient freedom for carbene precursor geometries differing by 10° to yield the same final geometry,[21] although the proposition that the strained oxirane **10b** and the diazo precursor should give isoenergetic nascent carbene appears unreasonable to us. Equally unlikely we feel is the proposal that the insertion and addition reactions are insensitive to energetic factors, although it may be argued that thermal equilibration to a common vibrational level of the same state occurs prior to insertion or addition. Certainly if equilibration of the singlet and triplet states of phenylcarbene occurs more rapidly than insertion and addition, as has been proposed,[25c] then the product distribution would not reflect the properties of the nascent carbene.

A study of the photolability of the acetophenone pinacol carbonates **1d** and **1e** has also been conducted and on the basis of preliminary photolysis experiments (254 nm) it is clear that both the meso and *dl* isomers (**1d** and **1e**, respectively), like the corresponding sulfites,[4] undergo [5 → 2 + 2 + 1] photocycloelimination to give methylphenylcarbene.[34] The requisite *meso*- and *dl*-α,α'-dimethylhydrobenzoin carbonates (**16** and **17**, respectively) were prepared by treatment of the corresponding hydrobenzoins with diethyl carbonate[15] and phosgene,[14] respectively. Irradiation of **1d** or **1e** in methanol affords α-phenethyl methyl ether (20%) and acetophenone identified by GLC analysis using enrichment techniques with authentic samples. Additional evidence that the photolysis of **1d** and **1e** affords methylphenylcarbene was obtained by photolysis (254 nm) of these carbonates in cyclohexane, whereupon α-methylbenzylcyclohexane is produced. A more detailed comparative study of the photochemistry of **1d** and **1e** as well as the corresponding sulfites and isomeric 2,3-diphenyl-2,3-dimethyloxiranes, which are all methylphenylcarbene precursors, is in progress.

Experimental Section

Apparatus. Irradiation were conducted in serum-capped 15 cm × 12.6 mm i.d. fused quartz tubes (unless otherwise specified) in an air-cooled Rayonet RPR-100 chamber reactor (The Southern New England Ultraviolet Co., Middletown, Conn.) utilizing the stated number of G8T5 (254 nm) or F8T5/BLB (350 nm) 8-W low-pressure lamps at a temperature of approximately 40°. All samples were degassed by nitrogen sparging for at least 10 min prior to irradiation. A Rayonet MGR-100 merry-go-round apparatus (The Southern New England Ultraviolet Co., Middletown, Conn.) was employed in all kinetic studies to ensure uniform radiation of the individual samples which were rotated at 5 rpm during the course of photolysis. The quartz tubes used in all kinetic investigations were fabricated from a single length of 12.6 mm i.d. fused quartz tubing to ensure that the vessels used in any given run had identical properties. Several additional precautions were taken in all kinetic investigations; the solutions involved were thermally equilibrated to 25° in a water bath, and the ultraviolet lamps and chamber reactor were allowed to stabilize for a 10-min period prior to sample insertion.

Analytical gas chromatograms were obtained on either Perkin-Elmer Model 810 or Model 900 gas chromatographs equipped with flame ionization detectors. Support-coated open tubular (SCOT) capillary columns proved particularly effective in the isomer separation problems encountered in this study. Absolute yields were obtained by determination of the gas chromatographic response factors utilizing authentic mixtures of known concentration of an internal standard (phenylcyclohexane or *n*-amylbenzene) and authentic samples of the reaction products. All lamp emission spectra were determined on an Aminco-Bowman spectrophotofluorimeter.

The proton magnetic resonance spectra were determined on a Varian A-60 ^{1}H NMR spectrometer with 1% tetramethylsilane as an internal standard. A Hitachi Perkin-Elmer RMU-6E mass spectrometer was used for all mass spectral analyses. Ultraviolet absorption spectra were recorded on a Cary Model 15 spectrophotometer in rectangular cells of 1 cm path length with flat optical quartz or Suprasil windows. All melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Silica gel G (PF_{254}) on glass plates was used for thin and thick layer chromatographic separations. Resolution was confirmed by exposure of the chromatogram to short-wavelength ultraviolet light (Blak-Ray UVL-21) and/or developed in iodine vapor. Liquid–liquid partition chromatographic separations were obtained on a 164 cm × 42 mm i.d. glass column utilizing Celatom Filter Aid as the solid support; the column eluents were monitored on a Perkin-Elmer Model 202 ultraviolet–visible spectrometer and fractions were collected with an automatic fraction collector.

Preparation of Benzopinacol Carbonate (1a). The method used for the preparation of **1a** is a modification of that employed by Mosher, Steffgen, and Lansbury.[15] A solution of 95 ml of acetic acid and 75 ml of acetic anhydride which contained a 2.00-g (6.05 mmol) sample of tetraphenylethylene was treated with 1.21 g (12.0 mmol) of chromium trioxide in the presence of 5.86 g (60 mmol) of potassium acetate. The crude product mixture deposited upon addition of 200 ml of water, and the compounds were separated by thick layer chromatography using a solvent system of 4:1 benzene–carbon tetrachloride. The carbonate was collected on a filter and recrystallized from aqueous ethanol to give 410 mg (17%) of benzopinacol carbonate (**1a**), mp 170–171° (lit.[16] mp 170–171°).

Preparation of Tetraphenyloxirane (5). To a stirred solution of 4.00 g (1.21 × 10^{-2} mol) of tetraphenylethylene in 140 ml of

chloroform was added 2.67 g (1.32×10^{-2} mol) of solid *m*-chloroperbenzoic acid (85%) while the temperature was maintained at 20° with a water bath. The resulting mixture was stirred at room temperature overnight, and the disappearance of tetraphenylethylene was monitored by TLC utilizing an eluent mixture of benzene–carbon tetrachloride (4:1). Upon completion of the reaction, the excess peracid was destroyed by slow addition of sufficient 10% aqueous sodium sulfite solution to render the solution neutral to starch–iodide paper. The mixture was then transferred to a separatory funnel and washed repeatedly with 10% aqueous sodium bicarbonate solution. The organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The resulting residue was recrystallized from methanol and 2.61 g (62%) of tetraphenyloxirane (**5**), mp 204–205° (lit.[35a] mp 204–205°, 208–210° [35b]) was obtained.

Preparation of Benzhydryl Methyl Ether (3). The desired ether **3** was prepared from benzhydrol by a modification of the method outlined by Gillis[36] and the procedures are described in detail elsewhere.[4] Purification of **3** was achieved by distillation under reduced pressure, bp 105–106° (4 mm) [lit.[37] 146–148° (12 mm)].

Relative Rates of Formation of Diphenylcarbene from Benzopinacol Carbonate (1a) and Tetraphenyloxirane (5). In each of two identical clear fused quartz tubes was placed 2.47×10^{-2} mmol of the compound to be irradiated [9.70 mg of benzopinacol carbonate (**1a**) or 8.61 mg of tetraphenyloxirane (**5**)]. A 10-ml aliquot of anhydrous methanol containing 2.18×10^{-3} g (1.36×10^{-5} mol) of phenylcyclohexane was added to each tube by means of a 10-ml volumetric pipet. The tubes were sealed, degassed by nitrogen sparging, equilibrated at 25° in a water bath, and irradiated for a total of 14 min using eight G8T5 low-pressure mercury lamps. Aliquots (3 ml) of the solutions under study were withdrawn by syringe during the photolysis after total exposure times of 4 and 9 min. The resulting solutions were concentrated under reduced pressure and analyzed by GLC utilizing an Apiezon L SCOT 50 ft capillary column (The Perkin-Elmer Corp., Norwalk, Conn.) operated isothermally at 200°. Enrichment techniques employing authentic samples of benzhydryl methyl ether (**3**) and the internal standard (phenylcyclohexane) permitted identification of the peaks in the resulting gas chromatograms. Multiple runs of each sample were made, and the requisite peak areas were determined by multiplication of peak height by peak width at one-half peak height. The peak areas due to **3** and phenylcyclohexane were tabulated and their ratios compared. Absolute yields were obtained by determination of the GLC response factors using known solutions of phenylcyclohexane and **3**. Subsequent TLC analysis (4:1 benzene–carbon tetrachloride) revealed that no detectable tetraphenyloxirane (**5**) was present in the carbonate photolysis mixture.

Irradiation of Benzopinacol Carbonate (1a) in Methanol. A 106-mg (2.72×10^{-4} mol) sample of benzopinacol carbonate (**1a**) was dissolved in 5 ml of methanol in a 15 cm × 24 mm i.d. clear fused quartz tube which had been modified to accept an aerosol compatibility head assembly[38] or alternatively a Griffin-Worden pressure vessel was employed.[39] The sample was then degassed using the freeze–thaw method prior to irradiation for 14 hr using 16 G8T5 low pressure mercury lamps. Upon completion of the photolysis, the gases evolved were examined mass spectrometrically, and found to contain a substantial amount of carbon dioxide. The mass spectrometer was calibrated against air prior to analysis of the effluent gases from the reaction mixture. The excess methanol was then removed under reduced pressure from the reaction mixture, and the resulting residue was separated by TLC utilizing an eluent mixture of 2:1 benzene–carbon tetrachloride. The following pure photolysis products were isolated, and are listed in order of decreasing R_f values: 9,10-diphenylphenanthrene (**4**, 10%) [spectroscopically identical with authentic sample prepared by photolysis (254 nm) of tetraphenylethylene in methanol[17]], benzhydryl methyl ether (**3**, 60%), and benzophenone (15%), both identical with authentic samples. No residual carbonate **1a** or tetraphenyloxirane could be detected by TLC [benzene–carbon tetrachloride (4:1)].

Irradiation of Benzopinacol Carbonate (1a) in Methanol at 350 nm. A 58-mg (1.4×10^{-4} mol) sample of benzopinacol carbonate (**1a**) was dissolved in 10 ml of methanol in a 15 cm × 1.8 cm i.d. Pyrex tube, and irradiated for 16 hr utilizing 16 F8T5/BLB low pressure mercury lamps (350 nm). Upon completion of the irradiation, the volatile solvent was removed under reduced pressure and subsequent analysis of the residue by infrared and TLC (4:1 benzene–carbon tetrachloride) confirmed that no detectable photoproducts were formed upon irradiation of **1a** under these conditions.

Preparation of *meso*-Hydrobenzoin (6b). *meso*-Hydrobenzoin was prepared by sodium borohydride reduction of benzil as described by Fieser.[40] The crude product was recrystallized from aqueous ethanol, mp 136–137° (lit.[40] mp 136–137°).

Preparation of *meso*-Hydrobenzoin Carbonate (1b). A modification of the procedure employed by Ludwig and Piech[14] for the preparation of cyclic 1,3-diol carbonate esters was utilized. A solution of 500 mg (2.33 mmol) of *meso*-hydrobenzoin (**6b**) in pyridine was placed in a three-necked round-bottom flask, equipped with a gas dispersion tube, thermometer, and an exhaust outlet. Phosgene was introduced slowly into the stirred solution which had been previously cooled to 15° at a rate sufficient to maintain the reaction temperature at approximately 35°. After an excess of phosgene had been added to the mixture, the reaction vessel was protected with a drying tube and the resulting solution stirred for 6 hr at room temperature. The system was subsequently flushed with nitrogen and the solvent and excess phosgene subsequently removed under reduced pressure while exercising the usual precautions for disposing of phosgene. The resulting residue was taken up in methylene chloride and washed twice with water and once with a saturated cupric nitrate solution. The resulting organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure. Recrystallization of the residue from aqueous ethanol afforded 270 mg (48%) of pure *meso*-hydrobenzoin carbonate (**1b**), mp 126–127° (lit.[15] mp 127°).

Preparation of *dl*-Hydrobenzoin (6c). The compound was prepared by an adaptation of the method described by Berti and Bottari.[41] *trans*-2,3-Diphenyloxirane (**10b**) was treated with trifluoroacetic acid to give the monoester, which was then treated with ethanolic potassium hydroxide according to the procedure outlined by Jenevein.[42] Isolation of the crude product and subsequent recrystallization from heptane yielded the desired *dl*-glycol **6c**, mp 120–121° (lit.[42] mp 120–121°).

Preparation of *dl*-Hydrobenzoin Carbonate (1c). An aliquot (4.0 g) of a solution of phosgene in benzene (12.5%) was added slowly with stirring to a solution containing 500 mg (2.30 mmol) of *dl*-hydrobenzoin (**6c**) and 460 mg (5.80 mmol) of pyridine in 25 ml of anhydrous benzene. The rate of addition was controlled to maintain the temperature of the reaction mixture between 30 and 35°. After addition was completed, the resulting mixture was stirred overnight and the crude carbonate **1c** was isolated in a manner identical with that described for the meso isomer and recrystallized from aqueous ethanol to give 300 mg (54%) of *dl*-hydrobenzoin carbonate (**1c**), mp 110.0–110.5° (lit.[43] mp 110°).

Preparation of *trans*-2,3-Diphenyloxirane (10b). The procedure used was identical with that previously described for the preparation of tetraphenyloxirane (**5**). A 6.0-g (33 mmol) sample of *trans*-stilbene upon treatment with *m*-chloroperbenzoic acid afforded 4.12 g (63%) of *trans*-2,3-diphenyloxirane (**10b**), mp 69–70° (lit.[35b] mp 69–70°).

Preparation of Phenyldiazomethane. Phenylhydrazone was prepared by treatment of benzaldehyde with hydrazine hydrate and barium oxide according to the method outlined by Curtius and Pflug.[44] Yellow mercuric oxide was added to the phenylhydrazone in pentane as described by Staudinger and Gaule,[45] and the resulting suspension shaken for 3 hr. The mixture was then filtered, and the volatile solvents removed under reduced pressure to give the desired reddish-brown phenyldiazomethane, which was prepared freshly and used immediately in all experiments.

Preparation of Benzyl Methyl Ether (9). The ether **9** was prepared by an adaption of the method outlined by Gillis[36] and employed for benzhydryl methyl ether **3** and has been described previously.[4] Distillation at atomospheric pressure gave the pure benzyl methyl ether (**9**), bp 169–170° (lit.[46] bp 170°).

Irradiation of *meso*- and *dl*-Hydrobenzoin Carbonates (1b and 1c, respectively) in Methanol at 254 nm. The carbonates **1b** and **1c** were irradiated in methanol under conditions described for the photolysis of benzopinacol carbonate in methanol. The resulting products, benzyl methyl ether (**9**) and benzaldehyde, were identified by GLC using enrichment techniques.

Irradiation of *meso*- and *dl*-Hydrobenzoin Carbonates (1b and 1c, Respectively) at 350 nm. In two 15 cm × 18 mm i.d. Pyrex tubes were placed 50 mg (2.1×10^{-4} mol) samples of the *meso*- and *dl*-hydrobenzoin carbonates (**1b** and **1c** respectively) in 10 ml of methanol. The solutions were irradiated using 16 F8T5/BLB mercury lamps (350 nm) for a period of 14 hr. Removal of the volatile solvent under reduced pressure and subsequent infrared and TLC [benzene–carbon tetrachloride (4:1)] analyses of the resi-

due revealed that **1b** and **1c** are photostable under these conditions.

Preparation of Benzylcyclohexane (7). Benzylcyclohexane was prepared as described earlier[4] by treatment of cyclohexanone with benzylmagnesium bromide to give the 1-benzylcyclohexanol,[47] which was subsequently dehydrated with iodine in toluene and then hydrogenated using palladium on charcoal as a catalyst. Purification was achieved by distillation, bp 141° (26 mm) [lit.[48] bp 132° (19 mm)].

Relative Rates of Formation of Phenylcarbene from *dl*-Hydrobenzoin Carbonate (1b) and *trans*-2,3-Diphenyloxirane (10b) in Cyclohexane. In each of two identical, clear fused quartz tubes was placed 4.07×10^{-2} mmol of the compound under investigation [9.80 mg of *dl*-hydrobenzoin carbonate (**1b**), or 8.81 mg of *trans*-2,3-diphenyloxirane (**10b**)]. A 10-ml aliquot of cyclohexane containing 2.16 mg (1.35×10^{-2} mmol) of phenylcyclohexane was transferred to each tube by means of a 10-ml volumetric pipet. The tubes were degassed, sealed, and photolyzed using the "merry-go-round" technique for a total of 7 min utilizing four G8T5 8-W low-pressure mercury lamps. Irradiations were interrupted after total exposure times of 1 and 4 min, and 3-ml aliquot samples were withdrawn with a syringe as previously described. The samples were concentrated under reduced pressure, and analyzed by GLC using a single DC-550 SCOT 50 ft capillary column operated isothermally at 150°. Enrichment techniques employing authentic samples of benzylcyclohexane (**7**) and the internal standard (phenylcyclohexane) permitted confirmation of the identity of these peaks in the resulting gas chromatograms. Multiple runs of each sample were made, and the requisite peak areas were obtained by multiplying peak height by peak width at one-half peak height. The peak areas due to **7** and phenylcyclohexane were tabulated and their ratios compared. Enhancement studies with authentic samples also demonstrated the presence of benzaldehyde and bicyclohexyl among the photolysis products of both the oxirane **10b** and the carbonate **1b.** Subsequent TLC analysis [benzene–carbon tetrachloride (4:1)] revealed no photoisomerism of either **10b** or **1b** under the reaction conditions, and no detectable oxirane **10b** was found among the carbonate photoproducts.

Preparation of 2- and 3-Benzylpentane (11 and 12, Respectively). The synthesis of **11** and **12** was accomplished by techniques previously described in detail.[4] The requisite 1-phenylhexane (**13**) was purchased (Aldrich Chemical Co., Inc., Milwaukee, Wis.).

Insertion of Phenylcarbene Generated from Other Sources in *n*-Pentane. In each of four identical, fused quartz tubes was placed 3.30×10^{-2} mmol of the substrate to be studied. The specific amounts employed were as follows: 7.94 mg of *meso*-hydrobenzoin carbonate (**1b**), 7.93 mg of *dl*-hydrobenzoin carbonate (**1c**), 6.48 mg of *trans*-2,3-diphenyloxirane (**10b**), and 3.90 mg of phenyldiazomethane. A 10-ml aliquot of a 1.0×10^{-5} *M* solution of amylbenzene in *n*-pentane (99%) was transferred to each tube by means of a 10-ml volumetric pipet. The tubes were sealed, degassed by nitrogen sparging, equilibrated to 25° in a water bath, and irradiated for 25 min utilizing the "merry-go-round" technique with eight G8T5 low-pressure mercury lamps. A duplicate sample of phenyldiazomethane was irradiated for 4 hr utilizing 16 F8T5/BLB mercury lamps (350 nm). Upon completion of the irradiations, the samples were concentrated at room temperature under reduced pressure and analyzed by GLC. Satisfactory resolution of the resulting benzylpentanes, **11, 12,** and **13,** was obtained using a DC-550 SCOT 50 ft capillary column and temperature programming from 75° to 145° at 2°/min. The programmed temperature rise was begun simultaneously with sample injection, and the final temperature was held for 2 min upon termination of each run. Enrichment methods using authentic samples of each of the benzylpentane isomers **11, 12,** and **13** and the internal standard (amylbenzene) confirmed the identity of these peaks in the resulting gas chromatograms. Each sample was injected several times, and the resultant peak areas were obtained by multiplying peak height by peak width at one-half peak height. In this manner, the areas of the peaks corresponding to **11, 12,** and **13** and amylbenzene were determined and tabulated. The ratios of the isomers were calculated and compared for each separate carbene precursor. Absolute yields were obtained by determination of the GLC response factors utilizing standard solutions of amylbenzene and authentic samples of the reaction products. Further enhancement studies demonstrated that benzaldehyde is also present in the photolysis mixtures obtained from the oxirane **10b,** and both the carbonates **1b** and **1c.** Subsequent TLC analysis employing an eluent mixture of benzene–carbon tetrachloride (4:1) revealed that no photoisomerism to give the alternate isomer occurs with either the oxirane **10b** or the isomeric carbonates **1b** and **1c.** Furthermore, neither *cis*- nor *trans*-2,3-diphenyloxirane (**10a** and **10b,** respectively) was detected as a photoproduct of photolysis.

Preparation of *syn*-, *anti*-, and *trans*-2,3-Dimethyl-1-phenylcyclopropanes (8a, 8b, and 8c, Respectively). Authentic samples of the cyclopropanes **8a** and **8b** were prepared from *cis*-2-butene and phenylcarbene generated photochemically from *trans*-2,3-diphenyloxirane (**10b**). A 2.00-g (0.01 mol) sample of *trans*-diphenyloxirane (**10b**) was dissolved in 20 ml of *cis*-2-butene (99.91 mol %) and placed in a 15 cm × 24 mm i.d. quartz tube which had been modified to accept an aerosol compatibility head.[38] Alternatively a Griffin-Worden quartz pressure vessel may be used.[39] The head was secured and the solution degassed by the multiple "freeze–thaw" method prior to irradiation for 24 hr employing 16 G8T5 low-pressure mercury lamps. The excess *cis*-2-butene was then removed by short-path distillation and the residue subjected to preparative GLC using a 12 ft × 0.25 in. 10% Dow Corning silicone high vacuum grease on Chromosorb P column operated isothermally at 150°. Judicious collection procedures yielded two of the pure cis isomers with the following ^{1}H NMR spectral characteristics which agree with previously reported data:[24] syn [^{1}H NMR (CCl_4) τ 2.80 (s, 5, phenyl), 9.05 (s, 6, methyl)] and anti [^{1}H NMR (CCl_4) τ 2.92 (s, t, phenyl), 8.87 (s, 6, methyl)] (**8a** and **8b,** respectively). The mass spectra in both cases exhibited the expected molecular ion, *m/e* 146.

A sample of **8c** was obtained by a similar photolysis of *trans*-2,3-diphenyloxirane (**10b**) in *trans*-2-butene (99.63 mol %). Isolation procedures as outlined for **8a** and **8b** afforded the pure trans isomer **8c** [^{1}H NMR (CCl_4) τ 2.02 (s, 5, phenyl), 9.22 (d, 6, methyl)]. The mass spectrum of **8c** displayed the anticipated molecular ion, *m/e* 146.

Addition of Phenylcarbene Generated from Diverse Sources to *cis*-2-Butene. Irradiations were conducted in 150 × 24 mm i.d. fused quartz tubes which had been modified to accept an aerosol compatibility head assembly[38] or alternatively in a Griffin-Worden pressure vessel.[39] The substrate to be photolyzed was placed in the quartz pressure tube, and the head secured prior to evacuation of the system. The assembly was then immersed in a dry ice–acetone bath, and sufficient *cis*-2-butene (99.91 mol %) was admitted by means of a coupling tube to obtain a solution which was approximately 5.0×10^{-3} *M*. The specific weights of the compounds employed follow: 15.32 mg (7.88×10^{-5} mol) of *trans*-2,3-diphenyloxirane (**10b**), 15.31 mg (6.40×10^{-5} mol) of *meso*-hydrobenzoin carbonate (**1b**), and 11.13 mg (4.65×10^{-5} mol) of *dl*-hydrobenzoin carbonate (**1c**). The solutions were degassed using the multiple "freeze–thaw" method, and irradiated for 9 min at 254 nm using eight G8T5 low-pressure mercury lamps. Upon completion of photolysis, the excess *cis*-2-butene was collected and subsequent GLC analysis revealed that no isomerization of this substrate had occurred under the reaction conditions. A 1-ml aliquot of a methylene chloride solution containing 0.543 mg (3.34×10^{-6} mol) of 1-phenylhexane was added to each reaction mixture by means of a 1-ml volumetric pipet. The reaction mixtures were then concentrated under reduced pressure and analyzed by GLC. Satisfactory resolution of the isomeric cyclopropanes formed during photolysis was acheived utilizing two DC-550 50 ft SCOT capillary columns in series, and temperature programming from 100 to 128° at 0.5°/min. The programmed temperature rise was begun simultaneously with sample injection. Sample enrichment techniques employing authentic samples of each of the isomeric 2,3-dimethyl-1-phenylcyclopropanes **8a, 8b,** and **8c** and the internal standard (1-phenylhexane) allowed identification of these peaks in the resulting gas chromatograms. Multiple runs of each sample were made, and the resulting peaks were sufficiently symmetrical to permit the peak areas to be determined by multiplication of peak height by peak width at one-half peak height. In this manner, the areas of the peaks corresponding to **8a, 8b, 8c,** and 1-phenylhexane were determined and tabulated. The ratios of the isomers were calculated and compared for each of the carbene precursors studied. Subsequent TLC analysis employing an eluent system of benzene–carbon tetrachloride (4:1) revealed that no isomerism of the oxirane substrate **10b** or carbonates **1b** and **1c** occurs under the reaction conditions. Furthermore, there was no evidence of the related *cis*- or *trans*-oxiranes (**10a** or **10b,** respectively) in either of the carbonate photolysis mixtures.

Preparation of *meso*-α,α'-Dimethylhydrobenzoin (16). The procedure reported by Stocker and co-workers involving the addition of 2 mol of methyllithium to benzil was utilized for the preparation of this diol.[49] Two recrystallizations of the crude product

from benzene–heptane provided *meso*-α,α'-dimethylhydrobenzoin (16), mp 120–121° (lit.[49] mp 120–121°).

Preparation of *meso*-α,α'-Dimethylhydrobenzoin Carbonate (1d). A solution of 500 mg (1.90 mmol) of *meso*-α,α'-dimethylhydrobenzoin (16) was heated under reflux with 10 mg (0.10 mmol) of sodium methoxide and 250 mg (2.10 mmol) of diethyl carbonate in 30 ml of anhydrous toluene for 2 hr following the method outlined by Sarel and co-workers.[15] The ethanol which is formed was distilled and collected. The toluene and excess diethyl carbonate were removed under reduced pressure, and the resulting residue was dissolved in methylene chloride and worked up in the manner previously described for **1b**. A total of 200 mg (99%) of *meso*-α,α'-dimethylhydrobenzoin carbonate (**1d**), mp 129–130° (lit.[16] mp 129.5–130°), was obtained.

Preparation of *dl*-α,α'-Dimethylhydrobenzoin (17). This pinacol was prepared by the addition of freshly distilled biacetyl to phenyllithium as outlined by Stocker and co-workers.[49] Several recrystallizations of the crude product from heptane were required to obtain the diol in the desired state of purity, mp 124–125° (lit.[49] mp 124–125°).

Preparation of *dl*-α,α'-Dimethylhydrobenzoin Carbonate (1e). The procedure used for the preparation of **1e** is a modification of that described by Ludwig and Piech.[14] A solution containing 1.12 g (4.60 mmol) of *dl*-α,α'-dimethylhydrobenzoin (17) and 0.90 g (11.6 mmol) of anhydrous pyridine in 30 ml of anhydrous benzene was placed in a three-necked round-bottom flask, and a 5.92-g aliquot of a cold solution of 12.5% phosgene in benzene was added dropwise at a rate sufficient to maintain the reaction temperature below 30°. The resulting mixture was stirred overnight and isolation achieved in the manner described previously for **1c**. A total of 0.41 g (37%) of the desired *dl*-α,α'-dimethylhydrobenzoin carbonate (**1e**), mp 119–120° (lit.[16] mp 120.5–121°), was obtained.

Irradiation of *meso*-α,α'-Dimethylhydrobenzoin Carbonate (1d) in Methanol. A solution of 0.027 mg (1×10^{-4} mol) of *meso*-α,α'-dimethylhydrobenzoin carbonate (**1d**) in 10 ml of methanol was degassed by nitrogen sparging and irradiated in a quartz tube (254 nm, Hanovia 250 W) for 2 hr. The reaction mixture was concentrated under reduced pressure and examined by GLC [2% OV-17 on Chromosorb W, ⅛ in. × 6 ft (6 mm × 2 m), 110°C]. Two products were observed and determined to be α-phenethyl methyl ether and acetophenone in the ratio of 2:1 The yield of α-phenethyl methyl ether was determined to be 20% using phenylcyclohexane as an internal GLC standard.

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Registry No.—**1a**, 15855-93-3; **1b**, 19456-17-8; **1c**, 28521-60-0; **5**, 470-35-9; **6b**, 579-43-1; **6b**, 655-48-1; **8a**, 7653-96-5; **8b**, 25181-26-4; **8c**, 7653-95-4; **10b**, 1439-07-2; **14**, 19455-94-8; **15**, 28521-61-1; tetraphenylethylene, 632-51-9; diphenylcarbene, 3129-17-7; *trans*-stilbene, 103-30-0; phenylcarbene, 3101-08-4.

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(9) Properly substituted 1,3-dioxoles also give carbenes upon photolysis through cycloeliminations of the [5 → 4 + 1] rather than [5 → 2 + 2 + 1] type. In this case it is the atom flanked by the oxygen atoms which is extruded in the divalent form. R. M. G. Nair, E. Meyer, and G. W. Griffin, *Angew. Chem.*, **80**, 442 (1968); *Angew. Chem., Int. Ed. Engl.*, **7**, 462 (1968).

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Kinetics and Mechanism of the Hydrolysis of 2,2,2-Trifluoro-*N*-(3-methyl-2-cyclohexenylidene)ethylamine—an α,β-Unsaturated Schiff Base

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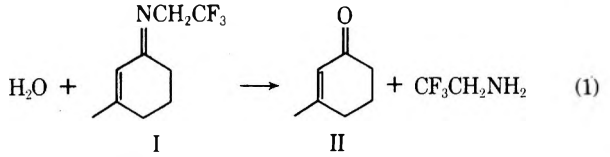
The kinetics of the hydrolysis of 2,2,2-trifluoro-*N*-(3-methyl-2-cyclohexenylidene)ethylamine (I) has been investigated in the range $H_0 = -1.5$ to pH 13 at 25°. The reaction rate is almost independent of pH from pH 0 to pH 13, varying by a factor of less than 3. We propose a mechanism involving rate-determining attack of water on protonated I (IH^+) at pH 0–7; at pH > 7 attack of hydroxide ion on IH^+ is the slow step; and at $H_0 < 0$ breakdown of the carbinolamine is rate determining. Observed solvent isotope effects (k_{H_2O}/k_{D_2O}) of 2.44 (pH ~2) and 1.68 (pH 11–12) are consistent with this interpretation. Rates of hydrolysis for I are compared with those for a closely related β,γ-unsaturated Schiff base and found to be at least 300-fold slower at pH values near neutrality.

The kinetics of the formation and hydrolysis of Schiff bases has been investigated in detail in the last two decades and the general features of the mechanism are now well established.[1] However, virtually all of the work to date has dealt with Schiff bases derived from either aromatic or saturated aliphatic carbonyl compounds. In this report we describe the first detailed examination of the kinetics and mechanism of the hydrolysis of an α,β-unsaturated Schiff base, 2,2,2-trifluoro-*N*-(3-methyl-2-cyclohexenylidene)ethylamine (I).[2]



I II (1)

The mechanism of the hydrolysis of Schiff bases of α,β-unsaturated carbonyl compounds is of particular interest since α,β-unsaturated Schiff bases derived from enzymatic amine residues have been suggested to be involved in the mechanism of several enzymes, among them dehydroquinase,[4] 5-keto-4-deoxy-D-glucarate dehydratase,[5] and, possibly, maleylacetoacetate isomerase[6] and other isomerases.[7] In addition, compounds of this type are involved in the visual process[8] and perhaps in the NAD-mediated biological reduction of Δ^4-3-keto steroids.[9] Amine catalysis of elimination from β-acetoxy ketones,[10] β-ketol dehydration,[11] and isomerization of β,γ-unsaturated ketones[7,12] have also been shown to proceed through α,β-unsaturated imines.

Results

The hydrolysis of 2,2,2-trifluoro-*N*-(3-methyl-2-cyclohexenylidene)ethylamine (I) was studied from $H_0 = -1.59$ to pH 13.17 at 25.0° ($\mu = 1.0$). In the pH range 3.3–10.6, acetate, phosphate, or carbonate buffers were used to control the pH as appropriate; outside this range, NaOH, HCl, H_2SO_4, or $HClO_4$ were employed. At pH ≤8 the kinetics were monitored by observing the decrease in absorbance with time at 268 nm due to the loss of the protonated Schiff base; at pH >8 the change in absorbance was followed at 237 nm. Most reactions exhibited good pseudo-first-order kinetic behavior through at least 90% reaction.

The only *substantial* deviations from strict pseudo-first-order behavior occurred in HCl solutions in the pH range 0–3. It appeared that two exponential functions with similar time constants were needed to accurately describe the observed decay. Analysis of several runs using the observed infinity points showed initial rates about 10–20% higher than obtained by the best first-order fit to the entire curve. Conversely, analysis of only the last 30% reaction gave rate constants 10–15% lower than those calculated using all the experimental points. A possible explanation for this behavior is the existence of syn and anti forms of the protonated Schiff base (IH^+) which may hydrolyze at slightly different rates. We have previously shown[7] that the interconversion of these isomers is slow on the NMR time scale and it may also be nonnegligible under the conditions for hydrolysis. A similar explanation has been advanced to account for biphasic kinetics in the hydrolysis of *N*-methylacetimidates.[13] Since we were unable to separate the two decay processes, we used the computer calculated rate constants for the entire reaction (standard deviations less than 2% in all cases).

The product was identified on the basis of the ultraviolet spectra. Uv spectra of several reaction mixtures taken after completion of the reaction showed a peak at 240 nm. An authentic sample of 3-methyl-2-cyclohexenone showed an absorbance maximum at 241 nm (ϵ 1.4 × 10^4). Routine checks of the infinity absorbance at 240 nm at various pH values indicated 85–95% conversion of I to II. The other 5–15% of material may be present as 3-hydroxy-3-methylcyclohexanone since α,β-unsaturated imines are known to be able to add water across the double bond.[11]

The rate of hydrolysis of I varies very little with pH throughout the entire range (Figure 1). The slight downward trend at about pH 6, however, suggests that the protonated Schiff base (IH^+) is the reactive species (pK_a of $IH^+ = 6.76$).[14] The independence of rate on pH above pH 8 could then be accounted for by reaction of hydroxide ion with protonated Schiff base. In the pH range 1 to 13, the observed pseudo-first-order rate constants were analyzed in terms of eq 2, where K_a is the acid dissociation constant

$$k^{obsd} = k^{H_2O} + k^{OH^-}[OH^-] + k^{B}[B]\left(\frac{[H^+]}{[H^+] + K_a}\right) \quad (2)$$

of protonated I and k^{H_2O}, k^{OH^-}, and k^B are rate constants for the reaction of IH^+ with water, hydroxide ion, and a general base, respectively. The previously measured value of 1.66×10^{-7} *M* was used for K_a. Both acetate and phosphate buffers strongly catalyze the reaction in their base forms but not as acids; carbonate buffers showed marginal catalytic ability. Analysis of the observed rate constants was performed in the usual manner by plotting $k^{corr} = k^{obsd}/[[H^+]/([H^+] + K_a)]$ vs. $[B]_{total}$ at constant pH. Intercepts of these plots gave the rate constant in the absence of buffer (k_0). Plots of k_0 vs. $[OH^-]$ gave $k^{OH^-} = 1.93 \pm 0.27 \times$

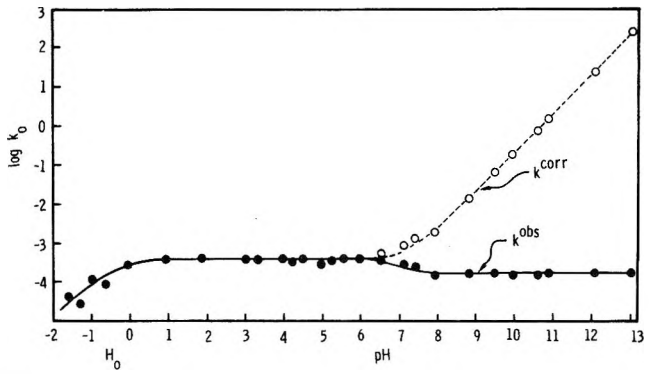


Figure 1. pH–rate profile for the hydrolysis of 2,2,2-trifluoro-*N*-(3-methyl-2-cyclohexenylidene)ethylamine at 25.0° in the absence of buffers. The actual observed rate constant is given by k^{obsd} and the observed rate constant corrected for the ionization of substrate (see text) is designated by k^{corr}. Below pH 6, k^{corr} and k^{obsd} are identical.

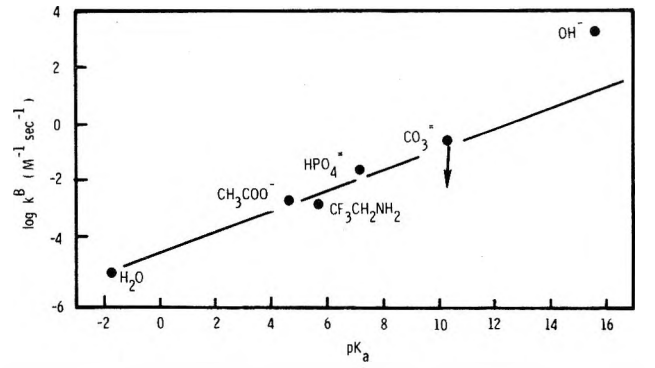


Figure 2. Bronsted plot of the catalytic constants for general-base-catalyzed attack of water on 2,2,2-trifluoro-*N*-(3-methyl-2-cyclohexenylidene)ethylammonium ion at 25.0°. The point for carbonate represents an upper limit.

10^3 M^{-1} sec^{-1} and k^{H_2O} = 3.55 ± 0.42 × 10^{-4} sec^{-1}. Values of k^B were obtained by plotting the slopes of the buffer plots vs. [B]/([B] + [BH^+]). Calculated values of these parameters are given in Table I. A Bronsted plot generated from these catalytic constants gives a reasonably good straight line with β = 0.4, although the point for hydroxide ion deviates from the line by about 3 log units (Figure 2).

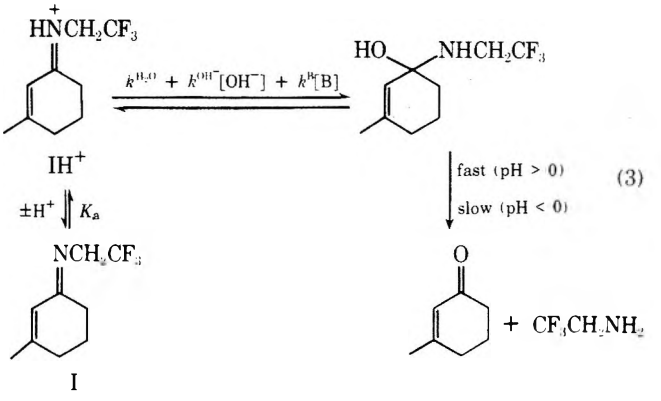
A plot of the corrected rate constants (k^{corr}) at zero buffer concentration is shown in Figure 1. Between pH 1 and 6, k^{corr} is independent of pH. At pH values greater than 6, the rate constant begins to increase with increasing pH, whereas at pH (H_0) < 0, k^{corr} falls off with increasing acid concentration in both sulfuric and perchloric acid solutions. These results suggest a change in mechanism at ca. pH 6 and a change in rate-determining step at ca. pH 0.

In addition to the kinetic measurements in water, rate constants were determined in deuterim oxide solutions of DCl, NaOD, and acetate buffers. The results for the unbuffered solutions are presented in Table II. In both acidic and basic solutions the rate constant is larger in water than in D_2O by a factor of about 2. The measured value of $k_{D_2O}^B$ for the acetate-catalyzed hydrolysis is 1.00 ± 0.12 × 10^{-3} M^{-1} sec^{-1}, giving an isotope effect for this process of $k_{H_2O}^B/k_{D_2O}^B$ = 2.2 ± 0.4.

Discussion

The general features of the kinetics of the hydrolysis of I in aqueous solution are very similar to those found previously for the hydrolysis of Schiff bases derived from aromatic or saturated aliphatic carbonyl compounds.[1,15-18] The rate of the reaction is proportional to the concentration of protonated Schiff base (IH^+) and shows rate terms in hydroxide ion (k^{OH^-}) and general bases (k^B) in addition to a spontaneous reaction rate (k^{H_2O}). The decrease in rate at pH (H_0) less than zero has precedent in the hydrolysis of other types of Schiff bases.

We interpret these kinetic results in terms of the same mechanism postulated earlier for the hydrolysis of Schiff bases of other carbonyl compounds (eq 3).[15-18] In the pH range 1–6, the rate-determining step is attack of water on the protonated Schiff base to give an intermediate carbinolamine which rapidly breaks down to products. This reaction is buffer catalyzed, probably involving true general base catalysis of attack of water on the iminium ion (eq 4). Support for this contention comes from the fact that catalysis by general bases occurs even with the completely protonated Schiff base, ruling out a mechanism involving hydroxide ion attack on I assisted by general acid protonation of the nitrogen.[16] The β of ca. 0.4 for this reaction is compa-



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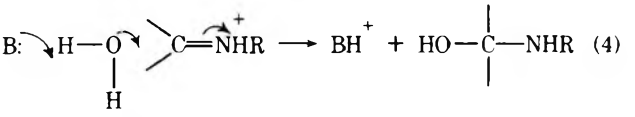


(4)

Table I
Catalytic Constants of Various Bases for the Hydrolysis of 2,2,2-Trifluoro-*N*-(3-methyl-2-cyclohexenylidene)ethylamine at 25.0° (μ = 1.0)

Base	pK_a	k^B, M^{-1} sec^{-1} [a]
H_2O	−1.7	6.40 ± 0.75 × 10^{-6} [b]
$CH_3CO_2^-$	4.7	2.15 ± 0.35 × 10^{-3}
$CF_3CH_2NH_2$	5.7	1.40 ± 0.23 × 10^{-3} [c]
$HPO_4^{=}$	7.2	2.88 ± 0.38 × 10^{-2}
$CO_3^{=}$	10.3	8.0 ± 5.0 × 10^{-2} [d]
OH^-	15.7	1.93 ± 0.27 × 10^3

[a] Rate constant for general-base-catalyzed attack of water on IH^+. No corrections for statistical factors are included; errors are standard deviations. [b] k^{H_2O} divided by 55.5 M. [c] Reference 7. [d] Upper limit.

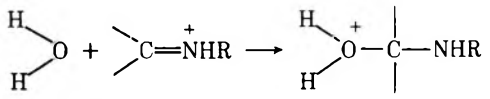
Table II
Solvent Isotope Effects on the Hydrolysis of 2,2,2-Trifluoro-*N*-(3-methyl-2-cyclohexenylidene)ethylamine

Solution	k^{obsd}, sec^{-1}	$k_{H_2O}^{obsd}/k_{D_2O}^{obsd}$
HCl–H_2O [a]	3.52 ± 0.06 × 10^{-4}	2.44
DCl–D_2O [b]	1.44 ± 0.03 × 10^{-4}	
NaOH–H_2O [c]	1.09 ± 0.03 × 10^{-4}	1.68
NaOD–D_2O [d]	6.50 ± 0.15 × 10^{-5}	

[a] Average of three runs at 10^{-3} to 10^{-1} M HCl. [b] Average of two runs at 1.95 × 10^{-2} and 3.90 × 10^{-2} M DCl. [c] Average of two runs at 10^{-2} and 10^{-3} M NaOH. [d] Average of two runs at 10^{-2} and 10^{-3} M NaOD.

rable to the Bronsted coefficient of 0.27 observed by Cordes for the analogous general-base-catalyzed attack of water on benzhydrylidenedimethylammonium ion.[17]

The solvent isotope effect, k^{H_2O}/k^{D_2O}, of 2.44 obtained for the pH-independent pathway may be compared with the value of 2.3 calculated from isotopic fractionation factors for the complete conversion of two LO bonds to two LO^+ bonds and one NH^+ bond to an NH bond.[19] The mechanistic implication of the close correspondence between the measured solvent isotope effect and the maximum calculated one, of course, is that the transition state

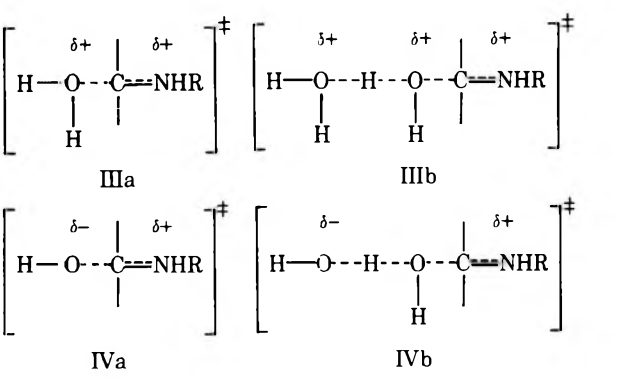


(5)

more closely resembles the protonated carbinolamine than the reactants. Cordes has come to a similar conclusion for the attack of water on the conjugate acids of substituted *N*-benzylidene-1,1-dimethylethylamines on the basis of measurements of secondary deuterium isotope effects.[20]

Above pH 6, attack of hydroxide ion on the protonated Schiff base becomes competitive with attack of water. Support for hydroxide ion acting as a nucleophile comes from the large positive deviation (ca. 10^3-fold) of hydroxide ion in the Bronsted plot. Although hydroxide ion often deviates in the Bronsted relationship,[21] a large positive deviation is usually considered to be evidence for nucleophilic attack.[22] A similar deviation of hydroxide ion from the Bronsted plot in Schiff base hydrolysis[17] has also been attributed to nucleophilic attack.[1] Further evidence for hydroxide ion as a nucleophile is seen in the measured solvent isotope effects for this reaction at high pH ($k_{OH^-}{}^{obsd}/k_{OD^-}{}^{obsd} = 1.68$). This number may be converted to a value for the isotope effect for direct attack of OH^- (OD^-) on the protonated Schiff base (k^{OH^-}/k^{OD^-}) by using the relationship $K^{H_2O}/K^{D_2O} = 3.4$ for nitrogen acids[19] and the difference in the autoprotolysis constants of water and deuterium oxide ($K_w{}^{H_2O}/K_w{}^{D_2O} = 7.5$).[23] Applications of these corrections gives $k^{OH^-}/k^{OD^-} = 0.8$, in agreement with the expected inverse isotope effect for nucleophilic attack of hydroxide ion. Calculation of the theoretical isotope effect for hydroxide ion attack on the protonated Schiff base gives a value of 0.5 for a transition state resembling the carbinolamine and 1.0 for one resembling reactants.[19] The observed value of 0.8 indicates that in the transition state the incipient carbon–oxygen bond is formed to a lesser extent for hydroxide ion as the nucleophile than for water attack. This interpretation is in accord with the conclusions of Cordes and Jencks[16] about the nature of the transition states for attack of water and hydroxide ion on substituted benzylidene-1,1-dimethylethylammonium ions. On the basis of substituent effects they concluded that the transition state for water attack on the iminium ion comes later along the reaction coordinate than the one for attack of hydroxide ion. However, more recent work of Cordes[20] using secondary isotope effects in this system indicates that both reactions have transition states with the carbon–oxygen bond almost fully formed.

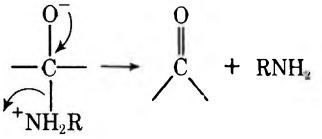
It should be pointed out here that our conclusions about the structure of the transition states involved rest on the assumption that no other water molecules participate in the actual attack of the nucleophile. In other words we are assuming that the transition states for attack of water and hydroxide ion look like IIIa and IVa, respectively, rather than IIIb and IVb, or some variation of them which may include more than one additional water molecule, although we have no evidence to bear on this question at present.



IIIa IIIb

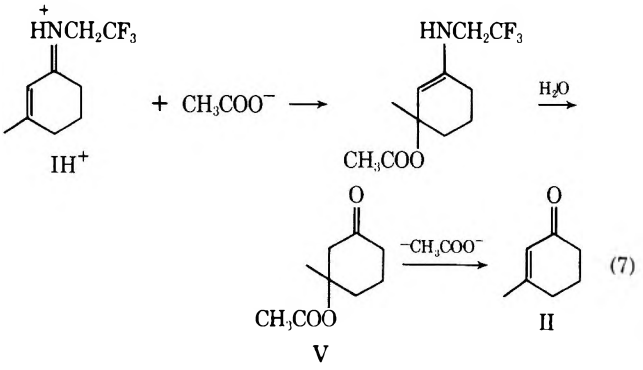
IVa IVb

The break in the pH–rate at pH 0 can be accounted for by a change in rate-determining step from formation of the carbinolamine at pH >0 to breakdown of the carbinolamine at pH (H_0) <0. This change in rate-determining step is generally observed in the hydrolysis of Schiff bases, although it usually comes at somewhat higher pH.[1] Base catalysis in more concentrated acid solution can be accounted for by invoking a zwitterionic carbinolamine intermediate which breaks down to products (eq 6), as has been suggested earlier.[1]



(6)

Although the above mechanism involving general-base-catalyzed attack of water on the protonated Schiff base is consistent with the experimental results and has ample precedent in the hydrolytic reactions of saturated Schiff bases, the existence of a conjugated double bond in I compels us to consider the possibility of an alternate mechanistic pathway. Specifically, buffer catalysis might occur by Michael addition to the α,β-unsaturated system, followed by hydrolysis of the enamine and elimination of the nucleophile (shown for acetate as the nucleophile in eq 7). An



(7)

analogous mechanism has been observed in the deamination of cytosine derivatives catalyzed by bisulfite ion.[24,25]

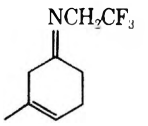
The observation of a substantial solvent isotope effect for the acetate-catalyzed hydrolysis ($k_{H_2O}{}^B/k_{D_2O}{}^B = 2.2$) suggests that nucleophilic catalysis is not operating. An isotope effect of this magnitude is indicative of a proton transfer in the rate-limiting step[19] and is generally interpreted to mean that general base catalysis is occurring.[26] In order to substantiate this conclusion, we synthesized the β-acetoxy ketone V and found that the rate constants for its conversion to the α,β-unsaturated ketone in 0.2 *M* acetate buffers (pH 3.35, 4.43, and 5.00) are at least 10^2-fold slower than the overall rate constants for acetate-catalyzed conversion of I to II in these buffers. Consequently, V cannot be an intermediate in the overall reaction, ruling out

nucleophilic catalysis at the carbon–carbon double bond, at least in the case of acetate ion.

Another alternative, direct nucleophilic attack on the carbon–nitrogen double bond of IH^+, may be discarded since it should show a kinetic solvent isotope effect of about 1.0. Furthermore, this mode of catalysis cannot be operating with trifluoroethylamine as a catalyst since the nucleophile in this case would be the same moiety as the leaving group.

The overall conclusion which can be drawn from the above discussion is that the hydrolytic behavior of α,β-unsaturated Schiff bases is very similar to that for Schiff bases derived from either aromatic or saturated aliphatic carbonyl compounds. There is, however, a quantitative difference in the rates of hydrolysis of I and saturated Schiff bases. Investigations of hydrolytic rates of saturated Schiff bases have shown that these reactions are generally very rapid, often in the stopped flow range,[18,27,28] substantially faster than what is observed for I. The structural dissimilarity of I and the previously investigated compounds, however, makes a direct comparison difficult.

In order to make a more valid comparison between the rates of hydrolysis of a saturated and an α,β-unsaturated Schiff base, we can estimate the rate of hydrolysis of 2,2,2-trifluoro-*N*-(3-methyl-3-cyclohexenylidene)ethylamine (VII) at several pH values. This compound differs from I



VII

only in the location of the double bond (β,γ rather than α,β). We have previously shown[7] that the trifluoroethylamine-catalyzed isomerization of 3-methyl-3-cyclohexenone to 3-methyl-2-cyclohexenone proceeds via formation of VII in a rapid reversible step followed by isomerization to I and subsequent hydrolysis. We can set a lower limit on the rate of formation of VII from trifluoroethylamine and 3-methyl-3-cyclohexenone by simply noting that this rate must be at least as fast as the overall reaction to the α,β-unsaturated Schiff base (I). At pH's 4.85, 5.77, and 6.90 with 0.5 *M* trifluoroethylamine buffer (pK_a = 5.77), the rate constants for formation of I are 4.6×10^{-3}, 1.4×10^{-2}, and 6.5×10^{-3} sec^{-1}, respectively.[7] Using an estimate for the equilibrium constant for Schiff base formation ($K \sim 0.1\ M^{-1}$),[29] we can calculate the following *minimum* rate constants for hydrolysis of VII in the presence of 0.5 *M* trifluoroethylamine buffer: 1.0 (pH 4.85), 5.6×10^{-1} (pH 5.77), and 1.5×10^{-1} sec^{-1} (pH 6.90). The corresponding rate constants for hydrolysis of I under these conditions are 4.2×10^{-4} (pH 4.85), 6.0×10^{-4} (pH 5.77), and 4.6×10^{-4} sec^{-1} (pH 6.90).[7] It can readily be seen that near neutral pH the β,γ-unsaturated Schiff base (VII) hydrolyzes more than 300-fold faster than the corresponding α,β-unsaturated isomer (I).

If one assumes a pK_a of 2.8[31] for $VIIIH^+$ (protonated VII), then minimum rate constants for the hydrolysis of $VIIIH^+$ in these buffers may be calculated to be 1.0×10^2 (pH 4.85), 5.6×10^2 (pH 5.77), and 1.5×10^3 sec^{-1} (pH 6.90). These results give a rate increase for hydrolysis of $VIIIH^+$ over IH^+ of ca. 10^6-fold under these conditions.[34] A large fraction (if not all) of this rate difference can be accounted for simply in terms of the relative pK_a's of the Schiff bases. The observed rate difference of ca. 10^6-fold for a difference in pK_a of the Schiff base of ca. 4 is similar to what was observed by Cordes and co-workers[17] for substituted benzylidene-1,1-dimethylethylamines. They found that the rate constant for attack of water on the cationic Schiff bases varies slightly more than a factor of 10 for each change of 1 pK_a unit in the protonated Schiff base, similar to what we observe for $VIIIH^+$ and IH^+.

Experimental Section

Materials. 2,2,2-Trifluoro-*N*-(3-methyl-2-cyclohexenylidene)-ethylamine was available from a previous study.[7] A 3.22×10^{-3} *M* stock solution in freshly distilled acetonitrile was prepared and stored under refrigeration. There was no indication of decomposition of the imine as evidenced from the initial absorbances obtained from the spectrophotometric kinetic curves. 3-Acetoxy-3-methylcyclohexanone (V) was synthesized by the following procedure which is analogous to that used by Spencer[10] for the synthesis of 9-acetoxy-10-methyl-*cis*-decalone-2.

3-Methyl-2-cyclohexenone Oxide. A solution of 10.0 g (91 mmol) of 3-methyl-2-cyclohexenone in 70 ml of methanol was cooled to 10° and 75 ml of cold 30% hydrogen peroxide was added. Then 35 ml of 3 *N* sodium hydroxide was added dropwise with stirring over 30 min, keeping the solution at about 10°. When addition was complete, the mixture was allowed to attain room temperature, and stirring was continued for an additional 30 min. The reaction mixture was then diluted with 200 ml of saturated NaCl solution and extracted with methylene chloride (5 × 50 ml). The organic fractions were combined, backwashed with saturated NaCl solution (2 × 100 ml), and dried over Na_2SO_4. The solvent was evaporated to yield 6.44 g (56%) of crude 3-methyl-2-cyclohexenone oxide: NMR ($CDCl_3$) δ 1.40 (s, 3, $-CH_3$), 2.96 (s, 1, –OCH-CO–).

3-Methylcyclohexane-1,3-diol. A solution of 6.44 g (51 mmol) of crude 3-methyl-2-cyclohexene oxide in 50 ml of dry tetrahydrofuran was added dropwise over 20 min to a stirred suspension of 5.0 g of lithium aluminum hydride (132 mmol) in 250 ml of ether. When addition was complete the reaction mixture was diluted with 250 ml of anhydrous ether and then stirred at room temperature for 15 min, followed by heating under gentle reflux for 3 hr. At the end of this time, the reaction mixture was cooled to 0° and 125 ml of saturated NaCl solution was slowly added to destroy the excess hydride. A saturated solution of Na_2SO_4 sufficient to form a clear supernatant ether–THF solution (ca. 200 ml) was then added. The organic layer was decanted, dried over $CaSO_4$, and the solvent evaporated to yield 3.23 g of crude product. The aqueous layer was continuously extracted with ether for several hours, the ether fraction dried over $CaSO_4$, and the solvent evaporated to yield 3.09 g (95% total yield) of crude 3-methylcyclohexane-1,3-diol: NMR ($CDCl_3$) δ 1.12 and 1.14 (s, 3 $-CH_3$).

1,3-Diacetoxy-3-methylcyclohexane. A solution of 5.62 g (43 mmol) of crude 3-methylcyclohexane-1,3-diol, 70 ml of isopropenyl acetate, and 15 mg of toluenesulfonic acid was heated under gentle reflux overnight. The reaction mixture was cooled to room temperature and then diluted with 500 ml of ether. The resulting solution was washed with 5% $NaHCO_3$ solution (2 × 250 ml) followed by saturated NaCl (2 × 250 ml). The organic fraction was dried over $CaSO_4$ and the solvent evaporated to yield 6.7 g of crude product. The aqueous washings were combined and back-extracted with ether (2 × 250 ml). These organic extracts were combined and dried over $CaSO_4$, and the solvent was evaporated to yield 0.7 g (80% total yield) of crude 1,3-diacetoxy-3-methylcyclohexane: NMR ($CDCl_3$ δ 1.44 (s, 3, $-CH_3$), 1.92 (s, 6, H_3CCOO-); ir (CCl_4) 1730 cm^{-1} (C=O), no detectable 3600-cm^{-1} (–OH) absorption.

3-Methyl-3-acetoxycyclohexanol. A solution of 1.0 g (25 mmol) of sodium hydroxide in 50 ml of water and 30 ml of methanol was added to a stirred solution of 5.41 g (25 mmol) of crude 1,3-diacetoxy-3-methylcyclohexane in 175 ml of methanol over 2 min at 0°. When addition was complete, the reaction mixture was stirred at 0° for 20 min, and then allowed to attain room temperature over about 40 min with continued stirring. At the end of this time the reaction mixture was diluted with 300 ml of ether. The resulting solution was washed with saturated NaCl (4 × 100 ml). The organic fraction was then dried over $CaSO_4$ and excess solvent was evaporated to yield 2.77 g of crude product. The aqueous washings were combined and back-extracted with ether (4 × 100 ml). These ether extracts were dried over $CaSO_4$ and the solvent was evaporated to yield 0.90 g (77% total yield) of crude 3-methyl-3-acetoxycyclohexanol: NMR (CCl_4) δ 1.42 (s, 3, $-CH_3$), 1.94 (s, 3, H_3CCOO); ir (CCl_4) 3600 (OH), 1725 cm^{-1} (C=O).

3-Methyl-3-acetoxycyclohexanone. Jones reagent[35] (6.0 ml, 24 mmol, [O]) was added to a stirred solution of 2.85 g (15 mmol) of crude 3-methyl-3-acetoxycyclohexanol in 100 ml of reagent-grade acetone at 0°. After 20 min at 0°, 60 ml of methanol was

added to quench the excess Jones reagent. The reaction mixture was then poured into 300 ml of saturated NaCl solution and extracted with methylene chloride (3 × 150 ml). The organic extracts were dried over $MgSO_4$ and the solvent was evaporated to yield 2.71 g (96%) of crude 3-methyl-3-acetoxycyclohexanone. Although the product β-acetoxy ketone could be separated from most of the impurities by GLC, it proved to have a retention time identical with that of the reactant, 3-methyl-3-acetoxycyclohexanol, on all columns which were tried. In order to eliminate this impurity, a mixture of 400 mg of crude product from above, 10 ml of isopropenyl acetate, and 3 mg of toluenesulfonic acid was heated at reflux for 3 hr to convert the remaining acetoxycyclohexanol to diacetate. Work-up in the usual manner gave 378 mg of crude material. Purification was effected by GLC (10% DC550 silicon on Chromosorb 60/80, acid washed, 5 ft × 0.25 in., 105°, flow rate 100 ml/min, retention time 14 min). This material showed no absorbance in the uv at 240 nm in water, but had a strong absorbance at 240 mn in 0.1 *N* NaOH (ε 13600) due to elimination to give II (ε 14000). On this basis, the product is ca. 97% pure: NMR (CCl_4) δ 1.48 (s, 3, $-CH_3$), 1.86 (s, 3, CH_3COO-), 2.27 [s, 2, $AcOC(CH_3)CH_2CO-$]; ir (CCl_4) 1740 and 1725 cm^{-1}.

Anal. Calcd for $C_9H_{14}O_3$: C, 63.51; H, 8.29. Found: C, 63.26; H, 8.34.

Kinetic Procedures. Distilled water was used for all kinetic runs. Deuterium oxide solutions were prepared using 99.87% D_2O. The deuterium chloride used was a 38% solution of DCl in D_2O containing 99% D, obtained from Stohler Isotope Chemicals. The sodium hydroxide-*d* used was a 40% solution in D_2O from Bio-Rad Laboratories. The ionic strength of all solutions was maintained at 1.00 with either 1.00 *M* NaCl or 1.00 *M* KCl solutions for aqueous solutions and 1.00 *M* NaCl in D_2O for deuterium oxide solutions. Buffers were reagent grade and used without purification. All kinetic measurements were carried out spectrophotometrically at 25.0 ± 0.1°C in a thermostated cell compartment of Gilford instruments, Model 2400 or 2400-2. pH measurements were made on a Radiometer Model 26 pH meter and spectra were obtained on a Cary Model 16K spectrophotometer. Kinetic runs were initiated by the addition of 5–20 μl of a stock solution of the imine in acetonitrile (ca. 10^{-2} *M*) to 3.0 ml of the solution in the cell compartment of the spectrophotometer. The reaction was monitored by following the disappearance of the protonated imine vs. time at 268 nm at low pH. At pH 8.75–13.0, the disappearance of the unprotonated imine was followed at 237 nm. Most reactions exhibited first-order behavior through at least 4 or 5 half-lives. All first-order rate constants were obtained by a nonlinear least-square regression analysis and linear plots were analyzed by a weighted least-squares program which assumed an equal percent error for all ordinate points. Standard deviations were, in most cases, less than 1% of the observed first-order rate constants except for the reactions in HCl solutions (pH 0–3) which showed kinetic behavior which was not *strictly* first order. Although these deviations were not large, it was apparent that the observed process was somewhat more complex (see Results).

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Registry No.—I, 57256-10-7; II, 1193-18-6; V, 57256-11-8; 3-methyl-2-cyclohexenone oxide, 21889-89-4; 3-methylcyclohexane-1,3-diol, 57256-12-9; 1,3-diacetoxy-3-methylcyclohexane, 57256-13-0; isopropenyl acetate, 108-22-5; 3-methyl-3-acetoxycyclohexanol, 57256-14-1.

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Azaindolizines. 3. Formylation Studies on 6-Azaindolizines

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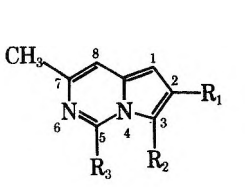
The Chichibabin reaction between an α-halo ketone and 4-methylpyrimidines has been used to synthesise the 6-azaindolizines (**2–5**); 2,4,6-trimethylpyrimidine has been shown to yield the 6-azaindolizine (**4**) rather than the reported isomeric 8-azaindolizine (**14**). The ^{1}H NMR spectra of the 6-azaindolizines (**1–6**) and the formyl-6-azaindolizines (**7–13**) have been elucidated. Vilsmeier formylation was shown to occur at C-3 and C-1; the 5,7-dimethyl-6-azaindolizines **4** and **5** yielded in addition to their formyl derivatives the 4-formyl-5-azacycl[3.2.2]azines **19** and **21**.

The 6-azaindolizines were synthesized by the Chichibabin procedure[1,2] which involved quaternization of 4,6-dimethyl- or 2,4,6-trimethylpyrimidine with phenacyl bromide, bromoacetone, or 3-bromobutanone followed by bicarbonate cyclization. 4,6-Dimethylpyrimidine can only give rise to a 6-azaindolizine whereas 2,4,6-trimethylpyrimidine may give either a 6- or an 8-azaindolizine depending on whether cyclization occurs via the 4- or 2-methyl groups, respectively. The ^{1}H NMR spectra of the azaindolizines are shown in Table I. The assignments of the ring and methyl hydrogen signals were made on the basis of the proximity of the protons to nitrogen, and also with the assistance of double irradiation. The C-1 and C-3 protons were readily identified[3,4] by deuterium exchange.[5]

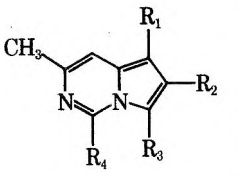
The Chichibabin reaction between 2,4,6-trimethylpyrimidine and phenacyl bromide has been reported by Ochiai[6] to give the 8-azaindolizine (**14**) together with a substituted pyrrole which was thought to be formed by breakdown of the isomeric 6-azaindolizine (**4**), and was assigned the acetonyl pyrrole structure (**15**). We have reinvestigated this reaction and have also obtained an azaindolizine and a small amount of a pyrrole derivative. This pyrrole and its *p*-nitrophenylhydrazone gave melting points consistent with those reported by Ochiai.[6] The pyrrole now has been shown to be 3-acetyl-2-methyl-5-phenylpyrrole (**16**), since its ^{1}H NMR spectrum indicated it to be trisubstituted containing a methyl group (δ 2.43, CH_3), a phenyl group (δ 7.04–7.56, C_6H_5), and an acetyl group (δ 2.59, $COCH_3$), and the position of the groups was established by an alternative Hantzsch synthesis between phenacyl bromide, acetylacetone, and ammonia. Presumably the pyrrole is formed in the Chichibabin reaction by interaction between phenacyl bromide and a degradation product from the pyrimidine or pyrimidinium nucleus.

The azaindolizine isolated by us forms a picrate the melting point of which is identical with that previously recorded.[6] Its ^{1}H NMR spectrum showed a complex multiplet (δ 7.20–7.70) due to the phenyl protons, two 3 H singlets (δ 2.34 and 2.64) both due to methyl protons, and three lower field 1 H singlets at δ 6.52, 6.88, and 7.34. By deuterium exchange[5] H-1 and H-3 were assigned as the 1 H singlets at δ 6.52 and 7.34, respectively; thus the 1 H singlet at δ 6.88 may be assigned to either H-6 of the 8-azaindolizine (**14**) or H-8 of the 6-azaindolizine (**4**). Sharpening of the signal at δ 6.88 only occurred by irradiation at the frequency of the higher field methyl signal at δ 2.34, assigned to the 7-methyl of structure **4**. Since in the 8-azaindolizine (**14**) both methyl groups would be expected to cause a sharpening of the signal at δ 6.88, the 6-azaindolizine structure (**4**) is preferred.

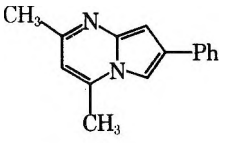
2,4,6-Trimethylpyrimidine has been shown to react analogously with bromoacetone to give a small amount of the acetyl pyrrole (**17**) and the corresponding 6-azaindolizine



	R_1	R_2	R_3
1	Ph	H	H
2	CH_3	H	H
3	CH_3	CH_3	H
4	Ph	H	CH_3
5	CH_3	H	CH_3
6	CH_3	CH_3	CH_3



	R_1	R_2	R_3	R_4
7	H	CH_3	CHO	H
8	H	CH_3	CHS	H
9	CHO	CH_3	CH_3	H
10	H	CH_3	CHO	CH_3
11	CHO	CH_3	CH_3	CH_3
12	CHO	CH_3	H	CH_3
13	CHO	Ph	H	CH_3



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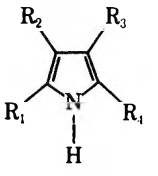
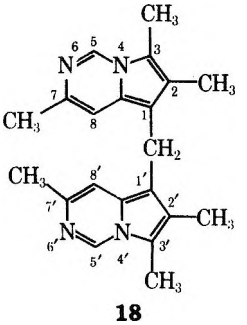


	R_1	R_2	R_3	R_4
15	H	Ph	H	CH_3COC
16	Ph	H	CH_3CO	CH_3
17	CH_3	H	CH_3CO	CH_3



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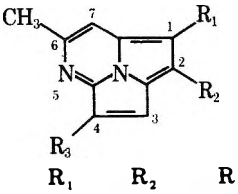
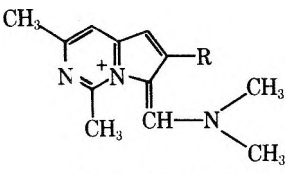
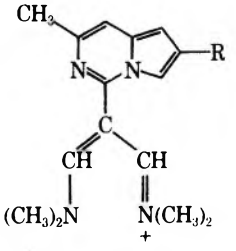


	R_1	R_2	R_3
19	H	Ph	CHO
20	H	Ph	H
21	H	CH_3	CHO
22	H	CH_3	H
23	CHO	Ph	H
24	CHO	CH_3	H



25, R = CH_3 or Ph



26, R = CH_3 or Ph

Table I[a]
Chemical Shifts (δ) in the 100-MHz ^{1}H NMR Spectra of 6-Azaindolizines 1–6 in $CDCl_3$

Structure	R_1	R_2	R_3	7-CH_3	H-1	H-8
1	7.30–7.70 (complex)	7.53	8.70	2.40	6.56	7.00
2	2.25	7.05	8.58	2.29	6.08	6.90
3	2.22	2.36	8.46	2.38	6.07	6.90
4	7.20–7.70 (complex)	7.34	2.64	2.34*	6.52	6.88*
5	2.30	6.94	2.62	2.36	6.13	6.85
6	2.16	2.60	2.86	2.28*	6.00	6.69*

[a] Unless otherwise stated values given refer to singlet absorption, d = doublet, complex = complex multiplet absorption. Coupling constants (hertz) are in parentheses; weakly coupled peaks indicated by double irradiation are marked by an asterisk.

Table II[a]
Chemical Shifts (δ) in the 100-MHz ^{1}H NMR Spectra of Formyl-6-azaindolizines 7–13 in $CDCl_3$

Structure	R_1	R_2	R_3	R_4	7-CH_3	H-8
7	6.23	2.54	9.85 (3-formyl)	10.26	2.60	7.16
8	6.35*	2.51*	10.71 (3-thioformyl)	11.63	2.53	7.24
9	10.6 (1-formyl)	2.43	2.43	8.63	2.51	7.80
10	6.26	2.45	9.97 (3-formyl)	2.98	2.59	7.00
11	10.02 (1-formyl)	2.39	2.66	3.01	2.42	7.73
12	10.06 (1-formyl)	2.51	6.95	2.74	2.49	7.74
13	9.98 (1-formyl)	7.36–7.60 (complex)	7.18	2.81	2.52	8.04

[a] See footnote *a*, Table I.

(5), but no identifiable products were isolated from the reaction with 3-bromobutanone. Further evidence that a 6- rather than an 8-azaindolizine was isolated from these Chichibabin reactions with 2,4,6-trimethylpyrimidine was obtained from formylation studies.

Vilsmeier formylation of 2,7-dimethyl-6-azaindolizine (2) gave either a formyl or thioformyl 2,7-dimethyl-6-azaindolizine depending on whether the reaction mixture was poured into sodium hydroxide or sodium hydrogen sulfide.[7] Comparison of the ^{1}H NMR spectrum of **2** with those of its formylated or thioformylated products indicates that reaction occurs at position 3, since the H-5, *not* the H-8, signals showed large peri shifts (168 and 305 Hz) due to the anisotropic deshielding effect of the 3-formyl and 3-thioformyl groups, respectively. The products must therefore have structures **7** and **8**. Furthermore, reduction of **7** with lithium aluminium hydride–aluminium chloride gave 2,3,7-trimethyl-6-azaindolizine (**3**) which was alternatively synthesized from 4,6-dimethylpyrimidine and 3-bromobutanone. Formylation of **3** gave 1-formyl-2,3,7-trimethyl-6-azaindolizine (**9**), as indicated by comparing the ^{1}H NMR spectrum of **9** with that of its precursor **3** (see Table II). Introduction of the 1-formyl group causes the disappearance of the H-1 singlet (δ 6.07) of **3** and a large downfield shift (90 Hz) in the position of the H-8 signal due to its peri orientation with respect to the formyl group. That C-1 substitution proceeds when the 3 position is blocked is also shown by the formation of the di-6-azaindolizylmethane (**18**) in the reaction of 2,3,7-trimethyl-6-azaindolizine (**3**) with formaldehyde. Compound **18** had no exchangeable hydrogens and its ^{1}H NMR spectrum was similar to that of its precursor (**3**) except that the lowest field aromatic singlet of **3** was no longer present and a new 2 H singlet at δ 3.97 due to the methylene protons appeared. These reactions showing formylation to occur preferentially at C-3[9] and then at C-1 agree in the main with theoretical calculations which point to the 3 and 1 positions as the preferred sites of electrophilic substitution.[10]

Formylation of 5,7-dimethyl-2-phenyl-6-azaindolizine (**4**) gave two aldehydes. The ^{1}H NMR spectrum of one was consistent with it being 1-formyl-5,7-dimethyl-2-phenyl-6-azaindolizine (**13**) showing a considerable peri shift of the H-8 proton (δ 8.04) with respect to the H-8 proton (δ 6.88) of the parent 6-azaindolizine (**4**). The other aldehyde has been shown to be 4-formyl-6-methyl-2-phenyl-5-azacycl[3.2.2]azine (**19**), since the 6-methyl-2-phenyl-5-azacycl[3.2.2]azine (**20**), synthesized by Boekelheide's 1,3-dipolar addition procedure,[2] gave on formylation approximately equal yields of the 1- and 4-formyl derivatives **23** and **19**. The interpretation of the ^{1}H NMR spectra of these cyclazines is shown in Table III. In structure **23** the two aromatic protons at C-3 and C-4 occur as doublets (J = 4.0 Hz) and the C-7 proton, because of its peri orientation to the formyl group and weak coupling to the 6-methyl group, occurs as a lower field broad singlet. Since the ^{1}H NMR spectrum of the other formyl derivative showed only singlets for the 1 H signals it must be either the 3- or 4-formyl-6-methyl-2-phenyl-5-azacycl[3.2.2]azine. As carbon protonation of **20**[2] has been inferred to occur at C-1 and C-4 we suggest that the formyl group is located at position 4. This is supported by the fact that the introduction of the formyl group into **20** does not result in a significant shift of the resonance position of the phenyl protons; and it is consistent with the recent results of Fuentes and Paudler.[11]

Unequivocal proof that a 6-azaindolizine (**5**) is indeed formed in the reaction of 2,4,6-trimethylpyrimidine with bromoacetone was obtained from the following reactions. Formylation of compound **5** gave the two formyl-6-azaindolizines **10** and **12** together with the 5-azacycl[3.2.2]azine **21**, the structures of which can be assigned on the basis of their ^{1}H NMR spectra. Reduction of compound **10** with lithium aluminium hydride–aluminium chloride gave the

Table III[a,b]
Chemical Shifts (δ) in the 100-MHz ^{1}H NMR Spectra of 5-Azacycl[3.2.2]azines 19–24 in $CDCl_3$

Structure	R_1	R_2	R_3	6-CH_3	H-3	H-7
19	7.42	7.30–8.06 (complex)	10.50 (4-formyl)	3.01*	8.37	7.67*
20	7.24	7.34–8.06 (complex)	7.20 (7.91) d, $J \simeq 4.0$Hz	2.93*	7.91 (7.20) d, $J \simeq 4.0$Hz	7.58*
21	6.98*	2.71*	10.49 (4-formyl)	2.99*	8.10	7.57*
22	6.81*	2.70*	7.10 (7.70) d, $J \simeq 4.0$Hz	2.93	7.70 (7.10) d, $J \simeq 4.0$Hz	7.52
23	10.22 (1-formyl)	7.48–7.92 (complex)	7.30 (7.86) d, $J \simeq 4.0$Hz	2.98*	7.86 (7.30) d, $J \simeq 4.0$Hz	8.20*
24	10.29 (1-formyl)	2.96	7.24 (7.82) d, $J \simeq 4.0$Hz	2.96	7.82 (7.24) d, $J \simeq 4.0$Hz	8.02

[a] See footnote *a*, Table I. [b] H-3 and H-4 δ values are tentative and are quoted in parentheses.

tetramethylazaindolizine (**6**) which could be further formylated. This formylazaindolizine showed the expected large peri shift of the one remaining aromatic proton (H-8, 104 Hz) with respect to the lowest field signal (H-8) of **6** and must therefore be 1-formyl-2,3,5,7-tetramethyl-6-azaindolizine (**11**). Finally, compound **10** on heating with solid potassium hydroxide afforded 2,6-dimethyl-5-azacycl[3.2.2]azine (**22**), which was also prepared by reaction of dimethyl acetylenedicarboxylate with 2,7-dimethyl-6-azaindolizine (**2**) followed by hydrolysis and decarboxylation.

There would appear to be two possible routes whereby the 4-formyl-5-azacycl[3.2.2]azine structures **19** and **21** could be formed from the 6-azaindolizines. Cyclization could occur through an intermediate cation such as **25**, formed by attack of the Vilsmeier electrophile[12] on the electron-rich C-3 site of the azaindolizine, followed by formylation of the resulting azacycl[3.2.2]azine. Alternatively attack by the electrophile[12] on the active 5-methyl group[13] of the azaindolizine could give an intermediate such as **26**[14] which on cyclization followed by hydrolysis would yield the 4-formyl-5-azacycl[3.2.2]azine. Presumably the formation of 3-formyl-2,5,7-trimethyl-6-azaindolizine (**10**) from **5** has occurred via cation **25** (R = CH_3), so that the 4-formylazacycl[3.2.2]azine (**21**) could be formed from **5** via this cation. However, formylation of 5,7-dimethyl-2-phenyl-6-azaindolizine (**4**) gave no 3-formyl derivative, suggesting that the access of the Vilsmeier electrophile to the C-3 site is hindered, and yet the 4-formylazacycl[3.2.2]azine **19** was isolated. This infers that the 4-formylazacycl[3.2.2]azines **19** and **21** are more likely to be formed through intermediate **26**. This inference is supported by the fact that formylation of the azacycl[3.2.2]azines **20** and **22** gave approximately equal mixtures of the corresponding 1- and 4-formyl derivatives together with unchanged azacyclazine, whereas formylation of the 6-azaindolizines **4** and **5** gave, inter alia, the 4-formyl-5-azacycl[3.2.2]azines **19** and **21** but no 1-formyl-5-azacycl[3.2.2]azines **23** and **24**; further no unformylated azacyclazines **20** and **22** were isolated.

Experimental Section

Melting points were determined by the capillary method and are uncorrected. Elemental analyses were performed by the analytical laboratories of Aberdeen University. Infrared spectra were measured for Nujol mulls with a Unicam SP200 spectrometer. Ultraviolet spectra were measured with a Unicam SP800 spectrometer. Light absorption data refer to solutions in ethanol, principal maxima are italicized, br = broad, infl = inflection. ^{1}H NMR 100-MHz spectra were recorded with a Varian HA-100D spectrometer using tetramethylsilane as an internal standard. Unless otherwise stated values given on the δ scale refer to singlet absorption, coupling constants in hertz, and integration values and signal assignment are in parentheses. For multiplets d = doublet, m = complex multiplet. Mass spectra were measured with an AEI MS30 spectrometer.

Procedures. Solutions were dried over anhydrous magnesium sulfate and solvents evaporated at reduced pressure on a rotary film evaporator. Column chromatography was carried out with Woelm neutral alumina. Thin layer chromatography was carried out on Merck Kieselgel GF_{254} using benzene–ethyl acetate (3:1) as eluent unless otherwise stated. Petroleum ether refers to the fraction bp 80–100° except when otherwise indicated.

The synthesis of 7-methyl-2-phenyl-6-azaindolizine (**1**) has been previously reported.[2] The following general procedure was used in the Chichibabin synthesis of **2,7-dimethyl- (2), 2,3,7-trimethyl- (3), 2,5,7-trimethyl- (5), and 5,7-dimethyl-2-phenyl-6-azaindolizine (4).** Deviations are given in individual cases. The α-bromo ketone was added to the pyrimidine in a small volume of ethanol. The solution was left overnight and if required the quaternization reaction completed by evaporating off the ethanol. Water was added to the resulting viscous oil. This was extracted several times with ether and warmed to remove the dissolved ether, before adding an excess of sodium hydrogen carbonate. After the effervescence had ceased, the resulting solution was steam distilled. The steam distillate was extracted several times with ether, the combined ether extracts were washed with water and dried, and the ether was evaporated to leave a crude residue of the 6-azaindolizine.

4,6-Dimethylpyrimidine (16.2 g, 0.15 mol) and bromoacetone (12.6 ml, 0.15 mol) gave **2,7-dimethyl-6-azaindolizine (2)** as a brown oil. This was taken up in petroleum ether and chromatographed on a short column (5 cm). Elution and evaporation gave a light brown solid which vacuum distilled at 160° (20 mm) to give 2,7-dimethyl-6-azaindolizine (**2**) as a cream, waxy solid (2.7 g, 10%), mp 63–65°, which darkened on standing: λ_{max} 291, 280 (br), 270 (infl), *239* nm (log ε 3.61, 3.57, 3.44, 4.31, respectively); ir 780, 860, 1240, 1615 cm^{-1}.

Anal. Calcd for $C_9H_{10}N_2$: C, 73.9; H, 6.9; N, 19.2. Found: C, 73.8; H, 7.2; N, 19.0.

4,6-Dimethylpyrimidine (21.6 g, 0.2 mol) and 3-bromo-2-butanone (21.4 ml, 0.2 mol) gave **2,3,7-trimethyl-6-azaindolizine (3,** 4.17 g, 15%) as a brown oil which solidified on cooling. Distillation at 100° (12 mm) gave **3** as yellow, waxy needles, mp 55–57°, which darkened slowly on standing: λ_{max} 293, 282, 272 (infl), *240* nm (log ε 3.76, 3.74, 3.73, 4.42, respectively); ir 760, 880, 1190, 1250, 1355, 1420, 1635 cm^{-1}.

Anal. Calcd for $C_{10}H_{12}N_2$: C, 75.0; H, 7.6; N, 17.5. Found: C, 74.7; H, 7.7; N, 17.2.

2,4,6-Trimethylpyrimidine (12.2 g, 0.1 mol) and bromoacetone (8.4 ml, 0.1 mol) gave the crude 2,5,7-trimethyl-6-azaindolizine (**5**) as a golden-brown oil. Distillation of this oil (20 mm) gave as the first fraction unreacted 2,4,6-trimethylpyrimidine (3.0 g). **2,5,7-Trimethyl-6-azaindolizine (5)** was then collected at 110° (2 mm) as a pale yellow oil (0.86 g, 6%) which slowly turned blue green on standing; λ_{max} 350 (br), 290, 279, 250 (infl), *235* nm (log ε 3.26, 3.92, 3.89, 3.97, 4.59, respectively); ir 770, 930, 1165, 1295, 1535, 1625 cm^{-1}.

Anal. Calcd for $C_{10}H_{12}N_2$: C, 75.0; H, 7.6; N, 17.5. Found: C, 74.8; H, 7.6; N, 17.3.

2,4,6-Trimethylpyrimidine (12.2 g, 0.1 mol) and phenacyl bromide (19.9 g, 0.1 mol) gave on evaporation of the ether extract from the aqueous bicarbonate solution a dark-colored liquid residue. This residue was distilled at 130° (5 mm) to give as the first fraction unreacted 2,4,6-trimethylpyrimidine (2.2 g). Distillation at 180–200° (1 mm) then gave **5,7-dimethyl-2-phenyl-6-azaindolizine (4)** as a yellow oil which solidified to a hard, compact

mass (1.5 g, 7%): mp 89–92° dec; λ_{max} 290 (infl), *257*, 212.5 nm (log ϵ 3.81, 4.61, 4.19, respectively); ir 690, 730, 770, 860, 1200, 1410, 1540, 1625 cm^{-1}.

Anal. Calcd for $C_{15}H_{14}N_2$: C, 81.2; H, 6.3; N, 12.6. Found: C, 81.5; H, 6.0; N, 12.3.

3-Acetyl-2,5-dimethyl- (17) and 3-acetyl-2-methyl-5-phenylpyrrole (16) were isolated from the reaction of 2,4,6-trimethylpyrimidine with bromoacetone or phenacyl bromide, respectively. The ether extracts of the aqueous solutions of the quaternary salts resulting from the reaction between 2,4,6-trimethylpyrimidine and the bromo ketone were evaporated to leave brown oils which, by TLC, gave the pyrrole which was finally recrystallized from petroleum ether.

3-Acetyl-2,5-dimethylpyrrole (17, 0.092 g) was obtained as white needles: mp 93–94°;[15,16] λ_{max} 294, *246* nm (log ϵ 3.77, 3.96, respectively); ir 950, 1225, 1360, 1531, 1630, 1639, 3175, 3240 cm^{-1}; ^1H NMR ($CDCl_3$) 2.19 (3 H, 5-Me), 2.35 (3 H, 2-Me), 2.48 (3 H, 3-acetyl-Me), 6.15 (1 H, H-4), 8.60 (1 H, NH).

Anal. Calcd for $C_8H_{11}NO$: C, 70.0; H, 8.1. Found: C, 69.9; H, 8.4.

3-Acetyl-2-methyl-5-phenylpyrrole (16, 0.028 g) was obtained as pale green needles: mp 179–181°;[17] λ_{max} 310, 288, *242*, 236 (infl), 229 (infl) (log ϵ 4.06, 4.31, 4.34, 4.31, 4.22, respectively); ir 775, 812, 930, 952, 1238, 1561, 1600, 1629, 3220 cm^{-1}; ^1H NMR ($CDCl_3$) 2.43 (3 H, 2-Me), 2.59 (3 H, 3-acetyl-Me), 6.77 (1 H, H-4), 7.04–7.56 (5 H, 5-Ph), 8.78 (1 H, NH).

Anal. Calcd for $C_{13}H_{13}NO$: C, 78.4; H, 6.6; N, 7.0. Found: C, 78.4; H, 6.5; N, 6.7.

The *p*-nitrophenylhydrazone derivative of **16** gave mp 235–237°.[6] Calcd mass for $C_{19}H_{18}N_4O_2$: 334.1429. Found: M^+ (35% base peak) 334.1429.

3-Acetyl-2-methyl-5-phenylpyrrole was synthesized by the Hantzsch procedure[18] as follows. To a mixture of phenacyl bromide (1.99 g, 0.01 mol) and acetylacetone (1.00 g, 0.01 mol) was added slowly excess aqueous ammonia (20 ml, sp gr 0.88) and the mixture gently warmed before refluxing for 15 min. The reaction mixture was evaporated to dryness, the residue extracted with chloroform, and the chloroform extract evaporated to leave a red gum which after TLC gave the pyrrole **16** (0.084 g, 4.2%) with identical melting point and spectral characteristics as cited above.

6-Methyl-2-phenyl-5-azacycl[3.2.2]azine (**20**) was synthesized according to Boekelheide's procedure.[2]

2,6-Dimethyl-5-azacycl[3.2.2]azine (22). 2,7-Dimethyl-6-azaindolizine (**2,** 1.00 g) in nitrobenzene[19] (20 ml) was added to dimethyl acetylenedicarboxylate (3 g) in nitrobenzene (20 ml). The resultant red solution was refluxed (1 hr) and the solvent evaporated. The resulting black tar gave after TLC a slow-moving bright yellow band which after extraction and distillation (160–180°, ~0.1 mm) followed by recrystallization (ethyl acetate) gave **3,4-dicarbomethoxy-2,6-dimethyl-5-azacycl[3.2.2]azine** (0.208 g, 11%) as orange prisms: mp 143–145°; λ_{max} 438, 315, 263, *239* nm (log ϵ 3.93, 4.07, 4.36, 4.51, respectively); ir 792, 1060, 1131, 1153, 1190, 1229, 1261, 1700, 1726 cm^{-1}.

Anal. Calcd for $C_{15}H_{14}N_2O_4$: C, 62.9; H, 4.9; N, 9.8. Found: C, 62.8; H, 5.1; N, 10.0.

To the diester (0.10 g) in warm methanol (2 ml) was added a solution of potassium hydroxide (5.2 g) in methanol (13 ml). A fine precipitate formed and the reaction mixture was warmed (50°) for 1 hr to ensure complete hydrolysis. The precipitate was collected, dissolved in water, and acidified with 6 *M* hydrochloric acid. The crude diacid (0.064 g, 71%) was collected, dried, and refluxed with copper powder (0.25 g) and aniline (50 ml) for 2 hr. The copper powder was filtered and the filtrate evaporated to remove the bulk of the aniline. The residue after TLC [benzene–ethyl acetate (25:1) and then petroleum ether (60–80°)–ethyl acetate (10:1)] gave a bright yellow band which afforded **2,6-dimethyl-5-azacycl[3.2.2]azine (22,** 0.008, 19%) as yellow crystals: mp 40–43°; λ_{max} 433, 306, 291, *249* nm (log ϵ 3.54, 3.54, 3.75, 4.62, respectively); ir 710, 719, 741, 1332, 1515, 1525, 1590 cm^{-1}.

Calcd mass for $C_{11}H_{10}N_2$: 170.0843. Found: M^+ (base peak) 170.0843.

General Formylation Procedure. Formylation was carried out by treatment of the 6-azaindolizine or azacycl[3.2.2]azine with dimethylformamide and phosphoryl chloride at room temperature by a procedure similar to that reported in a previous paper.[20]

2,7-Dimethyl-6-azaindolizine (1.46 g) gave **3-formyl-2,7-dimethyl-6-azaindolizine (7,** 1.08 g, 62%) as yellow needles: mp 109–110°; λ_{max} 367, 360 (infl), 264, 253 (infl), 247, *228* nm (log ϵ 4.22, 4.17, 3.97, 4.01, 4.07, 4.27, respectively); ir 720, 780, 960, 1130, 1260, 1625, 1675 cm^{-1}.

Anal. Calcd for $C_{10}H_{10}N_2O$: C, 69.0; H, 5.8. Found: C, 69.2; H, 6.1.

2,3,7-Trimethyl-6-azaindolizine (**3,** 1.6 g) gave **1-formyl-2,3,7-trimethyl-6-azaindolizine (9,** 1.28 g, 68%) as straw-colored needles: mp 143–146°; λ_{max} 340, 274 (infl) 264 (infl), *240* nm (log ϵ 4.10, 3.37, 3.71, 4.41, respectively); ir 780, 870, 1045, 1250, 1360, 1510, 1615, 1660 cm^{-1}.

Anal. Calcd for $C_{11}H_{12}N_2O$: C, 70.3; H, 6.4. Found: C, 70.2; H, 6.7.

2,3,5,7-Tetramethyl-6-azaindolizine (**6,** 0.032 g) gave **1-formyl-2,3,5,7-tetramethyl-6-azaindolizine (11,** 0.002 g, 5%) as white needles from petroleum ether: mp 166°; λ_{max} 349, 279 (infl), 267 (infl), *239* nm (log ϵ 4.14, 3.30, 3.60, 4.40, respectively); ir 965, 1438, 1519, 1610, 1647 cm^{-1}. Calcd mass for $C_{12}H_{14}N_2O$: 202.1106. Found: M^+ (base peak) 202.1104.

5,7-Dimethyl-2-phenyl-6-azaindolizine (**4,** 0.22 g) gave after TLC two bands. The faster moving band afforded **1-formyl-5,7-dimethyl-2-phenyl-6-azaindolizine (13,** 0.01 g, 4.0%) as small needles from petroleum ether: mp 167–169°; λ_{max} 348, 282 (infl), *242* nm (log ϵ 4.19, 3.79, 4.50, respectively); ir 719, 1490, 1508, 1610, 1641 cm^{-1}. Calcd mass for $C_{16}H_{14}N_2O$: 250.1106. Found: M^+ (base peak) 250.1107.

The slower moving yellow band afforded **4-formyl-6-methyl-2-phenyl-5-azacycl[3.2.2]azine (19,** 0.005 g, 1.9%) as orange needles from petroleum ether–benzene: mp 178–179°; λ_{max} 454, 342, 283, 253 (infl), *245*, 230 nm (infl) (log ϵ 3.98, 4.36, 4.22, 4.52, 4.59, 4.46, respectively); ir 685, 770, 1150, 1410, 1505, 1528, 1591, 1659 cm^{-1}. Calcd mass for $C_{17}H_{12}N_2O$: 260.0949. Found: M^+ (base peak) 260.0946.

2,5,7-Trimethyl-6-azaindolizine (**5,** 1.0 g) gave after TLC three main bands. The fastest moving band gave unchanged starting material (0.17 g, 17%). The middle band afforded **3-formyl-2,5,7-trimethyl-6-azaindolizine (10,** 0.19 g, 20%) as prisms from petroleum ether: mp 100–101°; λ_{max} *365*, 355 (infl), 260 (infl), 253 (infl), 246, 228 nm (log ϵ 4.29, 4.23, 3.99, 4.03, 4.06, 4.26, respectively); ir 790, 850, 1263, 1319, 1410, 1518, 1630 cm^{-1}.

Anal. Calcd for $C_{11}H_{12}N_2O$: C, 70.2; H, 6.4; N, 14.9. Found: C, 70.1; H, 6.5; N, 15.2.

The slowest moving band gave orange crystals (0.127 g) which on fractional crystallization (petroleum ether–benzene, 10:1) gave **4-formyl-2,6-dimethyl-5-azacycl[3.2.2]azine (21,** 0.072 g, 7%) as long yellow needles: mp 202.5°; λ_{max} 435 (infl), 428, 315, 309, 281, *249*, 224 nm (log ϵ 3.98, 3.99, 4.01, 4.01, 4.20, 4.47, 4.33, respectively); ir 870, 1139, 1410, 1534, 1592, 1664 cm^{-1}.

Anal. Calcd for $C_{12}H_{10}N_2O$: C, 72.7; H, 5.1; N, 14.1. Found: C, 72.9; H, 5.0; N, 14.3.

The mother liquors from the fractional crystallization were evaporated and the residue after TLC [acetone–petroleum ether (60–80°), 5:2] gave two overlapping bands. The lower portion of the slower moving component afforded **1-formyl-2,5,7-trimethyl-6-azaindolizine (12,** 0.022 g, 2.2%) as prisms from petroleum ether: mp 127–129°; λ_{max} 338, 261 (infl), *232* nm (log ϵ 4.16, 3.60, 4.39, respectively); ir 961, 1278, 1441, 1523, 1610, 1649 cm^{-1}.

Anal. Calcd for $C_{11}H_{12}N_2O$: C, 70.2; H, 6.4. Found: C, 70.4; H, 6.5. Calcd mass: 188.049. Found: M^+ (base peak) 188.049.

Formylation of 6-methyl-2-phenyl-5-azacycl[3.2.2]azine (**20,** 0.016 g) gave after TLC (benzene–ethyl acetate, 50:3) three well-separated bands, the fastest moving one being starting material (0.003 g, 20%). The middle band gave **1-formyl-6-methyl-2-phenyl-5-azacycl[3.2.2]azine (23,** 0.004 g, 29%) as orange needles from petroleum ether: mp 163–164°; λ_{max} 438, 315 (infl), *297*, 284 (infl), 233 (infl), 255 nm (log ϵ 3.97, 4.27, 4.46, 4.42, 4.33, 4.40, respectively); ir 709, 760, 794, 1362, 1529, 1588, 1643 cm^{-1}. Calcd mass for $C_{17}H_{12}N_2O$: 260.0949. Found: M^+ (84% base peak) 260.0946.

The slowest moving band gave **4-formyl-6-methyl-2-phenyl-5-azacycl[3.2.2]azine (19,** 0.004 g, 28%). It showed identical melting point and spectral characteristics with the sample obtained from the formylation of 5,7-dimethyl-2-phenyl-6-azaindolizine (**4**).

Formylation of 2,6-dimethyl-5-azacycl[3.2.2]azine (**22,** 0.017 g) gave after TLC (benzene–ethyl acetate, 50:3) three well-separated bands, the fastest moving band being starting material (0.004 g, 24%). The middle band gave **1-formyl-2,6-dimethyl-5-azacycl-[3.2.2]azine (24,** 0.003 g, 20%) as small yellow crystals from petroleum ether: mp 152–160°; λ_{max} 424, 312, 286 (infl), 267 (infl), *258*, 227 nm (log ϵ 3.92, 4.00, 4.03, 4.33, 4.45, 4.38, respectively); ir 720, 781, 1324, 1365, 1422, 1518, 1533, 1590, 1640 cm^{-1}. Calcd mass for $C_{12}H_{10}N_2O$: 198.0793. Found: M^+ (75% base peak) 198.0791.

The slowest moving band gave **4-formyl-2,6-dimethyl-5-aza-**

cycl[3.2.2]azine (**21**, 0.004 g, 27%) showing identical melting point and spectral characteristics with those of sample obtained from the formylation of 2,5,7-trimethyl-6-azaindolizine (**5**).

Thioformylation of 2,7-dimethyl-6-azaindolizine (**2**, 0.250 g) was carried out by treatment of **2** with dimethylformamide (2 ml) and phosphoryl chloride (0.35 g) at room temperature. The reaction mixture was poured into a 2 *M* aqueous sodium hydrogen sulfide[7] solution (30 ml) and extracted with chloroform. Evaporation of the chloroform followed by column chromatography using benzene and recrystallization from benzene–cyclohexane (1:5) gave **2,7-dimethyl-3-thioformyl-6-azaindolizine** (**8**, 0.190 g, 58%) as red needles: mp 175–176°; λ_{max} *439*, 433 (infl), 420 (infl), 370, 308, 300 (infl), 253 (infl), 238 (infl), *227* nm (log ϵ 4.20, 4.15, 3.98, 3.65, 3.76, 3.72, 3.91, 4.02, 4.20, respectively); ir 870, 980, 1135, 1258, 1318, 1510, 1610 cm^{-1}.

Anal. Calcd for $C_{10}H_{10}N_2S$: C, 63.1; H, 5.3; N, 14.7. Found: C, 63.4; H, 5.4; N, 15.0.

Reduction of aldehydes **7** and **10** to give, respectively, **2,3,7-trimethyl-6-azaindolizine** (**3**) and **2,3,5,7-tetramethyl-6-azaindolizine** (**6**) was carried out with lithium aluminum hydride–aluminum chloride in ether by a procedure similar to that reported in a previous paper.[20] 3-Formyl-2,7-dimethyl-6-azaindolizine (**7**, 0.5 g) gave a brown oil (0.21 g). This oil after TLC afforded as the main band 2,3,7-trimethyl-6-azaindolizine (**3**, 0.01 g, 2%) which showed identical spectral characteristics with the sample obtained from the Chichibabin reaction between 4,6-dimethylpyrimidine and 3-bromo-2-butanone.

3-Formyl-2,5,7-trimethyl-6-azaindolizine (**10**, 0.20 g) after TLC gave 2,3,5,7-tetramethyl-6-azaindolizine (**6**, 0.05, 27%) as needles: mp 64–67°; λ_{max} 358 (br), 295, 284, 277 (infl), *240* nm (log ϵ 3.15, 3.82, 3.83, 3.71, 4.39, respectively); ir 868, 1287, 1363, 1436, 1530, 1630 cm^{-1}. Calcd mass for $C_{11}H_{14}N_2$: 174.1156. Found: M^+ (base peak) 174.1157.

2,6-Dimethyl-5-azacycl[3.2.2]azine (22) from 3-Formyl-2,7-dimethyl-6-azaindolizine (10). A mixture of 3-formyl-2,7-dimethyl-6-azaindolizine (**10**, 0.05 g) and potassium hydroxide (2.0 g) were quickly fused in a sealed, evacuated tube. Immediately a yellow vapor formed and droplets of a yellow-brown liquid condensed. After cooling, the contents of the tube were extracted with ether, the ether evaporated, and the residue after TLC gave as an intense yellow band 2,6-dimethyl-5-azacycl[3.2.2]azine (**22**, 0.012 g, 27%) which showed identical melting point and spectral characteristics with those of the sample obtained after hydrolysis and decarboxylation of the product from the 1,3-dipolar addition reaction between 2,7-dimethyl-6-azaindolizine and dimethyl acetylenedicarboxylate.

Methylene-1,1′-(2,2′,3,3′,7,7′-hexamethyl)di-6-azaindolizine (18). Addition of 40% aqueous formaldehyde (2.0 ml) to a solution of 2,3,7-trimethyl-6-azaindolizine (**3**, 0.8 g, 5 mmol) in ethanol (3 ml) gave on gentle reflux for 15 min a cloudy solution from which yellow needles of the symmetrical di-6-azaindolizylmethane (**18**, 0.73 g, 88%) precipitated. Recrystallization from ethyl acetate gave the compound **18**: mp 238–240° dec; λ_{max} 376, 299, 287, 277 (infl), *243* nm (log ϵ 3.22, 3.91, 3.91, 3.83, 4.53, respectively); ir 850, 1120, 1175, 1240, 1350, 1420, 1620 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.04 (6 H, 2- and 2′-Me), 2.32 (6 H, 3- and 3′-Me), 2.39 (6 H, 7- and 7′-Me), 3.97 (2 H, bridge methylene), 6.68 (2 H, H-8 and H-8′), 8.44 (2 H, H-5 and H-5′).

Anal. Calcd for $C_{21}H_{24}N_4$: C, 75.9; H, 7.3; N, 16.8. Found: C, 76.0; H, 7.5; N, 17.1.

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Registry No.—**1**, 57139-15-8; **2**, 57108-98-2; **3**, 57108-99-3; **4**, 57109-00-9; **5**, 57109-01-0; **6**, 57109-02-1; **7**, 57109-03-2; **8**, 57109-04-3; **9**, 57109-05-4; **10**, 57109-06-5; **11**, 57109-07-6; **12**, 57109-08-7; **13**, 57109-09-8; **16**, 13219-97-1; **16** *p*-nitrophenylhydrazone, 57109-10-1; **17**, 1500-94-3; **18**, 57109-11-2; **19**, 57109-12-3; **20**, 57109-13-4; **21**, 57109-14-5; **22**, 57109-15-6; **23**, 57109-16-7; **24**, 57109-17-8; 4,6-dimethylpyrimidine, 1558-17-4; bromoacetone, 598-31-2; 3-bromo-2-butanone, 814-75-5; 2,4,6-trimethylpyrimidine, 22114-27-8; phenacyl bromide, 70-11-1; acetylacetone, 123-54-6; 3,4-dicarbomethoxy-2,6-dimethyl-5-azacycl[3.2.2]azine, 57109-18-9.

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Stereospecific Epoxidation of Dihydrophthalates

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Carboxylate groups exert specific syn-directing effects on the epoxidation of adjacent double bonds in the absence of steric or conformational effects. Peracid epoxidation of dimethyl *trans*-1,2-dihydrophthalate is stereospecific and gives a 90:9.5:0.5 mixture of diepoxides **2**, **3**, and **4** in 95–98% yields. Epoxidation converts monoepoxide **5** to diepoxide **2** in 100% selectivity, and dimethyl 1,4-dihydrophthalate to a 75:25 mixture of the cis and trans monoepoxides. Cis diepoxide **4** is obtained by thermal rearrangement of endo peroxide **11**. Irradiation of **11** in cyclohexane gives a mixture of **4** and unsaturated diol **12**. Both catalytic hydrogenation and lithium aluminum hydride reduction of diepoxide **2** are regiospecific and give alcohols **13** and **14**.

Epoxidation[1] and photooxygenation[2] are valuable for stereospecific introduction of oxygen into olefins. The stereochemistry of epoxidations and of ring opening reactions of epoxides has been extensively studied.[3] There is considerable interest in syntheses and reactions of cyclohexadiene diepoxides[4–6] and in 1,4-endo peroxides (1,4-epidioxide compounds)[7] as precursors to cis diepoxides by thermal[8] or photochemical rearrangements.[9] Recently, iso-

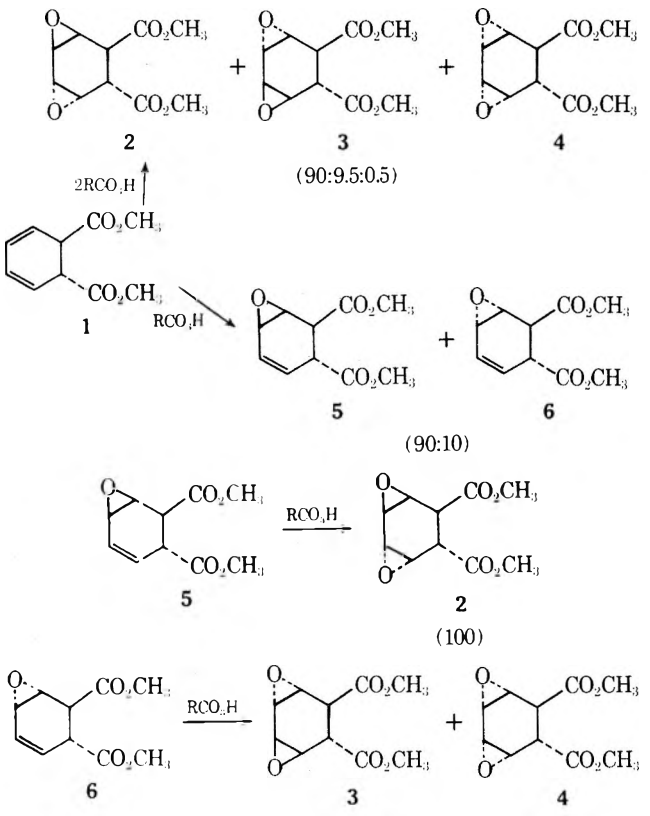
meric di- and triepoxides of benzene and annulenes have been reported.[10]

The stereospecific syn-directing effects of allylic alcohols in epoxidations were first described by Henbest[11] and Albrecht[12] in 1957. Much has been published since on the stereochemistry of epoxidation and directive effects of polar substituents. For studying the latter, substituted 1,3-cyclohexadiene is a good system; it is nearly flat and has no steric or conformational interferences. We have been studying the chemistry or dihydrophthalic acid derivatives[13] and here report our results on stereospecific epoxidations of the dihydrophthalates, regiospecific reductions of the epoxides, and the preparation, rearrangement, and reductions of 1,2-dihydrophthalate endo peroxides.

Results

Epoxidation of dimethyl *trans*-1,2-dihydrophthalate (**1**) with excess *m*-chloroperbenzoic acid in chloroform gave 95–98% yields of a 90:9.5:0.5 mixture of all three possible diepoxides **2**, **3**, and **4** and 2–5% dimethyl phthalate (Scheme I). The ratio of products showed little dependence

Scheme I

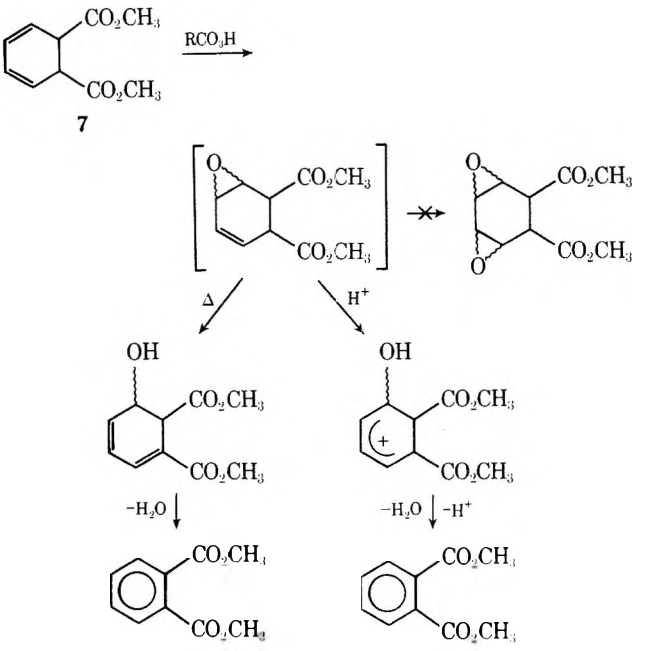


on solvent, temperature, or peracid. Diepoxide **2** was formed with 87–93% selectivity in methylene chloride, chloroform, or benzene at 20–80° using perbenzoic, *m*-chloroperbenzoic, or peracetic acid buffered with sodium carbonate. Alkaline hydrogen peroxide in methanol converted **1** to dimethyl phthalate and dimethyl 1,4-dihydrophthalate (**8**).

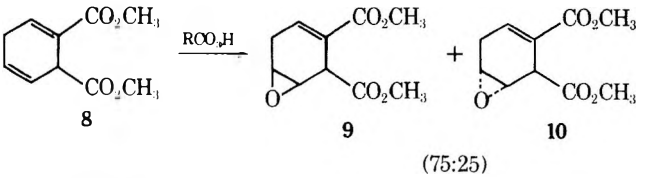
Reaction of **1** with 1 equiv of *m*-chloroperbenzoic acid gave high yields of a 9:1 mixture of monoepoxides **5** and **6** plus 2–5% dimethyl phthalate. Further reaction of the monoepoxides with peracid gave the same mixture of diepoxides **2**, **3**, and **4** obtained directly from **1**. Monoepoxides **5** and **6** are particularly reactive as they are allylic ethers and contain tertiary hydrogens activated by carbomethoxy groups. In the presence of acid or base, or on attempted chromatography over silica gel or alumina, they are rapidly converted to dimethyl phthalate. An isomerically pure sample of cis monoepoxide **5** was obtained by diazomethane esterification of the corresponding diacid, which is the exclusive product from peracid monoepoxidation of *trans*-1,2-dihydrophthalic acid.[14] Epoxidation of cis monoepoxide **5** was 100% stereospecific; **2** was the only diepoxide formed. To account for the 0.5% yield of cis diepoxide **4**, trans monoepoxide **6** must be converted to diepoxides **3** and **4** in a ratio of 95:5.

Reaction of dimethyl *cis*-1,2-dihydrophthalate (**7**) with *m*-chloroperbenzoic acid, under conditions that gave high yields of diepoxides from *trans*-1,2-dihydrophthalate (**1**), led exclusively to formation of dimethyl phthalate (Scheme II).

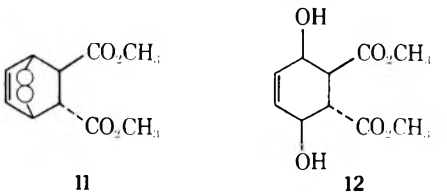
Scheme II



Reaction of dimethyl 1,4-dihydrophthalate (**8**) with 1 or more equiv of *m*-chloroperbenzoic acid in refluxing chloroform gave 95% of monoepoxides and 5% of dimethyl phthalate. Epoxidation of **8** was less stereospecific than epoxidation of **1**; a 75:25 mixture of cis and trans epoxides **9** and **10** was formed. The homoallylic monoepoxides **9** and **10** were more stable than monoepoxides **5** and **6**; they could be chromatographed on silica gel, but were converted to dimethyl phthalate on alumina.



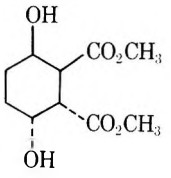
As cis diepoxide **4** was obtained in such low yield (0.5%) by direct epoxidation of diene **1**, we studied an alternative route, the rearrangement of 1,4-endo peroxides to cis diepoxides.[2,7,9,10] The required endo peroxide **11**[15] was prepared



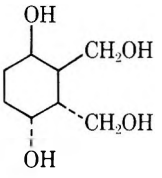
in 98% yield by reaction of **1** in acetone with singlet oxygen generated photochemically using rose bengal as the sensi-

tizer. In refluxing xylene **11** was converted to cis diepoxide **4** (35% yield) and dimethyl 3-hydroxyphthalate. The endo peroxide was also isomerized to cis diepoxide **4** photochemically by irradiation in methanol or cyclohexane solution. In cyclohexane, unsaturated diol **12** was formed (15% yield) in addition to **4** (6% yield) by trapping of the intermediate diradical[9] by solvent in competition with intramolecular addition of the dioxygen diradical to the double bond (Scheme IV).

Catalytic hydrogenation of diepoxide **2** in methanol using palladium on carbon catalyst gave a mixture of diols from which a single crystalline diol **13** was isolated in 70% yield. Lithium aluminum hydride reduction of **13** afforded



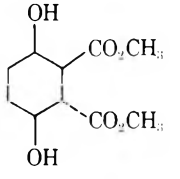
13



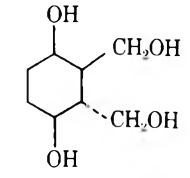
14

tetraol **14** in high yield. Reduction of **2** with lithium aluminum hydride in tetrahydrofuran gave the same stereoisomer **14**, isolated in 54% yield, and overreduced products (diols and hydrocarbons).

Isomeric diols **15** and **17** and a tetraol **16** were needed to aid in the characterization and assignment of stereochemistry to the major product from epoxidation of **1** and its reduction products. We prepared **15**[15] in 80% yield by cata-



15



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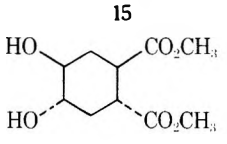

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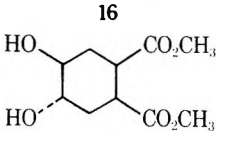


18

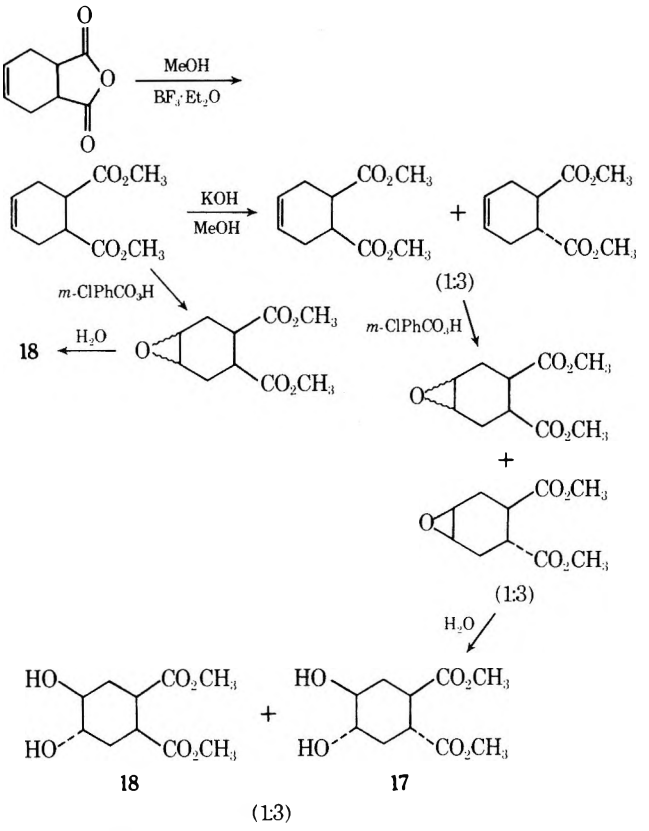
lytic hydrogenation of endo peroxide **11** in methanol over a palladium on carbon catalyst. Lithium aluminum hydride reduction of **15** in tetrahydrofuran gave tetraol **16**.

The syntheses of 4,5-dihydroxyhexahydrophthalates **17** and **18** are outlined in Scheme III. Epoxidation of dimethyl *cis*-1,2,3,6-tetrahydrophthalate gave a mixture of monoepoxides that was converted by aqueous hydrolysis to the trans 4,5-diol (**18**) of *cis*-tetrahydrophthalate,[16] which is a noncrystallizable viscous oil. Epimerization of dimethyl *cis*-1,2,3,6-tetrahydrophthalate in methanolic potassium hydroxide gave a 3:1 mixture of *trans*- and *cis*-1,2,3,6-tetrahydrophthalates which was converted to a 3:1 mixture of **17** and **18** by epoxidation and hydrolysis. The trans 4,5-diol (**17**) of *trans*-tetrahydrophthalate is crystalline, and was isolated from the mixture by crystallization from benzene.

Discussion

Diepoxide **4**, formed in 0.5% yield from bisepoxidation of **1**, was identified by comparison with diepoxide obtained by thermal rearrangement of endo peroxide **11**. Assignment of stereochemistry to the major diepoxide of **1** as that indicated by **2** rather than **3** was based on the following evidence: it was reduced to **13** and **14**, the diaxial alcohols expected from trans-coplanar epoxide ring opening of **2**, and not **24**, the diol expected from reduction of **3**; and it was identical with the dimethyl ester of $3\alpha,8\beta$-dioxatricyclo[5.1.0.$0^{2,4}$]octane-$5\alpha,6\beta$-dicarboxylic acid (the diacid corresponding to structure **2**), obtained by peracid epoxidation of *trans*-1,2-dihydrophthalic acid.[14] The product formed in 9.5% yield was isomeric with diepoxides **2** and **4** and, therefore, must have structure **3**.

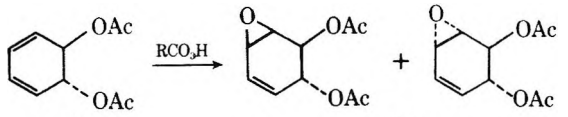
Scheme III



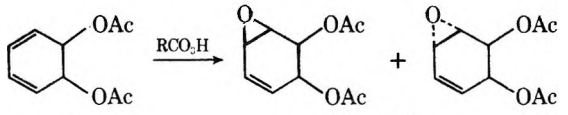
The stereochemistry of epoxidations is determined by the ease of approach of the peracid to the more stable conformer of a substituted olefin. In the absence of directing effects from polar substituents, epoxidation would take place from the less hindered side to give trans epoxides. As **1** is nearly planar, there should be no steric or conformational preferences for epoxidation syn or anti to the carboxylate substituents. It is surprising, therefore, that epoxidation of **1** proceeded in 90% stereospecificity to monoepoxide **5**, and to diepoxide **2**. We propose that a carboxylate group exerts a syn-directive effect on the stereochemistry of peracid epoxidations and that, in the absence of steric effects, syn epoxidation will predominate to give epoxide cis to the carboxylate (cis epoxide).

Although much has been published on the stereochemistry of epoxidations and the syn directive effects of allylic alcohols,[1] little is known about directive effects of carboxylate substituents. The stereospecific directive effect of allylic hydroxyl groups is due to stabilization of the transition state leading to cis epoxides by hydrogen bonding to the peracid.[11,12,17] This interaction is more effective when the directing group is in the pseudoequatorial position.[18,19] Where no such hydrogen bonding is possible, as for allylic ethers, trans epoxides are formed. Epoxide substituents do not show syn directive effects, so epoxidation of epoxycyclohexenes gives mainly trans diepoxides.[4,5,10] Epoxidation of allylic acetates is not very stereospecific, but generally gives more of the cis epoxides than expected on the basis of steric interactions alone.[18] Carboxylate and acetate substituents show specific directing effects on the stereochemistry of the mechanistically closely related Simmons–Smith cyclopropanation reaction, but are not as effective as hydrox-

yl groups.[20] A free carboxylic acid is a more effective syn directing group than a carboxylate ester, as peracid epoxidation of *trans*-1,2-dihydrophthalic acid gave only the cis monoepoxide.[14] An ester is a better syn-directing group than acetate. Epoxidation of *trans*-5,6-diacetoxycyclohexa-1,3-diene (**19**) gave a 2:1 mixture of cis and trans monoepoxides,[17] compared to a 9:1 mixture of **5** and **6** from the corresponding dicarboxylate **1**. Cis diacetate **20** gave 90% trans monoepoxide;[21] apparently the steric influence of the pseudoaxial acetate in **20** overcomes any directive effect of the acetate group.

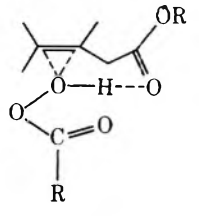


19 (2:1)

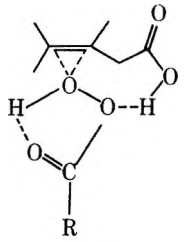


20 (1:9)

The high degree of stereochemical control found for allylic carboxylates may be due to stabilization of the transition state (possibly **21** and/or **22** for carboxylic acids) leading to syn epoxidations when the carboxylate is pseudoequatorial and there are no interfering steric or conformational effects. The relative order of effectiveness for syn-directing allylic substituents is $-OH \gg -CO_2H > -CO_2R \gg -O_2CR$.



21

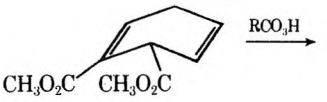


22

Monoepoxides **5** and **6** could not be separated and isolated in a pure state, owing to their tendency to aromatize to dimethyl phthalate by loss of water. They were characterized as a mixture of 90% **5** and 10% **6** by peracid conversion to a 90:9.5:0.5 mixture of **2**, **3**, and **4**. Epoxidation of **5**, obtained isomerically pure by esterification of the diacid,[14] was 100% stereospecific to **2**, owing to a combination of the syn directive effect of the allylic pseudoequatorial carboxylate and the steric effect of the adjacent epoxide group. In epoxidation of **6** there is a competition between the carboxylate directing effect to give **4**, and the epoxide steric effect to give **3**. The latter dominated almost completely, as the ratio of **3** to **4** was 95:5 (Scheme I).

We were not able to isolate epoxides of dimethyl *cis*-1,2-dihydrophthalate (**7**). Reaction of **7** with peracid gave dimethyl phthalate, presumably by acid-catalyzed or thermal isomerization or an intermediate monoepoxide and dehydration (Scheme II). Epoxidation of the monoepoxide is expected to be very slow, as approach of peroxy acid from either side of the double bond is sterically hindered by the epoxide or pseudoaxial carboxylate.

Epoxidation of dimethyl 1,4-dihydrophthalate (**8**) gave only monoepoxides, as the double bond conjugated to the carboxylate is deactivated toward attack by electrophilic peracid reagent. The reaction was less stereospecific and gave a 75:25 mixture of cis and trans epoxides **9** and **10**, due to the conformational effects in 1,4-cyclohexadienes. In the more stable flattened-boat conformation of **8**, the pseudoequatorial carboxylate would direct syn epoxidation to the more sterically crowded inside face. Thus, attack of peracid from the unhindered side, leading to trans epoxide, is expected to be more important than in the absence of this conformational effect.[4,22,23]



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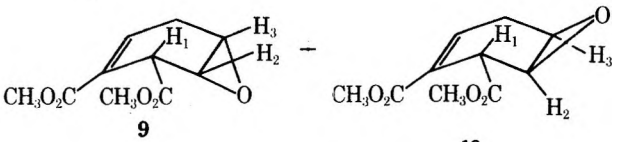
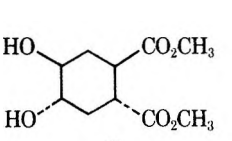


9 **10**

Assignment of stereochemistry to **9** and **10** was made by comparison of their NMR spectra. Multiplets assigned to H_1 at δ 3.25, H_2 (H_3) at 4.10, and H_3 (H_2) at 3.48 in the major product were shifted 0.10–0.15 ppm higher in the minor product, whereas the other ring hydrogens had the same chemical shifts in both isomers. Inspection of models of each isomer showed that in structure **10** H_1, H_2, and H_3 are closer to the oxirane oxygen or the carboxylate group than in structure **9**. As the deshielding anisotropic effects of these substituents are expected to increase the chemical shifts of adjacent hydrogens, the higher chemical shifts found for H_1, H_2, and H_3 in the minor product show that it is the trans epoxide **10**, and that the major product is **9**.

The structures of diols **15**, **17**, and **18** and tetraol **16** were unambiguously determined by their methods of synthesis. Both catalytic hydrogenation and lithium aluminum hydride reductions of **2** were regiospecific and gave products with the same stereochemistry; tetraol obtained by hydride reduction of **2** was identical with the product from hydrogenation of **2** followed by hydride reduction.

The hydrogenation product of **2** was assigned structure **13**, rather than the other possible isomers **17** or **23**, and the



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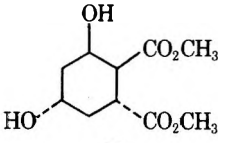

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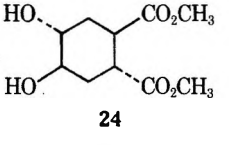
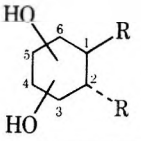


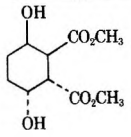
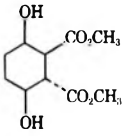
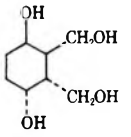
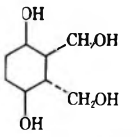
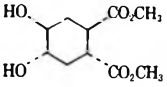
24

hydride reduction product was characterized as **14**, based on the following evidence. Diol **17** was prepared by an independent synthesis and was different than the hydrogenation product. The hydrogenation product gave a negative periodate test for *vic*-glycols, as did the 1,4-diol **15**. Structure **24**, the product expected from reduction of diepoxide **3**, was ruled out because it is expected to give a positive periodate test,[24] as did the 1,2-diols **17** and **18**. The NMR spectra of **13** and **14** are consistent with the proposed structures, are similar to the spectra of stereoisomers **15** and **16**, and are different from **17** and spectra expected for structure **23**. NMR spectral data and assignments for compounds **13**, **14**, **15**, **16**, and **17** are shown in Table I. Structure **13** is identical with **15**, and **14** is identical with **16**, except for the stereochemistry at C_3. H_3 and H_6 have the same chemical shifts in **13** (δ 4.40) as H_6 in **15** (δ 4.40); H_3 and H_6 have the same chemical shifts in **14** (δ 4.14) as H_6 in

Table I
NMR Spectra[a] of Substituted Cyclohexane Diols of General Structure



(R = CH_2OH or CO_2CH_3)

Compd		H_1	H_2	H_3	H_4	H_5	H_6	CH_2OH	CO_2CH_3
	(13)	3.12 s	3.12 s	4.40 s	1.80 m	1.80 m	4.40 s		3.70 s
	(15)	2.94 s	2.88 d[b]	~3.7[b]	1.80 m	1.80 m	4.40 s		3.70 s, 3.73 s
	(14)	1.85 m	1.85 m	4.14 s	1.75 m	1.75 m	4.14 s	3.66 m	
	(16)	(1.4–2.0 m)		3.6–4.0 m	(1.4–2.0 m)		4.18 s	2.6–4.0 m	
	(17)	3.00 m	3.00 m	1.94 m	3.85 s	3.85 s	1.94 m		3.72 s

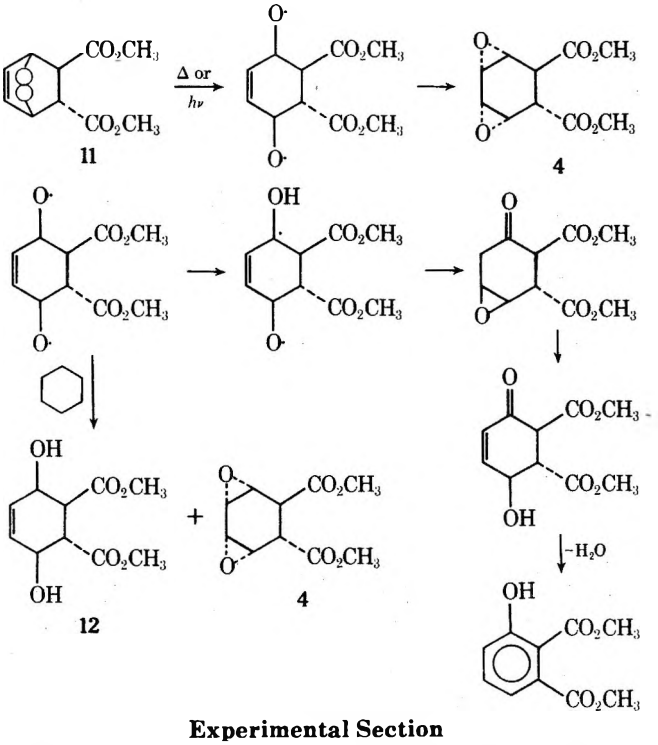
[a] All spectra were run in D_2O; chemical shifts (δ, 100 MHz) were measured in parts per million from TSP (sodium 3-trimethylsilylpropionate-d_4). [b] H_2 is a doublet, $J_{H_2-H_3}$ = 9 Hz; H_3 is partially buried under the methyl ester peak at 3.70.

16 (δ 4.18). The cis coupling constants between H_1 and H_6 in all four structures and between H_2 and H_3 in 13 and 14 are expected to be small,[14] and the observed couplings are less than 1 Hz.

Hydride reductions of substituted cyclohexene oxides are generally quite regiospecific. The stereochemistry is determined by trans-coplanar (diaxial) attack of hydride on the more stable conformer, and in conformationally rigid systems the axial alcohol is formed.[3,25] Tetraol 14 is the product expected from diaxial opening of both epoxide groups and reduction of the esters in 2. Catalytic hydrogenation gave the diaxial diol 13, which is the stereoisomer predicted by approach of the diepoxide from its less hindered side to the hydrogenated metal surface.

Cis diepoxides are not formed to any appreciable extent by direct epoxidation of dienes. Thermal[8] or photochemical[9] rearrangements of endo peroxides, readily available by Diels–Alder reactions of conjugated dienes and singlet oxygen,[2] produce cis diepoxides stereospecifically. Some endo peroxides are so prone to undergo this transformation that they cannot be isolated at room temperature;[10] others are stable at 200°.[26] Endo peroxide 11 was thermally stable at 100°, and required higher temperatures to effect isomerization. The same products are obtained and the same mechanism is proposed for thermal as for photochemical rearrangements of endo peroxides.[9] Isolation of 12 from irradiation of a cyclohexane solution of 11 (Scheme IV) is good evidence for the proposed dioxygen diradical intermediate. Common side products in these isomerizations are β,γ-epoxy ketones or products derived from these by a 1,2-hydride shift in the diradical and ring closure. The formation of dimethyl 3-hydroxyphthalate can be explained in this way.

Scheme IV



Experimental Section

NMR spectra were recorded on a Joel H-100 spectrometer and are reported in parts per million (δ) downfield from internal Me_4Si or TSP (for D_2O solvent). Infrared spectra were recorded on a Perkin-Elmer 237B spectrophotometer. GC analyses were obtained on a Hewlett-Packard Model 5750 gas chromograph attached to a Varian Aerograph Model 477 digital integrator, using a 15 ft ×

0.125 in. column packed with 10% OV 210 (methyl silicone with 50% trifluoropropyl groups) on Chromosorb W (80/100). Melting points are uncorrected.

Dimethyl 3α,8β-Dioxatricyclo[5.1.0.0^{2,4}]octane-5α,6β-dicarboxylate (2). A solution of 6.30 g (32 mmol) of 1[13] and 13.50 g (66.5 mmol) of 85% *m*-chloroperbenzoic acid in 250 ml of $CHCl_3$ was refluxed for 4 hr. The solution was extracted with 5% $NaHCO_3$ (4 × 200 ml) and H_2O (200 ml). The $CHCl_3$ solution was dried, filtered, and evaporated to dryness under reduced pressure to give 7.30 g of a 90:9.5:0.5 mixture of **2**, **3**, and **4** (98%) and dimethyl phthalate (2%). The product mixture was dissolved in 20 ml of warm CCl_4; 10 ml of hexane was added and the solution was cooled to 0° and filtered. **2**, 4.75 g, was obtained as a white, crystalline solid, mp 96–100°. A second recrystallization from carbon tetrachloride–hexane (5:1) raised the melting point to 104–105°: ir (Nujol) 1737, 1440, 1300, 1280, 1250, 1235, 1190, 1180, 1020, 987, 895, 768, 750 cm^{-1}; NMR ($CDCl_3$) δ 3.40 (s, 2 H), 3.52 (s, 4 H), 3.80 (s, 6 H); *m/e* (M^+) 228.0643 (calcd, 228.0634).

Anal. Calcd for $C_{10}H_{12}O_6$: C, 52.6; H, 5.3. Found: C, 52.5; H, 5.1.

Dimethyl 3β,8α-Dioxatricyclo[5.1.0.0^{2,4}]octane-5α,6β-dicarboxylate (3). Recrystallization of the mother liquors from above, containing a 70:28:2 ratio of **2**, **3**, and **4**, from CCl_4–hexane (2:1) gave a second crop of **2** (96% pure) and filtrates that consisted of 48% **2**, 49% **3**, and 3% **4**. Solvent was removed and the residue was recrystallized from acetone to give a 90:10 mixture of **3** and **2**. Pure **3** was obtained by recrystallization of this enriched mixture from CCl_4–hexane (2:1): mp 139.0–139.5°; ir (Nujol) 1742, 1725, 1435, 1270, 1245, 1015, 1005, 900, 875, 840, 765, 725, 690 cm^{-1}; NMR ($CDCl_3$) δ 3.50 (m, 2 H), 3.64 (m, 2 H), 3.82 (s, 8 H); *m/e* (M^+) 228.0625 (calcd, 228.0634).

Anal. Calcd for $C_{10}H_{12}O_6$: C, 52.6; H, 5.3. Found: C, 52.4; H, 5.3.

Dimethyl 3α,8α-Dioxatricyclo[5.1.0.0^{2,4}]octane-5α,6β-dicarboxylate (4). Removal of most of the diepoxides **2** and **3** from the products obtained by epoxidation of **1** left a viscous oil that contained about 20% of diepoxide **4**, which was identified in this mixture by GC and NMR by comparison with spectra of diepoxide isolated by thermal rearrangement of **11**.

4 by Thermal Rearrangement of Endo Peroxide 11. A solution of 2.40 g of **11** in 50 ml of *p*-xylene was refluxed for 20 hr. The solution was decanted from a small amount of an insoluble gum and the xylene was distilled at reduced pressure, leaving a yellow, viscous oil (2.20 g). NMR and GC analysis of the product mixture showed that it contained 35 wt % of **4**. Fractions containing a total of 0.58 g (25%) of **4** were obtained by column chromatography of the crude products over silica gel, using benzene as eluent. Recrystallization from Et_2O at −78° gave 0.48 g of **4** as a crystalline solid, mp 76–78°. **4** was further purified by recrystallization from CCl_4: mp 79–80°; ir (Nujol) 1735 (shoulders at 1745 and 1725), 1470, 1440, 1300, 1280, 1265, 1245, 1230, 1170, 1150, 1020, 960, 945, 920, 865, 785, 770, 735 cm^{-1}; NMR ($CDCl_3$) δ 3.20 (m, 1 H), 3.24 (m, 2 H), 3.40 (m, 1 H), 3.50 (m, 2 H), 3.76 (s, 6 H); *m/e* 229 (P + 1).

Anal. Calcd for $C_{10}H_{12}O_6$: C, 52.6; H, 5.3. Found: C, 52.4; H, 5.1.

Elution of the silica gel column, containing the products from thermal reaction of **11**, with $CHCl_3$ gave 1.20 g (about 50%) of a gummy solid, that was mainly dimethyl 3-hydroxyphthalate:[27] ir (Nujol) 3400, 1715, 1600, 1575, 1325–1200, 1125, 1065, 885, 880, 800, 785, 765, 710 cm^{-1}; NMR ($CDCl_3$) δ 7.74 (m, 1 H), 7.3–6.8 (m, 3 H), 3.92 (s, 3 H), 3.86 (s, 3 H); *m/e* 210.

Dimethyl 7β-Oxabicyclo[4.1.0]hept-4-ene-2β,3α-dicarboxylate (5). Monoepoxide **5** was prepared by esterification with diazomethane of the corresponding diacid, obtained by monoepoxidation of *trans*-1,2-dihydrophthalic acid[13] according to the procedure described by Berchtold.[14] It was pure by GC: ir (film) 1737, 1435, 1305, 1275, 1195, 1165, 1020, 980, 860, 755 cm^{-1}; NMR ($CDCl_3$) δ 3.14 (m, 1 H), 3.40 (m, 1 H), 3.55 (m, 1 H), 3.72 (m, 4 H), 3.80 (s, 3 H), 6.00 (m, 2 H).

Dimethyl 7β- and 7α-Oxabicyclo[4.1.0]hept-4-ene-2β,3α-dicarboxylates (5 and 6) by Epoxidation of 1. A solution of 4.85 g (24.7 mmol) of **1** and 5.20 g (25.6 mmol) of 85% *m*-chloroperbenzoic acid in 200 ml of $CHCl_3$ was refluxed for 2 hr. The reaction product was worked up as described above. A yellow oil (5.20 g) was obtained that contained 3% of dimethyl phthalate (by NMR) and 4% of **2** (by GC). The ir and NMR spectra of the product mixture were similar to those of pure **5**. Chromatography over alumina, silica gel, or Florisil converted **5** and **6** to dimethyl phthalate. Relative composition could not be determined by GC as the monoepoxides partially decomposed to dimethyl phthalate and unidentified products: *m/e* (on mixture of **5** and **6**) 212 (76), 210 (1.6), 196 (7.3), 194 (14). The composition of **5** and **6** was shown to be 90:10 by reaction of the mixture with 1 equiv of *m*-chloroperobenzoic acid to give 90% **2** (from **5**), 9.5% **3**, and 0.5% **4** (from **6**).

Dimethyl 7β- and 7α-Oxabicyclo[4.1.0]hept-3-ene-2β,3-dicarboxylates (9 and 10). A solution of 4.60 g (23.4 mmol) of 8[13] and 5.30 g (26.2 mmol) of 85% *m*-chloroperbenzoic acid in 100 ml of chloroform was refluxed for 6 hr. A viscous oil (4.90 g, 98% yield) was obtained that consisted of **9** (69%), **10** (23%), dimethyl phthalate (4%), and unidentified products (~4%). The monoepoxides were purified and partially separated by chromatography over silica gel. Preparative GC afforded pure samples of **9** and **10**.

9: ir (film) 1736, 1720 (shoulder), 1662, 1435, 1365, 1312, 1265, 1200, 1174, 1125, 1095, 1055, 1035, 1015, 950, 825, 807, 760, 735 cm^{-1}; NMR ($CDCl_3$) δ 2.74 (m, 2 H), 3.25 (m, 1 H), 3.48 (m, 1 H), 3.72 (s, 6 H), 4.10 (m, 1 H), 6.80 (m, 1 H); *m/e* 212.

Anal. (M^+) Calcd for $C_{10}H_{12}O_5$: 212.06847. Found: 212.06735.

10: ir (film) 1740, 1717, 1660, 1435, 1360, 1300, 1262, 1225, 1198, 1170, 1035, 1025, 785, 760 cm^{-1}; NMR ($CDCl_3$) δ 2.74 (m, 2 H), 3.36 (m, 1 H), 3.64 (m, 1 H), 3.72 (s, 3 H), 3.76 (s, 3 H), 4.20 (m, 1 H), 6.80 (m, 1 H); *m/e* 212.

Anal. (M^+) Calcd for $C_{10}H_{12}O_5$: 212.06847. Found: 212.06735.

Dimethyl 7,8-Dioxabicyclo[2.2.2]oct-2-ene-*trans*-5,6-dicarboxylate (11).[15] A solution of 2.00 g (10.2 mmol) of **1** in 550 ml of acetone containing 50 mg of rose bengal was irradiated through a Pyrex filter by a Hanovia 450-W medium-pressure mercury immersion lamp at 22° for 30 min. A stream of oxygen was bubbled through the solution at a rate of 150 ml/min during the irradiation. Acetone was removed under reduced pressure. The residue was dissolved in Et_2O and filtered. Removal of solvent left 2.28 g (98%) of **11** as a pale yellow, viscous oil. The product was purified by chromatography in benzene over silica gel. Pure **11** (1.58 g) was obtained: ir (film) 1737, 1440, 1375, 1325, 1290, 1265, 1240, 1210, 1180, 1055, 980, 940, 875, 760, 705 cm^{-1}; NMR (CCl_4) δ 2.95 (m, 1 H), 3.63 (s, 3 H), 3.74 (s, 3 H), 3.78 (m, 1 H), 4.93 (m, 2 H), 6.54 (m, 2 H); MS *m/e* (rel intensity) 228 (2.6), 197 (6.9), 196 (12.1), 169 (2.1), 164 (12.1), 137 (100.0), 136 (20.2).

Anal. Calcd for $C_{10}H_{12}O_6$: C, 52.6; H, 5.3. Found: C, 52.7; H, 5.1.

Dimethyl 1β,4β-Dihydroxycyclohex-5-ene-2β,3α-dicarboxylate (12). A solution of 1.02 g of **11** in 500 ml of cyclohexane was irradiated as above. The solvent was removed under vacuum. The residue was taken up in benzene and filtered to give 0.15 g (15%) of **12**. Examination of the mother liquor by NMR showed the presence of about 6% **4**. Recrystallization of **12** from acetone–benzene (1:1) gave a pure product: mp 160.5–161.5°; ir (Nujol) 3275, 1740, 1725, 1440, 1335, 1225, 1200, 1187, 1135, 1070, 1050, 1030, 970, 950, 900, 880, 820, 790, 755 cm^{-1}; NMR (D_2O) δ 3.0 (m, 2 H), 3.74 (s, 3 H), 3.78 (s, 3 H), 4.20 (m, 1 H), 4.55 (m, 1 H), 5.92 (s, 2 H); MS *m/e* (rel intensity) 230 (1.9), 198 (4.0), 154 (9.7), 152 (9.5), 136 (100), 122 (10.4).

Irradiation of a solution of **11** (1.0 g) in methanol (550 ml) as above gave a 10% yield of **4** (by NMR and GC). None of **12** was obtained.

Dimethyl 1β,4α-Dihydroxycyclohexane-2β,3α-dicarboxylate (13). **1** (2.0 g) in 100 ml of methanol was hydrogenated in a rocking autoclave using 0.50 g of 5% Pd/C, under a pressure of 500 psi of hydrogen at 23° for 17 hr. After filtering, removing solvent at reduced pressure, and recrystallizing from benzene, we obtained 1.39 g (68%) of **13**: mp 134–135° (after two recrystallizations from benzene); ir (Nujol) 3550, 3500, 3450 (shoulder), 1735, 1718, 1440, 1315, 1300, 1240, 1220, 1190, 1175, 1167, 1115, 1050, 1035, 1000, 967, 900 cm^{-1}; NMR (Table I); MS *m/e* (rel intensity) 233 (1.3), 232 (0.0), 214 (3.7), 145 (100.0), 113 (90.0).

Anal. Calcd for $C_{10}H_{16}O_6$: C, 51.7; H, 7.0. Found: C, 51.6; H, 7.0.

1β,4α-Dihydroxy-2β,3α-bis(hydroxymethyl)cyclohexane (14). A solution of 1.19 g (5.13 mmol) of **13** in 10 ml of THF was added slowly to a stirred suspension of 1.10 g (29.0 mmol) of lithium aluminum hydride in 25 ml of THF at 10–20° under nitrogen. The mixture was stirred at 10° for 30 min, then refluxed for 2 hr. To the cooled reaction mixture, 1 ml of water was added with rapid stirring, followed by 1 ml of 15% sodium hydroxide and 3 ml of water. The solids were filtered and washed with THF (300 ml). The solution was dried, filtered, and evaporated to dryness under vacuum to give 0.81 g (90%) of **14**. Two recrystallizations from acetone gave a pure product: mp 132–133°; ir (Nujol) 3400–3200, 1420, 1360, 1288, 1200, 1185, 1100, 1075, 1015, 980, 940, 905, 865, 820 cm^{-1}; NMR (Table I); MS *m/e* (rel intensity) 177 (1.0), 176 (0.3), 158 (0.5), 140 (18.0), 110 (20.0) 85 (62.0), 79 (25.0), 54 (100.0).

Anal. Calcd for $C_8H_{16}O_4$: C, 54.5; H, 9.2. Found: C, 54.4; H, 9.0.

14 by Hydride Reduction of 1. A solution of 4.42 g (19.4 mmol) of **1** in 30 ml of THF was added to a stirred suspension of 4.00 g

(105 mmol) of lithium aluminum hydride in 100 ml of THF. The mixture was refluxed for 2 hr and the products were isolated as above. Recrystallization of the crude products from acetone gave 1.85 g (54%) of **14**, which was identical with the product from hydride reduction of **13**.

Dimethyl 1β,4β-Dihydroxycyclohexane-2β,3α-dicarboxylate (15).[15] **11** (0.98 g) dissolved in 100 ml of methanol was hydrogenated in a rocking autoclave using 0.50 g of 5% Pd/C under a 500 psi pressure of hydrogen at 23° for 17 hr. The catalyst was removed and the solvent evaporated under vacuum. Recrystallization of the residue from benzene gave 0.75 g (80%) of **15**: mp 131°; ir (Nujol) 3300, 1743, 1720, 1485, 1435, 1377, 1365, 1260, 1217, 1200, 1180, 1165, 1130, 1070, 1050, 1030, 1015, 987, 950, 930, 880, 775 cm^{-1}; NMR (Table I); MS *m/e* (rel intensity) 233 (0.1), 214 (0.1), 155 (7.0), 146 (29.6), 145 (85.2), 114 (66.2), 113 (100.0).

Anal. Calcd for $C_{10}H_{16}O_6$: C, 51.7; H, 7.0. Found: C, 51.8; H, 6.9.

1β,4β-Dihydroxy-2β,3α-bis(hydroxymethyl)cyclohexane (16). A solution of 2.85 g (12.3 mmol) of **15** in 80 ml of THF was added to a stirred suspension of 4.08 g (107 mmol) of lithium aluminum hydride in 100 ml of THF. The mixture was refluxed for 2 hr and the products were isolated as above to give 1.65 g (76%) of **16**. Two recrystallizations from methanol–benzene (1:1) gave 1.19 g (55%) of pure **16**: mp 180–181°; ir (Nujol) 3300–3150, 1485, 1340, 1315, 1280, 1215, 1190, 1100, 1087, 1060, 1040, 995, 975, 940, 900, 855, 820, 730 cm^{-1}; NMR (Table I); MS *m/e* (rel intensity) 177 (5.4), 159 (1.5), 141 (9.8), 140 (6.8), 123 (9.1), 110 (21.1), 87 (25.0), 85 (44.3), 54 (100.0).

Anal. Calcd for $C_8H_{16}O_4$: C, 54.5; H, 9.2. Found: C, 54.4; H, 9.0.

Dimethyl 4α,5β-Dihydroxycyclohexane-1β,2β-dicarboxylate (18). A solution of 12.0 g (59 mmol) of 85% *m*-chloroperoxybenzoic acid and 9.90 g (50 mmol) of dimethyl *cis*-1,2,3,6-tetrahydrophthalate[13] in 300 ml of benzene was stirred at room temperature for 2.5 days. The precipitated *m*-chlorobenzoic acid was removed and the benzene solution was extracted with 5% sodium bicarbonate (4 × 200 ml). The solution was dried, filtered, and evaporated under vacuum to give 9.67 g (90%) of a light yellow oil, that consisted of a 5:1 mixture of trans and cis epoxides of *cis*-1,2,3,6-tetrahydrophthalate.

The monoepoxide (1.0 g) was refluxed in 50 ml of water for 2 hr. Water was removed under vacuum and the residue was extracted with Et_2O (4 × 200 ml). Removal of the solvent left 1.08 g (100%) of **18** as a colorless, viscous oil: ir (film) 3450, 1735, 1440, 1265, 1215, 1165, 1065, 1015, 1000, 945, 920, 890, 850, 820, 785, 690 cm^{-1}; NMR (D_2O) δ 1.70 (m, 2 H), 2.3 (m, 2 H), 2.9 (m, 1 H), 3.2–3.6 (m, 3 H), 3.68 (s, 6 H).

Anal. Calcd for $C_{10}H_{16}O_6$: C, 51.7; H, 7.0. Found: C, 51.8; H, 6.8.

Dimethyl 4α,5β-Dihydroxycyclohexane-1β,2α-dicarboxylate (17). Dimethyl *cis*-1,2,3,6-tetrahydrophthalate (16 g) was epimerized to a 74:26 mixture of *trans*- and *cis*-1,2,3,6-tetrahydrophthalates by refluxing in 200 ml of CH_3OH containing 1.96 g of potassium hydroxide. The solvent was removed under vacuum. The residue was dissolved in benzene and extracted with water. The solution was dried, filtered, and distilled at 75–80° (9.5 Torr) to give 9.60 g (48.5 mmol) of a mixture of 76% *trans*- and 24% *cis*-1,2,3,6-tetrahydrophthalate. This was stirred with 10.6 g (52 mmol) of 85% *m*-chloroperbenzoic acid in 300 ml of $CHCl_3$ at room temperature for 20 hr. This mixture of monoepoxides (6.50 g) was refluxed in 300 ml of water for 4 hr. Water was removed under vacuum to give 6.67 g (97%) of a 3:1 mixture of **17** and **18**. **17** was isolated by crystallization from benzene. A second recrystallization from benzene gave pure **17**: mp 123–124°; ir (Nujol) 3350, 3275, 1730, 1335, 1280, 1250, 1205, 1185, 1162, 1050, 1035, 940, 915, 887 cm^{-1}; NMR (Table I).

Anal. Calcd for $C_{10}H_{16}O_6$: C, 51.7; H, 7.0. Found: C, 51.8, H, 6.8.

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Registry No.—**1**, 26549-64-4; **2**, 57236-59-6; **3**, 57236-60-9; **4**, 57236-61-0; **5**, 57197-04-3; **8**, 38201-52-4; **9**, 57197-05-4; **10**, 57236-62-1; **11**, 57197-06-5; **12**, 57197-07-6; **13**, 57197-08-7; **14**, 57197-09-8; **15**, 57236-63-2; **16**, 57236-64-3; **17**, 57197-10-1; **18**, 57236-65-4; dimethyl 3-hydroxyphthalate, 36669-02-0; *cis*-dimethyl-1,2,3,6-tetrahydrophthalate, 4841-84-3.

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Proton and Carbon-13 Nuclear Magnetic Resonance Spectra of Equilibrating Organic Cations. Evidence for a Six-Membered-Ring Halonium Ion in Equilibrium with a Tertiary Carbonium Ion

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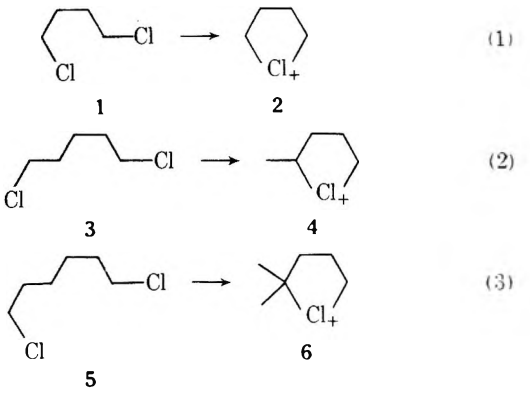
1,7-Dichloroheptane, 1,5-dichloro-5-methylhexane, and 1,4-dichloro-4-methylhexane ionized in SbF_5–SO_2 solution at −78° to give a mixture consisting principally of the following cyclic chloronium ions in equilibrium with appropriate tertiary carbonium ions: 1,1-dimethylpentamethylenechloronium ion, 1-methyl-1-ethyltetramethylenechloronium ion, and 1,1,4-trimethyltetramethylenechloronium ion. With time or higher temperatures the NMR spectrum indicated conversion of the mixture of ionic species into 1,1,4-trimethyltetramethylenechloronium ion. The three equilibrium constants for the reaction halonium ion ⇄ carbonium ion were 6.8 ± 2.0, 0.53 ± 0.07, and 0.055 ± 0.027, respectively, at −59.7° as determined by ^{13}C NMR chemical shifts. These results show that the six-membered-ring chloronium ion is predominantly converted to open carbonium ion at equilibrium, whereas five-membered chloronium ions exist predominantly as the cyclic species. The energy and entropy terms which may account for these results are discussed.

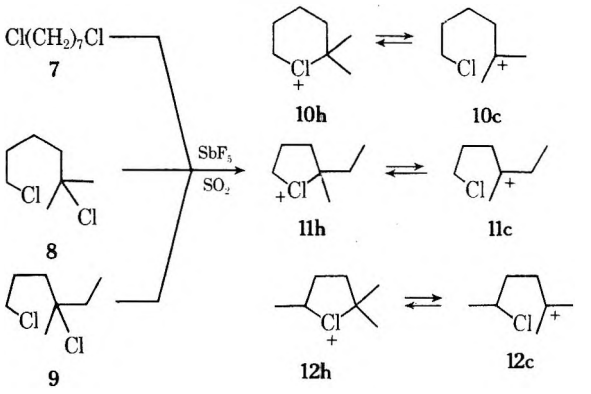
In previous work[2] the following reactions (eq 1–3) of polymethylenedihalides with SbF_5 in SO_2 have been observed. The ion **4** is presumably formed from 1,4-dichloropentane (**3**) in a process involving hydrogen shift, whereas



hydrogen and carbon shifts are involved in the formation of **6** from 1,5-dichloropentane.

We have now studied the products of reaction of the next member of the series, 1,7-dichloroheptane (**7**). In contrast with the clean reactions of dihalides **1**, **3**, and **5**, the reaction of 1,7-dichloroheptane produced a complex ^1H NMR spectrum (Figure 1) in which some of the chemical shifts were not readily attributable to known types of halonium or carbonium ion. Both the relative amounts and *positions* of some of the peaks seemed to vary from experiment to experiment. Below we shall describe observations which indicate that the rapidly equilibrating carbonium ion–halonium ion systems, **10h** ⇄ **10c** and **11h** ⇄ **11c**, sometimes accompanied by **12h** ⇄ **12c**, were the major products present. As we shall point out again, still unidentified components also were formed in some experiments. As shown in Scheme I, the products, **10**, **11**, and **12** were obtained also upon ionization of the branched dihalides **8** and **9**. Temperature dependence of the equilibrium constants and slow conversion of the ions to the most stable equilibrating system, **12h** ⇄ **12c**, were responsible for the apparently variable results of early experiments. (The letters **h** and **c** designate halonium and carbonium ion forms, respectively). Comparable rapid equilibria between halonium ions and carbonium ions have previously been reported in the case of five-membered-ring chloronium ions.[3a] Although six-membered-ring iodonium and bromonium ions were previously reported,[4] there has been no previous NMR detection of a six-membered-ring chloronium ion.

Scheme I



Results

Both the ^1H and the ^{13}C spectra of the ionized solutions obtained from 1,7-dichloroheptane were complex (Figures 1 and 2, Tables I and II). Nevertheless, the ^{13}C spectrum clearly indicated the presence of three seven-carbon ions or equilibrating groups of ions. The most notable features of the hydrogen spectrum (approximately −65°) were an apparent triplet at δ 3.43 showing the unusually small J value 4 Hz and an upfield triplet at δ 1.19, J = 7 Hz. The appearance of the downfield triplet is reminiscent of the spectrum of the *gem*-dimethyl group of the *tert*-amyl cation,[5] which shows long-range coupling (J = 5 Hz), However, the chemical shift, δ 3.43, is substantially upfield from that of *tert*-amyl cation (δ 4.12). An equilibrating mixture of **10d** and a lesser amount of **10h** is, however, consistent with our observations. The triplet at δ 3.75 also is in an appropriate position for the CH_2Cl methylene hydrogens in **10c** ⇄ **10h**. More definitive evidence for the presence of the structure **10c** ⇄ **10h** is provided by ^{13}C NMR spectroscopy and quenching experiments, to be described.

That the second species present in the mixture contained an ethyl group was suggested by the presence of the previously mentioned triplet at δ 1.19. The structure **11h** ⇄ **11c**, equilibrating ions with the halonium ion form predominating, are reasonable possibilities. As expected, if a small amount of the carbonium ion form contributes to the averaged spectrum, the assigned methyl resonance, at δ 2.53 (Figure 1) shows significant broadening, attributable to

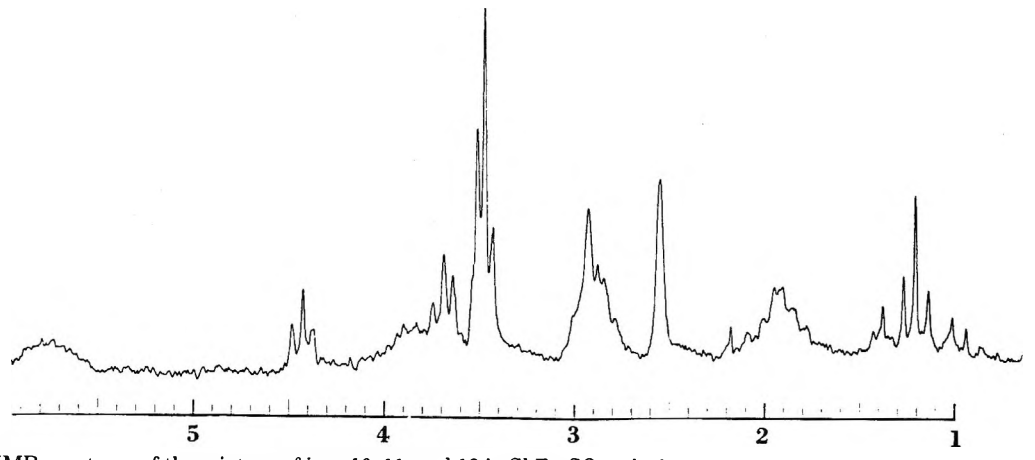


Figure 1. ^1H NMR spectrum of the mixture of ions **10**, **11**, and **12** in SbF_5–SO_2 solution.

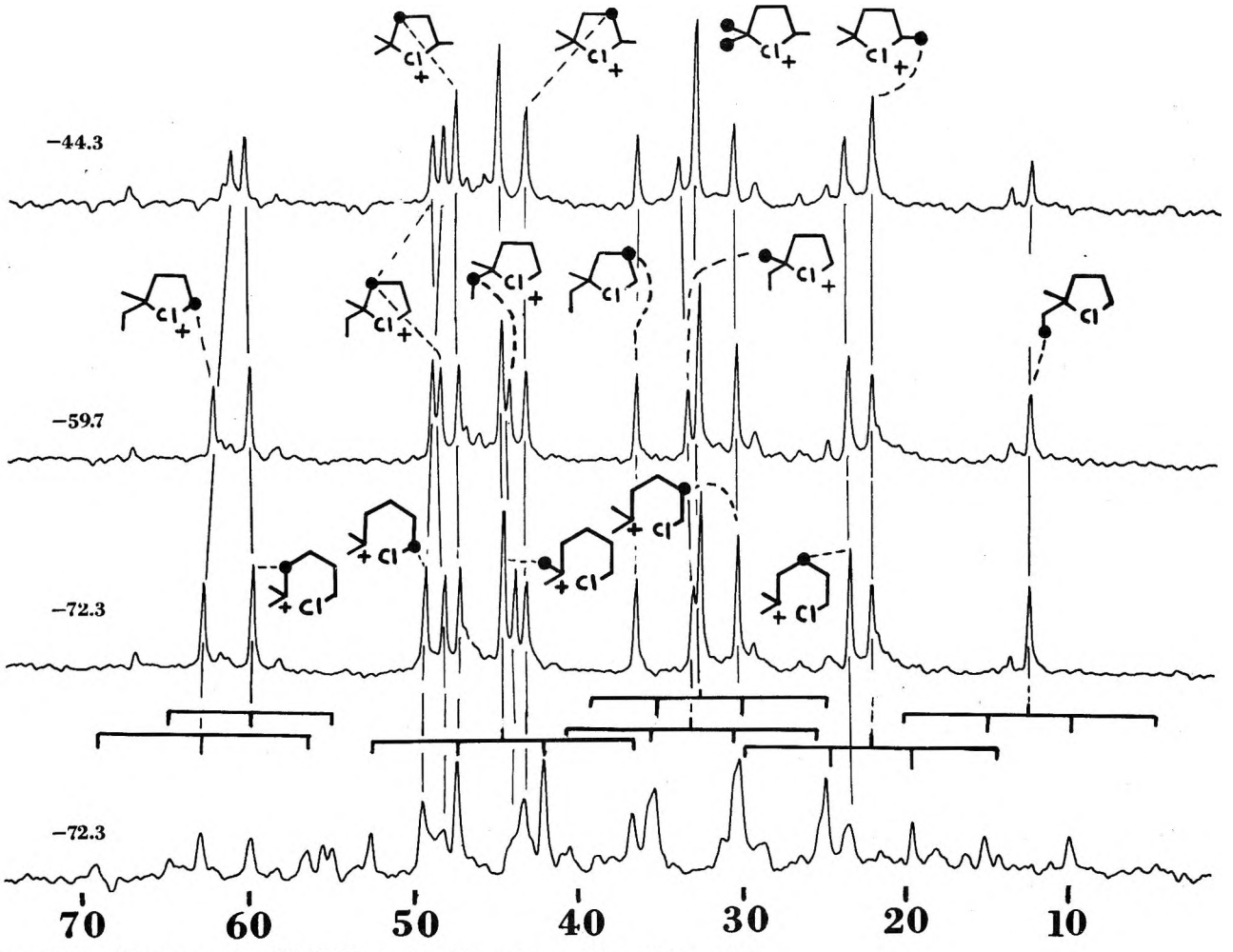


Figure 2. Variable-temperature ^{13}C NMR spectra of the mixture of ions **10**, **11**, and **12**.

long-range coupling. However, spectra taken at high temperatures showed a partially resolved unassigned second peak in this region. The triplet at δ 4.42 (Figure 1) is attributable to the CH_2Cl^+ methylene hydrogens in **11**. Additional evidence for the presence of **11h** ⇄ **11c** was provided by ^{13}C NMR and quenching experiments, to be described.

The third species, **12** (Scheme I), was present only in small amounts immediately following ionization of **7** at −78°, as indicated by the small size of its singlet at δ 2.2 (Figure 1). However, the spectrum of **12**, which was known from previous work,[3] became the dominant feature a sample of which was stored overnight at −65°. The identification of **12**, confirmed by ^{13}C NMR and quenching experiments, simplified the spectroscopic studies of ion mixtures, since allowing for the presence of **12** (if present) in effect reduced the structural problem to that of a two-component mixture. In addition to the features of the hydrogen spectra of ion mixtures which have been described, additional unassigned peaks were present in some of the ion mixtures, including those shown near δ 5.75 in Figure 1, downfield peaks in the region δ 8.5–10, and lines at δ 3.76 and 4.27 (not present in Figure 1).

During ^{13}C NMR experiments, peaks for **12** increased irreversibly, especially at higher temperatures. After allowing for these peaks, the upfield region still showed considerable complexity (Figure 2). A striking feature is that a

Table I
^{1}H NMR Spectra of Equilibrating Ions

Ions	$-CH_2Cl^+-$ or CHCl	$-CH_3$
10h and 10c	~4.4 t[a]	3.43 t
11h and 11c	4.32 t	2.63 s and 1.20 t
12h and 12c	6.55 m	2.19 s and 1.85 d

[a] Temperature dependent.

in equilibrium with a smaller amount of the carbonium ion analogous to **10c**. Other species were present, probably including an ethylated ion analogous to **11**. However, 1,5-dibromo-5-methylhexane was difficult to purify as it decomposed badly on distillation, and no detailed work was done with the slightly impure material available.

Calculations. Equilibrium constants for the reaction cyclic halonium ⇄ carbonium ion were calculated by the previously described method[3] from the chemical shifts of the

Table II
^{13}C NMR Chemical Shifts of Equilibrating Ions

Ions	Temp, °C	C–X$^+$[a]	C–CH_2C[a]	CH_3[a]
10h ⇄ 10c	−72.1	49.1, 309.3	23.3, 30.2, 61.6	44.4
	−59.7	48.7, 310.9	23.4, 30.3, 59.9	44.6
	−44.3	48.0, 313.5	23.7, 30.4, 60.2	44.7
11h ⇄ 11c	−72.1	62.7, 213.1[b]	36.3, 43.6, 48.0	12.4, 32.9
	−59.7	62.1, 219.3	36.2, 44.1, 48.2	12.3, 33.2
	−44.3	61.0, 226.2	36.2, 44.7, 48.7	12.2, 33.8
12h ⇄ 12c	−72.1	99.2, 154.1	43.0, 47.1	22.0, 32.4
	−59.7	98.9, 155.6	43.1, 47.1	22.0, 32.5
	−44.3	98.3, 158.4	43.0, 47.3	21.9, 32.7

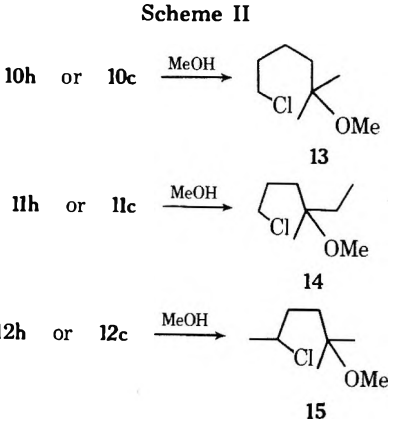
[a] For tentative assignment see Figure 2. [b] Measured at −72.3°.

number of the frequencies were temperature dependent, some shifting upfield with increasing temperature whereas others shift downfield. Spectra taken at five temperatures (three shown in Figure 2) showed that some peaks reversed their relative positions as the temperature was changed. The temperature dependence provides strong evidence that equilibrating halonium–carbonium ion systems are present, by analogy with the systems which we previously studied.[3a] As in the earlier study the lines which shifted downfield with increasing temperature were assigned to carbons near the carbonium ion center, whereas those which shifted upfield were assigned to carbon atoms in the vicinity of the primary chlorine in the carbonium ion, as expected if the percentage of carbonium ion increases with temperature. The coupled spectrum (Figure 2) served to distinguish CH_2 carbons from others. Based on the features mentioned above, plus comparison of chemical shifts with those from our earlier papers, a tentative assignment (Figure 2) was made for all major lines. Although our ability to find peaks in the expected regions which exhibit the expected temperature dependence provides additional evidence for the presence of structures **10** and **11**, the most useful information gained from the ^{13}C NMR spectrum is the evidence (from temperature dependence) that equilibrating systems were present. As in the earlier study, the chemical shifts of the tertiary carbons, which were especially temperature dependent, were used in the calculation of equilibrium constants (see below).

Although we postulated the identity of ions **10**, **11**, and **12** from NMR studies, reaction of the ion solution with methanol to give ethers **13**, **14**, and **15** (Scheme II) provided probably the most unequivocal evidence for the presence of structures **10** and **11**. The ^{1}H and ^{13}C NMR spectra of the products corresponded with those of compounds prepared by methanolysis of the corresponding tertiary dichlorides (cf. Scheme II). The extraordinary power of ^{13}C NMR spectroscopy for identification of mixtures was illustrated by examination of distillation fraction containing **13**, **14**, and **15**. Both the presence of these ethers and the absence of others in appreciable amounts was demonstrated, although some lower boiling alkenes were present in some fractions.

1,5-Dibromo-5-methylhexane, the bromine analogue of **8**, also ionized in SbF_5–SO_2 solution at −78° to give a solution whose ^{1}H and ^{13}C NMR spectra were consistent with the presence of a six-membered-ring ion analogous to **10h**

Scheme II



tertiary carbons in **10**, **11**, and **12** with the equation $K = (\nu_h - \nu_0)/(\nu_0 - \nu_c)$ where ν_h = chemical shift of the halonium ion, ν_c = chemical shift of the carbonium ion, and ν_0 = the observed averaged chemical shift. Chemical shifts in parts per million from Me_4Si were estimated as follows. For **10c** and **12c** the shift of the tertiary carbon was assumed to be the same as that of *tert*-amyl cation, 334.7 ppm.[3] For **11c** the value 338.5 ppm was used. The shift of 148.7 ppm, which was previously used for the tertiary carbon in 1,1-dimethyltetramethylenechloronium ion, was used for **10h** even though there is an obvious risk in assuming that corresponding carbons in five- and six-membered rings have the same chemical shift. The chemical shifts of the 1 carbons in tetramethyleneiodonium ion and pentamethyleneiodonium, for example, differ by 13.1 ppm.[3] The difference for the corresponding bromonium ions is only 7.5 ppm, however, so that it is reasonable that a negligible difference occurs for chloronium ions.

The shift of the tertiary carbon in **11h** was taken to be 156.4 ppm based on the previously measured shift of the 1 carbon in 1-ethyltetramethylenechloronium ion, 121.1 ppm, and the observed downfield shift of 35.3 ppm caused by a 1-methyl substituted on the carbon to which it is attached. As before,[3] a shift of 145.7 ppm was used for the tertiary carbon in **12h**.

From the assumed and observed chemical shifts the equilibrium constants and free-energy differences shown in Table III were computed. The errors shown are based on an error of ±0.01 ppm in the measured chemical shifts, ±2° in

Table III
Equilibrium Constants and ΔG Values for Halonium Ion–Carbonium Ion Equilibria

Ion	Temp, °C	Equilibrium constant	ΔG, kcal/mol
10	−44.3	7.9	−0.93
	−59.7	6.8 ± 2.0	−0.82 ± 0.1
	−72.3	6.3	−0.73
11	−44.3	0.62	0.22
	−59.7	0.53 ± 0.07	0.27 ± 0.05
	−71.8	0.45	0.32
12	−36.0	0.081[a]	1.19[a]
	−44.3	0.072	1.20 ± 0.2
	−54.3	0.061[a]	1.22
	−59.7	0.055 ± 0.03	1.23 ± 0.2
	−67.8	0.049[a]	1.24[a]
	−72.3	0.046	1.23

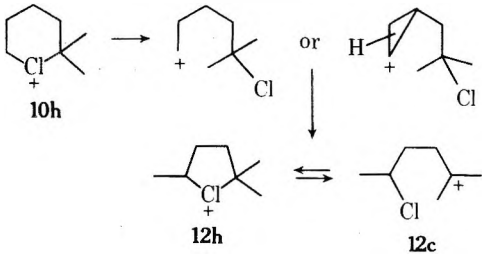
[a] From ref 2.

the temperature and ±5 ppm in the assumed chemical shifts. Although the latter value (±5 ppm) was used as a basis of calculation, a larger value (±10 ppm) would not affect our conclusions or discussion. Referees have expressed some skepticism regarding the reliability and accuracy of our calculations because of the assumptions involved. Let us consider in more detail the data for ion **10**. The observed tertiary carbon shift (approximately 310 at −60°) is 24 ppm from the estimated values for the tertiary cation (334.7) and enormously far from that of the chloronium ion (148.7). The open cation **10c** differs from the *tert*-amyl cation only in having attached carbons at the γ and δ positions, plus a chlorine at the ϵ position. The average shift produced by a γ carbon is only −2.5 ppm, and δ and ϵ effects are usually much less. Our assumed error is based on consideration of these values. Since the ^{1}H NMR spectrum indicates that a *predominantly open* cation such as **10c** is present, and since **11c** is expected to be predominantly closed based on our earlier work, there is little reason to doubt that the temperature-dependent peak near 310 ppm is that of **10c**. In summary, we have cited what appears to us to be a sound basis for our calculations and conclusions, although evidence presently unknown to us could lead to a modification of our interpretation.

Discussion

It is interesting that the dimethylated six-membered-ring chloronium ion **10h** has now been observed as a component of an equilibrating system. Its rearrangement reaction (Scheme III) involving the breaking of the bond between chlorine and the unmethylated carbon (to give a primary carbonium ion or its protonated cyclopropane equivalent) is relatively slow. In contrast, the unsubstituted six-membered-ring chloronium ion apparently rearranged too rapidly to allow its preparation.[3] This inference is based on the observation that the corresponding iodonium ion was relatively stable whereas the six-membered-ring bromonium ion rearranged fairly rapidly.[3] Although the primary cationic transition states for rearrangement of unsubstituted and dimethylated chloronium ion should be of similar stability, the presumed difference in rates of rearrangement can be understood in terms of ground-state stabilization of the dimethylated reactant, **10h**. Substantial stabilization of three-membered-ring halonium ions by methyl substituents has been observed, and smaller stabilization of larger rings has been suggested.[4,6] We note that this stabilization, if present, slows but does not prevent rearrangement of **10** to trimethylated ion **12** (Scheme III) at higher temperature or longer reaction times.

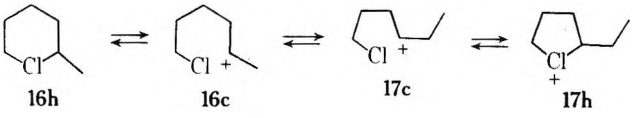
Scheme III



Having accounted for the formation of trimethylated ion **12** in terms of the less favored opening of the six-membered-ring **10h** at the primary position (Scheme III), it remains for us to note that rearrangement of the tertiary ion **10c**, present in large amount, accounts for the formation of the methylethyl species **11h** ⇄ **11c**. A similar rearrangement occurs in the *tert*-amyl cations, resulting in carbon scrambling.[7] Our results do not show whether **10** and **11** are present in a thermodynamically controlled equilibrium or whether they are formed in the observed proportions in a kinetically controlled process during the initial reaction of halide precursors.

Completing our survey of the status of primary, secondary, and tertiary six-membered-ring chloronium ions, we note that presently unknown secondary chloronium ions such as **16h** (Scheme IV) should be in rapid equilibrium

Scheme IV



with small amounts of the corresponding secondary carbonium ions. This conclusion is implied by the observation that hydrogen scrambling broadens the hydrogen multiplet of the CH_3 group of ethylated ion **19h** at −65°.[3] Since the six-membered ring is a minor component in the mixture, we infer that monoalkylated five-membered-ring **17h** is more stable than the comparable six-membered-ring **16h**.

This inference leads us to a discussion of the direction of the halonium ion–carbonium ion equilibria observed in this study and the earlier one. The most noteworthy result is that the six-membered-ring **10h** is predominantly opened to **10c**, whereas five-membered rings have all been present predominantly in the closed form. Although molecular orbital energy levels may play a part in these ring size effects (cf. ref 4), the observed effect may actually be due to a mixture of enthalpy and entropy effects which should be considered in detail. In principle, both enthalpy and entropy differences for the equilibria may be determined from the data in Table III. However, the values so determined may not be accurate enough for meaningful comparison. It is apparent, however, that the closed species is favored by enthalpy for both the five-membered-ring ions and the six-membered-ring ion, since the open-chain species increases in concentration with higher temperature for all cases and $d(\ln K)/d(1/T) = -\Delta H/R$. Therefore, at least for **10** the entropy difference is the overriding factor in determining to which side the equilibrium lies. For hydrocarbons equilibria between open and closed species have been found to favor the closed species more highly when a five-membered ring rather than a six-membered ring is involved.[8] Comparable effects could account for part or all of the preference for five-membered-ring formation observed in our study. However, still another effect remains to be considered. The carbonium ions in equilibrium with five-membered rings

are probably destabilized relative to those derived from six-membered rings because the electronegative halogen substituents of the former are closer (by one methylene group) to the positive charge. If the magnitude of the effect is comparable to that in transition states for solvolyses, the available data suggest that a threefold effect on the ratio of K values might be expected from this factor alone.[9]

Conclusion

The value of ^{13}C NMR in the analysis of equilibria involving a complex mixture of equilibrating ions is illustrated by the present study. Since there are very few systems in which equilibrium constants can be determined in ring-forming reactions, the system described here presents a rare opportunity to assess factors governing the energetics of formation of five- and six-membered rings.

Experimental Section

The ^1H NMR spectra were obtained on Varian A-60 and XL-100-15 instruments. Chemical shifts were referenced to a capillary of Me_4Si in SO_2 or internal Me_4Si in carbon tetrachloride. The ^{13}C NMR spectra were obtained by the Fourier transform method on the Varian XL-100-15 with noise decoupling and between 500 and 1000 pulses. Chemical shifts were measured from CF_2BrCF_2Br in a 5-mm tube within the 12-mm tube and were corrected to capillary Me_4Si using a value of 115.32 ppm for the difference in chemical shifts between Me_4Si and $(CF_2Br)_2$. Temperature measurements were made as previously described.[3]

Ionic Solutions. The ion solutions were made in 5-mm NMR tubes by addition of 0.27 mmol of one of the dichlorides to 0.5 ml of a 1.25 M solution of SbF_5 (Ozark Mahoning, redistilled) in SO_2 (0.68 mmol of SbF_5). The solutions were cooled in a dry ice–acetone bath during the addition with stirring with a Nichrome wire. Similar proportions were used in the preparation of samples in 12-mm tubes for ^{13}C spectroscopy. Some NMR samples were also taken from solutions prepared in a volumetric flask for reaction with methanol (see below).

1,7-Dichloroheptane was prepared by reaction of 18.51 g of 1,7-heptanediol (0.14 mol) with 36.64 g of thionyl chloride (0.31 mol) in 25.31 g of pyridine (0.32 mol). The product was separated after extraction by spinning-band distillation, bp 95–97° (13 mm).

Anal. Calcd for $C_7H_{14}Cl_2$: C, 49.72; H, 8.34. Found: C, 49.66; H, 8.43.

1,4-Dichloro-4-methylhexane. To a solution of 24.51 g (0.20 mol, Aldrich) of γ-chlorobutyric acid in 150 ml of dry ether in a dry, nitrogen-flushed flask was added dropwise 278 ml (0.50 mol, Lithcoa) of methyllithium solution. Total addition time was 1.5 hr, after which 60 ml of water was added dropwise with cooling in ice. The ether solution was washed twice with water and dried over Na_2SO_4. Spinning-band distillation gave 13.2 g (55%) of 5-chloro-2-pentanone, bp 73–75° (22 mm).

In a 500-ml, dry, nitrogen-flushed flask were placed 2.67 g (0.11 mol, MCB for Grignard) of magnesium turnings and 50 ml of dry ether. A solution of 11.99 g (0.11 mol) of ethyl bromide in 50 ml of ether was added dropwise with cooling in ice. The solution was allowed to warm to room temperature and then was stirred for 0.5 hr after which 12.06 g (0.10 mol) of the 5-chloro-2-pentanone was added with cooling. After the solution had returned to room temperature, 15 ml of a saturated solution of ammonium chloride was added to precipitate the magnesium salts. The ether solution was filtered, and solvent was removed by distillation. The remaining liquid was stirred with concentrated HCl for 20 min, then was extracted into CH_2Cl_2. The CH_2Cl_2 solution was washed once with 7 N sulfuric acid, once with saturated $NaHCO_3$ solution, and with water. Spinning-band distillation resulted in 8.9 g of product boiling at 68–69° (6 mm) (58% yield from the ketone), ^1H NMR (CCl_4) δ 3.50 m, 2 H; 1.5–2.0 m, 6 H; 0.98 t, 3 H.

Anal. Calcd for $C_7H_{14}Cl_2$: C, 49.72; H, 8.34. Found: C, 49.73; H, 8.34.

1,5-Dibromo-5-methylhexane. Hydrogen bromide was bubbled through a solution of 35.01 g (0.35 mol, Aldrich) of δ-valerolactone in 500 ml of anhydrous ethanol for 3 hr. The solution was poured into 250 ml of water which was then extracted five times with CH_2Cl_2. The organic solution was dried with Na_2SO_4 and distilled to give 23.4 g of ethyl 5-bromopentanoate: bp 63° (0.4 mm); yield 32%; ^1H NMR δ 4.05 t, 3.35 t, 2.24 m, 1.80 m, 1.22 t.

A Grignard reaction was carried out using 20.7 g (0.1 mol) of ethyl 5-bromopentanoate, 31.2 g (0.22 mol) of methyl iodide, and 5.35 g (0.22 mol) of magnesium. The procedure was the same as that used above for 1,4-dichloro-4-methylhexane. The liquid remaining after removal of the ether was allowed to react with 100 ml of concentrated hydrobromic acid for 20 min. The product was extracted into CH_2Cl_2 which was then washed with saturated $NaHCO_3$ solution and a saturated solution of $Na_2S_2O_3$. Attempted distillation on a spinning-band column gave a material having olefinic peaks in the ^1H NMR spectrum. The remaining material was extracted with concentrated sulfuric acid, then with sodium bicarbonate solution, then water. A short-path distillation (90°, 0.2 mm) led to 1.55 g of clear liquid: ^1H NMR δ 1.72 s, 3.35 t.

Anal. Calcd for $C_7H_{14}Br_2$: C, 32.59; H, 5.47. Found: C, 32.71; H, 5.35.

1,5-Dichloro-5-methylhexane was prepared from δ-valerolactone (35.0 g) by the same procedure used for 1,5-dibromo-5-methylhexane except that ring opening was accomplished with hydrogen chloride gas.

Distillation gave ethyl 5-chloropertanoate, 26.1 g (46%), bp 85–90° (12 mm). A portion of the ester (24.6 g) was allowed to react with methylmagnesium iodide to give an ether extract which was allowed to react with 100 ml of 12 M HCl for 1 hr. Distillation of the ether extract gave 16 g, bp 30–63° (2 mm), in five fractions, shown by NMR to contain an impurity thought to be 1-iodo-5-chloro-5-methylhexane: ^1H NMR δ 1.55 s, 1.70, 3.50 t.

Anal. Calcd for $C_7H_{14}Cl_2$: C, 49.72; H, 8.35. Found: C, 49.72; H, 8.34.

Reaction of Ions with Methanol. Ionic solutions prepared from 1,7-dichloroheptane and 1,5-dichloro-5-methylhexane were allowed to react with methanol, and the products were collected by distillation. The procedure for the solution prepared from 1,5-dichloro-5-methylhexane is described in detail. The 1,5-dichloro-5-methylhexane (12.50 g, 0.07 mol) was dissolved in 40 ml of sulfur dioxide. This solution was added to a mixture of 40.07 g of SbF_5 (0.18 mol) and 50 ml of sulfur dioxide with agitation. The ^1H NMR and the ^{13}C NMR spectra of the resulting solution indicated that there were roughly equal concentrations of the three ions **10**, **11**, and **12**. (The solution from 1,7-dichloroheptane contained a larger relative concentration of **12**, possibly owing to heating by the reaction.)

The SO_2 solution was poured into 100 ml of methanol containing 10 g of K_2CO_3. The temperature was maintained below 40°. The solution was allowed to evaporate at room temperature and was poured into 100 ml of H_2O and 100 ml of CH_2Cl_2. A yellow precipitate was removed by filtration, and the CH_2Cl_2 solution was washed with saturated $NaHCO_3$ and H_2O. An emulsion formed which was partially broken by addition of saturated NaCl. Removal of solvent and spinning band distillation gave 15 fractions (Table IV).

Table IV

Fraction	Temp, °C	Pressure, mm	Weight, g
1	42–49	13	0.37
2–5	49–59	13	0.82
6–11	61–68	13	3.16
12–14	70–72	13	0.94
15	60	1.5	0.80

^1H NMR spectra of the undistilled material and fractions 2, 5, 6, 7, 10, 13, 14, and 15 were recorded. All of the fractions were also analyzed by VPC (DC 550, 163°, glass column). Unfortunately, variable results indicated that some elimination occurred during VPC analysis even with the glass column. Furthermore, while there was no large olefinic peak in the ^1H NMR spectrum of the undistilled material, the spectra of fractions 2 and 5 had substantial intensity between δ 4.9 and 5.1 indicating that some elimination also occurred during distillation.

The NMR spectra of fractions 5, 6, and 7 showed that 2-chloro-5-methoxy-5-methylhexane (**15**), derived from 1,1,4-trimethyltetramethylenechloronium ion, was the major component, but some olefin was also present. The ^1H NMR spectrum of fraction 10 had much smaller olefinic peaks, and the ^{13}C NMR spectrum and the VPC analysis matched that of authentic **15**.

The ^1H and ^{13}C NMR spectra of fraction 15 indicated that it was a mixture of chloro ethers **13** and **14**, whose spectra were available from reference samples described below. Fractions 13 and 14 were mixtures of **13**, **14**, and **15** and also contained olefin. The ethers **13** and **14** are the expected products of reaction of 1,1-di-

methylpentamethylenechloronium ion and 1-methyl-1-ethyltetramethylenechloronium ion, respectively.

Solutions of chloro ethers **13**, **14**, and **15** were prepared by solvolysis of 0.005 mol of the corresponding dichlorides in 5 ml of methanol containing 1.0 g of $NaHCO_3$. The reactions were followed by VPC (DC 550, 163°, glass column) and required about 9 hr reflux for completion. The products were isolated in 5 ml of CCl_4 which was washed twice with 5-ml portions of water. The ^1H NMR spectra of the products indicated that some elimination occurred during solvolysis. Nevertheless, only very minor peaks in the ^{13}C NMR spectra of the undistilled products could not be assigned to the desired substitution products, except for the solvolysis which yielded **14**. In this instance, olefin was removed by distillation at ~1 mm pressure before the NMR spectra of the undistilled residue were obtained.

The ^{13}C NMR spectrum of **13** was recorded at room temperature in CCl_4. Chemical shifts relative to the solvent peak were converted to Me_4Si reference by subtraction of 96.0 ppm. The chemical shifts (parts per million from Me_4Si) follow: 73.5, *t*-C; 48.6, OCH_3; 44.1, $-CH_2Cl$; 39.6, $-CH_2-$; 33.1, $-CH_2-$; 24.8, $-CH_3$; 21.1, $-CH_2-$.

The ^{13}C NMR chemical shifts of **14** follow: 45.0, $-CH_2Cl$; 34.4, $-CH_2-$; 30.0, $-CH_2-$; 26.7, $-CH_2-$; 22.0, $-CH_3$; 17.9, $-CH_3$. (The methoxy peak was weak in all of the spectra, probably owing to a long relaxation time, and was not always observed with certainty.)

The ^{13}C NMR chemical shifts of **15** follow: *t*-C, 58.3, C-Cl; 37.0, $-CH_2-$; 34.3, $-CH_2-$; 25.5, 25.1, and 24.8, $-CH_3$. (Note that the three methyl groups are nonequivalent owing to the asymmetric carbon.)

Acknowledgment. We are grateful to Mr. William Fahey for making initial observations at St. Louis University on the system produced from 1,7-dichloroheptane in SbF_5–SO_2 solution. Support by the National Science Foundation (Grant GP 30683) is gratefully acknowledged.

Registry No.—**7**, 821-76-1; **8**, 54305-92-9; **9**, 54305-94-1; **10c**, 57256-52-7; **10h**, 57256-53-8; **11c**, 57256-54-9; **11h**, 57256-55-0; **12c**, 57256-56-1; **12h**, 50635-30-8; **13**, 57256-57-2; **14**, 57256-58-3; **15**, 57256-59-4; 1,7-heptanediol, 629-30-1; γ-chlorobutyric acid, 627-00-9; 5-chloro-2-pentanone, 5891-21-4; 1,5-dibromo-5-methylhexane, 54305-93-0; δ-valerolactone, 542-28-9; ethyl 5-bromopentanoate, 14660-52-7; ethyl 5-chloropentanoate, 2323-81-1.

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Notes

The Rapid HI Cleavage of Ethers and Ketals in Acetonitrile. Catalysis by CH_3OCHI_2 and Preparation of Formates

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The use of ethers as alcohol protecting groups in synthesis has aroused recent interest.[1] Ganem noted "the dearth of gentle yet effective techniques for releasing the parent alcohol". We wish to report that the use of acetonitrile as solvent with diiodomethyl methyl ether (DIME) catalysis promotes the classic HI cleavage[2] into the gentle and effective category at least for primary and secondary alkyl methyl ethers. Methyl ethers may be cleaved in good yield in 30 min or less at room temperature (Table I). At the cost of increasing the reaction time to hours, cleavage may be accomplished with 1 equiv of HI generated in controlled fashion by the addition of toluenesulfonic acid hydrate to excess sodium iodide. Other gentle and selective reagents are available for ether cleavage.[3,4]

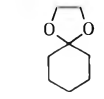
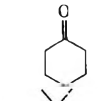
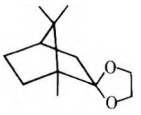
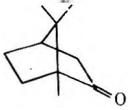
The HI cleavage of ethers in acetonitrile exhibits all the hallmarks of the classic reaction.[2]

$$ROCH_3 + HI \rightleftarrows ROH(CH_3)^+ \begin{cases} \nearrow ROH + CH_3I \\ \searrow R^+ \longrightarrow RI \end{cases}$$

When R is primary or simple secondary alkyl group, the methyl–oxygen bond is cleaved. When R^+ is a good carbonium ion, such as tertiary alkyl or benzyl, iodide is the predominant product. *exo*-Norbornyl shows intermediate behavior, yielding a 50:50 mixture of iodide:alcohol. Chiral 2-octyl methyl ether is cleaved with complete retention of the C-2–O bond. Ethers which are strong Lewis bases, such as tetrahydrofuran, 7-oxanorbornane, epoxides, and, of synthetic importance, ketals, are all cleaved readily. Cyclohexanone and camphor are regenerated in excellent yield from their ethylene glycol ketals in 5 min at room temperature in the presence or absence of DIME. Ethers which are weak Lewis bases such as tetrahydropyran, dibutyl ether, and anisole are unaffected at room temperature.[5]

DIME, prepared in situ from 1,1-dichloromethyl ether (DCME) and sodium iodide, catalyzes ether cleavage and yields formate as the predominant product. Initial speculation suggested that the oxonium ion CH_3OCHI^+ acted as a Lewis acid catalyst for the cleavage in the same manner as the reported catalysis by acetyl derivatives.[6] However, unyielding experiments showed that if all reagents are rigor-

Table I
Ether Cleavage at Room Temperature in Acetonitrile

Registry no.	Ether ($ROCH_3$)	Reaction conditions[a] NaI:DCME:H_2O	% yield of products[b,c] ROOCH	RI	ROH	$ROOCCH_3$
929-56-6	1-Octyl methyl ether	A 4:2:1	43	40	2	8
		A 4:2:2	60	28	11	*d*
		A 8:2:2	41	41	0	*d*
		A 8:4:4	61	22	15	*d*
		B 8:4:4	75	13	2	2
					(69)	
		C 4:2:3.5		25	42	9
56711-42-3	2-Octyl methyl ether	A 4:2:2	48	35	0	*d*
		A 8:4:4	75	14	7	*d*
		A 8:2:10	0	*d*	*d*	*d*
		B 8:4:4	75	8	9	5
					(84)	
		C 8:4:4		7	87	
57132-05-5	2,4-Dimethyl-3-pentyl methyl ether	A 8:4:1	47	5		
		B 8:4:4	41	*d*	9	*d*
					(35)	
		C 8:4:3			48	
5614-37-9	Cyclopentyl methyl ether	A 4:2:2	70	14		2
931-56-6	Cyclohexyl methyl ether	A 8:4:4	52	6		
32122-44-4	1-Methylcyclohexyl methyl ether	A 4:2:2	0	16	0	0
10395-53-6	*exo*-Norbornyl methyl ether	A 8:4:3	35	37[e]	0	0
		B 8:4:4	40	40	0	0
				(32)	(18)	
		C 4:2:14		37	36	
5331-32-8	Borneol methyl ether	B 8:3:5	75			
		C 5:1:19			83	
100-66-3	Anisole	A 8:4:4	0	0	0	0
538-86-3	Benzyl methyl ether	A 4:2:2	0	*f*	0	0
929-56-6	1-Octyl ethyl ether	A 8:4:2	11	17		
42-96-1	Di-1-butyl ether	A 8:4:2	0	0	0	0
		C 8:8:36	0	*d*	0	0
109-99-9	Tetrahydrofuran[g]	A 4:4:2	80	8	7	5
		A 4:2:2	85	11	*d*	*d*
		C 4:4:0.5		27	32	
96-47-9	2-Methyltetrahydrofuran[h]	A 8:5:2	59	32		
142-68-7	Tetrahydropyran[i]	A 4:4:2	0	0	0	0
		C 8:8:36		5	5	2
279-49-2	7-Oxanorbornane[j]	A 4:2:2	57	0	31	
		C 8:2:1.5			73	
		A 8:4:0[k]			95	
177-10-6		C 8:4:0.25[k]			95	
18501-53-6		A 8:4:4[k]			87	
		B 4:2:0[k]			(83)	

[a] A and B reaction times 20–30 min. A, DIME reactions run on ca. 5 mmol of ether in 10 ml of MeCN. Numbers following refer to equivalents of NaI, DCME, and H_2O, respectively. B, DIME reactions run on preparative scale of at least 0.1 mol. The second line gives the isolated yield of alcohol after hydrolysis with KOH in aqueous ethanol. C, HI reactions run on ca. 5 mmol of ether in 10 ml of MeCN. Numbers following refer to equivalents of NaI, $TsOH \cdot H_2O$, and the time in hours, respectively. [b] GC yields with internal standard. Yields for type B reactions are GC determinations on isolated crude mixture. Numbers in parentheses are isolated yields. [c] R is identical in starting ether and product unless noted. Structures were confirmed by comparison with authentic samples, by ir and NMR spectroscopy, and in the case of formates, by hydrolysis to alcohol starting materials. [d] Present in low yield; actual quantity not determined. [e] Stereochemistry established by comparison of NMR spectrum with that of authentic sample: H. C. Brown, N. R. DeLue, and E. N. Peters, submitted for publication. [f] Benzyl iodide formed in good yield; actual quantity not determined. [g] R = 4-iodobutyl. [h] R = 5-iodo-2-pentyl. [i] R = 5-iodopentyl. [j] R = *trans*-4-iodocyclohexyl. Confirmed by ir [Y. Takeoka, *Bull. Chem. Soc. J.*, 35, 1371 (1962)] and ^{13}C NMR. [k] Reaction time 10 min.

ously dried, there is no ether cleavage except for limited reaction of the most reactive ethers. Addition of 1 or more equiv of water regenerates reactivity. Furthermore, when excess proton specific base, 2,4,6-tri-*tert*-butylpyridine,[7] is present no cleavage occurs over several hours. Thus the mechanistic aspects of DIME catalysis remain obscure, but its practical efficacy is apparent (Figure 1). The alcohol could be an intermediate in the reaction, as it was demonstrated that alcohol could be converted to formate and incompletely to iodide under reaction conditions. Formate and iodide are stable to reaction conditions. The importance of iodide nucleophilicity was demonstrated not only by the selectivity for methyl cleavage, but also by the cleavage of 2-methyltetrahydrofuran to give 5-iodo-2-pentyl formate with no detectable 4-iodo-1-pentyl formate. Several other reaction solvents were tested. Methylene chloride, cyclohexane, and dimethylformamide gave very little cleavage product. Acetone was suitable for reactive ethers, but mesityl oxide condensation is faster than ether cleavage in most cases. Nitromethane gave similar results to acetonitrile, but more slowly.

Water content and temperature have a significant effect

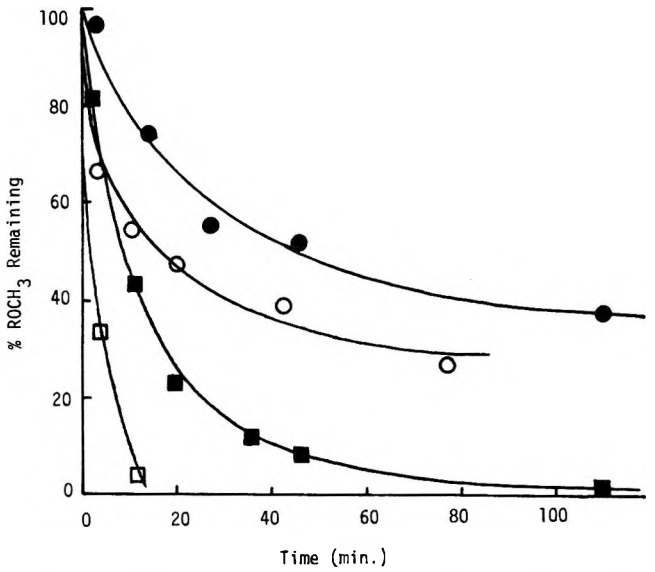


Figure 1. Cleavage of 2-octyl methyl ether at 27° (solid) and 47° (open) with DIME (squares) and HOTs–NaI (circles).

on formate/iodide product ratio. With limited water, iodide becomes the predominant product even with 1-octyl methyl ether. The use of 4 equiv of water reduces the iodide fraction to less than 10%. (Table II). Experiments with ^{18}O-labeled water showed that there was no label incorporation (2% detectable) in the ester oxygen of the formate.[8] It is interesting to note that the specific rotation of 2-octyl iodide derived from cleavage of (*R*)-2-octyl methyl ether was 33.6° (52% inversion)[9] with 0.5 equiv of water but only 12.9° (20% inversion) with 4 equiv. Higher temperatures decrease the formate/iodide ratio. In preparative scale reactions, if no cooling is applied during the exothermic addition of DCME to the reaction mixture, formate/iodide ratios may approach 1:1 rather than the room temperature value of approximately 10:1.

In addition to formate, alcohol, and iodide, iodine and the acetate ester of the alcohol are normally formed in small amounts (1–2%). The acetate presumably arises from acid-catalyzed alcoholysis of the acetonitrile solvent. Both acetate and formate may be hydrolyzed to alcohol by stirring with aqueous base during work-up.

An interesting sidelight in the chemistry of DIME is that when sodium iodide and dichloromethyl ether are mixed in acetonitrile under strictly anhydrous conditions, a substantial quantity of carbon monoxide is evolved over 3 hr. Nucleophilic displacement by iodide of the methyl group on CH_3OCHI^+ to give unstable formyl iodide is an appealing rationale.

Table II
Influence of Water on Product Ratio[a]

Ether ($ROCH_3$)	Reaction conditions NaI:DCME:H_2O	% yield of products ROOCH	RI	ROH
1-Octyl methyl ether	A 8:4:0.5	*d*	44	0
	A 8:4:1	22	70	0
	A 8:4:3	57	15	11
	A 8:4:4	61	22	15
	A 8:4:5	51	17	11
2-Octyl methyl ether	A 8:4:0.5	35	53	0
	A 8:4:1	57	43	0
	A 8:4:4	75	14	7
Tetrahydrofuran	A 4:4:0	29	18	0
	A 4:4:0.5	64	30	0
	A 4:4:2	80	8	7

[a] See Table I for footnotes. Reaction time 20 min, DCME added in two lots, half originally and half after 10 min.

Experimental Section

GC analysis was performed on a Varian 90-P3 instrument using a 10 ft × 0.25 in. 10% SE52 on Chromosorb W AW/DMCS with helium carrier gas. Infrared spectra were recorded on neat samples between salt plates on Perkin-Elmer 137 or 727 spectrophotometers. Nuclear magnetic resonance spectra were recorded on Perkin-Elmer R-32 and Varian A-60A, XL-100, and CFT-20 spectrometers. All spectra are reported in parts per million from internal tetramethylsilane. Rotations (Na D line, 1-dm cell, absolute ethanol) were measured on a Zeiss polarimeter.

Materials. The materials were standard commercial reagents. Acetonitrile (Mallinckrodt) was used without purification for preparative reactions and was distilled from CaH_2 for small-scale reactions. Sodium iodide (Mallinckrodt) was used as obtained; sodium iodide (Baker) contained *ca.* 7% water and was dried before use. DCME was prepared by the method of Reiche, Gross, and Hoft.[10] Chemical and spectral analysis demonstrated its purity. Anal. Calcd for $C_2H_4OCl_2$: C, 20.90; H, 3.51; Cl, 61.68. Found: C, 21.06; H, 3.48; Cl, 61.78. Methyl ethers were prepared by standard methods[11,12] and properties were consistent with the literature.

3-Methoxy-2,4-dimethylpentane was prepared in 67% yield using the NaH–MeI procedure:[11] bp 119–122°; ir 3.33, 3.38, 3.44, 3.50, 6.8, 7.2, 7.3, 9.0, 9.1, 10.0, 10.6, 11.1 μ; NMR δ 3.44 (s, OCH_3), 2.51 (t, *J* = 5.5 Hz, C_3H), 1.75 (m, C_2H C_4H), 0.92 (d, *J* = 7 Hz, CH_3). Anal. Calcd. for $C_8H_{18}O$: C, 73.78; H, 13.93. Found: C, 73.74; H, 13.85.

Ether Cleavage Procedure. Type A. The cleavage of (−)-(*R*)-2-octyl methyl ether is illustrative of a type A cleavage (A 844). (−)-(*R*)-2-octyl methyl ether[13] ($[\alpha]^{22}D$ −7.03 ± 0.15°, 720 mg, 5.0 mmol) was dissolved in dry MeCN (50 ml) together with NaI (6.0 g, 40 mmol) and water (360 μl, 20 mmol) in a side arm 100-ml flask equipped with magnetic stirrer, drying tube, and rubber stopple. DCME (0.95 ml, 10 mmol) was added by syringe with stirring. NaCl precipitation occurred immediately. After 10 min a second addition of DCME (10 mmol) was made to the yellow solution. After a total time of 20 min, the reaction mixture was poured into saturated $NaHCO_3$ solution (50 ml) layered with ether (50 ml) in a 1-l. beaker (foam). A few crystals of $Na_2S_2O_3$, to remove the iodine, and solid K_2CO_3 were added until CO_2 evolution ceased. The ether layer was washed with water (4 × 100 ml) and NaCl solution (100 ml), dried, and evaporated. GC analysis (internal standard, *p*-bromotoluene) showed (*R*)-2-octyl formate[14] (75%, $[\alpha]^{22}D$ 6.09°), (*S*)-2-octyl iodide (14%, $[\alpha]^{22}D$ 12.94°), 2-octanol (7%, activity not determined), and a trace of 2-octyl acetate. Samples for rotation measurements were obtained by preparative GC and checked for purity by reinjection. (*R*)-2-octyl formate (300 mg, $[\alpha]^{22}D$ 6.09°) was stirred for 10 min with NaOH (200 mg) in 50% aqueous ethanol (6 ml). GC analysis showed complete hydrolysis. Ether extraction and preparative GC gave pure (*R*)-2-octanol ($[\alpha]^{22}D$ −9.13°). The original (*R*)-2-octanol had $[\alpha]^{22}D$ −9.29°.

The reactions shown in Figure 1 were run in constant-temperature baths; in synthetic reactions, the temperature was not controlled and there was a slight exotherm at the start of the reaction.

Iodide Exchange Rate of 2-Octyl Iodide. A sample of GC pure (+)-(*S*)-2-octyl iodide (245 mg, 1.0 mmol $[\alpha]^{22}D$ 33.94°) was dissolved with 4.00 mmol of NaI in 8.0 ml of acetonitrile. DCME (2.0 mmol) was added by syringe, and the reaction mixture was stirred at room temperature for exactly 20 min. The iodide was isolated and purified by GC in the manner described previously. Its specific rotation was $[\alpha]^{22}D$ 26.26°. The specific rate constant for iodide exchange is estimated to be 4×10^{-2} l. mol^{-1} min^{-1}.

Type B. The procedure given under type A was followed with direct scale-up, but MeCN was not rigorously dried. The reaction vessel was placed in an ice-water bath to maintain a temperature of 25–40° until the heat from the DCME additions was dissipated (ca. 15 min total). Reaction times as long as 30–40 min were sometimes employed. The course of the reaction may be monitored by GC. Product was isolated by distillation at either the formate or alcohol stage.

Type C. The cleavage of (−)-(*R*)-2-octyl methyl ether is illustrative (C 84). The ether (2 mmol, $[\alpha]^{22}D$ −6.88°) was stirred with NaI (8 mmol) in MeCN (15 ml) and $HOTs \cdot H_2O$ (4 mmol) was added. Sodium tosylate precipitated immediately and the mixture was stirred for 20 min. Product was isolated by the procedure given above. Recovered ether had specific rotation −7.08°. (*R*)-2-octanol had rotation −9.40°. No 2-octyl iodide was observed by GC. In

preparative reactions, the time for the reaction is best determined by GC analysis as reaction proceeds. In one experiment with 2-octyl methyl ether, 1 equiv of HOTs-H_2O was dissolved in the minimum volume of MeCN and added to the solution dropwise over 30 min, and reaction was >95% complete in 2 hr.

Influence of 2,4,6-Tri-*tert*-butylpyridine. When 2 or more equiv of 2,4,6-tri-*tert*-butylpyridine per equivalent of DCME are present in the initial solution, no cleavage of THF or cyclohexanone ketal was detected in 3 hr. If 1 equiv of the pyridine is used, THF yields ca. 50% cleavage products and cyclohexanone ketal is cleaved completely.

Cleavage of Ketals. Camphor and cyclohexanone ethylene glycol ketals were prepared by standard methods.[15] Cleavage was accomplished by the methods given above (Table I), but reaction time was always less than 5 min.

Carbon Monoxide Formation. DCME (10 mmol) and NaI (20 mmol) were dissolved in MeCN (20 ml of Spectrograde) and stirred at room temperature. Gas was evolved over 3 hr (134 ml, 6 mmol) and was collected in a gas buret. Mass spectroscopy and ir analysis identified the gas as CO. CO evolution was also detected during the ether cleavage reactions, but the quantities were smaller.

^{13}C Spectra of *exo*- and *endo*-Norbornyl Iodide. ^{13}C spectra were recorded on CFT-20 with proton noise decoupling on neat samples containing internal Me_4Si and acetone-d_6. Assignments were made on the basis of off-resonance proton-decoupled spectra.[16] Exo: 47.9, C-1; 45.1, C-3; 37.9, C-4; 36.2, C-7; 29.3, C-2; 28.6, 28.4, C-5 and C-6, not distinguished. Endo: 45.1, C-1; 43.7, C-3; 37.3, C-4; 36.3, C-7; 32.4, C-2; 29.9, 28.7, C-5 and C-6, not distinguished.

Acknowledgments. C.A.S. gratefully acknowledges the support of an NSF Graduate Fellowship. The Perkin-Elmer R-32 and Varian CFT-20 NMR spectrometers were purchased with NSF Departmental Grants 8370 and 7842, respectively. The support of a Frederick Gardner Cottrell grant from the Research Corporation is gratefully acknowledged.

Registry No.—Acetonitrile, 75-05-8; 1,1-diiododimethyl ether, 57132-06-6; hydriodic acid, 10034-85-2; dichlorodimethyl ether, 4885-02-3; (+)-(*S*)-2-octyl iodide, 1809-04-7; 2,4,6-tri-*tert*-butylpyridine, 20336-15-6; *endo*-norbornyl iodide, 57173-48-5; *exo*-norbornyl iodide, 30983-85-8.

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α-Hydroperoxy Acids via Direct Oxygenation[1]

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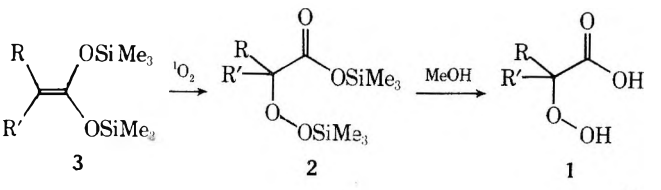
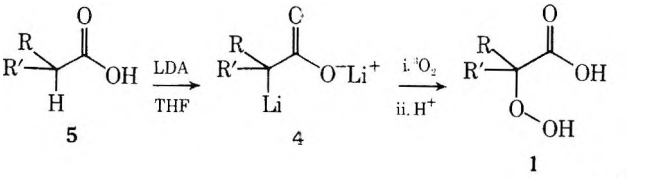
In the preparation of α-peroxylactones, which serve as active intermediates in bioluminescence,[2] we required the α-hydroperoxy acids **1** as precursors. We accomplished the preparation, isolation, and characterization of the first authentic α-hydroperoxy acids **1** by employing singlet oxygenation of the bis(trimethylsilyl) ketene acetals **3**, followed by desilylation of the bis(trimethylsilyl) derivative **2** with methanol (eq 1).[3] The success of our method rested on



(1)

the oxygenophilic nature of silicon, which promotes a silatropic shift with singlet oxygen, quite analogous to the classical ene reaction.[4] Simultaneously with oxygen fixation at the α carbon to the carbonyl group, the hydroperoxide and carboxylic acid functionalities are protected against base- and acid-catalyzed Grob fragmentation[5] of the hydroperoxy acid **1** by trimethylsilylation. The trimethylsilyl groups on one hand permit isolation and purification by distillation at reduced pressure, and on the other hand they permit quantitative release of the OOH and CO_2H functionalities by desilylation with neutral methanol.

The disadvantage of this novel oxygenation is that it lacks generality because secondary and primary alkyl groups in the ketene acetal **3** suffer prototropic shifts (ene reaction) with singlet oxygen. For this reason we investigated some time ago[6] the feasibility of the direct oxygenation of α-lithiocarboxylates **4**, derived from the corresponding carboxylic acids **5** by lithiation with LDA (lithium diisopropylamide), as shown in eq 2. A recent paper[7]



(2)

obliges us to communicate our results on this direct α-oxygenation of carboxylic acids **5** with triplet oxygen. Our experimental procedure is particularly advantageous for low molecular weight substrates which require special precautions in view of their thermal lability and high hygroscopic character. If the dianion **4** is prepared in the absence of HMPA, oxygenated at ca. −100 to −90° by slow addition of dianion **4** to an oxygen-saturated solution, protonated at −100°, and the work-up and purification carried out at subambient conditions, the degree of oxygenation can be effectively quantitative, affording crude α-hydroperoxide product in about 80%. Our recommended general procedure is described below and employed in the preparation of 2-hydroperoxy-2-methylpropionic acid (R = R′ = Me) and 3,3-dimethyl-2-hydroperoxybutyric acid (R = *t*-Bu; R′ = H).

Experimental Section

General Preparation of α-Hydroperoxy Acids. 1. α-Lithiation. A dry, 150-ml, two-necked, round-bottomed flask, provided with magnetic spinbar, rubber septum, and three-way stopcock, was attached to a nitrogen manifold and flushed with dry nitrogen for at least 5 min. While under a positive nitrogen pressure (ca. 50 mm, regulated with a mercury bubbler), the reaction vessel was charged by means of a syringe with 60 mmol of diisopropylamine (freshly distilled from calcium hydride) and 70 ml of anhydrous THF (freshly distilled from benzophenone ketyl radical). By means of a dry ice–methanol bath the reaction flask was cooled to −60 to −40° and while stirring vigorously, 63 mmol of *n*-butyllithium in *n*-hexane (standardized acidimetrically) was added with the help of a syringe. After complete addition (ca. 5 min), the cooling bath was removed and the reaction mixture allowed to reach room temperature (ca. 30°) while stirring. The reaction mixture was kept at room temperature for 10 min and cooled to −78° by means of a dry ice–methanol bath and a solution of 25 mmol of the carboxylic acid to be lithiated in 5 ml of anhydrous THF was added with the help of a syringe. Subsequently the reaction mixture was allowed to warm up to room temperature again and heated at 40° for 30 min while stirring. A pale yellow, clear solution of the dianion resulted, which exhibited a methyl iodide assay of better than 98% lithiation by NMR.

2. α-Oxygenation. A dry 250-ml, three-necked, round-bottomed flask, supplied with an efficient, hermetically sealed mechanical stirrer, a rubber septum, and a three-way stopcock, was attached to the nitrogen manifold and flushed with dry nitrogen. The flask was charged with 70 ml of anhydrous THF with the help of a syringe and cooled to −100 to −90° by means of a liquid nitrogen–THF bath, while keeping a positive nitrogen pressure (ca. 50 mm). The THF solution was saturated efficiently (ca. 10 min) with dry oxygen gas, allowed to enter through the rubber septum by means of a syringe needle. With the help of stainless steel capillary tubing (12G) as syphon, the dianion solution was transferred dropwise over a period of 1–2 hr (the dropping rate regulated with a blood serum proportionator which was attached to a nitrogen balloon) into the oxygen-saturated THF solution, keeping the oxygenation vessel at −100 to −90°, while passing a vigorous stream of dry oxygen gas through the reaction mixture during the entire process.

3. Hydrolysis. After complete addition of the dianion solution (ca. 1–2 hr), under efficient mechanical stirring and keeping the reaction mixture at −100 to −90°, by means of a syringe 120–125 mmol of a 15% aqueous hydrochloric acid solution was added. The resulting "sherbetlike" mixture was allowed to warm up to ca. −20° and transferred into a 500-ml separatory funnel, which contained 80 ml of NaCl-saturated ice water. The aqueous layer was efficiently extracted with ether (ca. 5 × 25 ml) and methylene chloride (ca. 3 × 25 ml), keeping the temperature during the extraction process between 0 and 5° by adding ice and NaCl. The combined organic extracts were dried over anhydrous $MgSO_4$ at 0°. The solvent was removed by rotary evaporation [−5 to 0° (3–4 mm)]. The oxygenation product was obtained as a colorless oil (ca. 95–100% crude yield), which crystallized on standing in the freezer. Iodometric analysis indicated a ca. 80% peroxide titer based on α-hydroperoxy acid. The crude product must be purified without delay at subzero temperature to minimize decomposition.

Preparation of 2-Hydroperoxy-2-methylpropionic Acid. Following the general procedure, 25 mmol of 2-methylpropionic acid was converted in 97% crude yield to the corresponding α-hydroperoxy acid, exhibiting a 81% peroxide titer by iodometry. In view of its low thermal stability in the impure state (above 10° it decomposes with gas evolution) and high hygroscopic nature (dry crystals allowed to come in contact with atmospheric moisture diffuse within seconds), the crude product was recrystallized immediately several times from ether–pentane mixture at 5° in a glove bag under a dry nitrogen atmosphere. The crystalline product was obtained as white needles, better than 97% pure by iodometry, mp 44–46°, with gas evolution at 74°. The spectral data follow: 60-MHz NMR (CCl_4) δ (Me_4Si) 9.7 (2 H, singlet, $-CO_2H$ and $-O_2H$) and 1.5 ppm (6 H, singlet, $-CH_3$); ir (CCl_4) 3660 and 3480 (–OOH and $-CO_2H$), 3000–2800 (aliphatic CH), 1710 (carbonyl), and 1380 and 1360 cm^{-1} (*gem*-dimethyl).

Preparation of 3,3-Dimethyl-2-hydroperoxybutyric Acid. Following the general procedure, 25 mmol of 3,3-dimethylbutyric acid was converted in 93% crude yield to its corresponding α-hydroperoxy acid, exhibiting 78% peroxide titer by iodometry. The crude product was purified immediately by repeated recrystallization from ether–hexane mixture, preventing exposure to atmospheric moisture. Colorless needles were obtained, better than 99% pure by iodometry, mp 68–70° (lit.[3] 69–70°), with gas evolution at 74°. The spectral data follow: 60-MHz NMR (CCl_4) δ (Me_4Si) 10.3 (2 H, singlet, $-CO_2H$ and $-O_2H$), 4.3 (1 H, singlet, CH), and 1.0 ppm (9 H, singlet, *tert*-butyl); ir (CCl_4) 3500–3000 ($-CO_2H$ and $-O_2H$), 2960 (aliphatic CH), 1715 (carbonyl), and 1370 cm^{-1} (*tert*-butyl).

Acknowledgment. Financial support by the National Science Foundation is gratefully appreciated.

Registry No.—**1** (R = R′ = Me), 57196-76-6; **1** (R = H; R′ = *t*-Bu), 36156-92-0; **5** (R = R′ = Me), 79-31-2; **5** (R = H; R′ = *t*-Bu), 1070-83-3.

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Studies Directed toward a Practical Synthesis of Brevicomin. IV. Formation and Hydrogenolysis of 5,7-Dimethyl-6,8-dioxabicyclo[3.2.1]octane under Catalytic Hydrogenation Conditions

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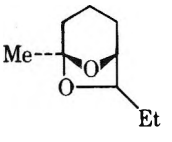
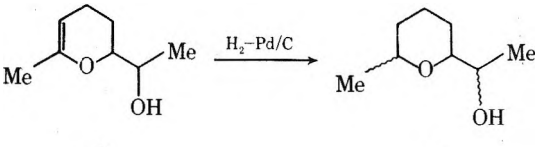
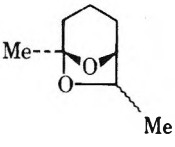
During the course of our investigations toward a practical synthesis of brevicomin (**1**), the aggregating sex pheromone of the pine bark beetle (*Dendroctonus brevicomis*),[1] we had the occasion to examine the hydrogenation of **2** → **3**. To our surprise we found a 13% yield of **4** as a secondary product of the reaction.[1c] In this paper we will present our findings on some of the unique chemistry associated with the reactions.



1



2 **3**



4

Attempts at utilizing this as a methodology for preparing, in high yield, bicyclic ketals of the type **4** met with uniform failure. Since we could not obtain increased yields of **4** we next decided to analyze whether or not **4** might simply be an intermediate in the reduction of **2** → **3**.

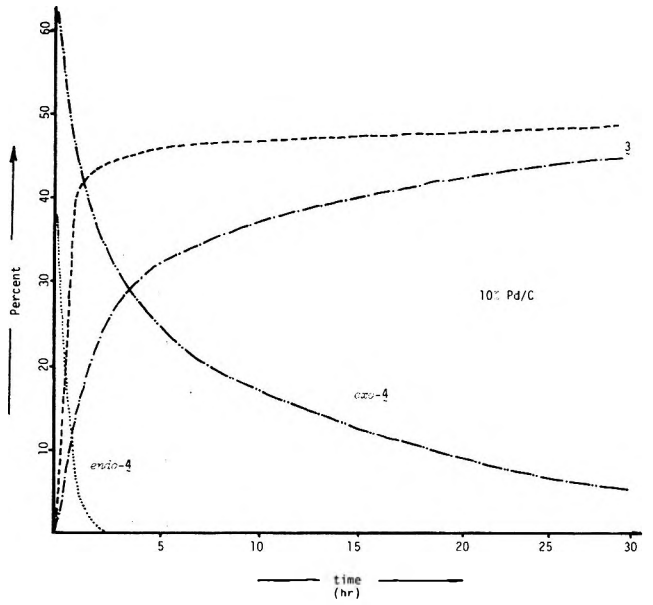
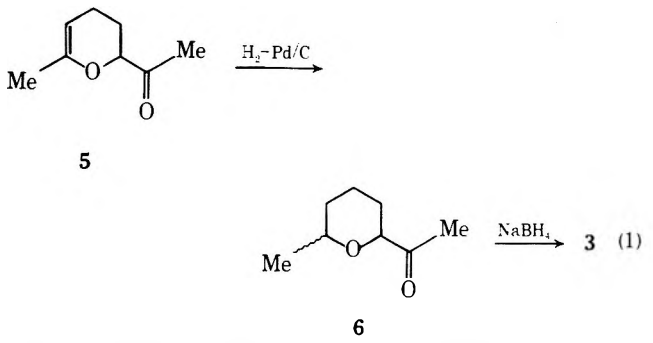


Figure 1. Hydrogenolysis of 5,7-dimethyl-6,8-dioxabicyclo-[3.2.1]octane.

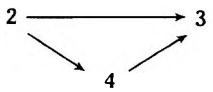
Beginning with a 60:40 mixture of *exo*- and *endo*-**4** it was observed that the endo isomer was rapidly hydrogenolyzed to the extent that in less than 3 hr this isomer could not be detected by GLC. The products of hydrogenolysis were the isomeric alcohols, **3**, which could be prepared by the unambiguous synthesis dilineated in eq 1. The exo isomer was



(1)

considerably less reactive, and even after 30 hr it could still be detected. Examination of molecular models suggested that the C-7 methyl group of the exo isomer might hinder approach of the ketal functionality to the catalyst surface. Figure 1 summarizes the hydrogenolysis results.

The catalytic hydrogenolysis of carbon–oxygen bonds in cyclic ethers and ketals is well documented.[2] The formation of ketals, however, under catalytic conditions is very rare indeed[3] and *this is the first bicyclic ketal to be prepared in such a fashion.* Formation of isomeric alcohols is thus suggested to arise from a multipath reaction (eq 2) in which some alcohol is formed via the more circuitous path involving ketal formation followed by hydrogenolysis.[4]



(2)

A relevant question, which now arises, is how did the bicyclic ketal form in the first place? In a recent study, Nishimura[1a] was able to classify two groups of metals as to their ability to form acetals. Osmium, ruthenium, and iridium belong to the group which catalyze acetal formation weakly while rhodium, palladium, and platinum belong to the group which catalyzes it efficiently. In total agreement with this we observed no ketalization of **2** using 5% ruthenium on carbon as catalyst. It is also known that hydrogen dissolved in or chemisorbed on palladium and platinum has been found to be positively charged.[5] This charge is weak, corresponding to $\frac{1}{15}$ of an electronic charge per atom, but in light of the propensity for enol ether **2** to cyclize[1c] it is not at all unreasonable to suggest that these metal catalysts are charged enough so as to act as an electrophile. Needless to say, when these experiments were repeated without catalyst, ketal formation was undetectable. In a similar way, when the reaction was run with **2** and catalyst, but without the hydrogen atmosphere, no cyclization to **4** could be detected. This suggests that cyclization does not occur by a palladation reaction and that the mixture of catalyst and hydrogen is required. The question of the electrophilicity of metal catalysts has been discussed before and it is maintained that there is enough hydronium ion character available to permit a pinacol type rearrangement of deoxydihydrowithaferin A to an *A*-nor-5-formyl derivative.[6] Likewise, we feel that enough hydronium-like character is present to allow the metal catalysts to act as an electrophile resulting in closure of **2** to 6,8-dioxabicyclic ketal **4**.

Experimental Section

Hydrogenation of 2-(1-Hydroxyethyl)-6-methyl-2,4-dihydropyran (2). See ref 1c.

Hydrogenolysis of *exo*- and *endo*-5,7-Dimethyl-6,8-dioxabicyclo[3.2.1]octane (4). Typically 1 g of ketal and 0.5 g of catalyst were added to 20 ml of anhydrous ethanol and shaken at ambient temperatures in a Parr low-pressure hydrogenation device at 30–35 psi hydrogen. The reaction was interrupted at various times and aliquots were directly withdrawn and analyzed by GLC on a 20% Carbowax column operating at 100°C, 40 psi He. Areas were calculated by triangulation methods. Since we were analyzing isomeric mixtures,[7] no attempt was made to calibrate the GLC instrument and peak areas were directly related to percent composition. The preparation of the alcohols by an unambiguous synthesis is presented below.

Preparation of 2-Acetyl-6-methyltetrahydropyran (6). One gram of **5**[1c] and 0.25 g of 10% Pd on carbon were placed in 20 ml of anhydrous ethanol and hydrogenated with 40 psi hydrogen gas for 24 hr at ambient temperature. GLC analysis (10% Ucon-50 on Chromosorb W) indicated that no starting material remained. The product was distilled, bp 97° (20 mm). The NMR spectrum exhibited the following characteristics: δ 1.2, 3 H, doublet, J = 6 Hz; 2.05–1.40, 6 H, multiplet; 2.19, 3 H, singlet; 3.25–3.93, 2 H, multiplet. The infrared spectrum (NaCl disk) exhibited a carbonyl (1715 cm^{-1}) and the loss of enol ether. MS: calcd and found, 142.

Anal. Calcd for $C_8H_{14}O_2$: C, 67.61; H, 9.86. Found: C, 67.23; H, 9.41.

Preparation of 3. Reduction of **6** with sodium borohydride was carried out in routine fashion, giving an isomeric mixture of **3**. The NMR spectrum exhibited (for the mixture) δ 1.10, 3 H, overlapping doublets, J = 6 Hz; 1.20–2.0, 6 H, methylene envelope; 3.0, 1 H, singlet; 3.05–3.85, 3 H, multiplet. The mass spectrum gave a molecular weight of 144.

Anal. Calcd for $C_8H_{16}O_2$: C, 66.66; H, 11.11. Found: C, 66.50; H, 10.98.

Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this work. Financial assistance of the USDA, Forest Service, is also acknowledged.

Registry No.—**1**, 20290-99-7; **3**, 56057-17-1; *exo*-**4**, 56057-15-9; *endo*-**4**, 56057-16-0; **5**, 28450-02-4; **6**, 57015-77-7.

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(4) We have no proof for the competitive reduction of **2** and hydrogenolysis of **4**. However, the quantitative conversion of **5** to **6** demonstrates that the enol ether functionality is quite receptive to catalytic reduction; and thus it seems that some of the alkene bond of **2** might suffer similar reduction.

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Studies Directed toward a Practical Synthesis of Brevicomin. V. Isomer Enrichment of Bicyclic Ketals in the 6,8-Dioxabicyclo[3.2.1]octane Series by Complexation with Titanium Tetrachloride

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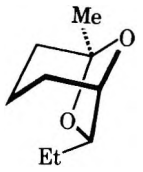
Received June 24, 1975

As part of a continuing effort directed toward a practical synthesis of brevicomin (1),[1] the aggregating sex pheromone of the pine bark beetle, *Dendroctonus brevicomis*, we initiated a study of methods for effecting isomer enrichment. Since it is well documented that powerful synergistic effects are noted for compound mixtures in testing, an effective method to remove unwanted isomers became quite important.[2] In our synthetic methodologies to date, we have always prepared a mixture isomeric about C-7.

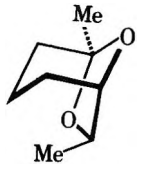
Since 1 has proven to be relatively difficult to obtain in quantity at this time, we chose to study the readily available 2 for our isomer enrichment study.[3]

exo-1

exo-2



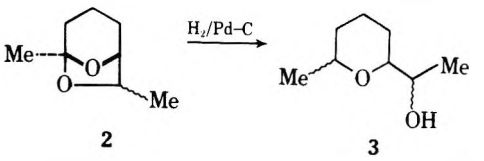
endo-1



endo-2

Substituted 1,3-dioxolane and dioxane derivatives have been generally observed to suffer cleavage and rearrangement to an appropriate ester in the presence of titanium tetrachloride.[4] Though this is a well-known Lewis acid capable of complexing ligands having heteroatom functionality,[5] *no ketal complexation has been reported.* We have observed, however, that titanium tetrachloride readily forms a complex with 2, and this complex can be hydrolyzed with water to recover 93% of the initial bicyclic ketal.

We had previously noted[6] that hydrogenolysis of *endo*-2 proceeded much faster than *exo*-2 (2 → 3). This was rationalized as a steric effect of the exo methyl group on the catalyst surface. Taking advantage of this observation we envisioned preparing a $TiCl_4$ "surface" on which one isomer might selectively interact. This was accomplished by preparing a dilute $TiCl_4$–CCl_4 frozen matrix at liquid nitrogen temperature. Typically, 0.005 mol of $TiCl_4$ in 20 ml of carbon tetrachloride was frozen in liquid nitrogen. To the surface formed was added 0.01 mol of ketal, and the solution was allowed to warm, unperturbed, to room temperature. The complex was filtered through a fritted glass filter and the filtrate was reduced in volume. GLC analysis indicated, that as expected, the endo isomer was selectively complexed. Hydrolysis of the filtered complex with water, followed by extraction with methylene chloride, yielded an enriched endo-isomer mixture. If the experiment is carried out without solvent, selectivity is decreased. This enrichment procedure can be repeated as many times as necessary to reach a desired isomeric purity. Starting with 2 having an exo–endo ratio of 15.9:9.4, three cycles increased the ratio to 16:2.7. This constitutes an enrichment of 71.5% by an experimentally simple procedure.



2 3

Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this work.

Registry No.—1, 20290-99-7.

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(1) (a) B. P. Mundy, R. D. Otzenberger, and A. R. DeBernardis, *J. Org. Chem.*, **36**, 2390 (1971); (b) K. B. Lipkowitz, B. P. Mundy, and D. Geeseman, *Synth. Commun.*, **3**, 453 (1973); (c) B. P. Mundy, K. B. Lipkowitz, and G. W. Dirks, *ibid.*, **5**, 7 (1975).

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Radical Decomposition of α-Hydroperoxy Ketones. A Facile Scission of Benzoyl Radical[1]

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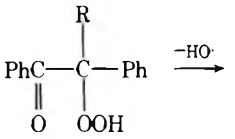
The β-scission of *tert*-alkoxy radicals has been established,[2] and previous reports include the information on the scission of halomethyl,[2a,h] alkoxymethyl,[2h,i] and alkoxycarbonyl radicals,[2h,i] and of acyl radical.[3,4] In the course of our study on the basic decomposition of α-hydroperoxy ketones,[5] 1, the facile fission of benzoyl radical was observed.

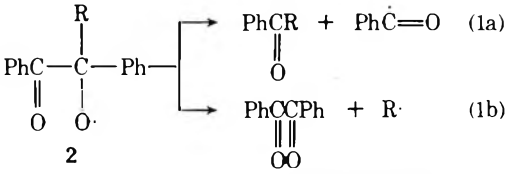
Table I
Radical Decomposition of α-Hydroperoxy Ketones (1)

Peroxide	Conditions	Products,[a] % PhCR (O)	$PhCO_2H$	Ph_2	PhCCPh (OO)	Others
		A. Pyrolysis GLC (250°)[b]				
1a	in PhH	95–100	68–80	1–6	0	None
1a	in PhMe	99	97	0	0	$PhCH_2CH_2Ph$ (7%); $PhCH_2OH$ (7%); PhCHO (17%)
1b	in PhH	90–95	75–90	1–7	6	None
		B. Fe^{2+}-Catalyzed Decomposition (70% MeOH, 25°)[c]				
1a	$FeSO_4$	96	*d*	0	16[e]	None
1a	$FeSO_4$–$FeCl_3$	100	*d*	0	<1[e]	$PhCO_2Me$ (61%)
1b	$FeSO_4$	80	*d*	0	18[e]	None
1b	$FeSO_4$–$FeCl_3$	82	*d*	0	3.9[e]	$PhCO_2Me$ (55%); $PhCH_2Cl$ (4.9%)

[a] Products were determined by GLC. [b] See Experimental Section. [c] [1] = 0.01 *M*, [$FeSO_4$] = 0.1 *M*, and [$FeCl_3$] = 0.05 *M*. [d] Not determined. [e] Mol/mol %. According to eq 2, this value should be duplicated.



1a, R = Ph
b, R = CH_2Ph



(1a)

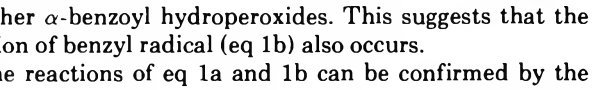
(1b)

2

Pyrolysis GLC of α-hydroperoxy-α,α-diphenylacetophenone (**1a**) at 250° as a solution in benzene gave benzophenone and benzoic acid together with a smaller amount of biphenyl (Table IA). When **1a** in toluene was pyrolyzed, bibenzyl, benzyl alcohol, and benzaldehyde were detected in place of biphenyl, suggesting a radical reaction. Biphenyl is formed probably via a sequence PhĊ=O → Ph· → Ph_2 in benzene.[6] These results suggest the predominant scission of benzoyl radical from **2** (eq 1a). Benzaldehyde may be produced by the hydrogen abstraction of PhĊ=O and/or oxidation of benzyl alcohol.

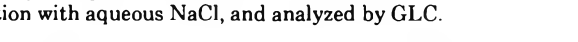
The thermal decomposition of α-hydroperoxy-α-phenyl-α-benzylacetophenone (**1b**) afforded benzil (6%) together with deoxybenzoin, benzoic acid, and biphenyl. The yield of benzil was unchanged even by a tenfold increase in the amount of **1b**, and its formation was not detected from **1a** or other α-benzoyl hydroperoxides. This suggests that the scission of benzyl radical (eq 1b) also occurs.

The reactions of eq 1a and 1b can be confirmed by the redox reaction of **1a** and **1b** with ferrous sulfate (Table IB). It is well known that the Fenton reaction of ROOH produces RO·.[2d,7] The predominant formation of monoketones shows the facile fission of PhĊ=O from **2**. The reaction of **1** with $FeSO_4$ afforded a considerable amount of benzil, much of which is formed by the dimerization of benzoyl radicals (eq 2). The reaction of **1** with Fe^{2+} is instantaneous, but the yield of benzil was not influenced by one-time or dropwise addition. Probably, PhĊ=O is efficiently trapped by Fe^{2+} to form a metastable complex[8,9] and benzil is formed by ligand transfer to another PhĊ=O.



(2)

Addition of $FeCl_3$ to the redox system reduced the yield of benzil but instead produced methyl benzoate (eq 3), substantiating the formation of free PhĊ=O. The formation of benzyl chloride from **1b** demonstrates the scission of benzyl radical (eq 1b).



(3)

These results at 25 or 250° together with no formation of α-hydroxy ketones clearly show that the scission of benzoyl radical from **2** is very facile and ca. 15–20 times faster than that of benzyl radical in view of the product ratio of PhCOR and PhCOCOPh: 90:6–80:3.9 in Table I. Since the scission of benzyl radical is known to be very fast,[2d,k,n] the scission of PhĊ=O (eq 1a) is probably the fastest one thus far known. This seems to be comprehensible, if it is considered that acyl radicals are stable and easily formed from aldehydes.[10] The scission of acyl radicals have been shown for a few cases,[2j,3,4] and its facility suggests a probable mechanism for the autoxidative α-fission of ketones.

Experimental Section

Materials. α-Hydroperoxy ketones, **1a** and **1b**, were prepared by basic autoxidation of ketones as described elsewhere.[5]

Pyrolysis GLC. Ca. 4 μl of a 0.01 *M* solution of **1** was injected into GLC (injection temperature 250°; column temperature 80–250°). Since the solvent was vaporized immediately, the thermal decomposition of **1** occurs in the vapor phase. Products were identified and determined by the usual GLC technique with three different columns (1 m): (1) Apiezon grease L, 15% on Celite 545; (2) PEG 20M, 2% on Chamelite CK; (3) PEG succinate, 13% on Chromosorb. Propiophenone or biphenyl were used as an internal standard.

Fe^{2+}-Catalyzed Decomposition. A methanolic solution of **1** (0.02 *M*, 5 ml) was added to the mixture of MeOH (2 ml), aqueous $FeSO_4$ (0.5 *M*, 2 ml), and H_2O (1 ml) at 25°. The reaction was instantaneously completed. Products were extracted with $CHCl_3$ after dilution with aqueous NaCl, and analyzed by GLC.

Acknowledgments. We are grateful to Dr. Shin Tsuge for the relevant discussions about pyrolysis GLC.

Registry No.—**1a**, 57196-77-7; **1b**, 57196-78-8; benzoyl radical, 2652-65-5.

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Synthesis of (±)-3-Methoxy-*N*-acetylnornantenine

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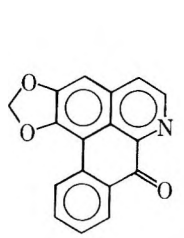
The heartwood of *Liriodendron tulipifera* has previously yielded two antimicrobial alkaloids, liriodenine (**1**) and dehydroglaucine (**2**),[1] and two nonbasic noraporphine alkaloids, one of which has been identified as (+)-*N*-acetylnornantenine (**3**) by direct comparison with an authentic sample.[2] A structure for the second alkaloid was tentatively assigned as (+)-3-methoxy-*N*-acetylnornantenine (**4**) based on spectroscopic evidence.[2] A total synthesis confirming this assignment has now been achieved.

Decomposition of ω-diazo-3,4-methylenedioxy-6-nitroacetophenone (**5**) in the presence of 2,3,4-trimethoxy-β-phenylethylamine (**6**) and silver oxide afforded the crystalline amide **7**. Compound **7** was smoothly cyclized in the Bishler–Napieralski reaction using phosphorus oxychloride in acetonitrile to the dihydroisoquinoline **8**. Reduction of **8** with sodium borohydride and acetylation with acetyl chloride produced the *N*-acetyl derivative **9**. The NMR spectrum of **9** clearly showed signals for each conformer which is characteristic of hindered rotation in 1-benzyl-1,2,3,4-tetrahydroisoquinolines.[3] Reduction of **9** with zinc dust and sulfuric acid gave **10**, which upon Pschorr cyclization following the method utilized by Weisbach and Douglas[4] gave (±)-3-methoxy-*N*-acetylnornantenine (**4**) which gave TLC, NMR, solution ir, and MS data identical with those of natural (+)-3-methoxy-*N*-acetylnornantenine (**4**).



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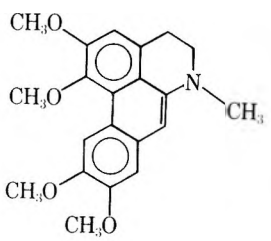

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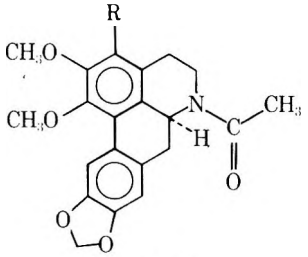
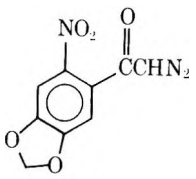


3, R = H
4, R = OCH_3



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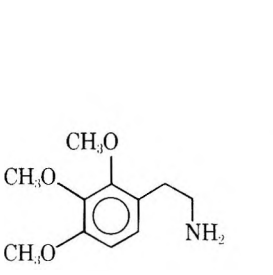

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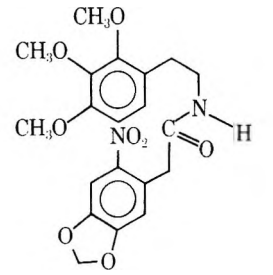

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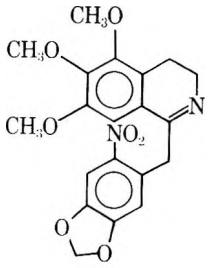

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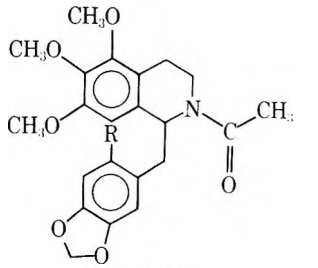

9, R = NO_2
10, R = NH_2

Experimental Section

All melting points were determined on a Thomas-Hoover Unimelt and are uncorrected. The infrared spectra were taken on a Perkin-Elmer 257 or Beckman IR-33 infrared spectrometer. Elemental analyses were performed by Scandinavian Microanalytical Laboratory, Herlev, Denmark. NMR spectra were recorded on a Jeol C-60HL spectrometer using deuterated chloroform as solvent and Me_4Si as internal standard, with chemical shifts recorded in δ (ppm) units. Uv spectra were obtained in methanol on a Beckman Acta III spectrophotometer. Mass spectral data were obtained on a Du Pont CEC 492 spectrometer.

***N*-(2,3,4-Trimethoxy-β-phenylethyl)-3′,4′-methylenedioxy-6′-nitrophenylacetamide (7).** To a solution of 7.2 g of ω-diazo-3,4-methylenedioxy-6-nitroacetophenone (**5**)[5] in 75 ml of dry benzene at 60° was added, with stirring, a solution of 7.4 g of 2,3,4-trimethoxy-β-phenylethylamine (liberated from 8.5 g of hydrochloride salt, obtained from Aldrich) in 30 ml of dry benzene and 513 mg of freshly prepared Ag_2O. The suspension was stirred at 60° for 0.5 hr and then an additional 300 mg of Ag_2O was added, followed by 1 hr of refluxing. After cooling, the solution was concentrated under reduced pressure to remove most of the benzene and then dissolved in boiling acetonitrile, filtered through Celite while hot, and evaporated to dryness to leave 10.2 g of amide **7**. Crystallization from acetonitrile gave 9.1 g: mp 181–182°; ir (KBr) 3300 (NH) and 1645 cm^{-1} (C=O).

Anal. Calcd for $C_{20}H_{22}N_2O_8$; C, 57.40; H, 5.30; N, 6.70. Found: C, 57.33; H, 5.27; N, 6.89.

1-(3′,4′-Methylenedioxy-6′-nitrobenzyl)-5,6,7-trimethoxy-3,4-dihydroisoquinoline (8).[6] Amide **7** (300 mg) was dissolved in 20 ml of acetonitrile at 60° and with stirring 3 ml of phosphorus oxychloride was added. After 2 hr at 60° the solution was evaporated under reduced pressure to give a red gum which yielded 77 mg of **8** upon crystallization from alcohol, mp 144–145°. Chromatography of the mother liquor on silica gel using benzene–acetone (8:1) as eluent gave an additional 69 mg: NMR ($CDCl_3$) δ 7.43, 6.95, and 6.85 (1 H each, PhH), 5.98 (2 H, s, OCH_2O), 4.30 (2 H, s, $NO_2PhCH_2C{=}N$), 3.87 (3 H, s, OCH_3), 3.80 (6 H, s, OCH_3), 3.55 (2 H, dd, J = 8, 8 Hz, $C{=}NCH_2CH_2$), 2.58 (2 H, dd, J = 8, 8 Hz, $-C{=}NCH_2CH_2$).

Anal. Calcd for $C_{20}H_{20}N_2O_7$; C, 59.98; H, 5.04; N, 6.99. Found: C, 59.72; H, 4.99; N, 6.72.

1-(3′,4′-Methylenedioxy-6′-nitrobenzyl)-2-acetyl-5,6,7-trimethoxy-1,2,3,4-tetrahydroisoquinoline (9). Dihydroisoquinoline (8, 1.11 g) was suspended in 150 ml of methanol and with stirring 800 mg of sodium borohydride was added in portions over 30 min. After an additional 1 hr the pH was adjusted to near pH 5 with acetic acid. After removal of all solvent under reduced pressure the residue was dissolved in $CHCl_3$, washed with dilute base and water, dried, and evaporated to dryness to give the tetrahydroisoquinoline as a white solid. This was immediately dissolved in 30 ml of pyridine and treated with 8 ml of acetyl chloride. After 3 hr at room temperature, the solution was treated with dilute base and extracted with $CHCl_3$. The combined organic layers were washed with 2% HCl and then water, dried over Na_2SO_4, filtered, and evaporated to dryness under reduced pressure. The residue was chromatographed over silica gel using benzene–acetone (8:1) as the eluent and afforded a yellow oil which crystallized from methanol to give 840 mg of **9**: mp 159–160°; ir ($CHCl_3$) 1630 cm^{-1} (C=O); NMR ($CDCl_3$) δ 7.66 and 7.53 (1 H total, s, PhH), 6.87 and 6.75 (1 H total, s, PhH), 6.63 and 6.57 (1 H total, s, PhH), 6.18 and 6.12 (2 H total, s, OCH_2O), 4.00–3.83 (9 H, OCH_3), 2.02 and 1.62 (3 H total, s, $NCOCH_3$).

Anal. Calcd for $C_{22}H_{24}N_2O_8$; C, 59.44; H, 5.45; N, 6.30. Found: C, 59.13; H, 5.49; N, 6.25.

1-(3′,4′-Methylenedioxy-6′-aminobenzyl)-2-acetyl-5,6,7-trimethoxy-1,2,3,4-tetrahydroisoquinoline (10). A 94-mg sample of **9** was suspended in 50 ml of methanol and with stirring 0.5 g of zinc dust was added slowly followed by 2 ml of 1 *N* H_2SO_4 added dropwise. The suspension was stirred for 30 min at room temperature, filtered, adjusted to pH 8 with NH_3, and then evaporated to dryness. The residue was taken up in $CHCl_3$, washed with water, dried, and evaporated to dryness, leaving a residue which was further purified by chromatography over silica gel. Elution with benzene–acetone (8:1) and crystallization from alcohol gave 55 mg of **10**: mp 189–190°; ir (KBr) 3440, 3350, 3240 (NH_2), and 1630 cm^{-1} (C=O).

Anal. Calcd for $C_{22}H_{26}N_2O_6$: C, 63.74; H, 6.33; N, 6.76. Found: C, 63.38; H, 6.31; N, 6.77.

(±)-3-Methoxy-*N*-acetylnornantenine (4). A 56-mg sample of **10** was added to a solution of 0.58 ml of glacial acetic acid and 0.04 ml of concentrated sulfuric acid at 10° and allowed to warm to 20°. A solution of sodium nitrite (11.6 mg in 0.1 ml of H_2O) was added and the solution was stirred at 20° for 50 min. The solution was allowed to warm to room temperature and then 1 mg of sulfamic acid, 0.5 mg of cuprous chloride, and 1.2 ml of acetone were added and the solution refluxed for 30 min. After cooling, the solution was concentrated to about 3 ml, adjusted to pH 8.5 with NH_4OH, and extracted with ether (5 × 10 ml). The combined extracts were dried and evaporated to give a yellow gum which was chromatographed over silica gel. Elution with benzene–acetone (8:1) and crystallization from alcohol gave 7 mg of racemic **4**, mp 174–175°. The synthetic product had the same R_f values in four TLC systems, the same NMR, uv, and mass spectra, and superimposable ir ($CHCl_3$) spectra as that of natural **4**.

Acknowledgment. This work was supported in part by a Faculty Research Grant, University of Mississippi, and the Research Institute of Pharmaceutical Sciences, School of Pharmacy, University of Mississippi. The authors are grateful to Dr. Stephen Billets, Research Institute of Pharmaceutical Sciences, School of Pharmacy, for determining the mass spectra.

Registry No.—(±)-**4**, 57236-56-3; **5**, 57196-56-2; **6**, 3937-16-4; **7**, 57196-57-3; **8**, 57237-60-2; **9**, 57196-58-4; **10**, 57196-59-5.

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Revision of the Structure of the Bisindole Alkaloid 14′,15′-Dihydropycnanthine. A Carbon-13 Nuclear Magnetic Resonance Study[1]

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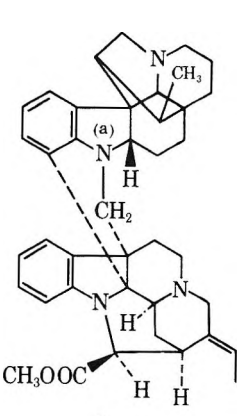
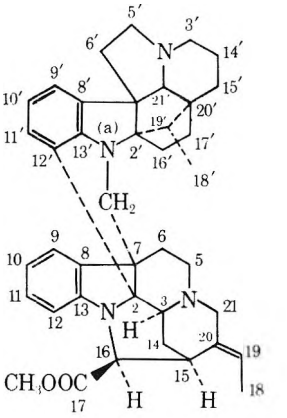
We wish to describe a ^{13}C nuclear magnetic resonance spectral analysis of the previously reported bisindole alkaloid 14′,15′-dihydropycnanthine (**1**)[2] and present evidence for the necessity of structural revision to **2**.



1



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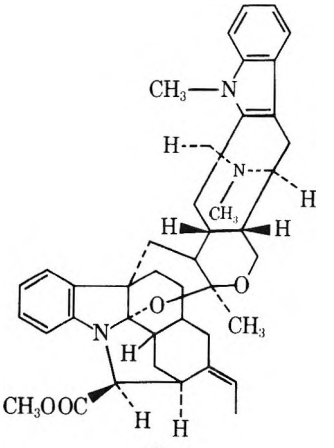


3

From the leaves of *Gonioma malagasy* Mgf. et P. Bt.[3] has been isolated a bisindole alkaloid [mp 247°; $[\alpha]^{22}D$ +243° (*c* 1.4, $CHCl_3$); *m/e* 614] [lit. mp 250°; $[\alpha]^{25}D$ +274 ± 10° (*c* 0.442, $CHCl_3$)] whose spectral characteristics (mass, ^1H NMR, uv, and ir) have indicated that it was identical in every respect with 14′,15′-dihydropycnanthine (**1**) having decarbomethoxy 14′,15′-dihydrovindolinine and 2,7-dihydropleiocarpamine moieties.[2,4]

The structure of the decarbomethoxy 14′,15′-dihydrovindolinine unit of 14′,15-dihydropycnanthine (**1**) had been

Table I
^{13}C Chemical Shifts

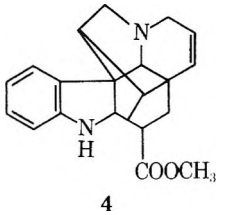
Compd	C-2	C-3	C-5	C-6	C-7	C-8	C-9	C-10	C-11	C-12
2	67.6	52.1	53.9	27.5[a]	46.3	135.8	121.0	117.7	126.6	108.8
3	92.2	51.5	53.1	28.6	44.2	132.9	120.9	118.1[a]	126.5	109.3
	C-13	C-14	C-15	C-16	C-17	C-18	C-19	C-20	C-21	$COOCH_3$
2	147.1	28.1	31.1	58.0	170.5	12.3	117.2	135.8	47.8	51.7
3	147.0	28.9	31.9	57.8	170.8	12.2	118.4[a]	136.4	47.5	51.9

	C-2′	C-3′	C-5′	C-6′	C-7′	C-8′	C-9′	C-10′	C-11′	C-12′	C-13′	C-14′
2	80.1	54.5	48.4	36.8	58.0	137.1	120.6	116.5	128.9	120.6	149.0	20.1
5	81.4	58.0	50.3	36.3	59.8	139.8	123.6	121.0	127.2	112.0	149.4	128.5
6	80.6	55.0	48.1	37.3	60.3	140.1	123.6	121.1	127.2	112.7	149.5	20.7
7	84.4	58.0	50.0	36.0	58.8	135.5	123.0	117.8	127.7	105.6	150.2	127.7
8	80.4	57.5	49.8	37.2	58.4	139.0	123.1	121.2	127.0	111.8	149.2	128.1

	C-15′	C-16′	C-17′	C-18′	C-19′	C-20′	C-21′	$N'CH_2'$ [a]	$'COOCH_3$	$COOCH_3$
2	32.4	27.0[a]	22.1	11.0	54.1	45.1	74.5	41.4		
5	130.7	39.2	29.1	7.4	48.4	46.2	78.0		174.2	51.8
6	31.2	40.2	29.0	7.5	51.0	44.5	78.8		175.0	52.0
7	130.8	37.0	28.0	9.0	47.0	45.6	77.0 NCH_3	30.0	174.0	52.0
8	131.0	42.7	31.4	10.1	51.2	44.2	74.2		172.8	51.2

[a] Assignments within the same compounds may be reversed.

proposed[2] by analogy with that of vindolinine (4) on the basis of their similar mass spectral fragmentation pattern.[5] However, a recent ^{13}C NMR analysis has led to the revision of the plane structure of vindolinine,[6] whose stereostructure 5[7] and absolute configuration[8] were later established. As a consequence, a reinvestigation of the structure of 14′,15′-dihydropycnanthine (1) became advisable.



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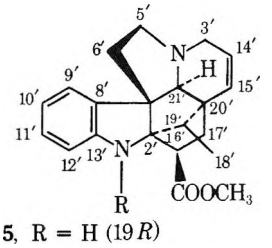


5, R = H (19*R*)
6, 14′,15′-dihydro-5 (19*R*)
7, R = CH_3 (19*R*)
8, 19′-epi-5 (19*S*)

Recently, complete signal assignments have been carried out in the ^{13}C NMR spectrum of villalstonine (3),[9] a 2,7-dihydropleiocarpamine unit containing bisindole alkaloid. Therefore, correlation of 14′,15′-dihydropycnanthine (1) with villalstonine (3), (19*R*)-vindolinine (5), and (19*S*)-vindolinine (8)[8] was sought through a study of their ^{13}C NMR spectra.

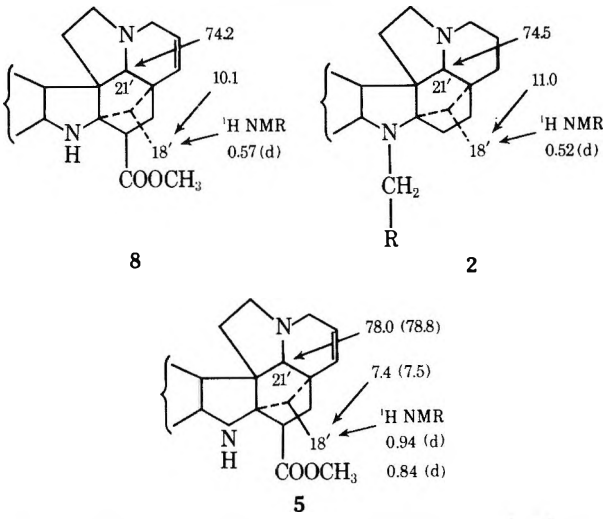
Noise, single-frequency, and noise off-resonance decoupled ^{13}C NMR spectra[10] of 14′,15′-dihydropycnanthine exhibited 12 nonprotonated carbons, 13 methines, 12 methylenes, and three methyl groups, suggesting that both of its indole nitrogens are substituted. Comparison of the ^{13}C NMR data of 14′,15′-dihydropycnanthine and villalstonine (3) afforded evidence (Table I) for the occurrence of a 2,7-dihydropleiocarpamine unit also in the former compound, substituted at C-2 and C-7 by carbon atoms and not as in 3 by an oxygen and by a carbon atom, respectively. The common fragment of the two bisindole alkaloids exhibited carbon signals identical both from the point of view of chemical shift and single-frequency decoupled multiplicity, except as expected, for the quaternary sites C-2, C-7, and C-8.

Thus by a substractive process, the signals representing the second moiety of 14′,15′-dihydropycnanthine could be easily deduced and their analysis could be undertaken. The three nonprotonated carbon signals at 80.1 (C-2′), 58.0 (C-7′), and 45.1 ppm (C-20′) indicated a vindolinine-like skeleton.[6] This interpretation was also in agreement with the chemical shift and single-frequency decoupled multiplicity of the remaining resonances, taking into account a decarbomethoxy 14′,15′-dihydro-(19*S*)-vindolinine unit. Signal assignments were based on our previous work[6] on the spectrum of (19*S*)-vindolinine (8) as well as on chemical shift rules.[11] As expected, C-16′ and C-17′ were strongly shielded in the spectrum of 14′,15′-dihydropycnanthine (2) with respect to the corresponding resonances of 8 as a result of the loss of α and β effects due to a carboxyl group.

The stereochemistry of the C-18′ methyl group of 14′,15′-dihydropycnanthine (2) is clearly of (19*S*)-vindolinine type. This interpretation was based on the chemical shift comparison of C-18′ and C-21′ of 14′,15′-dihydropycnanthine (2) and the corresponding signals of 5 and 8 as well as on the high-field resonance positions of the doublets due to the methyl protons in the ^{1}H NMR spectra of 2 and 8 (Chart I).[12]

The ^{13}C NMR data presented in Table I for 14′,15′-dihydropycnanthine (2) support well the previously suggested type of linkage for its monomeric units.[2] It is well known

Chart I[a]



[a] Chemical shifts in parentheses are those of 14′,15′-dihydro-(19*R*)-vindolinine (6).

that in the spectra of N_a-methyldihydroindole alkaloids the highest field aromatic carbon signal at 107 ± 2 ppm represents C-12.[6,14] By analogy with methyl substitution effects on simple indole models[15] a C-12′ linkage as depicted in **2** should strongly deshield this carbon and slightly shield C-9′ while not significantly influencing the other aromatic sites. The shift contrast between the aromatic carbon signals of the decarbomethoxy 14′,15′-dihydro-(19*S*)-vindolinine part of **2** and those of N'_a-methyl-(19*R*)-vindolinine (**7**) was in perfect agreement with a C-12′ attachment of the monomers. The second site of linkage is of course through the N'_a-CH'_2 carbon of the alkaloid. Two possibilities had then to be considered. The close shifts of C-7 of villalstonine (**3**)[9] and C-7 of **2** strongly suggested similar environments for this carbon in both compounds and was in consonance with previous conclusions.[2] The stereochemistry of this cis linkage could not be ascertained by NMR spectroscopy and has been put forward by analogy with all other related bisindole alkaloids having 2,7-dihydropleiocarpamine as a constituent part.[16] Based on the arguments presented above, structure **2** is proposed for 14′,15′-dihydropycnanthine.

Registry No.—**2**, 21400-49-7.

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(13) E. Wenkert, D. W. Cochran, E. W. Hagaman, F. M. Schell, N. Neuss, A. S. Katner, P. Potier, C. Kan, M. Plat, M. Koch, H. Mehri, J. Poisson, N. Kunesch, and Y. Rolland, *J. Am. Chem. Soc.*, **95**, 4990 (1973).
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The Dianion of Adipoin. A Model Study for the C Ring of Phorbol

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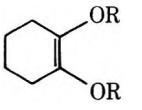
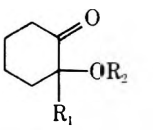
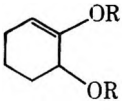
The acyloin condensation is a valuable method for ring formation and has been the subject of a recent reinvestigation[1] and review.[2] Although some details of the mechanism may be in question, enediolate **1a** is generally accepted as the stable species which on protonation gives adipoin **2a** or on silylation[3] gives bis silyl ether **1b**. The reverse reaction, however, i.e., treatment of an acyloin with base (**2a** → **1a**), is not so well known.



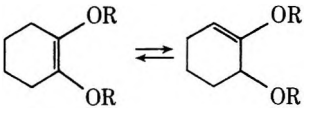
1a, R = Li
b, R = Me_3Si



2a, $R_1 = R_2 = H$
b, $R_1 = CH_3$; $R_2 = H$
c, $R_1 = CH_2CH_2CN$; $R_2 = H$
d, $R_1 = CH_2OH$; $R_2 = H$
e, $R_1 = H$; $R_2 = Me_3Si$
f, $R_1 = H$; $R_2 = Li$



3a, R = Li
b, R = Me_3Si



1a,b **2a,b**

A number of groups have reported the alkylation[4a-h] of acyloins on carbon (e.g., **2a** → **2b**), Michael addition[5a-c] (e.g., **2a** → **2c**), and aldol condensations[6] (e.g., **2a** → **2d**).

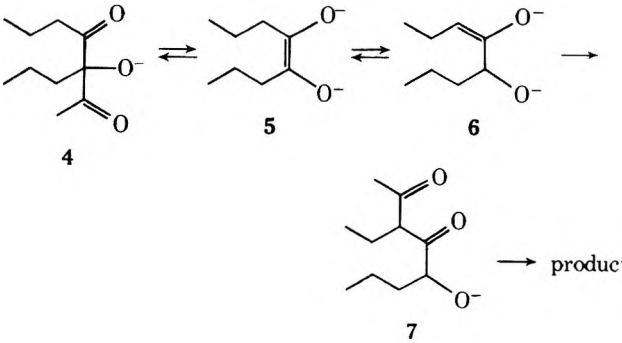
All published reports thus far on acyloin dianions, with one exception[7] (vida infra), however, evoke the structure of the well-known enediolate **1a**. We have determined that **1a** is in fact the "thermodynamic" enolate dianion and that compound **3a** is a readily accessible "kinetic" enolate dianion.[8]

When a THF solution of freshly distilled monomeric[9] adipoin **2a** is added dropwise to an excess of 2 equiv of lithium diisopropyl amide or 2,2,6,6-tetramethylpiperidide, a dianion is formed which on silylation gives predominantly the kinetic enolate cyclohexene-2,3-diol bis(trimethylsilyl) ether[13,14] (**3b**) in 73% yield (see Table I). This compound possesses the expected vinyl proton multiplet at δ 4.88 and methine adjacent to oxygen at δ 3.95.

If adipoin **2a** is refluxed in DMF with Me_3SiCl–Et_3N, conditions under which a "thermodynamic" mixture is to be expected,[15] the more stable bis silyl ether **1b** is the predominant bis silyl ether formed. These results are consistent with the observed site of reaction of acyloins which were conducted under equilibrating conditions.[4,5,6]

The observation[7] that enediolate **5**, obtained from acyloin condensation of ethyl butyrate, condenses with ethyl acetate to give a product derived from **7** can be best explained by the equilibrium in Scheme I. Condensation with

Scheme I



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

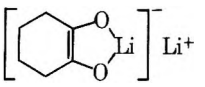
Table I
The Adipoin Dianions[a]

Entry	Conditions	% "thermodynamic" (1b)	% "kinetic" (3b)	% yield
1	Acyloin condensation (Na, Me_3SiCl)	89	11	68
2	Equilibrium (Et_3N, Me_3SiCl)	67	33	53
3	Kinetic (LDA)[b]	16	84	73
4	Kinetic (lithium 2,2,6,6-tetramethylpiperidide)	15	85	67

[a] Percentages determined by VPC. [b] Lithium diisopropylamide.

enediolate **5** gives a nonenolizable β-diketone which would revert to **5** in the presence of excess ethoxide. Some equilibrium concentration of enolate dianion **6** would eventually lead to product.

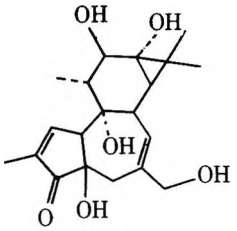
Under kinetic conditions the initially formed OLi group in salt **2f** hinders the approach of a second mole of base to that side of the carbonyl, thus yielding **3a**. The stability of the enediolate **1a** is presumably due to increased delocalization possible in structures such as **8**.



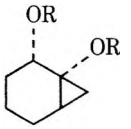
8

We have also repeated Rühlmann's[16] acyloin synthesis of **1b**. Our product contains ca. 10% of the "kinetic" enolate[17] **3b** which was isolated and fully characterized. This compound could arise by base-catalyzed equilibration of **1b** under the reaction conditions or may imply an alternative mechanism for the acyloin condensation.[1]

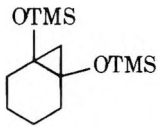
Our initial interest in acyloin dianions stemmed from model studies directed toward the construction of the C ring system of phorbol (**9**).[18] The interesting C ring of phorbol contains an unusual cyclopropyl–cyclopropylcarbinyl diol moiety. To develop a synthetic route to this diterpene we required a method for the construction of the 1,2-norcaranediol system **10a**.[19]



9



10a, R = H
b, R = Me_3Si



11

The synthesis of **10b** is easily achieved by the reaction of **3b** with a sixfold excess of Simmons–Smith[20,21] reagent in ether at room temperature, giving 83% of **10b** despite a report by Conia[13a] that attempted reaction of a similar system with Simmons–Smith reagent led to rearrangement. Compound **10b** possessed cyclopropane multiplets at δ 0.52 and 0.73 and methine adjacent to oxygen at δ 4.03. (The known[21] **11** was present as an impurity.)

The chemical shifts[22] of the cyclopropane hydrogens suggest that the methylene has been transferred as expected[23] from the side opposite the allylic $OSiMe_3$ grouping. Thus the various methods[11] available for the introduction of a hydroxyl α to carbonyl makes the 1,2-norcaranediol ring system accessible in three steps from a ketone via the heretofore unknown adipoin kinetic enolate dianion.[24]

Experimental Section

Infrared spectra were recorded on a Perkin-Elmer 237B spectrometer; ^1H NMR spectra were taken at 220 MHz in dilute $CDCl_3$ solution on a Varian HR220 referenced to Me_4Si (via residual $CHCl_3$). Mass spectra were obtained on Varian MAT CH-7 and AEI MS-9 mass spectrometers. Microanalyses were obtained from Spang Microanalytical Laboratory, Ann Arbor, Mich. VPC analyses were carried out on a Varian 920: column A is 5 ft × 0.25 in., 15% Carbowax 20M on Chromosorb W and column B is 5 ft × 0.25 in., 1.5% OV101 on Chromosorb P.

Cyclohexene-2,3-diol Bis(trimethylsilyl) Ether. A solution of lithium diisopropylamide in dry THF was prepared in the usual way under argon from 4.34 ml of *n*-butyllithium in hexane (2.3 *m*, Alfa) and 1.46 ml of diisopropylamine (distilled from CaH). The solution was then cooled to −76° and 0.32 g (2.8 mmol) of freshly distilled adipoin was added dropwise in THF. After stirring at −76° for 30 min 1.28 g (10 mmol) of trimethylsilyl chloride was added and the mixture allowed to warm to room temperature over 1 hr. The reaction mixture was then poured into cold $NaHCO_3$ and pentane.

After drying, the pentane was removed by rotavap and the residual oil distilled at 74° (1.1 mm) to give 0.53 g (73%) of bis silyl ethers **1b** and **3b**.

VPC analysis (column A, 110°C) showed only two components: compound **1b** (16%, t_R 1.9 min) and compound **3b** (84%, 2.2 min). Only a trace of the monosilyl ether **2e** (3.4 min) was detected. Column B at 85° showed **1b** (16%, t_R 8.1 min) and **3b** (84%, 9.5 min). Each component was purified by preparative VPC.

Compound **3b** showed ir 1653 cm^{-1}; NMR δ 4.88 (1 H, t), 3.95 (1 H, t), 1.0–2.2 (6 H, m), 0.23 (9 H, s), 0.16 (9 H, s); MS *m/e* (rel intensity) 258 (18), 230 (12), 215 (11), 169 (20), 168 (51), 147 (64), 75 (31), 73 (100).

Anal. Calcd for $C_{12}H_{26}O_2Si_2$: C, 55.81; H, 10.08; mol wt, 258.1473. Found: C, 55.91; H, 10.01; mol wt, 258.1480.

Compound **1b** showed ir 1689 cm^{-1}; NMR δ 1.95–2.35 (4 H, m), 1.65–1.85 (4 H, m) 0.2 (18 H, s); MS *m/e* (rel intensity) 258 (85), 146 (90), 75 (30), 73 (100).

Anal. Calcd for $C_{12}H_{26}O_2Si_2$: mol wt, 258.14713. Found: mol wt, 258.14925.

Norcarane-1,2-diol Bis(trimethylsilyl) Ether. In a 250-ml three-neck flask with magnetic stir bar was added 25 mg of AgOAc and 25 ml of glacial acetic acid. The vigorously stirred solution was heated with a microburner almost to reflux. Then 3.27 g (50 mmol, 20 mesh granular) of Zn was added in one portion. The solution was heated to reflux for 1 min, then cooled to room temperature in a water bath. The acetic acid was decanted and the Zn/Ag couple washed once with glacial acetic acid and six times with ether. The couple was then dried under vacuum for 1 hr. To the couple prepared above was added 45 ml of dry ether and a bit of silver wool. Then 3.86 ml (50 mmol) of CH_2I_2 was added and the mixture refluxed under argon for 2 hr, at which time most of the zinc had dissolved.

Two grams (7.74 mmol) of cyclohexene-2,3-diol bis(trimethylsilyl) ether (**3b**) was added and the reaction stirred at room temperature for 17 hr. At this time pyridine (about 10 ml) was added to the flask until no more precipitate formed. The precipitate was removed by filtration and an equal volume of benzene added. The solvents were evaporated on the rotavap and the residual oil distilled to give 1.75 g (83%) of a colorless liquid, bp 100° (6 mm). VPC (column A, 128°) showed compound **10b** (85%, 1.5 min) and the isomeric cyclopropane **11** (15%, 1.8 min).[21] Compound **10b** has ir no carbonyl or double bond; NMR δ 4.03 (1 H, m), 1.0–2.3 (6 H, m), 0.73 (2 H, m), 0.52 (1 H, m), 0.07 (9 H, s), 0.05 (9 H, s); MS *m/e* (rel intensity) 272 (14), 182 (15), 156 (17), 146 (66), 93 (14), 75 (43), 73 (100).

Anal. Calcd for $C_{13}H_{28}O_2Si_2$: C, 57.35; H, 10.29; mol wt, 272.1629. Found: C, 57.36; H, 10.29; mol wt, 272.1630.

"Thermodynamic" Enolate Mixture. To 0.5 g (4.4 mmol) of freshly distilled adipoin was added 1.24 g (10.5 mmol) of Me_3SiCl, 1.06 g (10.5 mmol) of triethylamine, and 50 ml of DMF. The mixture was refluxed under argon with stirring for 2 days. After cooling the mixture was poured into 100 ml of ice-cold saturated $NaHCO_3$ and rapidly extracted with 100 ml of ice-cold pentane. The pentane solution was dried over Na_2SO_4–K_2CO_3 and distilled to afford a single fraction, bp 104–106° (140 mm), 618 mg (54%) of a mixture of silyl ethers. VPC analysis showed (column B, 110°)

compound **2e** (trace, 2.8 min), compound **1b** (66%, 5.7 min), and compound **3b** (34%, 6.3 min). Compound **2e** was isolated by preparative VPC and showed ir 1720 cm^{-1}; NMR δ 4.39 (1 H, t), 1.3–2.6 (8 H, m), 0.2 (9 H, s); MS (70 eV) *m/e* (rel intensity) 186 (<0.1), 171 (42), 148 (18), 129 (23), 75 (100); MS (20 eV) 186 (<0.1), 171 (100), 148 (40), 129 (23), 75 (66), 73 (15).

Anal. Calcd for $C_9H_{18}O_2Si$: mol wt, 186.1056. Found: mol wt, 186.1056.

Acyloin Condensation of Diethyl Adipate. A 25-g sample of diethyl adipate was cyclized according to Rühlmann[16] to give after distillation 23.4 g of bis silyl ethers (68%). VPC analysis (column A, 110°) showed compound **1b** (89%, 1.9 min) and compound **3b** (11%, 2.2 min). Column B (110°) showed compound **1b** (89%, 5.7 min) and compound **3b** (11%, 6.3 min).

Registry No.—**1b**, 6838-67-1; **2a**, 533-60-8; **2e**, 53638-19-0; **3b**, 57173-86-1; **10b**, 57173-87-2; trimethylsilyl chloride, 75-77-4; diethyl adipate, 141-28-6.

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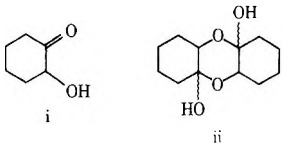
(7) R. B. Woodward and E. R. Blout, *J. Am. Chem. Soc.*, **65**, 562 (1943), footnote 12.
(8) The terms "thermodynamic" and "kinetic" enolate are used as defined by H. O. House, "Modern Synthetic Reactions", W. A. Benjamin, Menlo Park, Calif., 1972, p 502.
(9) Pure adipoin (i) is a mobile liquid of bp 194°. On standing for several hours i dimerizes[10] to a mixture of hemiacetals ii of mp 93–113°. Thus



comparison of melting points[11] of this dimer is probably not valid. This error has also been perpetrated in various compilations.[12]
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(11) G. M. Robottom, M. A. Vazquez, and D. R. Pelegrina, *Tetrahedron Lett.*, 4319 (1974).
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(13) To our knowledge there is only one such "kinetic" acyloin dianion bis silyl ether in the literature: H. Teichmann and V. Prey, *Justus Liebigs Ann. Chem.*, **732**, 121 (1970). Two acyloin dianion bis(trimethylsilyl) ethers substituted at the 2 position and consequently unable to form an enediolate have been reported: (a) J. P. Barnier, B. Garnier, C. Girard, J. M. Denis, J. Salaun and J. M. Conia, *Tetrahedron Lett.*, 1747 (1973); (b) P. Y. Johnson and M. A. Pries, *J. Am. Chem. Soc.*, **96**, 5618 (1974).
(14) All new compounds possessed satisfactory spectral and analytical data.
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(19) The corresponding 2-keto-1-norcaranol has been reported: J. V. Paukstelis and J. Kao, *J. Am. Chem. Soc.*, **94**, 4783 (1972).
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(21) Compound **1b** has been cyclopropanated and this isomeric 1,6-norcaranediol bis(trimethylsilyl) ether (**11**) is present as an impurity of 15% in compound **10b**: M. Audidrand, R. Le Goaller, and P. Arnaud, *C. R. Acad. Sci.*, **268**, 2322 (1969).
(22) W. G. Dauben and W. T. Wipke, *J. Org. Chem.*, **32**, 2976 (1967).
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(24) Since the submission of this manuscript another report has appeared [C. M. Cookson and G. H. Whitham, *J. Chem. Soc., Perkin Trans. 1*, 806 (1975) describing the isolation of the silylated "kinetic" enolate dianion from the modified acyloin condensation of ethyl acetate.

A Convenient Synthesis of (*S*)-(−)-Pulegone from (−)-Citronellol

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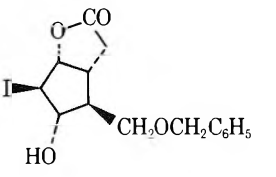
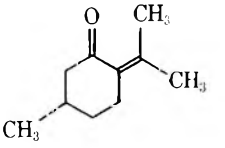
In connection with studies which have led to an efficient asymmetric synthesis of the levorotatory iodolactone **1**,[1] it became necessary to have a convenient source of (*S*)-(−)-pulegone (**2**). (*S*)-(−)-Pulegone occurs in the volatile oils of



1

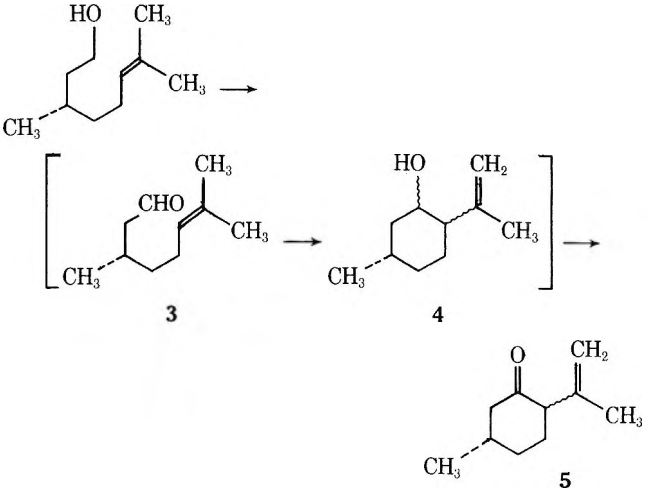


2

numerous plants;[2] however, there are at present no commercial suppliers.

The classical cation–olefin cyclization of citronellal to a mixture of isopulegols followed by oxidation offered a method for the preparation of **2** from (−)-citronellal;[3] however, the optical purity of (−)-citronellal isolated from natural sources is low.[4] A more convenient starting material appeared to be (−)-citronellol,[5] which is available by high-temperature hydroalumination of (+)-pinane, followed by oxidation of the acyclic organoaluminum compound.[6]

Treatment of (−)-citronellol, $[\alpha]^{20}D$ −4.1° (neat) (88% optically pure), with 2.5 equiv of pyridininum chlorochromate[7] in dry methylene chloride gave isopulegone (**5**) in one step via the intermediates citronellal (**3**) and the isopulegols (**4**). Treatment of **5** with ethanolic sodium hydroxide gave (−)-pulegone, $[\alpha]^{20}D$ −20° (neat), which was isolated in 70% overall yield.[8]



3 4 5

That pyridinium chlorochromate is sufficiently acidic to cause the cyclization of **3** to **4** was suggested by the observation that cis allylic alcohols are oxidized by the reagent to trans aldehydes.[7]

Optically pure (−)-**2** was prepared by recrystallization of its semicarbazone from ethanol. Treatment of the fully resolved semicarbazone (crystallized three times from ethanol), $[\alpha]^{22}D$ −65.2°,[9] with excess pyruvic acid[10] in glacial acetic acid gave (*S*)-(−)-pulegone, $[\alpha]^{23}D$ −22.5° (neat).[11]

Experimental Section

Preparation of (−)-Pulegone (2). To a suspension of 160 g (0.8 mol) of pyridinium chlorochromate in 1 l. of dry methylene chlo-

ride was added 40.0 g (0.26 mol) of (−)-citronellol, $[\alpha]^{23}D$ −4.1° (neat).[12] The slurry was stirred at 25° for 36 hr.[13] The mixture was filtered through Celite and the solids were washed thoroughly with methylene chloride. The solution was evaporated to ca. 500 ml and washed with 10% hydrochloric acid, 10% sodium bicarbonate, and water. The methylene chloride solution was evaporated to give a mobile oil (43 g). The oil was taken up in 300 ml of ethanol and treated with 600 mg (15 mmol) of sodium hydroxide. The solution was heated for 1 hr, then the ethanol was evaporated under reduced pressure and the residue was partitioned between 200 ml of ether and 100 ml of water. The ether was washed with 10% hydrochloric acid and then brine. Evaporation of the solvent and distillation of the residue gave 28 g (0.184 mol, 71%) of (−)-pulegone, bp 104–106° (18 mm), $[\alpha]^{22}D$ −20° (neat), homogeneous by gas chromatographic analysis.

Preparation of (*S*)-(−)-Pulegone Semicarbazone. To a solution of 35 g (230 mmol) of (−)-pulegone, $[\alpha]^{22}D$ −20° (neat), in 400 ml of ethanol and 200 ml of water cooled to 0° was added 55 g (404 mmol) of sodium acetate trihydrate and 40 g (359 mmol) of semicarbazide hydrochloride. The solution was stirred at 0° for 2 hr and then at 20° for 36 hr. The precipitated solid (53 g) was separated by filtration and was extracted three times with 200 ml of chloroform. Evaporation of the chloroform and recrystallization of the residue from ethanol gave 47 g (225 mmol, 98%) of the semicarbazone, mp 169–171°. This material was recrystallized twice from ethanol to afford 40.2 g (192 mmol, 83%), of pure semicarbazone: mp 170–171°; $[\alpha]^{23}D$ −65.2° (c 2.2, $CHCl_3$);[9] ir (CCl_4) 3522, 3489, 3419, 3200 (NH), 1689 (C=O), 1510 cm^{-1} (C=N); NMR ($CDCl_3$) δ 8.73 (1 H, s, NNH), 5.88 (2 H, bs, NH_2), 2.83–0.88 (16 H, m), 1.87 (3 H, s, allylic CH_3), 1.74 (3 H, s, allylic CH_3), 1.00 (3 H, d, J = 5.5 Hz, CH_3).

Regeneration of Optically Pure (−)-Pulegone (2). To 40 g (191 mmol) of (−)-pulegone semicarbazone dissolved in 100 ml of hot glacial acetic acid was slowly added (ca. 30 min) 35 g (398 mmol) of freshly distilled pyruvic acid. The solution was heated on a steam bath for 2 hr. The volume was reduced to ca. 50 ml under reduced pressure and the residue was partitioned between 200 ml of water and 400 ml of ether. The ether layer was washed with 200 ml of water, 200 ml of saturated sodium bicarbonate, and 50 ml of brine. The ether solution was dried ($MgSO_4$), evaporated, and distilled to give 25 g (164 mmol, 86%) of (−)-pulegone, bp 104–108° (22 mm), $[\alpha]^{23}D$ −22.5° (neat).[11,14]

Registry No.—**2**, 3391-90-0; 2 semicarbazone, 57237-90-8; (−)-citronellol, 7540-51-4; semicarbazide hydrochloride, 18396-65-1.

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(9) For lit. mp 171–172° and $[\alpha]^{20}D$ +61.7° (c 4.0, $CHCl_3$) for the semicarbazone of (+)-pulegone, see ref 3c; we observed mp 170–171° and $[\alpha]^{23}D$ +66° (c 2.05, $CHCl_3$).
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(13) The reaction can easily be followed by TLC (silica gel, methylene chloride). R_f values: citronellol, 0.17; citronellal, 0.65; isopulegols, 0.27 and 0.35; isopulegone, 0.41; pulegone, 0.36.

(14) This work was supported in part by a grant from the National Science Foundation.

Reactions of Cholesteryl Substrates with Chloride Ion in Aprotic Solvents. Synthesis of Epicholesteryl Chloride

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Shoppee,[2] after a review of the literature, concluded that, owing to homoallylic participation by the 5,6 π bond,[2,3] the hydroxyl group of cholesterol invariably undergoes replacement by chlorine with retention of configuration. Epicholesteryl chloride (3-α-chlorocholest-5-ene, **1**) was subsequently prepared by a variety of methods,[4,5] all of which involved replacement, with inversion, of a 3-α-hydroxyl group by chlorine prior to introduction of the 5,6 π bond by dehydration of a 5- or 6-ol. Column and thin layer chromatography were used to separate it from cholesta-3,5-diene (**2**). Recently, it has been shown that reaction of cholesterol with triphenylphosphine–carbon tetrachloride reagent does give rise to a small (~8%) amount of **1** within the product mixture.[6]

Since dipolar aprotic solvents are excellent media for SN2 reactions,[7] it might be possible to utilize them to prepare **1** by direct attack of chloride ion upon a suitable cholesteryl substrate. Several bimolecular inversions at C-3 of cholesteryl derivatives have been documented.[8] Plausible products from chloride-ion attack are indicated in Scheme I.

Reaction of cholesteryl *p*-toluenesulfonate (**3a**) with lithium chloride in refluxing acetone[9] was found to lead to a crude product, mp 91–92°, which after recrystallization gave pure cholesteryl chloride (3-β-chlorocholest-5-ene, **3b**), mp 95°. Unfortunately, neither crude nor purified yields are given but, from the small increase in melting point after recrystallization, it would appear that the reaction gave almost entirely substitution products, formed with retention of configuration. However, when the same reaction was carried out in refluxing acetonitrile,[6] a crude product was obtained which on chromatographic analysis yielded 8% **1**, 71% **3b**, and 18% **2**.

Scheme I

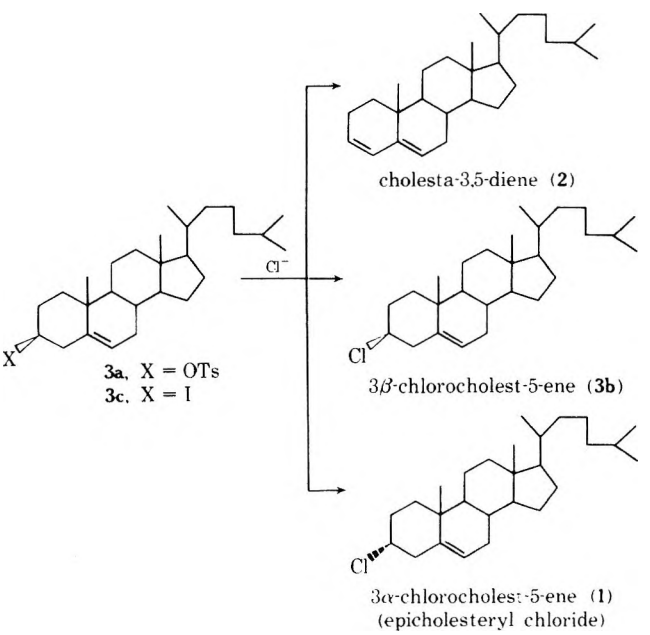


Table I
Product Studies for Reactions of Cholesteryl Substrates with Chloride Ion[a]

Entry	Reaction	% 2[b] Uv	% 2[b] ^{1}H NMR	% 1 ^{1}H NMR	% 3b ^{1}H MNR
1	3a, LiCl, CH_3CN, reflux	2	6	0	94
2	3a, LiCl, CH_3CN, reflux, TMU[c] (2 equiv)	2	6	0	94
3	3c, *n*-Bu_4NCl, acetone	46	39	37	24
4	3c, *n*-Bu_4NCl, acetone, TMU[c] (1 equiv)	56	59	41	0
5	3c, *n*-Bu_4NCl, acetone, TMU[c] (2 equiv)	64	58	42	0
6	3b, *n*-Bu_4NCl, acetone	1	1	0	99
7	3b, *n*-Bu_4NCl, acetone, TMU[c] (1 equiv)	0	3	0	97
8	3b, *n*-Bu_4NCl, HCl, acetone	0	0	0	100
9	1, *n*-Bu_4NCl, HCl, acetone	5	9	91	0

[a] Reaction at 50.0° unless otherwise noted and percentages are those within crude isolated product mixture (usually >90% recovery). [b] Especially for low percentages of conjugated diene, 2, the uv determination would be expected to give the more accurate value. [c] TMU = tetramethylurea.

The apparent contribution of a small SN2 component to the reaction in acetonitrile led us to consider the possibility of further modification of the conditions so as to substantially increase the fraction of inversion product; the procedure would then be preferable to the several-steps schemes for the synthesis of 1 devised by Shoppee and co-workers.[4,5]

The reaction of **3a** to give a small (8%) yield of 1 was, unfortunately, reported only in preliminary form[6] and, in particular, the concentration of lithium chloride within the refluxing acetonitrile was not specified. If it is assumed that 1 is formed by SN2 reaction and **3b** by SN1 reaction, then the product ratio would be directly related to the concentration of chloride ion. The reaction has been repeated with a substantial (0.236 *M*) concentration of lithium chloride. The ^{1}H NMR spectrum of the crude product did not show any signal at δ 4.50 for the 3-β hydrogen of 1 (Table I, entry 1); spectra of standard mixtures indicated that amounts in excess of 2% would have been detected. To see whether any **3b** was formed from 2 via an elimination–addition reaction,[10] the experiment was repeated in the presence of 2 equiv of tetramethylurea, a strong base which does not readily participate directly in substitution or elimination reactions.[11,12] Within experimental error, identical results were obtained (Table I, entry 2). The percentage of conjugated diene (~2%) and the absence of 1 are consistent with the claim by Madaeva[6] that reaction of **3a** with chloride ion in refluxing acetone led to the isolation of only **3b**. The present data are not necessarily inconsistent with the previous report,[6] provided that the unspecified concentration of lithium chloride used by the earlier workers was extremely large.

Table II
Second-Order Rate Coefficients, k_2 (M^{-1} sec^{-1}), and Fraction of Reaction Proceeding with Elimination, F_E, in Reaction of Cholesteryl Iodide (3c) with Tetra-*n*-butylammonium Chloride in Acetone at 50.0°

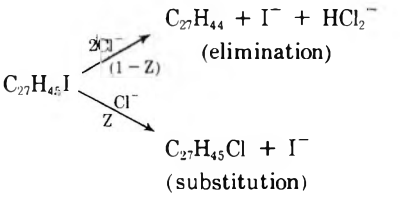
[3c]	[*n*-Bu_4NCl]	% reaction followed[a]	$10^4 k_2$[b]	F_E[c]
0.0400	0.0447	42	1.61	0.64
0.0400	0.0596	69	1.59	0.62
0.0200	0.0876	72	1.78	0.53
0.0400	0.0992	80	1.71	0.56
0.0400	0.117	80	1.74	0.58

[a] Of 3c. [b] Second-order rate coefficient for iodide ion formation. [c] Average value, as indicated by titration.

Since SN1 reaction leading to **3b** dominated the interaction of lithium chloride with **3a**, we attempted to obtain increased fractions of 1 within the product by introduction of a nucleofugic group which is somewhat better than tosylate in bimolecular reaction but much poorer in unimolecular reaction, namely iodide.[13] Cholesteryl iodide (**3c**) can be conveniently synthesized[14] from the commercially available chloroformate. Also, lithium chloride is only partially dissociated in dipolar aprotic solvents, with paired chloride ion of considerably less nucleophilic reactivity than free chloride ion, and the tendency to SN2 reaction can be considerably increased by substitution of tetra-*n*-butylammonium chloride.[15]

Under nonsolvolytic conditions, molecularity is frequently simply related to kinetics and we undertook a kinetic study of the reaction of cholesteryl iodide with tetra-*n*-butylammonium chloride in acetone at 50°. After due allowance for two chloride ions being consumed in elimination reaction but only one in substitution reaction (Scheme II), good second-order kinetics were observed, indicative of

Scheme II



a bimolecular process. Titration of acid developed relative to iodide developed indicated that, over an appreciable extent of reaction, ~60% of reaction was with elimination and ~40% was with substitution (Table II).

A product study, carried out using concentrations of reactants similar to those used in the kinetic study, led to a product which consisted of 37% 1, 24% **3b**, and only 39% 2 (Table I, entry 3). The discrepancy between the 39% of diene in the product study and the ~60% in the kinetic study was found to be due to an elimination–addition reaction[10] providing a route from **3c** to **3b** via 2. This reaction could be suppressed by the addition of excess tetramethylurea[11,12] and the product study then gave ratios consistent with those indicated by the kinetic study (Table I, entries 4 and 5).

While addition of tetramethylurea did not raise the fraction of 1, it did simplify its isolation insofar as that it only had to be separated from 2, rather than from a mixture of 2 and **3b**. Isolation of 1 was therefore from reactions carried out in the presence of excess tetramethylurea. Column chromatography on Florisil–Celite[16a] using pentane as eluent gave reasonably good separation but thin layer chro-

matography indicated that a small amount of diene remained within the epicholesteryl chloride fraction; to obtain analytically pure 1, this fraction had to be submitted to preparative thin layer chromatography. These difficulties paralleled those of Shoppee, Holley, and Newsoroff,[5] who also obtained, from column chromatography, samples of 1 contaminated with 2. Our scheme for synthesis of epicholesteryl chloride is considerably simpler than those previously available in the literature but it does share with the earlier schemes the need for thin layer chromatography for complete separation from simultaneously formed cholesta-3,5-diene.

Experimental Section[16b]

Materials. Cholesteryl iodide (3c) was prepared from cholesteryl chloroformate (Eastman) as described previously.[14] Cholesteryl *p*-toluenesulfonate (3a) was either the Eastman product or synthesized by the procedure of Wallis, Fernholtz, and Gephart.[17] A reference sample of epicholesteryl chloride (1) was prepared[4,5] by treatment of 6-ketocholestanol (Sigma) with phosphorus pentachloride to introduce the 3-α chlorine, followed by reduction of the keto group with lithium aluminum hydride and dehydration with phosphorus oxychloride–pyridine reagent. Tetra-*n*-butylammonium chloride and iodide (K and K) were recrystallized from acetone and dried under vacuum at 50°. Tetramethylurea was purified by distillation and used immediately. Acetonitrile[18] and acetone[19] were purified as described previously. A solution of dry hydrogen chloride in acetone was standardized against aqueous sodium hydroxide.

Analysis of Product Mixtures. The three predicted products from reaction of cholesteryl derivatives with chloride ion in aprotic solvents, **1**, **2**, and **3b**, did not, in our hands, separate completely by column chromatography. However, quite accurate analyses could be obtained from the integration of the ^{1}H NMR spectrum within the δ 3.5–6.5 range. Available spectra[20] reported, for **3b**, signals for the 3-α hydrogen at δ 3.76 and for the C-6 vinylic hydrogen at δ 5.36 and, for **2**, signals for the three vinylic protons at δ 5.41, 5.69, and 5.99. The authentic sample of **1** was found to exhibit signals at δ 4.50 for the 3-β hydrogen and at δ 5.38 for the C-6 vinylic hydrogen. Accordingly, the integrations at δ 3.76 and 4.50 are proportional to the concentrations of **3b** and **1** and, within the region of vinylic proton signals (δ 5.2–6.2), subtraction of the integrations at δ 3.76 and 4.50 (equal to those for the identical components at δ 5.36 and 5.38) leads to the integration for the three vinylic protons of the diene; one-third of this value can then be utilized together with the integrations at δ 3.76 and 4.50 to give the relative concentrations.

The percentage of conjugated diene, **2**, within the product mixture can also be determined from the ultraviolet spectrum, where its absorption swamps out those from the products with an isolated double bond. In cyclohexane, **2** has been shown[21] to exhibit absorption maxima with log ϵ 4.23 at 228 nm, log ϵ 4.27 at 235 nm, and log ϵ 4.07 at 244 nm. An average of the observed absorptions at each of these three wavelengths can be used to calculate the weight percentage, and hence the molar percentage, of a mixture with **1** and **3b**. For low concentrations of diene, this determination is preferable to the ^{1}H NMR determination, which has to be determined from a small difference between two relatively large numbers.

The above techniques have been used to determine the compositions of the product mixtures obtained in each of the following experiments (Table I).

Reaction of Cholesteryl *p*-Toluenesulfonate (3a) with Lithium Chloride. The **3a** (0.0185 *M*) was refluxed in acetonitrile with dry lithium chloride (0.236 *M*) for 16 hr. The solution was partitioned between ether and water. The ether layer was washed with a little water and dried over anhydrous $MgSO_4$, and the product mixture isolated by flask evaporation of solvent (Table I, entry 1). The experiment was also performed in the presence of 0.0370 *M* tetramethylurea (Table I, entry 2).

Reaction of Cholesteryl Iodide (3c) with Tetra-*n*-butylammonium Chloride. The **3c** (0.0400 *M*) and *n*-Bu_4NCl (0.200 *M*) were allowed to react in acetone for 72 hr at 50.0°. The solution was partitioned between ether and ice–water. The ether layer was dried over anhydrous $MgSO_4$ and the product mixture remained after flash evaporation (Table I, entry 3). The experiment was repeated in the presence of 0.040 and 0.080 *M* tetramethylurea (Table I, entries 4 and 5).

Control Experiments. Cholesteryl chloride (**3b**, 0.0400 *M*) was allowed to stand in acetone for 72 hr at 50.0° in the presence of *n*-Bu_4NCl (0.200 *M*). After partitioning between ether and water, a 90% recovery of cholesteryl chloride was made (Table I, entry 6). The experiment was repeated in the presence of 0.040 *M* tetramethylurea and a 97% recovery was made (Table I, entry 7).

An acetone solution of **3b** (0.0160 *M*) was allowed to stand for 72 hr in the presence of *n*-Bu_4NCl (0.200 *M*) and hydrogen chloride (0.0240 *M*). The solution was then partitioned between ether and water, and the ether layer was washed with a little water, dried over anhydrous $MgSO_4$, and flash evaporated to dryness (Table I, entry 8). The experiment was repeated with **1** substituted for **3b** (Table I, entry 9).

Column Chromatography. A 250-mg portion of the product from reaction of **3c** with *n*-Bu_4NCl in the presence of tetramethylurea (Table I, entries 4 and 5) was chromatographed, using pentane as eluent, on a 14 × 0.75 in. column packed with 45 g of a 4:1 Florisil–Celite[16a] mixture. Three fractions were collected, consisting of **2**, mp 80–81.5° (lit.[5] mp 79–80°), a mixture of **2** with **1**, and, finally, relatively pure **1**, mp 112–115° (lit. mp 105–107° [4], 114–117° [5]). Thin layer chromatography on silica with pentane as solvent showed for the first fraction one large spot (R_f 0.89), for the second fraction two spots (R_f 0.89 and 0.94), and for the third fraction a large spot (R_f 0.94), mp 115–117°, together with a small spot (R_f 0.89).

Kinetic Measurements. Solutions were made up by appropriate dilution of acetone solutions of **3c** and tetrabutylammonium chloride with acetone at 50.0°. After a few minutes for temperature equilibration, two 5-ml aliquots were withdrawn, followed by others at appropriate time intervals. One series of aliquots was added to 20 ml of acetone maintained at −78° (solid CO_2–acetone slush) and the acid developed, corresponding to elimination reaction, was titrated to Lacmoid (resorcinol blue) end point against a standard solution of sodium methoxide in methanol. The second series of aliquots was used to determine the iodide formation, corresponding to total reaction; the aliquot was introduced into 20 ml of concentrated HCl and 20 g of ice and titrated against a standard aqueous solution of potassium iodate. Starch was found to give an unsatisfactory end point, possibly owing to the presence of acetone, and the end point was determined by adding 5 ml of CCl_4 and titrating, with shaking after each drop near the end point, until the purple color of iodine within the organic layer changed to pale yellow.[22]

In analyzing the data in terms of second-order rate coefficients, it is necessary to take into account the consumption of one chloride ion in each act of substitution and two chloride ions in each act of elimination. The appropriate kinetic equation is

$$\frac{dx}{dt} = zk_2(a - x)(b - x) + (1 - z)k_2(a - 2x)(b - x)$$

where x is the concentration of iodide produced, a is the initial concentration of chloride ion, b is the initial concentration of **3c**, k_2 is the second-order rate coefficient for iodide production, and z is the fraction of reaction proceeding with substitution. Integrating:

$$k_2 = \frac{1}{[a + (z - 2)b]t} \ln \frac{b}{a}\left[\frac{a + (z - 2)x}{(b - x)}\right]$$

The second-order rate coefficients and fractions of reaction proceeding with elimination are listed in Table II.

An acetone solution 0.0387 *M* in **3c** and 0.0400 *M* in tetra-*n*-butylammonium iodide showed no acid formation after 24 hr at 50.0°.

Registry No.—**1**, 2863-79-8; **2**, 747-90-0; **3a**, 1182-65-6; **3b**, 910-31-6; **3c**, 2930-80-5; lithium chloride, 7447-41-8; *n*-Bu_4NCl, 1112-67-0; *n*-Bu_4NI, 311-28-4.

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Ring Enlargement of Geminal Dibromocyclopropanes with Silver Tosylate. An Approach to Medium Sized Rings

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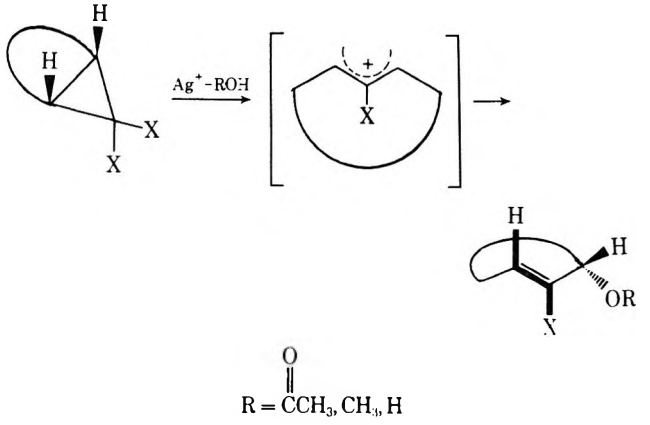
The reaction of geminal dihalocyclopropanes with silver perchlorate under solvolytic conditions has recently attracted attention as a synthetically useful approach for ring enlargement.[1-4] These reactions obey the Woodward–Hoffmann rules of conservation of orbital symmetry and proceed in a disrotatory manner.[5,6] The allylic system formed has been postulated to have the trans conformation, obtained by release of the exo halogen atom.

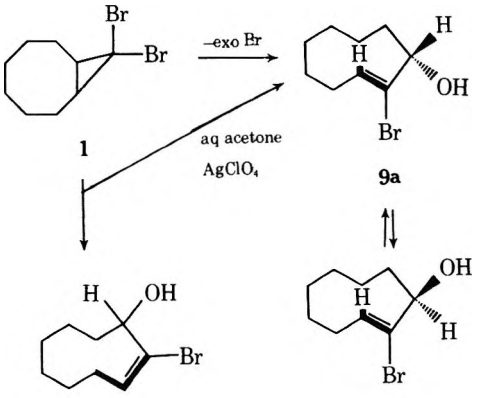


The nucleophile attacks at the same site of the incipient allylic system where the halogen atom is departing and thus leads to the formation of one single diastereoisomer in most cases.

In the absence of silver salts severing of the exo halogen atom is preferred on steric considerations, unless the expanded ring would become too small to accommodate a trans double bond. In the latter case the endo halogen is lost, leading to a cis allylic system.[7a,b]

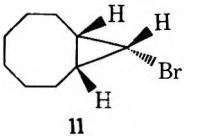
We now wish to present a highly stereospecific method to generate tosylated medium sized rings by ring opening of dibromocyclopropanes in one step and with excellent yields. Reaction of the bicyclic systems **1–4** for 2 hr with a slight excess of silver tosylate in refluxing acetonitrile led in a smooth reaction to the tosylates **5–8** (Table I). Examination of the reaction products (TLC, ^{1}H NMR) revealed that in all four cases one single diastereoisomer had been formed. The ring opening of **3** and **4** proceeds mechanistically in a similar fashion as the above-mentioned reactions. This could easily be demonstrated by synthesizing compounds **7** and **8** by tosylation of the corresponding alcohols with known stereochemistry.[1] Therefore, the tosylates **7** and **8** have the configuration as assigned in Table I.

The formation of tosylates **5** and **6** deserves some comment. Earlier literature concerning the silver perchlorate catalyzed solvolysis of **1** showed that two diastereoisomeric trans alcohols were formed, which were rapidly equilibrating at room temperature.[2] However, in our hands, besides the trans alcohols **9a,b**, also considerable and reproducible amounts of the cis alcohol **10** could be isolated (ca. 30%).[8]



Tosylation of the cis alcohol **10** gave the tosylate **4**, whereas the product obtained by reaction of the mixture of diastereoisomers **9a** and **9b** with tosyl chloride proved to be quite different (NMR spectrum displayed multiplet structures at δ 4.87 and 6.05 for the allylic part of the spectrum). A possibility of initial formation of a trans tosylate followed by an Ag^+-assisted isomerization to the cis conformer could be ruled out easily by refluxing the trans tosylate of **9a,b** with excess silver tosylate in acetonitrile; no traces of **5** could be detected.

Disrotatory ring opening of **1** with release of the sterically less accessible endo bromine atom leading to a cis-allylic system seems very improbable. Upon treating *endo*-9-bromobicyclo[6.1.0]nonane (**11**) with silver tosylate in refluxing acetonitrile no noticeable reaction was observed. A similar observation was made in the expansion of the nine-membered compound **2**.



11

In this case we found that besides the expected 2-bromo-3-hydroxy-*trans*-cyclodec-1-ene (**12**)[11] also the 2-bromo-3-hydroxy-*cis*-cyclodec-1-ene (**13**) could be isolated in 30% yield by ring expansion with silver perchlorate in 5% aqueous acetone.

The tosylate derived from **13** proved to be identical with **6**, whereas the trans alcohol **12** gave a tosylate displaying

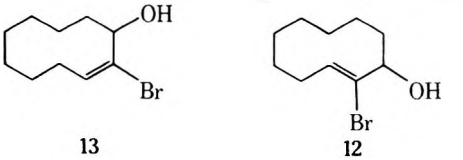
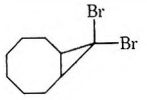
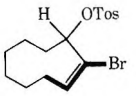
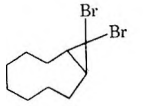
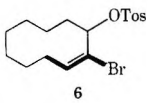
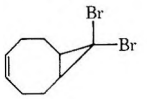
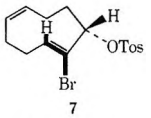
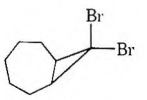
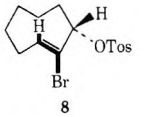


Table I

Starting compd	Product[a]	Mp, °C	Yield, %[b]	NMR data ($CDCl_3$), δ
 1	 5	91–93	93	6.04 (t, 1, olefin H, J = 8 Hz), 5.52 (dd, 1, methine H, J = 10 and 5 Hz), 2.40 (s, 3, CH_3)
 2	 6	108–111	81	5.75 (m, 2, olefin H and methine H), 2.41 (s, 3, CH_3)
 3	 7	89–91	89	5.85 (t, 1, olefin H, J = 8 Hz), 5.27 (m, 2, H cis double bond), 4.85 (dd, 1, methine H, J = 10 and 6 Hz), 2.39 (s, 3, CH_3)
 4	 8	80–82	85	6.10 (dd, 1, olefin H, J = 11 and 5 Hz), 4.92 (t, 1, methine H, J = 8 Hz), 2.42 (s, 3, CH_3)

[a] Satisfactory analytical data were obtained (±0.3% for C and H). [b] Yields are based upon isolated crude material (purity >95%).

triplets at δ 4.95 (J = 7 Hz) and 6.18 (J = 8.5 Hz). From these observations we must conclude that silver ion assisted ring opening of **1** and of **2** is leading initially to the free trans allylic cation which rapidly isomerizes to the cis allylic cation before reacting with the weakly nucleophilic tosylate anion.

The ring opening of **3** and of **4** leads exclusively to the trans allylic tosylates, because a free trans cation would require a sterically very unfavorable geometry, and therefore, these reactions must proceed completely concertedly leading to **7** and **8**.

Experimental Section

General. Starting materials **1–4** were prepared by the reaction of dibromocarbene with the appropriate olefins according to known procedures.[9] *endo*-9-Bromobicyclo[6.1.0]nonane (**11**) was obtained from reduction of **1** with tri-*n*-butyltin hydride.[8] Silver tosylate was prepared from silver oxide and *p*-toluenesulfonic acid, according to the procedure of Kornblum et al.[10] NMR spectra were obtained on a Varian T-60 spectrometer using Me_4Si as an internal standard. The ring expansion reaction with silver tosylate is exemplified with the preparation of **7**.

2-Bromo-3-tosyloxycyclonona-*trans,cis*-1,5-diene (7). To a solution of 2.80 g (0.01 mol) of **3** in 10 ml of acetonitrile was added a solution of 3.10 g (0.011 mol) of silver tosylate in 15 ml of acetonitrile. The mixture was stirred with gentle reflux for 2 hr. After cooling and addition of an equal volume of ether the precipitate was filtered and the filtrate evaporated to dryness. The resulting gummy product was chromatographed through a short silica gel column and afforded 3.3 g (89%) of white, crystalline tosylate **7**. Recrystallization from diisopropyl ether gave analytical material, mp 89–91°. Anal. Calcd for $C_{16}H_{19}BrO_3S$: C, 51.75; H, 5.12. Found: C, 51.64; H, 5.12.

2-Bromo-3-hydroxycyclonon-1-ene (9, 10). To a solution of 5.64 g (0.02 mol) of **1** in 50 ml of 5% aqueous acetone was added a solution of 5.36 g (0.026 mol) of silver perchlorate in 25 ml of 5% aqueous acetone. The mixture was stirred at ambient temperature for 2 hr. After addition of 50 ml of saturated sodium chloride solution stirring was prolonged for an additional 5 min. The precipitate was filtered; the filtrate was diluted with 200 ml of water and extracted with ether. Upon washing, drying, and evaporation of the organic phase 3.19 g (73%) of the product was left as a colorless oil. The product consisted of two components. Chromatography (silica gel, chloroform–2% methanol as eluent) afforded 0.89 g of the cis alcohol **10** (R_f 0.29) and 2.29 g of the diastereomeric mixture of trans alcohols **9a,b**[2a] (R_f 0.22). The cis alcohol was recrystallized from petroleum ether: mp 72–74°; NMR ($CDCl_3$) δ 4.75 (m, 1, methine H), 6.18 (t, 1, olefin H, J = 11 Hz). Anal. Calcd for $C_9H_{15}BrO$: C, 49.31; H, 6.84. Found: C, 49.29; H, 6.80.

2-Bromo-3-hydroxycyclodec-1-ene (12, 13). A solution of 5.92 g (0.02 mol) of **2** and 5.36 g (0.026 mol) of silver perchlorate in 75 ml of 5% aqueous acetone was stirred for 3 hr at room temperature. Work-up in a similar manner as described for **9** and **10** afforded 3.21 g (71%) of product. Chromatography over silica gel (chloroform–2% methanol as eluent) afforded 2.55 g of trans alcohol **12** (R_f 0.38) as a colorless oil: NMR ($CDCl_3$) δ 4.18 (dd, 1, methine H, J = 9 and 5 Hz), 6.24 (t, 1, olefin H, J = 9 Hz). The other component (0.75 g, R_f 0.44) was the cis alcohol **13**: mp 48–50° (petroleum ether); NMR ($CDCl_3$) δ 4.82 (t, 1, methine H, J = 8 Hz), 5.98 (dd, 1, olefin H, J = 12 and 6 Hz). Anal. Calcd for $C_{10}H_{17}BrO$: C, 51.50; H, 7.29. Found: C, 51.62; H, 7.31.

Registry No.—**1**, 32644-18-1; **2**, 57129-79-0; **3**, 54809-08-4; **4**, 52750-35-3; **5**, 57090-95-6; **6**, 57090-96-7; **7**, 57344-75-9; **8**, 57344-76-0; **10**, 32726-58-2; **12**, 57090-97-8; **13**, 57090-98-9; silver tosylate, 16836-95-6.

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(4) M. S. Baird and C. B. Reese, *Tetrahedron Lett.*, 4637 (1971).
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(8) M. S. Baird and C. B. Reese, *J. Chem. Soc. C*, 1808 (1969).
(9) L. Skattebøl, *Acta Chem. Scand.*, **17**, 1683 (1963).
(10) N. Kornblum, W. J. Jones, and G. J. Anderson, *J. Am. Chem. Soc.*, **81**, 4113 (1959).
(11) The two diastereoisomers of trans alcohol **12** equilibrate at room temperature at such a rate that only one NMR signal is observed.[2b]

Ring Opening of 5,7-Dimethyl-*v*-triazolo[1,5-*a*]pyrimidine by Halogenating Agents

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In earlier publications, we demonstrated that electrophilic attack by halogens took place in the five-membered ring

of pyrazolo[1,5-*a*]pyrimidines[1,2] and pyrazolo[1,5-*a*]-1,3,5-triazines.[3] Although a few derivatives of *v*-triazolo[1,5-*a*]pyrimidine have been synthesized by Sutherland and Tennant,[4] little is known about the chemistry of this ring system. The site of electrophilic attack on similar 10 π electron (bridgehead nitrogen) heterocycles has been explored by Lynch et al.[5] and by Jacquier et al.,[6] and therefore such a study on 5,7-dimethyl-*v*-triazolo[1,5-*a*]pyrimidine (**1**) seemed appropriate from a theoretical viewpoint (as well as a biological viewpoint[2,7]).

When **1** was treated with *N*-bromosuccinimide (NBS) in chloroform, two products were isolated, neither of which was the expected 3-bromo-5,7-dimethyl-*v*-triazolo[1,5-*a*]pyrimidine (**9**). The major product, which was isolated in up to 90% yield, was assigned the structure of 2-(α,α-dibromomethyl)-4,6-dimethylpyrimidine (**2**), as determined by mass spectrum, elemental analysis, ^{1}H NMR, and ^{13}C NMR (see Experimental Section). The application of ^{13}C NMR and ^{1}H NMR in the structural determination was employed to rule out the possibility that **2** might be 5-bromo-2-(α-bromomethyl)-4,6-dimethylpyrimidine.

The minor product was assigned the structure of 4,6-dimethylpyrimidine-2-carboxaldehyde diethyl acetal (**3**), also consistent with elemental analysis, ir, uv, ^{1}H NMR, and MS data, as well as ^{13}C NMR spectra. A search of the literature indicated that pyrimidine-2-carboxaldehyde and its derivatives had not been reported. Data from the ^{13}C NMR spectrum were particularly useful for structure determination, in this respect, because the ring carbons of **2** and **3** had essentially identical shieldings, but the signal for the α carbon of **3** occurred 51 ppm downfield from the α carbon of **2** (e.g., the substituted 2-methyl group of **2** and **3**). Such large deshielding effects had been demonstrated by Lauterbur[8] in alkoxy oxygen atoms. The acetal carbon in the ^{13}C NMR spectrum of neat methylaminoacetaldehyde dimethyl acetal was found to have the same shift (102.9 ppm) as that of **3**.

The origin of **3** presented a problem. Refluxing **2** in ethanol did not yield **3**, nor did **3** arise from adding NBS and a trace of ethanol to a solution of **2** in chloroform. It appeared that **3** did originate from a trace amount of ethanol in the solvent (when freshly dried chloroform was used, **3** was not isolated), but the addition of more ethanol during the bromination reaction did not substantially increase the yield of **3**. The bromination of **1** in methylene chloride with bromine at 0°, and in sodium hydroxide with bromine at 0°, gave only **2**.

In contrast to the above reactions, the bromination of **1** in ethanol at −20° gave a mixture of five products. From the GLC data of the crude mixture, it appeared that the decomposition of **1** was quantitative, giving approximately 60% of **3**, 10% of **2**, 20% of a derivative of the *v*-triazolo[1,5-*a*]pyrimidine ring, 9% of one new pyrimidine derivative, and 1% of another new pyrimidine.

Elemental analysis, uv, ir, and ^{1}H NMR substantiated the structure of one of the isolated products as being 3-bromo-5,7-dimethyl-*v*-triazolo[1,5-*a*]pyrimidine (**9**). As reported elsewhere,[6,7] the unique fluorescence of certain bridgehead nitrogen heterocycles (long-wavelength uv; silica gel TLC plate, as described in the Experimental Section), along with supporting uv data (e.g., the comparison of the uv data of **1** and **9**), helped to establish that the original ring system was still intact in compound **9**.

The remaining two products were identified by elemental analyses and spectra (ir, uv, and ^{1}H NMR). The material obtained in 9% yield was assigned the structure of 4,6-dimethyl-2-ethoxymethylpyrimidine (**8**) and the compound obtained in 1% yield was identified as 2-(α-bromoethoxymethyl)-4,6-dimethylpyrimidine (**7**). The latter (**7**) was not very stable and was also found to convert to **3** upon standing in ethanol at 25°, perhaps suggesting that **3** originated from **7** in the original reaction.

The reaction of **1** with *N*-chlorosuccinimide (NCS) gave the expected 2-(α,α-dichloromethyl)-4,6-dimethylpyrimidine (**5**). Normally, the use of iodine monochloride in the halogenation of nitrogen bridgehead heterocycles gives substitution of the ring with iodine, and hydrogen chloride is released.[2] When **1** was treated with this reagent, the product obtained was 4,6-dimethyl-2-(α-iodo-α-chloromethyl)pyrimidine (**4**).

It is possible that **1** may be in equilibrium with, or at least may coexist with, a 4,6-dimethylpyrimidinyl-2-diazomethane (**6**). Although we were unable to detect this species via low-temperature ^{1}H NMR and ^{13}C NMR spectra, such a structure is plausible. Sutherland and Tennant[4] suggested that a "diazonium cation" accounted for the decomposition of the 3-phenyl derivative of **1** in acetic acid. A similar equilibrium was demonstrated by Temple et al.[9,10] for 5,7-dimethyltetrazolo[1,5-*a*]pyrimidine, which was found to coexist with the 2-azidopyrimidine. Additionally, our earlier work[11] on the equilibria of the 8-phenyltetrazolo[1,5-*e*]pyrazolo[1,5-*a*]-1,3,5-triazine ring in the presence of bromine also supports this hypothesis.

All of the products appear to be consistent with a cationic mechanism, involving standard diazoalkane electrophile reactions,[12] as illustrated in Scheme I. Solvolysis by ethanol apparently accounts for **3** and **8**. From a general synthetic viewpoint, the reaction of diazoalkyl compounds with halogens to yield α,α-dihalomethyl derivatives has been of limited value in previous applications. However, the high yields of **2**, **4**, and **5** indicate that the present method is a potentially useful synthetic route to 2-substituted pyrimidines that are inaccessible or difficult to prepare by other methods.

Experimental Section

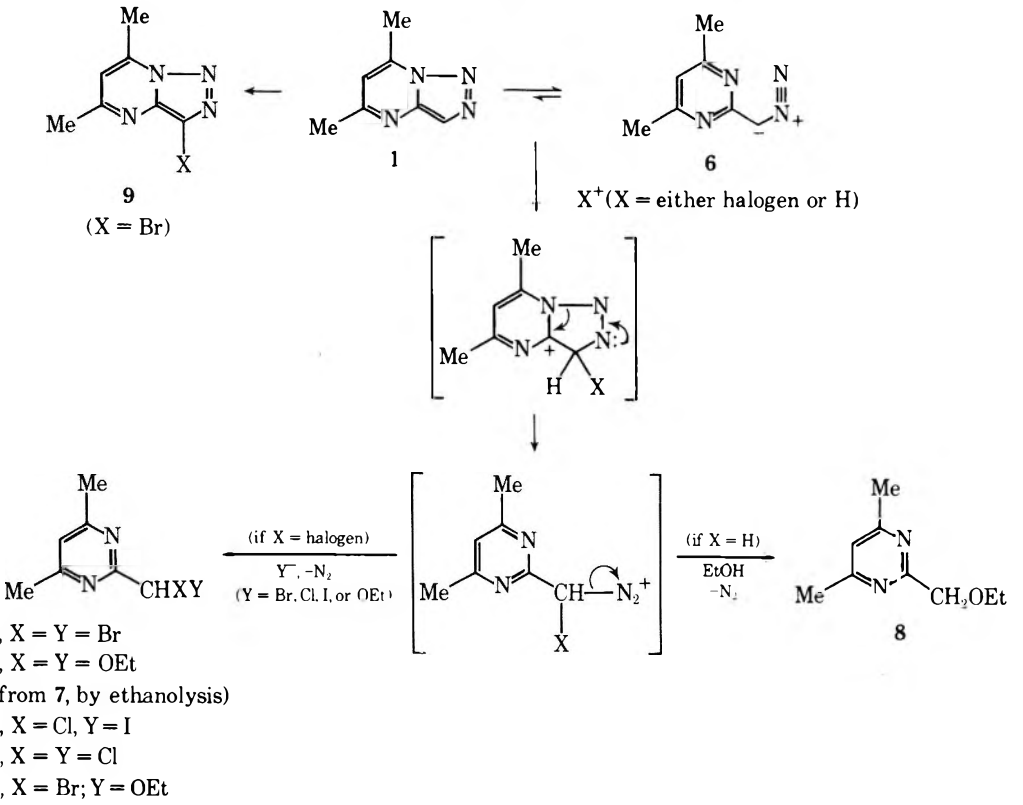
^{13}C NMR spectra were taken in 20% $CDCl_3$ solutions and recorded on a Bruker HX-90 spectrometer operating at 22.62 MHz in the Fourier transform mode at a probe temperature of 35°. A Nicolet 1074 signal averager with 4096 word memory was used for data accumulation and a PDP-8/e computer (Digital Equipment Corp.) for data processing. Chemical shifts were measured from $CDCl_3$ and then converted to the tetramethylsilane (Me_4Si) scale using the relationship $\delta_{Me_4Si} = \delta_{CDCl_3} + 77.2$ ppm. ^{1}H NMR spectra were taken in $CDCl_3$ with Me_4Si as an internal standard, recorded on a 60-MHz Hitachi Perkin-Elmer R20A spectrometer. Ir spectra were obtained in KBr disks if the sample was solid, and as a thin layer on NaCl cells if liquid, both being obtained on a Perkin-Elmer 257 spectrophotometer. Mass spectra were obtained on a Perkin-Elmer 270 high-resolution spectrometer. Gas–liquid chromatography was obtained on a Varian Model 2100 gas chromatograph equipped with flame ionization detector. A 3.8 mm × 6 ft glass column packed with 3% OV-101 was used at a column temperature of 220° and detector at 250°. Column chromatographic separations were performed on Woelm activity grade I neutral alumina, eluted with chloroform, unless otherwise noted. Analyses and molecular weight determination were performed by Galbraith Laboratories, Knoxville, Tenn.

5,7-Dimethyl-*v*-triazolo[1,5-*a*]pyrimidine (1). A mixture of 0.84 g (0.01 mol) of 5-amino-*v*-triazole[13] and 1.0 g (0.01 mol) of acetylacetone was refluxed in 10 ml of ethanol containing 2 drops of piperidine, for a period of 1 hr. The resulting solution was allowed to cool to room temperature and then it was evaporated at 25° (0.1 mm) to yield a gummy residue. The crude product was recrystallized from benzene–petroleum ether to yield 1.1 g (75%) of the product in the form of yellowish-white needles, mp 82–84°. The condensation was also performed in the absence of solvent (no piperidine), giving a 70% yield, and also in benzene, giving an 81% yield: mp 83–84°; ^{1}H NMR ($CDCl_3$) 2.67 (s, 3), 2.92 (s, 3), 6.78 (s, 1), and 8.16 (s, 1).

Anal. Calcd for $C_7H_8N_4$ (148.16): C, 56.74; H, 5.44; N, 37.82. Found: C, 57.02; H, 5.60; N, 38.05.

Bromination of 1. 2-(α,α-Dibromomethyl)-4,6-dimethylpy-

Scheme I



2, X = Y = Br
3, X = Y = OEt
(from 7, by ethanolysis)
4, X = Cl, Y = I
5, X = Y = Cl
7, X = Br; Y = OEt

rimidine (2). Method A. A solution of 1.0 g 1 in 50 ml of methylene chloride was cooled to 0° and 1.1 g of bromine was added dropwise over a 10-min period. The solvent was evaporated and the residue was recrystallized from methanol–water to yield 0.9 g (90%) of 2-dibromomethyl-4,6-dimethylpyrimidine (2) as yellowish-white needles, mp 82–84°. A second recrystallization, from ether, gave white cubettes, melting point unchanged. A mixture melting point depression of 60–65° was recorded when 1 and 2 were mixed.

Uv (MeOH) λ_{max} 225 nm (ϵ_{max} 6780), 250 sh (6510); ^{1}H NMR ($CDCl_3$) δ 6.96 (s, 1), 6.64 (s, 1), and 2.53 (s, 6); ^{13}C NMR ($CDCl_3$) 167.7 (C_2), 165.6 (C_4, C_6), 119.8 (C_5), 23.9 (Me at C_4, C_6) and 41.9 ppm ($CHBr_2$ at C_2).

Anal. Calcd for $C_7H_8N_2Br_2$ (279.96): C, 30.03; H, 2.88; Br, 57.08. Found: C, 29.82; H, 2.83; Br, 57.20.

Method B. A solution of 0.9 g of 1 in 50 ml of chloroform was cooled to 0° and 1.1 g (0.01 mol) of *N*-bromosuccinimide was added in small portions. The solution was then washed with ice-cold 1*N* NaOH (~ 100 ml), followed by water, and dried over Na_2SO_4. The chloroform was then evaporated at 20° (8 mm) to yield an oily residue. Chromatography of this material on alumina (Woelm, neutral, activity grade I) with chloroform gave two fractions. The first fracton, upon evaporation of the solvent, gave 120 mg (20%) of 2 as white needles, mp 82–84°. The second fraction, upon evaporation, gave 200 mg of a colorless oil which was judged sufficiently pure for analysis (GLC, as stated earlier). This material was shown to be **4,6-dimethylpyrimidine-2-carboxaldehyde diethyl acetal (3)**: bp 78–80 (0.1 mm); ^{1}H NMR ($CDCl_3$) δ 1.25 (t, 6), 2.5 (s, 6), 3.75 (q, 4), 5.5 (s, 1), and 7.0 (s, 1); ^{13}C NMR ($CDCl_3$) 167.1 (C_2), 165.2 (C_4, C_6), 119.6 (C_5), 23.9 (Me at C_4, C_6), 102.9 [$CH(OEt)_2$], 62.8 (OCH_2CH_3), 15.2 ppm (OCH_2CH_3); uv (MeOH) λ_{max} 250 nm (ϵ_{max} 8530).

Anal. Calcd for $C_{11}H_{18}N_2O_2$ (198): C, 60.58; H, 9.15; N, 14.13. Found: C, 60.40; H, 8.80; N, 14.44.

Method C. A solution of 1.0 g of 1 in 50 ml of water containing 1.0 g of sodium hydroxide was cooled to 0°. Then 1 ml of bromine was added dropwise over a 5-min period. The mixture was stirred for 30 min at 0°, then extracted with methylene chloride. The solvent was dried ($MgSO_4$) and evaporated. The residual oil was chromatographed on neutral alumina, as in method B. Only one fraction was obtained, and this gave 350 mg (40%) of 2, mp 82–84°, upon work-up (following the procedure given above).

4,6-Dimethyl-2-(α-iodo-α-chloromethyl)pyrimidine (4). A solution of 1.0 g of 1 in 50 ml of chloroform was cooled to 0° and 1.1 g of iodine monochloride was added, in small portions. Vigorous ebullition of nitrogen gas was observed at this temperature. The dark mixture was refrigerated for 24 hr, then filtered through 50 g of neutral alumina and eluted with chloroform. Upon evaporation of the eluent, a yellow oily residue was obtained, which soon solidified. Recrystallization of this solid from petroleum ether gave 1.2 g (48.6%) of pale yellow cubettes: mp 73–75°; ^{1}H NMR ($CDCl_3$) δ 2.53 (s, 6), 6.83 (s, 1), and 6.94 (s, 1); uv (MeOH) λ_{max} 230 nm (ϵ_{max} 7200), 260 sh (6830).

Anal. Calcd for $C_7H_8N_2ClI$ (282.5): C, 29.76; H, 2.85; N, 9.92. Found: C, 29.72; H, 2.88; N, 9.60.

2-(α,α-Dichloromethyl)-4,6-dimethylpyrimidine (5). A solution of 1.5 g (0.01 mol) of 1 in 70 ml of chloroform was cooled to −20° (dry ice–acetone bath) and 1.4 g (0.011 mol) of *N*-chlorosuccinimide in 20 ml of chloroform was added dropwise over a 5-min period. The mixture was stirred for 2.5 hr at −20°, then stored at 0° for 20 hr. The solution was then washed with aqueous sodium bicarbonate and the organic extract dried ($MgSO_4$) and evaporated in vacuo to yield an oily residue. Chromatography of the material on neutral alumina with chloroform gave 100 mg (10%) of the product, recrystallized from petroleum ether as white needles: mp 77–78°; ^{1}H NMR ($CDCl_3$) 2.55 (s, 6), 6.70 (s, 1), and 7.03 (s, 1); uv (MeOH) λ_{max} 228 nm (ϵ_{max} 7100), 250 sh (6200).

Anal. Calcd for $C_7H_8N_2Cl_2$ (191.1): C, 44.01; H, 4.22; N, 14.66. Found: C, 44.20; H, 4.35; N, 14.70.

Bromination of 1 in Ethanol. A solution of 1.0 g (6.7 mmol) of 1 in 25 ml of EtOH was cooled to −20° and 1.1 g of bromine in 10 ml of EtOH was added dropwise over a 10-min period, with stirring. A yellow precipitate formed, which decomposed with vigorous evolution of nitrogen, upon reaching 15–20°. The resultant clear, yellow solution was concentrated in vacuo to yield a gummy residue. The gum was dissolved in CH_2Cl_2 (50 ml) and washed with aqueous $NaHCO_3$ and then water, and the organic phase was dried ($MgSO_4$). Evaporation of the solvent gave an oil which was analyzed both by GLC and by TLC (percent isolated and R_f values are given for each compound below).

The crude mixture was chromatographed, giving in order of elution ($CHCl_3$) **2**, **9**, and **3**.

(a) **2** (130 mg, 8%, GLC 10%, R_f 0.79), mp 75–77° (ir and ^{1}H NMR compared with original).

(b) **3-Bromo-5,7-dimethyl-*v*-triazolo[1,5-*a*]pyrimidine (9)** (100 mg, 10%, GLC 20%, R_f 0.56), mp 103–104° dec, recrystallized from petroleum ether (bp 30–60°).

Anal. Calcd for $C_7H_7N_4Br$: C, 37.02; H, 3.10; N, 24.67. Found: C, 37.08; H, 3.16; N, 24.33.

^{1}H NMR ($CDCl_3$) δ 2.79 (s, 3), 2.90 (s, 3), 6.80 (s, 1); uv (MeOH)

λ_{max} 223 nm (ϵ_{max} 27120), 274 (3890), 284 (39740), and 310 (3200); ir (KBr) 1630, 1450, 1383, 1525, and 1322 cm^{-1}.

(c) **3** (400 mg, 43%, GLC 70%, R_f 0.43), bp 93–95 (0.5 mm) and 78–80 (0.1 mm), which was identical with the material obtained from the chloroform reaction (^1H NMR, uv, and ir).

Acknowledgment. The authors are grateful to L. Larek for mass spectra and GLC data, and to E. Banta and M. Strikaitis for other spectra. We would also like to thank R. Day for technical assistance and Drs. R. K. Robins, R. B. Meyer, Jr., L. N. Simon, B. Bhooshan, and A. A. Albert for helpful suggestions.

Registry No.—**1**, 57173-97-4; **2**, 57173-98-5; **3**, 57173-99-6; **4**, 57174-00-2; **5**, 57174-01-3; **7**, 57174-02-4; **9**, 57174-03-5; 5-amino-*v*-triazole, 30132-90-2; acetylacetone, 123-54-6; *N*-bromosuccinimide, 128-08-5; iodine monochloride, 7790-99-0; *N*-chlorosuccinimide, 128-09-6.

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Fluorometric Reagents for Primary Amines. Syntheses of 2-Alkoxy- and 2-Acyloxy-3(2*H*)-furanones

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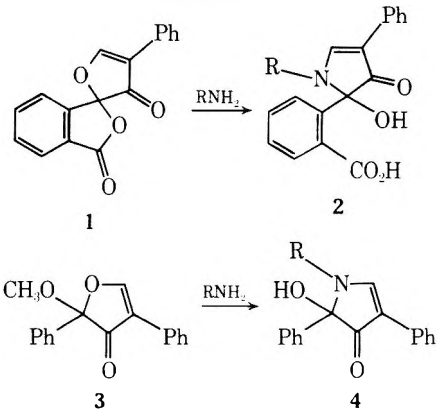
In recent years, fluorescamine, 4-phenylspiro[furan-2(3*H*),1′-phthalan]-3,3′-dione (**1**),[2] has become a widely used reagent for the fluorometric quantitation of primary amines. Fluorescamine reacts with primary amines (RNH_2) to form pyrrolinones of type **2** which upon excitation at 390 nm emit strong fluorescence at 475–490 nm (Scheme I). This reaction proceeds efficiently at room temperature in aqueous solutions[3] and allows the fluorometric estimation of submicromolar concentrations of amines, notably those of biological importance.[4] Many specific analytical applications of fluorescamine have been described in the recent literature, among them highly sensitive procedures for automated amino acid analyses[5,6] and for the assay of proteins.[7] Most recently, the use of fluorescamine has also been suggested for the colorimetric assay of amino acids.[8]

The structurally related compound, 2-methoxy-2,4-diphenyl-3(2*H*)-furanone (MDPF, **3**), which reacts similarly

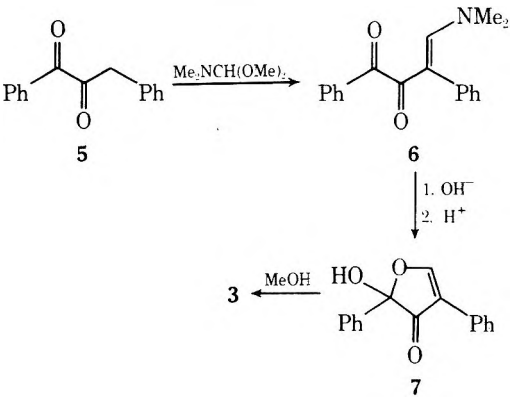
Scheme I



with primary amines to give fluorescent products of type **4**, was found particularly suitable for the fluorescent labeling of proteins and has been used in the preparation of fluorophoric immunoglobulin conjugates.[9] MDPF (**3**) has also been employed to derivatize α-amino acids for the purpose of determining their absolute configuration by chiroptical means.[10]

In this report we wish to describe in detail the syntheses of fluorescamine (**1**) and MDPF (**3**). As depicted in Schemes II and III, the carbon skeleton of these com-

Scheme II

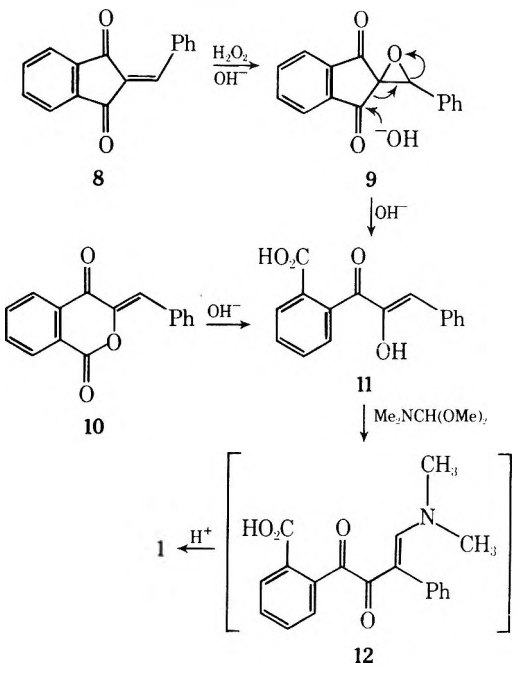


pounds was readily constructed by formylation of suitably substituted 1,2-propanediones.

Thus, in the case of MDPF (**3**), 1,3-diphenyl-1,2-propanedione (**5**)[11] was converted by reaction with *N,N*-dimethylformamide dimethyl acetal to the dimethylaminomethylene derivative **6** (Scheme II). Alkaline hydrolysis of this enamine, followed by acidic work-up, gave the hydroxyfuranone **7**, which was smoothly converted to the desired methoxy derivative **3** by heating in methanol at reflux temperature. Proof for the structure of **3**, in particular the establishment of its cyclic nature, has already been outlined in a previous communication.[2]

The hydroxycinnamoylbenzoic acid **11**, which was required for the synthesis of **1**, was initially obtained by hydrolysis of 3-benzylidene-1,4-isochromandione (**10**)[2] (Scheme III). However, the preparation of **10** according to literature procedures[12] was found to be cumbersome and inefficient. We therefore chose to prepare **11** by a novel route. Thus, 2-benzylideneindan-1,3-dione (**8**)[13] was converted by base-catalyzed oxidation with hydrogen peroxide in methanol to the epoxide **9**. Hydrolysis of **9** with sodium hydroxide led to cleavage of both the indandione and the oxirane ring (cf. **9**, arrows) to afford the desired 1,2-propanedione derivative **11**. The formylation of **11** was carried

Scheme III



out with *N,N*-dimethylformamide dimethyl acetal,[14] much like the conversion of **5** to **6**. However, in this case, it was not possible to isolate the analogous enamine intermediate **12**. Instead, aqueous work-up of the reaction mixture at pH 4 resulted directly in the formation of the desired spirolactone fluorescamine (**1**).

Experimental Section

General. Melting points were taken on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were obtained on a Perkin-Elmer 621 or a Beckman IR-9 spectrometer. Ultraviolet spectra were recorded on a Cary Model 16 spectrophotometer. NMR spectra were measured on a Varian HA-100 instrument and are reported in parts per million downfield from internal tetramethylsilane.

1-Dimethylamino-2,4-diphenyl-1-butene-3,4-dione (6). A solution of 44.8 g of 1,3-diphenyl-1,2-propanedione (**5**)[11] in 90 ml of *N,N*-dimethylformamide dimethyl acetal was allowed to stand at room temperature for 2 hr. It was then poured into 1 l. of ice water and the aqueous mixture was extracted three times with ether. The combined extracts were washed with water, diluted with benzene, dried over Na_2SO_4, and evaporated under reduced pressure. The oily residue was crystallized from ether–petroleum ether to give 43.3 g (77.5%) of **6**: mp 108°C; uv max (CH_3OH) 250 nm (ϵ 12200) and 300 (13300); ir ($CHCl_3$) 1780, 1765, 1605, 1570 cm^{-1}.

Anal. Calcd for $C_{18}H_{17}NO_2$: C, 77.39; H, 6.13; N, 5.01. Found: C, 77.38; H, 6.10; N, 4.91.

2-Methoxy-2,4-diphenyl-3(2*H*)-furanone (3). To a solution of 43.3 g of 1-dimethylamino-2,4-diphenyl-1-butene-3,4-dione (**6**) in 500 ml of ethanol was added 500 ml of 2% aqueous potassium hydroxide. The mixture was stirred at room temperature for 2 hr. It was then diluted with 3 l. of H_2O and acidified with 10% HCl. Solid 2-hydroxy-2,4-diphenyl-3(2*H*)-furanone (**7**) precipitated. It was filtered off with suction and washed on the filter with water. [A dried sample had uv max (MeOH) 244 nm (ϵ 18400) and 292 (6250); NMR ($CDCl_3$) δ 8.59 ppm (s, =CHO–).] The filter cake was dissolved (without further purification) in 500 ml of methanol, and the methanolic solution was heated at reflux temperature for 20 hr and then concentrated on a steam bath to ca. 350 ml. The desired product crystallized upon refrigeration. After two recrystallizations from methanol, there was obtained 31.3 g (76%) of 2-methoxy-2,4-diphenyl-3(2*H*)-furanone (**3**): mp 93–95°C; uv max (MeOH) 241 nm (ϵ 18750) and 307 (3500); ir ($CHCl_3$) 1735, 1705, 1618, 1595 cm^{-1}; NMR ($CDCl_3$) δ 8.69 (s, =CHO–), 3.43 ppm (CH_3O).

Anal. Calcd for $C_{17}H_{14}O_3$: C, 76.67; H, 5.30. Found: C, 76.65; H, 5.48.

3-Phenylspiro[oxirane-2,2′-indan]-1′,3′-dione (9). Into a 2-l. three-necked flask, equipped with a stirrer and a dropping funnel, were placed 96.0 g of 2-benzylidene-1,3-indandione (**8**),[13] 1 l. of methanol, and 60 ml of 30% hydrogen peroxide. The mixture was cooled to 5°C and 10 ml of 1 *N* sodium hydroxide was added dropwise at such a rate as to keep the temperature below 15°C. After completed addition, stirring was continued at room temperature for 30 min. The mixture was then poured into 4.5 l. of water and the resulting crystalline precipitate was collected by filtration, washed repeatedly on the filter with water, and dried under high vacuum at room temperature, affording 101.0 g (98.5%) of the epoxide **9**, mp 154–156°C, pure enough for the next step. An analytical sample, recrystallized from ethyl acetate, had mp 158°C; ir ($CHCl_3$) 1765, 1750 (sh), 1735 (sh), 1725, 905 cm^{-1}; NMR ($CDCl_3$) δ 4.72 ppm (s, –CHO–).

Anal. Calcd for $C_{16}H_{10}O_3$: C, 76.79; H, 4.03. Found: C, 77.07; H, 4.02.

***o*-(α-Hydroxycinnamoyl)benzoic Acid (11).** To a stirred suspension of 20.0 g of 3-phenylspiro[oxirane-2,2α-indan]-1′,3′-dione (**9**) in 200 ml of 10% aqueous sodium hydroxide was added 50 ml of methanol. The reaction became slightly exothermic and the temperature was kept below 35°C by external cooling. After 3.5 hr, the reaction mixture was diluted with 2 l. of water, and the resulting alkaline solution was washed with 500 ml of ether, acidified with 10% HCl, and extracted with chloroform. The extract was washed with water, dried (Na_2SO_4), and evaporated under reduced pressure. The crystalline residue was triturated with petroleum ether–ether (9:1) and filtered, giving 19.0 g (89%) of *o*-(α-hydroxycinnamoyl)benzoic acid (**11**): mp 106–115°C dec; uv max (Et_2O) 315 nm (ϵ 23300); ir (KBr) 1700, 1660, 1625, 1600 cm^{-1}; NMR (Me_2SO-d_6) δ 5.65 (1 s, –CH=), 7.21–8.17 (9 m, aromatic), 9.67 (1 s, –OH).

Anal. Calcd for $C_{16}H_{12}O_4$: C, 71.63; H, 4.51. Found: C, 71.73; H, 4.58.

4-Phenylspiro[furan-2(3*H*),1′-phthalan]-3,3′-dione (1). To a stirred solution of 16.08 g of *o*-(α-hydroxycinnamoyl)benzoic acid (**11**) in 60 ml of a 2 *N* dimethylamine solution in DMF was added 30 ml of *N,N*-dimethylformamide dimethyl acetal. The resulting mixture was kept at room temperature for 2 hr and was then poured into 500 ml of ice water. The aqueous solution was carefully acidified with 10% HCl to pH 4 and the resulting suspension was extracted with 3 × 600 ml of ether–benzene (1:1). After combination, the extracts were washed with 500 ml of 1% aqueous sodium bicarbonate and with water, dried over Na_2SO_4, and evaporated in vacuo. The solid residue was dissolved in 50 ml of warm methylene chloride and the resulting solution was diluted with 120 ml of ether. Upon refrigeration, 10.57 g (64%) of fluorescamine (**1**) precipitated; mp 154–155°C; uv max (Et_2O) 235 nm (ϵ 25900), 276 (3950), 284 (4100), and 306 (3800); ir ($CHCl_3$) 1810, 1745, 1722, 1625, 1600 cm^{-1}; NMR ($CDCl_3$) δ 8.71 (s, –OCH=).

Anal. Calcd for $C_{17}H_{10}O_4$: C, 73.38; H, 3.62. Found: C, 73.41; H, 3.57.

Registry No.—**1**, 38183-12-9; **3**, 50632-57-0; **5**, 23464-17-7; **6**, 36777-65-8; **7**, 54585-24-9; **8**, 5381-33-9; **9**, 43053-57-2; **11**, 43053-07-2; *N,N*-dimethylformamide dimethyl acetal, 4637-24-5.

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(14) Previously[2] we had used tris(dimethylamino)methane for this formylation. However, the present procedure utilizing *N,N*-dimethylformamide dimethyl acetal in the presence of dimethylamine was found to be superior.

Zwitterionic 2,4-Dioxopyrrolidines

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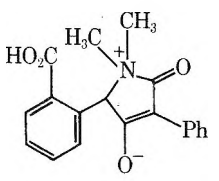
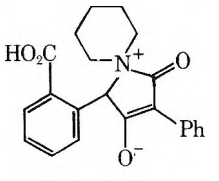
In the course of the development of the fluorogenic amine reagent fluorescamine,[2,3] we encountered the unusual ammonium acylides[4] **1** and **2**. The key step in the synthesis of fluorescamine (**3**) entails the formylation of o-(α-hydroxycinnamoyl)benzoic acid with *N,N*-dimethylformamide dimethyl acetal.[3] Presumably, a diketoenamine **4** (R = CH_3) is formed in this reaction, and is transformed during acidic work-up either directly (cf. **4**, arrows) or via the carbinolamine **5** (R = CH_3) to the spirolactone **6** (R = CH_3) and subsequently to the desired **3**. A minor by-product of this reaction sequence is the enol betaine **1**. The analogous reaction of *o*-(α-hydroxycinnamoyl)benzoic acid with tripiperidinomethane[5] affords only a small amount of the expected **3**, while the major product, obtained after hydrolysis, is the piperidinium acylide **2**. This compound is also formed when fluorescamine (**3**) is allowed to react with excess piperidine and subsequently with aqueous acid.

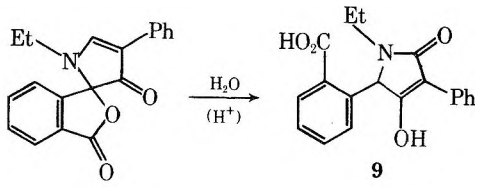


1

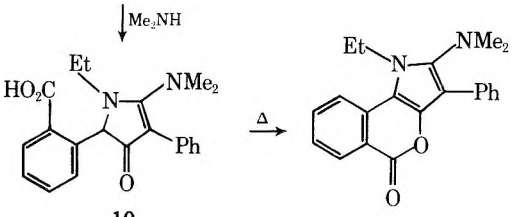


2

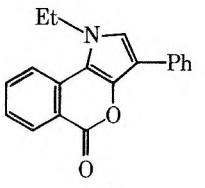
It thus appears that the proposed carbinolamine intermediate of type **5** can follow an alternative mode of cyclization leading to an intermediate of type **7** (instead of **6**), which upon intramolecular disproportionation gives rise to the observed products **1** and **2**. A first indication as to the structural nature of **1** and **2** was obtained from spectral comparisons of these materials with the related tetramic acid **9**, which was previously isolated from an acid catalyzed rearrangement of the spirolactone **8**.[6] For example,



8 **9**



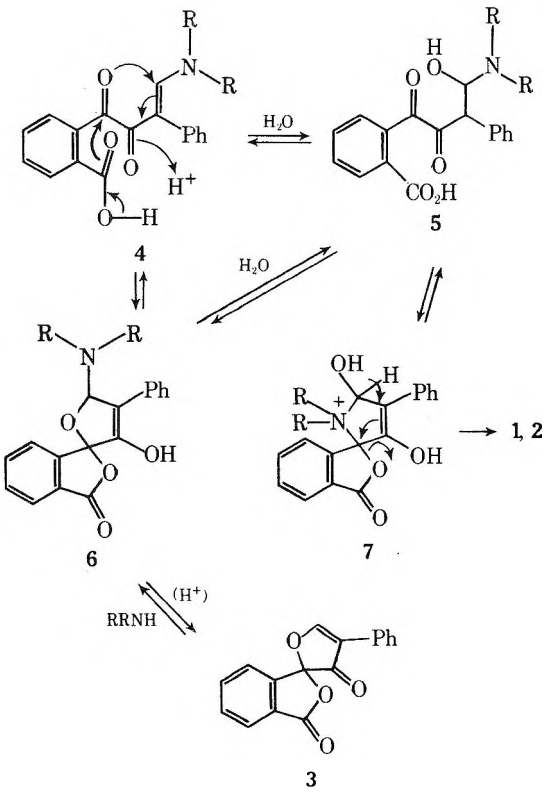
10 **11**



12

the ultraviolet spectra of **1** and **2** (measured in 0.1 *N* KOH) have an absorption maximum at 262 (ε 16500) and 263 nm (16800), respectively, while **9** (in 0.1 *N* KOH) absorbs maximally at 265 nm (ε 14500). Complete structure proof was furnished by an x-ray crystal structure analysis of **2**, the details of which are reported in the Experimental Section (cf. Figure 1).

In this connection, it is also interesting that **8**[6] rapidly reacts with dimethylamine at room temperature to afford the aminopyrrolinone **10**, a process which is strongly reminiscent of the reactions described above. At elevated temperatures, **10** is readily converted to the enol lactone **11**. The ultraviolet spectrum of **11** is remarkably similar in shape to that of **12**,[6] the first one having maxima (in methanol) at 233 (ε 27500), 313 (18500), and 390 nm (6200), the latter at 240 (ε 29750), 291 (19800), and 372 nm (5800). An x-ray crystal structure analysis of **10** (Figure 2) fully corroborated its assigned structure, thus securing also that of **11**.



3

Experimental Section

General. Melting points were taken on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were obtained on a Perkin-Elmer 621 or a Beckman IR-9 spectrometer. Ultraviolet spectra were recorded on a Carey Model 16 spectrophotometer. ^1H NMR spectra were measured on a Varian HA-100 instrument and are reported in parts per million downfield from internal tetramethylsilane.

5-(*o*-Carboxyphenyl)-1,1-dimethyl-2-oxo-4-oxy-3-phenylpyrrolidinium Inner Salt (1). A reaction of 16.08 g of *o*-(α-hydroxycinnamoyl)benzoic acid with 30 ml of *N,N*-dimethylformamide dimethyl acetal was carried out and worked up as described in the preceding paper[3] for the preparation of fluorescamine. The aqueous sodium bicarbonate washings (500 ml, 1% w/v), obtained in this process, were acidified with 1 *N* HCl. The resulting precipitate was extracted into chloroform, and the organic extract was washed with water, dried over Na_2SO_4, and evaporated to dryness under reduced pressure. The solid residue was crystallized from chloroform to afford 580 mg (3%) of the acylide **1** (as crystals containing ½ equiv of $CHCl_3$): mp 251–253°; uv max (0.1 *N* KOH) 262 nm (ε 16500); ir (KBr) 1770, 1690 cm^{-1}; NMR (Me_2SO-d_6) δ 2.54

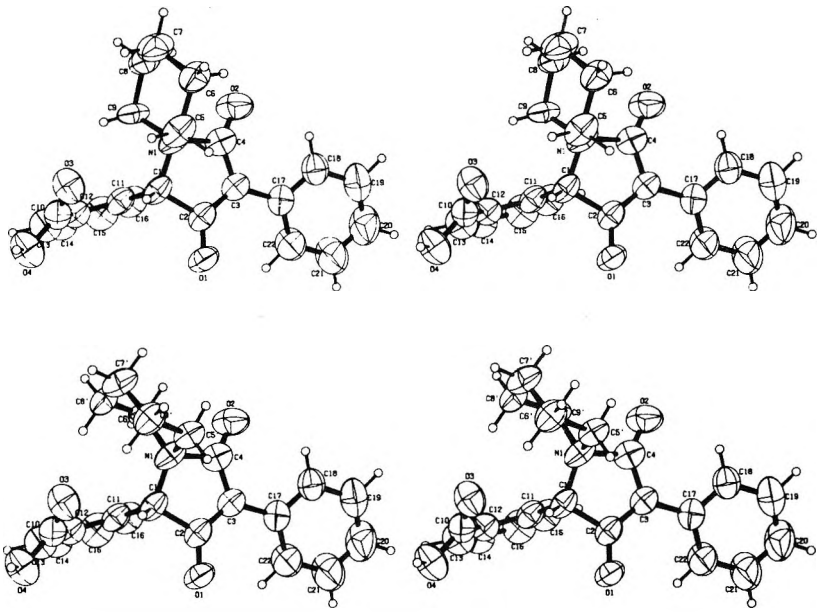


Figure 1. Computer-generated stereodrawing of **2**. The two conformers present in the crystal differ only in the conformation of the six-membered heterocyclic ring.

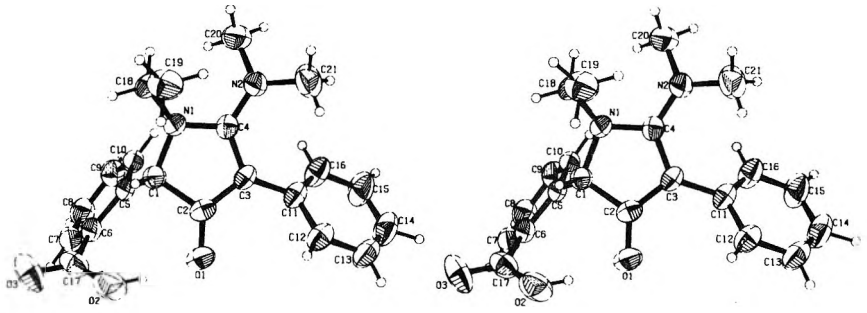


Figure 2. Computer-generated stereodrawing of **10**.

(3, s, NCH_3), 3.45 (3, s, NCH_3), 5.67 (1, s, benzylic CH), 7.0–8.4 (9, m, aromatic).

Anal. Calcd for $C_{19}H_{17}NO_4 \cdot \frac{1}{2}CHCl_3$: C, 60.36; H, 4.55; N, 3.60. Found: C, 60.60; H, 4.42; N, 3.57.

4-(*o*-Carboxyphenyl)-1-oxo-3-oxy-2-phenyl-5-azoniaspiro-[4.5]decane Inner Salt (2). A. To a solution of 1.34 g of o-(α-hydroxycinnamoyl)benzoic acid in 10 ml of *N,N*-dimethylformamide was added dropwise with stirring a solution of 2.0 g of tripiperidinomethane[5] in 5 ml of ether. The mixture was kept at room temperature for 16 hr and was then poured into 100 ml of ice-cold 1% HCl. The resulting precipitate was extracted into methylene chloride and the organic phase was extracted with 250 ml of 2% sodium bicarbonate. After drying and evaporation, the organic layer yielded 357 mg of fluorescamine (**3**).[3] The sodium bicarbonate phase was acidified and extracted with chloroform and the extract was washed with water, dried (Na_2SO_4), and evaporated in vacuo. Recrystallization of the solid residue from methylene chloride–ether afforded 1.12 g (61%) of the acylide **2**, mp 233°.

B. To a mixture of 15 ml of piperidine and 5 ml of water was added, in small portions, 1.39 g of fluorescamine (**3**). The resulting solution was left at room temperature for 5 hr and then poured onto crushed ice. Acidification with 2 *N* HCl produced a precipitate which was taken up in methylene chloride and the organic phase was then extracted with saturated sodium bicarbonate. After evaporation of the methylene chloride, 840 mg (60%) of fluorescamine was recovered. The bicarbonate extract was acidified and extracted with chloroform. The chloroform solution was dried (Na_2SO_4) and evaporated in vacuo. Recrystallization of the residue from methylene chloride–ether gave 294 mg (16%) of the acylide **2** (44%, based on unrecovered **3**): mp 233°; uv max (0.1 *N* KOH) 263 nm (ε 16800); ir (KBr) 1765, 1705 cm^{-1}; NMR (Me_2SO-d_6) δ 1.1–2.5 [6, m, $(CH_2)_3$], 3.3–3.9 (4, m, NCH_2), 6.29 (s, 1, benzylic CH), 7.0–8.1 (9, m, aromatic).

Anal. Calcd for $C_{22}H_{21}NO_4 \cdot \frac{1}{2}CH_2Cl_2$: C, 66.58; H, 5.46; N, 3.45; Cl, 8.74. Found: C, 66.60; H, 5.45; N, 3.43; Cl, 8.90.

1-Ethyl-2-dimethylamino-3-phenyl-5-(2-carboxyphenyl)-2-pyrrolin-4-one (10). To 4.50 g of 1′-ethyl-3′-phenylspiro[phthalan-1,5′(2)-pyrroline]-3,4′-dione (**8**)[6] in 200 ml of methylene chloride was added slowly, with ice cooling and stirring, 150 ml of a freshly prepared solution (10% w/v) of dimethylamine in methylene chloride. The mixture was kept in an ice bath for 30 min. Excess amine and solvent were then removed under reduced pressure and the residual oil was purified by chromatography on silica gel with chloroform–methanol (95:5) as the eluent. Fractions containing **10** were combined and concentrated at low temperature to a volume of 20 ml. After addition of 20 ml of methanol, the volume was further reduced in vacuo until the desired product started to crystallize. After refrigeration, there was collected 4.27 g (81%) of the pyrrolinone **10**: mp 197–200° dec; uv max (MeOH) 243 nm (ε 16400) and 302 (13650); ir (KBr) 1725 cm^{-1}; NMR (Me_2SO-d_6) δ 1.02 (3, t, NCH_2CH_3), 2.93 [6, s, $N(CH_3)_2$], 3.34 (2, q, NCH_2CH_3), 5.77 (1, s, benzylic CH), 7.02–7.85 (9, m, aromatic).

Anal. Calcd for $C_{21}H_{22}N_2O_3$: C, 71.98; H, 6.33; N, 7.99. Found: C, 71.97; H, 6.44; N, 8.02.

1-Ethyl-2-dimethylamino-3-phenyl[2]benzopyrano[4,3-*b*]pyrrol-5(1*H*)-one (11). A sample (600 mg) of **10** was melted in a pyrolysis tube by heating to 200°C. The melt was allowed to cool to room temperature and was then dissolved in methylene chloride. The solution was concentrated in vacuo and applied to preparative TLC plates (2 mm silica gel). The plates were developed in methylene chloride and a major band was collected by eluting with the same solvent. The eluate was evaporated and the residue was crystallized from ether to give 383 mg (67%) of the lactone **11**: mp 152–154°C; uv max (MeOH) 233 nm (ε 27500), 313 (18500), and 390 (6200); ir ($CHCl_3$) 1710, 1610, 1525, 1515 cm^{-1}; NMR ($CDCl_3$) δ 1.41 (3, t, NCH_2CH_3), 2.76 [6, s, $N(CH_3)_2$], 4.82 (2, q, NCH_2CH_3), 7.15–7.80 (9, m, aromatic).

Anal. Calcd for $C_{21}H_{21}NO_2$: C, 75.88; H, 6.07; N, 6.43. Found: C, 75.93; H, 6.09; N, 6.41.

Crystallography. Three-dimensional intensity data for **2** and

10 were measured on a Hilger-Watts four-circle diffractometer (θ–2θ scans, Ni-filtered Cu Kα radiation, pulse height discrimination). The data for 2 were corrected for absorption, but the data for 10 were not. Both structures were solved by a multiple solution procedure.[7] All refinements were carried out by full-matrix least square (FMLS). The unweighted discrepancy index is given by $R = \Sigma||F_o| - |F_c||/\Sigma|F_o|$ and the weighted index by $R_w = [\Sigma w||F_o| - |F_c||^2/\Sigma w|F_o|^2]^{1/2}$.

Crystal data for 2 ($C_{22}H_{21}NO_4 \cdot \frac{1}{2}CH_2Cl_2$) follow: monoclinic, space group $C2/c$ or Cc, a = 14.262 (8), b = 11.305 (6), c = 25.813 (15) Å, β = 99.80 (4)°, d_{obsd} = 1.31 (2), d_{calcd} = 1.314 g cm^{-3} for Z = 8, μ (Cu Kα) = 18.9 cm^{-1}. Of 3884 accessible reflections with θ < 70°, 2238 had intensities significantly greater than background [$I > 2.5\ \sigma\ (I)$]. The structure was obtained while working in the centrosymmetric space group $C2/c$. In the process of solving the structure, it was found that the crystal contains two different conformers of 2 which differ significantly only in the conformation of the heterocyclic six-membered ring. The presence of two conformers suggested the possibility that the space group was actually the noncentrosymmetric one, Cc. Since this space group has only four symmetry operations, the unique part of the unit cell would contain two independent molecules whose conformations need not be the same. The attempt to distinguish between $C2/c$ and Cc is described below.

The initial refinement of the structure was done in space group $C2/c$. The five carbon atoms of the heterocyclic six-membered ring were resolved into two sets of half-atoms corresponding to the two conformations of this ring. It was assumed that there are equal numbers of the two conformers in the crystal and that the two conformers are randomly distributed throughout the crystal, thus giving rise to a disordered structure. Isotropic temperature factors were used for the first few cycles of FMLS which were followed by several cycles of FMLS in which all atoms had anisotropic thermal parameters.

At this point the space group Cc was considered. There are two possible arrangements in Cc: (1) one independent molecule has conformation A and the other independent molecule has conformation B, and (2) vice versa. Refinements (isotropic temperature factors) of both arrangements were carried out. Both showed modest decreases in their R indices (R, R_w = 0.175, 0.228 and 0.174, 0.226 for the two trial structures in Cc) as compared to the corresponding values for the $C2/c$ refinement (R, R_w = 0.176, 0.240). Some decrease is expected because the number of independent variables is nearly doubled in Cc. Further refinement of these trial structures in space group Cc was not done because the reductions in the R values did not appear to be significant, particularly since both models showed almost equal decreases. Furthermore, the disordered model in $C2/c$ is more than adequate to establish the chemical structure.

The final refinement of the structure was carried out on the disordered model in space group $C2/c$. A difference Fourier calculated at the end of the anisotropic refinement showed peaks at reasonable positions for almost all the hydrogen atoms including those for the half-atoms. The idealized positions for all the hydrogen atoms were calculated and the hydrogen atoms were included in all subsequent calculations. In the final refinement, the hydrogen atoms were included in the structure factor calculations but their parameters were not refined. The final discrepancy index is R = 0.099 for the 2238 observed reflections. The final difference Fourier has only three features greater than 0.2 e Å^{-3} in magnitude. These are three peaks of about 0.5 e Å^{-3} which are located at 0.5–0.8 Å from the Cl atom of the solvent molecule. Stereodrawings of the two conformers of 2 are shown in Figure 1.

Crystal data for 10 ($C_{21}H_{22}N_2O_3$) follow: monoclinic, space group $P2_1/c$, a = 10.901 (5), b = 12.230 (5), c = 14.769 (12) Å, β = 112.09 (5)°, d_{calcd} = 1.275 g cm^{-3} for Z = 4, μ (Cu Kα) = 7.03 cm^{-1}. Of the 3716 accessible reflections with θ < 76°, 2187 were considered observed [$I > 2.5\sigma\ (I)$]. The structure was solved by a multiple solution procedure as implemented in the computer program MULTAN.[8] The structure was not found on any E map calculated from phase sets based on an expansion of eight reflections (three origin defining reflections and five reflections of unknown phases). The number of starting reflections was increased to 11 and the resulting 256 phase sets were generated. An E map calculated from the phase set with the highest absolute figure of merit (FOM = 1.132, Karle R factor 30.8%) revealed all atoms except the hydrogens. The hydrogen atoms were located from a difference Fourier calculated after refinement of the heavier atoms. For the final refinement, anisotropic thermal parameters were used for the heavier atoms and isotropic temperature factors were used for the hydrogens; the hydrogen atom parameters were refined. The final R is 0.050 for the 2187 observed reflections. There are no features on the final difference Fourier of intensity greater than ±0.1 e Å^{-3}.

Registry No.—1, 57109-19-0; 2, 57109-20-3; 3, 38183-12-9; 8, 36777-62-5; 10, 57109-21-4; 11, 57109-22-5; *o*-(α-hydroxycinnamoyl)benzoic acid, 43053-07-2; *N,N*-dimethylformamide dimethyl acetal, 4637-24-5; tripiperidinomethane, 22630-08-6; piperidine, 110-89-4.

Supplementary Material Available. Tables of the positional and thermal parameters for the structures of 2 and 10 (5 pages) will appear following these pages in the microfilm edition of this volume of the journal.

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Substituent Effects on the Electronic Nature of Carbon-Bonded Fluorine[1]

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We recently reported the surprising observation that certain lanthanide β-diketonates induce substantial shifts in the ^{1}H NMR spectrum of simple alkyl fluorides.[2] Here we wish to present results relevant to the nature of this interaction and describe its use to probe the electronic nature of organic fluorides.

Table I lists the magnitudes of selected ^{1}H and ^{19}F chemical shift, line width, and coupling constant differences induced by the addition of Yb(fod)$_3$ to a variety of alkyl fluorides. An examination of these results reveals that only relatively minor changes occur in the magnitude of the induced chemical shifts and spectral line widths as the steric bulk of adjacent centers is increased. Thus, steric factors do not have an overwhelming influence in determining the extent of substrate–lanthanide interaction. It is apparent, however, that the introduction of a second electronegative atom at the carbon bearing the fluorine atom produces a very significant *decrease* in both the induced chemical shifts and line widths while addition of Yb(fod)$_3$ has essentially no effect on the ^{1}H or ^{19}F spectra of compounds that contain two additional electronegative atoms at the fluorine-bearing carbon. Taken together, these results militate against a lanthanide–substrate interaction resulting from a principally electrostatic interaction between the electropositive lanthanide center and the electronegative end of the substrate molecular dipole since such an interaction, in contrast to what is observed, would be expected to increase as the resultant dipole moment of the substrate increases.

Table I
Influence of $Yb(fod)_3$ on Selected Values of the ^1H and ^{19}F Chemical Shifts, Line Widths, and Coupling Constants of Some Substituted Alkyl Fluorides[a]

Registry no.	Compd	^1H				^{19}F	
		$\Delta\delta_{CHF}$[b]	$\Delta\delta_{CH_3CF}$[b]	$\Delta W_{1/2}$[c]	ΔJ_{HCF}	$\Delta\delta$[d]	$\Delta W_{1/2}$
463-11-6	n-$C_8H_{17}F$	18.1		28.4	e	82	330
407-95-4	sec-$C_8H_{17}F$	10.0	11.4	25.0	e	99	400
75-10-5	CH_2F_2	0.49		9.0	0.0	1.6	<5
593-70-4	CH_2ClF	0.30		2.0	0.0	1.5	<5
75-45-6	$CHClF_2$	<0.01		<1.0	0.0	1.6	<5
75-43-4	$CHCl_2F$	<0.01		<1.0	0.0	0.3	<5
75-46-7	CHF_3	<0.01		<1.0	0.0	0.2	<5

[a] All chemical shift differences are reported in parts per million (ppm). Line widths and coupling constants are given in hertz. [R–F] = 0.2–0.3 M, [$Yb(fod)_3$] = 0.3–0.5 M in CCl_4 solution. [b] ^1H chemical shifts are reported relative to internal tetramethylsilane recorded at 100 MHz. [c] Unless otherwise indicated, these values refer to resonances corresponding to hydrogens on the fluorine-bearing carbon. [d] ^{19}F chemical shifts are relative to internal CCl_3F, recorded at 94.1 MHz. [e] Accurate coupling constants could not be determined because of extensive broadening in the presence of $Yb(fod)_3$.

Several additional observations pertinent to the nature of the interaction between alkyl fluorides and $Yb(fod)_3$ are noteworthy. First, the broad, featureless ^{19}F NMR spectrum of $Yb(fod)_3$ becomes significantly more detailed upon the addition of an alkyl fluoride. Similar effects, purportedly a consequence of substrate–lanthanide association, are observed when other heteroatom-containing substrates are added to either $Eu(fod)_3$ or $Yb(fod)_3$.[3] Second, numerous attempts to obtain the ^1H and ^{19}F spectra of *tert*-butyl fluoride were thwarted by the rapid, $Yb(fod)_3$-induced polymerization of this substance.[4] This same reagent also induced the decomposition of both *exo*-2-fluoronorborane and benzyl fluoride, although reaction in these instances was noticeably slower than that observed for *tert*-butyl fluoride.[5] Finally, GLC analysis of the reaction mixture produced by the addition of $Yb(fod)_3$ (1.12 g, 1.06 mmol) to a solution of *tert*-butyl fluoride (0.659 g, 8.55 mmol) in CCl_4 (3.8 ml) indicated a substantial yield (~57%, based on *tert*-butyl fluoride) of an unspecified olefinic hydrocarbon(s) (mol wt 168.185; calcd for $C_{12}H_{24}$, 168.188),[6] which presumably arises from the trimerization of the isobutylene produced by the decomposition of *tert*-butyl fluoride.[7]

These observations indicate that the structure of the alkyl groups bonded to the fluorine exerts an influence on the relative stability of the alkyl fluoride in the presence of $Yb(fod)_3$ which is consistent with a decomposition pathway involving a Lewis acid assisted ionization of the C–F bond. This conclusion further supports the suggestion that the mechanism of substrate–lanthanide interaction involves, at least in part, the coordination of a covalently bonded fluorine atom to an ytterbium center in a manner similar to and accompanied by basically the same magnetic interactions associated with related phenomena witnessed for organic substrates containing other heteroatom centers. Moreover, it is apparent that the effect which progressive substitution of electronegative α substituents has on substrate–lanthanide interaction parallels the progressive decrease in bond length and the corresponding increase in the degree of ionic character of the C–F bond in such systems.[8]

These results suggest that certain lanthanide shift reagents can provide a sensitive probe with which to examine the electronic nature of covalently bonded fluorine atoms. An illustration of this application is seen in the influence of $Yb(fod)_3$ on the ^1H NMR spectra of benzyl fluoride and fluorobenzene. While the spectrum of benzyl fluoride exhibits a typical pattern of well-separated ortho, meta, and para hydrogen resonances,[9] that of fluorobenzene shows only a reduction of spectral resolution, unaccompanied by any significant separation of resonances.

The differences in chemical shifts observed for these two substrates are presumably a reflection of the differing equilibrium constants which govern complex formation between substrate and lanthanide reagent. It follows that benzyl fluoride complexes more strongly with $Yb(fod)_3$ than fluorobenzene does. In light of the relatively minor role which steric factors play in determining the magnitude of the chemical shifts induced by $Yb(fod)_3$ in simple fluorocarbons, it further follows that these observed differences arise principally from the differences between the electronic character of the two fluorine centers.[10]

Experimental Section[11]

n-**Fluorooctane** was obtained from Pierce Chemical Co. **Difluoromethane, difluorochloromethane, dichlorofluoromethane, trifluoromethane, fluorobenzene,** and **benzyl fluoride** were obtained as commercial samples from PCR. Inc. **Chlorofluoromethane** (Freon 31) was purchased from E. I. du Pont de Nemours and Co. The shift reagent $Yb(fod)_3$ was purchased from Willowbrook Laboratories and stored over phosphorus pentoxide. ***sec*-Fluorooctane**[12] and ***exo*-2-fluoronorbornane**[13] were prepared by literature procedures. ***tert*-Butyl fluoride** was obtained from Cationics, Inc.

Preparation of Samples. All reagents and solvents including internal standards were stored over molecular sieves (5A) which had been activated at 250° at 0.1 Torr for at least 24 hr. This procedure greatly reduced but did not completely eliminate the extraneous water signal observed in certain samples. Control experiments established that a significant portion of this extraneous water originated in the shift reagent, which was very difficult to dry completely. Samples were prepared in a glove bag using documented techniques.[14]

Acknowledgment. The authors are indebted to Dr. Dorothy Z. Denney for assistance in obtaining ^{19}F NMR data.

Registry No.—$Yb(fod)_3$, 18323-96-1; fluorobenzene, 462-06-6; benzyl fluoride, 350-50-5; *exo*-2-fluoronorbornane, 765-92-4; *tert*-butyl fluoride, 353-61-7.

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(4) In the absence of $Yb(fod)_3$, solutions of *tert*-butyl fluoride in CCl_4 showed no evidence of polymerization after several days.
(5) ^1H NMR analysis indicated that both substances (~0.3 M in CCl_4) were >50% decomposed after 1 hr in the presence of $Yb(fod)_3$ (~0.5 M). Under similar conditions, the spectra of 1- and 2-fluorooctane remained unchanged.
(6) Ir 1628 (m, C=C), 904 (m), 895 cm^{-1} (s, C=CH); ^1H NMR δ (CCl_4, relative to Me_4Si) 5.00 (s), 5.31 (s) (C=CH). No other volatile hydrocarbons were observed.
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(10) This observation is also consistent with, but does not require, the proposal of fluorine lone pair participation in p → p_π back bonding in fluorobenzene. For a summary of the supporting and conflicting evidence regarding this proposal as well as a list of leading references, see ref 8.
(11) Infrared spectra were determined within sodium chloride cells on a Perkin-Elmer Model 225 grating spectrophotometer. NMR (^1H and ^{19}F) spectra were determined with a JEOL and Varian NMR spectrometers at 100 and 94.1 MHz, respectively. ^1H chemical shifts are reported in parts per million relative to internal tetramethylsilane. The internal standard for ^{19}F chemical shifts is as noted. All coupling constants are in hertz. Mass spectra were determined on a Hitachi Perkin-Elmer RMU-7E mass spectrometer. Samples for spectral analyses were purified on a Hewlett-Packard Model 700 thermal conductivity gas chromatograph. Analytical GLC analyses were performed on a Hewlett-Packard Model 5750 flame ionization instrument. Absolute yields of products were calculated from peak areas using internal standard techniques.
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Secondary Orbital Effects vs. Steric Effects in Some Diels–Alder Additions

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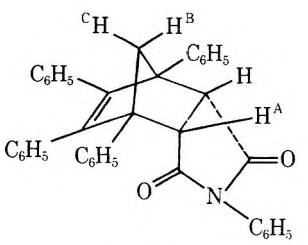
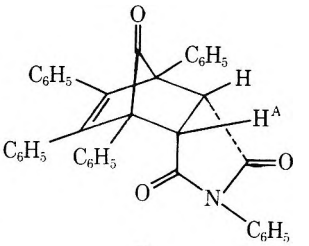
It has been found by several groups of workers that Diels–Alder addition of *N*-phenylmaleimide to heterocyclic dienes leads to formation of exo adducts.[1–4] The usual adduct, the endo isomer,[5] is not produced because either the nonbonded electrons on the heteroatom allow adequate overlap with the π electrons of the dienophile (*N*-phenylmaleimide) to produce the exo adduct or there is sufficient steric blocking to prevent formation of the endo adduct. The purpose of the study described below is to determine whether the possibility of exo-adduct formation results simply from steric hindrance or if the electronic interaction with π electrons of a bridged carbonyl group is operative.

We have determined the structures of endo adducts of *N*-phenylmaleimide to 1,2,3,4-tetraphenylcyclopentadiene (I) and 2,3,4,5-tetraphenylcyclopentadienone (II) which were isolated after 48 hr of reflux in xylene.



I
mp 241°

H_A (2 H, δ 4.26, singlet)
H_B (1 H, δ 2.36, doublet, J = 9 Hz)
H_C (1 H, δ 3.21, doublet, J = 9 Hz)



II
mp 226°

H_A (2 H, δ 4.28, singlet)

Several groups of workers have shown a four-bond spin–spin splitting coupling constant of approximately 3 Hz for the protons at the extremities of the fixed W formation in bicyclo[2.2.1]heptane systems;[6,7] specifically, the anti proton in the methylene bridge and the endo protons in the ethylene bridge show mutual splitting. The absence of coupling of H_A and H_C in I suggests the endo structure of the adduct.

The structure of II was shown by $Eu(fod)_3$-d_{27}–$CDCl_3$ NMR.[8,9] The exo hydrogens at δ 4.28 were shifted upfield as complexation with $Eu(fod)_3$-d_{27} took place. The aromatic hydrogens underwent no apparent shift. In order to determine complexation to be with the bridged carbonyl and not the imide carbonyls, the NMR of I with $Eu(fod)_3$-d_{27}–$CDCl_3$ was studied. The exo hydrogens at δ 4.26 underwent no apparent shift with $Eu(fod)_3$-d_{27}.[10]

The inclination for endo addition was ascribed by Alder and Stein[11] to the "maximum accumulation of double bonds". A quantum chemical restatement in terms of "secondary orbital interactions"[12] has emphasized the opinion[13–17] that secondary attractive forces in operation between centers not involved in eventual bond formation in the adduct account for the rule of endo addition.

There have been suggestions for the relative unimportance of secondary orbital relationships in favor of a steric repulsion hypothesis.[18–22] In the past decade, there have been several reports of exo adducts formed from the addition of *N*-phenylmaleimide to heterocyclic dienes.[1–4] The heteroatoms, each having at least one pair of nonbonded electrons, can participate in a secondary orbital effect leading to transition states which give rise to exo adducts. The carbonyl of 2,3,4,5-tetraphenylcyclopentadienone apparently does not sufficiently participate in secondary overlap in the transition state to form an exo adduct (instead, II is formed).

Experimental Section

***endo*-1,2,3,4-Tetraphenylbicyclo[2.2.1]hept-2-ene-5,6-dicarboxylic Acid *N*-Phenylimide (I).** A solution of 5.000 g (0.0135 mol) of 1,2,3,4-tetraphenylcyclopentadiene and 2.48 g (0.014 mol) of *N*-phenylmaleimide in 100 ml of dry xylene was refluxed for 3–48[23] hr and cooled, and solid was recrystallized twice (first from *p*-xylene, second from anhydrous ethanol) to give 5.36 g (73%) of colorless crystals (the endo isomer): mp 241°; NMR, vide supra.

Anal. Calcd for $C_{39}H_{29}NO_2$: C, 86.16; H, 5.38; N, 2.58. Found: C, 86.42; H, 5.36; N, 2.61.

***endo*-1,2,3,4-Tetraphenylbicyclo[2.2.1]hept-2-en-7-one-5,6-dicarboxylic Acid *N*-Phenylimide (II).** A solution of 5.000 g (0.0130 mol) of 2,3,4,5-tetraphenylcyclopentadienone and 2.57 g (0.015 mol) of *N*-phenylmaleimide in 100 ml of dry xylene was refluxed for 3–48[23] hr and cooled, and the colorless crystals which separated were collected by filtration and recrystallized once from *p*-xylene to give 4.21 g (58%) of the endo isomer: mp 226°; NMR, vide supra.

Anal. Calcd for $C_{39}H_{27}NO_3$: C, 84.00; H, 4.88; N, 8.61. Found: C, 83.83; H, 5.17; N, 2.61.

Acknowledgment. The author wishes to thank the American Philosophical Society for its generous support.

Registry No.—I, 57066-03-2; II, 57128-65-1; *N*-phenylmaleimide, 941-69-5; 1,2,3,4-tetraphenylcyclopentadiene, 15570-45-3; 2,3,4,5-tetraphenylcyclopentadienone, 479-33-4.

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Thermal and Base-Catalyzed Decomposition of Ester and Nitrile Derivatives of 2-(2,2-Dicarboxyvinyl)-1,1,1-trimethylhydrazinium Hydroxide Inner Salt

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Curtius (path a) or Stevens (path b) rearrangements may be initiated by thermal decomposition of appropriately substituted aminimides derived from carboxylic acids (**1**).[1]

$$\underset{\mathbf{1}}{RCONN^{+-}(Me)_2R'} \xrightarrow{a} RNCO + Me_2R'N \quad (R' = \text{alkyl or aryl})$$

$$\underset{\mathbf{1}}{RCONN^{+-}(Me)_2R'} \xrightarrow{b} RCONR'N(Me)_2 \quad (R' = \text{allyl or benzyl})$$

This note reports the results of our study of the thermal and base-catalyzed decomposition of three vinylogous aminimides (**2**) which were first synthesized by Brown[2] in 1967.

$$(CH_3)_3\overset{+-}{N}NCH{=}CR_1R_2$$

2a, $R_1 = R_2 = CO_2Et$
b, $R_1 = CN$; $R_2 = CO_2Et$
c, $R_1 = R_2 = CN$

Brown[2] reported that the diester **2a** decomposes in refluxing chloroform to give trimethylamine and unidentified products. The latter observation was of interest to us since **2a** is incapable of undergoing a Curtius-type rearrangement and the unidentified products could therefore derive from the vinyl nitrene, $NCH{=}C(CO_2Et)_2$. Although the odor of trimethylamine was apparent during the thermolysis of **2a** in refluxing chloroform, we have established that the major pathway for the thermal decomposition of **2a** is β elimination of trimethylammonium ion to give the trimethylammonium salt of diethyl cyanomalonate (**3**). Attempts to initiate similar eliminations by heating the more stable nitrile derivatives **2b** and **2c** in *N,N*-dimethylformamide at 140° gave recovered starting materials and tarry, unidentified products.

$$\underset{\mathbf{2a}}{(Me)_3\overset{+-}{N}NCH{=}C(CO_2Et)_2} \longrightarrow \underset{\mathbf{3}}{(Me)_3\overset{+}{N}H\ \overset{-}{N}CC(CO_2Et)_2}$$

When treated with 1 equiv of sodium ethoxide in refluxing ethanol, **2a** eliminated trimethylamine and was converted to diethyl sodiocyanomalonate (**4a**). Similar treatment of **2b** and **2c** afforded ethyl sodiodicyanoacetate (**4b**) and sodium tricyanomethide (**4c**), respectively.

$$\underset{\mathbf{2}}{(Me)_3\overset{+-}{N}NCH{=}CR_1R_2} \xrightarrow[EtOH]{NaOEt} (Me)_3N + \underset{\mathbf{4}}{NaC(CN)R_1R_2}$$

a, $R_1 = R_2 = CO_2Et$
b, $R_1 = CO_2Et$; $R_2 = CN$
c, $R_1 = R_2 = CN$

These nitrile-forming β-eliminations find precedence in our previously reported base-catalyzed conversion of aldehyde quaternary hydrazones to nitriles.[3]

Experimental Section

Melting points are uncorrected and were determined with a Mel-Temp apparatus. NMR spectra were determined on a Perkin-Elmer R-20 spectrometer utilizing hexamethyldisiloxane as an internal standard.

Thermolysis of 2-(2,2-Dicarbethoxyvinyl)-1,1,1-trimethylhydrazinium Hydroxide Inner Salt (2a) in Chloroform. A solution containing 2.5 g of **2a**[2] in 50 ml of chloroform was heated under reflux for 10.5 hr. Removal of the chloroform in vacuo afforded 2.5 g of the crude semisolid trimethylammonium salt of diethyl cyanomalonate. Recrystallization from ethanol–ether gave hygroscopic white crystals: mp 109–110°; NMR ($CDCl_3$) δ 2.86 (s, 9), 1.15 (t, 6, J = 8 Hz), 4.05 (q, 4, J = 8 Hz); ir (KBr) 2170 (CN, m), 1690 cm^{-1} (CO, s).

Anal. Calcd for $C_{11}H_{20}N_2O_4$: N, 11.5. Found: N, 11.3.

The salt was identical (ir, NMR) with that precipitated by addition of anhydrous ether to a solution prepared by adding diethyl cyanomalonate[4] to methanolic trimethylamine.

Reaction of Aminimides with Ethanolic Sodium Ethoxide. Ten percent ethanolic solutions of **2a, 2b,** and **2c** containing 1 equiv of sodium ethoxide were heated under reflux for 5, 18, and 15 hr, respectively. Trimethylamine was evolved and was identified (from **2b**) by conversion to its picrate, mp 220–225° (ir identical with that of an authentic sample). The ethanol was evaporated in vacuo to give the crude sodium salts (**4a, 4b,** and **4c**).

Crude diethyl sodiocyanomalonate (**4a**) from 2.0 g of **2a** was acidified with 10 ml of 6 *N* HCl and the resultant solution extracted with chloroform. Evaporation of the dried extract gave 1.0 g (66%) of pure diethyl cyanomalonate, which was identified by comparison of its NMR and ir spectra with those of an authentic sample.[4]

Crude ethyl sodiocyanoacetate (**4b**) obtained from 4.0 g of **2b** was recrystallized from ethanol–ether, affording 1.5 g (54%) of product whose structure was established to be **4b** by comparison of its NMR and ir spectra (KBr) with those of an authentic sample.[5] The NMR spectrum (CD_3COCD_3) indicated contamination with <5% of **4b**.

The crude sodium tricyanomethide (**4c**) obtained from 2.0 g of **2c** displayed an ir spectrum identical with that of an authentic sample.[6]

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Registry No.—**2a**, 18248-91-4; **2b**, 18248-92-5; **2c**, 18248-93-6; **3**, 57196-67-5; **4a**, 22466-42-8; **4b**, 4513-68-2; **4c**, 36603-80-2; chloroform, 67-66-3; sodium ethoxide, 141-52-6; diethyl cyanomalonate, 4513-67-1.

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Radical Reactions in the Coordination Sphere. III.[1] Reactions of Dichloro- and Trichloroacetic Acid Esters with 1-Olefins Catalyzed by Dichlorotris(triphenylphosphine)ruthenium(II)

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Although transition metal complex or salt catalyzed addition reactions of polyhaloalkanes with olefins give the 1:1 adducts which have a straight carbon-chain structure,[2] the course of addition reactions of polychloroacetic acid esters depends upon the type of the catalyst used for the reactions. Thus, under the catalytic influence of binuclear metal carbonyls of molybdenum and iron, methyl trichloroacetate undergoes lactonization reaction with olefins to afford 4-alkyl-2,2-dichloro-γ-butyrolactone,[3] whereas, in

$$CCl_3COOCH_3 + R_1R_2C{=}CH_2 \xrightarrow[[CpFe(CO)_2]_2]{[CpMo(CO)_3]_2\ \text{or}} R_1R_2C(-CH_2)-O-C(=O)-CCl_2 \quad (1)$$

the presence of copper salts, methyl or ethyl trichloroacetate adds to olefins to give methyl or ethyl 2,2,4-trichlorocarboxylates as 1:1 adduct.[4] In the latter cases, the yields of

$$CCl_3COOR' + RCH{=}CH_2 \xrightarrow{\text{copper salts}} RCHClCH_2CCl_2COOR' \quad (R' = CH_3, C_2H_5) \quad (2)$$

the products were at best 40–60% based on the olefin charged.

In the course of our investigation on the synthetic utility of the radical reactions brought about by the interaction between a transition metal homogeneous catalyst and an organic halide, we have found that, in the presence of dichlorotris(triphenylphosphine)ruthenium(II), the reaction of polyhalomethanes such as carbon tetrachloride and chloroform with olefins proceeded smoothly under mild conditions to give the corresponding 1:1 adducts in good yields.[1,5] We now report the results of the ruthenium complex catalyzed addition reactions of polychloroacetic acid esters with some 1-olefins. The general feature of the reactions is indicated by the results summarized in Table I.

Addition of methyl trichloroacetate to 1-octene was simply accomplished by heating a benzene solution of the halide, the olefin, and the ruthenium complex (molar ratio 1.7:1:0.004) in a sealed tube at 120°C for 23 hr. Thus, methyl 2,2,4-trichlorodecanoate was obtained in a yield of 95% (based on the olefin consumption) from this reaction. The reaction can be carried out without any added solvent, but the use of a solvent such as benzene gave somewhat better results. Under almost the same conditions, the reaction of ethyl trichloroacetate with 1-octene resulted in the formation of 93% yield of ethyl 2,2,4-trichlorodecanoate. Similarly, the reaction of methyl trichloroacetate with 1-hexene afforded methyl 2,2,4-trichlorocapryrate in 97% yield.

Although the reactions were conducted using benzene as solvent, which was said to be the best solvent for lactonization reaction,[3] no lactonization products could be detected in these reactions. Thus, the ruthenium catalyst favors the formation of esters over that of lactones in the reaction of chloro esters.

It was further found that the ruthenium complex catalyzed addition reaction can be extended to easily polymerizable olefins such as styrene, acrylonitrile, methyl methacrylate, and methyl vinyl ketone. The reactions could be carried out with considerable success using an equimolar mixture of ethyl trichloroacetate and the olefins, but we have obtained best results with a 2:1 mixture of the reactants. Thus, heating a 2:1 mixture of ethyl trichloroacetate and styrene with 0.5 mol % of the ruthenium complex at 120°C for 10 hr gave ethyl 2,2,4-trichloro-4-phenylbutyrate in 95% yield. Similarly, the reaction of the same halide with acrylonitrile, methyl methacrylate, and methyl vinyl ketone gave ethyl 2,2,4-trichloro-4-cyanobutyrate, ethyl 2,2,4-trichloro-4-carbomethoxyvalerate, and ethyl 2,2,4-trichloro-5-ketocaproate in a yield of 85, 80, and 80%, respectively.

When methyl dichloroacetate was allowed to react with 1-octene in the presence of 0.7 mol % of the ruthenium complex at 120°C for 20 hr, only methyl 2,4-dichlorodecanoate was obtained in 95% yield. Thus, the present reaction

$$CHCl_2COOCH_3 + C_6H_{13}CH{=}CH_2 \begin{cases} \xrightarrow{RuCl_2(PPh_3)_3} C_6H_{13}CHClCH_2CHClCOOCH_3 \\ \xrightarrow{\text{peroxide}} C_6H_{13}CH_2CH_2CCl_2COOCH_3 \end{cases} \quad (3)$$

exhibits a striking contrast to the peroxide catalyzed reaction which finds chiefly methyl 2,2-dichlorodecanoate as an adduct.[6] This result can be rationalized in terms of the mechanism of the ruthenium catalysis (eq 4–6 in Scheme I). The reaction is likely to involve a ligand transfer process

Scheme I

$$\text{—Ru—} + CHCl_2COOCH_3 \rightarrow \text{—Ru(Cl)—} + \cdot CHClCOOCH_3 \quad (4)$$

$$\cdot CHClCOOCH_3 + C_6H_{13}CH{=}CH_2 \rightarrow C_6H_{13}\dot{C}HCH_2CHClCOOCH_3 \quad (5)$$

$$C_6H_{13}\dot{C}HCH_2CHClCOOCH_3 + \text{—Ru—Cl} \rightarrow C_6H_{13}CHClCH_2CHClCOOCH_3 + \text{—Ru—} \quad (6)$$

(eq 6) in which the adduct radical abstracts a chlorine atom from the ruthenium complex with at least one labile chlorine ligand in its coordination sphere.[2a,5] Hence the chlorine abstraction in the ruthenium catalysis is associated with lower energy requirements compared to the hydrogen abstraction from the starting ester. It follows that the formation of methyl 2,4-dichlorodecanoate will become a predominant pathway in the present case.

Supporting evidence for the homolytic nature of the present reaction comes from the result that the reaction was inhibited by adding a small amount of galvinoxyl to the reaction mixture (Figure 1).

The results accumulated in Table I indicate that the ruthenium complex catalyzed addition reaction has many advantages over the existing methods for the preparation of chloro esters of moderate molecular weight from polychloroacetic acid esters and olefins. E.g., (a) the reaction can afford the 1:1 adducts in high yields with 1-olefins including vinyl monomers. Peroxide catalysis gives predominantly

Table I
Reactions of Trichloro- and Dichloroacetic Acid Esters with 1-Olefins in the Presence of Dichlorotris(triphenylphosphine)ruthenium(II)[a]

Chloro ester	Registry no.	Olefin	Registry no.	Conditions	Adduct[b]	Yield, %[c]	Conversion, %[d]
CCl_3COOCH_3	598-99-2	1-Octene	111-66-0	120°C, 23 hr	$C_6H_{13}CHClCH_2CCl_2COOCH_3$ (1)	95 (88)	100
$CCl_3COOCH_2CH_3$	515-84-4	1-Octene		120°C, 19 hr	$C_6H_{13}CHClCH_2COOCH_2CH_3$ (2)	93 (83)	92
CCl_3COOCH_3		1-Hexene	592-41-6	120°C, 21 hr	$C_4H_9CHClCH_2CCl_2COOCH_3$ (3)	97 (90)	96
$CCl_3COOCH_2CH_3$		Styrene	100-42-5	120°C, 10 hr	$C_6H_5CHClCH_2CCl_2COOCH_2CH_3$ (4)	95 (82)	100
$CCl_3COOCH_2CH_3$[e]		Acrylonitrile	107-13-1	120°C, 20 hr	$(CN)CHClCH_2CCl_2COOCH_2CH_3$ (5)	84 (71)	100
$CCl_3COOCH_2CH_3$[e]		Methyl methacrylate	80-62-6	120°C, 10 hr	$(COOCH_3)(CH_3)CClCH_2CCl_2COOCH_2CH_3$	80 (62)	100
$CCl_3COOCH_2CH_3$[e]		Methyl vinyl ketone	78-94-4	120°C, 10 hr	$CH_3COCHClCH_2CCl_2COOCH_2CH_3$ (7)	80 (64)	100
$CHCl_2COOCH_3$[f]	116-54-1	1-Octene		120°C, 20 hr	$C_6H_{13}CHClCH_2CHClCOOCH_3$[g] (8)	94 (89)	100

[a] Reactions were carried out in benzene with a 1.5–1.7:1 mixture of a chloro ester and an olefin, the catalyst concentration being 0.4 mol % based on the olefin charged without otherwise indicated. [b] All new compounds in the table gave satisfactory elemental analyses. [c] Yields are based on the olefin consumed (via GLC). In parenthesis are given isolated yields. [d] Conversion is (moles of olefin consumed)/(moles of olefin charged). [e] A 2:1 mixture of a chloro ester and an olefin was used. The catalyst concentration was 0.5 mol %. [f] The catalyst concentration was 0.7 mol %. [g] This adduct was obtained as a 1:1 mixture of the diastereomers 8a and 8b.

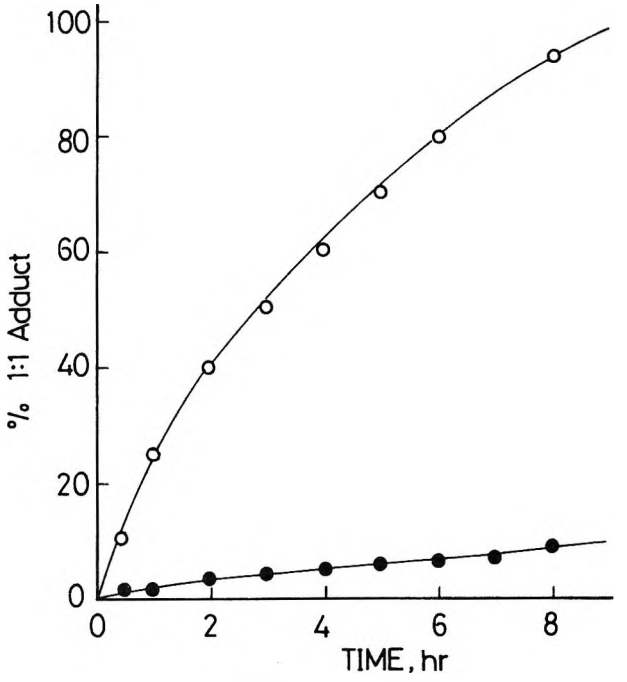

Figure 1. Formation of methyl 2,2,4-trichlorodecanoate from the addition reaction with 0.10 mmol of $RuCl_2(PPh_3)_3$ using (○) 10 mmol of 1-octene, 20 mmol of methyl trichloroacetate, and 3 ml of benzene; (●) 0.81 mmol of galvinoxyl added to the mixture.

telomers of high molecular weight in the reaction of the halides with vinyl monomers.[7] (b) For the addition of ethyl trichloroacetate to the olefins the ruthenium catalysis gives 60–80% isolated yields of the adducts, while copper salts catalyzed reactions give 10–40% yields.[4a]

Experimental Section

Boiling points are uncorrected. Infrared spectra were recorded on a Hitachi Model EPI-G3 spectrophotometer with neat samples. NMR spectra were taken on a Varian Model A-60D instrument using tetramethylsilane as an internal standard in carbon tetrachloride solvent. GLC analyses were carried out with an Okura Model 802 gas chromatograph equipped with a thermal conductivity detector. Teflon columns (200 × 0.4 cm) packed with 20% Silicone KF-96, 20% Carbowax 20M, 25% DCQF-1, and 25% polydiethylene glycol adipate on 60–80 mesh Chromosorb W were utilized for analytical studies. Corrections were made for thermal conductivity of the various components.

Commercially available ethyl trichloroacetate, methyl trichloroacetate, methyl dichloroacetate, 1-octene, 1-hexene, styrene, acrylonitrile, methyl methacrylate and methyl vinyl ketone were purified by distillation under nitrogen prior to use. Dichlorotris(triphenylphosphine)ruthenium(II) was prepared by Wilkinson's procedure.[8]

The addition reactions were carried out in a sealed Pyrex tube containing a Teflon-covered stirring bar. Only typical examples are shown below.

Reaction of Methyl Trichloroacetate with 1-Octene Catalyzed by Dichlorotris(triphenylphosphine)ruthenium(II). A mixture of 6.25 g (58.2 mmol) of 1-octene, 15.65 g (102 mmol) of methyl trichloroacetate, 0.20 g (0.21 mmol) of the ruthenium complex, and 10 ml of benzene was introduced into a Pyrex tube, cooled in liquid nitrogen, degassed (two times) at 0.1 mm, sealed, and heated for 23 hr at 120°C with stirring. After the reaction, the tube was cooled in liquid nitrogen and then opened. GLC analysis of the resulting mixture indicated that the olefin had been almost completely consumed and that the 1:1 adduct had been produced in 95% yield based on the olefin consumption. The mixture was then diluted with 40 ml of *n*-pentane to precipitate the catalyst which was removed by filtration. The solvents were evaporated from the filtrate under reduced pressure and subsequent distillation gave 14.8 g (88% yield) of methyl 2,2,4-trichlorodecanoate in 97% purity, bp 112–113°C (1.2 mm). The structure of the product was confirmed by spectral data and elemental analysis. These data are shown in Table II.

Reaction of Ethyl Trichloroacetate with Styrene Catalyzed by the Ruthenium Complex. The addition reaction was carried out at 120°C for 10 hr using 2.24 g (21.6 mmol) of styrene, 8.55 g (44.6 mmol) of ethyl trichloroacetate, 0.10 g (0.10 mmol) of the ruthenium complex, and 5 ml of benzene as described above. GLC analysis of the resulting solution disclosed that the olefin had been almost completely consumed and that the 1:1 adduct had been produced in 95% yield. The mixture was then diluted with 30 ml of *n*-pentane and the precipitated catalyst was removed by filtration. After removal of the solvents, distillation gave 5.20 g (82% yield) of ethyl 2,2,4-trichloro-4-phenylbutyrate, bp 139–142°C (1.8 mm).

Reaction of Methyl Dichloroacetate with 1-Octene Catalyzed by the Ruthenium Complex. The addition reaction was carried out at 140°C for 20 hr using 4.01 g (35.8 mmol) of 1-octene, 10.91 g (76.3 mmol) of methyl dichloroacetate, 0.24 g (0.25 mmol) of the ruthenium complex, and 10 ml of benzene as described

above. The resulting mixture was worked up as described above. Subsequent distillation gave 9.14 g (89% yield) of methyl 2,4-dichlorodecanoate as a 1:1 mixture of the diastereomers, bp 110–113°C (2.0 mm). The structure of each diastereomer was confirmed by spectral data and elemental analysis after isolation by preparative GLC.

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Registry No.—**1**, 57196-88-0; **2**, 53781-38-7; **3**, 33037-20-6; **4**, 57196-89-1; **5**, 34405-09-9; **6**, 57196-90-4; **7**, 57196-91-5; **8a**, 57196-92-6; **8b**, 57196-93-7; $RuCl_2(PPh_3)_3$, 15529-49-4.

Supplementary Material Available. Table II, reporting the physical properties of adducts 1–8 (2 pages), will appear following these pages in the microfilm edition of this volume of the journal.

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A Stereoselective Total Synthesis of *exo*- and *endo*-Brevicomin

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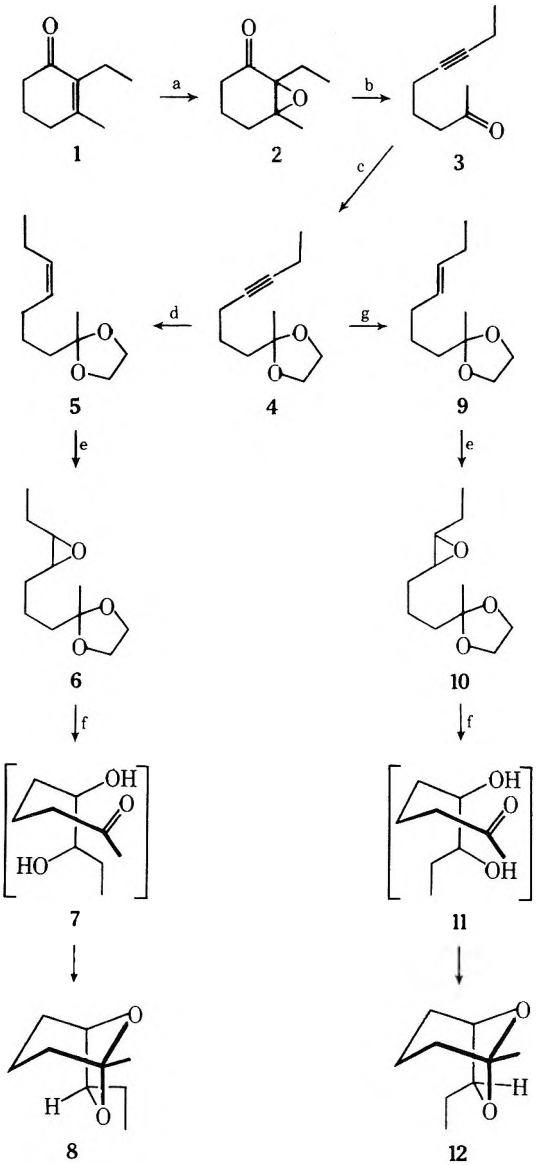
In 1968, Silverstein and co-workers[1] reported the structure determination of *exo*-brevicomin (**8**),[2] the principal sex attractant of the western pine beetle *Dendroctonus brevicomis*. The unusual 6,8-dioxabicyclo[3.2.1]octane skeleton has since been demonstrated in two other sex pheromones: frontalin, from the southern pine beetle *Dendroctonus frontalis*,[3] and multistriatin, from the elm bark beetle *Scolytus multistriatus*.[4] Since the use of *exo*-brevicomin for the manipulation of the mating habits of *D. brevicomis* may provide an ecologically advantageous means for the population control of this destructive insect,[5] we have developed a practical stereoselective synthesis of both *exo*-brevicomin (**8**) and the corresponding endo isomer **12**[6] which should be amenable to large-scale preparation. With one exception,[8] previous syntheses of **8** are inefficient and/or nonstereoselective.[7-10]

The preparation of both *endo*- and *exo*-brevicomin required that our synthetic plan incorporate an intermediate which was sufficiently flexible to permit conversion to both products. The acetylenic ketal **4** seemed ideally suited for this purpose since stereoselective reductions of acetylenes to the requisite cis or trans olefins are well established.

Scheme I[a]



[a] a, H_2O_2–NaOH/MeOH; b, *p*-$TsNHNH_2$/CH_2Cl_2–HOAc; c, $HOCH_2CH_2OH$, H^+; d, BH_3·Me_2S–ether, HOAc; e, *m*-$ClC_6H_4CO_3H$; f, 0.1 *N* $HClO_4$; g, Na–NH_3.

Thus the fulcrum of the synthesis, **4**, was prepared in three steps (73% overall) from the known cyclohexenone **1**[11] as shown in Scheme I. Eschenmoser fragmentation[12] of the epoxy ketone **2** yielded 6-nonyn-2-one (**3**) which incorporated the carbon skeleton appropriately functionalized for eventual conversion to the desired products.

The *exo*-brevicomin (**8**) was prepared in 42% overall yield[13] from the acetylenic ketal **4** by a three-step sequence involving reduction of the acetylene with BH_3·Me_2S followed by protonolysis to give first the cis olefin **5** (75%).[15] Epoxidation of **5** (73%) followed by stereospecific acid-catalyzed cleavage of the resultant cis epoxide **6**[16] with concomitant hydrolysis of the ketal function afforded *exo*-brevicomin (**8**, 72%). No attempt was made to isolate or detect the presumed threo keto diol intermediate **7**. The *exo*-brevicomin thus obtained was contaminated with <1% of the endo isomer **12** by VPC analysis.

Similarly, *endo*-brevicomin (**12**) was prepared in three steps (77% overall) from the acetylenic ketal **4** by Na–NH_3 reduction of **4** to the trans olefin **9** (96%).[15] Epoxidation of **9** (93%) followed by acid hydrolysis gave the intermediate erythro keto diol **11** which cyclized under the reaction con-

ditions to give *endo*-brevicomin (**12**, 86%) which was contaminated with <1% of the exo isomer **8** by VPC analysis.

In contrast with the previous syntheses of **8**,[7-10] the procedure reported herein derives considerable advantage from the fact that all nine carbons of the brevicomin skeleton are already present in the starting enone **1**. Since the starting material is relatively inexpensive and since each step proceeds in good to excellent yield, the sequence described should provide an economical and highly stereoselective source of *exo*- and *endo*-brevicomin.

Experimental Section

Infrared spectra were obtained with a Perkin-Elmer 457 spectrometer; NMR spectra were recorded with Varian A-60 or HA-100 instruments in CCl_4 solution using Me_4Si as internal standard. All yields quoted are based on products by isolated simple distillation. Purity of products was ascertained by VPC using a Perkin-Elmer 3920 gas chromatograph with thermal conductivity detectors. Unless otherwise stated, 4 ft × 0.25 in. 10% SE-30 and/or 10% Carbowax 20M on Chromosorb P (60–80 mesh) columns were used throughout. The *m*-chloroperbenzoic acid (85%) obtained from Eastman Organics was used without further purification. The BH_3-Me_2S was obtained from Aldrich Chemical Co.

2-Ethyl-3-methyl-2,3-epoxycyclohexan-1-one (2). To a solution of 20.2 g (0.146 mol) of 2-ethyl-3-methylcyclohex-2-en-1-one (**1**)[11] in 150 ml of methanol cooled to 10° was added with magnetic stirring 55 ml (0.438 mol) of 30% hydrogen peroxide. While maintaining the temperature between 15 and 20°, 12.2 ml of 6 *N* NaOH (0.073 mol) was added dropwise over 5 min. After addition was complete, the reaction mixture was stirred for 3 hr at 20–22°. The reaction mixture was poured into 600 ml of water and extracted with 2 × 60 ml of ether. The combined organic layers were washed with 2 × 30 ml of water, dried over $MgSO_4$, concentrated in vacuo, and the resultant oil distilled to give 19.2 g (85%) of **2** as a colorless oil: bp 48–49° (0.3 mm); ir (CCl_4) 1710 cm^{-1}; NMR (60 MHz, CCl_4) δ 0.9 (t, 3 H), 1.39 (s, 3 H), 1.5–2.5 (br m, 8 H).

6-Nonyn-2-one (3). To a magnetically stirred solution of 17.7 g (0.115 mol) of epoxy ketone **2** in 115 ml of CH_2Cl_2 and 57 ml of HOAc at 0–2° was added 21.3 g (0.115 mol) of *p*-toluenesulfonylhydrazide in one portion. Stirring was continued at 0–2° for 3 hr followed by 3 hr at room temperature. The reaction mixture was poured into 450 ml of water and extracted with 2 × 200 ml of hexane. The combined organic layers were washed with 2 × 100 ml of water followed by 2 × 50 ml of saturated $NaHCO_3$. After drying over $MgSO_4$ and concentration in vacuo, the resultant oil was distilled to afford 14.5 g (91%) of **3** as a colorless oil: bp 50–51° (0.5 mm); ir (CCl_4) 1712 cm^{-1}; NMR (100 MHz, CCl_4) δ 1.11 (t, 3 H, J = 8 Hz), 1.68 (quintet, 2 H, J = 7 Hz), 2.06 (s, 3 H), 2.0–2.3 (m, 4 H), 2.47 (t, 2 H, J = 7 Hz).

6-Nonyn-2-one Ethylene Ketal (4).[7] A mixture of 14.5 g (0.105 mol) of **3**, 7.15 g (0.115 mol) of ethylene glycol, and 10 mg of *p*-TsOH in 120 ml of benzene was refluxed for 8 hr using a water separator. The cooled solution was washed with 2 × 25 ml of saturated $NaHCO_3$, dried over $MgSO_4$, and concentrated in vacuo. Distillation afforded 18.0 g (94%) of the ketal **4** as a colorless oil: bp 64–65° (0.3 mm); ir (CCl_4) 1070 cm^{-1}; NMR (100 MHz, CCl_4) δ 1.10 (t, 3 H, J = 7 Hz), 1.23 (s, 3 H), 1.4–1.8 (m, 4 H), 1.95–2.30 (m, 4 H), 3.83 (s, 4 H).

***cis*-Non-6-en-2-one Ethylene Ketal (5).** To a magnetically stirred solution of 8.00 g (43.9 mmol) of **4** in 80 ml of ether at 0° was added 1.5 ml (15.8 mmol) of BH_3-Me_2S dropwise via syringe over 5 min. After addition was complete the mixture was allowed to stir under nitrogen at 0° for 30 min whereupon 8 ml of glacial acetic acid was added. Ether was distilled off until the internal temperature reached 60°, an additional 12 ml of acetic acid was added, and the mixture was stirred at 60° for 1.5 hr. The reaction mixture was then poured with rapid magnetic stirring into a solution of 20 g of NaOH in 50 ml of water containing ~50 g of crushed ice. The product was extracted into 2 × 40 ml of hexane, washed with 50 ml of water, dried over $MgSO_4$, and concentrated in vacuo. Distillation afforded 6.29 g (75%) of **5** as a colorless oil:[17] bp 60–62° (0.4 mm); ir (CCl_4) 1060 cm^{-1}; NMR (CCl_4) δ 5.27 (m, 2 H), 3.80 (s, 4 H), 1.8–2.3 (m, 4 H), 1.3–1.8 (m, 4 H), 1.20 (s, 3 H), 0.97 (t, 3 H).

***cis*-6,7-Epoxynonan-2-one Ethylene Ketal (6).** To a magnetically stirred solution of 8.00 g (43.4 mmol) of **5** in 70 ml of CH_2Cl_2 was added 9.45 g (47.6 mmol) of 85% *m*-chloroperbenzoic acid in portions over 30 min while maintaining the temperature below 7°. Stirring was continued at 0° for an additional 30 min after which the mixture was extracted with 25 ml of saturated $NaHSO_3$ and 2 × 50 ml of 1*N* NaOH. Distillation of the product obtained after drying over $MgSO_4$ and concentration in vacuo afforded 6.35 g (73%) of **6** as a colorless oil: bp 86–89° (0.4 mm); ir (CCl_4) 1060 cm^{-1}; NMR (CCl_4) δ 3.8 (s, 4 H), 2.7 (m, 2 H), 1.3–1.8 (m, 8 H), 1.22 (s, 3 H), 1.02 (distorted t, 3 H).

***exo*-Brevicomin (8).** A mixture of 2.86 g (14.3 mmol) of **6** and 14.3 ml of 0.1 *N* $HClO_4$ was rapidly stirred at ambient temperature for 2.5 hr. The product was extracted into 2 × 30 ml of ether and dried over $MgSO_4$. The solvent was removed in vacuo (bath temperature 20°) with a rotary evaporator and the residue distilled via Kugelrohr to give 1.72 g (77%) of *exo*-brevicomin (**8**), bp 70° (bath) (20 mm), having ir and NMR spectra identical with those published of the natural product.[18] The exo isomer (retention time 14.6 min) was contaminated with <1% of the endo isomer **12** (retention time 20.2 min) by VPC (10 ft × 0.25 in. 10% Carbowax 2000 on Chromosorb W, 150°, He flow 20 ml/min).

***trans*-Non-6-en-2-one Ethylene Ketal (9).** To a solution of 7.35 g (40 mmol) of **4** in 70 ml of anhydrous liquid NH_3 at −78° was added 3.0 g (0.13 g-atom) of sodium metal piecewise over a 10-min period. After addition was complete, the blue-colored reaction mixture was allowed to stir at −78° for 30 min. Sufficient solid ammonium chloride was added to discharge the blue color. After evaporation of the ammonia, the residue was dissolved in 75 ml of water and extracted with 2 × 50 ml of ether. The combined ether layers were washed with 2 × 30 ml of water, dried over $MgSO_4$, and concentrated in vacuo. Distillation afforded 7.11 g (96%) of the trans olefin **9** as a colorless oil: bp 50–51° (0.2 mm); ir (CCl_4) 1065, 970 cm^{-1}; NMR (100 MHz, CCl_4) δ 0.97 (t, 3 H, J = 7 Hz), 1.20 (s, 3 H), 1.25–1.70 (m, 4 H), 1.80–2.20 (m, 4 H), 3.81 (s, 4 H), 5.35 (m, 2 H).

***trans*-6,7-Epoxynonan-2-one Ethylene Ketal (10).** To a magnetically stirred solution of 6.24 g (33.9 mmol) of **9** in 65 ml of CH_2Cl_2 cooled to 0° was added in one portion 6.90 g (33.9 mmol) of 85% *m*-chloroperbenzoic acid. After stirring at 0° for 1 hr, the reaction mixture was extracted with 2 × 35 ml of 0.1 *N* KOH and washed with 30 ml of water, and the organic layer was dried over $MgSO_4$. Concentration in vacuo followed by distillation afforded 6.30 g (93%) of the epoxide **10** as a colorless oil: bp 75–78° (0.3 mm); ir (CCl_4) 1250, 1055, 860 cm^{-1}; NMR (100 MHz, CCl_4) δ 0.96 (t, 3 H), 1.22 (s, 3 H), 1.3–1.8 (m, 8 H), 2.4–2.6 (m, 2 H), 3.82 (s, 4 H).

***endo*-Brevicomin (12).** A heterogeneous mixture of 5.15 g (25.7 mmol) of **10** and 25 ml of 0.1 *M* $HClO_4$ was rapidly stirred at ambient temperature for 2.5 hr. The product was extracted into 2 × 50 ml of ether, dried over $MgSO_4$, and concentrated with a rotary evaporator (bath temperature 20°). Kugelrohr distillation [bath temperature 60° (20 mm)] afforded 3.45 g (86%) of *endo*-brevicomin (**12**) which gave ir and NMR spectra identical with those published.[18] Analysis by VPC (10 ft × 0.25 in. 10% Carbowax 2000 on Chromosorb W, 150°, He flow 20 ml/min) showed *endo*-brevicomin (retention time 20.2 min) contaminated with <1% of the exo isomer (retention time 14.6 min).

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Registry No.—**1**, 13679-27-1; **2**, 57237-88-4; **3**, 57237-89-5; **4**, 24403-63-2; **5**, 24381-26-8; **6**, 24381-28-0; **8**, 20290-99-7; **9**, 24381-27-9; **10**, 24381-29-1; **12**, 22625-19-0; ethylene glycol, 107-21-1.

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(9) K. Mori, *Tetrahedron*, **30**, 4223 (1974).
(10) B. P. Mundy, K. B. Lipkowitz, and G. W. Dirks, *Synth. Commun.*, **5**, 7 (1975), and references cited therein.
(11) The 2-ethyl-3-methylcyclohex-2-en-1-one was prepared by hydrolysis and decarboxylation of commercial (Aldrich) 2-ethyl-3-methyl-4-carboethoxycyclohex-2-en-1-one as described: L. I. Smith and G. F. Rouault, *J. Am. Chem. Soc.*, **65**, 631 (1943). The decarboxylation reaction did not occur spontaneously under the reaction conditions reported. However, acidification of the crude reaction mixture resulted in vigorous evolution of CO_2 to afford the desired cyclohexenone **1** in 84% yield after one recycling of recovered starting material.
(12) R. K. Müller, D. Felix, J. Schreiber, and A. Eschenmoser, *Helv. Chim. Acta*, **53**, 1479 (1970), and references cited therein.
(13) No attempt has been made to optimize the yields.
(14) To our knowledge, this reaction represents the first application of the relatively inexpensive and safe BH_3·Me_2S reagent for the reductive hydroboration of an acetylene. The use of BH_3·THF or disiamylborane in THF offered no advantage in yield or stereoselectivity and was considerably more expensive.
(15) We were unable to effect a separation of the cis and trans olefins **5** and **9** by VPC. However, an assay of the stereoselectivity of the reduction reactions was possible by an analysis of the corresponding epoxides **6** and **10** which were readily separable (see ref 7). Both **6** and **10** were contaminated with <1% of the corresponding isomer.
(16) J. G. Buchanan and H. Z. Sable in "Selective Organic Transformations", Vol. 2, B. S. Thyagarayan, Ed., Wiley, New York, N.Y., 1972, pp 8–11.
(17) Although the acetic acid was dried by reaction with acetic anhydride in the presence of a trace of *p*-TsOH and every effort maintained to exclude moisture from the reaction mixture during protonolysis of the vinylborane, the product obtained invariably contained anywhere from a trace to ~15% of *cis*-non-6-en-2-one. Reketalization afforded the desired ketal **5**.
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Communications

Synthetic Photochemistry with the Imide System. Norrish Type II Cyclization of Alicyclic Imides[1,2]

Summary: On irradiation a series of *N*-alkyl-substituted succinimides and glutarimides readily underwent photocyclization to afford ketolactams with ring enlargement by the two-carbon unit derived from the side chain in moderate yields; the efficiencies of the photoreactions of the alicyclic imides were distinctly larger than that for the aromatic counterparts (phthalimides), being comparable with that for simple ketones; the Norrish type II processes were proposed as the mechanism and general synthetic utility of the reaction was discussed.

Sir: In contrast to the extensive studies on photochemistry of common carboxylic acid derivatives such as esters and amides, the photochemical behavior of imides has been scarcely investigated. As part of broadly based studies of synthetic photoreactions of carbonyl derivatives, we have recently explored reactions of the excited states of an *aromatic* imide system, phthalimides.[3] We now wish to report a scheme which characterizes the photochemistry of *alicyclic* imides, and to present evidence which indicates its general synthetic utility.

A series of N-substituted succinimides **1a–i** and glutarimides **1j–m** were irrddiated[4] and the results are listed in Table I. Each major photoproduct was purified in most runs by vacuum distillation and identified by its ir, uv, NMR, and mass spectra and elemental analysis. In all cases ketolactams having two additional carbons in their rings were readily obtained in moderate isolated yields, accompanied by some elimination products (succinimide or glutarimide, 10–30%). In a representative example, the structural assignment for **2c** was based on (i) the presence of a carbonyl [uv 283 nm (ϵ 27); ir 1700 cm^{-1}] and an amide (ir 1660 mm^{-1}); (ii) the presence of the β [NMR 3.80 ppm ($C_\beta H$, m)] and the γ [NMR ~2.6 ppm ($C_\gamma H_2$)] carbons, methyl [1.35 ppm (d)], and NH (7.05 ppm); (iii) the molecular weight and composition, $C_7H_{11}NO_2$ (mass *m/e* 141; elemental analysis). Only one isomer (cis), **2g** and **2m**, was isolated from **1g** and **1m**, respeciively, hhereas a mixture of two stereoisomers, **2h** and **2i**, were obtained from **1h** and **1i**.

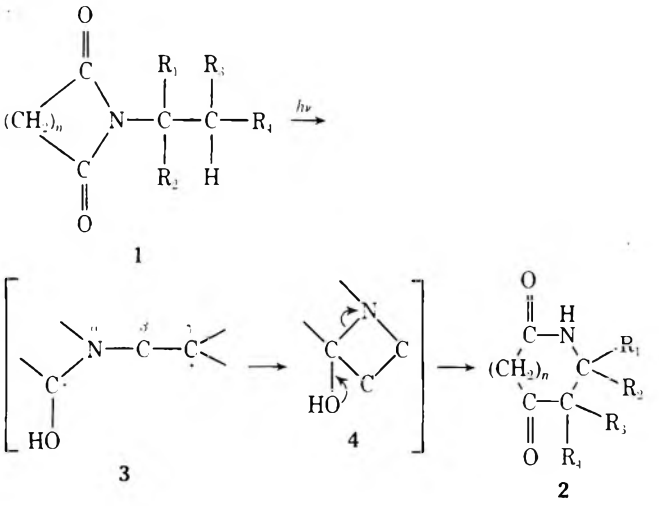
Table I
Products of Photolysis of the Cyclic Imides 1[a]

	1				2	
Compds	R_1	R_2	R_3	R_4	%	Mp, °C
			n = 2			
a	H	H	H	H	45	139–140
b	H	H	CH_3	H	42	120–121
c	H	CH_3	H	H	56	139.5–140.5
d	H	H	C_2H_5	H	31	85–87
e	H	H	CH_3	CH_3	33	109–110
f	CH_3	CH_3	H	H	49	175–176
g	H	$-(CH_2)_3-$		H	50	192.5–193.5
h	H	$-(CH_2)_4-$		H	42	Mixture
i	H	$-(CH_2)_5-$		H	38	Mixture
			n = 3			
j	H	H	H	H	37	117–118
k	H	H	CH_3	H	52	141–142
l	H	H	C_2H_5	H	33	149–150
m	H	$-(CH_2)_3-$		H	28	220–221.5

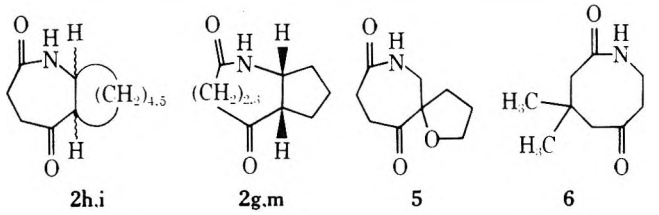
[a] A 60-W low pressure mercury lamp was used for 30 min, 10m*M* solution in acetonitrile.

The principal feature of the Norrish type II processes of the alicyclic imides is not the elimination but rather the cyclization forming ketolactams with ring enlargement by the two-carbon unit derived from the side chain (Scheme I). Quantum yield of the formation of **2a** was 0.64,[7] which is notably larger than that for the reactions of phthalimides, the aromatic counterparts, by a factor of 50,[8] indicating practical efficiency of the photolysis of the alicyclic imide system. General synthetic potential of the reaction on the basis of structural variation of the substrates is as follows.

Scheme I



Variation of the N substituents (including heteroatoms and cyclic systems) may lead to a wide variety of products. For example, *N*-tetrayydrofurfurylsuccinimide gave the expected spiro azepinone **5** (mp 96–98°, 27%). In view of their multifunctionality, these photoproducts will further be used as synthetic intermediates. By activation due to introduction of heteroatoms into the side chain, extensive type II processes seem possible involving δ (or other) hydrogen abstraction.[9] The ring size of the imides (n) could be increased beyond three. In addition, the ring may carry substituents as desired. For example, 1-ethyl-4,4-dimethylglutarimide readily produced **6** (mp 173–174°, 27%).



Piperylene quenches the formation of **2a** from 1a indicative of a triplet intermediate. A Stern–Volmer plot in acetonitrile (up to 1 m*M*) is linear with a slope $k_q\tau = 670$ M^{-1}.[12] As a plausible mechanism the biradical intermediate **3** is postulated (Scheme I) which is generally accepted in the type II processes of ketones as summarized by Wagner.[13] Such a biradical would either lead to elimination or undergo cyclization to form **4** followed by retrotransannular ring opening[14] giving rise to the ring-enlarged products **2**. Since these cyclic imides are starting materials which can be relatively easily prepared, this method may provide a novel versatile synthetic entry to otherwise rather unaccessible type of compounds including medium-sized and other various heterocyclic systems. Further synthetic scope and the mechanism of the photochemistry of the imide system are under investigation.

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(4) To our knowledge very few photochemical studies of aliphatic imides previously reported include vapor-phase photolysis of succinimide,[5] which is, however, of little interest from the synteetic point of view. Examination as well as the literature survey[5,6] of the uv spectra of aliphatic imides revealed that 2537-Å light of a low pressure mercury lamp is convenient for exciting the aliphatic imide carbonyl. Tests on the wavelength dependency of the formation of **2** indeed showed that only the range 230–270 nm is effective with the maximum around 240 nm in accord with the uv of **1a**.
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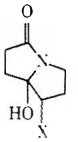
(6) O. H. Wheeler and O. Rosando in "The Chemistry of Amides," J. Zabicky, Ed., Interscience-Wiley, New York, N.Y., 1970, p 358.
(7) Formation of **2a** (degassed acetonitrile solution, 10 m*M*) was monitored by gas chromatography, and the quantum yield was determined by potassium ferrioxalate actinometry using 2537-Å light on a merry-go-round.
(8) Quantum yield of photocyclization of N-(*o*-tolyl)phthalimide is on the order of 0.01: Y. Kanaoka, K. Koyama and Y. Hatanaka, unpublished data.
(9) For example, photolysis of succinimides with ether and sulfide moieties in the alkyl chains gave i,[10] which are the products from δ-hydrogen abstraction. Maruyama and Kubo have independently reported some related results.[11]



i, X = OCH, SCH

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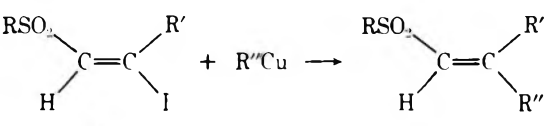
Organocopper Chemistry. The Coupling of (*E*)-2-Iodo-1-alkenyl Sulfones with Monocopper(I) Reagents

Summary: Monocopper(I) reagents (**2**) couple stereospecifically with (*E*)-2-iodo-1-alkenyl sulfones (**1**) to form β-alkylated 2-alkyl-1-alkenyl sulfones (**3**) with retained configuration.

Sir: The preparation and some of the reactions of 2-iodo- and 2-bromo-1-alkenyl sulfones has been the subject of several recent investigations.[1,2] The stereospecific organocopper coupling of vinyl iodides with organocopper reagents[3,4] has recently been reported as a method for the synthesis of alkenes of known configuration. This work prompts us to report on our preliminary results concerning the stereospecific coupling of a variety of (*E*)-2-iodo-1-alkenyl sulfones with a variety of monocopper(I) reagents.

Monoalkyl and monoarylcopper(I) reagents couple in good to excellent yields (Table I) with (*E*)-2-iodo-1-alkenyl sulfones and with complete retention of configuration. The presence of a single isomer is verified by a single set of proton absorptions in the ^{1}H NMR and the absence of absorptions for the isomeric structures. The assignment of configuration is based upon ^{1}H NMR chemical shift data and alternate synthesis.[5]



1 2 3

Table I[a]
2-Alkyl-1-alkenyl Sulfones[b]

3	R	R'	R''	% yield
a	CH_3CH_2	n-C_4H_9	CH_3	96
b	CH_3CH_2	n-C_4H_9	n-C_4H_9	93
c	CH_3CH_2	n-C_4H_9	C_6H_5	55
d	CH_3CH_2	C_6H_5	CH_3	80
e	CH_3CH_2	C_6H_5	n-C_4H_9	90
f	CH_3CH_2	t-C_4H_9	CH_3	47
g	p-$CH_3C_6H_4$	n-C_4H_9	CH_3	64
h	p-$CH_3C_6H_4$	n-C_4H_9	n-C_4H_9	99
i	C_6H_5	C_6H_5	C_6H_5	50

[a] All reactions are carried out in THF as solvent. [b] Characterized by ir, ^1H NMR, and elemental analysis.

Table II[a]
Yne Ene Sulfones[b]

3	R	R'	% yield	Temp, °C	Time, hr	Mp, °C
j	p-$CH_3C_6H_4$	H	75.5	RT	24	121–122.5
k	p-$CH_3C_6H_4$	CH_3	75.3	RT	48	103–104.5
l	p-$CH_3C_6H_4$	C_6H_5	58.3	130	23	81.0–82.5
m	p-$CH_3C_6H_4$	n-C_4H_9	71.9	RT	72	Oil[c]
n	p-$CH_3C_6H_4$	n-C_6H_{13}	59.7	RT	72	Oil[c]
o	C_6H_5	H	63.0	RT	24	72–74
p	C_6H_5	CH_3	62.3	RT	72	71–73
q	C_6H_5	C_6H_5	67.7	69	22	85.5–87.5
r	CH_3CH_2	CH_3	~50.0	RT	48	Oil[c]
s	CH_3CH_2	C_6H_5	76.3	100	19	76.5–77.5
t	CH_3	CH_3	53.0	RT	72	43–44
u	CH_3	C_6H_5	67.5	60	16	67.5–69.5

[a] In all examples R'' is $C_6H_5C{\equiv}C-$. [b] All compounds were purified by column chromatography; characterized by ir, ^1H NMR, and elemental analysis. [c] No boiling point was obtained.

Unlike other substitutions on vinyl halides, which usually require the use of lithium diaryl- or lithium dialkylcuprates, low temperatures (between −20 and −78°C), and long periods of time, substitutions involving (*E*)-2-iodo-1-alkenyl sulfones proceed rapidly, <30 min at 0°C being sufficient for completion. Also, under these reaction conditions, the presence of a complexing agent, e.g., diisopropyl sulfide, is not required.[5]

In contrast to the alkyl- and arylcopper species, the less reactive cuprous phenylacetylide[6] requires more vigorous reaction conditions to achieve coupling. Cuprous phenylacetylide in pyridine, at room temperature or on heating, reacts with the (*E*)-2-iodo-1-alkenyl sulfones to yield the coupled products with high stereospecificity and in fair to good yields for the examples studied, as shown in Table II.

The compounds in Table II were characterized in detail by ir, ^1H NMR, and elemental analysis. In all cases the couplings proceeded stereospecifically with retention of configuration to yield the (*E*)-yne ene sulfones. In the crude ^1H NMR, traces of the isomeric products were observed in some cases; however, the yields listed in Table II represent yields of the purified (*E*)-yne ene sulfones.

The assignment of stereochemistry is based upon ^1H NMR coupling constants and chemical shift arguments as well as supporting ir absorption data. An in depth description of the stereochemical arguments will be presented at a later date upon conclusion of another study which involves the preparation of the isomeric (*Z*)-yne ene sulfones. The following procedures are representative.

(*Z*)-1-Ethanesulfonyl-2-phenyl-1-hexene (3e). Into an oven-dried and nitrogen-flushed, 100-ml flask, equipped with a stoppled side arm, an adapter tube with stopcock connected to a mercury bubbler, and a magnetic stirring bar, was placed 2.44 g (12.52 mmol) of cuprous iodide and 60 ml of dry THF. This suspension was cooled to 0°, when 6.5 ml of 1.94 *M* *n*-butyllithium (12.44 mmol) in hexane was added. This was followed by 2.0 g (6.22 mmol) of (*E*)-1-ethanesulfonyl-2-iodo-2-phenylethylene in 30 ml of THF. After 10 min at 0°C, the reaction mixture was poured into a saturated NH_4Cl solution, extracted with ether, and dried over $MgSO_4$, and solvent was removed in vacuo to yield an oil. Short-path distillation at 140°C and 0.2 mm Hg afforded 1.20 g (90%) of (*E*)-1-ethanesulfonyl-2-phenyl-1-hexene.

(*E*)-1-Ethanesulfonyl-2,4-diphenylbut-1-en-3-yne (3s). Into a 200-ml, three-neck, round-bottom flask, fitted with a nitrogen inlet and outlet tube, reflux condenser, magnetic stirrer and stirring bar, oil bath, and paraffin oil bubbler, previously flame dried and purged with nitrogen, was placed 3.29 g (20 mmol) of cuprous phenylacetylide. Dry pyridine, 50 ml, was added to serve as solvent. Then 6.44 g (20 mmol) of (*E*)-2-iodo-1-ethanesulfonyl-2-phenylethene dissolved in 50 ml of dry pyridine was added. The mixture was heated to 100°C for 11 hr, then poured into 500 ml of H_2O, and extracted with four 200-ml portions of Et_2O. The other extracts were extracted successively with three 100-ml portions of H_2O, three 100-ml portions of 10% HCl, three 100-ml portions of H_2O, and one 100-ml portion of saturated aqueous NaCl. The ether extracts were dried over $MgSO_4$ and decolorized with activated carbon for 2 hr and vacuum filtered, and the ether was removed in vacuo to yield a solid material. The solid was purified by column chromatography on silica gel with benzene as eluent, then recrystallized from 95% EtOH to yield 4.52 g of material melting at 76.5–77.5°C for a 76.3% yield.

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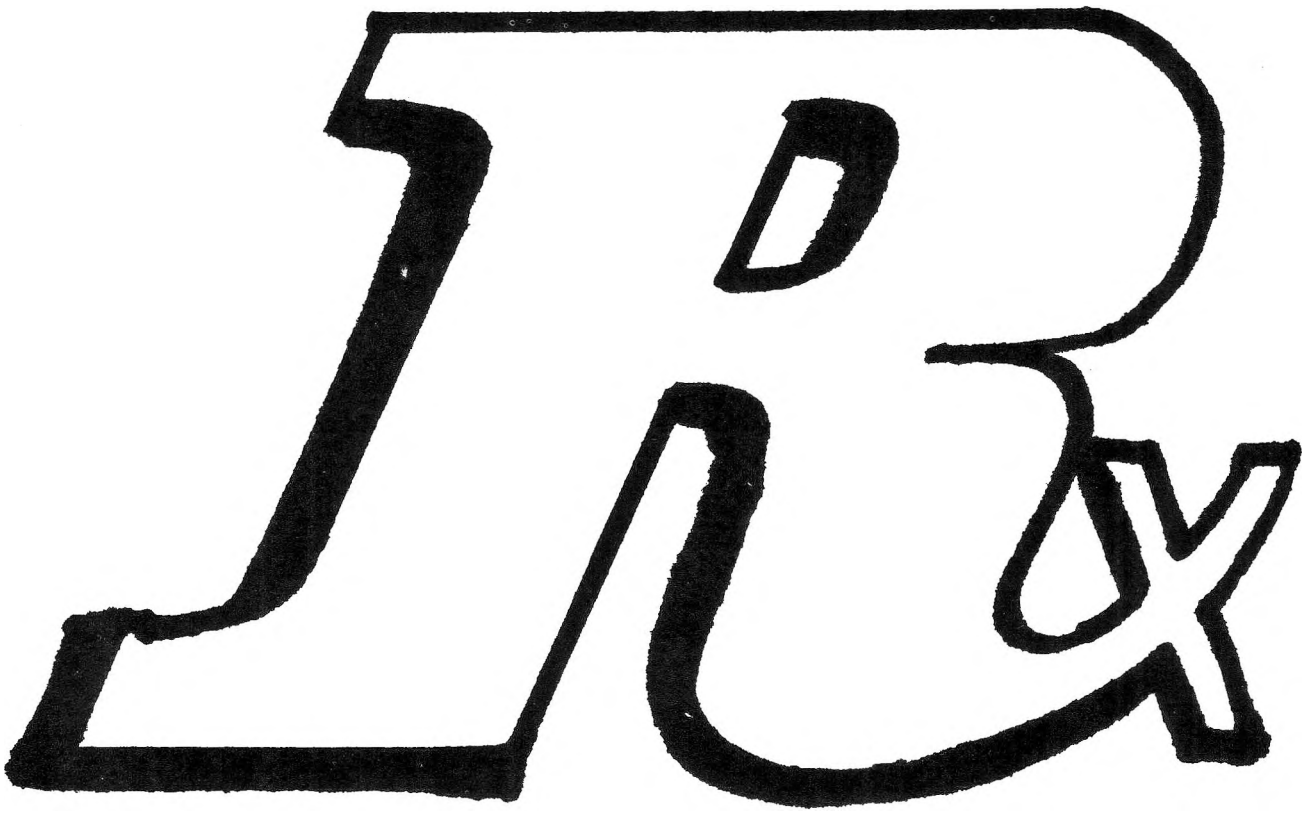
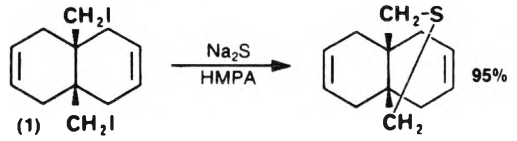
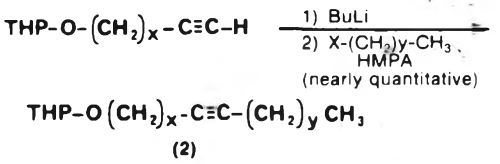


Hexamethylphosphoramide {HMPA}

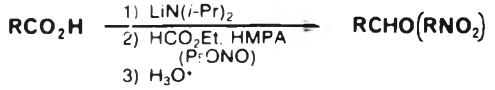
Hexamethylphosphoramide (HMPA, hexamethylphosphoric triamide), an excellent polar aprotic solvent, possesses remarkable solvent properties in that many S_N2 reactions proceed more readily in **HMPA** than in DMSO or DMF. Displacement reactions of neopentyl-type halides such as **1** are normally difficult to perform yet proceed easily in **HMPA**.[1]



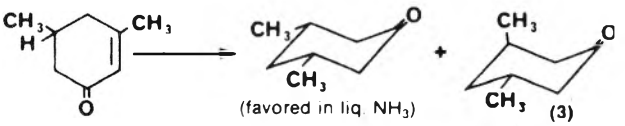
Sodium or lithium acetylides react with alkyl halides in higher yield in **HMPA** than in either liquid ammonia or tetrahydrofuran (THF).[2] Insect sex attractant intermediates (**2**) are readily formed from the reaction of a lithium acetylide and an alkyl halide in **HMPA** whereas solubility problems are encountered with the use of liquid ammonia.[3]



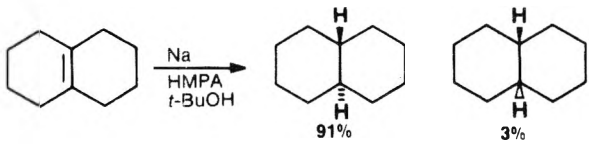
Other alkylations are readily effected in **HMPA**. Magnesium enolates formed from Grignards and ketones are C-alkylated in high overall yields whereas other metallated derivatives afford more O-alkylation.[4] Amines, alcohols and carboxylic acids react rapidly with NaH in **HMPA** and then can be easily alkylated.[4] **HMPA** also enables a facile transformation of carboxylic acids to aldehydes or nitroderivatives.[5]

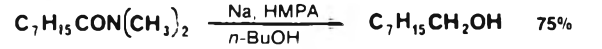


Birch reductions of α,β-unsaturated ketones are easily performed in **HMPA** with sodium or lithium to give the saturated ketone in which the less stable epimer (**3**) is favored.[6]

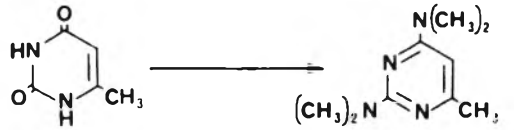


Solutions of sodium in **HMPA** containing *t*-butanol reduce alkenes,[7] ketones,[8] and tertiary amides.[9]





In addition to its powerful solvent properties, **HMPA** also undergoes useful reactions with various substrates. Carboxylic acids form *N,N*-dimethylamides (50-90% yield) when heated at 180-200° in **HMPA**.[10] In heterocycle synthesis, hypoxanthines and uracils react to form dimethylamino derivatives.[11]



α-Bromoketones[12] and alkyl halides[13] are dehydrohalogenated with little rearrangement to the respective α,β-unsaturated ketones and olefins. Secondary alcohols are dehydrated in **HMPA** to give unrearranged olefins.[14]

Preliminary results of an inhalation toxicity study of **HMPA** recently released by DuPont showed the development of nasal tumors in rats exposed to 400 and 4,000 ppb **HMPA** daily after 8 months of exposure. Although there is no data available on the toxic effects of **HMPA** in humans, we recommend that **HMPA** be handled with the precautions appropriate for a potential carcinogen.

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