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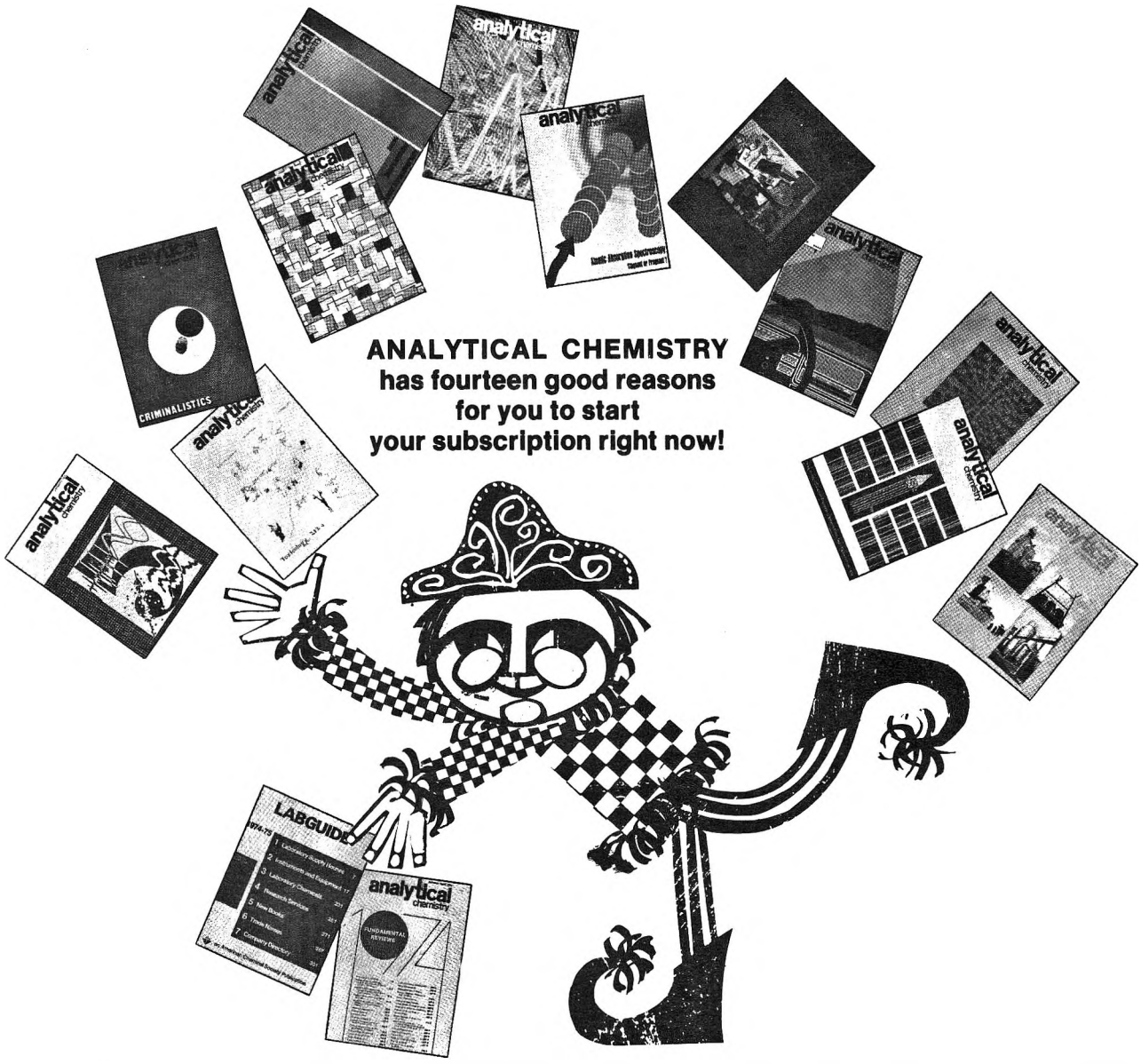

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THE JOURNAL OF Organic Chemistry®

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JULY 25, 1975

C-Glycosyl Nucleosides. VI. Synthesis of Several 3- and 5-(β-D-Ribofuranosyl)isoxazoles

Hans P. Albrecht, David B. Repke, and John G. Moffatt*

Contribution No. 114 from the Institute of Molecular Biology, Syntex Research, Palo Alto, California 94304

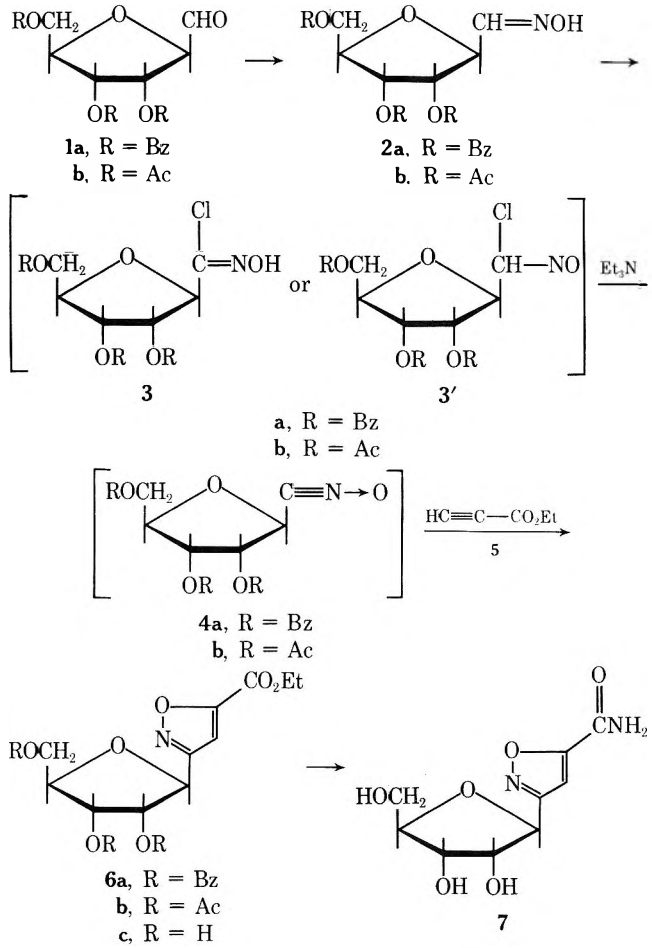
Received February 11, 1975

The oximes of several derivatives of 2,5-anhydro-D-allose were chlorinated at low temperature and then treated with triethylamine to generate nitrile oxides. The latter underwent 1,3-dipolar cycloaddition reactions with ethyl propiolate and with dimethyl acetylenedicarboxylate to form 3-(β-D-ribofuranosyl)isoxazolecarboxylates in good yield. Various sequences of deblocking then gave rise to several substituted isoxazole *C*-glycosyl nucleosides. Condensation of 2,5-anhydro-3,4,6-tri-*O*-benzoyl-D-allose with acetonylidenetriphenylphosphorane gave the unsaturated ketone (**13a**) which was converted to its oxime and oxidatively cyclized with iodine. Deblocking of the resulting product then gave 3-methyl-5-(β-D-ribofuranosyl)isoxazole.

In a previous paper in this series we have described the synthesis of a number of variously substituted derivatives of 2,5-anhydro-D-allose (e.g., **1**, **9a**).[1] Such compounds provide versatile starting materials for the synthesis of *C*-glycosyl nucleosides through elaboration of the aldehyde function into heterocyclic systems. In this vein we have already described a facile synthesis of the antibiotic showdomycin[2] and of a number of 4-(β-D-ribofuranosyl)pyrazoles.[3] In the present paper we describe the conversion of suitable 2,5-anhydro-D-alloses into several 3- and 5-(β-D-ribofuranosyl)isoxazoles.

Of the various methods available for the synthesis of isoxazoles[4] the most convenient for our purpose appeared to be the 1,3-dipolar cycloaddition of nitrile oxides to activated acetylenes.[5] With this in mind 2,5-anhydro-3,4,6-tri-*O*-benzoyl-D-allose (**1a**) was converted into its oxime (**2a**), which was isolated as a syrup in 91% yield as a roughly 4:1 mixture of geometrical isomers as judged by TLC. Without any further purification **2a** was converted into the α-chloro oxime **3** by reaction with chlorine in ether at −60° according to the general procedure of Casnati and Ricca.[6] During this treatment the solution assumed a greenish-blue color and deposited a precipitate, but following evaporation of the solvent the chloro oxime (**3a** or its nitroso tautomer **3'a**) was obtained as a colorless syrup with a TLC mobility somewhat greater than that of **2a**. The course of the chlorination of the oximes of several aldehydo sugars has been carefully examined by Tronchet et al.[7] and the crude product is expected to be a mixture of **3a**, **3'a**, and the nitroso dimer. Without purification or further examination this product was treated with triethylamine in the presence of ethyl propiolate (**5**). The procedure is expected to convert the chloro oxime into the nitrile oxide **4**, which undergoes 1,3-dipolar cycloaddition with **5** to form 3-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-5-ethoxycarbonylisoxazole (**6a**), a product that was isolated in 67% yield as a homogeneous syrup.

It is well known that in the absence of overriding steric or electronic influences, 1,3-dipolar cycloadditions of nitrile oxides to acetylenecarboxylates takes place predominantly

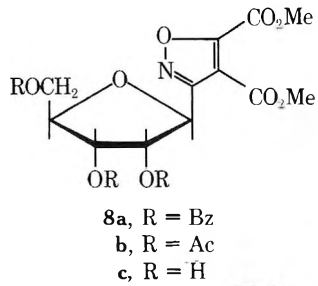


in the fashion leading to 3-substituted isoxazole-5-carboxylates similar to **6**.[5,8] Frequently, however, substantial amounts of the isomeric 3-substituted isoxazole-4-carboxylates are also formed.[8] In the present case we have observed only the formation of a single isomer which was shown by NMR spectroscopy to have the structure **6a**,

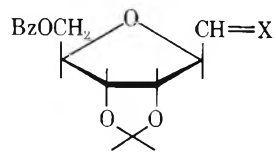
since C_4H of the isoxazole ring appeared as a singlet at 6.94 ppm. Earlier work has shown that C_4H in a variety of 5-alkoxycarbonylisoxazoles appears close to 7.0 ppm[8,9,10] while the vinyl proton adjacent to oxygen in the isomeric 4-alkoxycarbonylisoxazoles is located at 9.0 ppm.[8,9,11] During the course of our work Tronchet et al.[12] described the 1,3-dipolar cycloaddition of nitrile oxides derived from several 5-aldehydofuranoses and 6-aldehydopyranoses to acetylenes and also observed only formation of single isomers. They have not, however, examined any derivatives of 2,5-anhydroaldoses and, hence, have not prepared any D-aldofuranosyl *C*-glycosides.

The reaction of **6a** with methanolic ammonia at room temperature required 5 days to reach completion but gave crystalline 3-(β-D-ribofuranosyl)isoxazole-5-carboxamide (**7**) in 90% yield. Attempted debenzoylation of **6a** with a catalytic amount of methanolic sodium methoxide at room temperature for 16 hr, however, led to the formation of a number of unidentified products. In order to facilitate deblocking of the sugar under less vigorous conditions the above synthesis was repeated starting with 3,4,6-tri-*O*-acetyl-2,5-anhydro-D-allose (**1b**). The latter compound was readily regenerated from its previously described diphenylimidazolidene derivative[1] by brief treatment with *p*-toluenesulfonic acid. Without purification, this compound was converted in an overall yield of 76% into the oxime **2b**, which, from its NMR spectrum, appeared to be a single isomer. The oxime was chlorinated, converted to the nitrile oxide **4b**, and treated with ethyl propiolate as above to give 3-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)-5-ethoxycarbonylisoxazole (**6b**) in an overall yield of 46% from **2b**. Once again, the direction of cycloaddition was apparent from the NMR spectrum of **6b**, which showed C_4H as a singlet at 6.97 ppm. In this case deacetylation could be readily accomplished under acidic conditions via treatment with ethanolic hydrogen chloride at room temperature. By this treatment **6b** was converted into crystalline 5-ethoxycarbonyl-3-(β-D-ribofuranosyl)isoxazole (**6c**) in 49% yield. This yield was achieved by direct crystallization and could doubtless be increased by chromatography of the mother liquors.

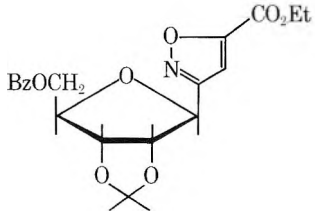
The nitrile oxides **4a** and **4b** were also generated in the presence of dimethyl acetylenedicarboxylate, giving rise to the 4,5-dimethoxycarbonyl-3-β-D-ribofuranosylisoxazole esters (**8a** and **8b**) as analytically pure syrups. Deacetyla-



8a, R = Bz
b, R = Ac
c, R = H



9a, X = O
b, X = NOH



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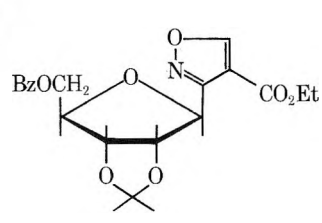

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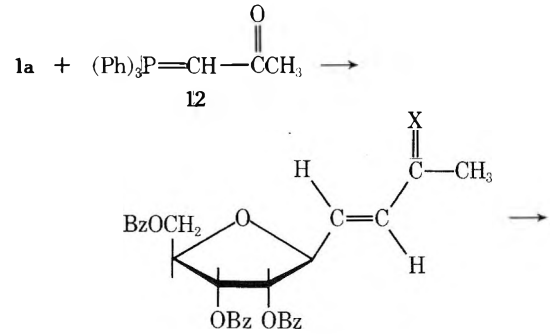
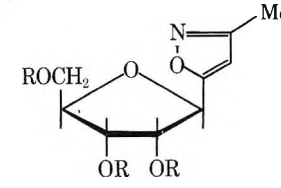
tion of **8b** under acidic conditions as above gave the crystalline *C*-glycoside **8c** without difficulty. Attempted debenzoylation of **8a** with sodium methoxide, however, gave rise to an analytically impure, syrupy compound the NMR spectrum of which was grossly similar to that of **8c** with respect to the carbohydrate moiety. The compound only appeared to contain one methyl ester group at a chemical shift quite different from those in **8c** and it once again appears that the isoxazole ring underwent degradation under the strongly basic conditions.

The previously described 2,5-anhydro-6-*O*-benzoyl-3,4-*O*-isopropylidene-D-allose (**9a**)[1] was also used as a starting material for isoxazole *C*-glycosides by routes similar to those above. Thus **9a** was converted into the crystalline oxime **9b** and thence, by chlorination and reaction with ethyl propiolate in the presence of triethylamine, into the isoxazole **10** in an overall yield of 62%. While this material gave a single spot by TLC, its NMR spectrum showed the presence of roughly 15% of an isomer, presumably **11**. The major component (**10**) showed C_4H of the isoxazole ring as a singlet at 6.88 ppm while the isoxazole proton in the putative **11** appeared at 8.84 ppm. Without purification, crude **10** was treated first with 90% trifluoroacetic acid to remove the isopropylidene group, and then with methanolic ammonia to give a 71% yield of the amide **7** identical with that obtained from **6b**. In order to characterize pure **10** the triol **6c** was converted to its 2′,3′-*O*-isopropylidene derivative and, without purification of this intermediate, then benzoylated. The product from this sequence, isolated in an overall yield of 80%, proved to be identical with the major product (**10**) obtained via the oxime **9b**.

In order to prepare a 5-ribosylisoxazole, a totally different route was explored via oxidative cyclization of an α,β-unsaturated ketoxime.[13] To this end **1a** was treated with acetonylidenetriphenylphosphorane (**12**)[14] in methylene chloride at room temperature to give, after chromatography on silicic acid, an 83% yield of *trans*-5,8-anhydro-6,7,9-tri-*O*-benzoyl-1,3,4-trideoxy-D-*allo*-non-3-enulose (**13a**). The pure trans stereochemistry of **13a** was evident



13a, X = O
b, X = NOH



14a, R = Bz
b, R = H

from its NMR spectrum, which showed the two vinyl protons as well-separated signals with $J_{3=4}$ = 16 Hz.[15] This material was then converted to the oxime **3b** and treated with iodine, potassium iodide, and sodium bicarbonate in aqueous methanol[13] to give 5-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-3-methylisoxazole (**14a**) in 51% yield. Debenzoylation of **14a** with methanolic ammonia then gave the crystalline free *C*-glycoside (**14b**) in 63% yield. The method of synthesis makes the orientation of the isoxazole substit-

uents unambiguous, and the structure and homogeneity of the product is further supported by NMR spectroscopy.

The methods described in this paper allow the synthesis of a number of differently substituted 3- and 5-(β-D-ribofuranosyl)isoxazoles for biological evaluation. Future papers in this series will extend this work to the synthesis of other heterocyclic *C*-glycosides.

Experimental Section

General Methods. Thin layer chromatography was done using 250-μ layers of Merck silica gel GF, and preparative TLC using 20 × 100 cm glass plates coated with a 1.3-mm layer of Merck silica gel HF. Nuclear magnetic resonance (NMR) spectra were obtained using a Varian HA-100 spectrometer and are recorded in parts per million downfield from an internal standard of tetramethylsilane. We express our gratitude to Dr. M. L. Maddox and Mrs. J. Nelson for their help with NMR studies. Elemental analyses were obtained by Dr. A. Bernhardt, Elbach über Engelskirchen, Germany, or by the staff of the Analytical Laboratories of Syntex Research. Melting points are corrected.

2,5-Anhydro-3,4,6-tri-*O*-benzoyl-D-allose Oxime (2a). *p*-Toluenesulfonic acid monohydrate (7.03 g, 37 mmol) was added with stirring at 0° to a solution of1,3-diphenyl-2-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)imidazolidine (10.0 g, 15 mmol)[1] in methylene chloride (150 ml) and stored for 45 min. The mixture was filtered and after addition of pyridine (3 ml) the filtrate was evaporated to a syrup. The latter was dissolved in pyridine (75 ml) and ethanol (75 ml) containing hydroxylamine hydrochloride (5.2 g, 75 mmol) and heated under reflux for 2 hr. The solvent was evaporated and the residue was dissolved in chloroform and washed with 5% aqueous sodium bisulfate, sodium bicarbonate, and water. Evaporation of the dried ($MgSO_4$) organic phase left 6.68 g (91%) of **2a** as a syrup that contained only a trace contaminant by TLC. For analytical purposes a sample was further purified by preparative TLC using ether–hexane (2:1): $[\alpha]^{23}D$ 12.9° (c 0.2, MeOH); λ_{max} (MeOH) 229 nm (ε 37,000), 273 (2700), 280 (2200); NMR ($CDCl_3$) 4.5–4.9 (m, 4, C_2H, C_5H, C_6H_2), 5.73 (m, 2, C_3H, C_4H), 7.25–7.45 (m, 9, Ar), 7.48 (d, 1, $J_{1,2}$ = 2 Hz, C_1H), 7.8–8.1 (m, 6, Ar), 8.19 ppm (br s, 1, NOH).

Anal. Calcd for $C_{27}H_{23}NO_8$ (489.46): C, 66.24; H, 4.74; N, 2.86. Found: C, 66.25; H, 4.90; N, 2.87.

3,4,6-Tri-*O*-Acetyl-2,5-anhydro-D-allose Oxime (2b). A solution of *p*-toluenesulfonic acid monohydrate (3.94 g, 21 mmol) in acetone (20 ml) and methylene chloride (30 ml) was added to a solution of 1,3-diphenyl-2-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)imidazolidine (4.0 g, 8.3 mmol).[1] After 30 min at room temperature the precipitated salt was removed by filtration and washed with methylene chloride. Evaporation of the combined filtrates left the essentially homogeneous aldehyde (**1a**), which was immediately dissolved in ethanol (100 ml) and pyridine (100 ml) containing 1.16 g (16.6 mmol) of hydroxylamine hydrochloride. The mixture was heated under reflux for 2.5 hr, cooled, and evaporated to dryness. The residue was dissolved in chloroform, washed with saturated aqueous sodium bicarbonate and with water, dried ($MgSO_4$), and evaporated. The resulting syrup was chromatographed on a column of silicic acid (250 g) using chloroform–ethyl acetate (9:1), giving 1.90 g (76%) of **2b** as a clear syrup: $[\alpha]^{23}D$ 21.7° (c 1.0, $CHCl_3$); NMR ($CDCl_3$) 2.05, 2.07 (s, total 9, OAc), 4.20 (m, 1, C_5H), 4.20 (dd, 1, J_{gem} = 12, $J_{5,6a}$ = 3 Hz, $C_{6a}H$), 4.31 (dd, 1, $J_{5,6b}$ = 3 Hz, $C_{6b}H$), 5.54 (dd, 1, $J_{1,2}$ = 6, $J_{2,3}$ = 5 Hz, C_2H), 5.25 (m, 2, C_3H, C_4H), 7.37 (d, 1, C_1H), 8.15 ppm (br s, 1, OH).

Anal. Calcd for $C_{12}H_{17}NO_8$ (303.27): C, 47.52; H, 5.65; N, 4.62. Found: C, 47.41; H, 5.81; N, 4.59.

3-(2,3,5-Tri-*O*-benzoyl-β-D-ribofuranosyl)-5-ethoxycarbonylisoxazole (6a). Dry chlorine gas was bubbled through a solution of the oxime (**2b**, 3.0 g, 6.2 mmol) in ether (60 ml) at −60° for 15 min. The greenish-blue solution, which contained some precipitate, was evaporated to dryness and the residue was coevaporated several times with benzene, leaving crude **3**, **3′** as a syrup with a TLC mobility somewhat greater than that of **2a** using CCl_4–ethyl acetate (5:1). This material was immediately dissolved in ether (100 ml) at −20° together with ethyl propiolate (2.4 g, 24.8 mmol). A solution of triethylamine (900 mg, 9 mmol) in ether (5 ml) was added dropwise and the mixture was then allowed to warm to room temperature over 1 hr. The solution was diluted to 700 ml with ether, washed twice with water, dried, and evaporated to dryness. The residue was chromatographed on a column of silicic acid using CCl_4–acetone (10:1) to give 2.4 g (67%) of **6a** as a homogeneous, colorless syrup: λ_{max} (MeOH) 229 nm (ε 44,800), 269 (3100), 274 (3300), 281 (2600); NMR ($CDCl_3$) 1.33 (t, 3, CH_3), 4.35 (q, 2, OCH_2), 4.67 (dd, 1, J_{gem} = 11.5, $J_{4',5'a}$ = 3 Hz, $C_{5'a}H$), 4.84 (dd, 1, J_{gem} = 11.5, $J_{4',5'b}$ = 3 Hz, $C_{5'b}H$), 4.7 (m, 1, $C_{4'}H$), 5.47 (m, 1, virtual coupling to $C_{3'}H$, $C_{1'}H$), 5.85 (m, 2, $C_{2'}H$, $C_{3'}H$), 6.94 (s, 1, C_4H), 7.4 (m, 9, Ar), 7.95 ppm (m, 6, Ar).

Anal. Calcd for $C_{32}H_{27}NO_{10}$ (585.55): C, 65.63; H, 4.65; N, 2.39. Found: C, 65.87; H, 4.70; N, 2.52.

3-(β-D-Ribofuranosyl)isoxazole-5-carboxamide (7). A. A solution of **6a** (800 mg, 1.34 mmol) in saturated methanolic ammonia (300 ml) was stored at room temperature for 5 days, at which point TLC [chloroform–methanol (5:1)] showed complete conversion to **7** and benzamide. Following evaporation of the solvent the syrupy residue was dissolved in water and washed several times with ethyl acetate. The aqueous phase was evaporated, leaving 300 mg (90%) of TLC-homogeneous crystalline **7**. After recrystallization from acetonitrile **7** had mp 148–149°: λ_{max} (MeOH) 224 nm (ε 11,900); $[\alpha]^{23}D$ −36.5° (c 0.5, MeOH); NMR (DMSO-d_6) 3.48 (m, 2, $C_{5'}H_2$), 3.8–4.1 (m, 3, $C_{2'}H$, $C_{3'}H$, $C_{4'}H$), 4.71 (d, 1, $J_{1',2'}$ = 5.5 Hz, $C_{1'}H$), 7.08 (s, 1, C_4H), 7.75 and 8.25 ppm (br s, 1, $CONH_2$).

Anal. Calcd for $C_9H_{12}N_2O_6$ (244.21): C, 44.26; H, 4.95; N, 11.47. Found: C, 44.32; H, 5.38; N, 11.61.

B. A solution of **10** (100 mg) in 90% trifluoroacetic acid (1.5 ml) was kept at room temperature for 10 min and then evaporated to dryness and coevaporated several times with ethanol and benzene. The residue was then treated with saturated methanolic ammonia for 5 days at room temperature and then purified by preparative TLC using chloroform–2-propanol (5:1), giving 41 mg (71%) of **7** identical with that from A.

3-(2,3,5-Tri-*O*-Acetyl-β-D-ribofuranosyl)-5-ethoxycarbonylisoxazole (6b). The oxime **2b** (1.60 g, 5.2 mmol) was converted into the chloro oxime by treatment in ether (50 ml) with chlorine gas at −70° for 15 min as above. The reaction could be followed by TLC [ethyl acetate–chloroform (7:3)], in which the mobility of **3b** is slightly greater than that of **2b**. After evaporation of the solvent in vacuo the residue was coevaporated with benzene and dissolved in ether (50 ml). The solution was stirred at −70° while solutions of ethyl propiolate (2.08 g, 21 mmol) and then triethylamine (800 mg, 8 mmol) in ether (10 ml each) were added dropwise. The mixture was then allowed to warm to room temperature over 2 hr, diluted with ether, and washed with water. The dried organic phase was chromatographed on a column of silicic acid (150 g) using chloroform–ethyl acetate (4:1), giving 950 mg (46%) of **6b** as a homogeneous syrup: λ_{max} (MeOH) 225 nm (ε 9400); $[\alpha]^{23}D$ −32.6° (c 1.0, $CHCl_3$); NMR ($CDCl_3$) 1.38 (t, 3, CH_2CH_3), 2.06, 2.07, and 2.08 (s, 3, OAc), 4.31 (m, 3, $C_{4'}H$ and $C_{5'}H_2$), 4.42 (q, 2, OCH_2CH_3), 5.15 (d, 1, $J_{2',3'}$ = 5.5 Hz, $C_{2'}H$), 5.32 (dd, 1, $J_{3',4'}$ = 9 Hz, $C_{3'}H$), 5.34 (s, 1, $C_{1'}H$), 6.97 ppm (s, 1, C_4H).

Anal. Calcd for $C_{17}H_{21}NO_{10}$ (399.37): C, 51.13; H, 5.30; N, 3.51. Found: C, 51.08; H, 5.28; N, 3.41.

5-Ethoxycarbonyl-3-(β-D-ribofuranosyl)isoxazole (6c). A saturated solution of hydrogen chloride in ether (10 ml) was added to a solution of **6b** (690 mg, 1.7 mmol) in anhydrous ethanol (25 ml) and the mixture was kept overnight at room temperature. The solvent was evaporated in vacuo and the residue was coevaporated several times with ethanol, leaving a residue that was crystallized from chloroform giving 230 mg (49%) of **6c** with mp 94–95°: λ_{max} (MeOH) 226 nm (ε 10,200); $[\alpha]^{23}D$ −36.3° (c 0.5, MeOH); NMR (DMSO-d_6) 1.30 (t, 3, CH_2CH_3), 3.50 (m, 2, $C_{5'}H_2$), 3.8–4.1 (m, 3, $C_{2'}H$, $C_{3'}H$, $C_{4'}H$), 4.34 (q, 2, OCH_2CH_3), 3.72 (d, 1, $J_{1',2'}$ = 6 Hz, $C_{1'}H$), 4.81 (t, 1, $J_{H,OH}$ = 5 Hz, $C_{5'}OH$), 4.97 (d, 1, $J_{H,OH}$ = 4 Hz, $C_{2' \text{ or } 3'}OH$), 5.17 (d, 1, $J_{H,OH}$ = 5 Hz, $C_{2' \text{ or } 3'}OH$), 7.30 ppm (s, 1, C_4H).

Anal. Calcd for $C_{11}H_{15}NO_7$ (273.25): C, 48.35; H, 5.53; N, 5.13. Found: C, 48.39; H, 5.65; N, 5.22.

3-(2,3,5-Tri-*O*-benzoyl-β-D-ribofuranosyl)-4,5-dimethoxycarbonylisoxazole (8a). A solution of the oxime **2a** (3.0 g, 6.1 mmol) in ether (75 ml) was converted into the chloro oxime **3a** as in the preparation of **6a** above. It was then treated with dimethyl acetylenedicarboxylate (3.4 g, 24 mmol) and triethylamine (0.90 g, 9 mmol) at −20° and allowed to warm to room temperature over 45 min. The solution was diluted with ether, washed with water, and evaporated to dryness, leaving a syrup that was purified by preparative TLC using carbon tetrachloride–acetone (9:1), giving 1.20 g (31%) of **8a** as a homogeneous syrup: λ_{max} (MeOH) 228 nm (ε 46,000), 275 (4600), 281 (4600); $[\alpha]^{23}D$ −24.5° (c 0.2, $CHCl_3$); NMR ($CDCl_3$) 3.83 and 3.94 (s, 3, OMe), 4.5–4.8 (m, 3, $C_{4'}H$, $C_{5'}H_2$), 5.65 (d, 1, $J_{1',2'}$ = 4.5 Hz, $C_{1'}H$), 5.90 (dd, 1, $J_{2',3'}$ = 5, $J_{3',4'}$ = 5.5 Hz, $C_{3'}H$), 6.19 (dd, 1, $C_{2'}H$), 7.4 (m, 9, Ar), 7.95 ppm (m, 6, Ar).

Anal. Calcd for $C_{33}H_{27}NO_{12}$ (629.56): C, 62.95; H, 4.32; N, 2.23. Found: C, 62.69; H, 4.48; N, 2.40.

3-(2,3,5-Tri-*O*-acetyl-β-D-ribofuranosyl)-4,5-dimethoxycarbonylisoxazole (8b). The chloro oxime **3b, 3'b** was generated as above from 1.90 g (6.27 mmol) of **2b** and evaporated to dryness, leaving a foamy residue after coevaporation with benzene. This was dissolved in ether (50 ml), cooled to −70°, and stirred while dimethyl acetylenedicarboxylate (3.54 g, 25 mmol) and then triethylamine (950 mg, 9.4 mmol) were added dropwise in ether (10 ml each). The mixture was allowed to warm to room temperature and kept for 2 hr before being diluted with chloroform and washed with water. Evaporation of the dried organic phase and chromatography of the residue on a column of silicic acid (300 g) using chloroform–ethyl acetate (9:1) gave 1.60 g (58%) of **8b** as a homogeneous syrup: λ_{max} (MeOH) 221 nm (ε 6600); $[\alpha]^{23}D$ −10.3° (c 1.0, $CHCl_3$); NMR ($CDCl_3$) 2.05 (s, 3, OAc), 2.09 (s, 6, OAc), 3.89 and 3.99 (s, 3, OMe), 4.3 (m, 3, $C_4'H$, $C_5'H_2$), 5.36 (d, 1, $J_{1',2'}$ = 5.5 Hz, $C_1'H$), 5.38 (dd, 1, $J_{2',3'}$ = 5.5 Hz, $C_3'H$),[16] 5.71 ppm (dd, 1, $C_2'H$).

Anal. Calcd for $C_{18}H_{21}NO_{12}$ (443.38): C, 48.76; H, 4.77; N, 3.16. Found: C, 48.58; H, 4.86; N, 3.13.

4,5-Dimethoxycarbonyl-3-(β-D-ribofuranosyl)isoxazole (8c). A solution of **8b** (1.1 g, 2.48 mmol) in anhydrous methanol (100 ml) was mixed with 6 *N* hydrogen chloride in ether (10 ml) and stored overnight at room temperature, at which point TLC [chloroform–methanol (9:1)] showed essentially complete reaction. Following evaporation of the solvent and coevaporation with methanol the syrupy residue solidified. Slow crystallization from benzene (175 ml) gave 250 mg (32%) of **8c** as needles with mp 73–74°. Chromatography of the mother liquors on a column of silicic acid using 2.5% methanol in chloroform gave a further 130 mg (total yield 48%) of crystalline **8c:** λ_{max} (MeOH) 222 nm (ε 6500); $[\alpha]^{23}D$ −7.3° (c 0.5, MeOH); NMR (DMSO-d_6–D_2O) 3.39 (m, 2, $C_5'H_2$), 3.8 (m, 2, $C_3'H$ and $C_4'H$), 3.82 and 3.91 (s, 3, OMe), 4.17 (dd, 1, $J_{1',2'}$ = 6.5, $J_{2',3'}$ = 5 Hz, $C_2'H$), 4.85 ppm (d, 1, $C_1'H$).

Anal. Calcd for $C_{12}H_{15}NO_9$ (317.26): C, 45.43; H, 4.77; N, 4.42. Found: C, 45.49; H, 4.85; N, 4.38.

2,5-Anhydro-6-*O*-benzoyl-3,4-*O*-isopropylidene-D-allose Oxime (9b). The free aldehyde (**9a**) was regenerated from its 1,3-diphenylimidazolidine derivative (5.0 g, 10 mmol) using *p*-toluenesulfonic acid as previously described.[1] The crude product was treated with hydroxylamine hydrochloride (1.5 g, 21.4 mmol) in pyridine–ethanol (1:1, 100 ml) under reflux for 2 hr and worked up as above for **2.** Crystallization from chloroform–hexane gave 1.55 g (53%) of **9b:** mp 120–125°; $[\alpha]^{23}D$ −4.5° (c 0.3, $CHCl_3$); NMR ($CDCl_3$) 1.35 and 1.55 (s, 3, CMe_2), 4.44 (m, 3, C_4H, C_5H_2), 4.59 (dd, 1, $J_{1,2}$ = 5.5, $J_{2,3}$ = 4 Hz, C_2H), 4.74 (m, 1, C_4H), 4.88 (dd, 1, $J_{3,4}$ = 6 Hz, C_3H), 7.43 (d, 1, C_1H), 7.45 (m, 3, Ar), 8.04 ppm (m, 2, Ar).

Anal. Calcd for $C_{16}H_{19}NO_6$ (321.32): C, 59.80; H, 5.96; N, 4.36. Found: C, 59.55; H, 5.95; N, 4.17.

3-(5'-*O*-Benzoyl-2',3'-*O*-isopropylidene-β-D-ribofuranosyl)-5-ethoxycarbonylisoxazole (10). A. Chlorine gas was bubbled through a solution of **9b** (315 mg, 1 mmol) in ether (30 ml) at −60° for 10 min. The resulting green solution was evaporated to dryness and the resulting white solid was coevaporated twice with benzene. The residue and ethyl propiolate (400 mg, 4 mmol) were dissolved in ether (15 ml) and cooled to −20° while triethylamine (150 mg, 1.5 mmol) in ether (5 ml) was added dropwise with stirring over 15 min. The mixture was then allowed to warm to room temperature and kept for 45 min. After dilution with chloroform the solution was washed with water, dried ($MgSO_4$), and evaporated, leaving a syrup that was purified by preparative TLC using ether–hexane (1:1), giving 260 mg (62%) of a syrup that consisted of **10** (see below) contaminated with roughly 15% of an isomer (probably **11**) which showed the isoxazole proton as a singlet at 8.84 ppm.

B. Perchloric acid (0.1 ml) was added to a solution of **6c** (50 mg) in acetone (5 ml) and 2,2-dimethoxypropane (0.2 ml). After 2 hr at room temperature the mixture was neutralized to ~pH 8 with methanolic ammonia and evaporated to dryness. The residue was partitioned between ethyl acetate and water and the dried organic phase was evaporated, leaving 60 mg of the almost pure [TLC, ether–hexane (1:1)] acetonide. This was dissolved in pyridine (5 ml) and treated with benzoyl chloride (100 mg) at 60° for 1.5 hr. The solvent was evaporated and the residue was dissolved in ethyl acetate, washed with aqueous sodium bicarbonate and with water, dried ($MgSO_4$), and evaporated. The residue was purified by preparative TLC using ether–hexane (1:1), giving 61 mg (80%) of pure **10** as a homogeneous (TLC and NMR) syrup: λ_{max} (MeOH) 228 nm (ε 21,500), 273 (1000), 280 (800); $[\alpha]^{23}D$ −59.4° (c 0.5, $CHCl_3$); NMR ($CDCl_3$) 1.34 (t, 3, CH_2CH_3), 1.39 and 1.60 (s, 3, CMe_2), 4.36 (q, 2, CH_2CH_3), 4.4 (m, 3, $C_4'H$, $C_5'H_2$), 4.83 (m, 1, virtual coupling to $C_3'H$, $C_1'H$), 5.17 (narrow m, 2, $C_2'H$, $C_3'H$), 6.89 (s, 1, C_4H), 7.45 (m, 3, Ar), 7.90 ppm (dd, 2, J_o = 8, J_m = 1.5 Hz, Ar).

Anal. Calcd for $C_{21}H_{23}NO_8$ (417.40): C, 60.42; H, 5.55; N, 3.36. Found: C, 60.53; H, 5.67; N, 3.49.

***trans*-5,8-Anhydro-6,7,9-tri-*O*-benzoyl-1,3,4-trideoxy-D-*allo*-non-3-enulose (13a).** 2,5-Anhydro-3,4,6-tri-*O*-benzoyl-D-allose (**1a**) was regenerated from its diphenylimidazolidine derivative (5.0 g, 7.5 mmol)[1] as described for the preparation of **2a.** This material was dissolved together with 4.80 g (15 mmol) of the ylide **12** in methylene chloride (800 ml) and then stored at room temperature for 4 hr. The mixture was then washed with water and the organic phase was evaporated and chromatographed on a column of silicic acid (500 g) using ether–hexane (2:1). Concentration of the major product gave 3.2 g (83%) of **13a** as a TLC-homogeneous syrup: λ_{max} (MeOH) 229 nm (ε 48,500), 274 (3500). 281 (3000), 318 (1600); $[\alpha]^{23}D$ −−21.5° (c 0.3, $CHCl_3$); NMR ($CDCl_3$) 2.16 (s, 3, $COCH_3$), 4.70 (m, 3, C_8H, C_9H_2), 4.88 (ddd, 1, $J_{4,5}$ = 4.5, $J_{5,6}$ = 5, $J_{3,5}$ = 1.5 Hz, C_5H), 5.47 (dd, 1, $J_{6,7}$ = 5 Hz, C_6H), 5.64 (dd, 1, $J_{7,8}$ = 5 Hz, C_7H), 6.40 (dd, 1, $J_{3,4}$ = 16 Hz, C_3H), 6.83 (dd, 1, C_4H), 7.4 (m, 9, Ar), 8.0 (m, 6, Ar).

Anal. Calcd for $C_{30}H_{26}O_8$ (514.51): C, 70.03; H, 5.09. Found: C, 69.68; H, 5.12.

5,8-Anhydro-6,7,9-tri-*O*-benzoyl-1,3,4-trideoxy-D-*allo*-non-3-enulose Oxime (13b). A solution of **13a** (2.5 g, 4.86 mmol) and hydroxylamine hydrochloride (840 mg, 12 mmol) in a mixture of pyridine (30 ml) and methanol (100 ml) was stirred at room temperature for 5 hr and then evaporated to dryness. The residue was coevaporated twice with toluene and chromatographed on a column of silicic acid using ether–hexane (2:1) to give 2.1 g (82%) of **13b** as a single isomer: λ_{max} (MeOH) 229 nm (ε 58,700), 272 (sh, 4500), 280 nm (sh, 3100); $[\alpha]^{23}D$ −43.8° (c 0.2, $CHCl_3$); NMR ($CDCl_3$) 1.92 (s, 3, C_1H_3), 4.54 (dd, 1, J_{gem} = 13, $J_{8,9a}$ = 3 Hz, $C_{9a}H$), 4.65 (m, 2, C_8H, $C_{9b}H$), 4.82 (ddd, 1, $J_{4,5}$ = 6, $J_{5,6}$ = 5.5, $J_{3,5}$ = 1 Hz, C_5H), 5.47 (dd, 1, $J_{6,7}$ = 5.5 Hz, C_6H), 5.67 (dd, 1, $J_{7,8}$ = 5 Hz, C_7H), 6.06 (dd, 1, $J_{3,4}$ = 16 Hz, C_4H), 6.50 (dd, 1, C_3H), 7.4 (m, 9, Ar), 8.0 ppm (m, 6, Ar).

Anal. Calcd for $C_{30}H_{27}NO_8$ (529.52): C, 68.04; H, 5.14; N, 2.65. Found: C, 68.21; H, 5.14; N, 2.56.

5-(2,3,5-Tri-*O*-benzoyl-β-D-ribofuranosyl)-3-methylisoxazole (14a). A solution of potassium iodide (580 mg, 3.5 mmol) and iodine (280 mg, 1.1 mmol) in water (6 ml) was added in the dark to a stirred solution of **13b** (530 mg, 1 mmol) and sodium bicarbonate (336 mg, 4 mmol) in a mixture of tetrahydrofuran (4 ml) and water (3 ml). The mixture was heated under reflux for 4.5 hr, cooled, diluted with saturated aqueous sodium bisulfite (10 ml), and extracted three times with ether. The extracts were dried ($MgSO_4$) and evaporated, leaving a residue that was chromatographed on a column of silicic acid (50 g) using chloroform–ethyl acetate (19:1) to give 270 mg (51%) of **14a** as a TLC-homogeneous clear syrup: λ_{max} (MeOH) 229 nm (ε 36,900), 274 (2800), 281 (2200); $[\alpha]^{23}D$ −32.4° (c 0.5, $CHCl_3$); NMR ($CDCl_3$) 2.22 (s, 3, C_3CH_3), 4.69 (dd, 1, J_{gem} = 12, $J_{4',5'a}$ = 2.5 Hz, $C_{5'a}H$), 4.7 (m, 1, $C_4'H$), 4.82 (dd, 1, $J_{4',5'b}$ = 2.5 Hz, $C_{5'b}H$), 5.40 (m, 1, with virtual coupling to $C_3'H$, $C_1'H$), 5.81 and 5.89 (dd, 1, $J_{1',2'}$, $J_{3',4'}$ = 2, $J_{2',3'}$ = 5 Hz, $C_2'H$, $C_3'H$), 6.17 (s, 1, C_4H), 7.4 (m, 9, Ar), 8.0 (m, 6, Ar).

Anal. Calcd for $C_{30}H_{25}NO_8$ (527.54): C, 68.30; H, 4.78; N, 2.66. Found: C, 68.24; H, 5.13; N, 2.67.

3-Methyl-5-(β-D-ribofuranosyl)isoxazole (14b). A solution of **14a** (390 mg, 0.74 mmol) in 25% saturated methanolic ammonia (50 ml) was kept at room temperature overnight and then evaporated to dryness. The residue was crystallized from ethyl acetate, giving 100 mg (63%) of **14b:** mp 108–109°; λ_{max} (MeOH) 216 nm (ε 6800); $[\alpha]^{23}D$ −38.3° (c 0.5, MeOH); NMR (DMSO-d_6) 2.20 (s, 3, C_3CH_3), 3.50 (m, 2, $C_5'H_2$), 3.9 (m, 3, $C_2'H$, $C_3'H$, $C_4'H$), 4.70 (d, 1, $J_{1',2'}$ = 6 Hz, $C_1'H$), 3.85 (t, 1, $C_5'OH$), 4.97 and 5.19 (d, 1, $C_2'OH$, $C_3'OH$), 6.35 (s, 1, C_4H).

Anal. Calcd for $C_9H_{13}NO_5$ (215.21): C, 50.23; H, 6.09; N, 6.51. Found: C, 50.40; H, 6.22; N, 6.49.

Registry No.—**1a,** 39037-99-5; **2a,** 50720-88-2; **2b,** 55267-78-2; **3a,** 50720-94-0; **3b,** 55267-79-3; (*S*)-**3b',** 55267-80-6; (*R*)-**3b',** 55331-41-4; **6a,** 50720-89-3; **6b,** 55267-81-7; **6c,** 50720-91-7; **7,** 50720-90-6; **8a,** 50720-93-9; **8b,** 55267-82-8; **8c,** 50720-96-2; **9a,** 39037-13-3; **9b,** 55267-83-9; **10,** 55267-84-0; **12,** 1439-36-7; **13a,** 55267-85-1; **13b,** 55267-86-2; **14a,** 55267-87-3; **14b,** 55267-88-4; 1,3-diphenyl-2-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)imidazolidine, 39038-02-3; 1,3-diphenyl-2-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)imidazolidine, 39037-09-7.

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Approaches to Analogs of Anhydrogliotoxin. 3.[1,2] Synthesis of a Desthiomethylene Analog

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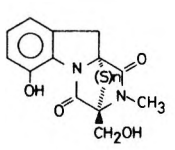
The reaction of *N*-benzyloxycarbonyl-L-cysteine (**7**) with the ethyl indolenino-2-carboxylate (**6**) gave two diastereomeric addition products, **8a** and **8b**. Deprotection of the amino group of **8a** yielded **9a**. On basification the free amine **10a** underwent ring closure by intramolecular aminolysis to yield **5**, a desthiomethylene analog of anhydrogliotoxin. The diastereomeric amine **10b** could also be converted into **5** in a reaction believed to proceed via **10a** by an autocatalyzed epimerization at C-9. Support for this mechanism was obtained by deuterium exchange studies. Recrystallization of **5** yielded a racemic and an optically active fraction. A CD spectrum of the latter supports an R_2S_9 absolute configuration, which is identical with that of gliotoxin **11**. The stereochemistry of the addition reaction is discussed: optically active product **5** results from a chiral component **7** whose configuration inverts during the reaction. The racemic, as well as the optically active compound **5**, is devoid of antiviral and antibacterial activity. This indicates that in natural products containing an epidithiodioxopiperazine moiety the disulfide bridge is essential for activity and the three-dimensional structure is of secondary importance.

Dehydrogliotoxin (**1**, n = 2) and sporidesmin (**2**, R = H) belong to a group of fungal metabolites characterized by a bridge of sulfur atoms across a dioxopiperazine ring.[3] Recently, a simple synthetic homolog, 3,6-epidithio-1,4-dimethyl-2,5-dioxopiperazine (**3**),[4-6] was found to have biological properties which are characteristic of this class of compounds.[5] On the other hand, the conversion of the complex natural products into their dithioalkylated derivatives is accompanied by complete loss of biological activity. From these observations Taylor concluded[4] that the sulfur bridged dioxopiperazine moiety, or a metabolite of it, might be responsible for the activity of these compounds. In this respect the activities of sporidesmin C, **4** (R = H),[7] having a methylene–disulfide bridge, and of monodesthiodehydrogliotoxin (**1**, n = 1)[8] are of interest. Taylor argues[3] that the low activity of the diacetate of **4** (R = $COCH_3$),[9] which is about 100 times less active than sporidesmin diacetate (**2**, R = $COCH_3$), can be accounted for by a contamination of **4** (R = $COCH_3$) with **2** (R = $COCH_3$).



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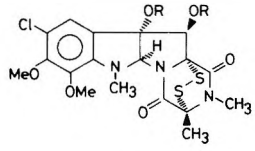

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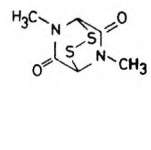

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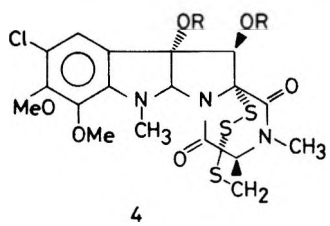

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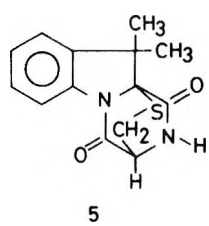


5

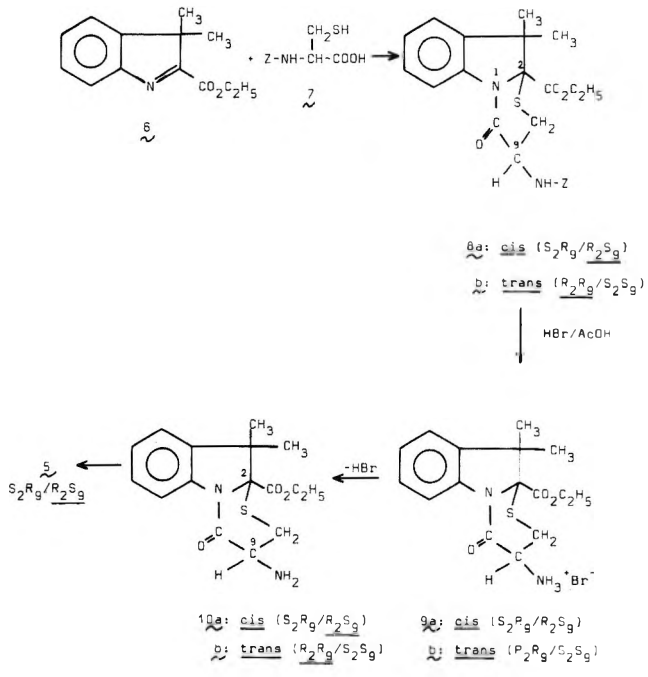
Here we wish to report on the synthesis of an anhydrogliotoxin analog **5** possessing a methylene sulfide bridge instead of a disulfide bridge. The three-dimensional structure will not be significantly altered by such a substitution and examination of **5** for biological activity might shed more light on the importance of the disulfide bridge in the activity of compounds such as **1–3**.

As we have previously reported,[2] β-mercaptopropionic acid reacts with the ethyl indolenino-2-carboxylate **6** to yield an indoline tetrahydrothiazone derivative. In an analogous reaction addition of *N*-benzyloxycarbonyl-L-cysteine[10] (**7**) to **6** gave in 95% yield a mixture of two compounds that could be separated by column chromatography. Both products, one an oil ($[\alpha]^{20}D$ −13.8°), the other crystalline ($[\alpha]^{20}D$ −19.2°) (ratio 5:6) were optically active. Elemental analyses and spectral data supported the diastereomeric indoline tetrahydrothiazone structures **8a** and **8b** (Scheme I). These compounds had nearly the same mass spectra, having parent peaks at m/e 454, differing only in that the oily component had a peak at m/e 408 (M − C_2H_5OH) in its spectrum which was missing in the spectrum of the crystalline material. Because intramolecular loss of C_2H_5OH seems more probable in a cis isomer, it was assumed that structure **8a** belongs to the oily material and the trans configuration **8b** to the crystalline product. This assumption could be substantiated as will be discussed below.

The *N*-benzyloxycarbonyl group was smoothly removed

from **8a** with HBr in acetic acid, yielding the crystalline hydrobromide **9a.** The free amino group was produced either by ion-exchange chromatography, or preferably, by adjusting the pH of a methanolic solution to 9.5 with sodium hydroxide followed by desalting on Sephadex LH-20. Surprisingly, **10a** could not be isolated as such, as it spontaneously underwent partial ring closure to **5.** This intramolecular aminolysis could be completed by refluxing the mixture in ethanol for 1 hr. This facile ring closure supports the assignment of the cis configuration **8a** to the oily fraction. Compound **5** thus obtained was found to be optically active: $[\alpha]^{20}D$ −10.2°. Structure proof is based on elemental analysis and the usual spectral data. Recrystallization yielded a racemic, crystalline product (mp 212–213°) leaving an optically active, amorphous residue, $[\alpha]^{20}D$ −63°.

Scheme I



When the trans compound **8b** was subjected to the same operations, homogeneous free amino **10b** could be isolated. It was anticipated that **10b** would not react further, since the ester and amino group are in a trans position. Surprisingly, this amine could also be ring closed, though slowly, by refluxing in ethanol for 20 hr. The compound thus obtained was identical in all respects with that prepared from **10a,** except for the rotation, this being $[\alpha]^{20}D$ −52°. Recrystallization of this material again yielded a racemic, crystalline fraction (mp 213–214°) but the optically active amorphous residue had $[\alpha]^{20}D$ −156°.

Evidently, the diastereomers **10a** and **10b** are interconvertible, with the cis product **10a** being removed from the mixture because of irreversible ring closure (**10a** → **5**). A priori, epimerization of **10b** might happen at either C-2 or C-9. To distinguish between these possibilities, the amino deuterated trans compound **10b** was refluxed in deuterated methanol after which compound **5** was isolated with 100% deuterium at C-9. Proton exchange after ring closure of **10a** was ruled out by the following experiment. Reflux of a solution of **5** in deuterated methanol with 1 equiv of amino deuterated aniline did not lead to incorporation of deuterium. Thus epimerization of **10b** probably occurs at C-9, with the amino group functioning as an autocatalyst.

The specific rotations of the amorphous residues of **5** differed, but were in both cases negative, indicating that in

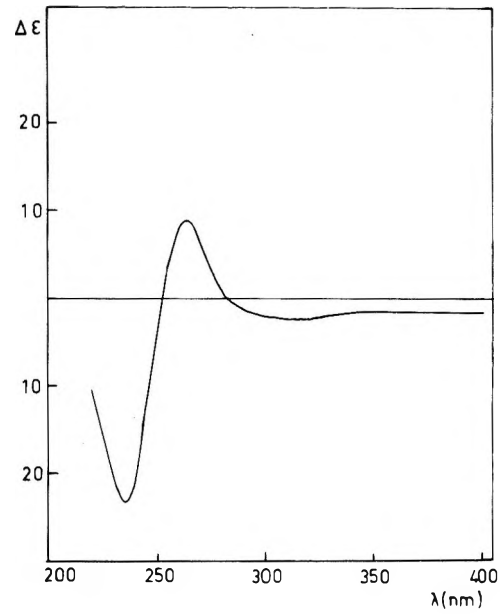
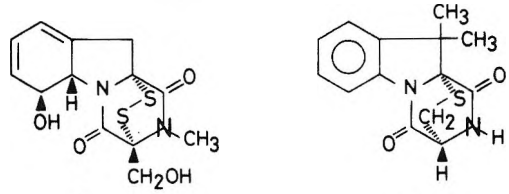


Figure 1. Circular dichroism curve of **5,** $[\alpha]^{20}D$ −156°, 0.2325 mg/ml of absolute MeOH, path length 2 mm.

both fractions the same enantiomer of **5** predominated. The absolute configuration of the fraction of **5** having $[\alpha]D$ −156° was derived from a CD spectrum (Figure 1).

The negative Cotton effect at 235 nm ($\Delta\epsilon_{max}$ −23.3) is due to a n,π^* transition of a peptide bond.[11] The natural product gliotoxin **11**, similarly having two chiral centers in the dioxopiperazine ring,[12] also shows a negative Cotton effect at 230 nm ($\Delta\epsilon_{max}$ −33).[13] From this, the tentative conclusion is drawn that compound **5,** with $[\alpha]^{20}D$ −156°, consists mainly or entirely of the enantiomer **5**-R_2S_9. In the



11 **5**-R_2S_9

partially racemic end product **5,** whether obtained directly from the cis isomer **10a** or via epimerization at C-9 from the trans isomer **10b,** the levorotating R_2S_9 isomer apparently predominates. Thus the intermediate **10a** must have contained more R_2S_9 isomer. Similar enantiomer ratios must also have been present in the addition products **8a** and **8b** after separation, because alterations in these ratios after that stage are not possible by epimerization but only via racemization, which is very improbable under the experimental conditions used.

On the other hand, the initially formed addition products from the achiral starting compound **6** and optically pure (*R*)-cysteine can only have been the diastereomers (R_2R_9)-**8** and (S_2R_9)-**8** since benzyloxycarbonylamino acids are known for their low tendency toward racemization.[14] Apparently the addition step proceeds rather stereoselectively, leading mainly to the R_2R_9 isomer, which undergoes epimerization at C_9 before it is separated from the minor product S_2R_9. The occurrence of epimerization at C_9 in the addition product **8** under the experimental conditions of the addition reaction could be demonstrated by refluxing a pure sample of **8b** in benzene. Chromatography of the solution revealed that a new spot, having an R_f value equal to that of **8a,** had appeared. Treatment of **8b** with sodium deuteroxide in deuterated methanol gave complete ex-

change of one proton (mass spectrum). The NMR spectrum showed that the C_9 proton had been exchanged and that the isomers **8a** and **8b** were present in the ratio 3:2. The relatively facile epimerization of **8** may be caused by the formation of a dehydroalanine derivative via β-elimination.[15] Thus it can be concluded that optically active product **5** results from a chiral component **7**, whose configuration inverts during the reaction.

Activity Tests. The racemic compound **5**, as well as the optically active residue with $[\alpha]D$ −156°, were found to be devoid of antiviral and antibacterial activity.

The activity of both fractions toward the reverse transcriptase[16] which is known to be involved in the integration of viral genomes into the host DNA was tested according to Verma et al.[17] At the concentration used (6.1×10^{-5} mol/l.) no inhibition was observed with either of the compounds (1 and 4 ml of each solution, containing 16 and 64 μg, respectively), whereas the reference compound, chetomin,[18] reduced the activity to about 85 and 20%, respectively (10^{-5} mol/l., using 7 and 28 μg, assumed mol wt 710). The same result was obtained when the endogenous reaction[19] of dissociated Rauscher leukemia virus was used for the activity test. The antibacterial activity was also tested.[20] No growth-inhibitory activity against *Bacillus subtilis, Sarcina lutea,* or *Pseudomonas solanacearum* was found. The compounds did not show antifungal activity in a test with *Candida utilis.*

These results support the supposition that in the natural products containing the epidithiodioxopiperazine moiety the disulfide bridge is essential for the biological activity and the three-dimensional structure might be of secondary importance.

Experimental Section

Infrared spectra were measured with a Perkin-Elmer spectrophotometer, Model 257. Proton magnetic resonance spectra were measured on a Varian Associates Model A-100 spectrometer. Chemical shifts are reported as δ values (parts per million) relative to tetramethylsilane as an internal standard; deuteriochloroform was used as solvent. Mass spectra were obtained with a double-focusing Varian Associates SMI-B mass spectrometer. CD spectra were measured with a Cary 60 using a 8.5×10^{-4} *M* solution (MeOH) in a 2-mm cell. Melting points were taken on a Kofler hot stage and are uncorrected. Thin layer chromatography (TLC) was carried out using Merck precoated silica gel F-254 plates, thickness 0.25 mm. Spots were visualized with a uv hand lamp, iodine vapor, a 0.1% solution of ninhydrin in methanol–1-butanol–2 *N* acetic acid (20:10:1 v/v) or according to Reindel and Hoppe.[21] Solvent systems used: A, 8% ethanol in toluene; B, hexane–2-butanol–acetic acid (3:1:1 v/v); C, 1-butanol–acetic acid–water (4:1:1 v/v). For column chromatography Sephadex LH-20 (Pharmacia) was used (up to 150 mg—column A, 2.4 × 90 cm, eluent 80% methanol, flow rate 18 ml/hr, 3.6-ml fractions; up to 2.0 g—column B, 3.4 × 167 cm, eluent 83% methanol, flow rate 52 ml/hr, 15 ml fractions). The eluent was monitored continuously by measuring the uv absorption at 254 nm with an LKB Uvicord 8300A apparatus. Fractions were collected with a remote-controlled LKB-Ultrarac fraction collector 7000-2.

Benzyloxycarbonyl-L-cysteine (7). This compound was prepared from *N,N'*-dibenzyloxycarbonylcystine[22] according to Wieland and Sarges.[10] The crystalline material (mp 61–63°, yield 98%) thus obtained showed only one spot on TLC (system B) which was sodium nitroprusside positive. By treatment of a sample of **7** with iodine in ethyl acetate, optically pure starting material was obtained quantitatively [$[\alpha]D$ −88° (AcOH); starting material −90.6°; lit.[22] −91.7°] indicating that no racemization had occurred during reduction.

2-Carbethoxy-3,3-dimethylindolino[2,1-*b*]-9-carbobenzoxyaminotetrahydrothiazone-8 (8a and 8b). A solution of **7** (25.9 g, 100 mmol) in 125 ml of refluxing, dry benzene was allowed to react with the indolenine ester **6** (1.30 g, 6 mmol) for 10 days in a simplified Soxhlet apparatus, filled with sodium sulfate as drying agent. The apparatus was filled with argon. After 10 days no further progress of the reaction could be detected on TLC (system A; two new spots with R_f values higher than and identical with that of **6**, respectively). After removal of the solvent under vacuum, ethyl acetate and water were added; the organic layer was washed with 5% $NaHCO_3$ solution, water, 1 *N* HCl solution, water until neutral, and finally brine.[23] After drying (Na_2SO_4), filtration, and removal of the solvent under vacuum, 7.7 g of a light-yellow oil was isolated which was subjected to column chromatography on Sephadex LH-20 in five aliquots, column B. After elution of **6**, two partially overlapping peaks were observed in the uv diagram with elution volumes of 1500 and 1610 ml. The compound with the smaller elution volume had the lower R_f value on TLC (system A) and was assigned structure **8a**; the other peak contained **8b**. Only those fractions were pooled which showed a single spot on TLC, so that rechromatography of the fractions in the overlapping region was necessary. Of **8a**, 1.22 g (2.47 mmol, 41.5%) was isolated as a chromatographically pure, colorless oil, which could not be brought to crystallization. The trans compound **8b** (1.470 g, 3.24 mmol, 54%) was obtained in a crystalline form, mp 140–141° (ethanol–hexane). Structures were assigned on the following basis.

Cis compound 8a: ir ($CHCl_3$) 3400 (NH), 2950, 1720 (br, ester and urethane), 1660 (amide), 1495, 1480, 1452, and 1390 cm^{-1}; NMR ($CDCl_3$) δ 8.24 (m, 1 H, C_7 H), 7.20 (m, 8 H, C_{4-6} H and C_6H_5), 6.10 (d, 1 H, NH, *J* (NH–C_9 H) = 5 Hz), 5.10 (s, 2 H, $C_6H_5CH_2$), 4.48 (six lines, 1 H, C_9 H, *J* (C_9 H–C_{10} H_A) = 12.5 Hz, *J* (C_9 H–C_{10} H_B) = 5 Hz, ABCX spectrum[24]), 4.08 (q, 2 H, CH_2CH_3, *J* = 7 Hz), 3.34 (four lines, 1 H, C_{10} H_A, *J* (C_{10} H_A–C_{10} H_B) = 14 Hz), 2.80 (four lines, 1 H, C_{10} H_B), 1.44 (s, 3 H, C_3 $C_\alpha H_3$), 1.32 (s, 3 H, C_3 $C_\beta H_3$), 1.10 (t, 3 H, CH_2CH_3); mass spectrum (70°) *m/e* 454 (M^+), 408 ($M^+ - C_2H_5OH$), 381 ($M^+ - CO_2C_2H_5$), 346 ($M^+ - C_6H_5CH_2O$), 274 ($M^+ - C_6H_5CH_2OCOOC_2H_5$) (base peak); $[\alpha]^{20}D$ −13.8° (MeOH).

Anal. Calcd for $C_{24}H_{26}N_2O_5S$: C, 63.42; H, 5.77; N, 6.16. Found: C, 63.42; H, 5.71; N, 6.13.

Trans compound 8b: ir ($CHCl_3$) identical with that for **8a**, except for the position of the amide carbonyl absorption at 1670 cm^{-1}; NMR ($CDCl_3$) δ 8.19 (m, 1 H, C_7 H), 7.22 (m, 8 H, C_{4-6} H and C_6H_5), 6.26 (d, 1 H, NH, *J* (NH–C_9 H) = 5 Hz), 5.12 (s, 2 H, $C_6H_5CH_2$), 4.50 (five lines, 1 H, C_9 H, *J* (C_9 H–C_{10} H_A) = 6 Hz, *J* (C_9 H–C_{10} H_B) = 11 Hz, ABCX spectrum), 4.22 (q, 2 H, CH_2CH_3, *J* = 7 Hz), 3.52 (four lines, 1 H, C_{10} H_A, *J* (C_{10} H_A–C_{10} H_B) = 11 Hz), 2.64 (three lines, 1 H, C_{10} H_B), 1.47 (s, 3 H, C_3 $C_\alpha H_3$), 1.31 (s, 3 H, C_3 $C_\beta H_3$), and 1.21 (t, 3 H, CH_2CH_3); mass spectrum (75°) identical with that for **8a**, except for the absence of *m/e* 408 ($M^+ - C_2H_5OH$); $[\alpha]^{20}D$ −19.2° (MeOH).

Anal. Calcd for $C_{24}H_{26}N_2O_5S$: C, 63.42; H, 5.77; N, 6.16. Found: C, 63.29; H, 5.74; N, 6.02.

(*S*$_2$*R*$_9$/*R*$_2$*S*$_9$)-2-Carbethoxy-3,3-dimethylindolino[2,1-*b*]-9-aminotetrahydrothiazone-8 Hydrobromide (9a). A solution of 1.05 g (2.31 mmol) of **8a** in 12 ml of a 40% solution of hydrobromic acid in acetic acid was stirred at room temperature for 60 min with exclusion of moisture. Solvent and excess reagent were removed in vacuo, after which the yellow residue was treated twice with dry ether, yielding 755 mg (1.89 mmol, 81%) of a crystalline material (mp 114–117°, methanol–ether) which was subjected to column chromatography on Sephadex LH-20, column B, to yield 648 mg (1.62 mmol, 70%) of a chromatographically pure (TLC, system C), ninhydrin-positive product: ir ($CHCl_3$) 3600 (sh) and 3420 (br, NH_3), 2960, 1730 (ester, sh), 1665 (amide), 1480, 1405, and 1205 cm^{-1}; NMR ($CDCl_3$) δ 8.74 (br s, 3 H, NH_3), 8.20 (m, 1 H, C_7 H), 7.04 (m, 3 H, C_{4-6} H), 4.73 (m, 1 H, C_{10} H_α), 4.15 (q, 2 H, CH_2CH_3), 3.62 (m, 2 H, C_9 H + C_{10} H_α), 1.36 (s, 3 H, C_3 $C_\alpha H_3$), 1.20 (s, 3 H, C_3 $C_\beta H_3$), 1.02 (t, 3 H, CH_2CH_3).

(*R*$_2$*R*$_9$/*S*$_2$*S*$_9$)-2-Carbethoxy-3,3-dimethylindolino[2,1-*b*]-9-aminotetrahydrothiazone-8 Hydrobromide (9b). A solution of 955 mg (2.11 mmol) of **8b** in 12 ml of a 40% solution of hydrobromic acid in acetic acid was treated and worked up as described for the preparation of **9a**, yielding 720 mg (1.80 mmol, 78%) of a crystalline (mp 134–135°, methanol–ether) material. After chromatography on Sephadex LH-20 (column B) 592 mg (1.48 mmol, 70%) of a ninhydrin-positive material was isolated, which showed only one spot on tlc (system C, R_f value identical with that of **9a**): ir ($CHCl_3$) 3600 (sh) and 3420 (br, NH_3), 1735 (ester, sh), 1675 (amide), 1490, 1415, and 1240 cm^{-1}; NMR ($CDCl_3$) δ 8.16 (br s, 4 H, NH_3 and C_7 H), 7.05 (m, 3 H, C_{4-6} H), 4.68 (m, 1 H, C_{10} H_α), 4.15 (q, 2 H, CH_2CH_3), 3.70 (m, 2 H, C_9 H + C_{10} H_α), 1.39 (s, 3 H, C_3 $C_\alpha H_3$), 1.29 (s, 3 H, C_3 $C_\beta H_3$), 1.09 (t, 3 H, CH_2 CH_3).

(*S*$_2$*R*$_9$/*R*$_2$*S*$_9$)-9,9a-Dihydro-2,9a-epimethylenethio-3,10-diketo-9,9-dimethylpiperazino[4,3-*a*]indole (5). Deprotonation of **9a** could be achieved by ion-exchange chromatography (Amberlite IRA-400) or by adjusting the pH to 9.5 with sodium hydroxide.

The latter method is the preferred one, as considerable losses of material occurred owing to irreversible binding to the ion-exchange resin.

From 9a. The pH of a stirred solution of **9a** (630 mg, 1.57 mmol) in 20 ml of 50% methanol was adjusted to 9.5 with a 0.5 *N* NaOH solution. This solution was evaporated under vacuum to a final volume of about 5 ml (water bath temperature kept below 40°) and subjected to column chromatography on Sephadex LH-20 (column B). Fractions in the peaks with elution volumes of 1500 ml (fraction 1) and 1900 ml (fraction 2) were pooled separately, to yield 330 mg (1.04 mmol) of **10a** and 100 mg (0.365 mmol) of ring-closed product **5**. A solution of fraction 1 in 10 ml of ethanol was refluxed for 1 hr, and the resulting solution, combined with fraction 2, was chromatographed on Sephadex LH-20, column B. Fractions in the peak with an elution volume of 1900 ml were pooled, yielding 245 mg (0.9 mmol, 57%) of a compound which on TLC (systems A or B) showed only one ninhydrin-negative, Reindal–Hoppe positive spot, $[\alpha]^{20}D$ −10° (MeOH). Recrystallization yielded crystalline, racemic crystals, mp 212–213° (methanol), and an amorphous residue, which was optically active, $[\alpha]^{20}D$ −63° (MeOH). Both fractions were chromatographically homogeneous.

Uv λ_{max} (MeOH) 286, 277, and 242 nm (ϵ 2.92, 3.60, and 9.5 × 10^3, respectively); ir ($CHCl_3$) 3380 (NH), 2960, 1705 (br, 2 amide), 1600, 1480, 1455, 1390, 1290, 1140, and 1105 cm^{-1}; NMR ($CDCl_3$) δ 7.95 (m, 2 H, disappearance of 1 H after addition of D_2O, C_7 H and NH), 7.25 (m, 3 H, C_{4-6} H), 4.56 [br s, 1 H, C_9 H; after addition of D_2O only slight sharpening up, indicating that J (C_9 H–NH) must be negligibly small; irradiation of signals at 3.12 and 3.54 revealed the presence of four overlapping lines [J (C_9 H–C_{10} H_A) = 3.5, J (C_9 H–C_{10} H_B) = 1 Hz], 3.54 [four lines, 1 H, C_{10} H_A, J (H_A–H_B) = 11 Hz], 3.12 (four lines, 1 H, C_{10} H_B), 1.68 (s, 3 H, C_3 $C_\alpha H_3$), and 1.54 (s, 3 H, C_3 $C_\beta H_3$); mass spectrum (100°) *m/e* 274 (M^+, base peak), 231 (M^+ − CONH), 228 (M^+ − SCH_2), 216 (M^+ − CONH, CH_3), and 213 (M^+ − SCH_2, CH_3).

Anal. Calcd for $C_{14}H_{14}N_2O_2S$: C, 61.29; H, 5.14; N, 10.21. Found: C, 61.59; H, 5.17; N, 10.25.

From 9b. 9b (580 mg, 1.28 mmol) was treated as described above. Column chromatography on Sephadex LH-20, column B, yielded 441 mg (1.26 mmol) of the trans amine **10b**, after pooling of the fractions in the peak having an elution volume of 1500 ml. A solution of this material in 10 ml of ethanol was refluxed for 20 hr, and the resulting solution was chromatographed on Sephadex LH-20, column B. Fractions in the peak with an elution volume of 1900 ml were pooled, yielding 190 mg (0.695 mmol, 55%) of a compound which had spectral properties identical with those described above, except for $[\alpha]^{20}D$ −52° (MeOH). Recrystallization of this material yielded a racemic crystalline fraction (mp 213–214°) and an optically active amorphous residue, $[\alpha]^{20}D$ −156° (MeOH). Both fractions were chromatographically homogeneous. A CD dispersion curve of the optically active fraction showed a positive and a negative Cotton effect at 235 and 263 nm, respectively (Figure 1).

Anal. Calcd for $C_{14}H_{14}N_2O_2S$: C, 61.29; H, 5.14; N, 10.21. Found: C, 61.48; H, 5.12; N, 10.27.

Ring Closure of 10b to C-9 Deuterated 5. To a solution of 49 mg (1.54×10^{-4} mol) of **10b** in 2 ml of CH_3OD was added 0.5 ml of D_2O. The resulting solution was evaporated to dryness. This procedure was repeated, after which a solution of the residue in 5 ml of CH_3OD was refluxed for 5 days. After evaporation the reaction mixture was subjected to column chromatography on Sephadex LH-20 (column A), yielding in addition to the deuterated starting material (5 mg, v_e 250 ml, M^+ *m/e* 321) and the corresponding methyl ester (4 mg, v_e 360 ml, M^+ *m/e* 307), 25 mg (59%, v_e 414 ml) of ring closed, C_9 deuterated material **5**, NMR ($CDCl_3$) identical with that described above, except for the absence of the four lines at δ 4.56 (C_9 D) and the presence of a simplified AB pattern at δ 3.53 and 3.11 (C_{10} H_A and C_{10} H_B, J (H_A–H_B) = 11 Hz), mass spectrum (110°) *m/e* 275 (M_D^+, base peak), 232 (M_D^+ − CONH), 229, 217, 214.

Deuterium Exchange in 8b and Its Epimerization. To an ice-cooled, stirred solution of 3 mmol of sodium deuterioxide in 2 ml of deuterated methanol [prepared by addition of 162 mg (3 mmol) of freshly prepared sodium methoxide to 0.5 ml of deuterium oxide in 1.5 ml of deuterated methanol] was added 90 mg (0.198 mmol) of **8b**. The reaction mixture was kept at 0° for 30 min, after which the reaction was stopped by the addition of acetic acid. The mixture was extracted with ethyl acetate subsequent to the addition of water; the organic layer was washed with 5% $NaHCO_3$ solution, water, 1 *N* HCl solution until neutral, and finally with saturated brine to yield 83 mg of an oil, which on TLC (system A) showed a spot on the origin, besides the two spots of the diastereomers **8a** and **8b**. Purification was achieved by column chromatography on Sephadex LH-20 (column A) to yield 42 mg (0.093 mmol, 47%) of a mixture of C_9-deuterated **8a** and **8b** in a ratio of 3:2 as an NMR spectrum showed. A mass spectrum indicated that the exchange was complete. NMR ($CDCl_3$), essentials only: δ 6.25 (s, 0.4 H, NH-**8b**), 5.97 (s, 0.6 H, NH-**8a**), 3.54 [two lines, 0.4 H, C_{10} H_A of **8b**, J (H_A–H_B) = 11 Hz], 3.36 [two lines, 0.6 H, C_{10} H_A in **8a**, J (H_A–H_B) = 14 Hz], 2.83 (two lines, 0.6 H, C_{10} H_B in **8a**), and 2.67 (two lines, 0.4 H, C_{10} H_B in **8b**); mass spectrum (120°) *m/e* 455 (M^+), 409 (M^+ − C_2H_5OH, characteristic for the cis compound), 382 (M − $CO_2C_2H_5$).

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Registry No.—(S_2R_9/R_2S_9)-**5**, 55400-05-0; (R_2S_9)-**5**, 55281-65-7; **6**, 41296-09-7; **7**, 53907-29-2; **8a**, 55281-66-8; **8b**, 55281-67-9; **9a**, 55281-68-0; **9b**, 55281-69-1; **10a**, 55281-70-4; **10b**, 55281-71-5.

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(24) Chemical shifts and coupling constants were calculated according to E. D. Becker, "High-Resolution NMR", Academic Press, New York, N.Y., 1970, p 157.

Synthesis of (−)-Pinidine and a Putative Biosynthetic Precursor: 5,9-Dioxodecanoic Acid

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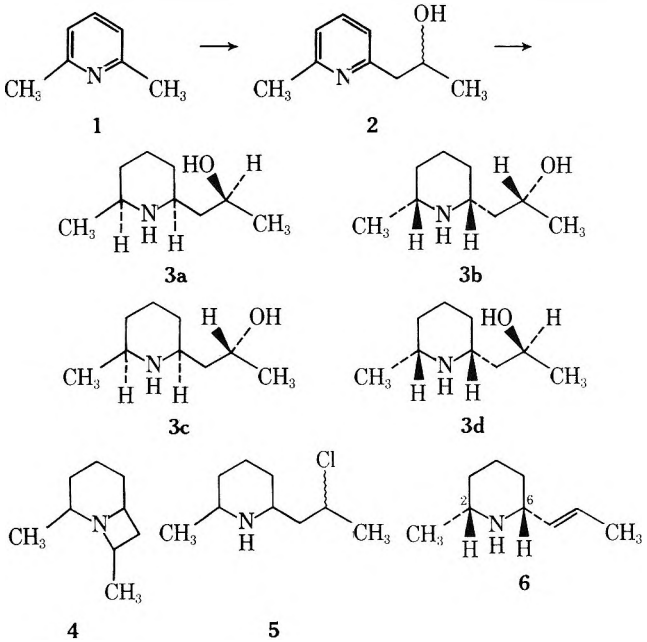
2-Methyl-6-(2-hydroxypropyl)pyridine (**2**) was obtained by reaction of the monolithium salt of 2,6-lutidine with acetaldehyde. Hydrogenation of the hydrochloride of **2** yielded *cis*-2-methyl-6-(2-hydroxypropyl)piperidine as a pair of diastereomers. Heating this alcohol with potassium bisulfate afforded (±)-pinidine, which was resolved with optically active 6,6′-dinitrodiphenic acid. [10-^{14}C]-5,9-Dioxodecanoic acid was prepared and fed to *Pinus jeffreyi* plants, as a potential precursor of pinidine. However, there was no significant incorporation of activity into the alkaloid, indicating that this compound is probably not an intermediate between acetate and pinidine.

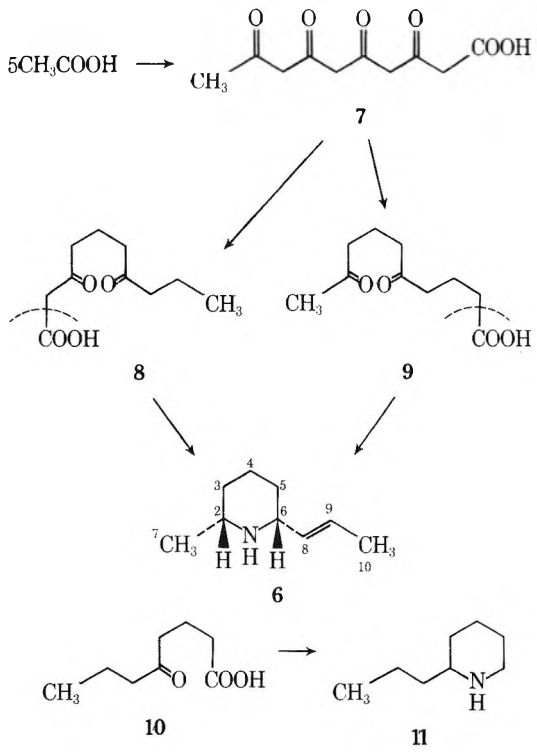
The alkaloid pinidine was isolated from various species of *Pinus* by Tallent et al.,[2] who established its structure as 2-methyl-6-(2-propenyl)piperidine.[3] Hill and coworkers deduced[4] the absolute configuration as illustrated in formula **6**: (*R*)-2-methyl-(*R*)-6-[(*E*)-2-propenyl]piperidine. This article describes the first synthesis of this simple piperidine alkaloid.

Reaction of the monolithium salt of 2,6-lutidine (**1**) with acetaldehyde afforded (*RS*)-2-methyl-6-(2-hydroxypropyl)pyridine (**2**).[5] Hydrogenation of the hydrochloride of **2** in ethanol in the presence of Adams catalyst yielded a pair of diastereomers. It has been shown that the hydrogenation of 2,6-dialkylpyridines leads almost exclusively to *cis*-dialkylpiperidines.[6] The pair of diastereomers can therefore be depicted by the structures **3a,b** and **3c,d.** Attempts to separate these isomers by TLC or GLC were unsuccessful. One pair of enantiomers, mp 80–81°, separated from ethyl acetate.[7] The *O*-acetyl derivatives of the mixture of alcohols **3** could be separated by GLC, the more abundant pair of enantiomers (58%) being identical with the *O*-acetyl derivative of the alcohol, mp 80–81°. The relative stereochemistry of the *O*-acetates could not be assigned by an examination of their NMR or ir spectra. Initial attempts to obtain pinidine from the alcohols **3** were unsuccessful. On heating the *O,N*-ditosylate of the alcohol, mp 80–81°, in dimethyl sulfoxide at 100° an oil was obtained which is considered to be 2,8-dimethyl-1-azabicyclo[4.2.0]octane (**4**).[8] Treatment of this oil with concentrated hydrochloric acid resulted in opening of the azetidine ring, affording 2-methyl-6-(2-chloropropyl)piperidine (**5**), identical with material obtained by the action of thionyl chloride on the alcohol, mp 80–81°. Heating the chloro compound **5** with potassium hydroxide in triethylene glycol failed to yield any pinidine. Only starting material was recovered when the mixture of alcohols **3** was heated with 85% phosphoric acid, or with sulfuric acid (50 or 98%). No dehydration was achieved when the hydrochloride of **3** was heated with hexamethylphosphoric triamide.[9] Smooth dehydration of the alcohols **3** was finally accomplished by heating their hydrochlorides with potassium bisulfate at 170°. The resultant (±)-pinidine was resolved with optically active 6,6′-dinitrodiphenic acid.[10] (−)-Pinidine (+)-6,6′-dinitrodiphenate separated from a mixture of methanol and ethyl acetate. The (−)-pinidine recovered from this salt as its hydrochloride was identical (mixture melting point, crystalline form, optical rotation) with the natural alkaloid isolated from *Pinus jeffreyi.* (+)-Pinidine crystallized from ethyl acetate as a salt with (−)-6,6′-dinitrodiphenic acid.

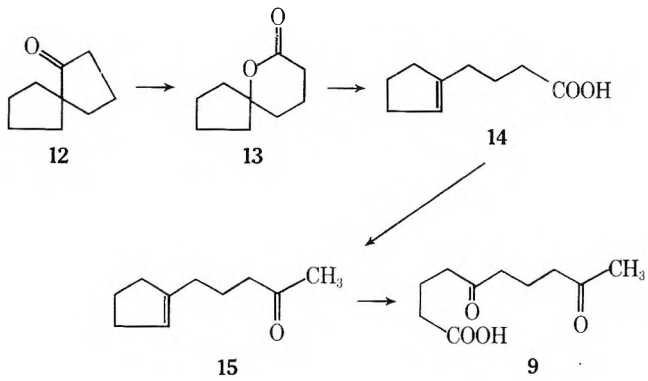


We have previously shown[11] that the administration of sodium [1-^{14}C]acetate to *Pinus jeffreyi* plants yielded radioactive pinidine which was labeled on the alternate carbons: C-2, -4, -6, and -9. This result is consistent with the hypothesis that the alkaloid is derived from the ten-carbon poly-β-keto acid **7,** with loss of the carboxyl group. Two alternate ways in which the acid **7** can be utilized for the formation of pinidine are illustrated in Scheme I. It is suggested that reduction affords either 3,7-dioxodecanoic acid (**8**) or 5,9-dioxodecanoic acid (**9**). Reaction with a nitrogen source, followed by reduction and dehydrogenation, would then afford pinidine.[12] Support for such intermediates as **8** and **9** is provided by the discovery that 5-oxooctanoic acid (**10**) is an excellent precursor of coniine (**11**) in the hemlock plant.[13] We have thus prepared [10-^{14}C]-5,9-dioxodecanoic acid by the method illustrated in Scheme II, and tested it as a precursor of pinidine. Spiro[4.4]-1-nonanone (**12**)[14] was subjected to a Baeyer–Villiger oxidation with *m*-chloroperbenzoic acid, affording the lactone **13,** which on hydrolysis and dehydration yielded 4-(1-cyclopentenyl)butanoic acid (**14**). The lithium salt of this acid was formed by reaction with 1 equiv of methyllithium. A second equivalent of [^{14}C]methyllithium then afforded [1-^{14}C]-5-(1-cyclopentenyl)-2-pentanone (**15**).[15] Oxidation of **15** with a mixture of sodium metaperiodate and potassium permanganate yielded [10-^{14}C]-5,9-dioxodecanoic acid (**9**).[16] This labeled acid was fed to 3-year-old *Pinus jeffreyi* plants by the wick method in two separate experiments (for 5 and 10 weeks). However, the resultant pinidine had very low activity, representing incorporations of only 0.0003 and 0.004%, respectively. We thus conclude that 5,9-dioxodecanoic acid is not

Scheme I



Scheme II



an intermediate between acetate and pinidine. Work is in progress to test the diketo acid 8, and its decarboxylation product, nona-2,6-dione, as precursors of pinidine.

Experimental Section[17]

(*RS*)-2-Methyl-6-(2-hydroxypropyl)pyridine (2). Butyllithium (0.178 mol) in hexane (90 ml) was added slowly to a solution of 2,6-lutidine (19 g, 0.178 mol) in THF (250 ml) maintained at −35°. Acetaldehyde (20 g, 0.45 mol) dissolved in THF (50 ml) was added slowly keeping at the same temperature. The reaction mixture was then allowed to warm to 0°, and water (100 ml) was added. Evaporation under reduced pressure removed the THF and the residual aqueous solution was extracted with ether. The residue obtained on evaporation of the dried ($MgSO_4$) extract was distilled (bp 65–67°, 0.5 mm) yielding 2 as a pale yellow oil (16.5 g, 61%). The hydrochloride of 2 was obtained by passing HCl gas into a solution of 2 in a mixture of ether and ethanol. Crystallization from a mixture of ethanol and ethyl acetate afforded colorless needles, mp 126–127°.

Anal. Calcd for $C_9H_{14}NOCl$: C, 57.60; H, 7.52; N, 7.46; Cl, 18.89. Found: C, 57.44; H, 7.34; N, 7.36; Cl, 19.03.

Hydrogenation of 2 to Yield a Mixture of Diastereomers of *cis*-2-Methyl-6-(2-hydroxypropyl)piperidine (3a–d). (*RS*)-2-Methyl-6-(2-hydroxypropyl)pyridine hydrochloride (4.48 g) in ethanol (200 ml) was hydrogenated in the presence of Adams catalyst (0.2 g) at 3 atm pressure for 6 hr. The filtered reaction mixture on evaporation yielded a white solid (4.56 g, 98%), mp 150–165°. This mixture of hydrochlorides was dissolved in water, made alkaline with potassium hydroxide, and extracted with ether. The dried ($MgSO_4$) extract on evaporation afforded a colorless oil (3.29 g) which was dissolved in ethyl acetate (50 ml) and cooled to −20°. Colorless prisms separated (0.36 g, 11%), mp 80–81°.

Anal. Calcd for $C_9H_{19}NO$: C, 68.74; H, 12.18; N, 8.91. Found: C, 68.48; H, 11.19; N, 8.84.

This alcohol afforded a hydrochloride, colorless plates, mp 193–194°.

Anal. Calcd for $C_9H_{20}NOCl$: C, 55.80; H, 10.41; N, 7.23. Found: C, 55.94; H, 10.73; N, 7.14.

***cis*-2-Methyl-6-(2-acetoxypropyl)piperidine.** The hydrochloride of the alcohol **3**, mp 80–81° (100 mg), was stirred with acetyl chloride (5 ml) for 4 hr at room temperature. Excess acetyl chloride was removed in vacuo, and the residue was dissolved in water, made basic with potassium carbonate, and extracted with ether. HCl gas was passed into the dried ($MgSO_4$) extract, affording the hydrochloride of 2-methyl-6-(2-acetoxypropyl)piperidine, mp 238–239° after crystallization from chloroform–ethyl acetate. It had an R_f of 0.30 by tlc on silica gel F-254 (Merck) developing with chloroform–methanol–concentrated NH_3 (85:15:1).

Anal. Calcd for $C_{11}H_{22}NO_2Cl$: C, 56.04; H, 9.41; N, 5.94. Found: C, 55.84; H, 9.21; N, 5.67.

The mixture of the hydrochlorides of the diastereomeric alcohols **3** was similarly acetylated and afforded a mixture which could be separated by TLC in the previously described system affording two compounds having R_f values of 0.30 and 0.36. These two compounds were also obtained by GLC (10% Carbowax 20M on 70:80 Chromosorb W at 136°). The compound with a shorter retention time (42%) afforded a hydrochloride, mp 225–226°.

Anal. Calcd for $C_{11}H_{22}NO_2Cl$: C, 56.04; H, 9.41; N, 5.94. Found: C, 56.05; H, 9.27; N, 5.85.

The more abundant (58%) pair of enantiomorphs yielded a hydrochloride, mp 238–239°, identical (ir, mixture melting point) with the hydrochloride of the acetyl derivative of the alcohol **3**, mp 80–81°.

***cis*-2-Methyl-6-(2-hydroxypropyl)piperidine *O,N*-Ditosylate.** The alcohol **3**, mp 80–81° (380 mg), was added to a rapidly stirred mixture of ether (10 ml) and water (5 ml) containing *p*-toluenesulfonyl chloride (1.93 g) and sodium hydroxide (0.5 g). After 5 hr the mixture was filtered, and the residue was dissolved in chloroform, washed with dilute sodium hydroxide, and dried over potassium carbonate. The residue obtained on evaporation was crystallized from ethanol–ether, affording colorless plates of the *O,N*-ditosylate (570 mg, 49%), mp 157–158°.

Anal. Calcd for $C_{23}H_{31}NO_5S_2$: C, 59.33; H, 6.71; N, 3.01. Found: C, 59.08; H, 7.00; N, 3.03.

Attempted Detosylation of *cis*-2-Methyl-6-(2-hydroxypropyl)piperidine *O,N*-Ditosylate. *cis*-2-Methyl-6-(2-chloropropyl)piperidine (5). The *O,N*-ditosylate (139 mg) dissolved in dimethyl sulfoxide (8 ml) was heated for 5 hr at 100°. Water (30 ml) was added to the mixture, which was then extracted with ether. Evaporation of the dried ($MgSO_4$) extract afforded an oil (23 mg), ir (neat) 1442 cm^{-1} (azetidine CH_2[19]), which was dissolved in ether and treated with HCl gas. The hydrochloride of **5** separated, mp 191–192°.

Anal. Calcd for $C_9H_{19}NCl_2$: C, 50.95; H, 9.03; N, 6.60. Found: C, 50.70; H, 9.06; N, 6.70.

This same compound was obtained by stirring the alcohol **3**, mp 80–81°, with thionyl chloride at room temperature for 18 hr.

(±)-Pinidine Hydrochloride. The hydrochlorides of the mixture of alcohols **3** (15 g) were ground with freshly fused potassium bisulfate (45 g) and heated in a round-bottomed flask for 75 min at 175°. The cooled reaction mixture was dissolved in water (300 ml), made basic with sodium hydroxide, and extracted with ether (4 × 100 ml). The residue obtained on evaporation of the dried ($MgSO_4$) extract was distilled, affording (±)-pinidine as a colorless oil (4.9 g, 45%), bp 175–177° (762 mm) [bp reported[2] for (−)-pinidine, 176–177° (751 mm)]. On passing HCl gas into an ether solution of the (±)-pinidine, its hydrochloride separated as colorless prisms: mp 192–193°; ir (KBr) 2524, 2400 (NH_2^+), 1578 (C=C), 966 cm^{-1} (C=CH trans); NMR ($CDCl_3$) δ 1.18–2.16 (12 H, m), 2.84–3.80 (2 H, m, $CHNH_2^+CH$), 5.69–6.26 (2 H, m, C=CH), 8.80–10.00 (2 H, NH_2^+); mass spectrum *m/e* 139 (M^+ − HCl).

Anal. Calcd for $C_9H_{18}NCl$: C, 61.52; H, 10.32; N, 7.97. Found: C, 61.58; H, 10.40; N, 7.93.

All spectra were identical with those of natural (−)-pinidine hydrochloride isolated from *Pinus jeffreyi*.[11] Hydrogenation of the

(±)-pinidine hydrochloride (0.3 g) in ethanol (45 ml) in the presence of Adams catalyst (0.15 g) for 4 hr afforded (±)-dihydropinidine hydrochloride (0.27 g), mp 218–220° (lit.[3] mp 219–220°), identical with an authentic specimen.

Resolution to Afford (−)-Pinidine (6) and (+)-Pinidine. (±)-Pinidine (2.92 g, 21 mmol) dissolved in methanol (50 ml) was mixed with a solution of (−)-6,6′-dinitrodiphenic acid[10] (3.49 g, 10.5 mmol) in methanol (50 ml), and the solution was allowed to evaporate slowly for 1 week. Ethyl acetate (50 ml) was then added, and after 2 more weeks the separated solid was removed. Crystallization of this solid from methanol afforded the (−)-6,6′-dinitrodiphenate salt of (+)-pinidine (1.32 g), mp 250–260° dec.

Anal. Calcd for $C_9H_{17}N{\cdot}C_{14}H_8N_2O_8$: C, 58.59; H, 5.34; N, 8.91. Found: C, 58.62; H, 5.52; N, 8.46.

This salt (1.3 g) was shaken with 10% HCl (200 ml) and ether (200 ml). The acid layer was made basic with potassium hydroxide and extracted with ether. HCl gas was passed into the dried ($MgSO_4$) extract, affording (+)-pinidine hydrochloride which was obtained as fine long needles (quite different from the racemic salt) from ethanol–ether (0.34 g), mp 243–244° (mixture melting point with natural pinidine 198–202°), $[\alpha]^{23}D$ (absolute EtOH, *c* 6.0) +10.2°.

(−)-Pinidine hydrochloride, mp 242–243°, $[\alpha]^{23}D$ (absolute EtOH, *c* 5.3) −9.5° (lit.[2] −11.1°), was similarly obtained from the racemic pinidine utilizing (+)-6,6′-dinitrodiphenic acid as the resolving agent.

4-(1-Cyclopentenyl)butanoic Acid (14). Spiro[4.4]-1-nonanone[13] [bp 75–79° (8 mm)] (15 g) and *m*-chloroperbenzoic acid (23.1 g, 85%) were dissolved in 1,2-dichloroethane (150 ml) and the mixture was refluxed for 6 hr. The reaction mixture was allowed to cool overnight and the separated *m*-chlorobenzoic acid was filtered off. The filtrate was extracted with 5% aqueous sodium bicarbonate. The residue obtained on evaporation of the dichloroethane was refluxed with 25% sodium hydroxide (150 ml) for 3 hr. This solution was extracted with chloroform and then acidified with concentrated hydrochloric acid. This solution was then extracted with chloroform (5 × 50 ml), dried ($MgSO_4$), and evaporated. The residue was refluxed with 20% hydrochloric acid (45 ml) for 3 hr, cooled, and extracted with chloroform. The liquid obtained on evaporation of the dried ($MgSO_4$) extract was distilled (bp 94–98°, 0.5 mm), affording 4-(1-cyclopentenyl)butanoic acid (13.6 g, 81%). This acid yielded an amide, mp 94–95° (lit.[20] mp 93°). Oxidation with potassium permanganate yielded 5-oxo-1,9-nonanedioic acid, mp 107–108° (lit.[20] mp 109°).

5-(1-Cyclopentenyl)-2-pentanone (15). In a nitrogen atmosphere a solution of methyllithium in ether (0.3 mol in 150 ml) was added slowly to a solution of 4-(1-cyclopentenyl)butanoic acid (19.2 g, 0.124 mol) in ether (200 ml) at room temperature. The mixture was then refluxed for 20 min. Water (100 ml) was then added to the cooled reaction mixture. The ether layer was dried ($MgSO_4$), evaporated, and distilled (bp 54–56°, 0.5 mm). Dry column chromatography on Woehm alumina (activity III), eluting with benzene, afforded the ketone **15** as a colorless oil (7.6 g, 40%): ir (neat) 1723 (C=O), 1655 cm^{-1} (C=C). This ketone afforded a 2,4-dinitrophenylhydrazone, mp 88–89° (lit.[15] mp 87°).

Anal. Calcd for $C_{16}H_{26}N_4O_4$: C, 57.82. H, 6.07; N, 16.86. Found: C, 58.17; H, 6.24; N, 17.12.

5,9-Dioxodecanoic Acid (9). The ketone **15** (0.5 g) was added to stirred solution of sodium metaperiodate (2.5 g), potassium permanganate (92 mg), and *tert*-butyl alcohol (75 ml) in water (200 ml). The solution was adjusted to pH 8 by the addition of potassium carbonate, stirred for 17 hr, and then acidified with concentrated hydrochloric acid. Addition of sodium metabisulfite resulted in the formation of a clear solution which was made basic by the addition of sodium bicarbonate. The *tert*-butyl alcohol was removed by evaporation under reduced pressure. The residual aqueous solution was acidified (HCl) and extracted continuously with ether for 12 hr. The residue obtained on evaporation of the dried (Na_2SO_4) extract was crystallized from benzene–petroleum ether to yield small, white prisms of 5,9-dioxodecanoic acid (0.28 g, 43%): mp 77–78° (lit.[16] mp 78–79°), R_f 0.52 by TLC on silica gel F-254, developing with ethyl acetate; ir (KBr) 1725, 1712, 1696 cm^{-1} (C=O); uv (95% EtOH) λ_{max} 274 nm (ϵ 64); mass spectrum *m/e* 201 ($M^+ + 1$), 200 (M^+), 182 ($M^+ - H_2O$).

Anal. Calcd for $C_{10}H_{16}O_4$: C, 59.98; H, 8.05. Found: C, 60.02; H, 7.91.

Its methyl ester, colorless plates, mp 39–40°, was obtained by stirring in methanol with 2,2-dimethoxypropane and a trace of HCl.

Anal. Calcd for $C_{11}H_{18}O_4$: C, 61.66; H, 8.47. Found: C, 61.89; H, 8.77.

[10-^{14}C]-5,9-Dioxodecanoic Acid. [^{14}C]Methyl iodide (0.43 g, 3 mmol, nominal activity 1 mCi, Amersham-Searle) in ether was added to lithium wire (87 mg, 12.4 mmol) suspended in ether (30 ml) under argon. After stirring for 35 min the mixture was added to a slurry of lithium 4-(1-cyclopentenyl)butanoate in ether [made by the addition of 4.0 mmol of methyllithium to 0.54 g (3.5 mmol) of **14** in 50 ml of ether]. The resultant ketone **15** was isolated as described before and oxidized with periodate–permanganate to yield [10-^{14}C]-5,9-dioxodecanoic acid (135 mg, 3.92×10^8 dpm/mmol).

Administration of [10-^{14}C]-5,9-Decanoic Acid to *Pinus jeffreyi* and Isolation of the Pinidine. In our previous feeding experiments with [1-^{14}C]acetate[11] optimum incorporations were obtained by feeding for a prolonged time in July and August. Similar conditions were used in the present work. [10-^{14}C]-5,9-Dioxodecanoic acid (76 mg, 1.49×10^8 dpm) dissolved in water was fed by the wick method to *Pinus jeffreyi* plants (3 year old) growing in soil in a greenhouse. The green needles and associated small twigs (fresh wt 903 g) were harvested 10 weeks later and extracted as previously described,[11] affording pinidine hydrochloride (485 mg), 12 dpm/mg. Another feed with 56 mg of the labeled acid was carried in May and June (for 5 weeks) and yielded pinidine hydrochloride (60 mg), 5 dpm/mg.

Registry No.—**1**, 108-48-5; **2**, 55267-89-5; **2** HCl, 55267-90-8; **3**, 55267-91-9; **3** HCl, 55267-92-0; **3** acetyl derivative HCl, 55267-93-1; **3** *O,N*-ditosylate, 55267-94-2; **3a,b**, 55331-42-5; **3a,b** HCl, 55399-20-7; **3a,b** acetyl derivative HCl, 55331-43-6; **3c,d**, 55331-44-7; **3c,d** HCl, 55399-21-8; **3c,d** acetyl derivative HCl, 55331-45-8; **5** HCl, 55267-95-3; **6** HCl, 55399-22-9; (±)-**6**, 55399-23-0; (±)-**6** HCl, 55448-41-4; (±)-**6** (−)-6,6′-dinitrodiphenate salt, 55448-43-6; (+)-**6** HCl, 55399-24-1; **9**, 34862-10-7; **9** Me ester, 55267-96-4; **12**, 14727-58-3; **14**, 20126-98-1; **15**, 55267-97-5; butyllithium, 109-72-8; acetaldehyde, 75-07-0; acetyl chloride, 75-36-5; *p*-toluenesulfonyl chloride, 98-59-9; (−)-6,6′-dinitrodiphenic acid, 50573-79-0; (+)-6,6′-dinitrodiphenic acid, 50573-78-9; *m*-chloroperbenzoic acid, 937-14-4; [10-^{14}C]-5,9-dioxodecanoic acid, 55267-98-6; [^{14}C]methyl iodide, 16170-82-4.

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A Biogenetic-Type Synthesis of the Cyclohexyl Constituents of the Boll Weevil Pheromone[1]

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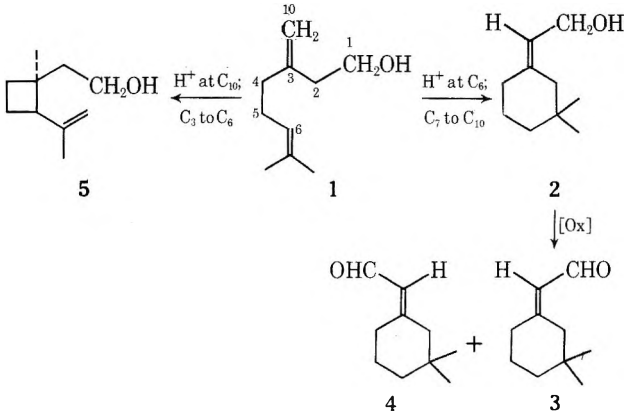
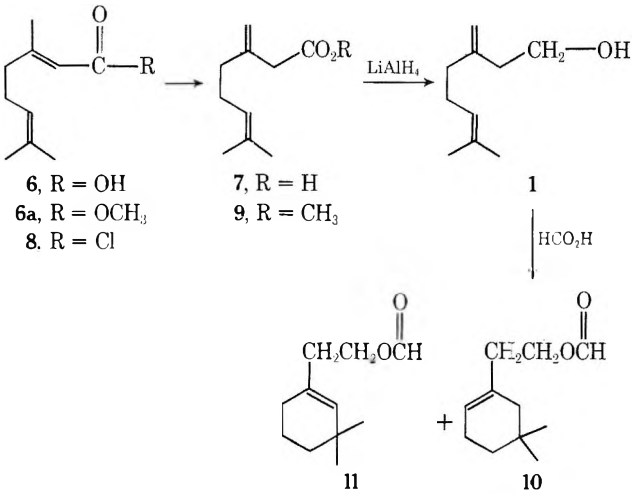
Treatment of the acid chloride of geranic acid (**6**) with triethylamine and methanol affords methyl γ-geranate (**9**) contaminated by ca. 10% of methyl geranate. Acid-catalyzed cyclization of methyl γ-geranate affords, in high yield, a mixture composed primarily of methyl 3,3-dimethylcyclohexenylacetates (**12** and **13**). The endocyclic unsaturated isomers **12** and **13** were converted to the desired conjugated, exocyclic isomers **15** and **16** by addition of hydrogen bromide followed by dehydrobromination with triethylamine. Lithium aluminum hydride reduction of **15** and **16** gave (*Z*)- and (*E*)-3,3-dimethyl-$\Delta^{1,8}$-cyclohexaneethanol (**2** and **2a**), which, in turn, were converted into the corresponding aldehydes by oxidation with manganese dioxide.

7-Methyl-3-methylene-6-octen-1-ol (**1**), henceforth referred to as γ-geraniol, has been postulated as the biosynthetic precursor for the four components, **2, 3, 4,** and **5,** of the boll weevil sex pheromone.[2,3,4] We have examined the acid-catalyzed cyclization of γ-geraniol and its derivatives and wish to report procedures which afford alcohol **2** and aldehydes **3** and **4** from readily available starting materials such as citral or geranic acid (**6**).[5]



5 1 2 4 3

γ-Geraniol (**1**)[7] is not commercially available, and γ-geranic acid (**7**) was not known prior to this work. These compounds are readily prepared from geranic acid (**6**) using a procedure to deconjugate a double bond suggested by Iwakura.[8] The acid chloride **8,** prepared from the sodium salt of geranic acid (**6**),[9,10] was treated with 1 equiv of triethylamine and methanol in benzene to give methyl γ-geranate (**9**),[11] contaminated by ca. 10% of methyl geranate (**6a**), in up to 83% isolated yield.[12] Essentially pure **9** can be obtained by distillation using a spinning band column. Lithium aluminum hydride reduction of **9** affords γ-geraniol (**1**).



6, R = OH
6a, R = OCH3
8. R = Cl

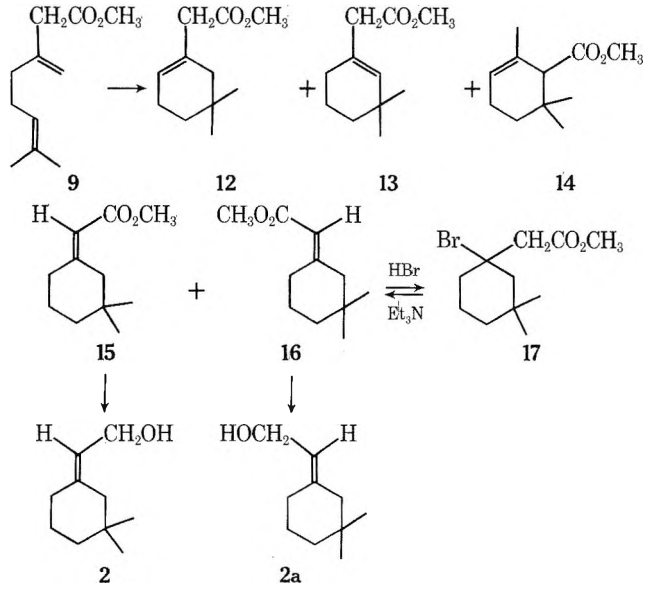
7, R = H
9, R = CH3

1

11 10

Formic acid catalyzed cyclization of **1** gave the more thermodynamically stable endocyclic isomers **10** and **11,** and only a trace of the formates of (*Z*)-**2** and (*E*)-**2a.** Lacking a convenient handle to effect double bond isomerization to the desired alcohols **2** and **2a,** we turned our attention to the cyclization of ester **9.**

Heating ester **9** with polyphosphoric acid gave, in 90% yield, a mixture of cyclized esters **12, 13, 14, 15,** and **16.**[13] In order to shift the double bond into the less stable conjugated position,[14] the ester mixture was treated with hydrogen bromide and the resulting bromide **17** was then dehydrobrominated with triethylamine to afford a mixture containing 80% of the exocyclic isomers **15** and **16.** If desired, the exocyclic isomers can be partially separated at this stage by distillation using a spinning band column.



9 12 13 14

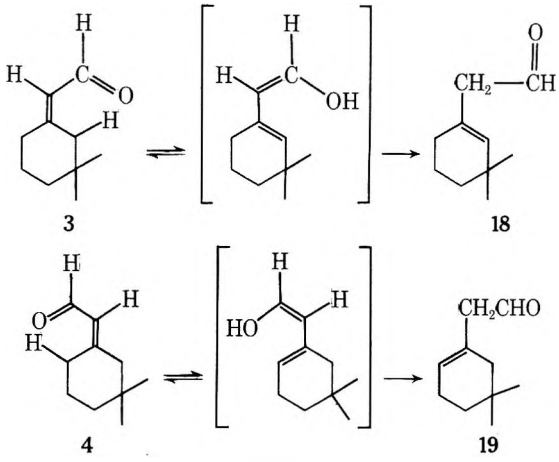
15 16 17

2 2a

The *Z* and *E* esters **15** and **16** were converted to the *Z* and *E* alcohols **2** and **2a** by reduction with lithium aluminum hydride. Oxidation of the alcohols using manganese dioxide affords the aldehydes **3** and **4** in high yield.

NMR analysis of **3** and **4** failed to indicate the presence of endocyclic isomers **18** and **19.** However, gas chromatographic analysis invariably showed the presence of these isomers. Samples of **3** and **4** collected by preparative GLC and determined to be pure by NMR were reanalyzed by GLC and once more showed the presence of **18** and **19.** We

conclude that **3** and **4** undergo 1,5-hydrogen transfer[15] in the gas chromatograph. Heating aldehydes **3** and **4** at 145° for 12 hr under a nitrogen atmosphere also gave a mixture containing ca. 20% of the endocyclic isomers **18** and **19**.



In conclusion, it is instructive to point out that two contrathermodynamic isomerizations permit the facile synthesis of the cyclohexyl constituents of the boll weevil pheromone. The failure to observe cyclobutane derivatives in the cyclization of **1** and **9** is undoubtedly related to the kinetically favored protonation of the Δ^6 double bond and the higher transition energy required to form a cyclobutane ring in the event that protonation at C-10 and subsequent C-3 to C-6 interaction does take place.

Experimental Section[16]

Methyl γ-Geranate (9). Ether (600 ml) was added in small portions to the gummy mixture resulting from the combination of 200 g (1.19 mol) of geranic acid (**6**) with 49 g (1.19 mol) of sodium hydroxide in 100 ml of water. The resulting white precipitate was removed by filtration through course filter paper and washed several times with ether. The salt was first dried on a steam plate and then in a vacuum oven at 70° for 24 hr.

To a suspension of 194 g (1.02 mol) of sodium geranate in 450 ml of benzene at 0° was added dropwise 130 g (1.06 mol) of thionyl chloride. After stirring for 2 hr at ambient temperature, the solvent and unreacted thionyl chloride were removed in vacuo. Benzene (300 ml) was added to the residue and the mixture was added at 0° over a 1-hr period to 200 ml of benzene containing 115 g (1.14 mol) of triethylamine and 37 g (1.16 mol) of methanol. The mixture was filtered and the solvents were removed. Vacuum distillation afforded 168 g of liquid containing 83% of **9** and 8% of methyl geranate (**6a**) according to GLC and NMR analysis. Pure methyl γ-geranate (**9**) was obtained by distillation using a spinning band column: bp 40° (0.15 mm); ir 3.4, 5.75, 6.08, 8.65, 9.9, and 11.2 μm; NMR ($CDCl_3$) 1.61 and 1.69 [s, 6, $C=C(CH_3)_2$], 2.11 (d, 4), 3.03 (s, 2, $-CH_2CO_2-$), 3.68 (s, 3, $-OCH_3$), 4.91 (s, 2, $-C=CH_2$), and 5.10 ppm (m, 1, $-CH=C-$); mass spectrum *m/e* (rel intensity) 182 (9), 139 (20), 123 (12), 109 (22), 108 (32), 107 (13), 69 (100), 68 (13), 67 (13), 41 (51), and 39 (11).

Anal. Calcd for $C_{11}H_{18}O_2$: C, 72.49; H. 9.95. Found: C, 72.39; H, 10.15.

γ-Geraniol (1). To a solution of 13.0 g (71 mmol) of **9** in 130 ml of dry ether was added 3.0 g (79 mmol) of lithium aluminum hydride. The mixture was stirred for 30 min and aqueous sodium hydroxide solution was slowly added. The mixture was filtered, and the filtrate was dried ($MgSO_4$) and distilled to yield 11.0 g of pure **1**: bp 51° (0.10 mm); $n^{20}D$ 1.4721 [lit.[7a] bp 83–86° (2–3 mm), $n^{20}D$ 1.4717]; ir 3.0, 6.08, 9.6, and 11.25 μm; NMR ($CDCl_3$) 1.63 and 1.70 [s, 6, $C=C(CH_3)_2$], 1.8–2.2 (m, 4), 2.30 (t, 2, J = 6 Hz, $-CH_2CH_2O$), 3.72 (t, 2, J = 6 Hz, $-CH_2CH_2O$), 4.88 (s, 2, $-C=CH_2$), and 5.10 ppm (m, 1, $CH=C-$).

Cyclization of γ-Geraniol (1). A solution of 0.50 g (3.2 mmol) of **1** and 1 ml of 90% formic acid was refluxed for 2 hr. Pentane was added, the solution was washed with water and dried ($MgSO_4$), and the solvent was evaporated, leaving 0.59 g of a mixture of formate esters **10** and **11** in 3:1 ratio as determined by GLC (DC-200 column) and NMR analysis: peaks at 0.90 (s, CH_3CCH_3), and 5.5 ppm ($-C=CH-$) were assigned to **10**; those at 0.93 (s, CH_3CCH_3) and 5.2 ppm (s, $-C=CH-$) to compound **11**; while those at 1.2–1.4 (m), 4.23 (t, 2, $-CH_2OCOH$), and 8.05 ppm (s, 1, $-OCHO$) were common to both isomers.

Cyclization of Methyl γ-Geranate (9). A mixture of 40 g (0.22 mol) of **9** (containing ca. 10% of methyl geranate) and 1.0 g of polyphosphoric acid was stirred at 130° for 2 hr. The products were distilled directly from the reaction vessel, yielding 36 g (90%) of liquid, bp 40–45° (0.1 mm). Preparative GLC using a 12 ft × 0.375 in. 15% Carbowax 20M column at 175° yielded five fractions. Compound **12** (53%, retention time 8.0 min): ir 5.73 μm; NMR ($CDCl_3$) 0.91 [s, 6, $-C(CH_3)_2$], 1.30 (t, 2), 1.5–2.2 (m, 4), 2.95 (s, 2, $-CH_2CO_2-$), 3.68 (s, 3, $-OCH_3$), and 5.55 ppm (s, 1, $-C=CH-$). Compound **13** (25%, retention time 6.3 min): ir 5.73 μm; NMR ($CDCl_3$) 0.96 [s, 6, $-C(CH_3)_2$], 1.2–2.6 (m, 6), 2.93 (s, 2, $-CH_2CO_2-$), 3.68 (s, 3, $-OCH_3$), and 5.30 ppm (s, 1, $-C=CH-$). Compound **14** (12%, retention time 5.1 min): ir 5.76 μm, NMR ($CDCl_3$) 0.92 [s, 6, $-C(CH_3)_2$], 1.65 (s, 3, $-C=CCH_3$), 1.7–2.5 (m, 4), 2.61 (s, 1, $-CHCO_2-$), 3.68 (s, 3, $-OCH_3$) and 5.60 ppm (s, 1, $-C=CH-$). Compound **15** (5%, retention time 8.8 min): ir 5.81 μm; NMR ($CDCl_3$) 0.91 [s, 6, $-C(CH_3)_2$], 1.2–1.9 (m, 4), 2.17 (t, 2, $-CH_2-$ trans to $-CO_2Me$), 2.68 (s, 2, $-CH_2-$ cis to $-CO_2Me$), 3.68 (s, 3, $-OCH_3$), and 5.68 ppm (s, 1, $-C=CH-$). Compound **16** (5%, retention time 9.6 min): ir 5.81 μm; NMR ($CDCl_3$) 0.90 [s, 6, $-C(CH_3)_2$], 1.3–1.9 (m, 4), 1.97 (s, 2, $-CH_2-$ trans to $-CO_2Me$), 2.78 (t, 2, $-CH_2-$ cis to $-CO_2Me$), 3.68 (s, 3, $-OCH_3$), and 5.58 ppm (s, 1, $-C=CH-$).

Isomerization of Esters 12 and 13 to 15 and 16. Hydrogen bromide was bubbled into a solution of 36 g of the mixture of **12, 13, 14, 15,** and **16** described above in 400 ml of methylene chloride at room temperature. The addition was complete (by NMR analysis) after 10 hr. The solvent and excess hydrogen bromide were removed in vacuo. The residue was taken up in benzene and 85 g of dry triethylamine and more benzene was added to bring the volume to 500 ml. The solution was refluxed for 36 hr, filtered, and washed twice with water, and the solvent was removed, leaving 35 g (97%) of liquid containing 75% of **15** and **16** as determined by GLC analysis. A portion of this material was distilled using a spinning band column and fractions boiling in the range of 47–48° (0.2 mm) collected. The initial fractions were enriched in **15** and the later ones in **16**.

(*Z*)-3,3-Dimethyl-$\Delta^{1,\beta}$-cyclohexaneethanol (*2*). To a solution of 9.0 g (49 mmol) of **15** (containing 25% of **16**) in 110 ml of dry ether was added 1.86 g (49 mmol) of lithium aluminum hydride. The mixture was stirred for 1 hr at ambient temperature, aqueous sodium hydroxide was added, the mixture was filtered and dried ($MgSO_4$), and the solvent was removed, affording 6.7 g of liquid which was purified by distillation using a spinning band column. Pure *Z* alcohol showed bp 44° (0.2 mm); ir 3.05, 6.0, 9.3, 9.7, and 10.0 μm; NMR ($CDCl_3$) 0.90 [s, 6, $-C(CH_3)_2$], 1.30–2.20 (m, 6), 1.98 (s, 2, $-CH_2-$ cis to $-CH_2OH$), 4.12 (d, 2, J = 7 Hz, $-CH_2OH$), and 5.50 ppm (t, 1, J = 7 Hz).

(*E*)-3,3-Dimethyl-$\Delta^{1,\beta}$-cyclohexaneethanol (2a). The *E* ester **16** (containing 14% of **15**) was reduced in the same manner to yield 90% of alcohol **2a** (containing 14% of **2**): bp 40° (0.15 mm); ir 3.05, 6.0, 9.3, and 10.0 μm; NMR ($CDCl_3$) 0.87 [s, 6, $-C(CH_3)_2$], 1.2–2.2 (m, 6), 1.90 (s, 2, $-CH_2-$ trans to $-CH_2OH$), 4.15 (d, 2, J = 7 Hz, $-CH_2OH$), and 5.32 ppm (t, 1, J = 7 Hz, $-C=CH-$).

Aldehydes 3 and 4. A mixture of 2.4 g (19.5 mmol) of alcohols **2** and **2a** in 100 ml of pentane and 10 g (115 mmol) of manganese dioxide was stirred at ambient temperature for 10 hr and filtered, and the solvent was removed, leaving 2.0 g (83%) of essentially pure aldehydes **3** and **4** showing properties consistent with those reported by Tumlinson:[3] ir 5.95 and 6.12 μ; NMR ($CDCl_3$) peaks at 0.97 (s), 2.24 (t, $-CH_2-$ trans to CHO), 2.49 (s, $-CH_2-$ cis to CHO), and 5.95 ppm (d, J = 8 Hz, $-C=CH-$) were assigned to **3**, while those at 0.92 (s), 2.10 (s, $-CH_2-$ trans to CHO), 2.68 (t, $-CH_2-$ cis to CHO), and 5.80 ppm (d, J = 8 Hz) were assigned to **4**. NMR peaks at 1.2–1.9 and 10.01 ppm (d, CHO) were common to both isomers.

A GLC-collected sample of a mixture of aldehydes **3** and **4** (shown to be pure by NMR), when injected again into a 12-ft DC-200 column employing an injector temperature of 235°, gave 15% of a broad peak with a lower retention time. This peak was collected and identified as a mixture of endocyclic aldehydes **18** and **19** on the basis of its ir and NMR spectra: peaks at 0.99 (s) and 5.35 ppm (s, $-C=CH-$) assigned to **18**, peaks at 0.91 (s) and 5.60 ppm (s, $-C=CH-$) assigned to **19**, and those at 1.2–2.4 and 2.98 ppm ($-CH_2CHO$) were common to both isomers.

Registry No.—**1**, 13066-51-8; **2**, 26532-23-0; **2a**, 30346-27-1; **3**, 26532-24-1; **4**, 26532-25-2; (*E*)-**6**, 4698-08-2; (*Z*)-**6**, 4613-38-1; (*E*)-**6a**, 1189-09-9; (*Z*)-**6a**, 1862-61-9; **9**, 55298-92-5; **10**, 55298-93-6; **11**, 55298-94-7; **12**, 55298-95-8; **13**, 55298-96-9; **14**, 28043-10-9; **15**, 30346-23-7; **16**, 30346-25-9; **18**, 36866-77-0; **19**, 55298-72-1.

References and Notes

(1) Presented in part at the VI International Congress of Essential Oils, San Francisco, Calif., Sept 1974.
(2) J. H. Tumlinson, R. C. Gueldner, D. D. Hardee, A. C. Thompson, P. A. Hedin, and J. P. Minyard, "Chemicals Controlling Insect Behavior", M. Beroza, Ed., Academic Press, New York, N.Y., 1970.
(3) For the isolation, identification, and synthesis of **2**, **3**, **4**, and **5** see J. H. Tumlinson, D. D. Hardee, R. C. Gueldner, A. C. Thompson, P. A. Hedin, and J. P. Minyard, *Science*, **166**, 1010 (1969); J. H. Tumlinson et al., *J. Org. Chem.*, **36**, 2616 (1971).
(4) For syntheses of grandisol (**5**) see (a) R. C. Gueldner, A. C. Thompson, and P. A. Hedin, *J. Org. Chem.*, **37**, 1854 (1972); (b) R. Zurflüh, L. L. Dunham, V. L. Spain, and J. B. Siddal, *J. Am. Chem. Soc.*, **92**, 425 (1970); (c) W. E. Billups, J. H. Cross, and C. V. Smith, *ibid.*, **95**, 3438 (1973); (d) G. Stork and J. F. Cohen, *ibid.*, **96**, 5270 (1974).
(5) Geranic acid is available from Fritzsche D & O, or can be synthesized by silver oxide oxidation of citral.[6]
(6) K. Bernhauer and R. Forster, *J. Prakt. Chem.*, **147**, 199 (1936).
(7) For earlier syntheses of γ-geraniol, see (a) H. C. Brown, K. Singh, and B. J. Garner, *J. Organomet. Chem.*, **1**, 2 (1963); (b) S. Watanabe and K. Suga, *Bull. Chem. Soc. Jpn.*, **36**, 1495 (1963); (c) A. I. Lebedeva and L. V. Kukhareva, *Zh. Obshch. Khim.*, **28**, 2782 (1958).
(8) Y. Iwakura, F. Toda, R. Iwata, and Y. Torii, *Bull. Chem. Soc. Jpn.*, **42**, 841 (1969).
(9) Geranic acid is a mixture of *E* and *Z* isomers.
(10) The reaction of geranic acid with thionyl chloride resulted in the addition of the by-product HCl to the $\Delta^{6,7}$ double bond.
(11) The nonconjugated ester **9** most likely forms by way of a vinyl ketene intermediate, as suggested by Iwakura.[8]
(12) Typical runs on a small scale yield 65% **9**.
(13) Compound **14** arises by cyclization of methyl geranate (**6a**), which was present in the sample of **9**.
(14) H. C. Brown, J. H. Brewster, and H. Shechter, *J. Am. Chem. Soc.*, **76**, 467 (1954); G. A. R. Kon and R. P. Linstead, *J. Chem. Soc.*, 1269 (1929).
(15) For examples of analogous 1,5-hydrogen transfers involving β,γ-unsaturated aldehydes, ketones, and esters see (a) G. Ohloff, *Tetrahedron Lett.*, **11**, 10 (1960); (b) G. Ohloff, J. Osiecki, and C. Djerassi, *Chem. Ber.*, **95**, 1400 (1962); (c) D. E. McGreer and N. W. K. Chiu, *Can. J. Chem.*, **46**, 2225 (1968).
(16) All boiling points are uncorrected. GLC analyses were performed using a 12 ft × 0.375 in. Carbowax 20M column at 175° except as otherwise noted. NMR spectra were determined with a Varian Associates A-60 spectrometer. Infrared spectra were recorded on a Perkin-Elmer Infracord spectrometer. Mass spectra were determined at 70 eV with a Hitachi RMU-6A mass spectrometer. Microanalyses were performed by Dr. C. S. Yeh and associates.

Regiospecific Alkylation of Enolate Ions in Liquid Ammonia–Tetrahydrofuran

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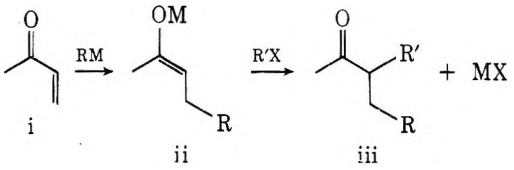
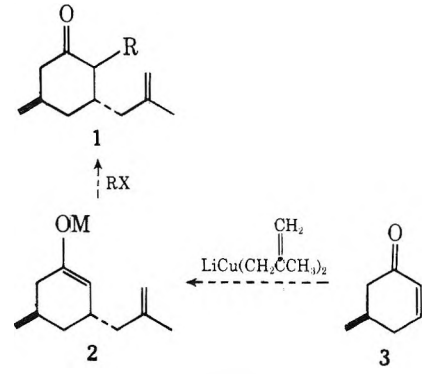
Specific cyclohexanone enolates are generated by cleaving the corresponding trimethylsilyl enol ethers with lithium amide in liquid ammonia. Butylation proceeds in high yield in this solvent, with little enolate equilibration. With corresponding sodium and potassium enolates, alkylation and enolate equilibration proceed at comparable rates.

Vicinal dialkylation of enones, by conjugate addition[1] and alkylation of the resulting specific enolate (i → ii → iii), is an important synthetic process which has received considerable recent attention.[2] The main problem is the



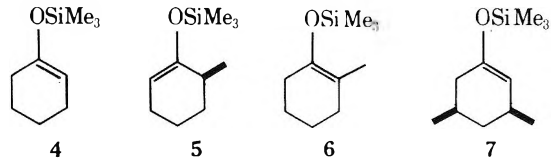
matter of proton exchange vs. alkylation. With very reactive electrophiles such as benzylic and allylic halides, alkylation is significantly more rapid than proton exchange, and regiospecific vicinal alkylation results.[2a,b,d] Coates found dimethoxyethane (DME) to be an effective solvent for promoting alkylation vis-à-vis proton transfer, although he still encountered substantial proton transfer in some cases.[2f]

In connection with a projected alkaloid synthesis, we required 2-alkyl-3-methallyl-5-methylcyclohexanones, in which the C-3 and C-5 substituents are trans (**1**). Since the conjugate addition of dialkylcuprates to 5-methylcyclohex-2-en-1-one is known to occur with good trans stereoselectivity,[3] the vicinal dialkylation process is an attractive route to **1**.



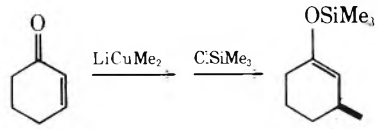
In the process of this study, we discovered that specific lithium enolates undergo alkylation in a mixture of liquid ammonia–tetrahydrofuran under conditions where proton transfer is an insignificant side reaction.[4] In this paper, we report the results of a limited study of this phenomenon.

Preparation of Alkylation Substrates. The ketone enolates which we have studied were prepared by cleavage of the appropriate silyl enol ether with methyllithium in the appropriate ether[4] or with lithium amide in liquid ammonia.[5] Silyl enol ethers **4**, **5**, and **6** were prepared by literature procedures.[6] Ether **7** was prepared in a similar manner from *cis*-3,5-dimethylcyclohexanone. This ether was contaminated with 10% of the *trans*-3,5-dimethyl isomer **9**,



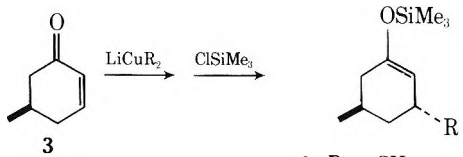
4 5 6 7

owing to the method by which it was prepared (see Experimental Section). Ether **8** was prepared in 69% yield by conjugate addition of lithium dimethylcuprate to cyclohex-2-en-1-one, followed by addition of chlorotrimethylsilane.[7]



8

Ethers **9** and **10** were prepared from enone **3** in yields of 71 and 86%, respectively, using the corresponding dialkylcuprates. Ether **9** was contaminated by 7% of the *cis*-3,5-dimethyl isomer **7**.

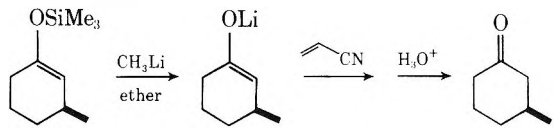


3

9, R = CH_3

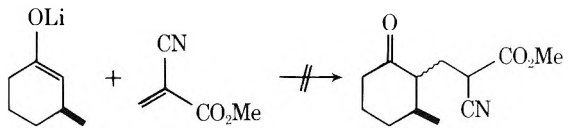
10, R = $CH_2C(CH_3)=CH_2$

Alkylation Results. We had hoped to alkylate enolate **2** with acrylonitrile or its equivalent. In our initial experiment toward this end, we treated enolate **11**, prepared in ether solution by treating **8** with methyllithium, with acrylonitrile. Not surprisingly, the reaction yielded no adduct but instead resulted in complete polymerization of the acrylonitrile; 3-methylcyclohexanone was the only product,



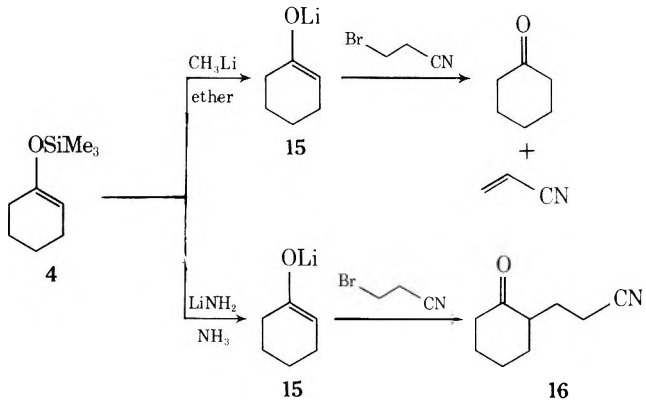
8 11 12

obtained in 80% yield. Enolate **11** also catalyzed the polymerization of methyl 2-cyanoacrylate (**13**). None of the desired product **14** could be detected.



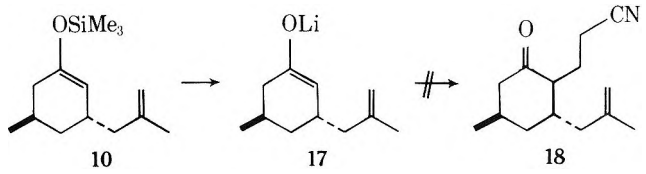
11 13 14

Having been thwarted in attempts to carry out Michael reactions on our specific enolates, we turned our attention to alkylation with 3-halopropionitriles. Enolate **15**, prepared in ether by treating silyl ether **4** with methyllithium, is not alkylated by 3-bromopropionitrile. The only products obtained are cyclohexanone and polyacrylonitrile. Because the C-2 protons in 3-bromopropionitrile are fairly acidic, E2 elimination predominates, and no alkylation is achieved. However, if the alkylation is carried out in liquid ammonia with excess β-bromopropionitrile, cyano ketone **16** is obtained in 48% yield. Unfortunately, we were unable to extend this result to the 3-methallyl-5-methyl system.



4 15 16

Enolate **17**, prepared by lithium amide cleavage of silyl ether **10**, failed to react with 3-bromopropionitrile or 3-iodopropionitrile. Apparently, the E2/SN2 ratio is lower in liquid ammonia than it is in ether. However, even in this solvent, the more hindered enolate **17** gives complete elimination of the 3-halopropionitrile.



10 17 18

The efficacy of liquid ammonia in reducing the proton-transfer process in the alkylation of **15** by 3-bromopropionitrile seemed interesting and worthy of further study. Consequently, we examined the butylation of enolate **17** and its sodium and potassium analogs in this medium. With the lithium enolate, the corresponding 2-butyl product **19** was obtained in 91% yield. With the sodium and potassium enolates, complex product mixtures were obtained. Representative data are shown in Table I.

Table I
Butylation of 17 in THF–NH_3[a]

	Product composition, %					
Cation	19	20	21	22	23	24
Li^{+c}	5.5	94.5	0	0	0	0
Na^{+b}	33.8	34.6	31.6	0	0	0
K^{+b}	7.7	49.0	13.7	5.5	8.3	15.8
$K^{+c,d}$	12.2	55.5	32.2	0	0	0

[a] Enolates were prepared by treating ether **10** with $LiNH_2$, $NaNH_2$, or KNH_2 in THF–NH_3 (40% THF, 60% NH_3). A fourfold excess of *n*-butyl iodide was added. Alkylation was allowed to proceed for 2 hr for M = Na and K and 6 hr for M = Li. [b] In these experiments, a 20% excess of the metal amide was used. [c] Only 1 molar equiv of MNH_2 was used. [d] Eight molar equivalents of *n*-butyl iodide.

Solvent systems containing hexamethylphosphoramide (HMPT) are also reported to be efficacious in promoting alkylation relative to proton transfer reactions.[8] We therefore studied the alkylation of **17** (M = Li) in a mixture of 80% THF and 20% HMPT at two different temperatures. The data are summarized in Table II. While this system provides up to 66% of the desired product **20** (after hydrolysis of the O,C-dialkylated product **24**), substantial amounts of the C-6 butyl product **21** and dibutylated products **22** and **23** are also produced. Clearly, with lithium enolates, the liquid ammonia–THF mixture is more effective in suppressing enolate equilibration than is HMPT–THF.

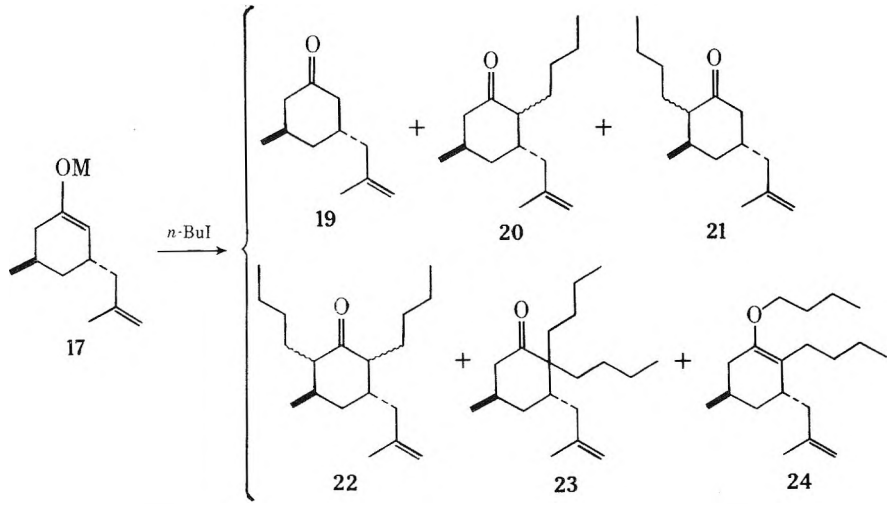


Table II
Butylation of 17 (M = Li) in THF–HMPT[a]

	Product composition, %					
Temp, °C	19	20	21	22	23	24
25	5.9	51.5	14.0	6.9	6.3	14.9
25[b]	5.9	66.4	14.0	6.9	6.3	0
55	10.9	42.5	23.1	5.6	5.3	12.3
55[b]	10.9	54.8	23.1	5.6	5.6	0

[a] The enolate was prepared by treating ether **10** with CH_3Li in THF. HMPT was added (20%), along with 4 molar equiv of *n*-butyl iodide. Alkylations were allowed to proceed for 10 hr. [b] After treating the total product with 5% aqueous HCl for 1 hr.

In order to establish the generality of the procedure, we have also carried out butylations of cyclohexanone enolates **15, 25, 26, 27,** and **28.** In all cases, the C-2 butylated product was obtained in high yield, uncontaminated by C-6 butylated or dibutylated products (Table III). Ketones **30, 31,** and **32** were each obtained as a mixture of C-2 epimers. In each case, the individual epimers were collected by preparative GLC and shown to be interconvertible under basic conditions (see Experimental Section).

Table III
Butylation of Lithium Enolates in NH_3–THF[a]

No.	Enolate	No.	Product	Yield,[b] %
15		29		74
25	OLi	30		70
26	OLi	31		83
27	OLi	32		90
28	OLi	33		92

[a] Enolates were prepared by treating the appropriate trimethylsilyl ether with $LiNH_2$ in THF-NH_3 (40% THF, 60% NH_3). A fourfold excess of *n*-butyl iodide was used. [b] Yield of distilled product, often contaminated with a small amount of the appropriate unbutylated ketone.

Experimental Section

Preparation of 1-Trimethylsiloxycyclohexane (4).[6] To a slurry of 10.5 g (0.25 mol) of 56.8% NaH oil dispersion in 200 ml of anhydrous DME was added 9.8 g (0.1 mol) of cyclohexanone. The resulting mixture was refluxed for 3 hr. At the end of this time the reaction mixture was cooled and 15 ml of both trimethylchlorosilane and triethylamine (50% excess of each) was added. After stirring for 15 min at room temperature, the reaction mixture was diluted with 400 ml of pentane and carefully quenched with 5% HCl. After the excess NaH was consumed the organic layer was washed with 200 ml of 5% HCl and 200 ml of 5% $NaHCO_3$ and dried over K_2CO_3. After solvent removal and distillation, 10.8 g (63%) of **4** was collected at 89–90° (20 Torr): ^1H NMR (CCl_4) τ 5.30 (m, 1, vinyl H), 9.85 (s, 9, $SiMe_3$).

Preparation of 1-Trimethylsiloxy-*cis*-3,5-dimethylcyclohexene (7). The silyl enol ether of *cis*-3,5-dimethylcyclohexanone was prepared using the procedure described above. Starting with 5.04 g (40 mmol) of ketone, obtained by the lithium–ammonia reduction of 3,5-dimethylcyclohex-2-en-1-one,[8] and 4.23 g (100 mmol) of 56.8% NaH oil dispersion in 40 ml of DME, 4.45 g (56%) of **7** was obtained, bp 96° (20 Torr). GLC analysis (6 ft × 0.25 in. 15% NPGS, 150°, 120 ml/min) indicated two components: 90% **7** (retention time 6.5 min) and 10% **9** (retention time 7.25 min). The trans isomer **9** arises from a comparable amount of *trans*-3,5-dimethylcyclohexanone produced in the lithium–ammonia reduction: ir (neat) 1665 cm^{-1} (enolate double bond stretching); ^1H NMR (CCl_4) τ 9.87 (s, 9, $SiMe_3$), 9.05 (d, 6, ring Me), 5.30 (broad s, 1, enolate vinyl H). Anal. Calcd for $C_{11}H_{22}SiO$: C, 66.58; H, 11.18. Found: C, 66.49; H, 10.83.

Preparation of 1-Trimethylsiloxy-2-methylcyclohexene (6). A 7:3 mixture of **6** and **5** was prepared in 85% yield from 2-methylcyclohexanone as described above. A 96.5% pure sample of **6,** bp 91–92° (20 Torr), was obtained by spinning band distillation: GLC (6 ft × 0.25 in. 15% NPGS, 100°, 120 ml/min) retention time 3.1 min; ^1H NMR (CCl_4) τ 8.40 (s, 3, vinyl Me), 9.80 (s, 9, $SiMe_3$).

Preparation of 1-Trimethylsiloxy-*trans*-3-methallyl-5-methylcyclohexene (10). To 14.6 g (100 mmol) of freshly distilled di-*n*-butyl sulfide was added with stirring 9.5 g (50 mmol) of purified copper(I) iodide,[9] and the resulting clear orange liquid complex was filtered and stored. A solution of 9.65 g (20 mmol) of this copper(I) iodide complex and 10 ml of dry ether was cooled to −78° under nitrogen and 80 ml (40 mmol) of a 0.5 *M* methallyllithium–ether solution[10] was slowly added. After 1 equiv of methallyllithium–ether solution had been introduced, the reaction mixture was a bright red slurry, which changed to a clear pale yellow solution upon addition of the second equivalent. This resulting lithium dimethallylcuprate solution was allowed to stir for an additional 15 min at −78°, and then a mixture of 1.84 g (16.7 mmol) of 5-methylcyclohex-2-en-1-one (**3**)[11] in 10 ml of dry ether was added dropwise. After the addition was complete, the mixture was stirred for an additional 15 min at −78° and then warmed to 0°. At this point, 6.1 ml of chlorotrimethylsilane was rapidly added, followed immediately by 7.6 ml of freshly distilled triethylamine and 3.8 ml of dry HMPT, and the resulting reaction mixture was stirred at room temperature for 1 hr. At the end of this time, the reaction mixture was diluted with 150 ml of pentane and the liquid layer was decanted from the insoluble copper salts. After this solid material

was washed with more pentane, the combined organic portions were washed successively with two 50-ml portions each of 5% HCl and 5% $NaHCO_3$, and then dried over magnesium sulfate. Solvent removal followed by distillation yielded 3.41 g (86% yield) of product which was collected at 74° (0.9 Torr): ir (neat) 1665 cm^{-1} (enolate double bond stretching); ^1H NMR (CCl_4) τ 9.83 (s, 9, $SiMe_3$), 9.03 (d, 3, ring Me), 8.30 (s, 3, vinyl Me). Anal. Calcd for $C_{14}H_{26}OSi$: C, 70.52; H, 10.99. Found: C, 70.26; H, 11.07.

Preparation of 1-Trimethylsiloxy-3-methylcyclohexene (8). To a cold (0°) slurry of 7.6 g (40 mmol) of copper(I) iodide in 92 ml of anhydrous ether was added 48 ml (72 mmol) of a 1.5 *M* methyllithium–ether solution. After the addition was complete, 1.92 g (20 mmol) of cyclohex-2-en-1-one in 18 ml of ether was added, the resulting mixture was stirred for 15 min at 0°, and 6.1 ml of trimethylchlorosilane, 7.6 ml of triethylamine, and 3.8 ml of HMPT were added. The mixture was then stirred at room temperature for 1 hr, after which time it was diluted with an equal volume of pentane. The resulting mixture was washed successively with two 50-ml portions each of 5% HCl and 5% $NaHCO_3$ and dried over $MgSO_4$. Solvent removal and distillation yielded 2.54 g (69%) of **8**: bp 35° (1.4 Torr); ^1H NMR (CCl_4) τ 5.37 (m, 1, vinyl H), 9.17 (d, 3, ring Me), 9.83 (s, 9, $SiMe_3$); ir (neat) 1660 cm^{-1} (enol ether).

Preparation of 1-Trimethylsiloxy-*trans*-3,5-dimethylcyclohexene (9). This silyl enol ether was prepared from 5-methylcyclohex-2-en-1-one **3**[11] using the above procedure. After distillation, **9** was collected in a yield of 70.5%, over a range of 43–44° (2.0 Torr). GLC analysis (6 ft × 0.25 in. 15% NPGS, 150°, 120 ml/min) indicated that 93% of the product was the desired trans material **9**, and that 7% of the cis isomer **7** was present: ir (neat) 1665 cm^{-1} (enolate double bond stretching); ^1H NMR (CCl_4) τ 9.85 (s, 9, $SiMe_3$), 9.03 (d, 6, ring Me), 5.33 (broad d, 1, enolate vinyl H). Anal. Calcd for $C_{11}H_{22}SiO$: C, 66.58; H, 11.18. Found: C, 66.55; H, 11.20.

Preparation of 2-Butyl-3-methallyl-5-methylcyclohexanone (20). A. A solution of 0.6 g (2.5 mmol) of **10** in 10 ml of dry tetrahydrofuran was slowly added to a slurry of lithium amide, formed from 0.0175 g (2.5 mg-atoms) of lithium, a crystal of ferric nitrate, and 13 ml of anhydrous ammonia. After stirring for 30 min at the reflux temperature of ammonia, a solution of 1.84 g (10 mmol) of butyl iodide in 5 ml of THF was added rapidly and the resulting mixture was stirred for 6 hr. At the end of this time solid ammonium chloride was added to quench any unalkylated enolate and the ammonia was allowed to evaporate. The resulting material was dissolved in 100 ml of ether and washed with two 50-ml portions of water and 50 ml of saturated NaCl solution and dried over magnesium sulfate. Solvent removal yielded 1.0 g of liquid. GLC analysis (6 ft × 0.25 in. 15% NPGS, 200°, 120 ml/min) indicated that two ketone components were present in addition to excess butyl iodide: 5.5% **19** (retention time 4.7 min) and 94.5% **20** (retention time 8.7 min). The above assignments were based on mass spectra,[12] ir, and ^1H NMR data. Excess butyl iodide was removed at reduced pressure to give 0.535 g of a mixture of **19** and **20**. Using the above composition, this corresponds to a 91% yield of **20**. An analytical sample of **20** was obtained by preparative glpc using the conditions described above: ir (neat) 1710 (carbonyl stretching), 892 cm^{-1} (methallyl double bond); ^1H NMR (CCl_4) τ 9.03 (d, 6, ring and butyl Me), 8.33 (s, 3, vinyl Me), 5.33 (d, 2, vinyl H). Anal. Calcd for $C_{15}H_{26}O$: C, 81.02; H, 11.79. Found: C, 81.09; H, 11.60.

B. The above reaction was repeated, using $NaNH_2$, rather than $LiNH_2$, to form the enolate. The enolate was prepared from 69 mg (3.0 mg-atoms) of sodium. Silyl ether **10** (600 mg, 2.5 mmol) was added, followed by 1.84 g (10 mmol) of butyl iodide. After 2 hr, the reaction was processed as above to obtain 470 mg of a ketone mixture, which was assigned (GLC) the following composition: 33.8% **19**, 34.6% **20**, and 31.6% **21** (equal amounts of two epimers). The two epimers of **21** were collected separately and shown to be interconvertible in a KOH–methanol solution.

C. 1. The butylation described above was repeated using 0.117 g (3.0 mg-atoms) of potassium. A yellow oil (615 mg) was isolated, which, upon GLC analysis (6 ft × 0.25 in. 15% NPGS column, 200°, 120 ml/min), was found to consist of seven components: 7.7% **19** (retention time 4.8 min), 15.8% **24** (retention time 6.0 min), 49.0% **20** (retention time 8.7 min), 13.7% **21** (both epimers in equal amounts with retention times of 9.8 and 11.0 min), 5.5% **22** (retention time 14.2 min), and 8.3% **23** (retention time 16.4 min). The two epimers of **21** were collected separately and shown to be interconvertible in a KOH–methanol solution.

2. The foregoing procedure was repeated using only 97.7 mg (2.5 mg-atoms) of potassium. After formation of the potassium enolate, 3.68 g (20 mmol) of butyl iodide was added. Upon normal work-up, there was obtained 490 mg of material which was shown by GLC to consist of 12.2% **19**, 55.5% **20**, and 32.2% **21**. No dialkylated material was detected.

D. 1. To a solution of 0.6 g (2.5 mmol) of **10** in 10 ml of anhydrous tetrahydrofuran at room temperature was added 1.25 ml (2.5 mmol) of a 2.0 *M* methyllithium–ether solution. The reaction was checked periodically by TLC (10% ether–hexane), which indicated that all of **10** had been converted to the lithium enolate **17** after 2 hr. At this point 1.84 g (10 mmol) of butyl iodide dissolved in 3 ml of anhydrous HMPT was added all at once and the resulting mixture was allowed to stir at room temperature for 10 hr. At the end of this time, the reaction mixture was added to a saturated NH_4Cl–water solution and extracted with two 100-ml portions of ether. The combined ether layers were washed with 100 ml of water and dried over $MgSO_4$. After solvent removal the resulting 600 mg of orange liquid was analyzed by GLC (6 ft × 0.25 in. 15% NPGS, 200°, 120 ml/min) and found to have the following composition: 5.9% **19**, 14.9% **24**, 51.5% **20**, 14.0% **21**, 6.9% **22**, and 6.8% **23**. After treatment with 5% HCl for 1 hr, all of **24** was converted to **20**, bringing its total up to 66.4%.

2. The foregoing experiment was repeated, only the enolate was allowed to alkylate for 10 hr at 55°. The GLC composition was found to be 10.9% **19**, 12.3% **24**, 42.5% **20**, 23.1% **21**, 5.6% **22**, and 5.6% **23**. Treatment with HCl increased the proportion of **20** to 54.8%.

Preparation of 2-Butylcyclohexanone (29). The silyl enol ether **4** (1.7 g, 10 mmol) was converted to its lithium enolate with a solution of $LiNH_2$ prepared from 84.8 mg (12 mg-atoms) of lithium and alkylated with butyl iodide using the same procedure developed for **20**, part A. The alkylation was allowed to proceed for only 2 hr. The product was distilled to obtain **29** in a yield of 74%. The product was collected at 65° (1.8 Torr) [lit. 70° (2.0 Torr)]. No dialkylated or unalkylated ketones were isolated. The structure of the product was confirmed by its mass spectrum:[13] major mass spectral peaks at *m/e* 154 (M^+), 98 ($M^+ - C_4H_8$, McLafferty), 70 ($M^+ - C_4H_8 - C_2H_4$), 55 ($M^+ - C_7H_{15}$, α cleavage); ir (neat) 1715 cm^{-1} (carbonyl); ^1H NMR (CCl_4) τ 9.06 (t, 3, butyl Me).

Preparation of 2-Butyl-*cis*-3,5-dimethylcyclohexanone (30). Compound **7** (1.0 g, 5 mmol) was converted into its lithium enolate (41.8 mg of lithium, 6 mg-atoms) and alkylated with butyl iodide as described in the foregoing preparation of **29**. The resulting product was distilled to obtain a mixture of unalkylated and butylated ketone in a ratio of 8:92. The butylated fraction was collected at 69° (3.0 Torr) in a yield of 70%. GLC analysis of this fraction (6 ft × 0.25 in. 15% NPGS, 150°, 120 ml/min) revealed the presence of three components: 90% **30** (two epimers, retention times 12.5 and 13.8 min) and 10% **31** (retention time 15.6 min). An analytical sample was obtained by preparative GLC using the above described conditions: ir (neat) 1700 cm^{-1} (carbonyl); ^1H NMR (CCl_4) τ 9.15 (d, 9, Me); major mass spectral peaks[13] at *m/e* 182 (M^+), 126 ($M^+ - C_4H_8$, McLafferty), 111 ($M^+ - C_4H_8 - CH_3$), 84 ($M^+ - C_4H_8 - C_3H_6$), 69 ($M^+ - C_8H_{17}$, α cleavage), 55. Anal. Calcd for $C_{12}H_{22}O$: C, 79.06; H, 12.12. Found: C, 79.13; H, 12.07.

The two epimers of **30** were collected separately and equilibrated using KOH–MeOH solution. At equilibrium the two epimers were present in a ratio of 89 (retention time 12.5 min) to 11 (retention time 13.8 min).

Preparation of 2-Butyl-*trans*-3,5-dimethylcyclohexanone (31). The silyl enol ether **9** was alkylated as described above, using 1.0 g (6 mmol) of **9**, 41.8 mg (6 mg-atoms) of lithium, and 3.68 g (20 mmol) of butyl iodide. The product was distilled and two fractions were collected, one boiling at 40° (0.5 Torr) and the second at 66° (0.5 Torr). The first fraction weighed 83 mg and was identified as *trans*-3,5-dimethylcyclohexanone by its mass spectrum. GLC analysis (6 ft × 0.25 in. 15% NPGS, 150°, 120 ml/min) of the second fraction (750 mg, 83% yield) revealed the presence of three components: 5.6% **30** (retention time 12.0 min) and 94.4% **31** (two epimers, retention time 14.5 and 16.0 min). An analytical sample was obtained by preparative GLC: ir (neat) 1690 cm^{-1} (carbonyl); ^1H NMR (CCl_4) τ 9.16 (d, 9, Me); major mass spectral peaks at *m/e* 182 (M^+), 126 ($M^+ - C_4H_8$, McLafferty), 111 ($M^+ - C_4H_8 - CH_3$), 84 ($M^+ - C_4H_8 - C_3H_6$), 69 ($M^+ - C_8H_{17}$, α cleavage), 55. Anal. Calcd for $C_{12}H_{22}O$: C, 79.06; H, 12.12. Found: C, 79.23; H, 12.19. The epimer percentages at equilibrium were obtained as before. This ratio was found to be 49.8 (retention time 14.5 min) to 50.2 (retention time 16.0 min).

Preparation of 2-Butyl-6-methylcyclohexanone (32). A 0.46-g (2.5 mmol) sample of **5**[4] was converted to its lithium enolate with a solution of $LiNH_2$ prepared from 17.5 mg (2.5 mg-atoms) of lithium and then alkylated with 10 mmol of butyl iodide, using the

procedure described above. After solvent and excess butyl iodide removal the resulting ketone mixture (90% recovery) was analyzed by GLC (6 ft × 0.25 in. 15% NPGS, 175°, 120 ml/min) and found to consist of 17% unalkylated ketone (retention time 2.5 min) and 83% **32** (two interconvertible epimers, retention times 8.75 and 9.3 min). Product identification was made from comparative GLC with **33** and mass spectral results.[13]

Preparation of 2-Butyl-2-methylcyclohexanone 33. The silyl enol ether **6**[4] was butylated exactly as described above. The product ketones were obtained in a yield of 92% and found to have the following compositions by GLC: 2.5% unalkylated ketone (retention time 3.8 min) and 97.5% **33** (retention time 9.5 min).

Preparation of 2-(2-Cyanoethyl)cyclohexanone (16). Using the procedure developed for **20**, part A, 1.7 g (10 mmol) of 4 was converted to its lithium enolate with a $LiNH_2$ solution prepared from 91.0 mg (13 mg-atoms) of lithium and then treated with 5.35 g (40 mmol) of 3-bromopropionitrile. After solvent removal, the resulting product was distilled, yielding 200 mg of cyclohexanone and 500 mg of **16** (48%), boiling at 118° (1.8 Torr): ir (neat) 1700 (carbonyl), 2230 cm^{-1} (-C≡N).

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Registry No.—**3**, 7214-50-8; **4**, 6651-36-1; **5**, 19980-33-7; **6**, 19980-35-9; **7**, 55373-57-4; **8**, 55373-58-5; **9**, 55373-59-6; **10**, 55373-44-9; **15**, 21300-30-1; **16**, 4594-78-9; **20**, 55373-32-5; **25**, 55373-60-9; **26**, 55373-61-0; **27**, 13670-83-2; **28**, 13670-84-3; **29**, 1126-18-7; **30** epimer 1, 55373-62-1; **30** epimer 2, 55373-63-2; **31** epimer 1, 55373-64-3; **31** epimer 2, 55373-65-4; *cis*-3,5-dimethylcyclohexanone, 7214-52-0; *trans*-3,5-dimethylcyclohexanone, 7214-49-5; lithium dimethallylcuprate, 55373-66-5; chlorotrimethylsilane, 75-77-4; lithium dimethylcuprate, 15681-48-8; cyclohex-2-en-1-one, 930-68-7; lithium amide, 7782-89-0; butyl iodide, 542-69-8; sodium amide, 7782-92-5; potassium amide, 17242-52-3; 3-bromopropionitrile, 2417-90-5.

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Mass Spectra of Some 2,3,5-Trialkylcyclohexanones

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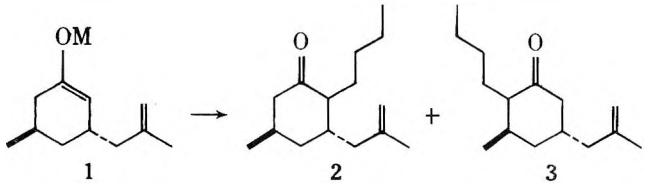
Mass spectra have been obtained for several pairs of isomeric 2,3,5-trisubstituted cyclohexanones. In all cases, the principle mode of fragmentation involves McLafferty rearrangement, followed by decomposition of the initial McLafferty ion. When there is an allylic group at C-3, the initial McLafferty ion simply loses allyl radical. When the allylic group is at C-5, the base peak corresponds to loss of the allylic substituent plus two hydrogens. A mechanism is proposed to rationalize the results.

In the accompanying paper, we report a study of the site-specific alkylation of enolate 1 and related enolates.[1] Under some conditions, enolate equilibration occurs and isomers **2** and **3** are produced. In searching for a method to assign

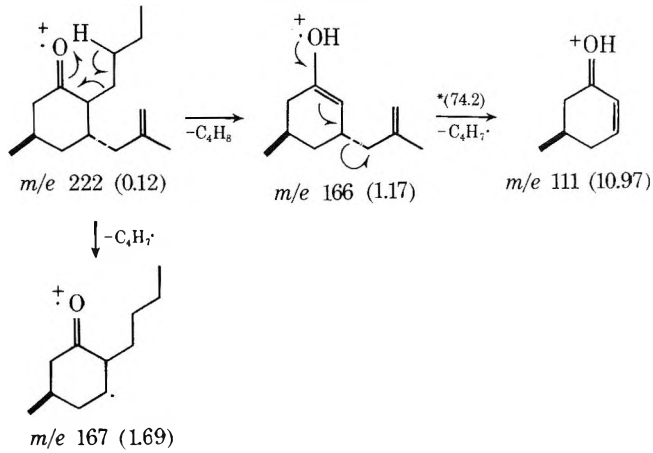


1 2 3

structures to such isomers, we examined the mass spectra of **2** and **3**. We were gratified to find that the two isomers differ markedly in their fragmentation patterns, and that structures may be readily assigned on this basis.

The 70-eV mass spectra of **2** and **3** are plotted in Figures 1 and 2. The base peak in the spectrum of **2** is *m/e* 111, at 10.97% of the total ion current (% TIC). The *m/e* 109 peak has an intensity of 3.19% TIC. For isomer **3**, the relative intensities of the *m/e* 109 and 111 peaks is reversed, with *m/e* 111 being 1.50% TIC and *m/e* 109 being 10.77% TIC. In addition to the *m/e* 109 and 111 fragments, both isomers show significant peaks at *m/e* 167 (loss of methallyl radical) and *m/e* 166 (McLafferty rearrangement). A rationale

Scheme I



for the principal fragmentations of compound **2** is outlined in Scheme I. A high-resolution spectrum of compound **2** confirmed that the *m/e* 111 fragment has the composition $C_7H_{11}O$. That this ion arises directly from a *m/e* 166 ion is shown by a significant metastable peak at *m/e* 74.2 (calcd, *m/e* 74.22).

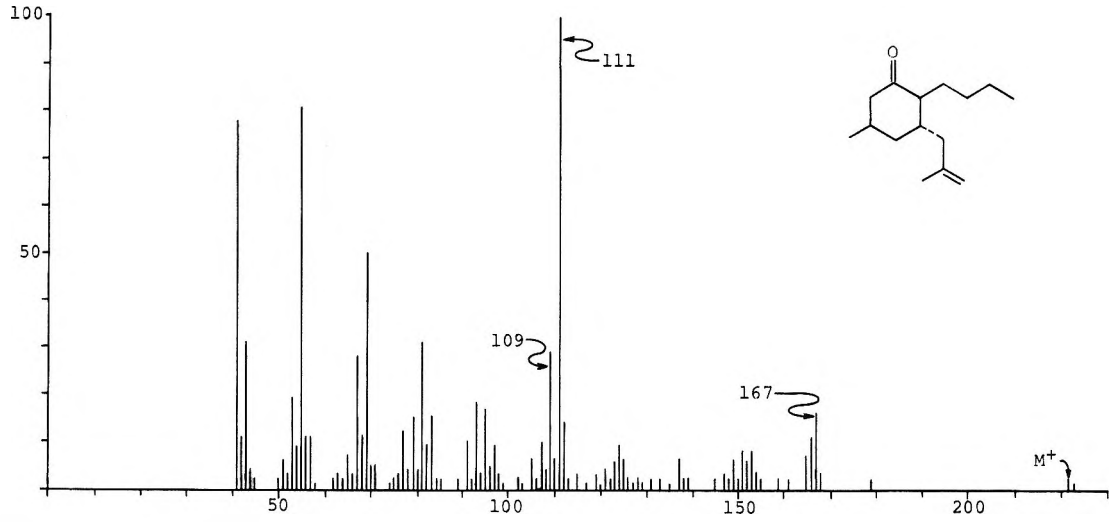


Figure 1. Mass spectrum of compound **2.**

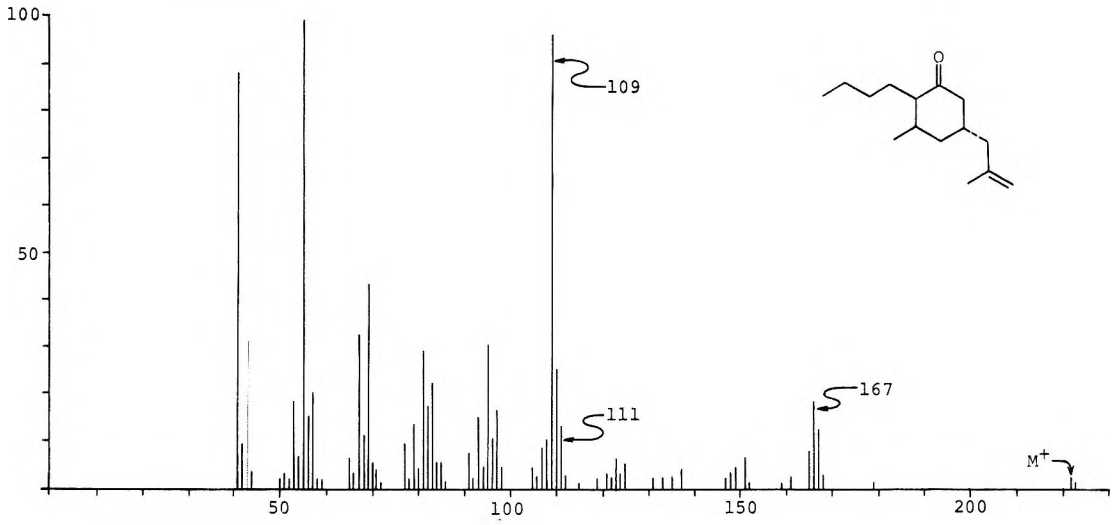
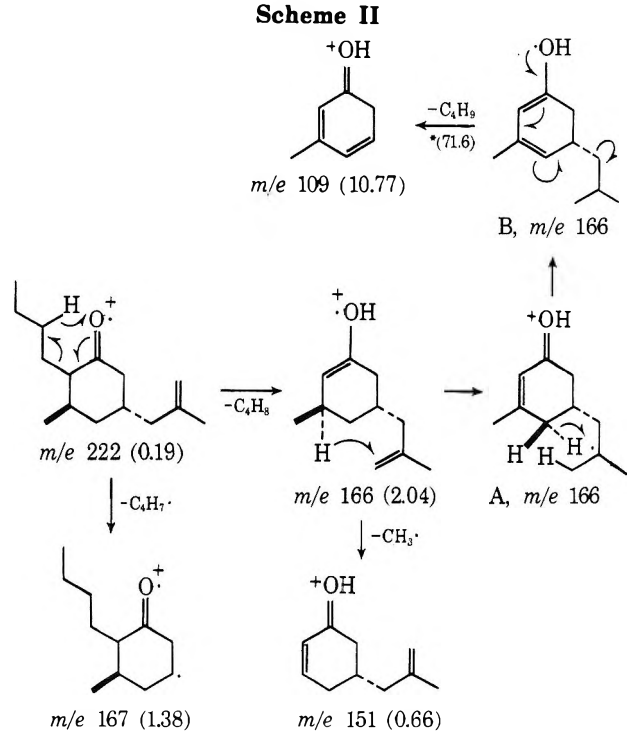


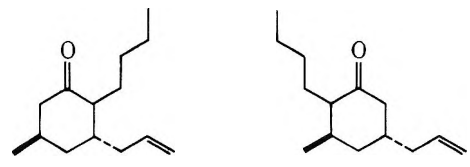
Figure 2. Mass spectrum of compound **3.**

For isomer **3** (Scheme II), the principal primary fragmentations are again loss of the methallyl chain (1.38% TIC) and McLafferty rearrangement (2.04% TIC). In this case, however, the McLafferty ion radical (*m/e* 166) cannot lose methallyl radical to give a stable oxonium ion, analogous to the *m/e* 166 → 111 fragmentation in Scheme I. Loss of methyl radical gives such an oxonium ion (*m/e* 151), but this fragmentation is not significant, probably because of the relatively high energy of CH_3·. Instead, we propose the path outlined in Scheme II. Transfer of the tertiary allylic hydrogen to the side-chain double bond gives a relatively stable oxonium ion A, which transfers a second hydrogen to give ion B. Finally, loss of isobutyl radical from ion B gives the stabilized oxonium ion with *m/e* 109. The *m/e* 109 fragment was shown to have the composition C_7H_9O by high-resolution studies. The observed metastable peak at *m/e* 71.6 (calcd, *m/e* 71.57) confirms the hypothesis that the *m/e* 109 ion arises directly from a fragment with *m/e* 166. Metastable ions corresponding to alternate origins of the *m/e* 109 fragment, which involve loss of the methallyl side chain and two hydrogens from the McLafferty ion, are not observed.

Scheme II

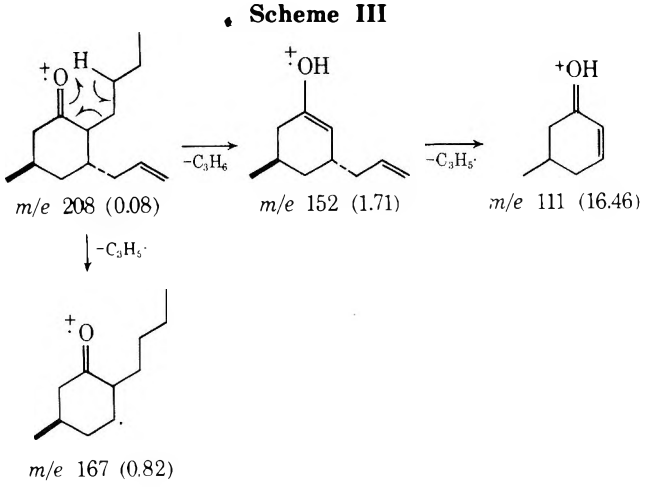


The generality of this fragmentation scheme is shown by the spectra of isomers **4** and **5**, in which the base peaks also

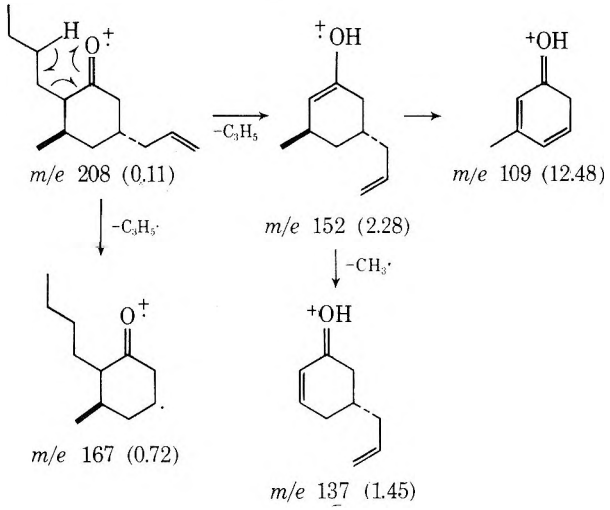


4 **5**

Scheme III

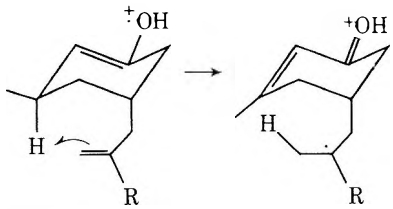


Scheme IV

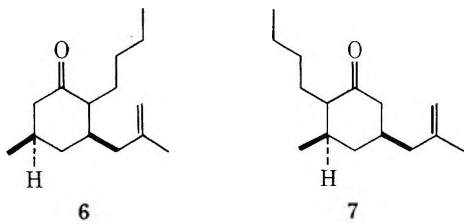


occur at *m/e* 111 and 109, respectively (see paragraph at end of paper regarding supplementary material). Principal fragmentations for the two isomers are shown in Schemes III and IV. Again, the reversal of the *m/e* 111 and 109 intensities is observed. Additionally, the McLafferty ion derived from **5** shows a greater tendency to lose CH_3· to give the *m/e* 137 ion (1.45% TIC). In the case of isomer **4**, the *m/e* 137 ion has only about one-third this intensity (0.45% TIC).

The intramolecular hydrogen transfers which are proposed to be involved in transforming the initial McLafferty ions into the *m/e* 109 ion would require that the allyl substituent be cis to the tertiary allylic hydrogen. To check



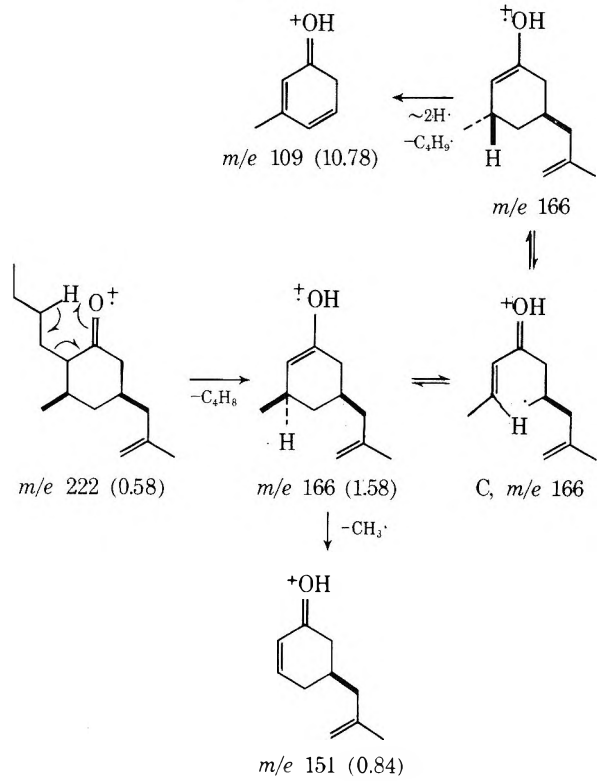
this hypothesis, we prepared isomers **6** and **7**, in which the methallyl side chain is trans to the relevent hydrogen. Iso-



6 **7**

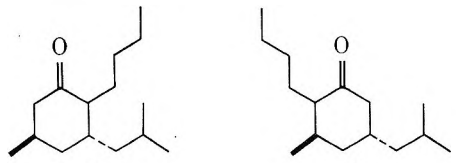
mer **6** behaves as expected, with the *m/e* 111 peak being 12.96% TIC, and the *m/e* 109 peak being only 3.68% TIC. However, we were surprised to find that the base peak in the spectrum of **7** is still *m/e* 109 (10.78% TIC), while the *m/e* 151 peak, which would result from loss of CH_3· from the McLafferty ion, is only 0.84% TIC (see paragraph at end of paper regarding supplementary material). These results are understandable in terms of the fragmentation

Scheme V



pathway in Scheme V. In other words, the cis and trans isomers may equilibrate in the McLafferty ion *via* ring-opened radical cation C.

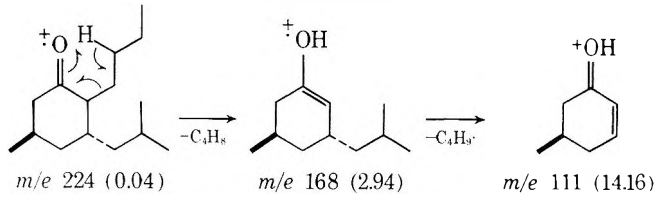
Compounds **8** and **9**, in which the methallyl group has been replaced by an isobutyl group, were prepared to test



8 **9**

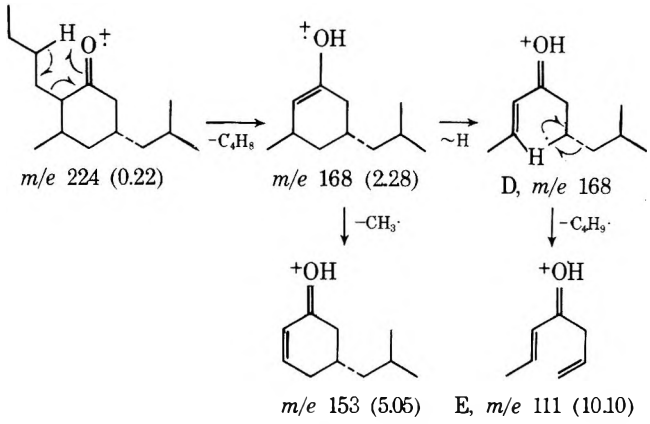
our hypothesis that intramolecular transfer of two hydrogens to the double bond is involved in the genesis of the *m/e* 109 fragments. As expected on the basis of this hypothesis, neither isomer gives a substantial fragment with *m/e* 109. The principal fragmentation path of **8** is McLafferty rearrangement, followed by expulsion of the isobutyl

Scheme VI



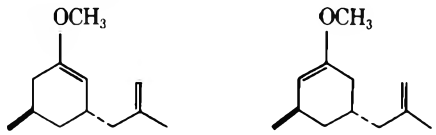
group to give the *m/e* 111 oxonium ion (Scheme VI, see paragraph at end of paper regarding supplementary mate-

Scheme VII



rial). For isomer **9** (Scheme VII), the McLafferty ion loses CH_3· to a significant extent, giving ion *m/e* 153 (5.05% TIC). The corresponding ion in the spectrum of **8** has an intensity of only 0.27% TIC. The *m/e* 111 peak in the spectrum of **9** is still substantial (10.10% TIC), and could arise via the ring-opened radical cation D. Expulsion of isobutyl radical would yield oxonium ion E.

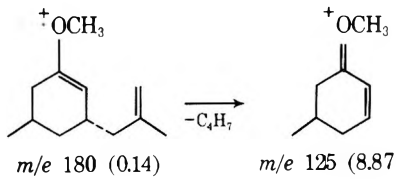
To further confirm the idea that the position of the double bond in the initial McLafferty ion governs the subsequent decomposition of the ion, the isomeric methyl enol



10 **11**

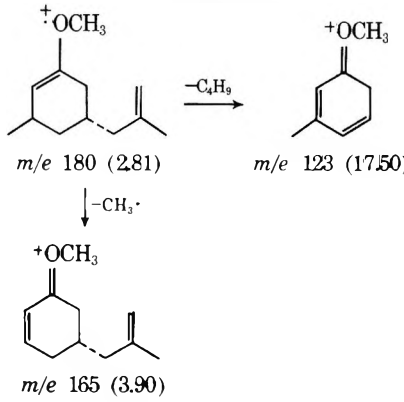
ethers **10** and **11** were prepared. As expected, the base peak in the spectrum of **10** has *m/e* 125, Scheme VIII. The M −

Scheme VIII



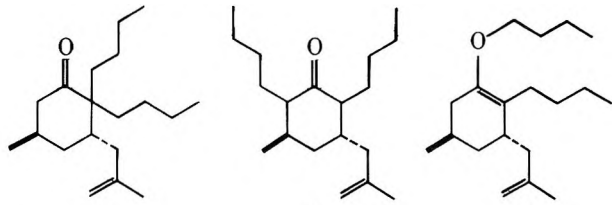
15 peak (*m/e* 165) is very weak, 0.10% TIC. For isomer **11**, the base peak is *m/e* 123, again corresponding to loss of methallyl and H_2 (Scheme IX). Additionally, the M − 15

Scheme IX



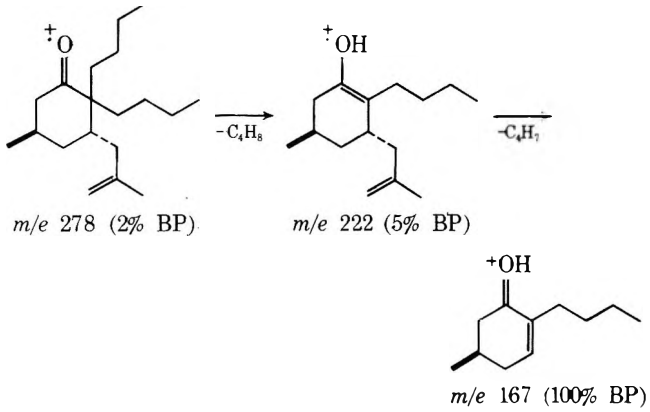
peak is now significant (3.90% TIC). (See paragraph at end of paper regarding supplementary material).

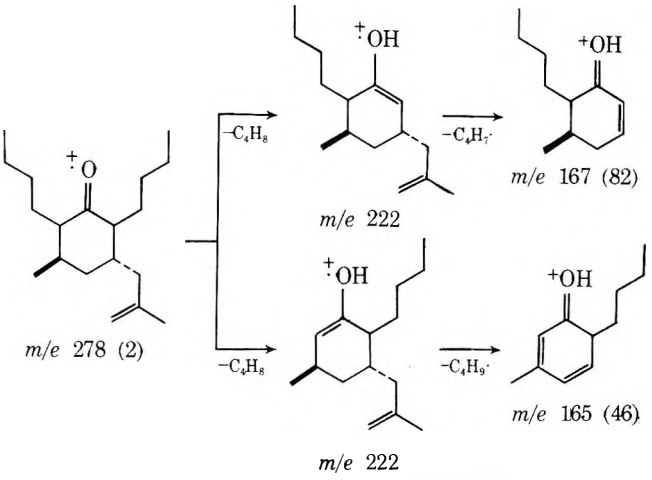
The fragmentation patterns which we have observed have been useful in assigning structure to some more highly alkylated materials prepared in our alkylation studies. For example, butylation of enolate **1**, when M = Na or K, gives three butylated products, **12**, **13**, and **14**, in addition to **2**



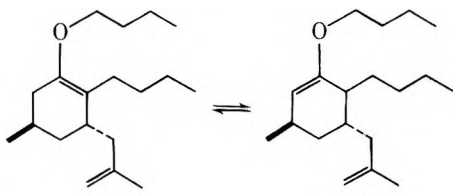
12 **13** **14**

and **3**. The structures of the three isomers were assigned on the basis of their mass spectra. The base peak in the spectrum of isomer **12** has *m/e* 167, corresponding to the fragmentation shown. Isomer **13** can undergo McLafferty rearrangement in either of two ways. Consequently, its spectrum shows ions which *m/e* (rel intensity) 167 (82) and 165 (46).





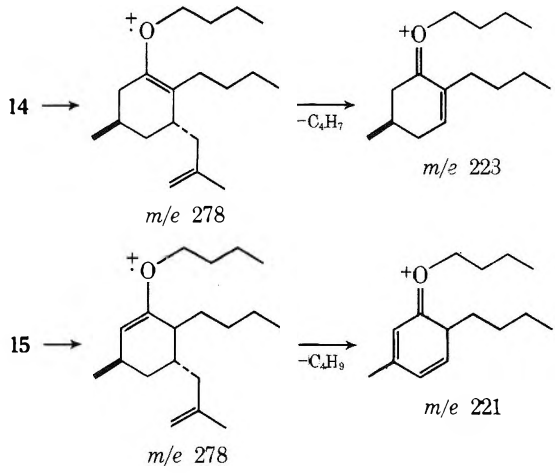
From its ir spectrum isomer **14** was suspected to be an enol ether with a tetrasubstituted double bond (ν 1675 cm^{-1}).[2] However, the double bond equilibrates upon GLC collection, so that the analytically pure material which we isolated by this method was actually a mixture of **14** and its double bond isomer **15**. Such facile equilibration was not



14 **15**

unexpected, since we had also encountered it with the isomeric enol ethers **10** and **11**. Correspondingly, the mass spectrum of the mixture shows fragments with *m/e* 121,

presumably deriving from **15**, and *m/e* 123, presumably deriving from **14**.



Experimental Section

Mass spectra were determined by Sherri Ogden on an MS-12 (low resolution) or CEC 21-110B (high resolution) instrument. Data were acquired with the Incos data acquisition system, Incos Corp., Berkeley, Calif.

Alkylation of Enolate 1. Isolation of Compounds 2, 3, 12, 13, and 14. The potassium enolate 1 (M = K) was alkylated as described in the accompanying communication.[1] Upon work-up, a mixture of butylated ketones was isolated which was shown by GLC (6 ft × 0.25 in. 15% NPGS, 200°, 120 ml/min) to have the following composition: 7.7% unalkylated ketone, 49.0% **2**, 13.7% **3**, 8.3% **12**, 5.5% **13**, and 15.8% **14**. Samples for mass spectral analysis were obtained by preparative GLC using the conditions described above. See Figures 1 and 2 for the spectra of **2** and **3**.

A sample of **14** was examined by ir as well as mass spectroscopy, ir (neat) 1675 cm^{-1} (enol ether). The sample of **14** was converted exclusively to **2** by treatment with 5% HCl.

Preparation of 2-Butyl-*trans*-3-allyl-5-methylcyclohexanone (4) and 2-Butyl-*trans*-3-methyl-5-allylcyclohexanone (5). Using conditions described elsewhere,[1,3] 48 mmol of a 0.98 *M* solution of allyllithium in ether, obtained by treatment of commercial tetraallyltin (Alfa-Ventron, Inc.) with phenyllithium,[4] was combined with 11.6 g (24 mmol) of copper iodide in 40 ml of anhydrous ether at −78° in an inert atmosphere to produce lithium diallylcuprate. This cuprate was in turn combined with 2.2 g (20 mmol) of 5-methylcyclohex-2-en-1-one, followed after 30 min by 6.1 ml of trimethylchlorosilane, 7.6 ml of triethylamine, and 3.8 ml of HMPT. After work-up and distillation, 3.0 g (76%) of 1-trimethylsiloxy-*trans*-3-allyl-5-methylcyclohex-1-ene was obtained: bp 58–60°C (1.0 Torr); ir (neat) 1660 cm^{-1} (enol ether); ^1H NMR (CCl_4) τ 4.33 (m, 1, vinyl H), 4.99 (m, 1, enol ether vinyl H), 5.30 (m, 2, vinyl H), 9.07 (d, 3, ring Me), 9.85 (s, 9, $SiMe_3$). Anal. Calcd for $C_{13}H_{24}OSi$: C, 69.57; H, 10.78. Found: C, 69.50; H, 10.96.

A solution of 560 mg (2.5 mmol) of the above silyl enol ether dissolved in 10 ml of dry tetrahydrofuran was added dropwise to a slurry of potassium amide prepared from 98 mg (2.5 mg-atoms) of potassium metal and 13 ml of ammonia. Following the procedure described earlier,[1] the resulting enolate was treated with 1.84 g (10 mmol) of butyl iodide to yield 550 mg of a ketone mixture upon work-up. GLC analysis (6 ft × 0.25 in. 15% NPGS, 225°, 120 ml/min) indicated that this mixture had the following composition: 7.2% unalkylated ketone (retention time 4.5 min), 54.0% **4** (retention time 7.2 min), 29.4% **5** (both epimers in equal amounts with retention times of 7.8 and 8.7 min), and 9.4% di-C-alkylated ketone (two compounds in equal amounts with retention times of 10.7 and 12.2 min). Samples for mass spectral analysis were again obtained by preparative GLC using the conditions described above. See Figures 3 and 4 (supplementary material) for the spectra of **4** and **5**.

Preparation of 2-Butyl-*cis*-3-methallyl-5-methylcyclohexanone (6) and 2-Butyl-*cis*-3-methyl-5-methallylcyclohexanone (7). Following a previously reported procedure,[5] a sample of 3-methallyl-5-methylcyclohex-2-en-1-one was prepared by treating methallylmagnesium chloride with 3-isobutoxy-5-methylcyclohex-2-en-1-one,[6] followed by hydrolysis of the resulting unsaturated alcohol with dilute HCl. A solution of 1.64 g (10 mmol) of the above unsaturated ketone, 0.7412 g (10 mmol) of *tert*-butyl alcohol, 4.0 ml of dry HMPT, and 5 ml of anhydrous ether was added dropwise to a dark blue solution of 0.153 g (22 mg-atoms) of lithium metal dissolved in 75 ml of anhydrous ammonia. After the addition was complete, the resulting mixture was stirred at the reflux temperature of ammonia for an additional 30 min. At the end of this time, the ammonia was allowed to evaporate under anhydrous conditions. The last traces of ammonia were removed by blowing nitrogen through the reaction flask for 2 hr. The resulting product was then dissolved in 50 ml of ether and treated with 6.1 ml of trimethylchlorosilane and 7.6 ml of triethylamine. The resulting mixture was stirred for 1 hr at room temperature and then diluted with 100 ml of pentane. This solution was washed successively with two 50-ml portions each of 5% HCl and 5% $NaHCO_3$ and then dried over magnesium sulfate. Solvent removal followed by distillation yielded 1.49 g (62.5% yield) of product which was identified as 1-trimethylsiloxy-*cis*-3-methallyl-5-methylcyclohex-1-ene: bp 73–74° (0.09 Torr); ir (neat) 1665 cm^{-1} (enol ether); ^1H NMR (CCl_4) τ 5.43 (m, 3, enol ether and methallyl vinyl H's), 8.36 (s, 3, vinyl Me), 9.10 (d, 3, ring Me), 9.87 (s, 9, silyl Me). Anal. Calcd for $C_{14}H_{26}OSi$: C, 70.52; H, 10.99. Found: C, 70.56; H, 10.91.

The $\Delta^{1,2}$ potassium enolate of *cis*-3-methallyl-5-methylcyclohexanone, prepared by treating 0.595 g (2.5 mmol) of the above silyl enol ether with 1 equiv of potassium amide, was combined with 1.84 g (10 mmol) of butyl iodide.[1] After work-up and solvent removal 500 mg of a ketone mixture was isolated and shown by GLC (6 ft × 0.25 in. 15% NPGS, 200°, 120 ml/min) to have the following composition: 31.3% unalkylated ketone (retention time 3.3 min), 30.5% **6** (retention time 5.5 min), 33.6% **7** (retention time 6.7 min), and 4.6% di-C-alkylated ketone (retention time 10.0 min). Samples for mass spectral analysis were prepared by preparative GLC. See Figures 5 and 6 (supplementary material) for the spectra of **6** and **7**.

Preparation of 2-Butyl-*trans*-3-isobutyl-5-methylcyclohexanone (8) and 2-Butyl-*trans*-3-methyl-5-isobutylcyclohexanone (9).[7] A solution of 5.5 g (60 mmol) of isobutyl chloride dissolved in 12 ml of anhydrous ether was added dropwise to 0.975 g (40 mg-atoms) of magnesium turnings covered with 25 ml of ether. The reaction was initiated with a crystal of iodine after a few drops of the halide solution had been added. Once the Grignard had begun to form, the addition was continued over a period of 45 min at room temperature, and the resulting mixture was allowed to stir for an additional 12 hr, during which time all of the magnesium was consumed. The resulting solution was then diluted with 25 ml of ether, cooled to 0°, and treated with 0.40 g of copper(I) iodide. To the resulting dark black mixture was slowly added a solution of 2.2 g (20 mmol) of 5-methylcyclohex-2-en-1-one[8] and 15 ml of ether. After the addition was complete, the resulting solution was stirred for an additional 1 hr at 0°. At the end of this time, 6.1 ml of trimethylchlorosilane, 7.6 ml of triethylamine, and 3.8 ml of HMPT was added successively and the resulting mixture was stirred for 1 hr at room temperature. This solution was then diluted with 100 ml of pentane, washed successively with two 50-ml portions each of 5% HCl and 5% $NaHCO_3$, and dried over magnesium sulfate. After solvent removal, the crude product was distilled, yielding 3.4 g (71%) of 1-trimethylsiloxy-*trans*-3-isobutyl-5-methylcyclohex-1-ene: bp 71° (0.9 Torr); ir (neat) 1665 cm^{-1} (enol ether); ^1H NMR (CCl_4) τ 5.30 (d, 1, vinyl H), 9.10 (m, 9, ring and isobutyl Me's), 9.83 (s, 9, silyl Me). Anal. Calcd for $C_{14}H_{28}OSi$: C, 69.93; H, 11.74. Found: C, 70.34; H, 11.38.

The above silyl ether (0.60 g, 2.5 mmol) was then converted to its potassium enolate with 1 equiv of potassium amide and treated with 1.84 g (10 mmol) of butyl iodide. Upon work-up and solvent removal, 500 mg of a ketone mixture was isolated, which was examined by GLC (6 ft × 0.25 in. 15% NPGS, 200°, 120 ml/min) and found to have the following composition: 7.2% unalkylated ketone (retention time 2.5 min), 53.4% **8** (retention time 4.5 min), 32.2% **9** (two epimers in a ratio of 3:2, retention times of 5.1 and 5.7 min), and 7.2% di-C-alkylated ketone (retention time 7.5 min). Spectral samples were obtained by preparative GLC (6 ft × 0.25 in. 15% NPGS, 175°, 120 ml/min). See Figures 7 and 8 (supplementary material) for the mass spectra of **8** and **9**.

Preparation of 1-Methoxy-*trans*-3-methallyl-5-methylcyclohex-1-ene (10) and 1-Methoxy-*trans*-3-methyl-5-methallylcyclohex-1-ene (11). A solution of 1-trimethylsiloxy-*trans*-3-methallyl-5-methylcyclohex-1-ene[1] (0.595 g, 2.5 mmol) in 10 ml of anhydrous THF was treated with 2.5 mmol of a methyllithium–ether solution for 2 hr at room temperature. The resulting lithium enolate solution was transferred by syringe to a clean, dry dropping funnel and added dropwise to a slurry of 1.03 g (5.0 mmol) of trimethyloxonium hexafluorophosphate (Alfa-Ventron, Inc.) in 5 ml of ether. After stirring for 15 min at room temperature, the so-

lution was diluted with 50 ml of ether and washed successively with 50 ml of water and 50 ml of saturated NaCl solution. After drying over potassium carbonate, the solvent was removed, yielding 400 mg of product. Analysis of this crude material by GLC (10 ft × 0.25 in. 15% NPGS, 175°, 120 ml/min) indicated that it consisted of three components: 36.2% **10** (retention time 4.0 min), 34.8% **11** (retention time 4.4 min), and 30.0% C-methylated ketone (retention time 8.2 min). This was rather surprising, since enolate equilibration is not usually encountered under the reaction conditions employed. To check if the observed equilibration was taking place in the chromatograph, the remaining product was purified by column chromatography (15 g of Silicar CC-7, 200–325 mesh, 10% ether–hexane elutant). This was indeed the case as the 200 mg of enol ether obtained from the chromatography column was identified as pure **10**. See Figure 9 (supplementary material) for the mass spectrum of **10**: ir (neat) 1665 (enol ether), 889 cm^{-1} (methallyl double bond); ^1H NMR (CCl_4) τ 5.33 (m, 1, vinyl H), 6.55 (s, 3, enol Me), 8.27 (s, 3, vinyl Me), 9.03 (d, 3, ring Me).

A sample of **11** was obtained by preparative GLC of the initial crude product. See Figure 10 (supplementary material) for the mass spectrum of **11**: ir (neat) 1665 (enol ether), 890 cm^{-1} (methallyl double bond).

Acknowledgment. The authors express their gratitude to the National Science Foundation for support of this research under Grant GP 31321X.

Registry No.—**1**, 55373-31-4; **2**, 55373-32-5; **3**, 55373-33-6; **4**, 55373-34-7; **5**, 55373-35-8; **6**, 55449-02-0; **7**, 55449-03-1; **8**, 55373-36-9; **9** epimer 1, 55373-37-0; 9 epimer 2, 55373-38-1; **10**, 55373-39-2; **11**, 55373-40-5; **14**, 55373-41-6; 1-trimethylsiloxy-*trans*-3-allyl-5-methylcyclohex-1-ene, 55373-42-7; potassium amide, 17242-52-3; butyl iodide, 542-69-8; 1-trimethylsiloxy-*cis*-3-methallyl-5-methylcyclohex-1-ene, 55400-55-0; isobutyl chloride, 513-36-0; 5-methylcyclohex-2-en-1-one, 7214-50-8; trimethylchlorosilane, 75-77-4; 1-trimethylsiloxy-*trans*-3-isobutyl-5-methylcyclohex-1-ene, 55373-43-8; 1-trimethylsiloxy-*trans*-3-methylallyl-5-methylcyclohex-1-ene, 55373-44-9.

Supplementary Material Available. Mass spectra of compounds **4–11** will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 24× reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 16th St., N.W., Washington, D.C. 20036. Remit check or money order for $4.50 for photocopy or $2.50 for microfiche, referring to code number JOC-75-2160.

References and Notes

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A Synthetic Approach to the Dendrobine Skeleton

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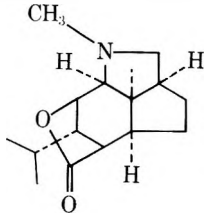
A possible synthetic route to the alkaloid dendrobine has been explored. Intramolecular Michael cyclization of unsaturated keto nitrile **17** yields only stereoisomer **18**. The stereochemistry of **18** has been established by the synthesis of a compound with the opposite stereochemistry of the cyanomethyl side chain (**28**). A rationale for the stereospecificity of the cyclization reaction is proposed.

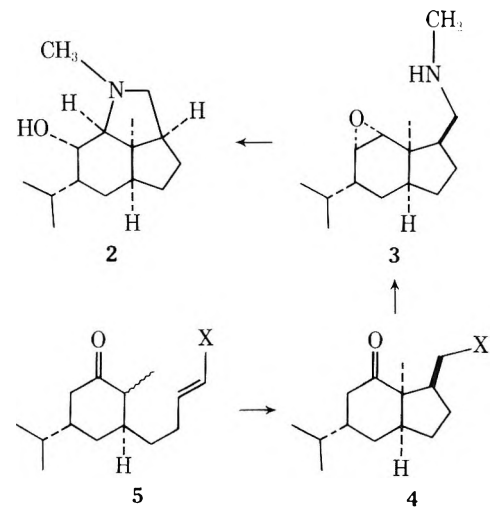
The sesquiterpene alkaloid dendrobine (**1**) occurs as a component of the Chinese drug Chin-Shih-Hu, which is prepared from the ornamental orchid *Dendrobium nobile* (Orchidaceae). It was first isolated from the stem of the



1

plant by Suzuki and coworkers.[1] Recently, the alkaloid, as well as a number of its congeners, has been extensively investigated by Hirata,[2] Inubushi,[3] and Okamoto,[4] who have determined the stereostructure shown in **1**. Dendrobine's interesting structure has elicited considerable attention from synthetic chemists, resulting in three total syntheses of the alkaloid itself[5–7] as well as a synthesis of the basic tricyclic skeleton.[8] In this communication we outline our own approach to the synthesis of the alkaloid.

In our projected synthesis of the basic skeleton, presented below in gross outline, the key step would be the Michael reaction **5** → **4**. The group X must be the synthetic

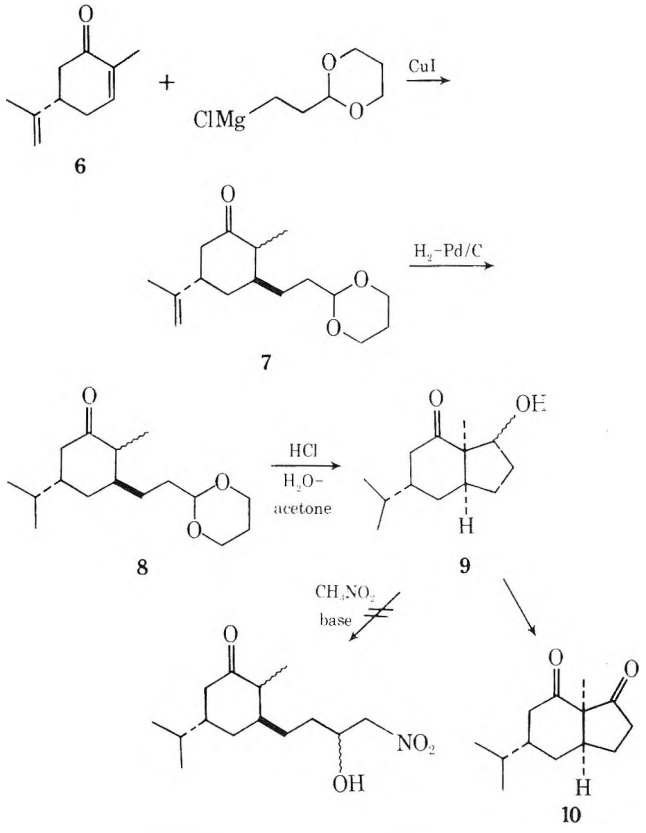


2 **3** **5** **4**

equivalent of $NHCH_3$, i.e., NO_2, CO_2R, CN, etc. Although the cis fusion of the product hydrindanone **4** could reasonably be expected,[9] the steric disposition of CH_2X in such a reaction is difficult to predict. As will be seen in the sequel, the desired intramolecular Michael reaction does indeed occur readily when X = CN, albeit in precisely the opposite steric sense. Although we were able to invert the stereo-

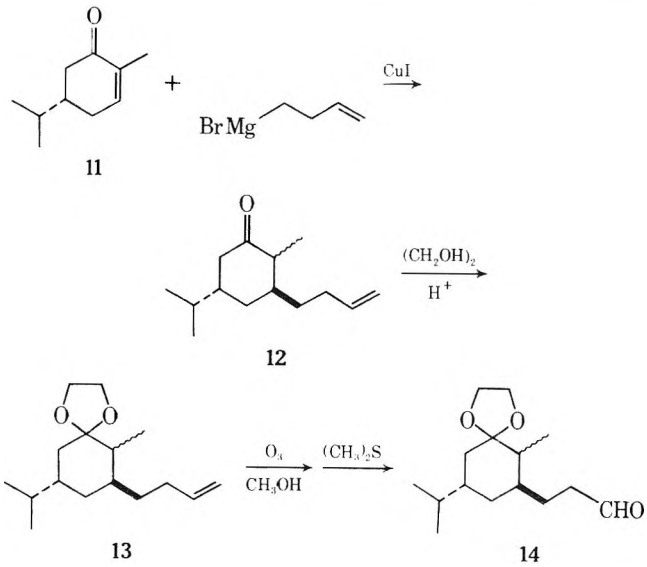
chemistry of the cyanomethyl side chain, the resulting synthesis of **4**, R = CN, is too awkward for use in a synthesis of the alkaloid.

For the preparation of compounds of type **5**, we began with (+)-carvone (**6**). Copper-catalyzed addition of the Grignard reagent derived from β-chloropropionaldehyde trimethylene acetal yields the keto acetal **7**, which is smoothly hydrogenated to **8**. The trans disposition of the groups at C-3 and C-5 is assumed by analogy with the conjugate addition of methylmagnesium bromide to 5-methylcyclohexenone.[10] Hydrolysis of **8**, even under very mild conditions, yields only the cyclic aldol **9**, which may be oxidized to dione **10** (ν_{max} 1755, 1710 cm^{-1}). Various attempts to utilize aldol **9** directly, e.g., in a Knoevenagel condensation with nitromethane, were unsuccessful.[11]

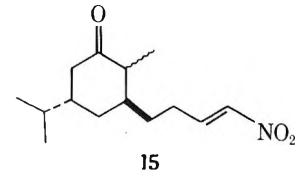


6 7 8 9 10

In order to circumvent this problem, we carried out the conjugate addition of 4-butenylmagnesium bromide onto (+)-carvotanacetone (**11**). The adduct **12** is smoothly ketalized and the resulting unsaturated ketal **13** reacts with ozone in methanol to give ketal aldehyde **14**. After numerous unsuccessful attempts to convert **13** or **14** into nitroalkene **15**,[11] we decided to explore the use of an α,β-unsaturated nitrile as the Michael acceptor group in formation of the cyclopentane ring. To this end, aldehyde **14** was condensed with diethyl cyanomethylphosphonate after the method of Wadsworth and Emmons.[12] Unsaturated nitrile **16** is produced in this research in good yield, as a mixture of geometric isomers. Hydrolysis of **16** yields the corresponding cyano ketone **17**, which reacts with potassium *tert*-butoxide in *tert*-butyl alcohol to yield hydrindanone **18**. The ^1H NMR spectrum of **18**, at 60 and at 220 MHz, shows the angular methyl group as a sharp singlet at δ 1.10 ppm, with an intensity 50% that of the isopropyl doublet at δ 0.92 ppm, suggesting that a single stereoisomer is produced in the cyclization.



11 12 13 14



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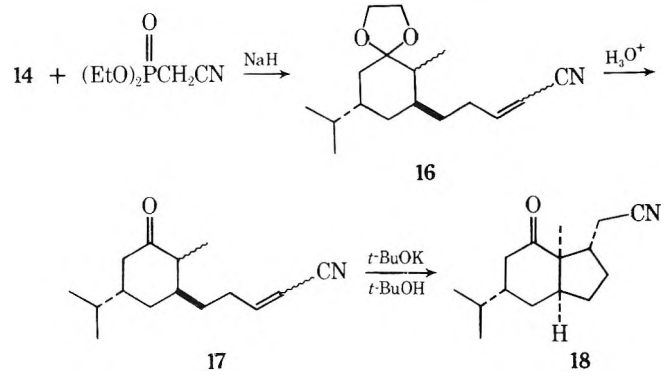
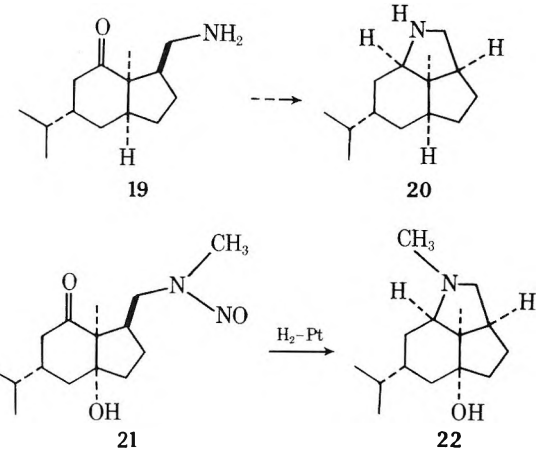


16 17 18

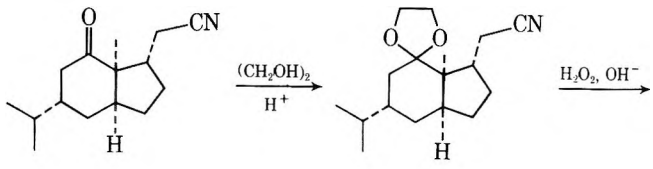
In order to determine the stereochemistry of the cyanomethyl side chain in **18**, we decided to convert it into an amino ketone, which should undergo reductive amination to yield the tricyclic amine **20** if the cyanomethyl group is trans to the angular methyl (e.g., **19**). The related bicyclic amine *N*-nitroso-6-hydroxynornobilonine (**21**) has previously been cyclized to yield dendramine (**22**) by treatment with hydrogen at atmospheric pressure over Adams catalyst.[13] Examination of Dreiding stereomodels suggests that the ring closure is not possible when the aminomethyl group is cis to the angular methyl.



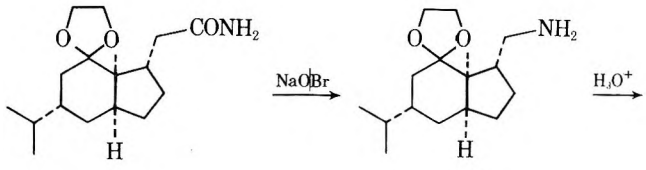
19 20 21 22

Toward this end, **18** was ketalized and ketal **23** was hydrolyzed to amide **24**. Hofmann degradation of **24** yields amine **25**, which may be hydrolyzed to amino ketone **26**. All attempts at the reductive cyclization of **26** failed,[11] suggest-

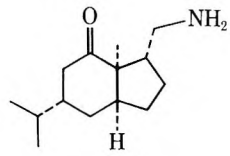
ing that the aminomethyl group indeed has the α configuration.[14]



18 23

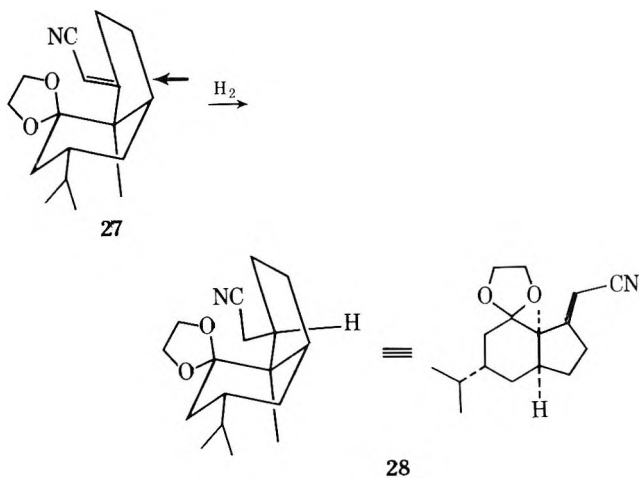


24 25



26

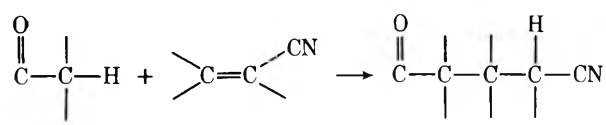
In order to provide more definitive evidence for the suspected stereochemistry of 18, we decided to invert the stereochemistry of the cyanomethyl group and examine the resulting epimer. Examination of Dreiding models reveals that the ketal oxygen so encumbers the β face of unsaturated nitrile 27 that catalytic hydrogenation of the double



27 28

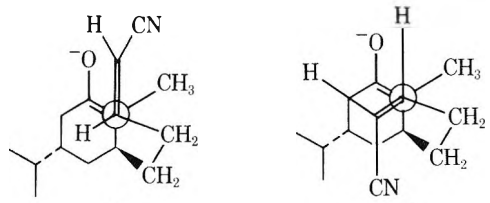
bond is highly likely to produce the desired β configuration[14] at the new chiral center. As suspected, compound 27, prepared from 23 by selenylation, followed by elimination of the derived selenoxide,[16] gives a ketal nitrile isomeric with 23 upon catalytic hydrogenation.

On the basis of the failure of 26 to cyclize and the β-face hindrance in 27, it seems clear that the cyanomethyl group is α in 23 and β in 28. In searching for an explanation for the observed stereospecificity, we must first ask whether the stereochemistry is established thermodynamically or kinetically. An estimate of the overall reaction energetics involved in the conversion of one carbon–carbon double bond into two carbon–carbon single bonds predicts $\Delta H^\circ \approx -18$ kcal mol^{-1}.[17] Thus, the reverse Michael reaction (18 → 17) must have $E_{act} \approx 18$ kcal mol^{-1} greater than for the forward reaction (17 → 18). From this estimate of ΔE_{act}, the ratio $k_{reverse}/k_{forward} \approx 3 \times 10^{-12}$. Furthermore, a simple experiment showed that the α hydrogens in octanonitrile are not exchanged for deuterium under conditions more drastic than the conditions required to convert 17 into 18.[18] Thus, it is reasonable to assume that the cyclization is effectively irreversible under the conditions employed and that 18 is, in fact, a kinetic product.



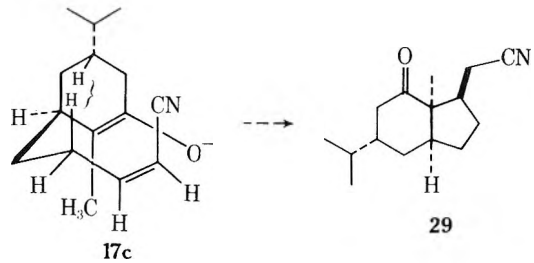
ΔH° = 142 kcal mol^{-1} − 2(80 kcal mol^{-1})

The observed stereochemical result probably has its origin in steric effects in the two alternate transition states. An examination of Dreiding stereomodels reveals that there are three reasonable conformations whereby the enolate ion derived from 17 may cyclize.[19] In two of the conformations, the two reacting double bonds are staggered relative to one another at a dihedral angle of approximately 60° (see structures 17a and 17b, below). Conformation 17b,



17a 17b

in which the side-chain double bond lies directly over the cyclohexane ring, appears to be far less stable than 17a, which gives rise to the observed product, 18. Like 17b, a third conceivable cyclizing conformation of 17, depicted below in a different perspective, would also yield the β-cyanomethyl stereochemistry (29). However, this conforma-



17c 29

tion suffers from a severe H–H interaction, as indicated. The internuclear distance between the two interacting hydrogens is only 1.6 Å.[20]

In principle, compound 28 may serve as a synthetic intermediate for further elaboration into dendrobine. However, in light of the success of other workers in synthesizing the alkaloid,[5–7] we have abandoned further work on the project.

Experimental Section

All melting and boiling points are uncorrected. The nuclear magnetic resonance (NMR) spectra were determined on a Varian T-60 or HR-220 spectrometer in CCl_4 solution containing tetramethylsilane as internal standard. Chemical shifts are given on the δ scale; the multiplicity, peak areas, and proton assignments are given in parentheses. The infrared (ir) spectra were measured as thin films between NaCl plates on a Perkin-Elmer 137 or 237 infrared spectrophotomer unless otherwise indicated. Consolidated 21-110B and AEI MS-12 mass spectrometers provided the mass spectra. Microanalyses were performed by the University of California Microanalytical Laboratory, Berkeley, Calif.

2-Methyl-3β-(3-trimethylenedioxypropyl)-5α-isopropenylcyclohexanone (7). To a 300-ml round-bottom flask equipped with a dropping funnel (pressure equalized), magnetic stirrer, reflux condenser, and a N_2 inlet tube was added 1.22 g (0.05 mol) of magnesium turnings. The N_2 purge was started and maintained throughout the reaction; the flask and dropping funnel were carefully flamed using a soft flame in order to remove traces of moisture. A 20-ml portion of dry tetrahydrofuran (THF) was added to

the flask along with a small crystal of iodine. A few drops of β-chloropropionaldehyde trimethylene acetal[21] were added and the stirred reaction mixture was refluxed for 15 min; however, the reaction failed to commence. A few drops of ethyl iodide were added and the mixture was refluxed briefly; the iodine coloration disappeared and was replaced by a faint cloudiness. Dropwise addition of a solution of the chloroacetal (7.53 g, 0.05 mol, 6.54 ml) in 10 ml of dry THF was started, and the reaction mixture now developed a dark color, indicating that the reaction was underway. The reaction mixture was occasionally heated to reflux during addition of the chloroacetal solution over a 45-min period.

After refluxing for 75 min, during which time almost all of the magnesium was consumed, the reaction mixture was diluted with 30 ml of dry THF and cooled to 0° by stirring in an ice bath for 20 min. Cuprous iodide (0.476 g, 0.0025 mol, 5 mol % based on Mg) was added to the stirred solution at 0°, and stirring was continued for an additional 20 min. A solution of (+)-carvone (7.51 g, 0.05 mol) in 10 ml of dry THF was added dropwise to the reaction mixture (0°) over a 10-min period and the solution was then stirred at 0° for 1 hr.

The mixture was poured into a cold (0°) aqueous solution (200 ml) of ammonia and ammonium chloride (pH ~8); the organic layer was separated and the aqueous layer was extracted with ether. The combined organic solutions were dried and the ether was evaporated. The residual liquid was fractionally distilled at reduced pressure to yield a forerun [bp 49–74° (2 mm), 1.69 g, mainly (+)-carvone and β-chloropropionaldehyde trimethylene acetal]. The main fraction was 5.43 g of **7** (41%) as a clear, viscous liquid, bp 157–167° (1 mm).

GLC analysis (20% Carbowax 20M, 60/80 Chromosorb W, 5 ft × 0.25 in., 206°, flow rate 80 ml/min) of the main fraction showed only one broad peak at 35.5-min retention time. There was no trace of either (+)-carvone or the chloroacetal in the product.

Ir 2980, 2870, (C–H), 1715 (C=O), 1650 (alkene), 1150, 1075, 1010 cm^{-1} (C–O–C); NMR δ 1.00 (m, 3, Me), 1.75 (s, 3, vinyl Me), 3.85 (m, 5, CH next to O), 4.72 (broad s, 2, CH_2=); low-resolution mass spectrum M^+ *m/e* 266.

Anal. Calcd for $C_{16}H_{26}O_3$: C, 72.14; H, 9.84. Found: C, 72.32; H, 9.68.

The above preparation was repeated using carefully redistilled (+)-carvone and chloroacetal, and the Grignard reagent was prepared at 48–50° for 20 hr to ensure complete reaction. Also, the conjugate addition reaction mixture was stirred at 0° for 8 hr instead of only 1 hr. These modifications gave, upon work-up in the above manner, 6.97 g (52.5%) of adduct **7**.

2-Methyl-3β-(3-trimethylenedioxypropyl)-5α-isopropylcyclohexanone (8). To a 125-ml round-bottom hydrogenation flask fitted with a ground glass joint and a Teflon-coated magnetic stirring bar were added the following: conjugate addition product **7** (3.81 g, 14.3 mmol), 10% Pd/C (191 mg, 5 wt % based on **7**), and ethyl acetate (50 ml). The stirred reaction mixture was hydrogenated at 23–24° over a 25.5-hr period during which 360.8 ml (92% of theory) of H_2 was taken up at atmospheric pressure. The catalyst was removed by filtration and the solvent was evaporated to give a residual yellow oil which was purified by distillation at reduced pressure to yield 2.89 g (75.4% of theory) of clear, colorless liquid product, bp 149–152° (0.5 mm).

GLC analysis (4% FFAP, 198°, flow rate ~120 ml/min) of the clear liquid product shows two major peaks: hydrogenated conjugate adduct (91%, 18.8 min) and starting conjugate adduct (9%, 21.2 min).

Ir 2980, 2880 (C–H), 1720 (C=O), 1150, 1080, 1010 cm^{-1} (C–O–C); NMR δ 0.93 (d, 9, CH_3 and isopropyl), 1.43 (m, CH_2), 3.90 (m, 5, CH next to O); high-resolution mass spectrum M^- *m/e* 268.2043 (calcd for $C_{16}H_{28}O_3$, 268.2041, Δ*m* = +0.2 mmu).

Anal. Calcd for $C_{16}H_{28}O_3$: C, 71.60; H, 10.52. Found: C, 71.35; H, 10.46.

3aα,4,5,7a-Tetrahydro-1-hydroxy-5α-isopropyl-7aα-methyl-7(6*H*)-indanone (9). To a 50-ml round-bottom flask equipped with a ground glass joint and a Teflon-coated magnetic stirring bar were added the following: keto acetal **7** (1.72 g, 6.4 mmol), 90% aqueous acetone containing 1.34% HCl (20 ml). The solution was stirred under N_2 at room temperature for 72 hr. After a normal work-up, aldol **9** was obtained as a dark yellow oil. Distillation at reduced pressure through a short-path still gave 0.816 g (60.7%) of nearly colorless, clear liquid product: bp 125–130° (0.5 mm); ir 3450 (HO), 2980 (C–H), 1710 (C=O), 1470, 1070 cm^{-1}; NMR δ 0.92 (d, 6, isopropyl), 1.11 (s, 3, angular CH_3), 3.52 (broad s, 1, HO), 4.42 (broad s, 1, CH next to OH); high-resolution mass spectrum M^+ *m/e* 210.1621 (calcd for $C_{13}H_{22}O_2$, 210.1619, Δ*m* = +0.2 mmu).

3aα,4,5,7a-Tetrahydro-5α-isopropyl-7aα-methyl-1,7(2*H*,6*H*)-indanedione (10). To a 50-ml round-bottom flask equipped with a Teflon-coated magnetic stirring bar and a reflux condenser fitted with a drying tube filled with Drierite were added CH_2Cl_2 (5 ml) and pyridine (0.273 g, 0.278 ml, 34.44×10^{-4} mol). The solution was stirred, and CrO_3 (0.1728 g, 17.28×10^{-4} mol) was added in one portion. The deep burgundy solution was then stirred at room temperature (29°) for 30 min. A solution of keto alcohol **9** (0.0603 g, 2.87×10^{-4} mol) in a small volume of CH_2Cl_2 was added in one portion; a black, tarry precipitate separated immediately. The solution was allowed to stir at room temperature (31°) for 30 min, after which ether (25 ml) was added, and the organic layer was washed with water (5 × 5 ml) followed by drying over anhydrous $MgSO_4$. The solvent was removed at reduced pressure (rotary evaporator, 40°, 1 hr) to give an amber oil still containing pyridine. The oil was dried in vacuo (1 mm, 55°, 3 hr) to give 0.0422 g (70.6%) of liquid product: ir 2950 (C–H), 1755 (cyclopentanone C=O), 1710 cm^{-1} (cyclohexanone C=O); NMR δ 0.93 (d, 6, isopropyl), 1.20 (s, 3, angular CH_3), 2.00 (m, 11, CH_2); low-resolution mass spectrum M^+ *m/e* 208.

Anal. Calcd for $C_{13}H_{20}O_2$: C, 74.96; H, 9.68. Found: C, 74.71; H, 9.42.

2-Methyl-3β-(3-butenyl)-5α-isopropylcyclohexanone (12). To a 200-ml round-bottom three-necked flask equipped with a pressure-equalized dropping funnel, mechanical stirrer (Teflon paddle), reflux condenser, and a N_2 purge bubbler was added 1.22 g (0.05 mol) of magnesium turnings. A solution of 6.75 g (0.05 mol) of 4-bromo-1-butene in 10 ml of dry THF was added to the dropping funnel; a few drops of alkenyl halide were added to the reaction flask along with a small crystal of iodine. The reaction was initiated by heating to reflux. The solution of alkenyl halide was added dropwise to the stirring, refluxing mixture of THF–Mg over a 50-min period. The solution was then refluxed for an additional 6 hr, after which almost all of the magnesium had been consumed. A 50-ml portion of dry THF was added and the solution was cooled to 0° over a 20-min period, during which a white precipitate formed in the dark solution.

To the stirring mixture at 0° was added 0.4883 g (2.56 mmol, 5.12 mol % based on Mg) of CuI in one portion. After 50 min at 0°, a solution of 7.61 g (0.05 mol) of carvotanacetone (**11**) in 10 ml of dry THF was added in a dropwise manner over a 15-min period. The reaction mixture was stirred overnight at 0° and was then poured into 400 ml of a cold solution of aqueous NH_3–NH_4Cl (pH ~8). The organic layer was separated and the aqueous phase was extracted with ether. The organic layers were combined, dried, and evaporated to give 8.95 g (86%) of amber oil which was distilled (9-in. Vigreux) to give fraction 1 [0.57 g, bp 63–103° (1.2 mmHg), carvotanacetone], fraction 2 [5.57 g, bp 107–108° (1.2 mmHg), 52.4%], and finally, by replacement of the fractionating column with a short-path still, fraction 3 [0.93 g, bp 169–172° (0.1 mmHg)].

GLC analysis of fraction 2 (4% FFAP, 10 ft × 0.25 in., 172°, 120 ml/min) shows the presence of ca. 98% pure product at retention time 2.6 min.

Ir 2950, 2930, 2870 (C–H), 1710 (C=O), 1640 (alkene), 910 (CH_2=); NMR δ 0.95 (d, 6, isopropyl), 0.95 (s, 3, CH_3 next to carbonyl), 4.99 (m, 2, CH_2=), 5.70 (m, 1, vinyl H next to CH_2=); high-resolution mass spectrum M^+ *m/e* 208.1821 (calcd for $C_{14}H_{24}O$: 208.1827, Δ*m* = −0.6 mmu).

Anal. Calcd for $C_{14}H_{24}O$: C, 80.71; H, 11.61. Found: C, 80.84; H, 11.82.

2-Methyl-3β-(3-oxopropyl)-5α-isopropylcyclohexanone Ethylene Ketal (14). A solution of 2.52 g of ketal **13** in 10 ml of methanol was cooled to −65° and ozonized on a commercial Welsbach ozonator (0.1 mmol O_3/min) for 100 min (10 mmol O_3). The cold solution was flushed with N_2 for 40 min and then 1.0 ml (13.5 mmol) of dimethyl sulfide was added. The solution was then stirred at −12 to −4° for 1 hr, then at ice-bath temperature (0°) for 1 hr, and finally at room temperature for 70 min. After evaporation of the solvent at reduced pressure, the residue was treated with 25 ml of water and 40 ml of light petroleum ether. The aqueous layer was separated and further extracted with petroleum ether. The combined organic layer was washed with water, dried, and evaporated to give 2.37 g (93.4% yield) of viscous, clear liquid.

GLC (4% FFAP, 10 ft × 0.25 in., 196°, 100 ml/min) shows the presence of ca. 95% pure ketal aldehyde (14.0 min) with a small amount of lower boiling material (1.75, 2.1, 3.1 min).

Ir 2990, 2900 (C–H), 2740 (aldehyde C–H), 1725 (CHO), 1170, 1150, 1095, 1075, 1040, 950 cm^{-1} (C–O–C); NMR δ 0.90 (t, 9, CH_3, isopropyl), 1.41 (m, CH_2), 3.82 (s, 4, OCH_2), 9.44 (t, 1, aldehyde H); low-resolution mass spectrum M^+ *m/e* 255; 141.

Anal. Calcd for $C_{15}H_{26}O_3$: C, 70.83; H, 10.30. Found: C, 70.59; H, 10.27.

2-Methyl-3β-(4-cyano-3-butenyl)-5α-isopropylcyclohexanone Ethylene Ketal (16). To a 25-ml round-bottom three-necked flask equipped with a Teflon-coated magnetic stirring bar, N_2 gas bubbler, and a serum cap was added NaH (0.21 g of a 57% dispersion in mineral oil, 0.120 g NaH, 5 mmol). The NaH was freed of mineral oil by washing with dry pentane. Dry glyme (5 ml) was added and the stirred suspension was cooled to 20°. Diethyl cyanomethylphosphonate (0.89 g, 5 mmol) was added dropwise over a 15-min period and the solution was stirred at room temperature for 35 min. At this point, a solution of ketal aldehyde **14** (1.27 g, 5 mmol) in dry glyme (2.5 ml) was added in a dropwise fashion over a 15-min period; during the addition a gummy precipitate separated. The reaction mixture was stirred at room temperature for 2 hr and then diluted with 30 ml of water. The resulting mixture was extracted with ether and the organic layer was washed with water and saturated aqueous NaCl, dried, and evaporated to give 1.18 g (86%) of amber liquid.

GLC analysis (4% FFAP, 10 ft × 0.25 in., 210°, 120 ml/min) showed two major components (*E* and *Z* stereoisomers) with retention times of 33.3 and 36.5 min.

Ir 3020, 2950, (C–H), 2240 (CN), 1630 (alkene), 1170, 1150, 1100, 1080, 1045, 950 cm^{-1} (C–O–C); NMR δ 0.89 (d, 9, CH_3, isopropyl), 1.42 (m, CH_2), 3.83 (s, 4, OCH_2CH_2O), 5.26 (m, 1, vinyl H α to CN), 6.56 (m, 1, vinyl H β to CN); low-resolution mass spectrum M^+ *m/e* 277.

Anal. Calcd for $C_{17}H_{27}NO_2$: C, 73.61; H, 9.81; N, 5.05. Found: C, 73.34; H, 9.66; N, 5.05.

2-Methyl-3β-(4-cyano-3-butenyl)-5α-isopropylcyclohexanone (17). A solution of 0.450 g (1.62 mmol) of ketal **16** in a mixture of 8 ml of formic acid and 2 ml of water was stirred at room temperature for 15 min and then poured into 50 ml of distilled water. After a normal work-up procedure, 0.354 g of ketone **17** was obtained as an amber liquid (94%).

GLC analysis (4% FFAP, 10 ft × 0.25 in., 249°, 120 ml/min) shows the presence of virtually pure product as a mixture of epimers and geometric isomers (50:50) about the double bond.

Ir 3020, 2940 (C–H), 2230 (α,β-unsaturated CN), 1710 (C=O), 1630 cm^{-1} (alkene); NMR δ 0.95 (t, 9, CH_3, isopropyl), 1.68 (m, CH_2), 2.22 (m, allylic CH_2), 5.36 (m, 1, vinyl H α to CN), 6.58 (m, 1, vinyl H β to CN); low-resolution mass spectrum M^+ *m/e* 233.

Anal. Calcd for $C_{15}H_{23}NO$: C, 77.21; H, 9.93; N, 6.00. Found: C, 76.89; H, 9.79; N, 6.27.

3aα,4,5,7a-Tetrahydro-1α-cyanomethyl-5α-isopropyl-7aα-methyl-7(6*H*)-indanone (18). To a 10-ml pear-shaped flask equipped with a Teflon-coated magnetic stirring bar were added potassium *tert*-butoxide (0.0052 g, 0.0465 mmol, 13.5 mol % based on ketone) and dry *tert*-butyl alcohol (0.3 ml). To the stirred solution at room temperature was added dropwise a solution of keto nitrile **17** (0.0798 g, 0.343 mmol) in dry benzene (0.2 ml). The solution was then stirred at 65–70° for 2 hr and reaction was then quenched by the addition of acetic acid (2.79 μl, 0.0465 mmol). The reaction mixture was poured into 20 ml of distilled water and extracted with ether. The organic layer was washed with water and saturated aqueous NaCl, dried, and evaporated at reduced pressure to give 0.0718 g (90%) of amber liquid.

GLC analysis (4% FFAP, 10 ft × 0.25 in., 248°, 120 ml/min) shows the almost completely pure product (85%) as a single isomer (13.0 min).

Ir 3020, 2940 (C–H), 2270 (CN), 1710 cm^{-1} (C=O); NMR δ 0.92 (d, 6, isopropyl), 1.10 (s, 3, angular CH_3), 1.67 (m, CH_2), 2.24 (m, allylic H) (14 H); low-resolution mass spectrum M^+ *m/e* 233.

Anal. Calcd for $C_{15}H_{23}NO$: C, 77.21; H, 9.93; N, 6.00. Found: C, 76.94; H, 9.69; N, 6.13.

The 220-MHz NMR spectrum shows the clear presence of isopropyl and angular CH_3 protons in a ratio of 2:1 in accord with a single bicyclic isomer.

3aα,4,5,7a-Tetrahydro-1α-cyanomethyl-5α-isopropyl-7aα-methyl-7(6*H*)-indanone Ethylene Ketal (23). To a 50-ml round-bottom flask equipped with a Teflon-coated magnetic stirring bar, small Soxhlet extractor containing a thimble filled with CaH_2 (4.2 g, 100 mmol), reflux condenser, and a N_2 gas bubbler were added keto nitrile 18 (0.268 g, 1.15 mmol), ethylene glycol (0.750 g, 12.10 mmol, 10.5 equiv), 2-naphthalenesulfonic acid (0.0228 g, 0.11 mmol, 9.6 mol %), and dry benzene (10 ml). The stirred reaction mixture was refluxed under N_2 for 22.5 hr, during which periodic GLC analysis (4% FFAP, 10 ft × 0.25 in., 250°, 120 ml/min) showed the disappearance of starting bicyclic keto nitrile (retention time 10 min) and the appearance of the product (retention time 11.5 min). The reaction mixture was cooled and poured into 20 ml of 5% aqueous $NaHCO_3$, and the mixture was extracted with ether. The combined organic solution was washed with 5% aqueous $NaHCO_3$, water, and saturated aqueous NaCl and dried. The solvent was removed at reduced pressure to give 0.315 g (99%) of amber liquid.

GLC analysis (4% FFAP, 10 ft × 0.25 in., 250°, 120 ml/min) showed the product to be virtually pure ketal.

Ir 3020, 2940 (C–H), 2260 (CN), 1120, 1050, 1035, 1000, 950 cm^{-1} (C–O–C); NMR δ 0.88 (d, 6, isopropyl), 1.00 (s, 3, angular CH_3), 1.42 (m, CH_2), 2.20 (m, allylic H), 3.82 (broad s, 4, OCH_2CH_2O); low-resolution mass spectrum *m/e* 277 (M^+), 234 (M^+ − 43, loss of isopropyl).

Anal. Calcd for $C_{17}H_{27}NO_2$: C, 73.61; H, 9.81; N, 5.05. Found: C, 73.27; H, 9.89; N, 4.97.

3aα,4,5,7a-Tetrahydro-1α-acetamido-5α-isopropyl-7aα-methyl-7(6*H*)-indanone Ethylene Ketal (24). To a 10-ml pear-shaped flask equipped with a Teflon-coated magnetic stirring bar were added bicyclic ketal nitrile **23** (0.0925 g, 0.333 mmol), 95% EtOH (0.328 ml), 30% aqueous H_2O_2 (0.133 ml, 1.15 mmol), and 5 *M* NaOH (0.016 ml, 0.08 mmol). The solution was stirred under N_2 at 69–70° for 2 hr and then poured into 20 ml of distilled water. The product amide was isolated as a viscous, clear oil (0.0742 g, 75%) by ether extraction in the normal manner.

GLC analysis (4% FFAP, 10 ft × 0.25 in., 250°, 120 ml/min) showed the product to be virtually pure (retention time 16.0 min).

Ir (10% w/v in CCl_4) 3450, 3320 (N–H), 3010, 2940 (C–H), 1670 (C=O, amide I band), 1610 (NH, amide II band), 1120, 1060, 1040, 1000, 950 cm^{-1} (C–O–C); NMR δ 0.88 (d, 9, CH_3, isopropyl), 1.43 (broad m, CH_2), 3.89 (broad s, 4, OCH_2CH_2O), 6.63 (broad, 2, amide NH_2); low-resolution mass spectrum *m/e* 295 (M^+), 252 (M^+ − 43, loss of isopropyl).

3aα,4,5,7a-Tetrahydro-1α-aminomethyl-5α-isopropyl-7aα-methyl-7(6*H*)-indanone Ethylene Ketal (25). To a cold mixture of 0.014 ml (0.276 mmol) of bromine, 0.502 ml (1.506 mmol) of 3 *M* NaOH, and 0.15 ml of water was added a solution of 0.0742 g (0.251 mmol) of amide **24** in 1.0 ml of 1,2-dimethoxyethane. The resulting mixture was stirred at room temperature for 0.5 hr and then at 70° for a further 1.5 hr. After this time, the mixture was diluted with 20 ml of water and extracted with ether. The ether extracts were washed well, dried, and evaporated to yield 0.0510 g of amine **25** (76%) as a clear oil: ir 3400, 3300 (N–H), 3000, 2930 (C–H), 1650 (N–H), 1120, 1040, 995, 950 cm^{-1} (C–O–C); NMR δ 0.89 (d, 9, CH_3, isopropyl), 1.43 (broad m, 16, CH_2 and NH_2), 3.89 (broad s, 4, OCH_2CH_2O); low-resolution mass spectrum *m/e* 267 (M^+), 252 (M^+ − 15, loss of CH_3), 224 (M^+ − 43, loss of isopropyl), 30 ($CH_2{=}NH_2^+$); high-resolution mass spectrum M^+ *m/e* 267.2205 (calcd for $C_{16}H_{29}NO_2$, 267.2198, Δm = 0.7 mmu).

Amine **25** was further characterized by conversion into its acetamide; 0.020 g of **25** was treated with 0.014 ml of acetic anhydride in 0.3 ml of pyridine at 100° for 1 hr. After a normal water–ether work-up, 0.020 g of the amide was obtained as a clear oil: ir (10% w/v in CCl_4) 3430 (N–H), 3010, 2930 (C–H), 1670 (C=O, amide I band), 1510 (NH, amide II band), 1115, 1035, 1000, 950 cm^{-1} (C–O–C); NMR δ 0.88 (t, 9, CH_3, isopropyl), 1.43 (broad m, CH_2), 1.82 (s, 3, CH_3CO), 3.00 (t, 2, CH_2N), 3.90 (broad s, 4, OCH_2CH_2O), 6.10 (broad, 1, NHCO); low-resolution mass spectrum *m/e* 309 (M^+), 266 (M^+ − 43, loss of acetyl or isopropyl), 72 ($CH_3CONHCH_2$), 43 (CH_3CO), 30 ($CH_2{=}NH^+_2$); high-resolution mass spectrum M^+ *m/e* 309.2335 (calcd for $C_{18}H_{31}NO_3$, 309.2303, Δm = 3.2 mmu).

3aα,4,5,7a-Tetrahydro-1α-aminomethyl-5α-isopropyl-7aα-methyl-7(6*H*)-indanone (26). A solution of 0.0195 g (0.073 mmol) of ketal amine **25** in 0.5 ml of 80% aqueous formic acid (80:20 HCO_2H–H_2O) was stirred at room temperature for 1 hr, then poured into 20 ml of H_2O and made basic with NaOH. The aqueous mixture was extracted with ether. After washing, the ether extract was dried and evaporated to yield 0.0150 g (92%) of amino ketone **26** as a clear oil: ir (10% w/v in CCl_4) 3420, 3300 (N–H), 3020, 2930 (C–H), 1710 (C=O), 1650 cm^{-1} (N–H); NMR δ 0.95 (d, 9, CH_3, isopropyl), 1.65 (broad m, 16, CH_2 and NH_2); low-resolution mass spectrum *m/e* 223 (M^+), 180 (M^+ − 43, loss of isopropyl), 30 ($CH_2{=}NH_2^+$); high-resolution mass spectrum M^+ − 43 *m/e* 180.1399 (calcd for $C_{11}H_{18}NO$, 180.1410, Δm = −1.1 mmu).

Amino ketone **26** resisted several attempts to convert it into a tricyclic amine. The following reaction conditions yielded only recovered starting material: (a) H_2 (15 psi) and Pt (200 wt %) in acetic acid at 25°; (b) H_2 (53 psi) and Pt (500 wt %) in acetic acid at 25°; (c) H_2 (1000 psi) and Pt (500 wt %) in acetic acid at 200°; and (d) $NaCNBH_3$ in a solution of 1 *M* HCl in methanol at 25° for 3 days.

3aα,4,5,7a-Tetrahydro-1-cyanomethylene-5α-isopropyl-7aα-methyl-7(6*H*)-indanone Ethylene Ketal (27). To a cold (0°) solution of 0.1458 g (1.03 mmol) of *N*-isopropylcyclohexylamine in 1.0 ml of THF was added 0.466 ml (1.00 mmol) of 2.145 *M* *n*-BuLi in hexane. The solution was allowed to warm to room temperature over a 30-min period, then was cooled to −76° and a solution of nitrile **23** (0.1387 g, 0.5 mmol) in 0.5 ml of dry THF was added over a 10-min period. After 35 min at −78°, the solution was warmed to room temperature and a solution of 0.1561 g (0.5 mmol) of diphenyl diselenide in 0.5 ml of dry THF was added dropwise over a 5-min period. The reaction mixture was stirred at room temperature for 2 hr and then diluted with 30 ml of water. The aqueous mixture was extracted with ether and the ether extract was washed well with cold 5% aqueous NaOH and water, and then dried. Evaporation of solvent gave a residual oil which was taken up in a mixture of 4 ml of ethyl acetate and 2 ml of THF. To this solution was added 0.13 ml (1.5 mmol) of 30% aqueous hydrogen peroxide and the resulting mixture was stirred at room temperature for 2 hr. It was then washed with water and 5% aqueous sodium carbonate and dried. Evaporation of solvent gave 0.1151 g of amber liquid.

GLC analysis (10% SF-96, 10 ft × 0.25 in., 240°, 120 ml/min) showed the presence of desired unsaturated nitrile **27** (8.1 min, ca. 50%) and starting nitrile **23** (8.8 min, 50%). The yield of product is, therefore, 42%. A pure sample of ketal nitrile **27** (19.4 mg) was collected by preparative GLC (4% FFAP, 10 ft × 0.25 in., 220°, 120 ml/min) along with starting ketal nitrile **23** (19.1 mg). The two compounds are separated under the column conditions used: **23** (13.5 min), **27** (10.0 min).

Ir (GLC fraction) 3020, 2930 (C–H), 2240 cm^{-1} (unsaturated CN); NMR (GLC fraction δ 0.86 (d, 6, isopropyl), 1.18 (s, 3, angular CH_3), 3.80 (broad s, 4, OCH_2CH_2O), 5.14 (t, 1, vinyl H next to CN); high-resolution mass spectrum M^+ *m/e* 275.1901 (calcd for $C_{17}H_{25}NO_2$, 275.1885, Δm = 1.6 mmu), $M^+ - 43$, 232.1366 (calcd for $C_{14}H_{18}NO_2$, 232.1338, Δm = 2.8 mmu).

3aα,4,5,6a-Tetrahydro-1β-cyanomethyl-5α-isopropyl-7aα-methyl-7(6*H*)-indanone Ethylene Ketal (28). To a 10-ml round-bottom flask equipped with a Teflon-coated magnetic stirring bar and a side arm bearing a serum cap were added 5% Pd/C (0.0198 g, 196 wt %) and a solution of unsaturated nitrile **27** (preparative GLC fraction) (0.0101 g, 0.0367 mmol) in absolute ethanol (0.72 ml). The stirred reaction mixture was hydrogenated at atmospheric pressure for 45 min, at which time GLC analysis (4% FFAP, 10 ft × 0.25 in., 220°, 120 ml/min) showed the absence of starting nitrile (13.8 min) and the presence of a new product (17.0 min). The reaction mixture was treated with K_2CO_3 to deactivate the catalyst, filtered, and evaporated under reduced pressure to give 0.0087 g (87%) of clear, colorless oil: ir (10% w/v in CCl_4) 3020, 2920 (C–H), 2270 (CN), 1185, 1130, 1115, 1100, 1035, 948 cm^{-1} (C–O–C); NMR δ 0.85 (d, 6, isopropyl), 1.18 (s, 3, angular CH_3), 1.44 (broad, CH_2), 3.86 (broad, 4, OCH_2CH_2O); low-resolution mass spectrum *m/e* 277 (M^+), 234 ($M^+ - 43$, loss of isopropyl); high-resolution mass spectrum M^+ *m/e* 277.2036 (calcd for $C_{17}H_{27}NO_2$, 277.2041, Δm = −0.5 mmu), $M^+ - 43$ 234.1493 (calcd for $C_{14}H_{20}NO_2$, 234.1493, Δm = 0.0 mmu).

Acknowledgment. We gratefully acknowledge financial support from the National Science Foundation under Grant GP 31321X.

Registry No.—**6,** 2244-16-8; **7,** 55267-99-7; **8,** 55268-00-3; **9,** 55268-01-4; **10,** 55268-02-5; **11,** 499-71-8; **12,** 55268-03-6; **13,** 55268-04-7; **14,** 55268-05-8; **16,** 55268-06-9; (*E*)-**17,** 55268-07-0; (*Z*)-**17,** 55331-46-9; **18,** 55268-08-1; **23,** 55268-09-2; **24,** 55268-10-5; **25,** 55268-11-6; **25** acetamide derivative, 55268-12-7; **26,** 55268-13-8; **27,** 55268-14-9; **28,** 55331-47-0; 4-bromo-1-butene, 5162-44-7; diethyl cyanomethylphosphonate, 2537-48-6; *n*-isopropylcyclohexylamine, 1195-42-2; β-chloropropionaldehyde trimethylene acetal, 13297-07-9.

References and Notes

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(14) The stereochemical notations α and β are used in the sense that they have been traditionally used in steroid nomenclature.[15] With the hydrindane written so that the six-membered ring is to the left and the angular methyl is at the top, the α configuration has the substituent below the general plane of the bicyclic system.
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(18) A. CH_3OD solution 0.8 *M* in octanonitrile and 0.8 *M* in CH_3ONa shows no detectable exchange after 91 hr at 25°. When the solution is 0.8 *M* in nitrile and 2.4 *M* in CH_3ONa, there is 10% exchange after 23 hr at 25° and 90% exchange after 20 hr at 120°.
(19) Note that **17** is approximately a 50:50 mixture of stereoisomers about the double bond. Since both stereoisomers yield the same product, double bond geometry is unimportant. We have illustrated the cyclizing conformation of **17** using the *Z* stereoisomer. The argument in favor of product **18** would appear to be even stronger for the *E* stereoisomer.
(20) For comparison, the internuclear distance between the bow and stern hydrogens in boat cyclohexane is 1.9 Å.
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Bridged Polycyclic Compounds. LXXXI. Rearrangements in Dibenzobicyclooctadiene Systems. The Nature of the Low-Energy Intermediates[1]

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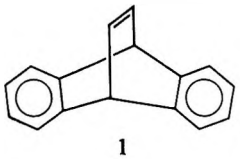
A number of addition reactions have been carried out with 10,11-dimethyldibenzobicyclo[2.2.2]octatriene (11) and with 10,11-dichlorodibenzobicyclo[2.2.2]octatriene (12). Some of these proceed without rearrangement and some with rearrangement to the dibenzobicyclo[3.2.1]octadiene ring system. This study was directed at determining whether reagents preferred attack at one side of the double bond or not and, if so, which orientation was preferred. No preference was noted with diborane, benzenesulfenyl chloride, iodine and silver acetate (Prevost reagent), or mercuric acetate. Of these, the first and the last give cis addition, the second trans addition, and the third addition with rearrangement. It is concluded that each of these reactions involves a cyclic process. On the other hand, bromine, chlorine, hydrogen bromide, and acetic acid show directional effects, with electrophilic attack preferred at the side anti to the dimethylbenzo ring in 11 and anti to the unsubstituted ring in 12. These results are rationalized as involving ring migration accompanying addition with the transition state resembling a phenyl-bridged ion (e.g., 6). The silver acetate assisted acetolyses of *trans*-7,8-dichloro-10,11,dimethyl- (or dichloro-) dibenzobicyclo[2.2.2]octadiene show similar migrating aptitude effects and are rationalized similarly.

Some time ago[2] we reported our initial results on the addition of a variety of electrophilic reagents to dibenzobicyclo[2.2.2]octatriene (1) which led, in general, to syn-8-exo- (or endo-) 4-substituted dibenzobicyclo[3.2.1]octadiene derivatives (2). The rearrangement reactions occurred with complete anti specificity. Similarly, solvolyses of cis-9,10 derivatives of dibenzobicyclo[2.2.2]octadiene (3) led stereospecifically to syn-8 compounds 2, while those of trans compounds 4 led only to the anti derivatives 5. In these solvolyses, the exo epimers of 2 or 5 were the principal products of kinetic control. When the exo epimers (Y = Cl, Br, $HOAc^+$) were allowed to stand or were warmed, they were rapidly converted to the endo epimers and, in most cases, were transformed more slowly, again sterospecifically and with anti migration, i.e. 2 to 3 and 5 to 4, to the thermodynamically stable [2.2.2] isomers.



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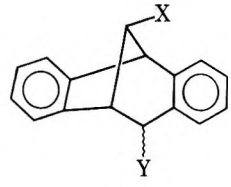

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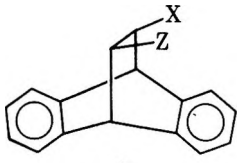

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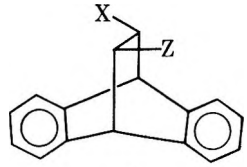

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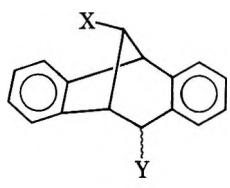

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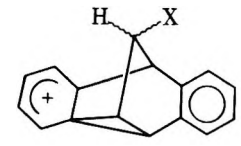
These results suggested[2] the intervention of the phenyl-bridged ions 6 and the benzylic ions 7 in the rearrangement reactions. The rapid exo–endo equilibration of 2 and 5 species, significantly faster than the [3.2.1] to [2.2.2] rearrangements, was interpreted as requiring the intermediacy of 7 species, as it was assumed that 6 could lead only to exo



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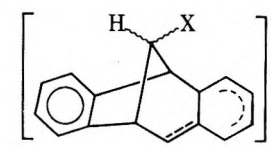

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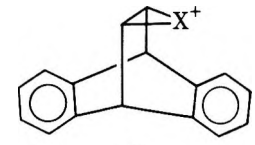

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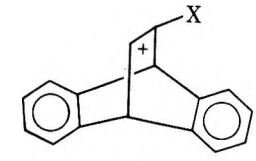

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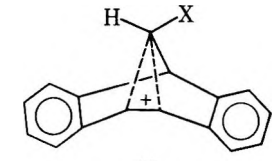

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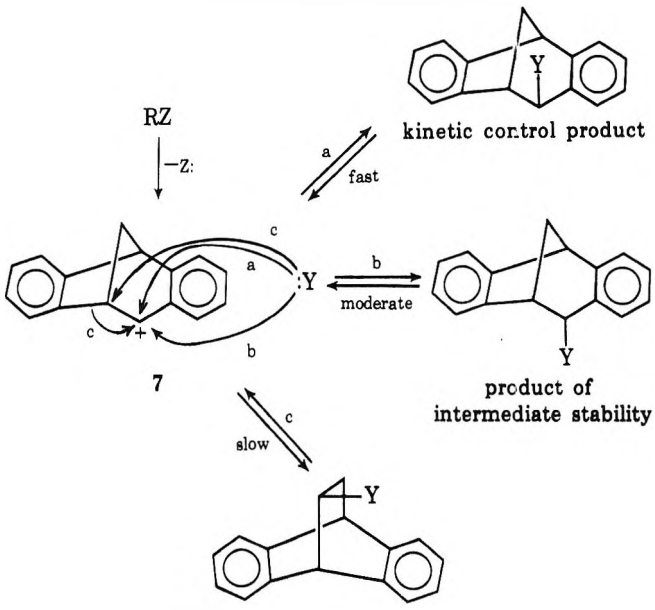
epimers or to [2.2.2] isomers. Thus, while 7 is required as an intermediate, 6 is not required. If in fact 6 is involved, it must be rapidly equilibrated with 7 to accommodate the exo–endo interconversion. On the other hand, as shown in Scheme I, the reactions may be interpreted by the assumption that 7 is the only cationic intermediate in the system, assuming the geitonodesmic[3] reaction (c). Since this early work, we have reported a number of experiments[4] consistent with these interpretations, with the further intervention of onium ions 8 in appropriate situations, and we have most recently noted[5] that cations of type 9 and 10, which are clearly not involved in most reactions, do intervene as high-energy species when the cationic systems are formed and consumed many times.

In this paper we return to the question of the number and nature of the low-energy cationic intermediates, and in particular to the question of the intermediacy of ions of type 6 in these rearrangements. We reasoned that we might be able to learn if the transition state for addition of X^+ to 1, or for loss of Z^- from 3 or 4, resembled 6 or 7, by appropriate nuclear substitution of 1, 3, or 4. Thus in additions to dimethyldibenzobarrelene (11), one would anticipate preferential migration of the substituted ring if the transition state for addition resembled 6 in electron distribution, while the unsubstituted ring should migrate preferentially if the transition state resembled 7. 12, which contains elec-

Scheme I
Pictorial Representation of
[2.2.2] ⇄ [3.2.1] Rearrangement
via Benzylic Ion Alone

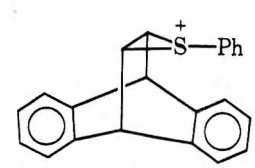


tron-withdrawing chlorine substituents, should react in an analogous fashion, but of course in the opposite sense. Similarly, if **13** were subjected to solvolysis, the chlorine anti to the substituted ring would react preferably if the transition state resembled **6**, and that anti to the unsubstituted ring would leave if the transition state resembled **7**. Again opposite predictions seemed reasonable for the dichloro derivative **14**.

Certain addition reactions involve cyclic processes, either via onium ions (π complexes) such as **8**, or via molecular cis additions. If the concepts described above are correct, if the substituents in **11** and **12** are small enough not to cause steric problems, and if the additions are irreversible, one might anticipate little or no directive influence upon the product mixture, whether the reaction leads to unrearranged [2.2.2] product or whether the intermediate analogous to **8** leads via **6** and/or **7** to [3.2.1] products. Thus study of **1**, **11**, and **12** with a variety of reagents offers not only an opportunity to learn about **6** and **7**, but also about the possibility of π complexes as product-determining intermediates in such reactions. Such intermediates are often used to rationalize stereochemical results (trans or cis addition), but our system allows a completely independent test for mechanism and may prove generally useful.

The addition of diborane to olefins involves a four-center transition state,[6] not involving cationic intermediates, and a study of its regioselectivity might be useful in testing the concept. Indeed **11**, when treated with diborane, followed by oxidation, gave equal amounts of the two alcohols **15**-OH and **16**-OH. Similarly **12** gave equal amounts of **17**-OH and **18**-OH.

Addition of sulfenyl chlorides is known to proceed via sulfonium ions,[7] and **1** has been shown[4a] to add benzenesulfenyl chloride stereospecifically trans and without rearrangement to give **4** (X = PhS; Y = Cl), obviously via attack of chloride ion on **19**. As anticipated, addition of benzenesulfenyl chloride to **11** gave equal amounts of **20** and **21**, confirming the intervention of the bis homologs of **19** as the product-forming intermediates.



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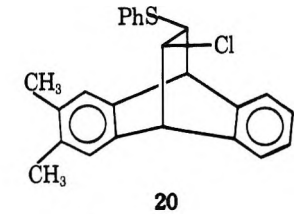

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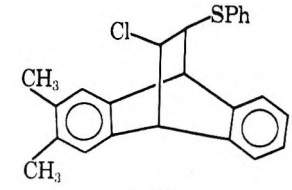
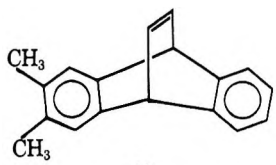


21

These three experiments thus seem to confirm the idea that processes involving cyclic additions to **1** and its analogs **11** and **12** will not show directive influences. Addition of positive halogen species to olefins may or may not involve cyclic onium intermediates,[8,9] and of the halogens, the likelihood of the formation of the **8** species decreases in the order iodine, bromine, chlorine. It has been reported[2d] that treatment of **1** with either iodine and silver acetate or bromine in acetic acid leads cleanly to syn-8-halo-4-exo acetate (**2**, X = halogen, Y = exo-OAc) and that[2b] chlorine gives the analogous dichloride (**2**, X = Cl, Y = exo-Cl), but the question remains open as to whether **8** (X = halogen) precedes **6** or **7** in the reaction scheme.

When **11** was treated with the Prevost reagent, the two rearranged iodoacetates **22**-I and **23**-I were obtained in equal amounts. The nature and amounts of the products allows the formulation of the ions **24**-I and **25**-I as product-determining intermediates, which then rearrange (**24** to **26** and/or **27** and **25** to **28** and/or **29**) on the path to product. On the other hand, addition of bromine in methylene chloride to **11** gave a mixture of **30** and **31** in a 2.1:1.0 ratio. Similarly **12** gave **32** and **33** in a ratio of 1.0:3.0. Thus, with bromine, rearrangement accompanies attack by electrophile and species analogous to **8** are bypassed. The facts that the dimethylbenzo ring migrates in preference to the



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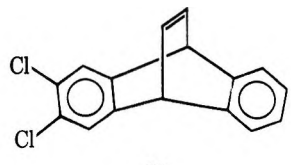

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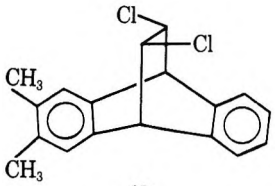

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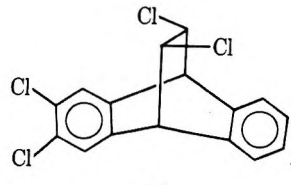

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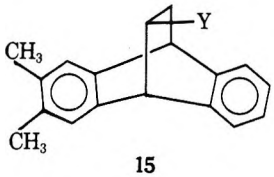

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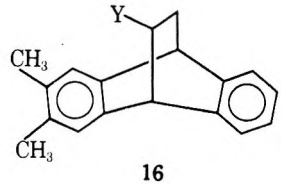

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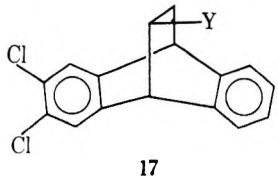

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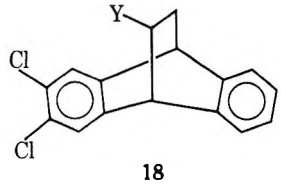

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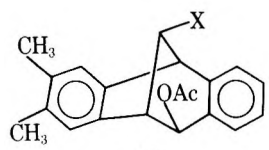
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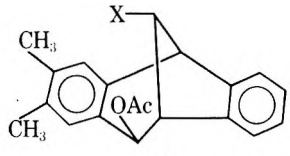
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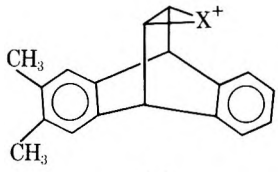
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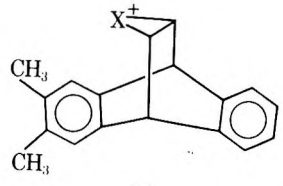
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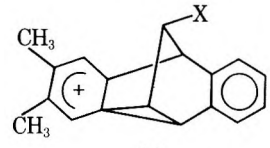
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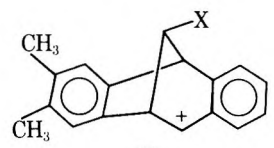
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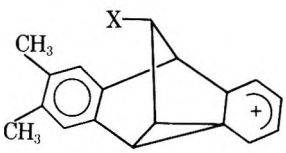
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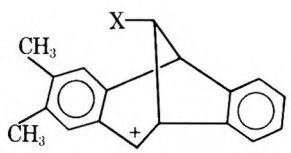
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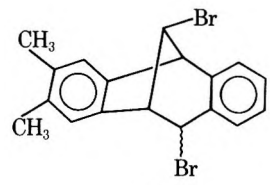
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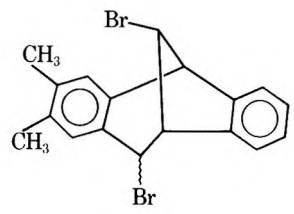
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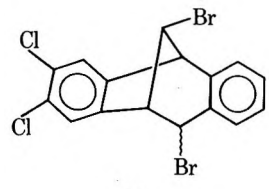
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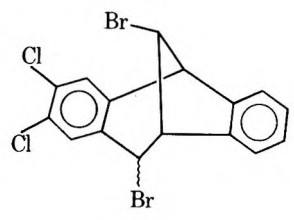
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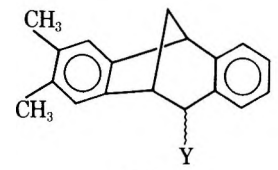
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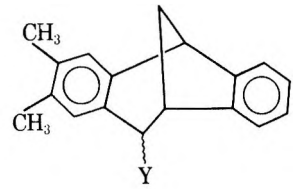
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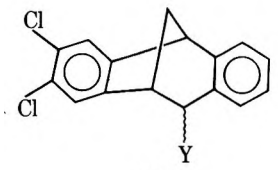
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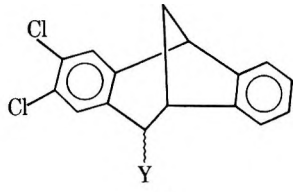
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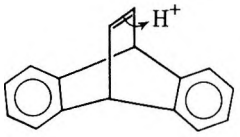
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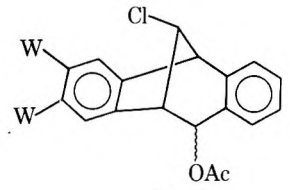
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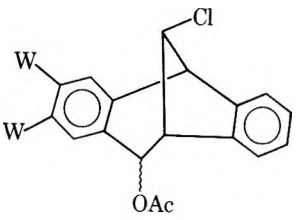
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benzo ring, which in turn migrates in preference to the dichlorobenzo ring, furnish excellent evidence that the transition state for addition resembles the bridged ion **6** rather than the benzylic ion **7**. Similar conclusions may be reached for chlorine addition (in methylene chloride) where the dichlorides analogous to **30** and **31** were produced in a ratio of 1.7:1.0, and those analogous to **32** and **33** in a ratio of 1.0:2.3.

Addition of protic species generally is assumed to proceed via carbenium ions, although π complexes (protonated double bonds) have been suggested occasionally as reaction intermediates.[10] When **11** was treated with hydrogen bromide in ether, **34**-Br and **35**-Br were produced in a ratio of 1.8:1.0. **12** gave **36**-Br and **37**-Br in a 1.0:2.1 ratio. Acetic acid addition to **1** is so slow[4c,5] that the [3.2.1] acetates (**2**, X = H; Y = OAc) are not found in the reaction products, but are instead isomerized to the [2.2.2] acetate (**3**, X = H; Y = OAc). As this [2.2.2] to [3.2.1] rearrangement is largely stereoselective,[4c,5] the information we are seeking may still be observed by addition regioselectivity. Thus **11** gave (with 5% sulfuric acid in acetic acid) a mixture of **15**-OAc and **16**-OAc in a ratio of 2.0:1.0, and **12** gave **17**-OAc and **18**-OAc in a ratio of 1.0:2.5. Clearly, just as with Br^+ and Cl^+ transfer, rearrangement accompanies proton transfer, and no protonated double bond species **38** intervenes. Again the migration aptitude results suggest the intervention of **6** rather than **7** as the first cationic intermediate.

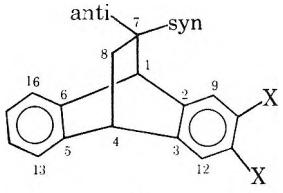
Oxymercuration of olefins, in particular addition of mercuric acetate, has been of considerable interest recently, with evidence adduced for[11] and against[12] cyclic processes, involving either mercurinium ions or concerted multicenter addition processes. A conservative viewpoint, to our mind, is that, as with other reactions, a multiplicity of mechanisms, often without large energy differences, is available so that evidence from one system is not necessarily transferable to others. Addition of mercuric acetate to **1** in acetic acid results in cis addition,[13] a result rationalized readily by the assumption of a concerted multicenter process. In accord with that assumption, similar treatment of **11**, followed by sodium borohydride reduction, gave equal amounts of acetates **15**-OAc and **16**-OAc. Treatment of **1** with mercuric acetate in aqueous acetone leads to trans addition without rearrangement,[13] probably via a mercurinium ion intermediate. It would be of interest to know how **11** reacts under these conditions, but we have not yet done that experiment. The results of such an experiment may be only difficultly interpretable, as mercurinium ions are known[14] to revert to olefin and mercuric ion, so that the requirement noted above of irreversible intermediate formation may not be met.

The data described above show clearly that migratory aptitude of groups is more important than benzylic stabilization, although the effects are not large. When the logarithms of relative k's are plotted against $\Sigma\sigma^+$ (we have used sums of σ^+_m and σ^+_p values[15] in these treatments), we get ρ values of -0.90, -0.67, -0.65, and -0.79 for addition of bromine, chlorine, hydrogen bromide, and acetic acid, respectively, under the conditions described above. These

rather low values suggest that the transition states for addition come quite early in the process, before much charge has leaked into the benzene rings. Solvolysis may be predicted to give a greater amount of benzene-ring participation, if results in the benzonorbornadiene–benzonorbornenyl system are applicable.[16] Accordingly the two trans dichlorides **13** and **14** were subjected to silver acetate assisted acetolysis. **13** gave a mixture of **39**-CH_3 and **40**-CH_3 in 5:1 ratio and **14** gave **39**-Cl and **40**-Cl in a 1:8 ratio. Again migratory aptitude leading to the phenyl-bridged species analogous to **6** prevailed; a ρ value of -1.8 resulted. This value is somewhat lower than those reported[16,17] for solvolysis of ring-substituted derivatives of 2-benzonorbornenyl chlorides or *p*-bromobenzenesulfonates, so that it would appear that π participation is somewhat less important in our system than in theirs. This may possibly be due in part to the silver ion assistance.

In all of the additions, and in the solvolyses as well, the products were largely exo at C-4. However, in most cases, small amounts of endo products accompanied the major epimers, as was noted in previous reactions with **1**.[2,4] We interpret these results as indicating that, while **6** is the first intermediate along the path from the [2.2.2] to [3.2.1] system, it comes into equilibrium with **7** (or begins to do so) before capture by nucleophile. Thus it may be assumed that bridged **6** ions lead to and from [2.2.2] molecules and may lead to and from exo [3.2.1] molecules, but that the latter species may arise from and give rise to benzyl cations **7**, as may the endo [3.2.1] molecules. There would appear to be no evidence requiring the intermediacy of geitonodesmic[3] reactions in these systems.

All of the product ratios were determined by ^{1}H NMR spectroscopy. In general, structure proof, other than syn-anti at C-8 or endo-exo at C-4 of the [3.2.1] systems, which are easily determined directly by ^{1}H NMR spectroscopy,[18] and often quantitative analysis as well, made use of conversion to the [3.2.1] 4-keto derivatives. We use the numbering systems shown in **41** and **42** in this paper, based upon the corresponding simple hydrocarbons.



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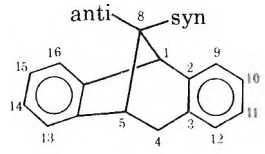
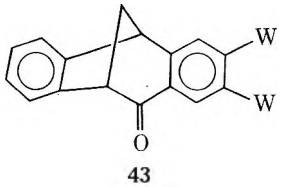


42

With the 4-keto substituent the ortho hydrogen (at C-12) resonance is shifted downfield by 0.4–0.9 ppm from the remainder of the aromatic multiplet and is therefore readily distinguishable. In ketones of type **43**, the proton resonance is a relatively sharp singlet, while in those of type **44**, the



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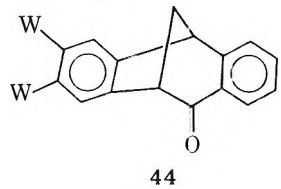

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proton resonance is seen as a doublet of doublets with important splittings between this proton and its ortho and meta neighbors. Once structures were established by conversion to ketones, we worked out procedures for analysis either by carrying out these conversions quantitatively and analyzing the ketone mixture, or by analysis of earlier product mixtures, again by ^{1}H NMR methods. The method used in each case is described in the Experimental Section.

Experimental Section

Proton magnetic resonance spectra were recorded with either Varian A-60A or HA-100 spectrometers, with tetramethylsilane as internal standard. Melting points were obtained with a Thomas-Hoover apparatus and are corrected. Microanalyses were performed by Galbraith Laboratories, Knoxville, Tenn.

Preparation of *trans*-7,8-Dichloro-10,11-dimethyldibenzobicyclo[2.2.2]octadiene (13). 2,3-Dimethylanthraquinone was prepared[19] and reduced with zinc and ammonia[20] to 2,3-dimethylanthracene. The reaction procedure was modified by using a two-phase system with a layer of toluene. The anthracene and *trans*-1,2-dichloroethene were combined to form **13** by the same method used for preparation of *trans*-7,8-dichlorodibenzobicyclo[2.2.2]octadiene.[2] Recrystallization of the product from petroleum ether (bp 60–70°) gave colorless crystals (mp 147.5–148.5°) with a ^{1}H NMR spectrum (CCl_4) indicating the assigned structure (δ 4.15, H-1, 4; 4.02, H-7, 8).

Anal. Calcd for $C_{18}H_{16}Cl_2$: C, 71.30; H, 5.32. Found: C, 71.23; H, 5.30.

Dehalogenation of 13 to 10,11-Dimethyldibenzobicyclo[2.2.2]octatriene (11). Dehalogenation of **13** by the established procedure in this laboratory[2] gave **11** (82%, mp 144–144.5°, recrystallized from ethanol). ^{1}H NMR analysis (CCl_4) confirmed the structure (δ 4.87).

Anal. Calcd for $C_{18}H_{16}$: C, 93.06; H, 6.94. Found: C, 92.94; H, 6.95.

Preparation of *trans*-7,8,10,11-Tetrachloridibenzobicyclo[2.2.2]octadiene (14). 2,3-Dichloroanthraquinone was prepared from *o*-dichlorobenzene and phthalic anhydride by the method of Fieser.[21] Conversion to 2,3-dichloroanthracene was the same as for 2,3-dimethylanthracene above. Treatment of 2,3-dichloroanthracene with *trans*-1,2-dichloroethene as above gave colorless crystals of **14** (86%, mp 179–180°). ^{1}H NMR analysis ($CDCl_3$) confirmed the structure (δ 4.12, H-1, 4; 4.30, H-7, 8).

Anal. Calcd for $C_{16}H_{10}Cl_4$: C, 55.85; H, 2.93. Found: C, 55.72; H, 2.83.

Dehalogenation of 14 to 10,11-Dichlorodibenzobicyclo[2.2.2]octatriene (12). Treatment of **14** in the same manner as **13** above resulted in **12** (90%, mp 227–228°). ^{1}H NMR analysis agreed with the assigned structure (δ 5.05, H-1, 4).

Anal. Calcd for $C_{16}H_{10}Cl_2$: C, 70.35; H, 3.69. Found: C, 70.13; H, 3.76.

Addition of Bromine to 11. The olefin **11** (348 mg, 1.5 mmol) was dissolved in 50 ml of methylene chloride. A solution of bromine (240 mg, 1.5 mmol) in 3 ml of CCl_4 was added dropwise with stirring in the dark over a 10-min period. The pale yellow solution was stirred for 10 min after the addition was completed. Sodium acetate (126 mg, 1.54 mmol) and 25 ml of glacial acetic acid were added, and the solution was heated on the steam bath until the chlorinated solvents were removed. The solution was then heated at reflux for 6 hr. The reaction mixture was poured into 25 ml of water and extracted with chloroform. The chloroform solution was washed with water and then neutralized with sodium bicarbonate. The chloroform was evaporated leaving a pale yellow oil containing by ^{1}H NMR analysis 90% *syn*-8-bromo-14,15-dimethyl-*exo*-4-dibenzobicyclo[3.2.1]octadienol acetate and *syn*-8-bromo-10,11-dimethyl-*exo*-4-dibenzobicyclo[3.2.1]octadienol acetate and 10% of their endo epimers. The oil was dissolved in 25 ml of anhydrous ether, and excess $LiAlH_4$ was added. The reaction mixture was stirred overnight. Water was then added dropwise until the excess $LiAlH_4$ was consumed, and magnesium sulfate was added. The ether solution was filtered and the reaction flask was rinsed with ether. Evaporation of the solvent left 459 mg (93%) of a colorless oil shown to be a mixture of 90% *syn*-8-bromo-14,15-dimethyl-*exo*-4-dibenzobicyclo[3.2.1]octadienol and *syn*-8-bromo-10,11-dimethyl-*exo*-4-dibenzobicyclo[3.2.1]octadienol with 10% of their endo epimers. The oil was dissolved in 5 ml of benzene, 5 ml of 0.33 *M* solution of sodium dichromate in acetic acid was added, and the solution was heated for 5 min on a steam bath, forming a dark green solution. Water was added, and the solution was extracted with benzene. The benzene solution was washed with water until the green color was removed. Evaporation of the benzene gave 417 mg (85.5% overall) of a pale yellow oil shown by ^{1}H NMR analysis to be the ketones *syn*-8-bromo-14,15-dimethyl-4-dibenzobicyclo[3.2.1]octadienone and *syn*-8-bromo-10,11-dimethyl-4-dibenzobicyclo[3.2.1]octadienone in a 2.1:1 ratio.

Preparation of the Bromine Derivatives of 11. Bromine was added to **11** as described above. The solvent was evaporated leaving a pale yellow oil, which was then dissolved in petroleum ether

(bp 85–100°). The dibromide **30** (***endo*-4-*syn*-8-dibromo-14,15-dimethyldibenzobicyclo[3.2.1]octadiene**) crystallized upon concentration of the solution: mp 150–151°; ^{1}H NMR (CCl_4) δ 3.79 (H-1), 5.80 (H-4), 3.57 (H-5), 4.63 (H-8), $J_{1,8}$ = 4.5, $J_{4,5}$ = 4.5 Hz.

Anal. Calcd for $C_{18}H_{16}Br_2$: C, 55.13; H, 4.11. Found: C, 55.46; H, 4.05.

Repeated crystallization of **30** and concentration of the mother liquor produced a small amount of **31** (***endo*-4-*syn*-8-dibromo-10,11-dimethyldibenzobicyclo[3.2.1]octadiene**), mp 154–157°, identified by the difference in the chemical shift for the C-8 proton: a mixture melting point with **30** was depressed; ^{1}H NMR (CCl_4) δ 3.79 (H-1), 5.80 (H-4), 3.57 (H-5), 4.68 (H-8), $J_{1,8}$ = 4.5, $J_{4,5}$ = 4.5 Hz.

Anal. Found: C, 55.28; H, 4.16.

Dibromide **30** was treated with 1 equiv of AgOAc in refluxing acetic acid for 4 hr. The reaction mixture was cooled, filtered, poured into an equal volume of water, and neutralized with aqueous $NaHCO_3$. Extraction with chloroform, followed by filtration of the chloroform solution through $MgSO_4$ and evaporation of the solvent under a stream of nitrogen, left a colorless oil, which crystallized upon dissolution in aqueous ethanol and standing. Recrystallization from ethanol gave ***syn*-8-bromo-14,15-dimethyl-*exo*-4-dibenzobicyclo[3.2.1]octadienol acetate:** mp 139–141°; ^{1}H NMR (CCl_4) δ 3.90 (H-1), 5.58 (H-4), 3.55 (H-5), 4.63 (H-8), $J_{1,8}$ = 3.8, $J_{4,5}$ = 1.4 Hz.

Anal. Calcd for $C_{20}H_{19}O_2Br$: C, 64.70; H, 5.15. Found: C, 64.89; H, 5.17.

$LiAlH_4$ reduction as described above gave ***syn*-8-bromo-14,15-dimethyl-*exo*-4-dibenzobicyclo[3.2.1]octadienol:** mp 173.5–175° (recrystallized from ethanol); ^{1}H NMR (CCl_4) δ 3.89 (H-1), 4.23 (H-4), 3.53 (H-5), 4.73 (H-8), $J_{1,8}$ = 4.4 Hz.

Anal. Calcd for $C_{18}H_{17}OBr$: C, 65.67; H, 5.20. Found: C, 65.49; H, 5.16.

Oxidation was carried out in the manner described above. Crystallization from EtOH gave a compound which was identified from its ^{1}H NMR spectrum as ***syn*-8-bromo-14,15-dimethyl-4-dibenzobicyclo[3.2.1]octadienone,** mp 171–172°, thus confirming the structure of **30**: ^{1}H NMR (CCl_4) δ 3.96 (H-1), 4.13 (H-5), 5.03 (H-8), $J_{1,8}$ = 4.6 Hz.

Anal. Calcd for $C_{18}H_{15}OBr$: C, 66.01; H, 4.62. Found: C, 66.23; H, 4.51.

Fractional crystallization (EtOH) of the ketone mixture from the product ratio determinations produced ***syn*-8-bromo-10,11-dimethyl-4-dibenzobicyclo[3.2.1]octadienone:** mp 185–188°; ^{1}H NMR (CCl_4) δ 3.96 (H-1), 4.13 (H-5), 4.98 (H-8), $J_{1,8}$ = 4.6 Hz.

Anal. Found: C, 66.16; H, 4.72.

$LiAlH_4$ reduction of this ketone gave ***syn*-8-bromo-10,11-dimethyl-*exo*-4-dibenzobicyclo[3.2.1]octadienol:** mp 146–148°; ^{1}H NMR (CCl_4) δ 3.89 (H-1), 4.23 (H-4), 3.53 (H-5), 4.73 (H-8), $J_{1,8}$ = 4.4 Hz.

Anal. Calcd for $C_{18}H_{17}OBr$: C, 65.67; H, 5.20. Found: C, 65.45; H, 5.24.

Acetylation of this alcohol in a 10:1 acetic anhydride–pyridine solution on a steam bath overnight gave the corresponding exo acetate, which after work-up and recrystallization from aqueous ethanol melted at 128–129°: ^{1}H NMR (CCl_4) δ 3.90 (H-1), 5.58 (H-4), 3.55 (H-5), 4.63 (H-8), $J_{1,8}$ = 3.8, $J_{4,5}$ = 1.4 Hz.

Anal. Found: C, 64.70; H, 5.15.

Addition of Bromine to 12. The addition of bromine to **12** was accomplished quantitatively when 15 ml of a 1 *M* solution of bromine was added over a 45-min period with an addition funnel to a stirred solution of 3.57 g (13 mmol) of **12** dissolved in 50 ml of methylene chloride and shielded from the light. Removal of the solvent by rotary evaporation left a colorless oil shown by ^{1}H NMR analysis to contain 53% *exo*-4-*syn*-8-dibromo-10,11-dichlorodibenzobicyclo[3.2.1]octadiene (*exo*-**33**), 13% *exo*-4-*syn*-8-dibromo-14,15-dichlorodibenzobicyclo[3.2.1]octadiene (exo-**32**), 22% *endo*-4-*syn*-8-dibromo-10,11-dichlorodibenzobicyclo[3.2.1]octadiene (*endo*-**33**), and 11% *endo*-4-*syn*-8-dibromo-14,15-dichlorodibenzobicyclo[3.2.1]octadiene (*endo*-**32**). These percentages were obtained upon expansion of the ^{1}H NMR spectrum of the exo and endo protons at C-4 with the HA-100 spectrometer. Fractional crystallization from petroleum ether (bp 85–100°) separated the four isomers.

exo-32: mp 165–170°; ^{1}H NMR ($CDCl_3$) δ 4.00 (H-1), 5.21 (H-4), 3.88 (H-5), 4.81 (H-8), $J_{1,8}$ = 4.5 Hz.

Anal. Calcd for $C_{16}H_{10}Cl_2Br_2$: C, 44.38; H, 2.33. Found: C, 44.40; H, 2.15.

***endo*-32:** mp 156–157°; ^{1}H NMR ($CDCl_3$) δ 4.00 (H-1), 5.90 (H-4), 3.62 (H-5), 4.75 (H-8), $J_{1,8}$ = 5.0, $J_{4,5}$ = 5.0 Hz.

Anal. Found: C, 44.46; H, 2.29.

exo-33: mp 178–182°; ^{1}H NMR ($CDCl_3$) δ 4.00 (H-1), 5.15 (H-4), 3.88 (H-5), 4.83 (H-8), $J_{1,8}$ = 4.5 Hz.

Anal. Found: C, 44.09; H, 2.32.

***endo*-33:** mp 140–160°; ^{1}H NMR ($CDCl_3$) δ 4.00 (H-1), 5.82 (H-4), 3.62 (H-5), 4.76 (H-8), $J_{1,8}$ = 5.0, $J_{4,5}$ = 5.00 Hz.

Anal. Found: C, 44.24; H, 2.30.

Each of the four dibromides was subjected to the reactions used for the structure proof of and the preparation of analytical samples from **30** above. The bromides of **33** were acetolyzed to ***syn*-8-bromo-10,11-dichloro-*exo*-4-dibenzobicyclo[3.2.1]octadienol acetate:** mp 141–146°; ^{1}H NMR ($CDCl_3$) δ 4.05 (H-1), 5.67 (H-4), 3.74 (H-5), 4.78 (H-8), $J_{1,8}$ = 4.5 Hz.

Anal. Calcd for $C_{18}H_{13}O_2Cl_2Br$: C, 52.46; H, 3.18. Found: C, 52.34; H, 3.14.

Reduction of the acetate gave ***syn*-8-bromo-10,11-dichloro-*exo*-4-dibenzobicyclo[3.2.1]octadienol:** mp 172–173°; ^{1}H NMR ($CDCl_3$) δ 4.03 (H-1), 4.44 (H-4), 3.65 (H-5), 4.86 (H-8), $J_{1,8}$ = 4.2 Hz.

Anal. Calcd for $C_{16}H_{11}OCl_2Br$: C, 51.93; H, 3.00. Found: C, 51.76; H, 2.93.

Oxidation produced *syn*-8-bromo-10,11-dichloro-4-dibenzobicyclo[3.2.1]**octadienone**: mp 200–201°; ^{1}H NMR ($CDCl_3$) δ 4.31 (H-1), 4.21 (H-5), 5.17 (H-8), $J_{1,8}$ = 5.0 Hz.

Anal. Calcd for $C_{16}H_9OCl_2Br$; C, 52.21; H, 2.46. Found: C, 52.40; H, 2.48.

The bromides of **32** formed upon acetolysis ***syn*-8-bromo-14,15-dichloro-*exo*-4-dibenzobicyclo[3.2.1]octadienol acetate:** mp 138–139°; ^{1}H NMR ($CDCl_3$) δ 3.99 (H-1), 5.71 (H-4), 3.74 (H-5), 4.76 (H-8), $J_{1,8}$ = 4.5 Hz.

Anal. Found: C, 52.51; H, 3.22.

Upon reduction the acetate was converted to ***syn*-8-bromo-14,15-dichloro-*exo*-4-dibenzobicyclo[3.2.1]octadienol:** mp 167–168°; ^{1}H NMR ($CDCl_3$) δ 3.95 (H-1), 4.48 (H-4), 3.65 (H-5), 4.89 (H-8), $J_{1,8}$ = 4.2 Hz.

Anal. Found: C, 51.86; H, 3.01.

Conversion was then accomplished to ***syn*-8-bromo-14,15-dichloro-4-dibenzobicyclo[3.2.1]octadienone:** mp 177–178°; ^{1}H NMR ($CDCl_3$) δ 4.33 (H-1), 4.23 (H-5), 5.10 (H-8), $J_{1,8}$ = 5.0 Hz.

Anal. Found: C, 52.26, H, 2.46.

Addition of Chlorine to 11. Elemental chlorine was bubbled through a sulfuric acid drying tower calibrated for known flow rate into a stirred solution of 238 mg (1.03 mmol) of **11** in 25 ml of methylene chloride until 2.0 equiv of chlorine had been delivered. The solvent was evaporated, leaving a colorless oil containing 80% of the dichlorides *endo*-4-*syn*-8-dichloro-14,15-dimethyldibenzobicyclo[3.2.1]octadiene and *endo*-4-*syn*-8-dichloro-10,11-dimethyldibenzobicyclo[3.2.1]octadiene and 20% of their exo epimers (^{1}H NMR analysis).

Conversion to the acetates, reduction to the alcohols, and oxidation to the ketones was accomplished by the procedure described above for bromine addition (89% overall yield). The ketone ratio was determined by ^{1}H NMR. The chlorine derivatives of **11** were isolated by fractional crystallization of the product mixtures. The following compounds were prepared in the course of this work.

***endo*-4-*syn*-8-Dichloro-14,15-dimethyldibenzobicyclo[3.2.1]octadiene:** mp 137–138°; ^{1}H NMR (CCl_4) δ 3.78 (H-1), 5.58 (H-4), 3.50 (H-5), 4.63 (H-8), $J_{1,8}$ = 4.5, $J_{4,5}$ = 5.0 Hz.

Anal. Calcd for $C_{18}H_{16}Cl_2$: C, 71.30; H, 5.32. Found: C, 71.03; H, 5.31.

***endo*-4-*syn*-8-Dichloro-10,11-dimethyldibenzobicyclo[3.2.1]octadiene:** mp 133–140°; ^{1}H NMR (CCl_4) δ 3.78 (H-1), 5.58 (H-4), 3.50 (H-5), 4.67 (H-8), $J_{1,8}$ = 4.5, $J_{4,5}$ = 5.0 Hz.

Anal. Found: C, 71.36; H, 5.33.

***syn*-8-Chloro-14,15-dimethyl-*exo*-4-dibenzobicyclo[3.2.1]-octadienol acetate:** mp 139–140°; ^{1}H NMR (CCl_4) δ 3.90 (H-1), 5.65 (H-4), 3.57 (H-5), 4.63 (H-8), $J_{1,8}$ = 5.0 Hz.

Anal. Calcd for $C_{20}H_{19}O_2Cl$: C, 73.50; H, 5.86. Found: C, 73.49; H, 5.91.

***syn*-8-Chloro-10,11-dimethyl-*exo*-4-dibenzobicyclo[3.2.1]-octadienol acetate:** mp 149–149.5°; ^{1}H NMR (CCl_4) δ 3.90 (H-1), 5.65 (H-4), 3.57 (H-5), 4.63 (H-8), $J_{1,8}$ = 5.0 Hz.

Anal. Found: C, 73.45; H, 5.86.

***syn*-8-Chloro-14,15-dimethyl-*exo*-4-dibenzobicyclo[3.2.1]-octadienol:** mp 184–185°; ^{1}H NMR (CCl_4) δ 3.87 (H-1), 4.37 (H-4), 3.48 (H-5), 4.72 (H-8), $J_{1,8}$ = 4.0 Hz.

Anal. Calcd for $C_{18}H_{17}OCl$: C, 75.92; H, 6.17. Found: C, 75.96; H, 5.90.

***syn*-8-Chloro-10,11-dimethyl-exo-4-dibenzobicyclo[3.2.1]-octadienol:** mp 158–158.5°; ^{1}H NMR (CCl_4) δ 3.87 (H-1), 4.37

(H-4), 3.48 (H-5), 4.72 (H-8), $J_{1,8}$ = 4.0 Hz.

Anal. Found: C, 76.12; H, 5.99.

***syn*-8-Chloro-14,15-dimethyl-4-dibenzobicyclo[3.2.1]octadienone:** mp 160–161°; ^{1}H NMR (CCl_4) δ 3.93 (H-1), 4.12 (H-5), 4.90 (H-8), $J_{1,8}$ = 4.4 Hz.

Anal. Calcd for $C_{18}H_{15}OCl$: C, 76.46; H, 5.35. Found: C, 76.27; H, 5.51.

***syn*-8-Chloro-10,11-dimethyl-4-dibenzobicyclo[3.2.1]octadienone:** mp 174–175°; ^{1}H NMR (CCl_4) δ 3.93 (H-1), 4.12 (H-5), 4.93 (H-8), $J_{1,8}$ = 4.4 Hz.

Anal. Found: C, 76.17; H, 5.46.

Addition of Chlorine to 12. When 229 mg (0.84 mmol) of **12** was treated under the same reaction conditions as described above, 200 mg (73% overall) of the ketones were obtained and used in the product ratio determination by ^{1}H NMR. The following compounds were prepared.

***exo*-4-*syn*-8,10,11-Tetrachlorodibenzobicyclo[3.2.1]octadiene:** mp 168–188°; ^{1}H NMR ($CDCl_3$) δ 3.97 (H-1), 4.92 (H-4), 3.77 (H-5), 4.77 (H-8), $J_{1,8}$ = 4.5 Hz.

Anal. Calcd for $C_{16}H_{10}Cl_4$: C, 55.85; H, 2.88. Found: C, 55.75; H, 2.88.

***exo*-4-*syn*-8,14,15-Tetrachlorodibenzobicyclo[3.2.1]octadiene:** mp 190.5–191.5°; ^{1}H NMR ($CDCl_3$) δ 3.97 (H-1), 4.94 (H-4), 3.77 (H-5), 4.73 (H-8), $J_{1,8}$ = 4.5 Hz.

Anal. Found: C, 56.04; H, 2.91.

***syn*-8,10,11-Trichloro-*exo*-4-dibenzobicyclo[3.2.1]octadienol acetate:** mp 141–143°; ^{1}H NMR ($CDCl_3$) δ 4.08 (H-1), 5.72 (H-4), 3.72 (H-5), 4.77 (H-8), $J_{1,8}$ = 4.5 Hz.

Anal. Calcd for $C_{18}H_{13}O_2Cl_3$: C, 58.80; H, 3.56. Found: C, 58.92; H, 3.36.

***syn*-8,14,15-Trichloro-*exo*-4-dibenzobicyclo[3.2.1]octadienol acetate:** mp 167–167.5°; ^{1}H NMR ($CDCl_3$) δ 4.08 (H-1), 5.73 (H-4), 3.72 (H-5), 4.75 (H-8), $J_{1,8}$ = 4.5 Hz.

Anal. Found: C, 58.69; H, 3.46.

***syn*-8,10,11-Trichloro-*exo*-4-dibenzobicyclo[3.2.1]octadienol:** mp 169–178°; ^{1}H NMR ($CDCl_3$) δ 3.97 (H-1), 4.40 (H-4), 3.63 (H-5), 4.85 (H-8), $J_{1,8}$ = 4.5 Hz.

Anal. Calcd for $C_{16}H_{11}OCl_3$: C, 59.02; H, 3.40. Found: C, 59.22; H, 3.29.

***syn*-8,14,15-Trichloro-*exo*-4-dibenzobicyclo[3.2.1]octadienol:** mp 166–167°; ^{1}H NMR ($CDCl_3$) δ 3.97 (H-1), 4.40 (H-4), 3.63 (H-5), 4.80 (H-8), $J_{1,8}$ = 4.5 Hz.

Anal. Found: C, 58.87; H, 3.30.

***syn*-8,10,11-Trichloro-4-dibenzobicyclo[3.2.1]octadienone:** mp 163–164°; ^{1}H NMR ($CDCl_3$) δ 4.17 (H-1), 4.28 (H-5), 5.12 (H-8), $J_{1,8}$ = 4.7 Hz.

Anal. Calcd for $C_{16}H_9OCl_3$: C, 59.40; H, 2.78. Found: C, 59.37; H, 2.92.

***syn*-8,14,15-Trichloro-4-dibenzobicyclo[3.2.1]octadienone:** mp 215–216°; ^{1}H NMR ($CDCl_3$) δ 4.17 (H-1), 4.28 (H-5), 5.11 (H-8), $J_{1,8}$ = 4.7 Hz.

Anal. Found: C, 59.10; H, 2.60.

Addition of Hydrogen Bromide to 11. In a two-necked flask (gas-inlet tube, Dry Ice condenser, magnetic stirrer) were placed 454 mg (1.95 mmol) of **11** and 5 ml of ether. Hydrogen bromide gas was bubbled from a lecture bottle until the volume of solution in the flask reached 15 ml. The reaction was stopped 45 min from the start of gas delivery by pouring the contents of the flask over ice. Extraction with ether, neutralization with $NaHCO_3$, and drying over $MgSO_4$ left an ether solution containing the exo bromides **34** (*exo*-4-bromo-14,15-dimethyldibenzobicyclo[3.2.1]octadiene) and **35** (*exo*-4-bromo-10,11-dimethyldibenzobicyclo[3.2.1]octadiene). Evaporation of the ether left a colorless oil, 560 mg (92%). A portion of the oil (331 mg, 1.06 mmol) was dissolved in 20 ml of acetone and water was added until the solution became cloudy. The solution was clarified with acetone and 0.5 ml of pyridine was added. The mixture was allowed to stand overnight. The acetone was removed by rotary evaporation and the contents of the flask were extracted with benzene. Evaporation of the benzene left a colorless oil which was dissolved in ether. Oxidation for 5 hr with 10 ml of the sodium dichromate solution described above gave a mixture of ketones 14,15-dimethyl-4-dibenzobicyclo[3.2.1]octadienone (44-Me) and 10,11-dimethyl-4-dibenzobicyclo[3.2.1]octadienone (43-Me) in 90% overall yield; these were used for the product ratio determination by ^{1}H NMR. The derivatives were prepared from compounds **34** and **35**, which were obtained by fractional crystallization from petroleum ether (bp 60–70°) solution of the oil obtained from HBr addition to **11**.

***exo*-34:** mp 115–116°; ^{1}H NMR ($CDCl_3$) δ 3.77 (H-1), 5.37 (H-4), 3.77 (H-5), 2.68 (H-8).

Anal. Calcd for $C_{18}H_{17}Br$: C, 69.02; H, 5.47. Found: C, 69.13; H, 5.40.

***exo*-35:** mp 107–108°; ^{1}H NMR ($CDCl_3$) δ 3.77 (H-1), 5.37 (H-4), 3.77 (H-5), 2.68 (H-8).

Anal. Found: C, 68.92; H, 5.55.

Treatment of **34** with acetone–H_2O gave 14,15-dimethyl-*exo*-4-dibenzobicyclo[3.2.1]octadienol, which was purified by sublimation at 130° (0.5 Torr): mp 169–170°; ^{1}H NMR ($CDCl_3$) δ 3.75 (H-1), 4.48 (H-4), 3.33 (H-5), 2.37 (H-8).

Anal. Calcd for $C_{18}H_{18}O$: C, 86.36; H, 7.25. Found: C, 86.52; H, 7.31.

Oxidation as described above gave 14,15-dimethyl-4-dibenzobicyclo[3.2.1]octadienone: mp 109–110°; ^{1}H NMR ($CDCl_3$) δ 3.97 (H-1), 4.10 (H-5), 2.71 (H-8a), 2.69 (H-8s).

10,11-Dimethyl-*exo*-4-dibenzobicyclo[3.2.1]octadienol: mol wt 250 (mass spectrum) (calcd 250); ^{1}H NMR ($CDCl_3$) δ 3.75 (H-1), 4.48 (H-4), 3.37 (H-5), 2.37 (H-8).

10,11-Dimethyl-4-dibenzobicyclo[3.2.1]octadienone: mol wt 248 (mass spectrum) (calcd 248); ^{1}H NMR ($CDCl_3$) δ 3.97 (H-1), 4.10 (H-5), 2.71 (H-8a), 2.69 (H-8s).

Addition of Hydrogen Bromide to 12. Under the conditions described above **12** showed no reaction with HBr. A heavy-walled Pyrex tube containing 410 mg (1.5 mmol) of **12** in 10 ml of ether was immersed in Dry Ice–acetone and hydrogen bromide gas was added until the total volume of solution was 30 ml. The tube was sealed and placed in a large Dewar flask at −30°. The tube was removed after 50 min, cooled to −70° and opened, and its contents were poured onto ice. The mixture was extracted with ether. The ethereal solution was neutralized with sodium bicarbonate. Evaporation of the ether left a colorless oil (405 mg, 93.5%) containing the bromides **37** (*exo*-4-bromo-10,11-dichlorodibenzobicyclo[3.2.1]octadiene) and **36** (*exo*-4-bromo-14,15-dichlorodibenzobicyclo[3.2.1]octadiene). Conversion to the ketones for ^{1}H NMR analysis was carried out as described above. The hydrolysis in aqueous acetone required 2 days at reflux for completion. The derivatives from this reaction were prepared from the [2.2.2] alcohols obtained in the hydroboration of **12**. Their preparation is described in the details of that reaction.

Addition of Acetyl Hypoiodite to 11. A mixture of 176 mg (0.76 mmol) of **11**, 201 mg (0.79 mmol), of iodine, and 263 mg (1.57 mmol) of AgOAc was stirred overnight in 25 ml of refluxing benzene. The solution was cooled to room temperature and filtered. Evaporation of the benzene under a stream of nitrogen left a pale yellow oil composed of 80% of the iodoacetates **22-I** (*syn*-8-iodo-14,15-dimethyl-*exo*-4-dibenzobicyclo[3.2.1]octadienol acetate) and 20% of their endo epimers. The oil was dissolved in ether and excess lithium aluminum hydride was added. The mixture was stirred for 5 hr. Water was carefully added until the excess hydride had been consumed, and magnesium sulfate was added. The ether was filtered, and the reaction flask was washed with dry ether. The ether was evaporated, and the resulting oil was dissolved in dry acetone. Oxidation with 0.3 ml of Jones reagent[22] for 10 min was followed by addition of 10 ml of water. The mixture was extracted with benzene. The benzene layer was washed with water and then evaporated to give a pale yellow oil (216 mg, 76% overall) containing the two ketones in a 1:1 ratio by ^{1}H NMR analysis. The ketones were separated by chromatography on Merck 71707 aluminum oxide, eluting with petroleum ether (bp 60–70°) and 20% benzene. The alcohols and acetates were prepared from the two ketones by $LiAlH_4$ reduction, then acetylation in acetic anhydride and pyridine as described. Each was recrystallized from EtOH.

22-I: mp 154–155°; ^{1}H NMR ($CDCl_3$) δ 4.00 (H-1), 5.75 (H-4), 3.72 (H-5), 4.78 (H-8), $J_{1,8}$ = 4.4 Hz.

Anal. Calcd for $C_{20}H_{19}O_2I$: C, 57.43; H, 4.58. Found: C, 57.62; H, 4.47.

23-I: mp 147–148°; ^{1}H NMR ($CDCl_3$) δ 4.00 (H-1), 5.75 (H-4), 3.72 (H-5), 4.78 (H-8), $J_{1,8}$ = 4.4 Hz.

Anal. Found: C, 57.30; H, 4.61.

***syn*-8-Iodo-14,15-dimethyl-*exo*-4-dibenzobicyclo[3.2.1]octadienol:** mp 180–182°; ^{1}H NMR ($CDCl_3$) δ 4.02 (H-1), 4.57 (H-4), 3.69 (H-5), 4.85 (H-8), $J_{1,8}$ = 4.5 Hz.

Anal. Calcd for $C_{18}H_{17}OI$: C, 57.46; H, 4.55. Found: C, 57.37; H, 4.61.

***syn*-8-Iodo-10,11-dimethyl-*exo*-4-dibenzobicyclo[3.2.1]octadienol:** mp 184.5–185°; ^{1}H NMR ($CDCl_3$) δ 4.02 (H-1), 4.57 (H-4), 3.69 (H-5), 4.85 (H-8), $J_{1,8}$ = 4.5 Hz.

Anal. Found: C, 57.40; H, 4.61.

***syn*-8-Iodo-14,15-dimethyl-4-dibenzobicyclo[3.2.1]octadienone:** mp 182–183°; ^{1}H NMR ($CDCl_3$) δ 4.13 (H-1), 3.97 (H-5), 5.00 (H-8), $J_{1,8}$ = 4.5 Hz.

Anal. Calcd for $C_{18}H_{15}OI$: C, 57.77; H, 4.04. Found: C, 57.50; H, 3.92.

***syn*-8-Iodo-10,11-dimethyl-4-dibenzobicyclo[3.2.1]octadienone:** mp 188–189°; ^1H NMR ($CDCl_3$) δ 4.13 (H-1), 3.97 (H-5), 5.03 (H-8), $J_{1,8}$ = 4.5 Hz.

Anal. Found: C, 57.93; H, 3.89.

Addition of Acetic Acid to 11. Into a 1.25 × 15 cm Pyrex tube were placed 1.04 g (4.5 mmol) of **11** and 5 ml of 0.5 *M* H_2SO_4 in HOAc. The tube was cooled, sealed, and then placed in a steam bath at 94° for 5 hr. The tube was cooled and opened, and its contents were poured into 5 ml of water. The mixture was extracted with CCl_4 which was then washed with water and neutralized with sodium bicarbonate. The carbon tetrachloride was removed by rotary evaporation, leaving 1.07 g (81.5%) of a brown oil which was shown by its ^1H NMR spectrum to be a 2:1 mixture of **15**-OAc and **16**-OAc. Analysis was by expansion and integration of the acetate methyl peak by HA-100 NMR. The peaks were also cut from the spectrum and weighed to determine the product ratio. The reaction was followed over a 3-day period and no significant change in the product ratio was detected.

Reduction of the acetate mixture with $LiAlH_4$ gave 915 mg (81.5%) of an oil, which contained the alcohols **15**-OH (10,11-dimethyl-*anti*-7-dibenzobicyclo[2.2.2]octadienol) and **16**-OH (10,11-dimethyl-*syn*-7-dibenzobicyclo[2.2.2]octadienol). Some separation of this mixture was effected by chromatography on silica gel (PF_{254} with $CaSO_4$), developing with 10% ether in benzene three times. The band with the smaller R_f value was removed and extracted with CH_2Cl_2, leaving a colorless oil upon evaporation of the solvent. A portion of the oil was acetylated and after work-up left an oil shown by ^1H NMR spectral analysis to be the acetate **15**-OAc. The remaining portion of the alcohol was converted to the *p*-toluenesulfonate using *p*-toluenesulfonyl chloride in dry pyridine for 2 days at room temperature. The solution was poured into water and extracted with ether. The ether was washed with cold dilute HCl, neutralized with aqueous $NaHCO_3$, and filtered through $MgSO_4$. The ether was evaporated and the oil which remained was dissolved in acetic acid containing 1 equiv of NaOAc and heated at reflux for 2 days. The solution was then poured into an equal amount of water and extracted with $CHCl_3$. After washing with $NaHCO_3$, the $CHCl_3$ was evaporated, giving a colorless oil which was then dissolved in ether. Excess lithium aluminum hydride was added to give the alcohol, which was converted with Jones reagent[22] to the ketone **44**-Me, identified by its ^1H NMR spectrum.

The analytical samples were prepared by recrystallizing the alcohols obtained in the TLC separation from CCl_4. Acetylation of the alcohols in acetic anhydride and pyridine gave the acetates **15**- and **16**-OAc, which were then recrystallized from EtOH–H_2O.

15-OAc: mp 140–141°; ^1H NMR ($CDCl_3$) δ 4.47 (H-1), 4.15 (H-4), 5.07 (H-7), 2.23 (H-8s), 1.45 (H-8a), 2.17 (CH_3), 1.83 (OAc).

Anal. Calcd for $C_{20}H_{20}O_2$: C, 82.16; H, 6.89. Found: C, 81.83; H, 6.85.

16-OAc: mp 132–133°; ^1H NMR ($CDCl_3$) δ 4.47 (H-1), 4.15 (H-4), 5.07 (H-7), 2.23 (H-8a), 1.45 (H-8s), 2.20 (CH_3), 1.86 (OAc).

Anal. Found: C, 81.94; H, 7.02.

15-OH: mp 188–189°; ^1H NMR ($CDCl_3$) δ 4.07 (H-1), 4.10 (H-4), 4.00 (H-7), 2.20 (H-8s), 1.23 (H-8a).

Anal. Calcd for $C_{18}H_{18}O$: C, 86.36; H, 7.25. Found: C, 86.48; H, 7.40.

16-OH: mp 230–231°; ^1H NMR ($CDCl_3$) δ 4.07 (H-1), 4.10 (H-4), 4.00 (H-7), 2.20 (H-8a), 1.23 (H-8s).

Anal. Found: C, 86.23; H, 7.32.

Addition of Acetic Acid to 12. The addition of HOAc to **12** was carried out in 0.5 *M* H_2SO_4 in HOAc at 110° in a sealed tube in an oil bath. The work-up was the same as in the addition to **11**, resulting in mixtures of the acetates **18**-OAc (10,11-dichloro-*syn*-7-dibenzobicyclo[2.2.2]octadienol acetate) and **17**-OAc (10,11-dichloro-*anti*-7-dibenzobicyclo[2.2.2]octadienol acetate). Reduction of the acetates to the alcohols was the same as above. TLC separation under the same conditions was possible to some extent. The band with the larger R_f value was removed and identified as **18**-OH in the same manner as **15**-OH. The addition of HOAc was followed for 3 days and the ratio of **18**-OAc to **17**-OAc decreased from over 2.5:1 to 1.5:1.[5]

17-OAc: mp 109–110°; ^1H NMR ($CDCl_3$) δ 4.47 (H-1), 4.17 (H-4), 5.02 (H-7), 2.22 (H-8s), 1.45 (H-8a), 1.85 (OAc).

Anal. Calcd for $C_{18}H_{14}O_2Cl_2$: C, 64.88; H, 4.23. Found: C, 64.70; H, 4.26.

18-OAc: mp 138.5–139°; ^1H NMR ($CDCl_3$) δ 4.47 (H-1), 4.17 (H-4), 4.97 (H-7), 2.22 (H-8a), 1.45 (H-8s), 1.88 (OAc).

Anal. Found: C, 65.01; H, 4.28.

17-OH: mp 191–193°; ^1H NMR ($CDCl_3$) δ 4.30 (H-1), 4.20 (H-4), 4.25 (H-7), 2.33 (H-8s), 1.37 (H-8a).

Anal. Calcd for $C_{16}H_{12}OCl_2$: C, 66.00; H, 4.15. Found: C, 65.84; H, 4.03.

18-OH: mp 206–207°; ^1H NMR ($CDCl_3$) δ 4.30 (H-1), 4.20 (H-4), 4.25 (H-7), 2.33 (H-8a), 1.37 (H-8s).

Anal. Found: C, 65.93; H, 4.19.

Addition of Mercuric Acetate to 11. Compound **11** (116 mg, 0.5 mmol) and 162 mg (0.5 mmol) of mercuric acetate were stirred in 20 ml of acetic acid for 4 hr at room temperature. The acetic acid was removed by rotary evaporation and 10 mg of sodium borohydride was added to the colorless oil in the flask. The mixture was stirred for 5 min in 5 ml of tetrahydrofuran and then 3 ml of 2 *M* NaOH was added. Stirring was continued for another 1 min. Water was added (10 ml) and the solution was extracted with $CHCl_3$. The $CHCl_3$ was evaporated to give 136 mg (93%) of an oil shown by its ^1H NMR spectrum to be a 1:1 mixture of the acetates **15**-OAc and **16**-OAc.

Hydroboration of 11. Hydroboration of **11** occurred when 232 mg (1.0 mmol) of **11** and 20 mg (0.62 mmol) of sodium borohydride were dissolved in 10 ml of dry diglyme and a solution of 100 mg of boron trifluoride etherate in 5 ml of diglyme was added dropwise with stirring. After addition had been completed the solution was stirred for 2 hr. Ten milliliters of 6 *M* NaOH was added very slowly and then 10 ml of 30% H_2O_2 was added. Stirring was continued for 15 min. The mixture was extracted with benzene and the benzene was evaporated, leaving a colorless oil which was acetylated in acetic anhydride and pyridine overnight at room temperature. Work-up as usual gave 251 mg (86% overall) of the acetates **15**-OAc and **16**-OAc in a 1:1 ratio by ^1H NMR analysis.

Hydroboration of 12. Hydroboration of **12** was carried out in the same way as that of **11**. In this case 273 mg (1.0 mmol) of **12** after hydroboration and acetylation yielded 249 mg (75%) of the acetates **17**-OAc and **18**-OAc in a 1:1 ratio by ^1H NMR analysis.

The alcohols **17**-OH and **18**-OH were separated by TLC. Formation of their *p*-toluenesulfonates and rearrangement to the [3.2.1] acetates followed by $LiAlH_4$ reduction and oxidation to ketones was the same as described above. The ketones were purified by crystallization from EtOH. PBr_3 reaction with the [3.2.1] alcohols gave the bromides **36**-Br and **37**-Br.

37-Br: ^1H NMR ($CDCl_3$) δ 3.83 (H-1), 5.26 (H-4), 3.83 (H-5), 2.67 (H-8), $J_{4,5}$ = 2.0 Hz; mol wt (mass spectrum) 354 (calcd 354).

36-Br: mp 182–184°; ^1H NMR ($CDCl_3$) δ 3.83 (H-1), 5.37 (H-4), 3.83 (H-5), 2.67 (H-8), $J_{4,5}$ = 2.0 Hz; mol wt (mass spectrum) 354 (calcd 354).

10,11-Dichloro-*exo*-4-dibenzobicyclo[3.2.1]octadienol (*exo*-37-OH): mp 116–117°; ^1H NMR ($CDCl_3$) δ 3.85 (H-1), 4.55 (H-4), 3.47 (H-5), 2.58 (H-8), $J_{4,5}$ = 2.0 Hz.

Anal. Calcd for $C_{16}H_{12}OCl_2$: C, 66.00; H, 4.15. Found: C, 65.73; H, 4.26.

14,15-Dichloro-*exo*-4-dibenzobicyclo[3.2.1]octadienol (*exo*-36-OH): mp 127–131°; ^1H NMR ($CDCl_3$) δ 3.85 (H-1), 4.60 (H-4), 3.47 (H-5), 2.58 (H-8), $J_{4,5}$ = 2.0 Hz.

Anal. Found: C, 65.72; H, 4.24.

10,11-Dichloro-4-dibenzobicyclo[3.2.1]octadienone (43-Cl): mp 135–137°; ^1H NMR ($CDCl_3$) δ 4.02 (H-1), 4.12 (H-5), 2.78 (H-8).

Anal. Calcd for $C_{16}H_{10}OCl_2$: C, 66.46; H, 3.49. Found: C, 66.43; H, 3.49.

14,15-Dichloro-4-dibenzobicyclo[3.2.1]octadienone (44-Cl): mp 178.5–180°; ^1H NMR ($CDCl_3$) δ 4.02 (H-1), 4.12 (H-5), 2.78 (H-8).

Anal. Found: C, 66.49; H, 3.36.

Silver Acetate Assisted Solvolysis of 13. Trans dichloride **13** (613 mg, 2.02 mmol) and 341 mg (2.04 mmol) of silver acetate were stirred for 4 hr in 25 ml of refluxing glacial acetic acid. The solution was cooled and the silver chloride was removed by filtration. The solution was poured into 25 ml of water and extracted with $CHCl_3$. The $CHCl_3$ solution was washed with water and dilute $NaHCO_3$. Evaporation of the $CHCl_3$ gave a colorless oil containing 33% unreacted **13** (^1H NMR analysis). The oil was dissolved in 25 ml of ether and excess $LiAlH_4$ was added. The mixture was stirred for 6 hr and water was carefully dropped in until the excess hydride had been consumed. The ether solution was dried over $MgSO_4$ and then filtered. The reaction flask was carefully rinsed with dry ether. Evaporation of the ether left 601 mg (94% based on initial percent reaction) of a colorless oil containing alcohols corresponding to **39** and **40** and the unreacted **13** by ^1H NMR analysis. Oxidation of this mixture by the Jones procedure gave 172 mg of a

mixture of the ketones (90% overall yield) which was analyzed by ^{1}H NMR. The major isomer of the two mixtures could be crystallized from EtOH solutions of the reaction mixtures. The minor isomers were not isolated, and their ^{1}H NMR spectra are taken from the mixtures with the other isomer. The mixture of alcohols was separated from the unreacted **13** by chromatography on Merck 71707 alumina. The trans dichloride was eluted with petroleum ether (bp 60–70°) and the alcohols were removed with benzene.

***anti*-8-Chloro-14,15-dimethyl-*exo*-4-dibenzobicyclo[3.2.1]-octadienol:** mp 217–218°; ^{1}H NMR (CCl_4) δ 3.94 (H-1), 4.65 (H-4), 3.47 (H-5), 4.83 (H-8), $J_{4,5}$ = 2.0 Hz.

Anal. Calcd for $C_{18}H_{17}OCl$: C, 75.92; H, 6.17. Found: C, 76.09; H, 5.94.

***anti*-8-Chloro-10,11-dimethyl-*exo*-4-dibenzobicyclo[3.2.1]-octadienol:** ^{1}H NMR (CCl_4) δ 3.94 (H-1), 4.65 (H-4), 3.47 (H-5), 4.83 (H-8), $J_{4,5}$ = 2.0 Hz.

***anti*-8-Chloro-14,15-dimethyl-4-dibenzobicyclo[3.2.1]octadienone:** mp 172–173°; ^{1}H NMR (CCl_4) δ 4.07 (H-1), 4.23 (H-5), 4.88 (H-8).

Anal. Calcd for $C_{18}H_{15}OCl$: C, 76.46; H, 5.35. Found: C, 76.32; H, 5.43.

***anti*-8-Chloro-10,11-dimethyl-4-dibenzobicyclo[3.2.1]octadienone:** ^{1}H NMR (CCl_4) δ 4.07 (H-1), 4.23 (H-5), 4.88 (H-8).

Silver Acetate Assisted Acetolysis of 14. Solvolysis of 688 mg (2.00 mmol) of **14** with 335 mg (2.00 mmol) of silver acetate in 15 ml of refluxing glacial acetic acid with stirring for 7 days was 75% complete by ^{1}H NMR analysis after work-up as described for **13**. The product was a colorless oil, 743 mg. ^{1}H NMR analysis of the acetates was used in determining the ρ values. The acetates were converted to the alcohols and ketones in the same procedure used for the derivatives of **13** in order to prove the structural assignments (overall yield 80%). The major isomer could be crystallized from an ethanol solution of the mixture obtained at each stage of the reaction sequence. The minor isomers were not separated, and ^{1}H NMR data are taken from mixtures.

***anti*-8,10,11-Trichloro-*exo*-4-dibenzobicyclo[3.2.1]octadienol acetate:** mp 199.5–200°; ^{1}H NMR ($CDCl_3$) δ 4.10 (H-1), 5.90 (H-4), 3.89 (H-5), 4.92 (H-8), $J_{4,5}$ = 2.5 Hz.

Anal. Calcd for $C_{18}H_{13}O_2Cl_3$: C, 58.80; H, 3.56. Found: C, 58.53; H, 3.48.

***anti*-8,14,15-Trichloro-*exo*-4-dibenzobicyclo[3.2.1]octadienol acetate:** ^{1}H NMR ($CDCl_3$) δ 4.10 (H-1), 5.95 (H-4), 3.89 (H-5), 4.98 (H-8).

***anti*-8,10,11-Trichloro-4-dibenzobicyclo[3.2.1]octadienone:** mp 204–205°; ^{1}H NMR ($CDCl_3$) δ 4.25 (H-1), 4.13 (H-5), 4.83 (H-8).

Anal. Calcd for $C_{16}H_9OCl_3$: C, 59.40; H, 2.78. Found: C, 59.21; H, 2.89.

***anti*-8,14,15-Trichloro-4-dibenzobicyclo[3.2.1]octadienone:** ^{1}H NMR ($CDCl_3$) δ 4.25 (H-1), 4.13 (H-5), 4.88 (H-8).

Addition of Benzenesulfenyl Chloride to 11. Benzenesulfenyl chloride (1.96 g, 13.6 mmol) in 50 ml of CCl_4 was added dropwise to 2.90 g (12.5 mmol) of **11** stirring in 50 ml of CCl_4. The orange color of the reagent disappeared instantly. Upon evaporation of the CCl_4 a pale yellow oil remained, 4.67 g (96%). The oil was dissolved in petroleum ether (bp 85–100°) and the two trans isomers **21** and **20** could be separated by fractional crystallization. Approximately equal amounts of each were obtained in this way.

In another reaction the mixture of trans isomers from the addition (476 mg, 1.27 mmol) and 227 mg (1.35 mmol) of AgOAc was refluxed with stirring in 25 ml of glacial acetic acid for 43 hr. Work-up as before, reduction with $LiAlH_4$, and oxidation gave a 97% yield of a mixture of syn and anti [3.2.1] ketones. When **20** was subjected to the reaction sequence above only *anti*-8-thiophenoxy-14,15-dimethyl-4-dibenzobicyclo[3.2.1]octadienone was formed, based on the ^{1}H NMR spectrum.

***anti*-8-Chloro-*syn*-7-thiophenoxy-10,11-dimethyldibenzobicyclo[2.2.2]octatriene (20):** mp 174–175°; ^{1}H NMR ($CDCl_3$) δ 4.23 (H-1), 4.12 (H-5), 3.95 (H-7), 3.42 (H-8).

Anal. Calcd for $C_{24}H_{21}SCl$: C, 76.46; H, 5.63. Found: C, 76.61; H, 5.77.

***syn*-8-Chloro-*anti*-7-thiophenoxy-10,11-dimethyldibenzobicyclo[2.2.2]octadiene (21):** mp 152–153.5°; ^{1}H NMR ($CDCl_3$) δ 4.23 (H-1), 4.12 (H-5), 3.95 (H-7), 3.42 (H-8).

Anal. Found: C, 76.26; H, 5.85.

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Registry No.—**11**, 55089-35-5; **12**, 55089-36-6; **13**, 55124-45-3; **14**, 55089-37-7; **15**-OAc, 55089-38-8; **15**-OH, 55089-39-9; **16**-OAc, 55123-06-3; **16**-OH, 55123-07-4; **17**-OAc, 55089-40-2; **17**-OH, 55089-41-3; **18**-OAc, 55123-08-5; **18**-OH, 55123-09-6; **20**, 55089-42-4; **21**, 55123-10-9; **22**-I, 55089-43-5; **23**-I, 55089-44-6; **30**, 55089-45-7; **31**, 55089-46-8; *exo*-**32**, 55089-47-9; *endo*-**32**, 55123-11-0; *exo*-**33**, 55089-48-0; *endo*-**33**, 55123-12-1; *exo*-**34**, 55089-49-1; *exo*-**35**, 55089-50-4; *exo*-**36**-Br, 55089-51-5; *exo*-**36**-OH, 55089-52-6; *exo*-**37**-Br, 55089-53-7; *exo*-**37**-OH, 55089-54-8; **43**-Cl, 55089-55-9; **44**-Cl, 55089-56-0; *syn*-8-bromo-14,15-dimethyl-*exo*-4-dibenzobicyclo[3.2.1]octadienol acetate, 55089-57-1; *syn*-8-bromo-14,15-dimethyl-*exo*-4-dibenzobicyclo[3.2.1]octadienol, 55089-58-2; *syn*-8-bromo-14,15-dimethyl-4-dibenzobicyclo[3.2.1]octadienone, 55089-59-3; *syn*-8-bromo-10,11-dimethyl-4-dibenzobicyclo[3.2.1]octadienone, 55089-60-6; *syn*-8-bromo-10,11-dimethyl-*exo*-4-dibenzobicyclo[3.2.1]octadienol, 55089-61-7; *syn*-8-bromo-10,11-dimethyl-*exo*-4-dibenzobicyclo[3.2.1]octadienol acetate, 55089-62-8; *syn*-8-bromo-10,11-dichloro-*exo*-4-dibenzobicyclo[3.2.1]octadienol acetate, 55089-63-9; *syn*-8-bromo-10,11-dichloro-*exo*-4-dibenzobicyclo[3.2.1]octadienol, 55089-64-0; *syn*-8-bromo-10,11-dichloro-4-dibenzobicyclo[3.2.1]octadienone, 55089-65-1; *syn*-8-bromo-14,15-dichloro-*exo*-4-dibenzobicyclo[3.2.1]octadienol acetate, 55089-66-2; *syn*-8-bromo-14,15-dichloro-*exo*-4-dibenzobicyclo-[3.2.1]octadienol, 55089-67-3; *syn*-8-bromo-14,15-dichloro-4-dibenzobicyclo[3.2.1]octadienone, 55089-68-4; *endo*-**4**-*syn*-8-dichloro-14,15-dimethyldibenzobicyclo[3.2.1]octadiene, 55089-69-5; *endo*-4-*syn*-8-dichloro-10,11-dimethyldibenzobicyclo[3.2.1]octadiene, 55124-04-4; *syn*-8-chloro-14,15-dimethyl-*exo*-4-dibenzobicyclo[3.2.1]octadienol acetate, 55089-70-8; *syn*-8-chloro-10,11-dimethyl-*exo*-4-dibenzobicyclo[3.2.1]octadienol acetate, 55089-71-9; *syn*-8-chloro-14,15-dimethyl-*exo*-4-dibenzobicyclo[3.2.1]octadienol, 55089-72-0; *syn*-8-chloro-10,11-dimethyl-*exo*-4-dibenzobicyclo[3.2.1]octadienol, 55089-73-1; *syn*-8-chloro-14,15-dimethyl-4-dibenzobicyclo[3.2.1]octadienone, 55089-74-2; *syn*-8-chloro-10,11-dimethyl-4-dibenzobicyclo[3.2.1]octadienone, 55089-75-3; *exo*-4-*syn*-8,10,11-tetrachlorodibenzobicyclo[3.2.1]octadiene, 55089-76-4; *exo*-4-*syn*-8,14,15-tetrachlorodibenzobicyclo[3.2.1]octadiene, 55089-77-5; *syn*-8,10,11-trichloro-*exo*-4-dibenzobicyclo[3.2.1]octadienol acetate, 55089-78-6; *syn*-8,14,15-trichloro-*exo*-4-dibenzobicyclo[3.2.1]octadienol acetate, 55089-79-7; *syn*-8,10,11-trichloro-*exo*-4-dibenzobicyclo[3.2.1]octadienol, 55089-80-0; *syn*-8,14,15-trichloro-*exo*-4-dibenzobicyclo[3.2.1]octadienol, 55089-81-1; *syn*-8,10,11-trichloro-4-dibenzobicyclo[3.2.1]octadiene, 55089-82-2; *syn*-8,14,15-trichloro-4-dibenzobicyclo[3.2.1]octadienone, 55089-83-3; 14,15-dimethyl-*exo*-4-dibenzobicyclo-[3.2.1]octadienol, 55089-84-4; 14,15-dimethyl-4-dibenzobicyclo-[3.2.1]octadienone, 55089-85-5; 10,11-dimethyl-*exo*-4-dibenzobicyclo[3.2.1]octadienol, 55089-86-6; 10,11-dimethyl-4-dibenzobicyclo[3.2.1]octadienone, 55089-87-7; *syn*-8-iodo-14,15-dimethyl-*exo*-4-dibenzobicyclo[3.2.1]octadienol, 55089-88-8; *syn*-8-iodo-10,11-dimethyl-*exo*-4-dibenzobicyclo[3.2.1]octadienol, 55089-89-9; *syn*-8-iodo-14,15-dimethyl-4-dibenzobicyclo[3.2.1]octadienone, 55089-90-2; *syn*-8-iodo-10,11-dimethyl-4-dibenzobicyclo-[3.2.1]octadienone, 55089-91-3; *anti*-8-chloro-14,15-dimethyl-*exo*-4-dibenzobicyclo[3.2.1]octadienol, 55123-13-2; *anti*-8-chloro-10,11-dimethyl-exo-4-dibenzobicyclo[3.2.1]octadienol, 55123-14-3; *anti*-8-chloro-14,15-dimethyl-4-dibenzobicyclo[3.2.1]octadienone, 55123-15-4; *anti*-8-chloro-10,11-dimethyl-4-dibenzobicyclo[3.2.1]-octadienone, 55123-16-5; *anti*-8,10,11-trichloro-*exo*-4-dibenzobicyclo[3.2.1]octadienol acetate, 55123-17-6; *anti*-8,14,15-trichloro-*exo*-4-dibenzobicyclo[3.2.1]octadienol acetate, 55123-18-7; anti-8,10,11-trichloro-4-dibenzobicyclo[3.2.1]octadienone, 55123-19-8; *anti*-8,14,15-trichloro-4-dibenzobicyclo[3.2.1]octadienone, 55123-20-1; 2,3-dimethylanthracene, 613-06-9; *trans*-1,2-dichloroethene, 156-60-5; 2,3-dichloroanthracene, 613-07-0; bromine, 7726-95-6; AgOAc, 563-63-3; chlorine, 7782-50-5; hydrogen bromide, 10035-10-6; acetyl hypoiodite, 6540-76-7; acetic acid, 64-19-7; mercuric acetate, 1600-27-7; sodium borohydride, 16940-66-2; benzenesulfenyl chloride, 931-59-9.

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Photochemical Transformations. XII. Photochemical Reduction of Some Dehydronorbornyl Derivatives[1]

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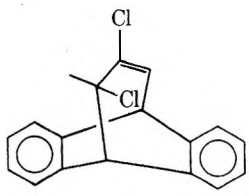
The photosensitized irradiation of exo and endo isomers of 5-chloronorbornene, 5-hydroxynorbornene, and 5-acetoxynorbornene, as well as of 5,5-dichloronorbornene, with a variety of sensitizers and solvents led to saturation of the double bond to give the corresponding norbornanes. No rearrangements, epimerizations, or solvolyses were observed.

Some years ago, it was discovered[3] that sensitized irradiation of **1** led to **2**, which is the photochemical equivalent of a Wagner–Meerwein rearrangement. That this is a true photochemical process, rather than a chain process, was clear from the fact that **1** is thermally stable with respect to **2**. The possibility that the photorearrangement involved carbenium ion–chloride ion pairs was suggested at that time and led to the idea that other systems which could accept triplet energy from photosensitizers and could undergo carbenium-ion formation readily might show similar interesting chemistry. Although the idea of carbenium-ion intervention remains to be proven or disproven,[4] it led to the discovery[5] that photosensitization of allylic chlorides and bromides results in the formation not only of products of 1,3-sigmatropic (allylic) rearrangement, but also of 1,2-rearrangement–cyclizations (allyl to cyclopropyl rearrangements). These reactions have been shown to be quite general.[1,4,6]



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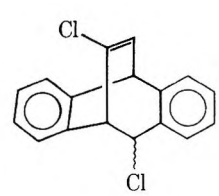

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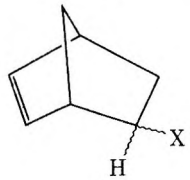

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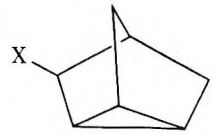
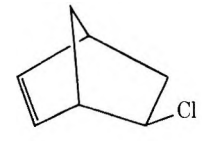


4

As the dehydronorbornyl (**3**)–nortricyclyl (**4**) system represents one in which reversible rearrangements attend carbenium ion processes,[7] we thought that photosensitized rearrangement of **3** to **4** might occur and that one might also possibly see some interesting stereochemical consequences of exo (**5**) and endo (**6**) isomerism in the halides. Accordingly, we subjected **5** and **6** to irradiation in acetone using thin-walled Pyrex filters ($\lambda > 280$ nm, $T\% > 10\%$). Both compounds were reactive under these conditions, but no trace of the isomeric nortricyclyl chloride (**4**-Cl) could be found. Instead, photoreduction occurred to give norbornyl chloride of retained stereochemistry (i.e., **5** → **7** and **6** → **8**) in yields of 10–20% as the only products of this volatility. Nortricyclyl chloride (**4**-Cl) was not reactive under similar conditions.



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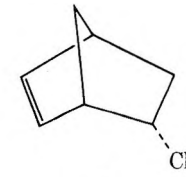

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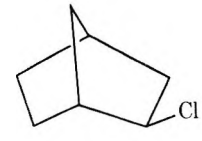

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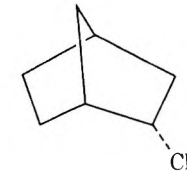
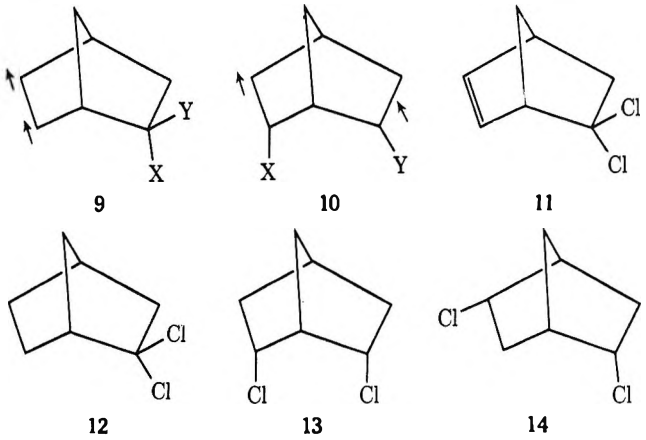


8

Sensitization of **6** with *m*-xylene (λ 254 nm) or with *p*-methoxyacetophenone ($\lambda > 280$ nm)[8] in pentane also gave

only 8 (no 4-Cl, 5, or 7 was noted) in the appropriate volatility range.

The photoreduction of norbornene and of its derivatives, as an accompaniment to dimeric, hydrodimeric, and radical solvent incorporation products both with sensitization and upon direct irradiation, has been known for some time,[9] and the yields which have been reported are consistent with those we have noted. In addition, we note that *exo*- and *endo*-dehydronorborneols and dehydronorbornyl acetates also give saturated products in similar yields. The mechanism of such reductions has not been clarified. Although cationic intermediates have been suggested, no evidence for their intervention seems at hand. Rather, as Scharf has suggested,[9] radicals seem to be involved. The fact that triplet sensitizers may be used suggests that the triplet biradical of the olefin (9) is an intermediate. This triplet might rearrange to 10 by a 1,3 shift of the endo substituent, assuming that it is long lived. Such a rearrangement would not be observable with 6 (X = Cl; Y = H), as hydrogen transfer from solvent to the 1,3-biradical still would give 8, but 5 (X = H; Y = Cl) would be expected to give appreciable amounts of 8, rather than 7, from preponderant hydrogen transfer from the exo side.[10] Failure to see exo–endo isomerism (or the reverse) speaks against such a process. Similarly, the clean photoreduction of 11 to 12, without the formation of 13 or 14 or of any of their epimers,



is of interest. While free-radical rearrangements of saturated radicals are rare at low temperatures, even in norbornyl systems,[10] rearrangements of triplet biradicals are quite common, both by 1,2 and 1,3 shifts,[11] and migration of halogen atoms occurs even in monoradicals.[12]

We have recently noted that chlorobenzene (ϵ 14, 280 nm) in acetonitrile is an excellent sensitizer for photoallylic rearrangements and that photosolvolysis occurs readily for certain allylic systems with chlorobenzene and methanol. When a mixture of 5 and 4-Cl was irradiated in the latter system, the 4-Cl was inert and the 5 was converted to 20% of 7. In chlorobenzene, irradiation of a mixture of 5 and 4-Cl again found 4-Cl inert; 5 was converted to higher molecular weight materials, and neither 6 nor 7 was produced.

In no case, then, have we observed either homolytic or heterolytic cleavage of the carbon–chlorine bond in these sensitized reactions. One rationalization might be that the reduction reactions are so fast as to overwhelm competing reactions. A preliminary quantum yield measurement for the 5 → 7 reaction in acetone was 0.007, and that for 6 → 8 was 0.002, so that the quantum yields for disappearance of these halides are in the order of 0.01–0.05, somewhat lower than those we have generally observed for the allylic and allyl to cyclopropyl chloride rearrangements. The results with the dehydronorbornyl chlorides thus offer no insight into the nature of the other rearrangements we have reported earlier.

Experimental Section

Proton magnetic resonance spectra were obtained with a Varian A-60A or A-60 spectrometer. Infrared spectra were run in carbon tetrachloride, using either Perkin-Elmer Model 337 or Model 137 spectrophotometers. Mass spectra were obtained on a Varian MAT Model CH-7 mass spectrometer. Analyses of some experiments were carried out on a Varian Aerograph Model A-90P-3 instrument, while preparative separations were carried out on an Aerograph Autoprep Model A-700 gas chromatograph. Irradiations were performed with a Hanovia 450-W mercury arc lamp (Engelhardt-Hanovia, Inc., Newark, N.J., Model L-639A-36) inserted into a water-cooled quartz immersion probe. In quantitative experiments, samples were placed into preconstricted 13 × 100 mm Pyrex test tubes, degassed on a vacuum line with five freeze–pump–thaw cycles and sealed at pressures less than 10^{-5} Torr. Sealed tubes were then irradiated in parallel with *cis*-2-pentene actinometer solutions[13] in a merry-go-round photolysis apparatus.

Materials. All solvents and sensitizers were spectroquality grade, except for chlorobenzene, which was twice distilled reagent-grade material. Nortricyclyl and *exo*- and *endo*-dehydronorbornyl chlorides[14] and acetates[15] were prepared as previously described, as was 5,5-dichloro-2-norbornene.[16] Norbornene, *exo*- and *endo*-norborneol, and *exo*- and *endo*-dehydronorbornyl alcohol were commercially available samples.

Irradiation of *exo*- (5) and *endo*- (6) Dehydronorbornyl Chloride in Acetone. *exo*-Dehydronorbornyl chloride (15 mg, 0.12 mmol) was dissolved in 0.6 ml of acetone in a Pyrex NMR tube, and 60 μl of *n*-heptane was added as internal standard. The tube was capped with a serum stopper and deaereated with nitrogen. After irradiation for 1.5 hr, analysis by gas chromatography (30% SE-30 on Chromosorb W 60/80 mesh, 20 ft × 0.375 in. Al column) indicated that total loss of starting material had occurred, and that the product mixture consisted of 15% of *exo*-norbornyl chloride (7) and 85% of unidentified higher molecular weight material. No nortricyclyl chloride (4-Cl), *endo*-dehydronorbornyl chloride (6), or *endo*-norbornyl chloride (8) were detected.

Similar treatment of *endo*-dehydronorbornyl chloride led to 10% formation of *endo*-norbornyl chloride (8) after 1.5 hr of irradiation. No other products of similar volatility were noted.

Irradiation of *endo*-Dehydronorbornyl Chloride (6) in *m*-Xylene and in *p*-Methoxyacetophenone–Pentane. *endo*-Dehydronorbornyl chloride (44 mg, 0.35 mmol) and 15.0 μl of *n*-heptane were dissolved in 0.6 ml of *m*-xylene in a quartz tube. The sample was treated as outlined above, and after 96 hr of irradiation, the product mixture contained 32% of 6, 13% of 8, and 54% of unidentified higher molecular weight material. No isomerization could be detected.

endo-Dehydronorbornyl chloride (21 mg, 0.16 mmol), 15 μl of *n*-heptane, and 60 μl of *p*-methoxyacetophenone in 0.6 ml of pentane was treated similarly and placed in a Pyrex NMR tube. After 1.5 hr the product mixture consisted of 95% of 6 and 4% of 8.

Irradiation of *exo*- and *endo*-Dehydronorborneols in Acetone. *endo*-Dehydronorborneol (15 mg, 0.14 mmol) and 15.0 μl of *n*-heptane was dissolved in 1.0 ml of acetone in a Pyrex NMR tube, and the sample was treated as described above. After 18 hr of irradiation 10% of *endo*-norborneol was obtained, but no isomerization was noted.

Similar treatment of *exo*-dehydronorborneol gave 15% of *exo*-norborneol after 18 hr. Again no isomerization was detected.

Irradiation of *exo*- and *endo*-Dehydronorbornyl Acetate in Acetone. *exo*-Dehydronorbornyl acetate (31 mg, 0.20 mmol) and 15.0 μl of *n*-heptane were dissolved in 1.0 ml of acetone in a Pyrex NMR tube, and the sample was treated as described above. After 6 hr of irradiation, the product mixture consisted of 15% of *exo*-norbornyl acetate, 0% of *exo*-dehydronorbornyl acetate, and 85% of higher molecular weight material. No isomerization was detected.

Similar treatment of the endo acetate gave 12% of *endo*-norbornyl acetate after 6 hr. Again, no isomerization was detected.

Irradiation of 5,5-Dichloro-2-norbornene (11) in Acetone. 5,5-Dichloro-2-norbornene (57 mg, 0.35 mmol) was dissolved in 0.5 ml of acetone and placed in a Pyrex NMR tube. The sample was handled as outlined above; after 4 hr of irradiation, total loss of starting material was noted. The product was analyzed by GC (3% SE-52 on Aeropak 30 100/120, 5 ft × 0.25 in. stainless steel), and it was found to consist of 20% of the saturated dichloride 12 and 80% of higher molecular weight material. No rearranged products could be detected.

Irradiation of Nortricyclyl Chloride (4-Cl) in Chlorobenzene and in Chlorobenzene–Methanol. Nortricyclyl chloride (200 mg, 1.6 mmol) was dissolved in 5.0 ml of chlorobenzene–

methanol (1:4) and placed in an 8 × 0.375 in. Pyrex tube. The sample was handled as outlined above; after 100 hr of irradiation, the ^{1}H NMR spectrum showed no change.

Nortricyclyl chloride (200 mg, 1.6 mmol) in 5.0 ml of chlorobenzene treated similarly showed no change in the ^{1}H NMR spectrum, even after 75 hr of irradiation.

Irradiation of *exo*-Dehydronorbornyl Chloride (5) in Chlorobenzene–Methanol. *exo*-Dehydronorbornyl chloride (250 mg, 1.94 mmol) was dissolved in 5.0 ml of chlorobenzene–methanol (1:4) solution and the sample was treated as outlined for nortricyclyl chloride. After 75 hr of irradiation, ^{1}H NMR analysis indicated that the product was composed of 20% of **5** and 80% of saturated compounds, of which at least 80% was dimeric or polymeric material. No absorption corresponding to –OMe could be detected.

Irradiation of *exo*-Dehydronorbornyl Chloride (5) in Chlorobenzene. To two Pyrex tubes were added, respectively, 47 mg (0.37 mmol) and 85 mg (0.66 mmol) of **5** in 1.0 ml of chlorobenzene. The samples were then treated as outlined above. After 100 hr of irradiation, ^{1}H NMR analysis indicated that the first tube contained 56% of **5** and 44% of dimeric or polymeric material, while the second contained 43% of **5** and 57% of dimeric or polymeric material. No isomerization was detected.

Quantum Yield Determination for *exo*-Norbornyl Chloride (7) and *endo*-Norbornyl Chloride (8). *exo*-Dehydronorbornyl chloride (**5**, 29.5 mg, 0.230 mmol) was diluted to 3.0 ml with acetone and placed in a preconstricted Pyrex test tube. The sample was degassed on a vacuum line and sealed at pressures less than 10^{-5} Torr. After irradiation for 48 hr, analysis by gas chromatography (25% Carbowax 20M on Chromosorb P 60/80, 6 ft × 0.25 in. Al column) indicated that the tube contained 20% of **7** (ϕ = 0.007).

endo-Dehydronorbornyl chloride (**6**) treated similarly gave 12% of **8** after 48 hr (ϕ = 0.002).

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Registry No.—**4-Cl**, 3509-46-4; **5**, 3721-19-5; **6**, 3721-18-4; **7**, 765-91-3; **8**, 2999-06-6; **11**, 4634-77-9; *endo*-dehydronorborneol, 694-97-3; *exo*-dehydronorborneol, 2890-98-4; *exo*-dehydronorbornyl acetate, 5257-37-4; *endo*-dehydronorbornyl acetate, 2890-95-1.

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Oxidations of Valencene

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Epoxidation of valencene (**1**) gives predominantly the β-epoxide **3**, and similarly, dihydrovalencene (**15**) gives predominantly **20**. Photosensitized oxidation of **1** gives 4α,10α-dimethyl-6β-isopropenyl-Δ^1-9β-octalol (**5**) and 4α,10α-dimethyl-6β-isopropenyl-Δ^8-1α-octalol (**6**). Epoxidation of nootkatone (**2**) gives β-epoxide **10**, which undergoes the Wharton–Bohlen rearrangement to β-octalol **5**. Hydroboration of dihydrovalencene (**15**) gives predominantly 4α,10α-dimethyl-6β-isopropyl-*trans*-1β-decalol (**16**). Stereochemical correlations are made and the results are discussed in reference to similar oxidations of other octalin derivatives.

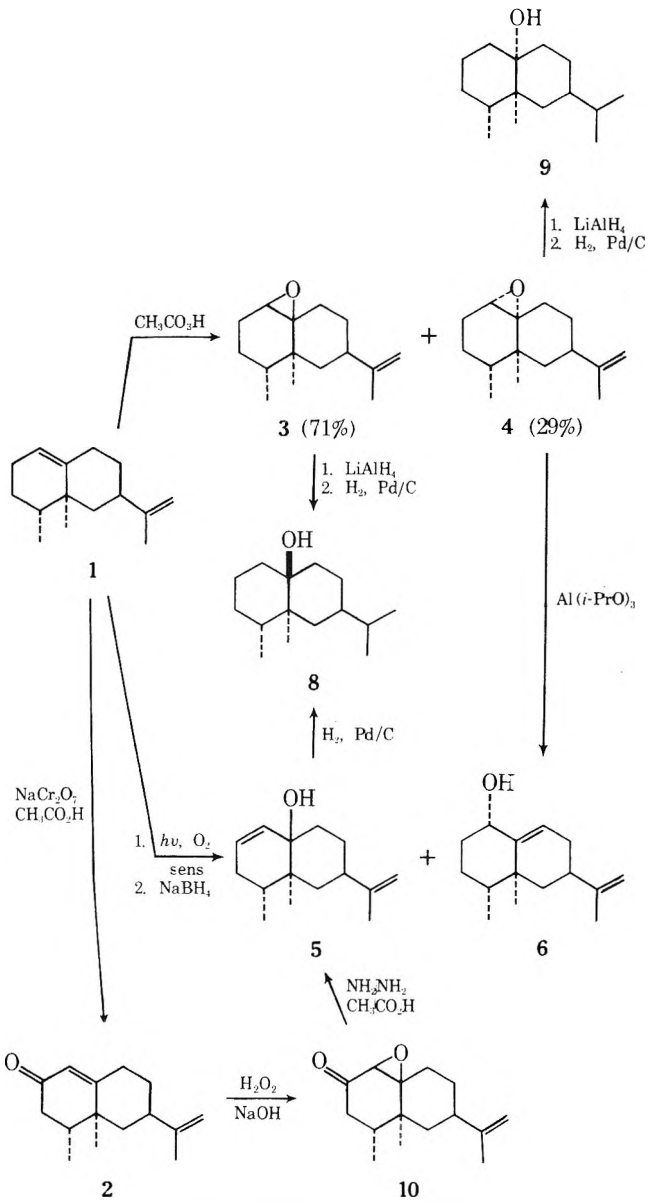
The sesquiterpene valencene (**1**),[1] which is present in valencia orange oil, has been of considerable interest both for the synthesis of nootkatone (**2**) and for the synthetic challenge posed by the 4α,10α-dimethyl substituents. Because of the desirable fragrance–flavor properties of nootkatone (**2**), we embarked on a study of some of the other oxidative chemistry of the parent hydrocarbon, valencene (**1**).

Epoxidation of valencene (**1**) by means of 40% peracetic acid afforded a mixture of mono- and diepoxides in a ratio of 3.5:1. The stereochemistry of the monoepoxides, isolated by distillation, was initially assigned by inspection of the NMR spectra. The epoxy hydrogens of *trans*-5,6-epoxy steroids and *trans*-1,9-epoxy-2,2,5,5,10-pentamethyldecalin resonate at higher field than the corresponding hydrogens of the cis isomers.[2] Since the NMR spectrum of the major valencene epoxide (71%) showed the epoxy hydrogen as a triplet at δ 2.90, whereas the minor epoxide (29%) had this corresponding triplet at δ 3.00, the major and minor epoxides were assigned structures **3** and **4** (Scheme I), respectively. Preferential epoxidation of **1** trans to the C-10 axial methyl group is consistent with the observation[3] that epoxidation of 10-methyl-1(9)-octalin gives 60% trans epoxide.

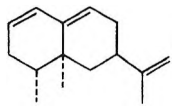
Support for this stereochemical assignment was obtained by correlation of the major epoxide with the major product derived from photosensitized oxidation of **1**, which was first reported by Ohloff.[7]

Photosensitized oxygenation of **1** followed by reduction

Scheme I



of the hydroperoxides with sodium borohydride gave two major alcohols, **5** and **6** (Scheme I), in 44 and 14% respective yield, and a considerable amount of nootkatene (**7**).[4,5]



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Alcohol **5** was isolated from the photooxidation mixture by preparative GLC on a Carbowax–KOH column and alcohol **6** was isolated by chromatography on a silica gel column. Except for the stereochemistry of the hydroxy groups, the structures of **5** and **6** were evident from their spectral data (see Experimental Section).

The stereochemistry of the major alcohols from type II photosensitized oxidation of cyclic olefins can normally be predicted. Attack of singlet oxygen occurs at either end of the double bond, preferentially from the face that allows concurrent abstraction of the quasi-axial allylic hydrogen.[6] Based on this mechanism, inspection of a molecular model of **1** shows that the hydroxyl group of tertiary alcohol **5** should have the β configuration and that of secondary alcohol **6** the α configuration.

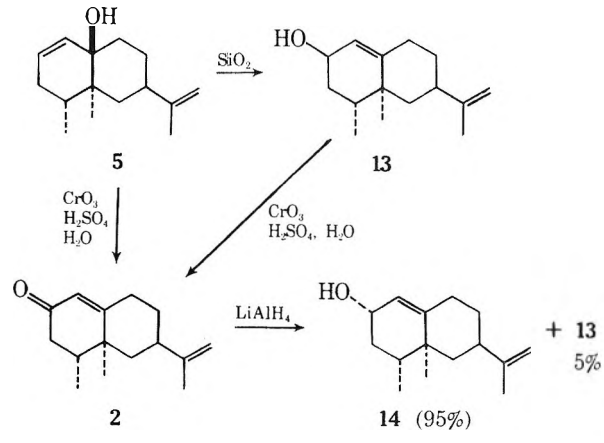
Ohloff and coworkers have also concluded[7] that **5** and **6** are the major products in 50 and 15% respective yields from photosensitized oxygenation of **1**. During their work, they were able to isolate and characterize the hydroxy epimers of **5** and **6**, both formed in 2% yield.

Reduction of a mixture of epoxides **3** and **4** (78% **3** by GLC) with lithium aluminum hydride, followed by hydrogenation over palladium catalyst, gave a 70:30 mixture of **8** and **9** which was separated by chromatography on silica gel. The major alcohol, **8**, was identical (ir and NMR spectra, GLC retention time) with the alcohol obtained by hydrogenation of **5**. This correlation of **3** with **5** substantiates the initial β stereochemistry assigned to the major valencene epoxide **3**.

Previously, a tertiary allylic alcohol of unknown stereochemistry had been derived[4] from the Wharton–Bohlen rearrangement[8] of nootkatone oxide (**10**). In order to correlate the stereochemistry of this alcohol with the other oxidation products of **1**, this reaction was repeated (Scheme I) and the alcohol obtained was identical (ir and NMR spectra, GLC retention time) with **5** isolated from the photosensitized oxidation of **1**. Alcohol **5**, as obtained crude from **10**, was essentially free of the epimeric alcohol, thus implying that epoxidation of nootkatone (**2**) with alkaline hydrogen peroxide occurs almost exclusively from the β face. The NMR spectrum of crude nootkatone oxide (**10**) shows a sharp singlet at δ 3.02 for the epoxide proton. There is no evidence in the spectrum of a second singlet near δ 3 as would be expected for the epimeric epoxide. The almost exclusive formation of **10** is in sharp contrast to the results[9] from 10-methyl-1(9)-octal-2-one and Δ^4-3-keto steroids, where epoxidation occurs predominantly cis to the axial bridgehead methyl group.

Alcohol **5**, when chromatographed on Merck silica gel, rearranged to epinootkatol (**13**) in 87% yield (Scheme II). A

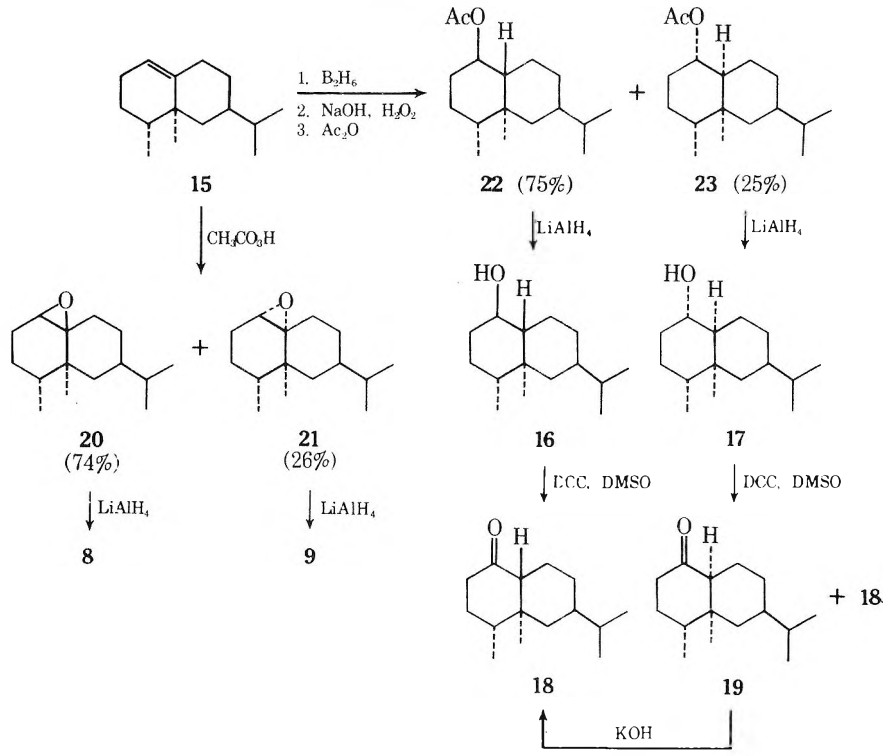
Scheme II



small amount (5%) of **13** was also present in the crude photooxidation mixture of **1**. The observation that **13** was a secondary allylic alcohol and oxidized quantitatively to nootkatone (**2**) established the general structure. Reduction of **2** with lithium aluminum hydride gave 95% of an alcohol epimeric with **13** and assigned structure **14**. The vinylic hydrogen NMR absorption of **14** appears as a broad singlet, consistent with a molecular model dihedral angle of nearly 90° between the vinylic and vicinal hydrogens, whereas the corresponding absorption of **13** appears as a doublet (J = 5 Hz), also consistent with the observed dihedral angle of 30–40°. Alcohol **5** can also be readily oxidized to **2**.

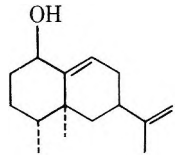
Rearrangement of the minor valencene epoxide **4** with aluminum isopropoxide gave one major alcohol, in addition

Scheme III

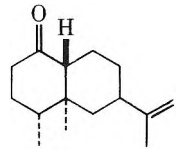


to considerable nootkatene (**7**), which was identical with the secondary allylic alcohol **6** isolated from photosensitized oxidation of **1** (Scheme I).

Major epoxide **3** in the presence of aluminum isopropoxide rearranged slowly as compared to **4** to give a series of products, none of which appear to be the expected[10] alcohol **11**. The major product has been tentatively identified as 4α,10α-dimethyl-6β-isopropenyl-*trans*-1-decalone (**12**),



11



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which could arise from epimerization of the corresponding *cis*-1-decalone. This implies that aluminum isopropoxide is functioning as a Lewis acid in the opening of epoxide **3**. Assuming the rearrangement of an epoxide to an allylic alcohol with aluminum isopropoxide to be a concerted reaction,[10] it is not obvious from molecular models why this rearrangement is not observed for epoxide **3**. This question, as well as the rearrangement of **3** and **4** under Lewis acid conditions, is presently under study.

Dihydrovalencene (**15**) was treated with diborane followed by alkaline hydrogen peroxide to give a mixture of alcohols which were separated as their acetates (**22** and **23**) by Nester–Faust spinning band distillation. The pure alcohols **16** and **17** were regenerated by reduction of the acetates with lithium aluminum hydride. Moffatt oxidation[11] of the major alcohol (75%) gave 4α,10α-dimethyl-6β-isopropyl-*trans*-1-decalone (**18**) (Scheme III). Similar oxidation of the minor alcohol (25%), after purification by chromatography on silica gel, gave a 1:1 mixture of **18** and *cis*-1-decalone **19**. When this mixture was allowed to react with 5% methanolic potassium hydroxide solution, the ratio of **18** to **19**, as determined by GLC analysis, changed from 56:44 to 89:11 thus establishing that **18** has a trans ring fusion. Consequently, the major alcohol obtained from hydroboration of dihydrovalencene is the β isomer **16**.

The stereochemical results for hydroboration of **15** almost exactly parallel the stereochemical results for epoxidation of **1**, although they differ from those of 10-methyl-1(9)-octalin, where hydroboration occurs 2:1 in favor of the cis isomer.[12]

The stereochemical results for epoxidation of dihydrovalencene (**15**) are identical with those for epoxidation of valencene (**1**). Reduction of 1,9-epoxydihydrovalencene (74% **20** and 26% **21** by GLC) with lithium aluminum hydride, followed by separation of the alcohols by chromatography on silica gel, gave 72% **8** and 28% **9** by GLC (Scheme III).

Although the 10-methyl group of the valencene skeleton is the only axial substituent, the stereochemical differences for epoxidation of **2** as compared to 10-methyl-1(9)-octal-2-one and for hydroboration of **15** as compared to 10-methyl-1(9)-octalin indicates that distal equatorial substituents, such as the 4-methyl group, must play a role in the steric determination of these reactions. Similar effects have been observed for oxidations of substituted cyclohexenes.[13]

Experimental Section

Infrared spectra were taken as neat samples on a Perkin-Elmer 457 and absorptions are reported as reciprocal centimeters, NMR spectra were taken on a Varian A-60A as chloroform-d_1 solutions and are reported as δ units relative to Me_4Si, and molecular weights were determined from mass spectra obtained with a Perkin-Elmer 270. Gas–liquid chromatography (GLC) was done, except where noted, on a 10% Carbowax 20M column (12 ft × 0.125 in.).

Valencene (1). Valencene (4α,10α-dimethyl-6β-isopropenyl-$\Delta^{1,9}$-octalin) was obtained by distillation of Valencia orange essence oil (Libbey, McNeil, and Libby, Inc.) where it is present in ca. 2% concentration: bp 98° (2 mm); $n^{20}D$ 1.5050; ir, 1637, 885 cm^{-1}; NMR δ 5.31 (1 H, vinylic H), 4.69 (2 H, broad s, terminal methylene H), 1.70 (3 H, vinylic methyl H), 0.95 (3 H, s, methyl H), 0.9 (3 H, d, J = ca. 5 Hz, methyl H).

The valencene (**1**) was contaminated with 2–3% of an antioxidant, 2,6-di-*tert*-butyl-4-methylphenol (BHT).

1α,9α- and 1β,9β-Epoxy-4α,10α-dimethyl-6β-isopropenyldecalin (4 and 3). To a stirred mixture of 175 g (0.858 mol) of valencene (1), 200 ml of benzene, and 22 g of sodium carbonate, was added, dropwise over 1 hr while controlling the temperature at 30–40°, a solution of 22 g of sodium carbonate in 220 g (1.16 mol) of 40% peracetic acid. After addition was completed, the mixture was stirred at 35° for 30 min and poured into 500 ml of cold water, the layers were separated, and the aqueous phase was extracted with benzene. The combined organic extract was washed with water, neutralized with 10% sodium hydroxide solution, washed with water, dried, filtered, and concentrated under reduced pressure. The residual oil (185 g) showed the following composition by GLC, in order of elution: 6% valencene (1), 21% 1α,9α-epoxy-4α,10α-dimethyl-6β-isopropenyldecalin (4), 52% 1β,9β-epoxy-4α,10α-dimethyl-6β-isopropenyldecalin (3), and 21% of the two diepoxides. The ratio of 4:3 was 29%:71%.

Distillation gave 118 g (63% yield) of a mixture of 3 and 4, bp 90–97° (1 mm), n^{20}D 1.4995–1.5000.

Anal. Calcd for $C_{15}H_{24}O$: C, 81.76; H, 10.98. Found: C, 81.83; H, 11.06.

Redistillation on a Nester-Faust Teflon spinning band column gave 75–80% pure 4, bp 78° (0.5 mm), and 99% pure 3, bp 84° (0.5 mm).

1α,9α-Epoxy-4α,10α-dimethyl-6β-isopropenyldecalin (4): ir 1640, 1236, 984, 968, 941, 914, 885 cm^{-1}; NMR δ 4.70 (2 H, broad s, terminal methylene H), 3.00 (1 H, t, J = 2 Hz, epoxy H), 1.71 (3 H, vinylic methyl H), 1.00 (3 H, s, methyl H), 0.93 (3 H, d, J = 7 Hz, methyl H); mass spectrum M^+ m/e 220.

1β,9β-Epoxy-4α,10α-dimethyl-6β-isopropenyldecalin (3): ir 1639, 954, 900, 884 cm^{-1}; NMR δ 4.72 (2 H, broad s, terminal methylene H), 2.90 (1 H, t, J = 2 Hz, epoxy H), 1.72 (3 H, vinylic methyl H), 0.99 (3 H, s, methyl H), 0.70 (3 H, d, J = 7 Hz, methyl H); mass spectrum M^+ m/e 220.

1α,9α- and 1β,9β-Epoxy-4α,10α-dimethyl-6β-isopropyldecalin (21 and 20). Dihydrovalencene (15, containing a few percent of BHT and tetrahydrovalencene) was epoxidized with peracetic acid as described above. The mixture of epoxides was 26% 1α,9α-epoxy-4α,10α-dimethyl-6β-isopropyldecalin (21) (eluted first from GLC) and 74% 1β,9β-epoxy-4α,10α-dimethyl-6β-isopropyldecalin (20): bp 108–110° (1 mm); ir 1455, 1375, 1358, 892, 725 cm^{-1}; NMR δ 2.85–3.07 (1 H, m, epoxy H), 0.93 (s, isopropyl methyl), 0.84 (s, methyl), 0.71 (d, J = 6.5 Hz, methyl); mass spectrum M^+ m/e 222 for both isomers.

Anal. Calcd for $C_{15}H_{26}O$: C, 81.02; H, 11.79. Found: C, 81.08; H, 11.95.

Photosensitized Oxidation of Valencene (1). A solution at 0° of 40.0 g (0.196 mol) of valencene (1) (containing about 8% of 2,6-di-*tert*-butyl-4-methylphenol, BHT), 0.5 g of Rose Bengal, 700 ml of methanol, and 500 ml of benzene was continuously aerated with oxygen and irradiated with a 400-W Lucalox lamp for 8 hr. After 4 hr of irradiation, an additional 0.5 g of Rose Bengal was added.

After irradiation, the solution was transferred to a three-necked flask and 10.0 g of sodium borohydride was added portionwise while keeping the temperature at 5–10°. After addition, the solution was allowed to warm to room temperature and was stirred overnight. The solution was concentrated under reduced pressure, diluted with water, and extracted with ether. The ethereal solution was washed with saturated sodium chloride solution, dried, filtered, and concentrated.

The residual oil (38.7 g) on GLC showed 57% unreacted valencene (1) and the following products in order of GLC elution: 31% nootkatene (7) and BHT, 44% 4α,10α-dimethyl-6β-isopropenyl-Δ^1-9β-octalol (5), 14% 4α,10α-dimethyl-6β-isopropenyl-Δ^8-1α-octalol (6), 5% 4α,10α-dimethyl-6β-isopropenyl-$\Delta^{1,9}$-2β-octalol (13), 2% 4α,10α-dimethyl-6β-isopropenyl-$\Delta^{1,9}$-2α-octalol (14, tentatively identified on the basis of identical GLC retention time with authentic 14), and 4% of several unidentified products.

Nootkatene (7) from the photooxidation mixture had an identical GLC retention time with that of synthetic nootkatene[4] but was not isolated from the mixture.

Octalol 5 was isolated by preparative GLC on a Carbowax–KOH column and was identical (ir and NMR spectra, GLC retention time) with the alcohol obtained from the Wharton–Bohlen rearrangement of nootkatone oxide (10).

Octalol 6 was isolated (80% pure) by chromatography of the crude photooxidation mixture on silica gel (50:1 benzene–ether). This alcohol was identical (ir and NMR spectra, GLC retention time) with the alcohol obtained from opening of 4α,10α-dimethyl-6β-isopropenyl-1α,9α-epoxydecalin (4) with aluminum isopropoxide.

Octalol 13 was isolated as crystalline material by continued elution of the silica gel chromatogram with 50:1 benzene–ether: mp 71–73.5°; ir 3370, 1635, 1044, 1004, 926, 882 cm^{-1}; NMR δ 5.46 (1 H, d, J = 5 Hz, vinylic H), 4.67 (2 H, broad s, terminal vinylic H), 4.05 (1 H, broad, α H), 1.70 (3 H, broad s, vinylic methyl), 0.90 (3 H, s, methyl), 0.90 (3 H, d, J = 5 Hz, methyl); NMR (DMSO) δ 4.30 (1 H, d, J = 5 Hz, hydroxy H); mass spectrum M^+ m/e 220.

Anal. Calcd for $C_{15}H_{24}O$: C, 81.76; H, 10.98. Found: C, 81.48; H, 11.06.

On GLC, 13 had an identical retention time with that of the minor epimer obtained by reduction of nootkatone (2) with lithium aluminum hydride. Jones oxidation[14] of 13 gave nootkatone (2).

Pure 5, when chromatographed on silica gel (Merck, 50:1 benzene–ether), rearranged to 13 in 87% yield.

When the crude photooxidation mixture was subjected to Jones oxidation,[14] alcohols 5, 13, and 14 were converted to nootkatone (2) in 45% isolated yield based on unrecovered valencene (1).

4α,10α-Dimethyl-6β-isopropyl-9α- and -9β-decalol (9 and 8). Reduction of 1,9-epoxyvalencene (22% 4, 78% 3 by GLC) with lithium aluminum hydride in diethyl ether under reflux gave 4α,10α-dimethyl-6β-isopropenyl-9α- and -9β-decalol: one peak on GLC; ir 3470, 1640, 885 cm^{-1}; NMR δ 4.60 (2 H, broad s, terminal vinylic H), 1.69 (3 H, broad s, vinylic methyl), 0.87 (3 H, s, methyl), 0.71 (3 H, d, J = 6.5 Hz, methyl); NMR (DMSO) δ 3.55 (25% α-ol, s, hydroxyl H), 3.40 (75% β-ol, s, hydroxyl H).

An ethanol solution of the crude alcohols was hydrogenated on a Parr apparatus with 5% palladium on carbon as catalyst to give 4α,10α-dimethyl-6β-isopropyl-9α- and -9β-decalol: two peaks on GLC, 70% 8, 30% 9; NMR (DMSO) δ 3.50 (24% α-ol, s, hydroxyl H), 3.32 (76% β-ol, s, hydroxyl H); mass spectrum m/e 206 ($M - H_2O$) for both epimers.

A sample (2.5 g) of the alcohols was chromatographed on 90 g of silica gel and 1% ether in hexane first eluted pure 8 (1.3 g) and then pure 9 (0.5 g).

4α,10α-Dimethyl-6β-isopropyl-9β-decalol (8): major alcohol; ir 3455, 1462, 1382, 1365, 1174, 1008, 964, 932, 918, 867 cm^{-1}; NMR δ 0.70, 0.80, 0.84, 0.86, 0.92 (methyl multiplet).

Anal. Calcd for $C_{15}H_{28}O$: C, 80.29; H, 12.58. Found: C, 80.21; H, 12.32.

4α,10α-Dimethyl-6β-isopropyl-9α-decalol (9): minor alcohol; ir 3475, 1465, 1381, 1364, 1138, 1045, 1019, 967, 923 cm^{-1}; NMR δ 0.81, 0.90, 1.00, 1.20 (methyl multiplet).

Anal. Calcd for $C_{15}H_{28}O$: C, 80.29; H, 12.58. Found: C, 80.14; H, 12.55.

The epoxides 20 and 21 obtained from epoxidation of dihydrovalencene (15) were reduced with lithium aluminum hydride and the alcohols were separated by chromatography on silica gel. The major alcohol (72% by GLC) was identical with 8 and the minor alcohol (28% by GLC) was identical with 9.

4α,10α-Dimethyl-6β-isopropenyl-Δ^1-9β-octalol (5) from Wharton–Bohlen Rearrangement of Nootkatone Oxide (10) and Reduction to 4α,10α-Dimethyl-6β-isopropyl-9β-decalol (8). By GLC and NMR analysis, nootkatone oxide (10)[4] is >95% of one isomer: ir, 1712, 886 cm^{-1}; NMR δ 4.72 (2 H, terminal vinylic H), 3.02 (1 H, s, epoxy H), 1.73 (3 H, vinylic methyl), 0.96 (3 H, s, methyl), 0.80 (3 H, d, J = 6 Hz, methyl). There was no evidence in the NMR spectrum of a second singlet near δ 3 for the isomeric epoxide.

4α,10α-Dimethyl-6β-isopropenyl-Δ^1-9β-octalol (5) was obtained[4,8] by the Wharton–Bohlen rearrangement of nootkatone oxide (10): ir 3450, 1644, 887 cm^{-1}; NMR δ 5.59 (2 H, vinylic H), 4.67 (2 H, terminal vinylic H), 1.73 (3 H, broad s, vinylic methyl), 0.80 (3 H, s, methyl), 0.80 (3 H, d, J = 6 Hz, methyl); NMR (DMSO) δ 3.77 (1 H, s, hydroxyl H). Alcohol 5 partially decomposes during GLC analysis to a hydrocarbon with an identical GLC retention time with that of synthetic nootkatene (7).[4] Jones oxidation[14] of 5 gave an essentially quantitative yield of nootkatone (2).

An ethanol solution of 5 was hydrogenated on a Parr apparatus using 5% palladium on carbon as catalyst until hydrogen uptake ceased (2.0 mol hydrogen consumed per mole of 5) to give predominantly one product (>95% pure by GLC, 1–2% of the epimeric alcohol could be present by GLC), which was identical (ir and NMR spectra, GLC retention time) with 4α,10α-dimethyl-6β-isopropyl-9β-decalol (8) obtained from reduction of the major isomer 3 of 1,9-epoxyvalencene.

Reaction of 1α,9α- and 1β,9β-Epoxy-4α,10α-dimethyl-6β-isopropenyldecalin (4 and 3) with Aluminum Isopropoxide. A solution of 1.0 g (0.005 mol) of 1α,9α-epoxy-4α,10α-dimethyl-6β-isopropenyldecalin (4, 80–85% pure, containing 10% of 3), 20 mg of

aluminum isopropoxide, and 10 ml of toluene was heated under reflux for 3 hr. The solution was allowed to cool to room temperature, washed with 30% sodium hydroxide solution, and then dried, filtered, and concentrated under reduced pressure. The residual oil (0.84 g) showed the following composition by GLC on a Carbowax–KOH column: 20% nootkatene (7), 40% unreacted 4, 9% 3, 20% 4α,10α-dimethyl-6β-isopropenyl-Δ⁸-1α-octalol (6), and 11% of several other minor components.

Nootkatene, collected from GLC, was identical (NMR spectrum, GLC retention time) with a synthetic sample.[4]

4α,10α-Dimethyl-6β-isopropenyl-Δ⁸-1α-octalol (6) was isolated by preparative GLC: ir 3350, 1637, 1039, 987, 882 cm^{-1}; NMR δ 5.55 (1 H, d of d, J = 4.5, 2.5 Hz, vinylic H), 4.69 (2 H, broad s, terminal vinylic H), 4.18 (1 H, t, J = 2 Hz, α H), 1.70 (3 H, broad s, vinylic methyl), 1.13 (3 H, s, methyl), 0.87 (3 H, misshapen d, J = 5–6 Hz, methyl); mass spectrum m/e 205 (M − CH_3), 202 (M − H_2O).

Anal. Calcd for $C_{15}H_{24}O$: C, 81.76; H, 10.98. Found: C, 81.52; H, 10.94.

When pure 6 was subjected to the above reaction conditions, a considerable amount of nootkatene was formed.

The rearrangement of 4 to 6 proceeded rapidly for 0.5–1 hr and then essentially stopped. The rearrangement resumed at a good rate when an additional 20 mg of aluminum isopropoxide was added.

1β,9β-Epoxy-4α,10α-dimethyl-6β-isopropenyldecalin (3), 95% pure, in the presence of aluminum isopropoxide under the above reaction conditions rearranged slower than 4 (half of the rate of 4 by GLC internal standard) to give a mixture of four products, including nootkatene (7). The major product was isolated from GLC and tentatively identified as 4α,10α-dimethyl-6β-isopropenyl-*trans*-1-decalone (12): ir, 1708, 1638, 885 cm^{-1}: NMR δ 4.68 (2 H, broad s, terminal vinylic H), 1.71 (3 H, broad s, vinylic methyl), 0.89 (3 H, d, J = 5.5 Hz, methyl), 0.68 (3 H, s, methyl). The other products, as yet unidentified, are two alcohols, neither of which appears to be 4α,10α-dimethyl-6β-isopropenyl-Δ⁸-1β-octalol (11).

4α,10α-Dimethyl-6β-isopropenyl-Δ^{1,9}-2α-octalol (14). Reduction of nootkatone (2) with lithium aluminum hydride gave a mixture of two alcohols: 95% 14 and 5% 13; ir 3310, 1640, 1020, 884 cm^{-1}; NMR δ 5.31 (1 H, broad s, vinylic H), 4.67 (2 H, broad s, terminal vinylic H), 4.20 (1 H, broad t, J = 7 Hz, α H), 1.70 (3 H, broad s, vinylic methyl H), 0.99 (3 H, s, methyl), 0.89 (3 H, d, J = 5.5 Hz, methyl); NMR (DMSO) δ 4.44 (1 H, d, J = 5.5 Hz, hydroxyl H of 14), 4.30 (very small, d, J = 5 Hz, hydroxy H of 13).

4α,10α-Dimethyl-6β-isopropyl-*cis*-decal-1α-ol (17) and 4α,10α-Dimethyl-6β-isopropyl-*trans*-decal-1β-ol (16). A solution of valencene (1) in ethanol was hydrogenated on a Parr apparatus at a hydrogen pressure of 50 psi using 5% palladium on carbon as catalyst until 1.1 mol of hydrogen per mole of valencene was consumed. The mixture, after filtration and concentration, showed the following composition by GLC in order of elution: 14% tetrahydrovalencene, 80% dihydrovalencene (15), and 2% valencene (1).

Pure dihydrovaleneene (15) was isolated by preparative GLC: NMR δ 5.3 (1 H, broad, vinylic H), no terminal methylene H; mass spectrum M$^+$ m/e 206.

Anal. Calcd for $C_{15}H_{26}$: C, 87.30; H, 12.70. Found: C, 87.24; H, 12.89.

A solution of borane in tetrahydrofuran (6 ml of 1 M solution, 0.006 mol) was added dropwise under nitrogen to an ice-cold solution of 2.0 g (0.008 mol of 15) of the above hydrocarbon mixture in 40 ml of tetrahydrofuran. After addition was complete, the solution was stirred for 30 min in the cold, allowed to warm to room temperature, and stirred overnight.

Water was cautiously added until the exothermic reaction ceased, a solution of 5 ml of 10% sodium hydroxide solution and 5 ml of 30% hydrogen peroxide was added dropwise, and the mixture was stirred at 50–60° for 1 hr. The mixture was diluted with 50 ml of water and extracted with ether. The ethereal extract was washed with water, washed with saturated ferrous sulfate solution, washed again with water, dried, filtered, and concentrated.

The residual oil (2.1 g) was chromatographed on 100 g of alumina (neutral III, 1.5 × 64 cm). Hexane and benzene eluted the unreacted hydrocarbons and impurities, and ether eluted a mixture of 4,10-dimethyl-6-isopropyl-2-decalols: 1.34 g (77% based on dihydrovalencene); 98% pure; one peak on GLC; NMR (DMSO) δ 4.09 and 4.15 (1 H, 2 d in ca. 70:30 ratio, J = 5.5 Hz, hydroxyl H).

A mixture of the corresponding acetates, prepared by allowing the above alcohols to react with refluxing acetic anhydride, was resolved by GLC into two peaks (ca. 25%:75%). The acetates were separated by distillation on a Nester-Faust Teflon spinning band (bp 105–114°, 0.5 mm).

1α-Acetoxy-4α,10α-dimethyl-6β-isopropyl-*cis*-decalin (23): minor isomer, distilled first, 85% pure; ir, 1735, 1248 cm^{-1}; NMR δ 4.7–5.3 (1 H, broad, α H), 2.02 (3 H, s, acetoxy methyl H), 0.84, 0.90, 0.97, 1.06 (12 H, methyl H); mass spectrum m/e 206 (M − HOAc).

1β-Acetoxy-4α,10α-dimethyl-6β-isopropyl-*trans*-decalin (22): major isomer, distilled last, 95% pure; ir 1740, 1248 cm^{-1}; NMR δ 4.5–5.0 (1 H, broad, α H), 2.00 (3 H, s, acetoxy methyl H), 0.75, 0.80, 0.90 (12 H, methyl H); mass spectrum m/e 206 (M − HOAc).

Reduction of the minor acetate with lithium aluminum hydride gave 4α,10α-dimethyl-6β-isopropyl-*cis*-decal-1α-ol (17): ir 3320 cm^{-1}; NMR δ 3.5–4.0 (1 H, broad, α H), 0.81, 0.90, 0.95, 1.04 (12 H, methyl H); NMR (DMSO) δ 4.16 (1 H, d, J = 5.5 Hz, hydroxyl H); mass spectrum M$^+$ m/e 224.

Anal. Calcd for $C_{15}H_{28}O$: C, 80.29; H, 12.58. Found: C, 80.21; H, 12.76.

Reduction of the major acetate with lithium aluminum hydride gave 4α,10α-dimethyl-6β-isopropyl-*trans*-decal-1β-ol (16): ir 3280 cm^{-1}; NMR δ 3.1–3.6 (1 H, broad, α H), 0.70, 0.81, 0.90 (12 H, methyl H); NMR (DMSO) δ 4.09 (1 H, d, J = 5.5 Hz, hydroxyl H); mass spectrum M$^+$ m/e 224.

Anal. Calcd for $C_{15}H_{28}O$: C, 80.29; H, 12.58. Found: C, 80.10; H, 12.56.

4α,10α-Dimethyl-6β-isopropyl-*cis*- and -*trans*-1-decalone (19 and 18). Moffatt oxidation[11] of 4α,10α-dimethyl-6β-isopropyl-*trans*-decal-1β-ol (16) (major alcohol from hydroboration of dihydrovalencene) gave 4α,10α-dimethyl-6β-isopropyl-*trans*-1-decalone (18): 91% pure; ir 1705 cm^{-1}; NMR δ 0.82, 0.91, 0.93 (9 H, isopropyl and methyl H), 0.63 (3 H, s, methyl H); mass spectrum M$^+$ m/e 222.

Anal. Calcd for $C_{15}H_{26}O$: C, 81.02; H, 11.79. Found: C, 81.29; H, 11.86.

Moffatt oxidation[11] of 4α,10α-dimethyl-6β-isopropyl-*cis*-decal-1α-ol (17) (minor alcohol from hydroboration of dihydrovalencene), after purification by chromatography on silica gel (50:1 benzene–ether), gave a 1:1 mixture of 18 and 4α,10α-dimethyl-6β-isopropyl-*cis*-1-decalone (19): ir 1705 cm^{-1}; NMR, same four methyl absorptions as above plus additional peaks at δ 0.87, 1.08, and 1.21; two peaks on GLC; mass spectrum M$^+$ m/e 222 for both isomers. When this mixture was allowed to react for a few minutes with 5% methanolic potassium hydroxide at room temperature, the GLC ratio of 19 to 18 (19 eluted first) changed from 44:56 to 11:89. After work-up, the NMR spectrum of the ketone obtained was identical with that obtained above for 18.

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Registry No.—1, 4630-07-3; 2, 4674-50-4; 3, 55255-23-7; 4, 55298-11-8; 5, 50763-63-8; 6, 50763-64-9; 8, 55281-72-6; 9, 55281-73-7; 10, 5090-66-4; 12, 22489-54-9; 13, 50763-66-1; 14, 50763-67-2; 15, 28940-75-2; 16, 55281-74-8; 17, 55281-75-9; 18, 16641-28-4; 19, 55255-24-8; 20, 55255-25-9; 21, 55298-12-9; 22, 55255-26-0; 23, 55281-76-0.

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Chlorination with *N*-Chloro Amides. I. Inter- and Intramolecular Chlorination[1a]

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Decomposition of a series of *N*-chloro amides in solution has been examined as a function of the solvent, the structure of the *N*-chloro amide, the mode of initiation, and the effect of additives. The reactions proceed by free-radical chain decomposition, affording products derived from intra- and intermolecular hydrogen abstraction. The light-initiated decompositions of *N*-chloro-*N*-methylacetamide (**1a**), *N*-chloro-*N*-*tert*-butylacetamide (**2a**), and *N*-chloro-*N*-(1,1-dimethyl-2-phenylethyl)acetamide (**3a**) in cyclohexane afforded chlorocyclohexane and the parent amide; the rates were inhibited by 2,4,6-trimethylpyridine. The decomposition of *N*-chloro-*N*-*tert*-butyl-2,2-dimethylpropionamide (**4a**) afforded *N*-*tert*-butyl-3-chloro-2,2-dimethylpropionamide (**4c**) derived from the rarely observed intramolecular 1,4-hydrogen transfer. The decomposition of *N*-chloro-*N*-(1,1-dimethylpentyl)-acetamide (**5a**) afforded *N*-(1,1-dimethyl-4-chloropentyl)acetamide (**5c**) in high yield, derived from 1,5-hydrogen transfer from carbon to nitrogen. The light-initiated decompositions of **4a** and **5a** were not inhibited by trimethylpyridine. The decompositions are interpreted in terms of chlorine atom–HCl chains (repressible by 2,4,6-trimethylpyridine) and of amidyl radical chains. Hydrogen abstraction takes place at the nitrogen and not at the oxygen of an amidyl radical.

Replacement of hydrogen of an amide (RCONHR′) by halogen (RCONXR′) affords a means for selective degradation of the amide under mild conditions. The synthetic utility of *N*-halo amides has been discussed.[2] The amidyl radical derived from the *N*-halo species may abstract a hydrogen atom by an intramolecular process analogous to the 1,5-hydrogen shift from carbon to nitrogen in the Hoffman–Loeffler–Freytag rearrangement.[3] A number of amides[4,5] (X = Cl, Br, I) and a few sulfonamides[6] have been halogenated on the acyl portion (R) by this method. The major products usually are derived from 1,5-hydrogen transfer, with minor products from 1,6 transfer in a few cases. Halogenation of the *N*-alkyl chain (R′) at the δ carbon also occurs by this method.[7] Amidyl radicals generated by the photolysis of *N*-nitroso amides undergo 1,5-hydrogen transfer from the *N*-alkyl chain.[8]

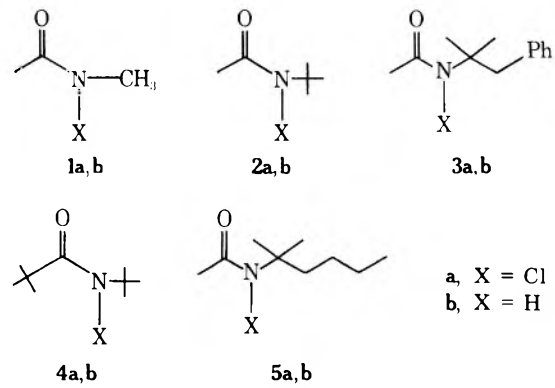
The objective of this work is to broaden our understanding of amidyl radicals, and to elucidate factors which affect the various free-radical chain decomposition paths of several *N*-chloro amides. Selectivity in hydrogen atom abstraction is taken up in Part II.[9]

Results

Preparation and Properties of *N*-Chloro Amides. *N*-Chloro amides **1a, 2a, 3a,** and **5a** were readily prepared by treating the parent amide with *tert*-butyl hypochlorite in methanol.[10] Compound **4a** required the use of chlorine monoxide in CCl_4. The N-tertiary alkyl compounds **2a, 3a, 4a,** and **5a** were stable over a period of months at 5° (in the dark). *N*-Chloro-*N*-methylacetamide (**1a**) was unstable in 2,3-dimethylbutane at 5° over a period of days.

The ultraviolet spectra of the *N*-chloro amides have maxima in the region of 260 mμ with broad tailing up to ca. 360 mμ, which permits light-initiated reactions to be carried out in Pyrex glassware. All of the *N*-chloro amides were stable toward 2,4,6-trimethylpyridine (TMP) under the reaction conditions but not stable to triethylamine or to pyridine. All (except **1a,** which was not tested) were stable toward trichloroethylene (TCE). The *N*-chloro amides **1a–5a** are readily soluble in cyclohexane, 2,2-dimethylbutane, 2,3-dimethylbutane, *n*-hexane, and benzene. The parent amides **1b–5b,** often major products of decomposition, are much less soluble and occasionally crystallize from solution after completion of the reaction.

Decomposition. The *N*-chloro amides are moderately stable in solution at 80° in the dark. In 2,3-dimethylbutane or cyclohexane, the values for $t_{1/2}$ (the time for decomposition of the first 50% of the *N*-chloro amide) follow: **2a** (20 days), **4a** (9 hr), **5a** (10 hr). Rates of decomposition are greatly accelerated by irradiation with a weak ultraviolet source or by use of dibenzoyl peroxide (azobisisobutyronitrile was ineffective). Rates are retarded by oxygen. The chain length for decomposition of *N*-chloro-*N*-*tert*-butylacetamide in cyclohexane at 80° in the dark initiated by dibenzoyl peroxide was ca. 2000.



1a, *N*-chloro-*N*-methylacetamide
2a, *N*-chloro-*tert*-butylacetamide
3a, *N*-chloro-*N*-(1,1-dimethyl-2-phenylethyl)acetamide
4a, *N*-chloro-*N*-*tert*-butyl-2,2-dimethylpropionamide
5a, *N*-chloro-*N*-(1,1-dimethylpentyl)acetamide

The products of decomposition are dependent on the *N*-chloro amide and on the reaction conditions. The results are summarized in the following paragraphs and in Tables I–IV.

***N*-Chloro-*N*-methylacetamide (1a) and *N*-Chloro-*N*-*tert*-butylacetamide (2a) (Table I and Eq 1).** The presence of 2,4,6-trimethylpyridine greatly reduced the rate of decomposition but had little effect on product composition.

$$\underset{\textbf{1a},\ R' = CH_3}{\underset{\textbf{2a},\ R' = \textit{tert}\text{-butyl}}{CH_3CONClR'}} \xrightarrow[h\nu,\ 25°]{\text{cyclohexane}} CH_3CONHR' + C_6H_{11}Cl \qquad (1)$$

***N*-Chloro-*N*-(1,1-dimethyl-2-phenylethyl)acetamide (3a) (Table II and Eq 2 and 3).** The irradiation of **3a** in degassed cyclohexane produced yields of 80–90% of the

Table I
Light-initiated Decomposition of *N*-Chloro Amides in Cyclohexane at 20–25°

N-Chloro amide	[*N*-Chloro amide], *M*	[TMP],[a] *M*	Yield of RCl, %	$t_{1/2}$,[b] min
1a	0.15		97	10
	0.15	0.22	94	320
2a	0.64		97	3
	0.64	0.19	89	125
3a	0.058		79	18
	0.058	0.15	46	430
4a	0.10		48[c,d]	3
	0.10	0.11	3[e]	6
5a	0.063		4[f]	9
	0.066	0.15	0.3[g]	6

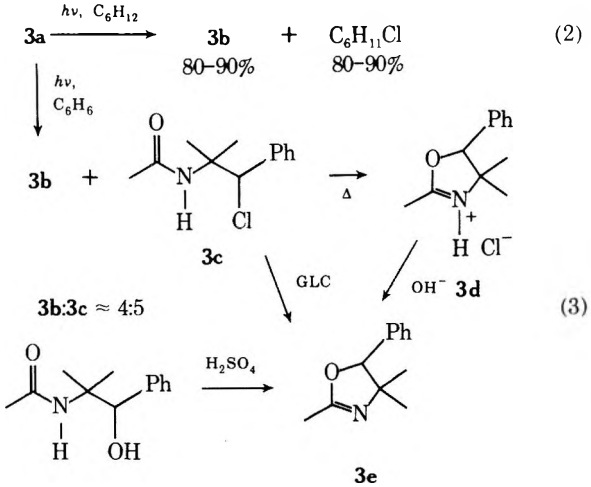
[a] TMP, 2,4,6-trimethylpyridine. [b] $t_{1/2}$ = time for 50% decomposition of *N*-chloro amide. [c] Solvent was a mixture of 2,3-dimethylbutane and cyclohexane. [d] Major product is **4c** (52%); see eq 4. [e] Major product is **4c** (97%); see eq 4. [f] Major product is **5c** (94%); see eq 6. [g] Major product is **5c** (100%); see eq 6.

Table II
Product Yields and Values for $t_{1/2}$ in the Light-Initiated Decomposition of *N*-Chloro-*N*-(1,1-dimethyl-2-phenylethyl)acetamide (3a) in Cyclohexane at 25°

[**3a**], *M*	Additive (*M*)	$t_{1/2}$, min[a]	Products[b] **3b**, %	Products[b] $C_6H_{11}Cl$, %
0.058	None	18	89	79
0.047	None	55	75	80
0.071	None	25	93	83
0.047	Ox[c]	102	90	88
0.058	TMP (0.15)[d]	430	52	46
0.047	TMP (0.05)[d]	430	57	53
0.047	TMP (0.05),[d] Ox	768	75	62

[a] $t_{1/2}$ = time for 50% decomposition of **3a**. [b] Percent yield determined by GLC using internal standards; **3b**, *N*-(1,1-dimethyl-2-phenylethyl)acetamide; $C_6H_{11}Cl$, chlorocyclohexane. [c] Undegassed, oxygen present. [d] TMP, 2,4,6-trimethylpyridine.

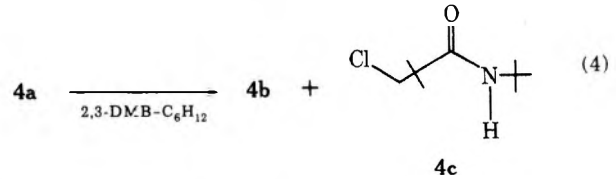
parent amide **3b** and chlorocyclohexane (Table II). The irradiation of **3a** in degassed benzene produced **3b** and *N*-(1,1-dimethyl-2-chloro-2-phenylethyl)acetamide (**3c**) in a ratio of ca. 4:5. On warming the benzene solution, **3c** isomerized to the hydrochloride salt **3d**. On washing with base,



3d gave 5-phenyl-2,4,4-trimethyl-2-oxazoline (**3e**), which was also collected from the GLC analysis of **3c**. An authentic sample of **3e** was prepared by an alternate route. Neither **3c** nor **3e** was a product in the irradiation of **3a** in cyclohexane.

The rate of the light-initiated decomposition of **3a** in cyclohexane was strongly inhibited by the addition of trimethylpyridine; the product yields were also reduced. Results are summarized in Table II. The decomposition of **3a** was two to four times faster in cyclohexane than in benzene.

***N*-Chloro-*N*-*tert*-butyl-2,2-dimethylpropionamide (4a).** The irradiation of **4a** in a mixture of 2,3-dimethylbutane and cyclohexane gave the parent amide **4b** and *N*-*tert*-butyl-3-chloro-2,2-dimethylpropionamide (**4c**) in ca. 1:1 ratio (Table III). No other amide products were observed. When **4a** was irradiated with trimethylpyridine present, or initiated with dibenzoyl peroxide (DBPO) at 80° (in the dark), the ratio **4b**:**4c** was ca. 5:95. The addition



of trimethylpyridine had only a small effect on the rate. The thermolysis was slow ($t_{1/2}$ 600 min), the peroxide-initiated reaction much faster ($t_{1/2}$ 7 min) at 80°.

Assignment of structure for the rearranged product as **4c** (rather than **4d**) was made on the basis of mass spectral

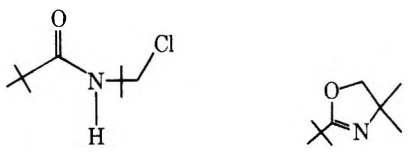


Table III
Products and Values for $t_{1/2}$ in the Decomposition of 0.10 *M* *N*-Chloro-*N*-*tert*-butyl-2,2-dimethylpropionamide (4a) in 2,3-Dimethylbutane and Cyclohexane (1.57:1 Molar Ratio)

Conditions[a]	$t_{1/2}$, min[b]	Products, % **4b**	Products, % **4c**
hν, 21°	3	48	52
hν, 21°, TMP[c] (0.11 *M*)	6	3	97
Dark, 80°	~600	6	94
Dark, 80°, DBPO[d] (5.6 mol %)	7	6	94

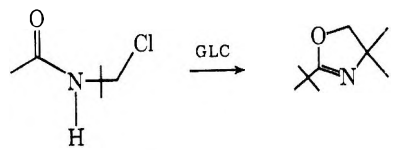
[a] All samples were degassed. [b] Time for 50% decomposition of **4a**. [c] TMP = 2,4,6-trimethylpyridine. [d] DBPO, dibenzoyl peroxide.

Table IV
Light-Initiated Decomposition of *N*-Chloro-*N*-(1,1-dimethylpentyl)acetamide (5a) in Cyclohexane at 25°

[**5a**], *M*	Additive (*M*)	$t_{1/2}$[a]	Products, %[b] **5c**	**5b**	$C_6H_{11}Cl$
0.063	None	9	94	6	4
0.075[c]	None	3	97	3	3
0.063	Ox[d]	89	6	83	78
0.066	TMP[e] (0.15)	6	100	0.3	0.3
0.066	TMP[e] (0.15), Ox[d]	110	86	3	3

[a] $t_{1/2}$ = time for 50% decomposition of **5a**. [b] Determined by GLC using internal standards: **5b**, *N*-(1,1-dimethylpentyl)acetamide; **5c**, *N*-(1,1-dimethyl-4-chloropentyl)acetamide. See eq 6. [c] Irradiated at 15°. [d] Undegassed, oxygen present. [e] TMP, 2,4,6-trimethylpyridine.

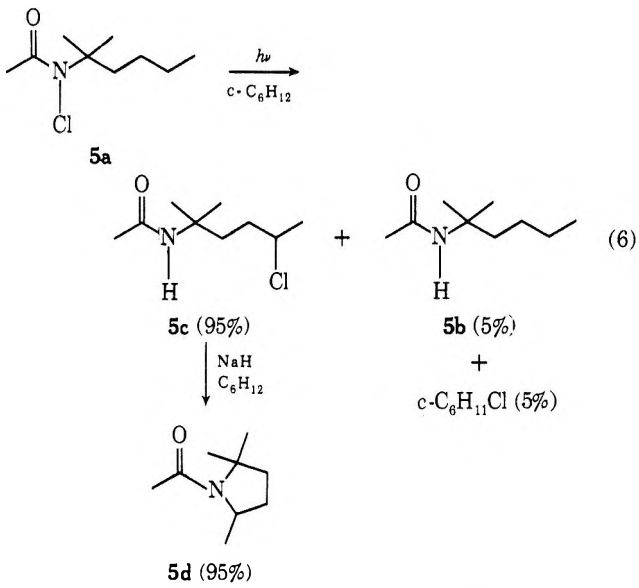
data which place the chlorine on the acyl portion of the amide (see Experimental Section). This assignment is supported by the thermal stability of **4c**, which could be collected unchanged from GLC. Under such conditions, amide **4d** would be expected to cyclize to the oxazoline **4e**,[11] as was found for **3c** (eq 3) and reported[4] for **2c** (eq 5).



(5)

2c

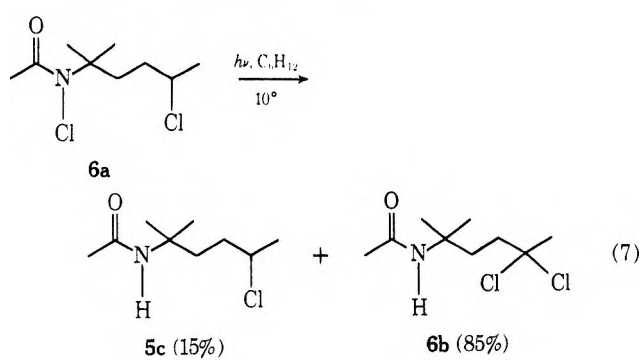
***N*-Chloro-*N*-(1,1-dimethylpentyl)acetamide (5a) (Table IV and Eq 6).** The only chlorinated amide product found was **5c**, based on NMR evidence, on cyclization to acetyl-2,2,5-trimethylpyrrolidine (**5d**) by treatment with sodium hydride in refluxing hexane, and on comparison with an authentic sample of **5c** prepared by an alternate route.



(6)

When solutions of **5a** were irradiated without degassing, the yields of the rearranged amide **5c** were greatly reduced (6–10%) and the yields of the parent amide **5b** and chlorocyclohexane correspondingly increased (74–78%) (Table IV). The samples that were not degassed also had a much longer time for 50% decomposition, characteristic of oxygen inhibition of free-radical chain reactions. The addition of trimethylpyridine raised the yield of the rearranged amide **5c** to ca. 100% in degassed samples and to 86% in samples not degassed. The base had very little effect on the rate of decomposition of **5a**.

Treatment of **5c** with *tert*-butyl hypochlorite in methyl alcohol afforded *N*-chloro-*N*-(1,1-dimethyl-4-chloropentyl)acetamide (**6a**), which on irradiation in degassed cyclohexane yielded ca. 15% **5c** and 85% *N*-(1,1-dimethyl-4,4-dichloropentyl)acetamide (**6b**).



(7)

Discussion

The sensitivity of the rates of decomposition to inhibition by oxygen and other additives and to acceleration by free-radical initiators and by weak irradiation indicates that the *N*-chloro amides **1a**–**5a** decompose by free-radical chain reactions of long chain length. The variations in rates and in product compositions as a function of additives point strongly to the operation of more than one kind of chain process.[12] The principal possibilities are summarized in Scheme I.

The "amidyl radical chain" simply involves abstraction of a hydrogen from the solvent or from within the amide (intramolecular) followed by atom transfer of a chlorine from another *N*-chloro amide to the intermediate carbon radical. The chlorine atom chain is essentially the Goldfinger mechanism[12,13] proposed for *N*-chlorosuccinimide. Neale[4] and others have shown that HCl rapidly reacts with *N*-chloro amide to generate Cl_2.

Effects of 2,4,6-Trimethylpyridine and Other Scavengers. The purpose of adding 2,4,6-trimethylpyridine (TMP) was to trap any HCl generated during the photolysis with the hope of limiting the reaction of the *N*-chloro amide to an amidyl radical chain (see Scheme I). This additive has a large inhibiting effect on the rates of decomposition of *N*-chloro-*N*-methylacetamide (**1a**), *N*-chloro-*N*-*tert*-butylacetamide (**2a**), and *N*-chloro-*N*-(1,1-dimethyl-2-phenylethyl)acetamide (**3a**) (see Table I), all of which give products of solvent chlorination. The rates for *N*-chloro-*N*-*tert*-butyl-2,2-dimethylpropionamide (**4a**) and *N*-chloro-*N*-(1,1-dimethylpentyl)acetamide (**5a**) show little or no inhibition when TMP is added (see Table I). Intramolecular hydrogen transfer leading to the *C*-chloro compound **5c** is the primary chain reaction path for **5a**. TMP does not inhibit the reaction, but does increase the yield of rearranged product **5c** (see Table IV), and essentially eliminates chlorination of the cyclohexane. A similar, but more dramatic, effect is observed for the irradiation of **4a** in cyclohexane. Without TMP, approximately 50% of the product is **4c** (intramolecular attack) and 50% is chloroalkane (intermolecular attack). Addition of TMP has little effect on rate but changes the product composition to 97% **4c** (intramolecular) and 3% chloroalkane (intermolecular). The simplest interpretation for cases **4a** and **5a** is (1) irradiation initiates both amidyl radical chains and chlorine atom chains; (2) the amidyl radicals abstract hydrogen intramolecularly, leading on to the *C*-chloro amides **4c** and **5c**; (3) these amidyl radical chains are not affected by TMP; and (4) chlorination of solvent comes from chlorine atom–HCl chains which are repressed by the acid-scavenging action of TMP.

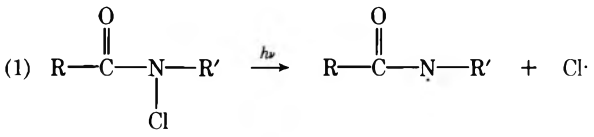
In the light-initiated decomposition of **1a**, **2a**, and **3a** the products indicate that the major reaction is chlorination of the solvent (cyclohexane or 2,3-dimethylbutane). The reaction could proceed by amidyl radical chains, by chlorine atom–HCl chains, or perhaps both. The strong inhibition by TMP suggests that HCl is important in the chain decomposition. In the presence of TMP presumably only the slower amidyl radical chain is available as the principal chlorination path.[14]

Effect of Oxygen on *N*-Chloro Amide Reactions. The rates of decomposition of all five of the *N*-chloro amides were inhibited by oxygen. Different product ratios and chlorination selectivities[9] were also observed, suggesting significant changes in the atom transfer steps involved.

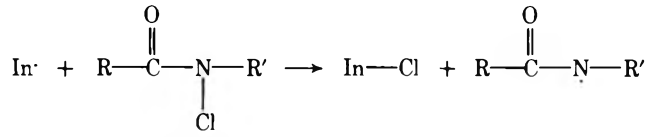
Light-initiated decomposition of **5a** in cyclohexane *in*

Scheme I
Free-Radical Chain Steps of *N*-Chloro Amides

Initiation



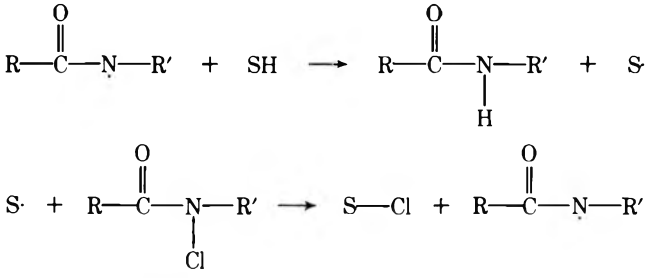
or (2) Initiator $\longrightarrow$ 2In·



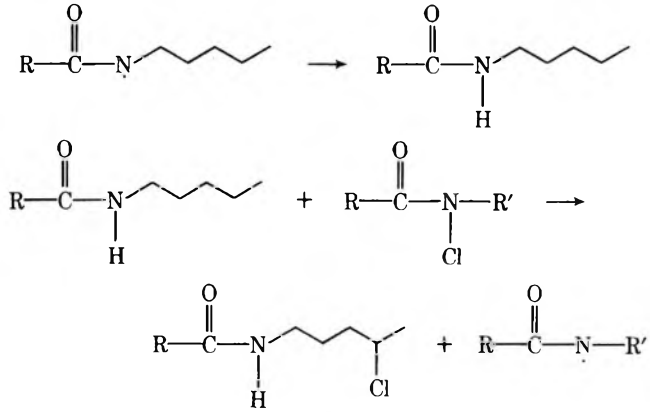
Propagation

(1) Amidyl radical chain

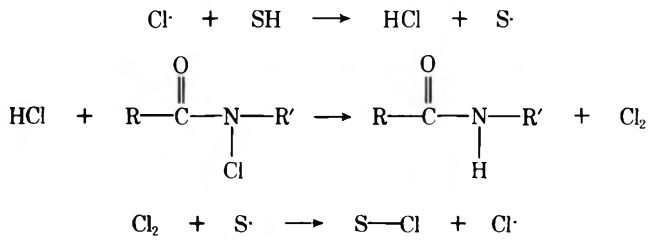
(a) Intermolecular



(b) Intramolecular



(2) Chlorine atom-HCl chain

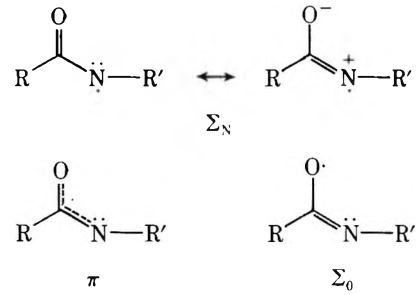


Termination (The results of this study are uninformative on this point; presumably the usual "like-" and "cross-termination" steps are involved.)

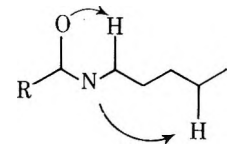
the presence of oxygen and absence of TMP greatly increases the importance of solvent chlorination (Table IV, lines 1 and 2 vs. line 3); in the presence of TMP, solvent chlorination with **5a** is unimportant and remains unimportant when oxygen is present (Table IV, lines 3 and 4). These results suggest that oxygen in some way enhances the chlorine atom–HCl chains. In accord with this, the light-initiated chlorinations of various alkanes with **2a** in the presence of oxygen show selectivities characteristic of chlorine atoms.[9] Again, this suggests that oxygen favors the HCl chain mechanism.

A study[15] of the allylic bromination of cyclohexene by *N*-bromosuccinimide (NBS) in carbon tetrachloride contains several observations relevant to the present case. Cyclohexenyl hydroperoxide increased the rate of allylic bromination, but the presence of oxygen inhibited the reaction. Thus, with the *N*-chloro amides of the present study, oxygen inhibits the free-radical chain reaction, and in the process forms hydroperoxides which react with the *N*-chloro amide to produce HCl and carry on the HCl chain. In this way the rate is inhibited, the yield of intermolecular chlorination products is raised in the case of **5a**, and chlorination with **2a** in the presence of oxygen is characteristic of chlorine atom.[9] The formation of amide peroxides may be the cause of the poor product balance in the irradiation of **5a** in the presence of oxygen.

Reactive Center of an Amidyl Radical. Amidyl radicals might be expected to show reactivity at both oxygen and nitrogen. An amidyl radical has several possible ground states (Σ_N, π, Σ_O). Evidence from ESR favors the π state for simple amidyl radicals.[16]



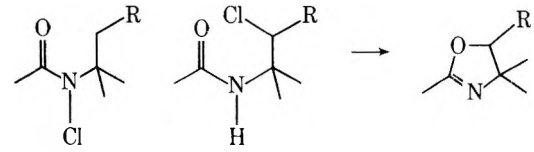
If we only consider the favored six-membered transition state (resulting in 1,5-hydrogen transfer), attack on the *N*-alkyl chain could result in two different products, depending on whether oxygen or nitrogen is the abstracting



species. We concur with Chow and Joseph that reactivity at oxygen is nil,[7] for the reasons given below.

When **5a** was irradiated (with trimethylpyridine to quench the HCl chain) in cyclohexane, a 100% yield of a single chloro amide (**5c**) was obtained, indicating a highly specific 1,5-hydrogen transfer from carbon to nitrogen. The 85% yield of **6b** from **6a** (eq 7) further suggests the preference for 1,5-hydrogen transfer to nitrogen, overcoming the expected low reactivity of the hydrogen at this δ carbon already holding one chlorine.[17-19]

The light-initiated decompositions of **2a** and **3a** in *cyclohexane* did not yield any of the rearrangement product (**2c** or **3c**), even when trimethylpyridine was added to quench

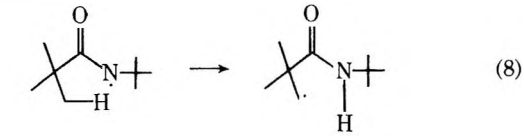


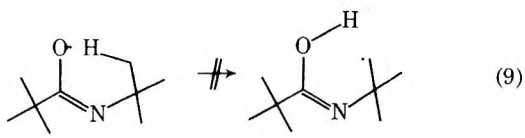
2a, R = H **2c**, R = H
3a, R = Ph **3c**, R = Ph

the HCl chain chlorination of cyclohexane. The large rate inhibition by trimethylpyridine on **2a** and **3a** (compared to the negligible inhibition for **4a** and **5a**, see Table I) also is consistent with a lack of intramolecular hydrogen abstraction. The light-initiated decompositions of **2a**[4,7] and **3a** in *benzene* do afford **2c** and **3c**, in all likelihood the result of intermolecular attack by amidyl radical or chlorine atom.

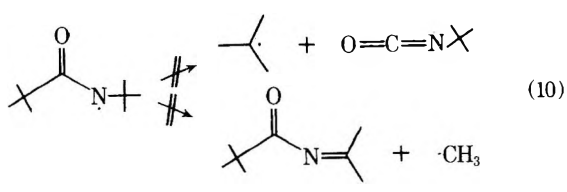
***N-tert*-Butyl-2,2-dimethylpropionamidyl Radical.** The decomposition of **4a**, like that of the other *N*-chloro amides of this study,[1,2] clearly takes place by a free-radical chain reaction (Table III). The major product (~97% from **4a** with $h\nu$, TMP), even in cyclohexane as solvent, is *N-tert*-butyl-3-chloro-2,2-dimethylpropionamide (**4c**) (eq 4). Apparently, the amidyl radical is so hindered that the unfavorable 1,4-hydrogen transfer is preferred over abstraction of hydrogen from the solvent. The 1,4-hydrogen transfer is quite unusual and has not been observed in rearrangements of alkoxy,[20a] aminium,[3] or amidyl[4-8] radicals. The major path where possible is 1,5-hydrogen transfer via a six-membered ring transition state. In some cases low yields of products of 1,6-hydrogen transfer have been observed.[5b] Products derived from 1,4-hydrogen transfer have been reported in some studies of carbonyl compounds.[20b] 1,4-Hydrogen transfer also has been observed in the 2,4,6-tri-*tert*-butylphenyl radical.[20c]

The fact that 1,4-hydrogen transfer from the acyl *tert*-butyl group (eq 8) occurs with **4a** is further evidence that amidyl radicals do not undergo hydrogen abstraction by oxygen (eq 9). Abstraction by an oxygen radical would involve a favorable 1,5-hydrogen transfer by attacking the *N-tert*-butyl group.


(8)


(9)

An alternative to hydrogen transfer would be β-scission of the amidyl radical (eq 10). This process is commonly observed for alkoxy radicals[20a,21] and has been proposed to explain some of the products from the photolysis of *N*-nitroso amides.[22] However, products of β-scission were not observed in the reactions of **4a**.


(10)

Experimental Section

Melting points are corrected. Reagent grade cyclohexane and 2,3-dimethylbutane were washed with concentrated sulfuric acid (until no discoloration) and distilled from sodium benzophenone ketyl.

Gas–liquid partition chromatographic analyses (GLC) were performed on an Aerograph 220 instrument with a thermal conductivity detector and with glass injection port liners. The following columns were used: column A, 2 ft × 0.25 in. aluminum tube packed with 15% silicone oil (SE-30) and 0.5% diethylene glycol succinate (DEGS) on Chromosorb W; column B, 6 ft × 0.25 in. aluminum tube packed with 15% Versamide 900 on Chromosorb W; column C, 6 ft × 0.25 in. aluminum tube packed with 15% silicone oil (SE-30) and 0.5% diethylene glycol succinate (DEGS) on Chromosorb W; column D, 6 ft × 0.25 in. aluminum tube packed with 20% silicone oil (SE-30) and 2% diethylene glycol succinate (DEGS) on Chromosorb P.

***N*-(1,1-Dimethylpentyl)acetamide (5b)** was prepared by the Ritter reaction[23] with 2-methyl-2-hexanol, acetonitrile, and concentrated H_2SO_4, as colorless needles (hexane): mp 53.0–54.5° (lit.[24] mp 65–67°); ir (CCl_4) 3430 (sh, NH), 3310 (br, NH), 1685 (s, C=O), 1540 (s, –NHC=O), 1385, and 1367 cm^{-1} [–$C(CH_3)_2$]; NMR δ 0.90 (t, J = 6 Hz, 3 H, –CH_2CH_3), 1.27 [s, 6 H, –$C(CH_3)_2$], 1.87 (s, 3 H, CH_3CO–), 1.1–1.7 [m, 6 H, –$(CH_2)_3CH_3$], and 5.9 ppm (s, 1 H, NH).

Anal. Calcd for $C_9H_{19}NO$: C, 68.74; H, 12.18; N, 8.90. Found: C, 68.48; H, 12.10; N, 8.95.

***N*-Chloro-*N*-(1,1-dimethylpentyl)acetamide (5a).** To a solution of 10.02 g (0.064 mol) of *N*-(1,1-dimethylpentyl)acetamide in 25 ml of methyl alcohol in a foil-wrapped flask was added 11 ml (10 g, 0.092 mol) of *tert*-butyl hypochlorite. After stirring for 2 hr the solvent and excess hypochlorite were removed on a rotoevaporator, leaving a colorless liquid. Distillation yielded 10.62 g (87%), bp 35.0–36.2° (0.36 mm). Iodometric analysis indicated 99.5 ± 1.5% active chlorine: ir (CCl_4) 1680 (s, C=O) and 1280 cm^{-1} (s); uv (isooctane) λ_{max} 257 mμ (ϵ 356); NMR (CCl_4) δ 0.92 (t, J = 6 Hz, 3 H, –CH_2CH_3), 1.41 [s, 6 H, –$C(CH_3)_2$], 2.16 (s, 3 H, CH_3CO–), and 1.1–1.9 ppm [m, 6 H, –$(CH_2)_3CH_3$].

Anal. Calcd for $C_9H_{18}NOCl$: C, 56.39; H, 9.46; N, 7.31. Found: C, 56.52; H, 9.36; N, 7.19.

***N*-Chloro-*N*-methylacetamide (1a)** was prepared by treating the amide with *tert*-butyl hypochlorite in methyl alcohol: bp 35–40° (14–18 mm); $n^{25.5}D$ 1.4563; ir (CCl_4) 1685 (C=O), 1320 cm^{-1} (s) [lit.[4] bp 42° (24 mm), $n^{23.5}D$ 1.4583]; iodometric analysis, 96.5 ± 1.0% active chlorine.

***N*-Chloro-*N*-*tert*-butylacetamide (2a)** was prepared by treating the amide with *tert*-butyl hypochlorite in methyl alcohol: bp 50° (9 mm); $n^{23.0}D$ 1.4506 [lit.[4] bp 44° (9 mm), $n^{23}D$ 1.4510]; ir (CCl_4) 1680 (s, C=O) and 1285 cm^{-1} (s); NMR (CCl_4) δ 1.43 [s, 9 H, –$C(CH_3)_3$] and 2.15 ppm (s, 3 H, CH_3CO–); iodometric analysis, 97.0 ± 1.0% active chlorine.

***N*-(1,1-Dimethyl-2-phenylethyl)acetamide (3b)** was prepared by treating α,α-dimethyl-β-phenethylamine with acetic anhydride in ether: mp 90.0–91.0° (lit.[25] mp 91.5–92.0°); ir (CCl_4) 3440 (sh, NH), 3300 (br, NH), 1682 (s, C=O), and 1502 cm^{-1} (s, –NHC=O); NMR (CCl_4) δ 1.22 [s, 6 H, –$C(CH_3)_2$], 1.69 (s, 3 H, CH_3CO–), 2.92 (s, 2 H, –$CH_2C_6H_5$), 6.16 (s, 1 H, –NH), and 6.97 ppm (s, 5 H, –C_6H_5); uv (isooctane) λ_{max} 259 mμ (ϵ 180).

***N*-Chloro-*N*-(1,1-dimethyl-2-phenylethyl)acetamide (3a)** was prepared by treating the amide with *tert*-butyl hypochlorite in methyl alcohol, yielding a viscous, colorless liquid: bp 73–77° (0.10 mm); $n^{26.2}D$ 1.5294; ir (CCl_4) 1663 (s, C=O) and 1290 cm^{-1} (s); NMR (CCl_4) δ 1.43 [s, 6 H, –$C(CH_3)_2$], 2.17 (s, 3 H, CH_3CO–), 3.13 (s, 2 H, –$CH_2C_6H_5$), and 7.14 ppm (s, 5 H, –C_6H_5); uv (isooctane) λ_{max} 259 mμ (ϵ 492); iodometric analysis, 98.0 ± 1.0% active chlorine.

Anal. Calcd for $C_{12}H_{16}NOCl$: C, 63.85; H, 7.15; N, 6.21. Found: C, 63.97; H, 7.15; N, 6.31.

***N-tert*-Butyl-2,2-dimethylpropionamide (4b)** was prepared by adding an excess of *tert*-butylamine to 2,2-dimethylpropionyl chloride in ether: mp 118–119° (hexane) (lit.[26] mp 118–119°); ir (CCl_4) 3480 (sh, NH), 1670 cm^{-1} (s, C=O); NMR (CCl_4) δ 1.15 (s, 9 H), 1.35 (s, 9 H), and 5.25 ppm (s, 1 H, NH).

***N*-Chloro-*N*-*tert*-butyl-2,2-dimethylpropionamide (4a).** To 5.9 g (0.038 mol) of the amide in 50 ml of CCl_4 in a foil-wrapped flask was added 115 ml of a 0.37 M solution of chlorine monoxide[27] in CCl_4. After stirring for 3 hr the solution was washed with 300 ml of water and dried ($MgSO_4$), the solvent was removed on a rotoevaporator, and the remaining pale yellow liquid was distilled: 4.32 g; bp 26° (0.04 mm); ir (CCl_4) 1672 (s, C=O), 1262 (s), and 1155 cm^{-1} (s); NMR (CCl_4) δ 1.35 (s, 9 H) and 1.45 ppm (s, 9 H); iodometric analysis, 96.0 ± 1.0% active chlorine. Attempts to N-chlorinate the amide with *tert*-butyl hypochlorite under a variety of conditions were unsuccessful.

Methods for the Decomposition of *N*-Chloro Amides. Some large-scale decompositions were done in 17-mm o.d. Pyrex test tubes which had been washed in a Lakeseal glass cleanser solution, rinsed, and dried. Reactions in which rates, product yields, or relative reactivities were determined were carried out in 5-mm o.d. Pyrex tubes. Lengths (0.4 m) of tubing were soaked in Lakeseal glass cleaner for 1 hr, rinsed with distilled water, soaked in 0.2 N HCl solution for 24 hr, rinsed, soaked in 0.2 N NH_4OH solution for 24 hr, and rinsed; each length was drawn out to make two tubes (each sealed at one end) and dried (150°).

Solutions of *N*-chloro amide (and added scavengers if specified)

were always made with freshly distilled solvents. Aliquots (0.5 ml) were placed in 5-mm o.d. Pyrex tubes, degassed by freezing (liquid nitrogen), evacuating (0.02–0.05 mm), and thawing five times, and then sealed. Sample tubes which were "not degassed" were loosely capped with no-air stoppers. In light-initiated reactions up to 16 sample tubes were rotated (to assure equal light exposure to each sample) in a clear Pyrex Dewar flask filled with water which was kept at a constant temperature during the run. The low-intensity long-wavelength uv light source was either a Blak-Ray uvl-22 lamp (Ultraviolet Products Co.) or a Burton Model 1910 lamp (Burton Manufacturing Co.). To measure the rates of decomposition, usually two sets of eight tubes were irradiated; samples were periodically removed from the light, immediately frozen, later thawed, opened, and analyzed iodometrically for positive chlorine. Samples were analyzed by GLC after disappearance of the *N*-chloro amide; yields were determined by adding an aliquot containing an internal standard after opening the tube. Thermally initiated samples were placed in a dark constant-temperature oil bath at 80.0 ± 0.1°; the rates and products were determined in the same manner as above.

Irradiation of *N*-Chloro-*N*-(1,1-dimethyl-2-phenylethyl)-acetamide in Benzene. Prepurified nitrogen was slowly bubbled through a solution of 6.10 g of the *N*-chloro amide in 65 ml of benzene for 75 min before irradiation, and a positive nitrogen pressure was maintained in the flask during photolysis. The solution was irradiated for 4 days at 20° with a Westinghouse 275-W sunlamp. Analysis by GLC (column B, 190°) indicated two major peaks at 1.2 and 5.3 min (ratio 1.26:1), the latter corresponding to *N*-(1,1-dimethyl-2-phenylethyl)acetamide. Removal of the benzene (rotoevaporator at room temperature) left a brown oil which was dissolved in 25 ml of CCl_4, seeded, and cooled at −22° for several days. The 2.10 g of off-white material collected was recrystallized three times (CCl_4), yielding 0.73 g of fine white crystals: mp 105.0–106.5° (solidified at 108–110°); second mp 176–179°; ir ($CHCl_3$) 3430 (sh, NH), 3300 (w, br, NH), 1678 (s, C=O), and 1505 cm^{-1} (s, –NHC=O); NMR ($CDCl_3$) δ 1.28 (s, 3 H, $-CCH_3$), 1.45 (s, 3 H, $-CCH_3$), 1.90 (s, 3 H, CH_3CO), 5.83 (s, 1 H, –CHClPh), 5.43 (s, 1 H, NH), and 7.38 (s, 5 H, $-C_6H_5$).

Anal. Calcd for $C_{12}H_{16}NOCl$: C, 63.84; H, 7.10; N, 6.21. Found: C, 63.86; H. 7.00; N, 6.09. When collected by GLC it has the same retention time (1.2 min) as 5-phenyl-2,4,4-trimethyl-2-oxazoline, and an identical ir spectrum.

In a separate experiment, attempts to crystallize this material from benzene–hexane resulted in the collection of fine white crystals: mp 170–175°; ir ($CHCl_3$) 3300–3400 (br, $-^+NH$), 2200–2500 (br, $-^+NH$), 1820 (br, NH), 1665 cm^{-1} (sh, C=O) (characteristic of ammonium salts); NMR ($CDCl_3$) δ 1.08 (s, 3 H, $-CCH_3$), 1.72 (s, 3 H, $-CCH_3$), 2.70 (s, 3 H, CH_3CO), 5.88 (s, 1 H, –OCHPh), and 7.50 ppm (s, 5 H, $-C_6H_5$).

Washing a chloroform solution of this material with a Na_2CO_3 solution produced a colorless oil with ir and NMR identical with those of 5-phenyl-2,4,4-trimethyl-2-oxazoline.

***N*-(1,1-Dimethyl-2-hydroxy-2-phenylethyl)acetamide** was prepared by treating 1-phenyl-2-amino-2-methyl-1-propanol (Commercial Solvents Corp.) with acetic anhydride in ether: mp 151.5–153.0° (benzene); ir ($CHCl_3$) 3280 (br) and 3420 (sh) (NH and OH), 1655 (s, C=O), 1510 (s, –NHC=O), and 1055 cm^{-1} (OH); NMR ($CDCl_3$) δ 1.17 (s, 3 H, $-CCH_3$), 1.37 (s, 3 H, $-CCH_3$), 1.70 (s, 3 H, CH_3CO), 4.50 (d, 1 H, J = 6 Hz, –CHOH), 5.83 (s, 1 H, NH), 6.18 (d, 1 H, J = 6 Hz, –CHOH), and 7.25 ppm (s, 5 H, $-C_6H_5$).

Anal. Calcd for $C_{12}H_{17}NO_2$: C, 69.53; H, 8.27; N, 6.76. Found: C, 69.78; H, 7.92; N, 6.65.

5-Phenyl-2,4,4-trimethyl-2-oxazoline was prepared by slowly adding 3.50 g (0.017 mol) of *N*-(1,1-dimethyl-2-hydroxy-2-phenylethyl)acetamide to 10 ml (0.19 mol) of concentrated H_2SO_4. The acid solution was poured onto crushed ice and neutralized (K_2CO_3), the product was extracted with ether and dried (Na_2SO_4), and the ether was removed, leaving 2.88 g (90%) of colorless oil. The ir, NMR, and analysis samples were collected by GLC (column B): ir (CCl_4) 1678 cm^{-1} (s, –OC=N–); NMR (CCl_4) δ 0.63 (s, 3 H, $-CCH_3$), 1.38 (s, 3 H, $-CCH_3$), 2.00 (s, 3 H, CH_3CO), 5.00 (s, 1 H, $-OCHC_6H_5$), and 7.26 ppm (s, 5 H, $-C_6H_5$).

Anal. Calcd for $C_{12}H_{15}NO$: C, 76.15; H, 7.99; N, 7.40. Found: C, 76.56; H, 8.33; N, 7.17.

***N*-tert-Butyl-3-chloro-2,2-dimethylpropionamide**[4c] was isolated from the dibenzoyl peroxide (1.74 mol %) initiated decomposition of 1.02 g (5.32 mmol) of *N*-chloro-*N*-tert-butyl-2,2-dimethylpropionamide (**4a**) in 10 ml of benzene at 80% (dark). The solution was saturated with prepurified nitrogen for 30 min before heating and a positive pressure of nitrogen was maintained during the 3.5 hr of heating. Analysis by GLC (column C, 120°) indicated two major peaks at 3.5 and 9.4 min (ratio 1:1.4), the first corresponding to *N*-tert-butyl-2,2-dimethylpropionamide. Attempts to separate the components by crystallization (hexane) were unsuccessful. The second peak was collected by GLC: mp 76.0–77.5°; ir (CCl_4) 3450 (sh, NH), 1675 (s, C=O), and 1505 cm^{-1} (s, –NHC=O); NMR (CCl_4) δ 1.20 [s, 6 H, $-(CH_3)_2$], 1.32 [s, 9 H, $C(CH_3)_3$], 3.54 (s, 2 H, CH_2Cl), 5.34 (s, 1 H, NH); mass spectrum (70 eV) *m/e* (rel intensity) 191 (3), 178 (3), 176 (9), 155 (5), 138 (5), 136 (16), 121 (3), 119 (8), 100 (5), 93 (10), 91 (28), 58 (25), 57 (100), 56 (86), 55 (21), 42 (11), 41 (31).[28]

Analysis by GLC of the products of the dibenzoyl peroxide initiated decomposition of *N*-chloro-*N*-tert-butyl-2,2-dimethylpropionamide in 2,3-dimethylbutane and cyclohexane in 5 mm degassed, sealed tubes indicated a ca. 95% yield of one component with the same retention time and virtually identical NMR (of the gross reaction mixture after removing volatile components) as those of the chloro amide described above.

***N*-(1,1-Dimethyl-4-chloropentyl)acetamide.** A 0.5 *M* solution of *N*-chloro-*N*-(1,1-dimethylpentyl)acetamide in cyclohexane (degassed) was irradiated (at 0°). Replacement of the cyclohexane by hexane and cooling at −22° for several days afforded crystals. Two recrystallizations from hexane yielded colorless needles: mp 31–34°; ir (CCl_4) 3430 (sh, NH), 3310 (br, NH), 1685 (s, C=O), 1540 (s, –NHC=O), 1387 and 1367 cm^{-1} [m, $-C(CH_3)_2$]; NMR (CCl_4) δ 1.27 [s, 6 H, $-C(CH_3)_2$], 1.47 (d, 3 H, J = 6 Hz, $-CHClCH_3$), 1.85 (s, 3 H, CH_3CO-), 1.6–1.9 (m, 4 H, $-CH_2CH_2CHCl-$), 3.86 (m, 1 H, J = 6 Hz, –CHCl–), and 7.15 (s, 1 H, NH).

Anal. Calcd for $C_9H_{18}NOCl$: C, 56.39; H, 9.46; N, 7.31. Found: C, 56.67; H, 9.53; N, 7.32. An authentic sample, prepared by the Ritter reaction of 5-chloro-2-methyl-2-hexanol[21,29] with acetonitrile, had identical melting point, ir and NMR spectra, and GLC retention time.

1-Acetyl-2,2,5-trimethylpyrrolidine. A 1.689-g sample of 62% NaH oil dispersion (0.043 mol) was washed with three 20-ml portions of cyclohexane and transferred by use of 25 ml of cyclohexane to a solution of 7.06 g (0.037 mol) of *N*-(1,1-dimethyl-4-chloropentyl)acetamide (obtained from the photolysis reaction) in 25 ml of cyclohexane. The mixture was brought to reflux and a few drops of tert-butyl alcohol were added. After 19 hr the reaction mixture was cooled, washed with two 25-ml portions of water and 15 ml of saturated $(NH_4)_2SO_4$ solution, and dried ($MgSO_4$). The solvent was removed, leaving 5.29 g of colorless oil (97%). Vacuum distillation produced 2.77 g: bp 33.0–35.0° (0.07 mm); $n^{21.0}D$ 1.4650; ir (CCl_4) 1645 cm^{-1} (s, C=O); NMR (CCl_4) δ 1.19 (d, 3 H, J = 6.5 Hz, $-NCHCH_3$), 1.32 (s, 3 H, CCH_3), 1.48 (s, 3 H, CCH_3), 1.6–2.2 (m, 4 H, $-CH_2CH_2-$), 1.93 (s, 3 H, CH_3CO), 3.95 ppm (m, 1 H, J = 6.5 Hz, CH_2CHCH_3; mass spectrum (80 eV) m/e (rel intensity) 155 (13), 140 (23), 99 (9), 98 (100), 81 (10), 55 (6), 44 (5), 43 (14), 42 (10), 41 (7).

Anal. Calcd for $C_9H_{17}NO$: C, 69.63; H, 11.04; N, 9.02. Found: C, 69.52; H, 11.20; N, 9.16.

***N*-Chloro-*N*-(1,1-dimethyl-4-chloropentyl)acetamide** was prepared by treating *N*-(1,1-dimethyl-4-chloropentyl)acetamide with tert-butyl hypochlorite in methyl alcohol in the manner previously described: 75% yield; bp 65–67° (0.25 mm); $n^{25.0}D$ 1.4780; ir (CCl_4) 1680 (s, C=O), 1290 cm^{-1} (s); NMR (CCl_4) δ 1.40 [s, 9 H, $(CH_3)_2C$], 1.48 (d, 3 H, J = 6 Hz, $-CHClCH_3$), 1.67–2.0 (m, 4 H, $-CH_2CH_2-$), 1.28 (s, 3 H, CH_3CO), and 3.86 ppm (m, 1 H, J = 6 Hz, $-CH_2CHClCH_3$).

***N*-(1,1-Dimethyl-4,4-dichloropentyl)acetamide.** A solution of 1.40 g (0.00892 mol) of *N*-(1,1-dimethylpentyl)acetamide and 2.8 g (0.026 mol) of tert-butyl hypochlorite in 5 ml of methyl alcohol was stirred for 1 hr. The solvent and volatile components were removed on a rotoevaporator. A cyclohexane solution (10 mol) of the residual *N*-chloro amide was degassed and sealed in a Pyrex test tube and irradiated for 12 hr at 0°. On removal of the cyclohexane, the solid residue was again chlorinated and irradiated by repeating the above procedure, yielding 1.77 g of white solid, mp 66.5–68.0°. Three recrystallizations (hexane) afforded 0.87 g of white needles: mp 71.0–73.0°; ir (CCl_4) 3340 (sh, NH), 3320 (br NH), 1682 (s, C=O), and 1500 cm^{-1} (m, NHC=O); GLC analysis indicated ca. 90% dichloro amide and 10% monochloro amide; NMR (of dichloro amide) (CCl_4) δ 1.32 [s, 6 H, $-C(CH_3)_2$], 1.90 (s, 3 H, CH_3CO), 2.13 (s, 7 H, $-CH_2CH_2CClCH_3$), and 7.2 (s, 1 H, NH); NMR (C_6H_6) δ 1.18 [s, 6 H, $-C(CH_3)_2$], 1.68 (s, 3 H, $-CCl_2CH_3$), 1.92 (s, 3 H, CH_3CO-), and 2.13 ppm (s, 4 H, $-CH_2CC_{-2}-$).

A solution of 0.681 g (0.0030 mol, 0.30 *M*) of *N*-chloro-(1,1-dimethyl-4-chloropentyl)acetamide in cyclohexane was degassed and irradiated for 8 hr; GLC analysis (column temperature 124°) indicated peaks at 1.4 and 2.6 min with relative areas (in percent) of 15 and 85%, corresponding in retention time with the mono- and dichloro amides.

Registry No.—**1a**, 5014-39-1; **1b**, 79-16-3; **2a**, 10271-73-5; **2b**, 762-84-5; **3a**, 55281-79-3; **3b**, 5531-33-9; **3c**, 55281-80-6; **3e**, 55281-81-7; **4a**, 55281-82-8; **4b**, 686-96-4; **4c**, 55281-83-9; **5a**, 55281-84-0; **5b**, 55281-85-1; **5c**, 55281-86-2; **5d**, 55281-87-3; **6a**, 55319-71-6; **6b**, 55281-88-4; *tert*-butyl hypochlorite, 507-40-4; α,α-dimethyl-β-phenethylamine, 122-09-8; acetic anhydride, 108-24-7; *tert*-butylamine, 75-64-9; 2,2-dimethylpropionyl chloride, 3282-30-2; chlorine monoxide, 14989-30-1; *N*-(1,1-dimethyl-2-hydroxy-2-phenylethyl)acetamide, 55281-89-5; 1-phenyl-2-amino-2-methyl-1-propanol, 34405-42-0; TMP, 108-75-8.

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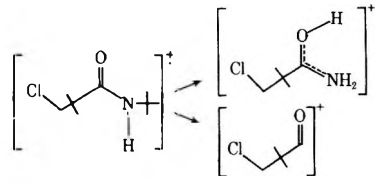

m/e	Rel intensity	
138	5.3	(4)
136	16.0	
121	2.0	(5)
119	8.0	

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Chlorination with *N*-Chloro Amides. II.[1a] Selectivity of Hydrogen Abstraction by Amidyl Radicals[1b]

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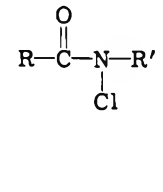
Selectivity in chlorinations of alkanes with *N*-chloro amides has been examined, providing evidence for several different hydrogen-abstracting species as a function of reaction conditions; e.g., for *N*-chloro-*N*-*tert*-butylacetamide (**2a**) with 2,3-dimethylbutane the relative reactivity of the tertiary hydrogen compared with the primary hydrogen, k_t/k_p, is 19 ($h\nu$, degassed), 4.8 ($h\nu$, oxygen present), 1.6 ($h\nu$, with 2,4,6-trimethylpyridine present, or benzoyl peroxide, 80°). In the presence of oxygen (and absence of base) the principal chain-carrying species are chlorine atoms; in the presence of the base (or under initiation by benzoyl peroxide, 80°) the principal chain-carrying species are considered to be amidyl radicals. Selectivity in amidyl radical, CH_3CONR, is markedly dependent on R; e.g., with 2,3-dimethylbutane $k_t/k_p \simeq 95$ for R = methyl, 1.6 for R = *tert*-butyl. Decomposition of **2a** by photochemical initiation in the absence of oxygen or trimethylpyridine proceeds more rapidly and shows higher selectivities than in the presence of either of these additives; the abstracting species under these conditions is not known. Steric effects in hydrogen abstraction reactions are briefly discussed.

In Part I,[1a] the decomposition of a series of *N*-chloro amides in alkane solvents was examined. The compounds decompose by free-radical chain reactions of long chain length and afford products of intermolecular and intramolecular chlorination. Rates and products showed marked dependence on the *N*-chloro amide, on oxygen, on 2,4,6-trimethylpyridine (TMP), and on mode of initiation ($h\nu$, 25° or dibenzoyl peroxide, 80°). The results were suggestive of the occurrence of two principal chain mechanisms: amidyl radical paths and chlorine atom–HCl paths. The amidyl



	R	R′
1a	CH_3	CH_3
2a	CH_3	*tert*-butyl
3a	CH_3	$C(CH_3)_2CH_2C_6H_5$
4a	*tert*-butyl	*tert*-butyl
5a	CH_3	$C(CH_3)_2CH_2CH_2CH_2CH_3$

radical path appeared to be operative in two situations: (a) initiation by light in the presence of 2,4,6-trimethylpyridine and (b) decomposition (in the absence of oxygen) of an *N*-chloro amide in which the resulting amidyl radical had the opportunity for intramolecular 1,5 hydrogen abstraction by the nitrogen atom. The chlorine atom–HCl

$$RCONR' + HS \longrightarrow RCONHR' + S\cdot \quad (1a)$$

$$S\cdot + RCONClR' \longrightarrow SCl + RCONR' \quad (1b)$$

$$Cl\cdot + HS \longrightarrow HCl + S\cdot \quad (2a)$$

$$HCl + RCONClR' \longrightarrow Cl_2 + RCONHR' \quad (2b)$$

$$S\cdot + Cl_2 \longrightarrow SCl + Cl\cdot \quad (2c)$$

path appeared to be operative in the decompositions in the absence of trimethylpyridine and to be of increased importance in decompositions in the presence of molecular oxygen. In order to provide further evidence on these points and to learn about the selectivity of amidyl radicals, decompositions of the *N*-chloro amides have been carried out in a series of hydrocarbons (*n*-hexane, cyclohexane, 2,3-dimethylbutane,[2] 2,2-dimethylbutane, and adamantane), analyzing for the chloroalkanes.[3] Selectivity in hydrogen abstraction was observed to depend markedly on reaction conditions. Various additives were examined as possible scavengers for chlorine atoms or HCl. Trichloroethylene, which has proved useful with alkyl hypochlorites,[4] had some effect. Much more effective was the hindered base 2,4,6-trimethylpyridine. Most of the work has been done with *N*-chloro-*N*-*tert*-butylacetamide (**2a**). The results are presented in Tables I–V. A summary of the selectivities in chlorinations with **2a**, relative to the primary hydrogen of *n*-hexane, is shown in Table VI.

Discussion

The principal findings regarding the selectivity of hydrogen abstraction for decomposition of *N*-chloro amide **2a** in alkane solvent are: (a) selectivity is markedly dependent on reaction conditions (e.g., k_t/k_p for 2,3-dimethylbutane: $h\nu$, degassed, 19; $h\nu$, undegassed, 4.8; $h\nu$, trimethylpyridine, 1.6); (b) in the presence of oxygen the selectivity is approximately the same as for Cl_2, $h\nu$ (Table VI, 4 vs. 5); (c) selectivity is increased severalfold by removal of oxygen (Table VI, 1 vs. 4); (d) selectivity is altered by the addition of 2,4,6-trimethylpyridine[5] (Table VI, 1 vs. 2) and is *not* the same as for Cl_2, $h\nu$ (Table VI, 2 vs. 5); (e) selectivity is approximately the same for initiation by $h\nu$, 25° in the presence of trimethylpyridine as for initiation by dibenzoyl peroxide, 80% (Table VI, 2 vs. 3).

Nature of the Reaction and Assessment of the Hydrogen-Abstracting Species. The results of this study of chlorinations with *N*-chloro amides provide evidence for three different hydrogen-abstracting species as a function of reaction conditions.[6]

A. RCON(Cl)R′, $h\nu$, 25°, Undegassed (Table VI, Line 4).

Assignment. Chlorine atom–HCl chains.

Basis. (a) The selectivities are approximately the same as for Cl_2, $h\nu$ (for some comments on how oxygen may increase the importance of the chlorine atom–HCl chains, see Part I[1a]); (b) the inhibition in rate and changes in selectivity observed upon the addition of trimethylpyridine are most simply ascribed to the scavenging of HCl by the base;

Table I
Light-Initiated Chlorination of 2,3-Dimethylbutane with 0.038 *M* *N*-Chloro-*N*-*tert*-butylacetamide (2a) at 25°

Scavenger[a] (*M*)	k_t/k_p per H	% yield[b]
None	14.5	97
None	15.5	100
Oxygen[a]	4.4	84
TCE (0.10)	16.0	93
TCE (0.50)	13.5	93
TCE (1.00)	11.0	84
TMP (0.05)	1.9	89
TMP (0.10)	1.9	74
TMP (0.50)	2.8	58
TMP (0.50), C_6H_6 (2.8)[c]	5.0	
C_6H_6 (4.0)[c]	25 (34)[d]	
C_6H_6 (4.0), Cl_2	20[d]	
Cl_2[e]	3.9[e]	

[a] Ox = sample was not degassed; TCE, trichloroethylene; TMP, 2,4,6-trimethylpyridine; C_6H_6, benzene. [b] Percent yield of 1- and 2-chloro-2,3-dimethylbutanes based on *N*-chloro amide. [c] **2a**, 0.054 *M*. [d] Reference 2. [e] Photochlorination with Cl_2 at 25°, ref 3.

Table II
Chlorination of 2,3-Dimethylbutane and Cyclohexane with *N*-Chloro-*N*-*tert*-butylacetamide (2a)

[2a], *M*	Conditions[a]	DMB/C_6H_{12} (mol ratio)	Relative reactivity per H		% yield[b]
			k_t/k_p	k_c/k_p	
0.18	$h\nu$, 25°	1.37	19	11	
0.08	$h\nu$, 21°, N_2[c]	2.34	7.7	3.7	
0.08	$h\nu$, 21°, Ox[d]	2.34	4.8	3.1	
0.12	$h\nu$, 25°, 0.11 *M* TMP	0.87	1.8	10.5	97
0.12	$h\nu$, 25°, 0.11 *M* TMP	2.81	1.6	9.8	91
0.06	$h\nu$, 25°, C_6H_{12}[e]				97
0.06	$h\nu$, 25°, C_6H_{12}, 0.19 *M* TMP[f]				89
0.12	80°, dark, 9 mol % DBPO		1.5		100
0.14	80°, dark, 5 mol % DBPO	1.57	1.6	9.5	98
0.12	80°, dark		5.3		93[g]
	Cl_2, $h\nu$, 40°[h]		3.9	2.7	

[a] TMP, 2,4,6-trimethylpyridine; DBPO, dibenzoyl peroxide. [b] Percent yield of all chloroalkanes. [c] Degassed by bubbling nitrogen through the solution for 10 min before irradiation. [d] Oxygen bubbled into the solution for 1 min before irradiation. [e] $t_{1/2}$ of 3 min. [f] $t_{1/2}$ of 125 min. [g] Approximately 55% of the *N*-chloro amide remained after 21 days at 80°. [h] Photochlorination with Cl_2, ref 3.

Table III
Chlorination of *n*-Hexane and Cyclohexane with 0.10 *M* *N*-Chloro-*N*-*tert*-butylacetamide (2a)

Conditions[b]	Relative reactivity[a] per H: k_s/k_p	k_c/k_p
$h\nu$, 25°[c]	7.3	
$h\nu$, 25°[d]	7.5	7.6
$h\nu$, 25°, not degassed	2.7	
$h\nu$, 25°, not degassed[d]	2.8	2.8
$h\nu$, 25°, TMP (0.05 *M*)[c]	4.5	
$h\nu$, 25°, TMP (0.05 *M*)[d]	4.4	4.2
Dark, 80°, DBPO (2.5 mol %)[c]	4.1	
Dark, 80°, DBPO (2.5 mol %)[d]	3.8	3.8
$h\nu$, 25°, Cl_2	2.8	

[a] $k_s \equiv$ rel $k_{secondary}$ for C-2 and C-3 together; $k_p \equiv$ rel $k_{primary}$ for C-1; $k_c \equiv$ rel $k_{cyclohexyl}$. [b] TMP, DBPO: see Table II, footnote *a*. [c] Chloroalkane yield determined, quantitative. [d] The mole ratio of *n*-hexane/cyclohexane was 1.65.

Table IV
Chlorination of 2,2-Dimethylbutane and Cyclohexane with 0.10 *M* *N*-Chloro-*N*-*tert*-butylacetamide (2a)

Conditions[b]	Relative reactivity per H[a]: k_{p1}/k_{p4}	k_s/k_{p4}	k_c/k_{p4}
$h\nu$, 25°[c]	0.84	8.0	
$h\nu$, 25°[d]	0.85	8.5	8.0
$h\nu$, 25°, not degassed	0.89	2.9	
$h\nu$, 25°, not degassed[d]	0.90	3.0	2.8
$h\nu$, 25°, TMP (0.06 *M*)[e]	0.11	0.45	
$h\nu$, 25°, TMP (0.05 *M*)[d]	0.10	0.38	4.7
80° dark, DBPO (2.5 mol %)[c]	0.10	0.52	
80° dark, DBPO (2.5 mol %)[d]	0.09	0.44	4.2
25°, $h\nu$, Cl_2	0.77	3.3	

[a] $k_{p1} \equiv k_{primary}$ at C-1; $k_{p4} \equiv k_{primary}$ at C-4; $k_s \equiv k_{secondary}$ at C-3; $k_c \equiv k_{cyclohexyl}$. [b] TMP, DBPO: See Table II, footnote *a*. [c] Chloroalkane yield determined, quantitative. [d] The mole ratio of 2,2-dimethylbutane/cyclohexane was 6.55. [e] Chloroalkane yield determined, 72%.

(c) the changes in intra- vs. intermolecular reaction discussed in Part I[1a] are most easily understood on the basis of this assignment.

B. RCON(Cl)R′, *hν*, 25°, 2,4,6-Trimethylpyridine, Degassed (Table VI, Line 2).

C. RCON(Cl)R′, Dibenzoyl Peroxide, 80°, Dark (Table VI, Line 3).

Assignment for B and C. Amidyl radical chains.

Basis. The selectivities observed under these two conditions are approximately the same. A feature that these two reaction conditions have in common is the absence of chlorine atom chains; toward some substrates selectivity in hydrogen abstraction is *lower* than for chlorine atom, toward others the selectivity is *higher* than for chlorine atom. The light-initiated reaction, B, would generate both amidyl radicals and chlorine atoms (eq 3), but the chlorine atom–HCl

$$\text{RCONClR}' \xrightarrow{h\nu} \text{RCONR}' + \text{Cl}\cdot \quad (3)$$

$$(C_6H_5COO)_2 \xrightarrow[\Delta]{} 2C_6H_5COO\cdot \longrightarrow R'' \quad (4a)$$

$$R''\cdot + \text{RCONClR}' \longrightarrow R''\text{Cl} + \text{RCONR}' \quad (4b)$$

(R″ = $C_6H_5\cdot$ or solvent-derived radical)

chain sequence (eq 2a–c) could be eliminated by the acid-scavenging action of the trimethylpyridine. (The lack of attack on the benzylic hydrogens of the trimethylpyridine is suggestive that amidyl radicals, like chlorine atoms,[3a] are more reactive toward alkyl H than toward benzyl H). Under initiation by dibenzoyl peroxide, reaction would proceed as shown in eq 4a,b with no path for initiation of chlorine atom chains. On these grounds, the principal hydrogen-abstracting species under conditions B and C is considered to be amidyl radicals. This conclusion is also consistent with the changes in intra- and intermolecular reactions as a function of reaction conditions discussed in Part I,[1a] and with the specific hydrogen atom selectivities observed, detailed examination of which is taken up after the fourth major reaction condition, D.

D. RCON(Cl)R′, *hν*, 25°, Degassed (Table VI, Line 1). Decomposition of **2a** under these conditions proceeds more rapidly and shows higher selectivities than decomposition in the presence of trimethylpyridine or oxygen (Table VI, 1 vs. 2 and 4). The abstracting species under these conditions is not known. Hydrogen chloride probably is involved in some way, since the addition of trimethylpyridine strongly inhibits the rate (e.g., Table II, line 6 vs. 7) and changes the

Table V
Relative Reactivities in the Light-Initiated Chlorination of Adamantane and 2,3-Dimethylbutane with 0.3 *M* *N*-Chloro-*N*-*tert*-butylacetamide (2a) at 16°

Conditions[a,b]	Relative reactivity per H[c]: k_t/k_p	k_{At}/k_{As}	k_{At}/k_p	k_{As}/k_p	Percent yield[d]
a	25.	5.1	42.	8.2	100
a	25.	5.5	40.	7.9	100
Ox	12.	2.9	14.	4.9	88
Ox	15.	3.7	21.	5.6	89
TMP (0.1 *M*)	1.7	35.	15.	0.44	76
TMP (0.2 *M*)	1.8	18.	14.	0.79	61
TMP (0.1 *M*), Ox	1.6	23.	18.	0.82	71
TMP (0.2 *M*), Ox	1.8	21.	20.	0.92	57
Cl_2, CCl_4, $h\nu$, 25°[e]		1.9			

[a] Ratio of 2,3-dimethylbutane to adamantane ~30. [b] Ox ≡ not degassed; TMP, 2,4,6-trimethylpyridine. [c] $k_t/k_p \equiv k_{tertiary}/k_{primary}$ for 2,3-DMB; $k_{At}/k_{As} \equiv k_{tert\ for\ adamantane}/k_{sec\ for\ adamantane}$. [d] Percent yield of chloroalkanes. [e] Reference 7.

selectivity. Some suggestions on the nature of the abstracting species under these conditions are taken up at the end of this paper.

Selectivity in Hydrogen Abstraction by the *N*-*tert*-Butylacetamidyl Radical. Conditions for amidyl radical chains: $h\nu$, 25°, trimethylpyridine, B, or dibenzoyl peroxide, 80°, C.

The selectivities in Tables I–VI show some striking changes from usual expectations. (a) The selectivity toward tertiary hydrogen of 2,3-dimethylbutane is low (k_t/k_p = 1.6), even lower than that of chlorine atom (k_t/k_p = 3.9). (b) The selectivity for cyclohexyl hydrogen vs. the primary hydrogen of 2,3-dimethylbutane is higher (k_c/k_p = 10.5) than that for chlorine atom (k_c/k_p = 2.7). (c) Selectivity for the secondary hydrogens of 2,2-dimethylbutane is very low, even less than for the primary hydrogens at C-4 of this molecule (k_s/k_{p4} = 0.38). (d) Selectivity for the primary hydrogens at C-1 of 2,2-dimethylbutane is much below that for the primary hydrogens at C-4 (k_{p1}/k_{p4} = 0.1). (e) Discrimination between the tertiary and secondary positions of adamantane is high (k_{At}/k_{As} = 35), much above that for chlorine atom (k_{At}/k_{As} = 1.9).[7]

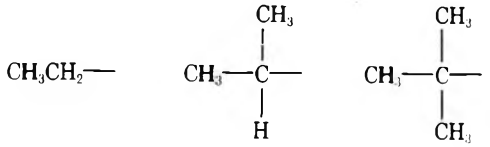
Steric hindrance appears to be an important factor in the selectivity of the *N*-*tert*-butylacetamidyl radical. The biggest reductions in rate are associated with abstraction of

Table VI
Summary of Reactivities in Chlorinations with *N*-Chloro-*N*-*tert*-butylacetamide Relative to the Primary Hydrogens of *n*-Hexane

Conditions[a]	*n*-Hexane		Cyclohexane	2,3-DMB[a]		2,2-DMB[a]			Adamantane	
	k_p	k_s	k_c	k_p	k_t	k_{p1}	k_{p4}	k_s	k_{As}	k_{At}
1 $h\nu$, 25°	1.0	7.5	7.6	0.69	13.	0.81	0.95	8.1	5.5	28.
2 $h\nu$, TMP, 25°	1.0	4.4	4.2	0.43	0.69	0.09	0.90	0.34	0.17	6.5
3 DBPO, 80°	1.0	3.8	3.8	0.39	0.62	0.09	0.90	0.40		
4 $h\nu$, Ox, 25°	1.0	2.8	2.8	0.90	4.2	0.90	1.0	3.0		
5 $h\nu$, Cl_2, 25°[b]	1.0	~2.8	~2.7	1	3.9	.8	1	3.3	(1/1.9)[c]	

[a] 2,3-DMB, 2,3-dimethylbutane; 2,2-DMB, 2,2-dimethylbutane; TMP, 2,4,6-trimethylpyridine; DBPO, dibenzoyl peroxide; Ox = samples not degassed. [b] Reference 3. [c] Reference 7.

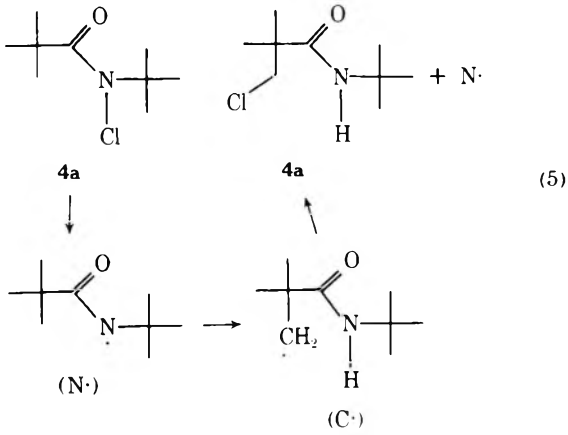
hydrogen from the tertiary position of 2,3-dimethylbutane and from hindered secondary positions (2,2-dimethylbutane and adamantane). One also notes a reduction in reactivity of primary hydrogen in the following series.[8]



	CH_3CH_2—	CH_3—C(H)—	CH_3—C(CH_3)—
relative reactivity per primary H	1	0.4	0.1

To test the importance of steric hindrance, some studies have also been carried out on a less hindered system, *N*-chloro-*N*-methylacetamide (**1a**), and on a more hindered one, *N*-chloro-*N*-*tert*-butyl-2,2-dimethylpropionamide (**4a**). The results of light-initiated chlorination of 2,3-dimethylbutane and cyclohexane with **1a** are summarized in Table VII. The degree of inhibition in the presence of trimethylpyridine was similar to that observed for **2a**. The selectivities in hydrogen abstraction with **1a** are high and, in contrast with **2a**, are largely unaffected by the presence of trimethylpyridine. A sample which was not degassed had a much lower selectivity. The high reactivity toward tertiary hydrogen in chlorination of 2,3-dimethylbutane with **1a** is consistent with hydrogen abstraction by a selective *N*-methylacetamidyl radical which lacks the steric hindrance of the *N*-*tert*-butylacetamidyl radical.

With the highly hindered *N*-chloro amide **4a**, efforts to effect chlorination of hydrocarbons under amidyl radical chain conditions resulted mainly (>95%) in conversion of **4a** into *N*-*tert*-butyl-2,2-dimethyl-3-chloropropionamide (eq 5).[1a] The yields of chlorinated solvent were too low to



4a **4a** (5)

(N·) (C·)

determine the selectivity for the intermolecular portion of the reaction.

The finding of a steric effect in the hydrogen abstraction step by CH_3CON-*tert*-butyl is of interest and may be of

Table VII
Light-Initiated Chlorination of 2,3-Dimethylbutane and Cyclohexane with *N*-Chloro-*N*-methylacetamide (1a)[a] at 25°

Additive (*M*)[b]	Relative reactivity k_t/k_p	Relative reactivity k_c/k_p	% yield[c]
	86		97
	81	24[d]	
Ox	14		77
TMP (0.036)	96	29[d]	
TMP (0.20)	94	29[d]	94
e	*f*		
TMP (0.22)[e]	*g*		
C_6H_6 (4.0)	65[h]		

[a] **1a** ~0.2 *M*. [b] Ox = sample was not degassed; TMP, 2,4,6-trimethylpyridine. [c] Percent yield of all chloroalkanes based on initial *N*-chloro amide. [d] The mole ratio of 2,3-dimethylbutane/cyclohexane is 1.44. [e] Cyclohexane solvent, **1a** 0.15 *M*. [f] Time for 50% consumption of **1a**, 10 min. [g] Time for 50% consumption of **1a**, 320 min. [h] Reference 2.

use in directing attack at unhindered positions in other chlorinations. Other examples also have been reported. In the chlorination of 3,3-diethylpentane by $C_6H_5SO_2NCl$-*t*-Bu, $k_s/k_p = 0.6$.[8,9] More recently, large variations in selectivity in chlorinations by R_2NCl, H_2SO_4, $h\nu$ as a function of the size of R have been reported and attributed to steric effects.[10] In contrast, an example of steric acceleration in a free-radical bromination reaction has also been reported.[11]

Mechanism of Light-Initiated Chlorination with *N*-Chloro Amides in the Absence of Trimethylpyridine and Oxygen, D. As indicated above, chlorinations with **2a** under these conditions are faster and generally severalfold more selective than in the presence of oxygen (chlorine atom chains) or in the presence of the base (amidyl radical chains). Chlorination of 2,3-dimethylbutane by the unhindered *N*-chloro amide **1a** under these conditions is also faster than in the presence of the base; in this case the selectivity in hydrogen abstraction is high and is largely unaltered by the presence of the base.[12] Chlorination of 2,3-dimethylbutane with the highly hindered *N*-chloro amide **4a** under these conditions (degassed, no trimethylpyridine) afforded a 50% yield of the chloroalkanes with $k_t/k_p = 30$ even though decomposition of **4a** under conditions B or C went largely via intramolecular 1,4-hydrogen transfer (eq 5) rather than attack on solvent. High selectivity (k_t/k_p for 2,3-dimethylbutane ≃ 20) was also observed under conditions D with **3a**. These results require a hydrogen-abstracting species more selective than chlorine atom and not subject to the steric effect shown by the amidyl radical derived from **2a**. One possibility considered was chlorine

atom complexed to an amide. However, chlorination of 2,3-dimethylbutane by Cl_2, $h\nu$ in the presence and absence of *N*-(1,1-dimethylpentyl)acetamide (0.09 *M*) showed no change in selectivity (k_t/k_p = 3.96 ± 0.08 vs. 3.92 ± 0.08). Other possibilities for species of the composition amidyl radical–HCl can be formulated. In the absence of additional evidence, further discussion is not warranted. It is worth stressing, however, that the selectivity with **2a** in hydrogen abstraction is considerably greater, and the rate of decomposition is faster, under these conditions ($h\nu$, degassed) than in the presence of oxygen or trimethylpyridine. Some high selectivities observed in chlorinations with *N*-chlorosuccinimide[13] may also be associated with complexities of the type described here.

Experimental Section

The preparation and characterization of the *N*-chloro amides and their amide products have been described, as have procedures for decomposition and columns for GLC analysis.[1a] The reaction solutions were directly analyzed by GLC after complete disappearance of the *N*-chloro amide. Typical retention times (in minutes) using column C[1a] (column temperature 60°, flow rate 60 ml/min) follow: 2-chloro-2,3-dimethylbutane (4.3), 1-chloro-2,3-dimethylbutane (5.9), chlorobenzene (7.7), chlorocyclohexane (10.3), *N*-*tert*-butylacetamide (14.7), and 2,4,6-trimethylpyridine (21.5). The products were stable to reaction and GLC analysis conditions, and were identified by comparison with authentic samples.

The chlorination products of *n*-hexane were analyzed on column D.[1a] The 2- and 3-chlorohexanes were not separable and formed a single symmetrical peak. The products were identified by comparison with authentic samples.

The chlorination products of 2,2-dimethylbutane were identified by comparison with authentic samples obtained from the photochlorination with Cl_2. The alkyl chlorides were collected by preparative GLC and structural assignments were made from the NMR spectra. A commercial sample of 4-chloro-2,2-dimethylbutane (Eastman) was also available. 1-Chloro-2,2-dimethylbutane: δ 0.83 (m, 3 H, CH_2CH_3), 0.93 [s, 6 H, $(CH_3)_2C$–], 1.29 (m, 2 H, CH_2CH_3), and 3.25 ppm (s, 2 H, $-CH_2Cl$). 3-Chloro-2,2-dimethylbutane: δ 1.00 [s, 9 H, $(CH_3)_3C$–], 1.40 (d, *J* = 7 Hz, 3 H, $-CHClCH_3$), and 3.80 ppm (q, *J* = 7 Hz, 1 H, $-CHClCH_3$). 4-Chloro-2,2-dimethylbutane: δ 0.93 [s, 9 H, $(CH_3)_3C$–], 1.70 (m, 2 H, $-CH_2CH_2Cl$), and 3.47 ppm (m, 2 H, $-CH_2CH_2Cl$).

Products from the chlorination of adamantane in 2,3-dimethylbutane were analyzed with column C.[1a] An authentic sample was used to identify 1-chloroadamantane, which had a shorter retention time than 2-chloroadamantane, as reported.[7]

The conditions and results are summarized in Tables I–VII.

Registry No.—**1a**, 5014-39-1; **2a**, 10271-73-5; *n*-hexane, 110-54-3; cyclohexane, 110-82-7; 2,3-DMB, 79-29-8; 2,2-DMB, 75-83-2; adamantane, 281-23-2; TMP, 108-75-8; DBPO, 94-36-0; oxygen, 7782-44-7; TCE, 79-01-6; Cl_2, 7782-50-5; 1-chloro-2,2-dimethylbutane, 6366-35-4; 3-chloro-2,2-dimethylbutane, 5750-00-5; 4-chloro-2,2-dimethylbutane, 2855-08-5.

References and Notes

(1) (a) Part I: R. A. Johnson and F. D. Greene, preceding paper in this issue. (b) Supported in part by the National Science Foundation. (c) Predoctoral Fellow of the National Institutes of Health, 1967–1970.
(2) Chlorination of this substrate by **1a** and **2a** in 4 *M* benzene has been reported: R. S. Neale, N. L. Marcus, and R. G. Schepers, *J. Am. Chem. Soc.*, **88**, 3051 (1966).
(3) For reviews on chlorination, see (a) M. L. Poutsma, *Methods Free-Radical Chem.*, 1, 79 (1969); (b) "Free Radicals", J. K. Kochi, Ed., Wiley, New York, N.Y., 1973, p 159.
(4) C. Walling and J. A. McGuinnes, *J. Am. Chem. Soc.*, **91**, 2053 (1969).
(5) Trichloroethylene (ref 4) has a much smaller effect on reactivity (see Table I).
(6) For evidence on changes in the chain-carrying species in *N*-bromosuccinimide brominations as a function of conditions, see J. G. Traynham and Y. Lee, *J. Am. Chem. Soc.*, **96**, 3590 (1974); J. C. Day, M. L. Lindstrom, and P. S. Skell, *Ibid.*, **96**, 5616 (1974).
(7) (a) G. W. Smith and H. D. Williams, *J. Org. Chem.*, **26**, 2207 (1961). (b) High discrimination between the tertiary and secondary positions of adamantane has also been observed with $Cl_3C\cdot$ [I. Tabushi, Y. Aoyama, S. Kojo, J. Hamuro, and Z. Yoshida, *J. Am. Chem. Soc.*, **94**, 1177 (1972)] and with photoexcited biacetyl [I. Tabushi, S. Kojo, and Z. Yoshida, *Tetrahedron Lett.*, 2329 (1973)] and attributed, in part, to steric effects.
(8) A trend in the same direction has also been seen in chlorinations with sulfonamide radicals: A. E. Fuller and W. J. Hickinbottom, *J. Chem. Soc.*, 3228 (1965), Table 5.
(9) For chlorination of 3,3-diethylpentane by Cl_2, $h\nu$ k_s/k_p = 1.4: M. Kosugi, K. Takeuchi, and T. Migita, *Bull. Chem. Soc. Jpn.*, **42**, 3354 (1969).
(10) N. C. Deno, R. Fishbein, and J. C. Wyckoff, *J. Am. Chem. Soc.*, **93**, 2065 (1971). See also R. Bernardi, R. Galli, and F. Minisci, *J. Chem. Soc. B*, 324 (1968).
(11) S. J. Cristol and H. W. Mueller, *J. Am. Chem. Soc.*, **95**, 8489 (1973).
(12) The similarity in selectivity with **1a** in the presence and absence of the base may be fortuitous; the hydrogen-abstracting species need not be the same under the two conditions.
(13) J. H. Markgraf, *J. Chem. Educ.*, **46**, 610 (1969); O. Cerny and J. Hajek, *Collect. Czech. Chem. Commun.*, **26**, 2624 (1961).

2*H*-Cyclopenta[*d*]pyridazines. Electrophilic Halogenation[1,2]

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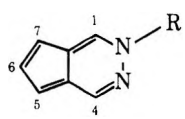
2-Methyl- and 2-phenyl-2*H*-cyclopenta[*d*]pyridazine (**1** and **2**) and the parent system (**3**) undergo electrophilic halogenation with *N*-halosuccinimides. The 5-, 7-, 5,7-, and 5,6,7-chloro and bromo derivatives, the 5,7-iodo derivative, and the 5-trifluoroacetyl-7-bromo and 5-bromo-7-trifluoroacetyl derivatives of **1** were prepared. Based on product yields, the relative position reactivities are 7 > 5 ≫ 6. Dipyridineiodonium nitrate was used to prepare the 5,6,7-triiodo derivative of **1**. The 5-, 7-, 5,7-, and 5,6,7-chloro derivatives of **2** and the 7-chloro and 5,7-dichloro derivatives of **3** were also obtained. The substituent long-wavelength spectral shifts for halogen and trifluoroacetyl were found to be qualitatively additive.

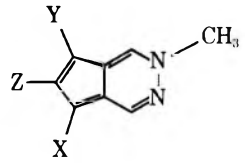
The preceding papers established the positions of protonation[6] and acylation[7] on the 2*H*-cyclopenta[*d*]pyridazine system for mono- and disubstitution. In the present study, electrophilic mono-, di-, and trihalogenation are reported for this heteroanalog of azulene containing both π-excessive and π-equivalent ring nitrogens.



1, R = CH_3
2, R = C_6H_5
3, R = H

Chlorination of **1**. As with azulene and cyclopenta-

[c]thiapyran,[8,9] the 2H-cyclopenta[d]pyridazine ring was found to react rapidly with N-halosuccinimides under mild conditions. The 2-methyl compound (1) was especially reactive, and it was necessary to employ an excess of 1 in the reaction with NCS[10] to obtain the monosubstitution products 4 and 5. These compounds (especially 4) were difficult



4, X = Cl; Y = Z = H
5, Y = Cl; X = Z = H
6, X = Y = Cl; Z = H
7, X = Y = Z = Cl
8, Y = Br; X = Z = H
9, X = Y = Br; Z = H
10, X = $COCF_3$; Y = Z = H
11, X = $COCF_3$; Y = Br; Z = H
12, Y = $COCF_3$; X = Z = H
13, X = Br; Y = $COCF_3$; Z = H
14, X = Y = Z = Br
15, X = Y = Cl; Z = Br
16, X = Y = I; Z = H
17, X = Y = Z = I

to separate from each other and from other impurities present and were somewhat unstable, particularly when impure. Complete purification was ultimately accomplished, after many attempts with other methods, by high-pressure liquid chromatography.

The structural assignments for 4 and 5 were determined by analogy with the characteristics found for the corresponding trifluoroacetyl compounds[6,11] and the 7-bromo compound (see below). Thus the major product, and the one for which the NMR chemical shift (δ) for H-4 was relatively larger than for H-1 and for which J for the vicinal five-ring hydrogen coupling was smaller (as would be expected if the non-charge-separated resonance structure is more important than the others), was designated to be the 7 isomer (5). This is also consistent with the major product arising from the intermediate for which the resonance structures indicate the greater stabilization,[6,9] and for which the π-electron localization energy is calculated to be the smaller.[11]

The by-product from the monochlorination was the 5,7-dichloro derivative 6, which was formed in high yield when slightly more than 2 equiv of NCS was used. The NMR spectrum for 6 shows a clean singlet at δ 6.95 for H-6 and peaks at δ 8.69 (H-1) and 8.51 (H-4).

1,3-Dichloroazulene undergoes further electrophilic substitution at the 5 position[12] and the formylation of 1,3-dialkylazulenes has been found to occur at both the 2 and 5 positions.[13] In contrast, attempts to effect the trichlorination of the π-excessive cyclopenta[c]thiapyran gave only polymer-like material. Compounds 1–3 have no substitutable atom corresponding to the 5 position of azulene, so trisubstitution, if it could be accomplished, would be expected to occur at the 6 position (corresponding to the azulene 2 position). Allowing 1 to react with an excess of NCS for a longer period of time gave a good yield of 7 which exhibited NMR peaks at δ 8.99 (H-1), 8.69 (H-4), and 4.34 (NCH_3). Further reaction of 6 with NCS also afforded 7. In the latter reaction, it was essential that 6 be pure and that an excess of NCS be avoided.

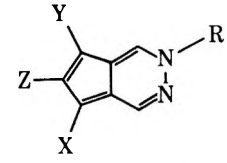
The presence of two trifluoroacetyl or carbomethoxy groups in the 5 and 7 positions of 1 deactivated the ring system such that treatment with NCS gave no further electrophilic substitution.

Bromination of 1. Reaction of 1 with 1 equiv of NBS gave a mixture of products. A low yield (11% based on NBS) of the 7-bromo compound (8) was obtained as an unstable oil. The identity of this material was shown by its NMR spectrum [singlets at δ 8.61 (broad, H-4) and 4.17 (NCH_3), doublets at 8.57 (J = 1 Hz, H-1) and 7.15 (J = 3 Hz, H-6), and a doublet of doublets at 6.61 (J = 3 and 1 Hz, H-5)] and its conversion to the stable 5-trifluoroacetyl-7-bromo derivative (11), identical with the product from the bromination of the 5-trifluoroacetyl compound (10). The major product (83% based on NBS) was the 5,7-dibromo compound (9) [NMR singlets at δ 7.17 (H-6) and 4.27 (NCH_3) and doublets at 8.75 (J = 1 Hz, H-1) and 8.54 (J = 1 Hz, H-4)], and some (37%) unchanged 1 was recovered. No substance corresponding to the 5-bromo derivative was detected. This was attributed to the 5-bromo compound being more reactive to disubstitution and also less stable to isolation than the 7-bromo isomer. The formation of 9 in high yield along with the recovery of unchanged 1 when 1 equiv of NBS was used indicates that the monobromo substitution products are comparable in reactivity to 1. Bromination of the 7-trifluoroacetyl compound (12) gave the stable 5-bromo-7-trifluoroacetyl derivative (13) of established structure.[11]

Tribromination of 1 took place readily to give 14 [singlets in the NMR spectrum at δ 8.89 (H-1), 8.57 (H-4), and 4.43 (NCH_3)], and the dichloro compound (6) also underwent bromination at the 6 position to yield 15, which showed NMR peaks (singlets) at δ 9.05 (H-1), 8.73 (H-4), and 4.34 (NCH_3).

Iodination of 1. From the treatment of 1 with 4 equiv of NIS was isolated a yellow solid which rapidly decomposed above 0°. Solutions in organic solvents were more stable and an NMR spectrum [singlets at δ 8.38 (H-1), 8.16 (H-4), 7.16 (H-6), and 4.20 (NCH_3)] consistent with that expected for the 5,7-diiodo compound (16) was obtained. Curiously, attempts to prepare the 5,6,7-triiodo compound (17) from 1 by reaction with excess NIS were not successful; only 16 was found. Yet reaction of 1 with 5 equiv of dipyridineiodonium nitrate produced the more stable 17 in 19% yield. The NMR spectrum for this compound showed singlets at δ 8.77 (H-1), 8.32 (H-4), and 4.26 (NCH_3). The formation of iodine during the reaction was observed, but 16 was found to be inert to iodine so the latter was not involved in the introduction of the third iodine atom.

Chlorination of 2 and 3.[14] The reaction of 2-phenyl-2H-cyclopenta[d]pyridazine (2) with 1 equiv of NCS afforded a mixture from which was isolated 20% of the 5-chloro (18) and 41% of the 7-chloro (19) derivatives. A small amount of the 5,7-dichloro compound (20) was formed. As with 4 and 5, the major monosubstitution product was judged to be the 7 isomer. Compounds 18 and 19 were considerably more stable than 4 and 5. The use of 2 equiv of NCS gave 20 in 90% yield, and further chlorination of 20 afforded 21 (74%).



18, X = Cl; Y = Z = H; R = C_6H_6
19, X = Z = H; Y = Cl; R = C_6H_5
20, X = Y = Cl; Z = H; R = C_6H_5
21, X = Y = Z = Cl; R = C_6H_5
22, X = H; Y = Cl; Z = R = H
23, X = Y = Cl; Z = R = H

Treatment of 3 with 1 equiv of NCS afforded 88% of a monochloro product. This was assigned the 7-chloro structure (22) [NMR absorption at δ 8.75 and 8.85 (H-1 and H-4), 6.82 (H-5) coupled with 7.22 (H-6) (J = 2 Hz), and a broad singlet at 3.0 (N-H)] on the basis that the 7-monosubstitution product is the major one in the established case of trifluoracetylation of 1, and is the exclusive product

Table I
Long-Wavelength Spectral Shifts for Substituted 2*H*-Cyclopenta[*d*]pyridazines

Substituent	λ_{max}[a] (obsd)	$\Delta\lambda_{max}$[a]	λ_{max}[a] (calcd)
2-CH_3[b]	395		
5-Cl-2-CH_3	405	10	
6-Cl-2-CH_3[c,e]			382
7-Cl-2-CH_3	413	18	
5,7-di-Cl-2-CH_3	420	25	423
5,6,7-tri-Cl-2-CH_3	407	12	
5-Br-2-CH_3[c,f]			403
6-Br-2-CH_3[c,g]			380
7-Br-2-CH_3	412	17	
5,7-di-Br-2-CH_3	420	25	
5,6,7-tri-Br-2-CH_3	405	10	
5,7-di-Cl-6-Br-2-CH_3	408	13	405
5-$COCF_3$-2-CH_3[d]	365	−30	
7-$COCF_3$-2-CH_3[d]	403	8	
5,7-di-$COCF_3$-2-CH_3[d]	370	−25	373
5-$COCF_3$-7-Br-2-CH_3	374	−21	382
5-Br-7-$COCF_3$-2-CH_3	415	20	411
5,7-di-I-2-CH_3	416	21	
6-I-2-CH_3[h]			393
5,6,7-tri-I-2-CH_3	414	19	
2-C_6H_5[b]	408		
5-Cl-2-C_6H_5	417	9	
7-Cl-2-C_6H_5	424	16	
5,7-di-Cl-2-C_6H_5	435	27	433
5,6,7-tri-Cl-2-C_6H_5	422	14	
2-H[b]	395		
7-Cl-2-H	403	8	
5,7-di-Cl-2-H	418	23	

[a] Nanometers. [b] Parent system. [c] Not known. [d] Reference 7. [e] Registry no., 55268-31-0. [f] Registry no., 55268-32-1. [g] Registry no., 55268-33-2. [h] Registry no., 55268-34-3.

when the 7-trifluoracetyl-2-methyl compound (**12**) is formed by methylation of the resonance hybrid anion of monotrifluoracetyl-2*H*-cyclopenta[*d*]pyridazine (which could yield either the 5- or 7-isomers or a mixture).[7] Reaction of **3** with 2 equiv of NBS produced the 5,7-dichloro derivative (**23**) in 82% yield.

Substituent Spectral Shifts. One of the unusual properties of substituted azulene compounds is the additivity of the long-wavelength absorption shifts caused by substituent groups. This was first recognized by Plattner for di-, tri-, and polyalkylazulenes[15] and later was shown to hold for a wide variety of other groups, especially in the 1 and 3 positions, by Cowles[16] and Anderson and coworkers.[17] The present results provided the first opportunity to examine this property with a π-excessive heteroanalog of azulene.[18]

Table I lists the long-wavelength spectral shifts observed for the 5- and 7-mono- and 5,7-disubstituted derivatives, and the values for the latter calculated by simple additivity. It is seen that the correlations are quite good, even in the two cases where quite different groups ($COCF_3$ and Br) are involved. Thus, the 2*H*-cyclopenta[*d*]pyridazine ring system retains the azulenic property of the additivity of substituent long-wavelength shifts. Therefore, it is likely that values for the 5,6,7-trisubstituted compounds provide the basis for qualitatively predicting the shifts for the monosubstituted halo derivatives not yet prepared.

The nonequivalent 5 and 7 positions in this ring system apparently respond differently to groups exerting different electronic effects. For example, chlorine or bromine on either position results in a bathochromic shift with that of the 7 position being the greater. The datum for the diiodo-2-methyl compound indicates that iodine behaves in the same manner. In contrast, the 5-trifluoroacetyl group causes a large hypsochromic and the 7-trifluoroacetyl group a small bathochromic shift. The trifluoroacetyl effect is similar to that of halogen, however, in that the shift for the 7 position is more bathochromic than for the 5 position. It is hoped that data from compounds having other groups will show whether or not these results fit a general pattern.

Experimental Section

Melting points are uncorrected. Uv and visible spectra were recorded on a Cary Model 14 recording spectrophotometer. Ir spectra were recorded with a Perkin-Elmer Model 21 instrument. NMR spectra were taken on a Varian Model A-60, T-60, or DA 60-II instrument with tetramethylsilane as internal reference. Mass spectra were recorded on an Associated Electrical Industries MS-9. Analyses were performed by A. Barnhardt, Elbach über Engelskircher, Germany; Chemalytics, Inc., Tempe, Ariz.; Midwest Microlab, Inc., Indianapolis, Ind.; or Mr. Dave Harsch, Department of Chemistry, University of Idaho, Moscow, Idaho. Hydrocarbon, acetonitrile, THF, alcohol, DMF, benzene, ether, and dichloromethane solvents were purified and dried prior to use. All other solvents were reagent grade. Petroleum ether was of bp 20–40°. Solvents were removed from reaction solutions with a rotary evaporator at or below room temperature unless otherwise specified.

5- and 7-Chloro-2-methyl-2*H*-cyclopenta[*d*]pyridazine (4 and 5). To a stirred solution of 400 mg (3.4 mmol) of **1** in 30 ml of CH_2Cl_2 was added dropwise a solution of 390 mg (2.9 mmol) of NCS in 20 ml of CH_2Cl_2 over a period of 30 min. The mixture was concentrated under N_2 to a volume of 10 ml and then was chromatographed on a 1.5 × 12 in. column of neutral alumina with 1:3 ether–petroleum ether as the eluate. The yellow eluate was collected as 60 20-ml fractions, the compositions of which were determined with a Waters Associates liquid chromatograph, Model ALC-100, using a 0.125 in. × 6 ft column of Corisil 2. The eluent was 1:4 *n*-hexane–CH_2Cl_2, the flow rate was 54 ml/hr, and the residual time on the column was ca. 35 min. Fractions 1–32, which contained one product, were combined and concentrated to ca. 5 ml volume. This solution was chromatographed on the Waters instrument except using a 0.375 in. × 6 ft Porasil column and a flow rate of 180 ml/hr. The elution time for the major fraction was ca. 2.5 hr with smaller fractions appearing at ca. 1.5 (**6**) and 3 hr (**5**). The major fraction was concentrated and the last few milliliters were then removed under a stream of N_2. Sublimation of the residue at 50° (10^{-4} mm) gave 40 mg (8.9%) of **4** as yellow crystals: mp 60–60.5°; NMR (acetone) slightly broadened singlets at δ 8.60 (H-1) and 8.55 (H-4), doublets at 7.03 (J = 4 Hz, H-6) and 6.63 (J = 4 Hz, H-7), and a singlet at 4.07 (NCH_3) of the corresponding areas; uv (ether) 247 nm (ϵ 26,488), 253 (25,857), 270 (15,767), 277 (sh, 12,610), 312 (4162), 318 (4919), 324 (4450), 332 (5171), and 405 (865).

Anal. Calcd for $C_8H_7N_2Cl$: C, 57.67; H, 4.23; N, 16.82. Found: C, 57.90; H, 4.24; N, 16.43.

Removal of the solvent from the combined fractions 33–54 (the last few milliliters under N_2) gave 270 mg (60%) of crude **5** which was further purified as described for **4**. The elution time was 3 hr with smaller fractions at 2.5 (**4**) and >4 hr (**1**). Further treatment as described for **4** gave 181 mg (40.2%) of **5** as yellow needles: mp 85–86°; NMR (acetone) slightly broadened singlet at 8.92 (H-4), partially resolved doublet at 8.78 ($J \simeq 1$ Hz, H-1), doublets at 7.24 (J = 3 Hz, H-6) and 6.74 (J = 3 Hz, H-5), and a singlet at 4.30 (NCH_3) of the corresponding areas; uv (ether) 248 nm (ϵ 27,800), 253 (27,000), 264 (20,800), 273 (sh, 15,600), 312 (sh, 3500), 317 (3950), 323 (3850), 331 (3850), and 413 (895).

Anal. Calcd for $C_8H_7N_2Cl$: C, 57.67; H, 4.23; N, 16.82. Found: C, 57.72; H, 4.36; N, 16.65.

5,7-Dichloro-2-methyl-2*H*-cyclopenta[*d*]pyridazine (6). A solution of 102.7 mg (0.778 mmol) of **1** and 230 mg (1.73 mmol) of NCS in 25 ml of CH_2Cl_2 was allowed to stand at room temperature for 1 hr. The solvent was removed and the dark green residue was chromatographed on a 6 × 8 in. silica gel (Merck GF-254) plate with CH_2Cl_2 as the eluent. The major band gave 130.3 mg (83.5%) of **6** as a bright yellow solid, mp 111–113°. Recrystallization from

aqueous acetone gave an analytical sample: mp 113–113.5°; NMR (acetone) singlets at δ 6.95 (M-6) and 4.18 (NCH_3) and doublets at 8.69 (J = 1 Hz, H-1) and 8.51 (J = 1 Hz, H-4); uv (ether) 250 nm (ε 26,000), 254 (26,000), 270 (18,000), 318 (sh, 4100), 324 (4900), 329 (sh, 4600), 337 (4900), and 420 (950).

Anal. Calcd for $C_8H_6N_2Cl_2$: C, 47.76; H, 2.98; N, 13.93; Cl, 35.52. Found: C, 47.60; H, 3.02; N, 13.70; Cl, 35.12

5,6,7-Trichloro-2-methyl-2H-cyclopenta[d]pyridazone (7). A. From 1. To a solution of 574 mg (4.25 mmol) of 1 in 15 ml of CH_2Cl_2 was added 1.775 g (13.30 mmol) of NCS. After the exothermic reaction had subsided, the stoppered flask was placed in a freezer for 24 hr. The mixture was then worked up as described for 6 and recrystallization of the yellow-brown solid obtained from the major band from aqueous ethanol gave 843.2 mg (83.5%) of 7 as yellow needles, mp 127–128.5°. The analytical sample was crystallized from aqueous acetone: mp 128–130°; NMR (acetone) singlets at δ 8.99 (H-1), 8.69 (H-4), and 4.34 (NCH_3); uv (ether) 260 nm (ε 31,000), 272 (sh, 19,000), 321 (3900), 336 (3300), and 407 (1100).

Anal. Calcd for $C_8H_5N_2Cl_3$: C, 40.76; H, 2.12; Cl, 45.22. Found: C, 40.71; H, 2.31; Cl, 45.18.

B. From 6. To a stirred mixture of 87 mg (0.5 mmol) of 6 in 15 ml of CH_2Cl_2 under N_2 was added a solution of 68 mg (0.51 mmol) of NCS in 10 ml of CH_2Cl_2 over a period of 30 min. Stirring was continued for an additional 4 hr. The solvent was removed and the residue was chromatographed on a short column of silica gel CG-7. CH_2Cl_2 removed the green by-products and the main yellow band. The concentrate from the latter was rechromatographed on a 12 × 1.5 in. column. CH_2Cl_2–ether (4:1) separated 7 from a small amount of 6. The major band afforded 72 mg (71%) of 7, mp 127–129.5°, identical (NMR) with the product from A.

5,7-Dibromo-2-methyl-2H-cyclopenta[d]pyridazine (9). Over a period of 10 min, 107 mg (0.603 mmol) of NBS was added to a solution of 79.6 mg (0.603 mmol) of 1 in 10 ml of CH_2Cl_2. After 90 min the mixture was worked up as described for 6 except that 2:1 and then 3:2 hexane–CH_2Cl_2 were used for successive elutions. Three fractions separated. The residue from the major, least polar band was sublimed at 50° (10^{-5} mm) and gave 72.6 mg (83% based on N-bromosuccinimide) of 9 as a yellow solid, mp 125–126.5° dec. An analytical sample was obtained by recrystallization from methanol and two sublimations: 125.3–126.5°; NMR (acetone) singlets at δ 7.17 (H-6) and 4.27 (NCH_3) and doublets at 8.75 (J = 1 Hz, H-1) and 8.54 (J = 1 Hz, H-4); uv (ether) 251 nm (ε 24,100), 256 (24,100), 270 (21,800), 320 (sh, 4550), 328 (5670), 339 (5430), and 420 (1170).

Anal. Calcd for $C_8H_6N_2Br_2$: C, 33.14; H, 2.08; N, 9.66. Found: C, 33.27; H, 2.01; N, 9.49.

The residue from the middle fraction after sublimation at 40° (10^{-5} mm) afforded 14.3 mg (11% based on NBS) of an unstable yellow solid partially characterized as 7-bromo-2-methyl-2H-cyclopenta[d]pyridazine (8): mp 87–88° dec; NMR (acetone) singlets at δ 8.61 (broad, H-4) and 4.17 (NCH_3) and doublets at 8.57 (J = 1 Hz, H-1), 7.15 (J = 3 Hz, H-6), and a doublet of doublets at 6.61 (J = 3 and 1 Hz, H-5); uv (ether) 254 nm (ε 28,000), 313 (sh, 4090), 318 (4640), 321 (sh, 4550), 332 (4750), and 412 (1080).

The most polar fraction afforded 29.1 mg (37%) of unchanged 1, mp 129–129.5°.

5,6,7-Tribromo-2-methyl-2H-cyclopenta[d]pyridazine (14). To a solution of 89.4 mg (0.676 mmol) of 1 in 10 ml of CH_2Cl_2 was added over a 10-min period 380.6 mg (2.13 mmol) of NBS. After 35 min, the dark green mixture was chromatographed on a 1 × 1 in. silica gel column using CH_2Cl_2 and then 1:1 CH_2Cl_2–$HCCl_3$ as eluents. Removal of the solvent from the bright yellow fraction gave 137.6 mg (55%) of 14 as a yellow solid which darkened and became green above 165° and melted at 177–178° dec before and after recrystallization from aqueous acetone: NMR (acetone) singlets at δ 8.89 (H-1), 8.57 (H-4), and 4.43 (N-CH_3); uv (ether) 264 nm (ε 30,100), 277 (sh, 23,100), 319 (3990), 337 (3180), and 405 (1190).

Anal. Calcd for $C_8H_5N_2Br_3$: C, 26.02; H, 1.35. Found: C, 26.16; H, 1.50.

5,7-Dichloro-6-bromo-2-methyl-2H-cyclopenta[d]pyridazine (15). A solution of 47 mg (0.234 mmol) of 6 and 136.4 mg (0.766 mmol) of NBS in 8 ml of CH_2Cl_2 formed needles 25 min after mixing. A small amount of acetone was added to dissolve the needles and the solution was chromatographed on a 1 × 5 in. silica gel column with acetone–CH_2Cl_2 as the eluent. Removal of solvent from the yellow and orange fractions gave a yellow-brown oil which was chromatographed on a 6 × 8 in. silica gel preparative plate with 3:2 CH_2Cl_2–petroleum ether as the eluent. The yellow oil from the major band was crystallized from aqueous ethanol and gave 13 mg (19.9%) of 15 as a yellow solid: mp 120–123°; NMR (acetone) singlets at δ 9.05 (H-1), 8.73 (H-4), and 4.34 (NCH_3); uv (ether) 262 nm (ε 26,000), 273 (sh, 17,000), 318 (3,200), 337 (2500), and 408 (940).

Anal. Calcd for $C_8H_5N_2Cl_2Br$: C, 34.29; H, 1.79; Cl, 25.36; Br, 28.57. Found: C, 34.31; H, 1.87; Cl, 25.42; Br, 28.56.

5-Trifluoroacetyl-7-bromo-2-methyl-2H-cyclopenta[d]pyridazine (11). A. From 5-Trifluoroacetyl-2-methyl-2H-cyclopenta[d]pyridazine (10). A mixture of 25.8 mg (0.113 mmol) of 10[7] and 34.3 mg of NBS in 10 ml of CH_2Cl_2 was stirred for 7 hr. The residue after removal of the solvent was chromatographed three times on a 20 × 30 cm silica gel preparative plate with CH_2Cl_2 as the eluent to afford 24.5 mg (74%) of 11 as yellow crystals, mp 213.5–215°. Recrystallization from hexane–CH_2Cl_2 gave an analytical sample: mp 214.5–215°; NMR (acetone, CAT) singlets at δ 9.13 (broad, H-1), 9.33 (broad, H-4) and 4.50 (NCH_3) and a quartet at 7.51 (J = 2 Hz, H-6); uv (ether) 248 nm (D 0.58), 260 (0.43), 267 (0.42), 292 (0.55), 299 (0.63), and 374 (0.29); ir ($HCCl_3$) 1647 cm^{-1}.

Anal. Calcd for $C_{10}H_6ON_2BrF_3$: C, 39.11; H, 1.97. Found: C, 39.05; H, 2.36.

B. From 8. A mixture of 14.3 mg (0.068 mmol) of 8, 3 drops of trifluoroacetic anhydride, 2 drops of triethylamine, and 1 ml of CH_2Cl_2 was allowed to stand for 2 days. Removal of the solvent and chromatography of the residue twice on a 14 × 25 cm silica gel preparative plate with CH_2Cl_2 as the eluent gave 19.7 mg (95%) of 11 as yellow crystals, mp 213–214.5°, which exhibited spectra (uv, ir) identical with those of the product from A.

5-Bromo-7-trifluoroacetyl-2-methyl-2H-cyclopenta[d]pyridazine (13). A solution of 23.4 mg (0.103 mmol) of 7-trifluoroacetyl-2-methyl-2H-cyclopenta[d]pyridazine (12)[7] and 22.7 mg (0.127 mmol) of NBS was stirred for 22 hr. The solvent was removed and the residue was chromatographed on a 25 × 30 cm silica gel preparative plate with CH_2Cl_2 as the eluent. A minor, less polar band was discarded and the major band afforded a yellow solid, mp 185–189°, which after sublimation at 100° (10^{-5} mm) amounted to 30.5 mg (97%) of 13, mp 187.5–189.5°. Recrystallization several times from hexane–CH_2Cl_2 gave an analytical sample: mp 190.5–191.0°; NMR (acetone) singlets at δ 9.42 (broad, H-4) and 4.47 (NCH_3), a doublet at 8.72 (J = 1 Hz, H-1), and a quartet at 7.58 (J = 2 Hz, H-6); ir ($HCCl_3$) 1632 cm^{-1}; uv (ether) 254 nm (ε 29,900), 288 (sh, 4750), 300 (sh, 4270), 339 (4670), and 415 (8180).

Anal. Calcd for $C_{10}H_6ON_2BrF_3$: C, 39.11; H, 1.97. Found: C, 39.42; H, 2.22.

Reaction of 1 with NIS. A solution of 41.9 mg (0.354 mmol) of 1 and 323.9 mg (1.42 mmol) of NIS[19] in 11 ml of CH_2Cl_2 was stirred for 20 min and then chromatographed on a 1 × 3 in. silica gel column using CH_2Cl_2 as the eluent. Removal of the solvent from the yellow band gave a yellow solid which rapidly decomposed above 0°. Solutions of this substance were more stable and exhibited spectra consistent with the structure of 5,7-diiodo-2-methyl-2H-cyclopenta[d]pyridazine (16): NMR (acetone) singlets at δ 8.38 (H-1), 8.16 (H-4), 7.16 (H-6), and 4.20 (NCH_3); uv (ether) 280 nm (sh, D 1.71), 275 (1.78), 258 (1.83), and on concentration 330 (0.99) and 344 (0.88); visible (ether) 416 nm.

5,6,7-Triiodo-2-methyl-2H-cyclopenta[d]pyridazine (17). To a solution of 1.644 g (4.75 mmol) of dipyridineiodine(I) nitrate[20] in 60 ml of $HCCl_3$ was added 105.2 ml (0.891 mmol) of 1. After 30 hr, the solvent was removed and the residue was chromatographed on a 1 × 3 in. silica gel column with CH_2Cl_2 as the eluent. The yellow band which followed the large I_2 fraction was collected and the solvent was removed. Trituration of the brown solid residue with a small amount of acetone, filtration, and washing with two small portions of CH_2Cl_2 gave 79.3 mg (19.3%) of 17 as yellow-brown crystals which darkened when heated but did not melt at 200°: NMR (dimethyl sulfoxide) singlets at δ 8.77 (H-1), 8.32 (H-4), and 4.26 (NCH_3); uv (ether) 271 nm (ε 31,000), 320 (sh, 5000) and 414 (1200).

Anal. Calcd for $C_8H_5N_2I_3$: C, 18.82; H, 0.98; N, 5.50; I. 74.41. Found: C, 18.80; H, 0.98; N, 5.32; I. 74.92.

5- and 7-Chloro-2-phenyl-2H-cyclopenta[d]pyridazine (18 and 19). To a stirred solution of 97 mg (0.5 mmol) of 2 in 20 ml of CH_2Cl_2 was added a solution of 67 mg (0.5 mmol) of NCS in 10 ml of CH_2Cl_2 over a 30-min period under a N_2 atmosphere. The mixture was concentrated to a small volume and then chromatographed on a 0.5 × 6 in. silica gel (CC-7) column with CH_2Cl_2 as the eluent. The concentrate from the yellow band was chromatographed on three 20 × 20 cm preparative silica gel plates with 2:1 CH_2Cl_2–heptane as the eluent. Four bands with R_f values of 0.33 (unchanged 2), 0.50, 0.58, and 0.70 (20) developed with a slight overlap of the middle two. The bands were physically separated.

Rechromatography of the second on a preparative silica gel plate with 5:2 CH_2Cl_2–heptane as the eluent separated a small amount of the third fraction. Crystallization of the second fraction from ether gave 23 mg (20%) of **18**, mp 120–126°. After sublimation at 50° (10^{-3} mm) the yellow-orange crystals melted at 124–126°: NMR (dimethyl sulfoxide) doublets at δ 9.60 (H-1), 8.90 H-4), 7.25 (H-6), and 7.00 (H-7) and a multiplet centered at 7.77 (5 H); uv (ether) 250 nm (ε 20,000), 258 (sh, 17,000), 289 (22,100), 320 (sh, 7500), and 417 (2680).

Anal. Calcd for $C_{13}H_9N_2Cl$: C, 68.27; H, 3.97; N, 12.25. Found: C, 68.07; H, 3.96; N, 12.28.

Rechromatography of fraction 3 combined with the portion separated from fraction 2 on a preparative silica gel plate with 2:1 CH_2Cl_2–heptane effected separation of the major band from small amounts of **18** and **20**. Sublimation at 50° (10^{-3} mm) of the yellow crystals, mp 76–79°, obtained from the major band gave 47 mg (41%) of **19** as yellow crystals: mp 78–79°; NMR (dimethyl sulfoxide) doublets at δ 9.40 (H-4), 8.27 (H-1), 7.30 (H-6), and 6.88 (H-7) and a multiplet centered at 7.77 (C_6H_5); uv (ether) 252 nm (ε 14,500), 259 (sh, 13,900), 287 (23,100), 322 (sh, 4470), and 424 (2100).

Anal. Calcd for $C_{13}H_9N_2Cl$: C, 68.27; H, 3.97; N, 12.25. Found: C, 68.30; H, 4.31; N, 11.78.

5,7-Dichloro-2-phenyl-2*H*-cyclopenta[*d*]pyridazine (20). To a stirred solution of 97 mg (0.5 mmol) of **2** in 20 ml of CH_2Cl_2 was added a solution of 133 mg (1.0 mmol) of NCS in 10 ml of CH_2Cl_2 over a 30-min period. After 1 hr, the mixture was concentrated to a small volume and chromatographed on a 20 × 20 cm preparative silica gel plate with 2:1 CH_2Cl_2–heptane as the eluent. Recrystallization of the solid, mp 102–104°, from the orange band from ether and then sublimation at 50° (10^{-3} mm) gave 120.2 mg (90%) of **20** as orange crystals: mp 109–109.5°; NMR (dimethyl sulfoxide) doublets at δ 9.40 and 8.90 (H-1 and H-4), multiplet centered at 7.77 (C_6H_5), and a singlet at 7.30 (H-6); uv (ether) 253 nm (ε 20,200), 260 (19,200), 290 (30,000), 331 (sh, 7400), and 435 (2660).

Anal. Calcd for $C_{13}H_8N_2Cl_2$: C, 59.35; H, 3.02; N, 10.65. Found: C, 59.50; H, 3.03; N, 10.83.

5,6,7-Trichloro-2-phenylcyclopenta[*d*]pyridazine (21). To a solution of 38 mg (0.2 mmol) of **2** in 10 ml of acetonitrile was added slowly 39 mg (0.29 mmol) of NCS. The progress of the reaction was monitored by TLC on silica gel and 5% ethyl acetate–95% pentane; no **2** was detected after 8 hr. After standing for 24 hr, orange crystals separated. The mixture was placed in a refrigerator overnight. The separated crystals were washed with cold acetonitrile and dried (vacuum desiccator) and this product (mp 179–180°) then sublimed (50°, 10^{-3} mm) to give 32 mg (74%) of **21**: mp 182–182.5°; NMR ($CDCl_3$) multiplet at δ 7.5–8.2 (5 H, C_6H_5) and a doublet at 8.9 (J = 1 Hz, H-1 and H-4); uv (ether) 258 nm (sh, ε 28,400), 265 (30,700), 294 (33,200), 326 (sh, 8100), and 422 (3200).

Anal. Calcd for $C_{13}H_7N_2Cl_3$: C, 52.44; H, 2.35; N, 9.41. Found: C, 52.46; H, 2.70; N, 9.29.

7-Chloro-2*H*-cyclopenta[*d*]pyridazine (22). To a stirred solution of 117 mg (1.0 mmol) of **3** in 50 ml of CH_2Cl_2 was added dropwise a solution of 119 mg (0.9 mmol) of NCS in 20 ml of CH_2Cl_2 over a period of ca. 10 min. The solvent was removed and the residue was chromatographed on a 0.75 × 6 in. column of SilicAR CC-7[21] with CH_2Cl_2 as the eluent. The combined yellow fractions were concentrated to a small volume and the residue was rechromatographed with a Waters Associates liquid chromatograph, Model ALC-100, using a 0.375 in. × 6 ft Porasil column and 93:7 CH_2Cl_2–ether as the eluent. The residual time on the column was ca. 1.5 hr. Small fractions of less polar (**3**) and more polar (**23**) material were discarded. Removal of the solvent from the major band and sublimation of the residue at 50° (10^{-3} mm) gave 120 mg (88%) of **22** as a yellow solid: mp 126–127°; NMR (acetone) closely spaced multiplets at δ 8.85 (H-4) and 8.75 (H-1), doublets at δ 7.22 (J = 2 Hz, H-6) and 6.82 (J = 2 Hz, H-5), and a broad singlet at 3.0 (NH); uv (ether) 244 nm (ε 33,700), 249 (32,300), 252 (19,100), 305 (4700), 312 (5300), 317 (5100), 325 (5400), and 403 (840).

Anal. Calcd for $C_7H_5N_2Cl$: C, 55.10; H, 3.30; N, 18.36. Found: C, 55.32; H, 3.26; N, 18.06.

5,7-Dichloro-2*H*-cyclopenta[*d*]pyridazine (23). A solution of 430 mg (3.22 mmol) of NCS in 50 ml of acetonitrile was added to a solution of 180 mg (1.53 mmol) of **3** in 15 ml of CH_3CN over a period of 20 min. The mixture was stirred at room temperature for 5 hr, at which time a thin layer chromatogram (silica gel, 9:1 CH_2Cl_2–ether) showed only one yellow spot. Removal of the solvent and chromatography of the residue on SilicAR CC-7[21] with CH_2Cl_2 gave **23** as fine, yellow crystals which were unstable in air. Rechromatography twice more with solvent removal under N_2 afforded 147.5 mg (82%) of long, yellow needles which decomposed at 115°; NMR (acetone-d_6) singlets at δ 8.80 (H-1 and H-4) and δ 7.06 (H-6), uv (ether) 248 nm (ε 23,880), 259 (18,080), 271 (sh, 15,510), 311 (sh, 4509), 318 (5230), 324 (5030), 331 (5046), and 418 (832).

Anal. Calcd for $C_7H_4N_2Cl_2$: C, 44.91; H, 2.14; N, 14.97. Found: C, 45.02; H, 2.10; N, 15.28.

Registry No.—**1**, 22291-85-6; **2**, 22291-84-5; **3**, 270-64-4; **4**, 55268-15-0; **5**, 55268-16-1; **6**, 55268-17-2; **7**, 55268-18-3; **8**, 55268-19-4; **9**, 55268-20-7; **10**, 32377-07-4; **11**, 55268-21-8; **12**, 35426-58-5; **13**, 32377-08-5; **14**, 55298-71-0; **15**, 55268-22-9; **16**, 55268-23-0; **17**, 55268-24-1; **18**, 55268-25-2; **19**, 55268-26-3; **20**, 55268-27-4; **21**, 55268-28-5; **22**, 55268-29-6; **23**, 55268-30-9.

References and Notes

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(2) Taken in part from the Ph.D. Theses of D. M. Forkey, 1967, L. D. Grina, 1970, and L. W. Hickernell, 1973.
(3) 3M Fellow, 1964–1965; National Science Foundation Summer Fellow, 1965.
(4) National Science Foundation Trainee, 1965–1966; National Defense Education Act Fellow, 1966–1968; National Institutes of Health Fellow, 1968–1970.
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Ring Transformations Involving Pyrido[1,2-*b*]cinnolin-6-ium Hydroxide Inner Salts

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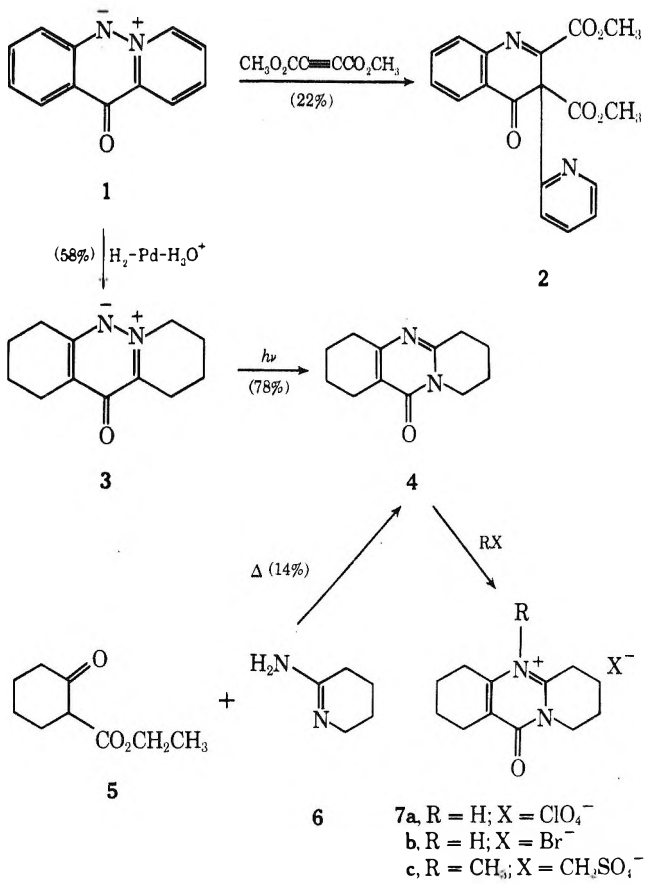
The heating of the mesoionic 5,11-dihydro-11-oxopyrido[1,2-*b*]cinnolin-6-ium hydroxide inner salt (1) with dimethyl acetylenedicarboxylate afforded 2,3-dicarbomethoxy-3,4-dihydro-3-(2-pyridyl)quinolin-4-one (2). The 1,2,3,4,7,8,9,10-octahydro derivative of 1 (3) undergoes photoisomerization, in high yield, to 1,2,3,4,6,7,8,9-octahydro-11*H*-pyrido[2,1-*b*]quinazolin-11-one (4). Structures of 2 and 4 (as the hydrobromide salt **7b**) were unambiguously established by X-ray crystallography. Compound 4 was also directly synthesized.

We recently reported[1] on the preparation and chemistry of 5,11-dihydro-11-oxopyrido[1,2-*b*]cinnolin-6-ium hydroxide inner salt (1)[2] and related compounds. In the course of further investigation of these novel substances, we encountered two products (2 and 4) which resulted from unusual rearrangements. The structures of these products were unambiguously established by X-ray crystallography. We wish to record these rearrangements as interesting examples of ring transformation reactions.[3]



Recent interest in dipolar cycloadditions involving six-membered mesoionic ring systems[4,5] prompted us to treat 1 with dimethyl acetylenedicarboxylate. The sluggishness of the reaction necessitated the heating (100°) of 1 in undiluted dimethyl acetylenedicarboxylate for 30 hr. The only product we could isolate from the complex reaction mixture was 2, obtained in 22% yield. Several aspects of the spectral properties of 2, especially the very different carbonyl frequencies (1760 and 1715 cm^{-1}) of the carbomethoxy groups, were inconsistent with simple 1:1 cycloadducts. The eventual assignment of structure 2 by X-ray crystallography confirmed our suspicion of the occurrence of an extensive rearrangement.

We have described earlier[1] the catalytic hydrogenation of 1 over Raney nickel in tetrahydrofuran to yield the octahydro derivative **3.** In the course of preparing larger amounts of compound **3,** we found that more consistent results were obtained if palladium on carbon and aqueous hydrochloric acid were used as catalyst and solvent, respectively. When 3 was photolyzed with a medium-pressure mercury lamp, isomerization occurred cleanly. The photoproduct[6] was isolated in 78% yield. After structure 4 was established by X-ray crystallographic analyses of its hydrobromide salt, **7b,** confirmation of 4 by synthesis was easily achieved by the condensation of 2-carbethoxycyclohexanone (5) with 2-iminopiperidine (6).

Several salts of 4 were prepared. The presence of the carbonyl bands (1700 cm^{-1}) in the infrared spectra of the perchlorate, hydrobromide, and the quaternary methylsulfonate salts **7a, 7b,** and **7c,** respectively, are consistent with protonation and alkylation on nitrogen rather than oxygen.

Mechanisms. Plausible mechanisms for the formation of 2 and 4 are shown in Scheme I. The initial 1,3-dipolar cycloaddition to 1 leading to intermediate A is reasonable.[5,7] Subsequent ring opening (to B) and reclosure as shown completes the transformation to the quinolinone **2.**

The most likely intermediate in the photolysis of **3** is the diaziridine[8,9] C. Ring-fused diaziridines have been isolated from photoisomerization of the ylide form of 1,5-dimethyl-6-phenyl-2,3-dihydrodiazepin-4-one,[10] and implicated in the photorearrangements of acyliminopyridinium *N*-ylides[11-14] and iminoquinolinium *N*-ylides.[15,16] The diaziridine C can open to the intermediate ketene D, which cyclizes to give **4.** It is of interest to note that the ketene intermediates B and D belong to the class of α-acyl-, α-thioacyl-, and α-imidoylketene intermediates which apparently readily undergo 1,4-cycloaddition reactions in the manner similar to those proposed here.[17]

Crystallography.[18] Crystal structure analyses were done for **2, 4,** and **7b.** The cell dimensions for each compound were obtained from a least-squares fit of 14 well-centered reflections with $30° < 2\theta < 40°$. Intensity data for all three compounds were measured on a Hilger-Watts four-circle diffractometer (θ–2θ scans, Ni filtered Cu Kα radiation, plus height discrimination). The structures of 2 and 4 were solved by a multiple solution procedure[19] and that of **7b** by Patterson and Fourier methods. All refinements were carried out by full-matrix least squares. 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 are: triclinic, space group $P\bar{1}$, a = 7.586 (5), b = 8.625 (4), c = 12.091 (6) Å, α = 86.93 (3), β = 86.19

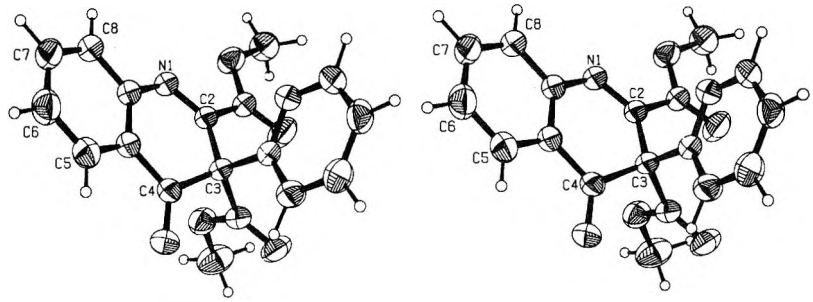
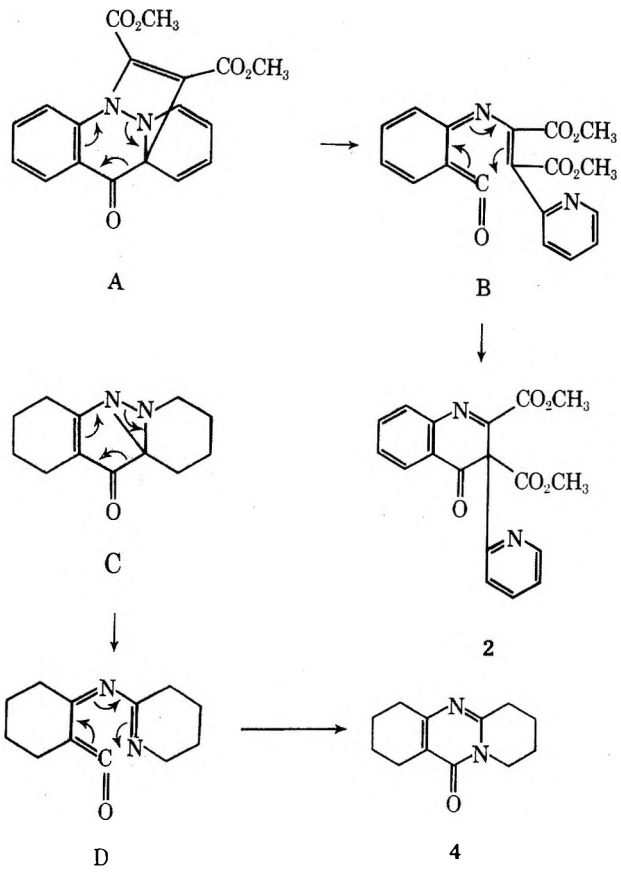


Figure 1. A stereodrawing of the structure of **2**.

Scheme I



(5), γ = 82.55 (4)°, Z = 2, μ (Cu Kα) = 9.04 cm^{-1}. The crystal used for data collection was 0.12 × 0.25 × 0.40 mm in size. Of the 3217 accessible reflections with $\theta < 76°$, 2571 had intensities which were significantly greater than background [$I > 2.5\sigma(I)$].

In the initial (isotropic) refinement of **2** the carbon and nitrogen atoms were all assigned the carbon scattering curve. The nitrogen atoms were identified at the conclusion of this refinement on the basis of their isotropic temperature factors. In the final refinement anisotropic thermal parameters were used for the heavier atoms and isotropic temperature factors for the hydrogen atoms. The hydrogen atom parameters were refined. The final R is 0.046 for the 2571 observed reflections. The final difference Fourier has no features greater than 0.1eÅ^{-3} in magnitude. The structure of **2** is shown by the stereodrawing in Figure 1. Using the numbering of the atoms in Figure 1 and indicating the nitrogen and carbon atoms of the pyridine ring as N′ and C′ respectively, the distances and angles about the two nitrogen atoms are, C(8a)–N(1), 1.418 (3) Å; N(1)–C(2), 1.271 (3) Å; C(8a)–N(1)–C(2), 119.2 (2)°; C(6′)–N(1′), 1.342 (3) Å; N(1′)–C(2′), 1.335 (3) Å; C(6′)–N(1′)–C(2′), 117.4 (2)°.

Crystal data for **4** are: monoclinic, space group Pn, a = 9.887 (6), b = 6.328 (5), c = 9.578 (8) Å, β = 117.05 (4)°, Z = 2, μ (Cu Kα) = 6.6 cm^{-1}. There were 1048 accessible reflections with $\theta < 76°$ of which 661 were considered observed. Although the gross structure was obtained easily, the analysis did not succeed in distinguishing between carbon and nitrogen atoms. Owing to this failure, an X-ray analysis of **7b** was undertaken.

Crystal data for **7b** are: orthorhombic, space group $P2_12_12_1$, a = 6.106 (5), b = 11.924 (10), c = 17.192 (15) Å, Z = 4, μ (Cu Kα) = 47.9 cm^{-1}. The size of the crystal used for data collection was 0.2 × 0.2 × 0.5 mm. Of the 2575 accessible reflections ($\theta < 76°$, hkl and $hk\bar{l}$ octants), 2166 were considered observed. These data were corrected for absorption. The crystal structure of **7b** was solved (except for the C vs. N ambiguity) by straightforward application of the heavy-atom method. In the preliminary stages of refinement all atoms except the oxygen and bromine were treated as carbon atoms and the imaginary part of the anomalous dispersion correction ($\Delta f''$) was set to zero. The first few cycles of least squares were done using isotropic temperature factors for all atoms. This refinement was followed by four cycles of least squares in which all atoms had anisotropic thermal parameters. At this point two sets of structure factors were calculated, one using the correct value of $\Delta f''$ and the other with the sign of $\Delta f''$ reversed (equivalent to refining the antipode). The absolute configuration of the crystal structure of **7b** was taken as the one corresponding to the lower R_w value (R_w = 0.082 and 0.088). The complete anomalous dispersion correction was used in all subsequent refinements.

It was apparent from the anisotropic thermal parameters that there was a disorder involving atoms C(12) and C(13) (see Figure 2 for the atom labeling scheme). That is, the ring containing these two atoms randomly assumes either of two conformations in the crystal. To account for this disorder, the two atoms C(12) and C(13) were replaced by four atoms, C(12)A, C(12)B, C(13)A, and C(13)B, each with an atom multiplier of 0.5. Isotropic temperature factors were used for these half-carbons in all subsequent refinements. Following refinement of the trial structure including the half-atoms a difference map was calculated. Peaks were found at reasonable positions for hydrogen atoms about those atoms not involved in the disorder, including a peak of 0.8 Å from the atom at position 4 [N(4) in Figure 2]. The positions of all hydrogen atoms were calculated. Two sets of eight half-hydrogens were used for the hydrogen atoms about the carbon atoms involved in the disorder. The refinement was continued for the structure including the hydrogen atoms. At the end of this refinement the discrepancy indices were R = 0.0453 and R_w = 0.0658.

All that remained to be done at this point was to identify the nitrogen atoms. It was assumed that both nitrogens were part of the central ring and that the atom bonded to O(1) was a carbon. Thus there were ten possible trial struc-

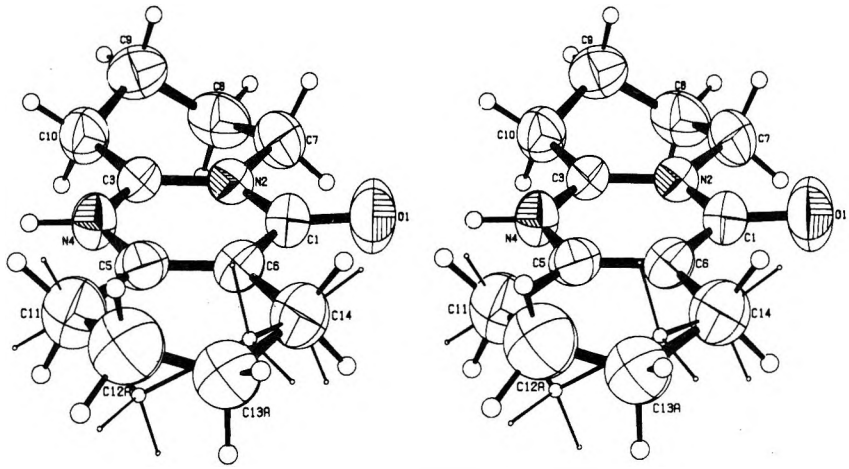


Figure 2. A stereodrawing of the cation of **7b**. The anisotropic atoms and C(12)A and C(13)A are scaled to the 50% probability level. The hydrogen atoms, including those which are part of the conformer containing C(12)A and C(13)A, are shown as spheres of a fixed arbitrary size. The carbon atoms C(12)B and C(13)B and the hydrogen atoms which are part of the other conformer are shown as very small spheres connected by thin bonds.

Table I
R Factors for the Various Trial Structures of 7b

Positions of nitrogen atoms	R	R_w
2,3	0.0447	0.0654
2,4	0.0386	0.0591
2,5	0.0441	0.0656
2,6	0.0440	0.0654
3,4	0.0456	0.0658
3,5	0.0490	0.0707
3,6	0.0494	0.0713
4,5	0.0442	0.0650
4,6	0.0446	0.0649
5,6	0.0491	0.0712

Table II
Distances and Angles about the Atoms Comprising the Central Ring of 7b as Indicated in Figure 2

C(6)–C(1)	1.433 (8) Å	C(6)–C(1)–N(2)	115.8 (4)°
C(1)–N(2)	1.423 (6)	C(1)–N(2)–C(3)	122.2 (4)
N(2)–C(3)	1.316 (6)	N(2)–C(3)–N(4)	119.5 (4)
C(3)–N(4)	1.320 (6)	C(3)–N(4)–C(5)	122.6 (4)
N(4)–C(5)	1.384 (6)	N(4)–C(5)–C(6)	119.9 (4)
C(5)–C(6)	1.324 (7)	C(5)–C(6)–C(1)	119.8 (4)
C(1)–O(1)	1.225 (7)	C(6)–C(1)–O(1)	124.7 (5)
N(2)–C(7)	1.485 (7)	N(2)–C(1)–O(1)	119.5 (5)
C(3)–C(10)	1.495 (7)	C(1)–N(2)–C(7)	115.1 (4)
C(5)–C(11)	1.497 (8)	C(3)–N(2)–C(7)	122.6 (4)
C(6)–C(14)	1.513 (7)	N(2)–C(3)–C(10)	122.3 (5)
		N(4)–C(3)–C(10)	118.2 (4)
		N(4)–C(5)–C(11)	114.5 (5)
		C(6)–C(5)–C(11)	125.6 (5)
		C(5)–C(6)–C(14)	121.5 (5)
		C(1)–C(6)–C(14)	118.6 (5)

tures in which the remaining five atoms of the central ring could be assigned as two nitrogen and three carbon atoms. The discrepancy indices for these ten trial structures are listed in Table I. The *R* factor ratio test of Hamilton[20] was used to compare the R_w values of the various trial structures in Table I with the R_w value of the structure with nitrogen atoms at positions 2 and 4. These other nine trial structures could be rejected at a significance level of 0.005 (two-dimensional hypothesis, 2023 degrees of freedom). Thus it is established that the nitrogen atoms are located at positions 2 and 4 (Figure 2).

Further evidence that N(4) is a nitrogen atom is provided by the fact that it is hydrogen bonded to the bromide ion. The N···Br distance is 3.23 Å and the N–H···Br angle is 177°. The bond distances and angles about the atoms comprising the central ring are given in Table II. In the final refinement isotropic temperature factors were used for the hydrogen atoms and the four half-weighted carbon atoms and anisotropic thermal parameters were used for all other atoms. The hydrogen atoms were included in the structure factor calculations, but they were not refined. The final discrepancy index is $R = 0.039$ for the 2166 observed reflections. There were two peaks (−0.5 and −0.6eÅ^{-3}), both about 0.85 Å from the bromide ion, on the final difference Fourier. There were no other peaks greater than 0.4eÅ^{-3} in magnitude.

Experimental Section

All melting points were taken in capillaries, heated in oil baths, and are corrected. Infrared spectra were determined on a Beckman IR-9 or a Perkin-Elmer 621 grating spectrometer, mass spectra on a Jeolco 01SG or a CEC-21-110 spectrometer, nuclear magnetic resonance spectra on a Varian A-60 or a Varian HA-100 spectrometer, using tetramethylsilane as internal standard, and ultraviolet spectra with a Cary 14M or 15 recording spectrometer. Solvents used were of reagent grade purity. Petroleum ether used boils at 30–60°. Unless otherwise specified, all solvents were evaporated on a Büchi Rotavapor evaporator under water-aspirator pressure using a water bath set at 30–80°. The progress of reactions was routinely followed by thin layer chromatography (TLC).

2,3-Dicarbomethoxy-3,4-dihydro-3-(2-pyridyl)quinolin-4-one (2). A mixture of 5,11-dihydro-11-oxopyrido[1,2-*b*]cinnolin-6-ium hydroxide inner salt[1] (**1**, 20.0 g, 10.2 mmol) and 60 ml of dimethyl acetylenedicarboxylate (Aldrich Chemical Co.) was heated in a stoppered flask on a steam bath for 30 hr. On cooling, the dark, viscous oil was triturated three times with 100-ml portions of boiling ether. The combined ethereal solutions were filtered and concentrated to near dryness, giving 3.0 g of slightly impure **2** as colorless prisms, mp 151–153°. The crystals were dissolved in ether. The ethereal solution was filtered through a pad of neutral alumina (10 g), which was then washed with ether. The combined ethereal filtrate and washing was evaporated. The solid residue was recrystallized from ethyl acetate–hexane to give 2.5 g of large, colorless prisms, mp 157–160°. These crystals were used for X-ray crystallographic analysis.

The ether-insoluble portion of the original product mixture was dissolved in a small volume of tetrahydrofuran and applied to the top of a short column of alumina (100 g of Woelm activity I grade) which was packed in ether. Elution of this column with ether afforded pure **2**, which after crystallization from ethyl acetate–hex-

ane weighed 5.1 g as colorless prisms, mp 156–159°. The total yield was 7.6 g (22%): ir (KBr) 1760, 1715, and 1685 cm^{-1}: uv max (CH_3CN) 244 nm (ε 30,800), 331 (4300); NMR (DMSO-d_6) δ 3.68 (s, 3, CH_3), 3.81 (s, 3, CH_3), 7.28–8.40 ppm (m, 8, aromatic); mass spectrum *m/e* 338 (M^+).

Anal. Calcd for $C_{18}H_{14}N_2O_5$: C, 63.91; H, 4.17; N, 8.28. Found: C, 63.64; H, 4.07; N, 8.09.

1,2,3,4,5,7,8,9,10,11-Decahydro-11-oxopyrido[1,2-*b*]cinnolin-6-ium Hydroxide Inner Salt (3).[1] A suspension of 90 g (0.46 mol) of 5,11-dihydro-11-oxopyrido[1,2-*b*]cinnolin-6-ium hydroxide inner salt (1) and 100 g of 10% palladium on carbon in 3 l. of 0.2 *N* aqueous hydrochloric acid was hydrogenated under 1 atm hydrogen at room temperature. After 20 hr the uptake of hydrogen became sluggish and TLC indicated that the reaction was essentially complete. The catalyst was removed by filtration. The filtrate was basified (pH 9) with 6 *N* sodium hydroxide. The product was isolated by extraction with methylene chloride. On crystallization from acetonitrile, 54.5 g (58%) of **3** was obtained, mp 198–200°. This material was identical with that which we reported earlier[1] (mp 196–198°).

1,2,3,4,6,7,8,9-Octahydro-11*H*-pyrido[2,1-*b*]quinazolin-11-one (4). A. From Photoisomerization of 3. A solution of 35.5 g (0.175 mol) of 3 in 4 l. of tetrahydrofuran was photolyzed under nitrogen with a 250-W medium-pressure mercury lamp (Hanovia 654A) through quartz. The quartz well was cleaned when it became coated with a brown film in the course of the photolysis. After 5 days, TLC indicated a clean and complete conversion. Solvent was evaporated. Trituration of the residue with ether afforded 27.7 g (78%) of amorphous **4**, mp 168–170°. Recrystallization from acetone–hexane afforded colorless prisms: mp 168–170°; ir (KBr) 1660 cm^{-1}; molecular ion *m/e* 204 (calcd 204); uv max (CH_3CN) 232 nm (ε 5660) and 276 (5460); NMR ($CDCl_3$) δ 1.6–2.1 (m, 8, 4 CH_2), 2.3–2.7 (m, 4, 2 CH_2), 2.85 (t, 2, CH_2), and 3.92 ppm (t, 2, CH_2).

Anal. Calcd for $C_{12}H_{16}N_2O$: C, 70.56; H, 7.90; N, 13.71. Found: C, 70.47; H, 7.75; N, 13.72.

B. By Synthesis. A solution of 2.5 g (18.5 mmol) of 2-iminopiperidine hydrochloride in 5.5 g (~32 mmol) of ethyl 2-cyclohexanone carboxylate (both reagents from Aldrich Chemical Co.) containing 0.5 ml of glacial acetic acid was heated under reflux, under nitrogen, for 20 hr. The reaction mixture was partitioned between methylene chloride and water which was basified with dilute ammonium hydroxide. The methylene chloride layer was washed with water, dried (Na_2SO_4), and evaporated. Crystallization of the residual oil from ether afforded 0.52 g (14%) of **4**, mp 162–165°. This material was found to be identical (TLC, ir) with the sample from the photoisomerization of **3** as described above.

The perchlorate salt (**7a**) was prepared by dissolving the free base 4 with a slight excess of concentrated perchloric acid (70%) in a mixture of methylene chloride and tetrahydrofuran. Solvents were evaporated. Crystallization from acetone–ether afforded the perchlorate salt in 76% yield as light tan prisms, mp 182–184°, ir (KBr) 1700 cm^{-1}.

Anal. Calcd for $C_{12}H_{16}N_2O \cdot HClO_4$: C, 47.30; H, 5.62; N, 9.19 Found: C, 47.53; H, 5.72; N, 9.30.

The hydrobromide salt (**7b**) was prepared by passing gaseous hydrogen bromide into a solution of the free base in methylene chloride. The salt crystallized from methylene chloride–ethyl acetate in 94% yield, mp 288–292° dec, ir (KBr) 1700 cm^{-1}. The crystals (light amber rods) used in X-ray crystallography were obtained by slow crystallization resulting from the solution of the free base in ethyl bromoacetate which contained some hydrogen bromide.

Anal. Calcd for $C_{12}H_{16}N_2O \cdot HBr$: C, 50.54; H, 6.01; N, 9.82; Br^-, 28.02. Found: C, 50.60; H, 6.03; N, 10.11; Br^-, 28.19.

Thermal Stability of 3. Three melting point capillaries containing **3** (mp 196–198°) were heated in an oil bath at 199–200°. The capillaries were withdrawn one at a time after 5, 15, and 45 min. TLC of the melted samples showed that the bulk of **3** was intact and that little or none of the photoproduct **4** was formed.

5-Methyl-1,2,3,4,6,7,8,9-octahydro-11-oxo-11*H*-pyrido[2,1-*b*]quinazolin-5-ium Methylsulfate (7c). A mixture of 4.08 g (20 mmol) of 4 and 10 ml of dimethyl sulfate was heated on a steam bath for 0.5 hr. The clear solution was diluted with ether, affording 4.6 g (70%) of light tan prisms, mp 155–157°. Recrystallizations from acetone afforded light tan needles, mp 153–155°, ir (KBr) 1700 cm^{-1}.

Anal. Calcd for $C_{14}H_{22}N_2O_5S$: C, 50.89; H, 6.71; N, 8.48. Found: C, 50.56; H, 6.79; N, 8.32.

Acknowledgment. We thank Dr. R. P. W. Scott and his staff in our Physical Chemistry Department, in particular, Dr. W. Benz for mass spectra, Dr. F. Scheidl for elemental analyses, Dr. V. Toome for uv measurements, Mr. S. Traiman for ir spectra, and Dr. T. Williams for NMR spectra. A special thanks is due to Mr. Ralph Nelson and Fred Sancilis for their efficient technical assistance in the X-ray laboratory.

Registry No.—**1**, 53114-16-2; **2**, 55450-47-0; **3**, 53114-22-0; **4**, 55450-48-1; **5**, 1655-07-8; **6** HCl, 16011-96-4; **7a**, 55450-49-2; **7b**, 55450-50-5; **7c**, 55450-52-7; dimethyl acetylenedicarboxylate, 762-42-5.

Supplementary Material Available. Tables of the positional and thermal parameters for the structures of **2** and **7b** will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (100 × 148 mm, 24× reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 16th St., N.W. Washington, D.C. 20036. Remit check or money order for $4.00 for photocopy or $2.50 for microfiche, referring to code number JOC-75-2201.

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Pyrimido[5,4-*e*]-*as*-triazines. VIII. Synthesis of 7-Azaaminopterin[1]

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7-Azaaminopterin (**25**) was prepared as a potential inhibitor of dihydrofolic reductase and the enzymes involved in the interconversions of tetrahydrofolates. The projected route for the preparation of **25** required an investigation of the preparation and reactions of 3-(halomethyl)pyrimido[5,4-*e*]-*as*-triazines. Amination of both 3-(chloromethyl)-5-methoxy- and 7-amino-5-(benzylthio)-3-(chloromethyl)pyrimido[5,4-*e*]-*as*-triazines (**1** and **19**), respectively, with ethyl *p*-aminobenzoate resulted in displacement of the 5 substituent to give ring-substituted products. Similarly, oxidative amination of 5-chloro-3-(chloromethyl)-1,2-dihydropyrimido[5,4-*e*]-*as*-triazine (**12**) with NH_3 in the presence of Ag_2O gave the corresponding 5-amino-3-(chloromethyl) derivative **7**. In contrast to the results obtained with **1** and **19**, treatment of **7** with ethyl *p*-aminobenzoate displaced the chloro group to give **9**. In the presence of KI, reaction of **19** with NaN_3 and *p*-aminobenzoyl-L-glutamic acid, respectively, replaced the chloro group to give the corresponding 3-methyl substituted products **22** and **23**. The interaction of **23** with NaN_3 resulted in displacement of the benzylthio group followed by conversion of the intermediate azido substituent to an amino group during the reaction to give 7-azaaminopterin (**25**). The latter showed no significant activity either against dihydrofolic reductase (pigeon liver) or in the KB cell culture screen, but was an inhibitor of *Streptococcus faecium* ATCC 8043.

The triazine ring of 7-azapteridines is easily reduced chemically, suggesting that the enzymatic reduction of appropriate derivatives of this ring system might also occur readily.[2-4] Previously, 7-azafolic acid (**24**) was prepared with the expectation that this compound would be a substrate for dihydrofolic reductase and produce hydro derivatives of **24** in vivo.[5] **24** was found not to be a substrate for dihydrofolic reductase from pigeon liver, but this lack of interaction was attributed to the electronic nature rather than to a structural effect of the 7-azapteridine ring. To increase the basicity of this ring system 7-azaaminopterin was prepared, which is not only a potential inhibitor of dihydrofolic reductase, but if a substrate for this enzyme, the resulting hydro derivatives might inhibit thymidylate synthetase[6] or other enzymes that utilize the reduced forms of folic acid.[7a] Earlier the preparation of 7-azafolic acid and the diethyl ester of 7-azaaminopterin from the corresponding diethyl glutamate derivative of a 4-(benzylthio)-7-azapteridine intermediate was described.[5] Simultaneously with the above investigation, work was carried out on the reactions of 6-(halomethyl)-7-azapteridines, which eventually led to the synthesis of 7-azaaminopterin [*N*-[*p*-[[(5,7-diaminopyrimido[5,4-*e*]-*as*-triazin-3-yl)methyl]amino]benzoyl]-L-glutamic acid] (**25**).

In nucleophilic displacement reactions, benzyl-type halides and haloheterocyclics are known to be more reactive than methoxyheterocyclics.[8] Previously, we reported the preparation of **1**,[9] which was chosen initially for the investigation of the preferred reaction site in the displacement of groups from the 4 position of the ring and from the 6-methyl group. Although treatment of **1** with ethyl *p*-aminobenzoate in refluxing dioxane was expected to give **2**, the only identified product obtained from this reaction was a 26% yield of **3**. This result indicated that the 4-methoxy group was activated more by the ring than the benzyl-type chloromethyl group. The amino group was chosen to circumvent this problem as it should be less susceptible to nucleophilic displacement from the ring than other heteroatom-containing groups. To prepare this type of compound, **4**[10] was treated with Br_2 in HOAc at reflux and appeared to be converted to some extent to the bromomethyl compound **5** (^{1}H NMR), but TLC data showed that the reaction product was a complex mixture containing unreacted **4**. Previously, reaction of **6** with Br_2 in $CHCl_3$ at room temperature was found to give a low yield of an α-bromoacetic acid derivative.[9] In an effort to increase the yield of this product, this reaction was repeated at 55°, but the crude product that precipitated was identified as the dibromo compound **10** by reaction with NaN_3, which gave a low yield of the diazido derivative **11**. This result suggested that the preparation of the monobromo derivative of **6** in high yield might be difficult. The successful route to the desired type of compound involved the oxidative amination of **12**.[9] Treatment of **12** with Ag_2O in a mixture of NH_3 and dioxane gave a good yield of **7**, presumably formed via the intermediate **8**. The structure of **7** was confirmed by the similarity of its uv spectrum with that of **4**. Since intermediate **8** contains the same leaving group in the ring and side chain, the obtainment of **7** provided additional support for the greater reactivity of substituents at C-4 compared to the chlorine of the chloromethyl group. However, the 4-amino group is not preferentially displaced and the amination of **7** with ethyl *p*-aminobenzoate gave **9** identified by its uv and ^{1}H NMR spectra.

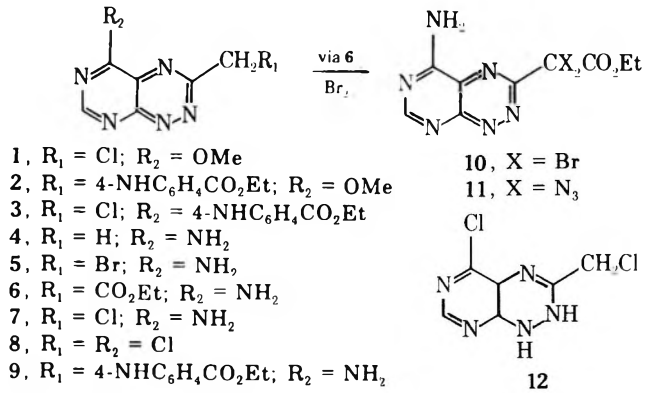
Simultaneously with the work on **6** described above, the bromination of **14**, prepared by the condensation of **13** with ethyl ortho(ethoxycarbonyl)acetate,[11] presumably via the air oxidation of the corresponding dihydro derivative, to give **15** was attempted. However, the conversion of **14** to **15** was unsuccessful, apparently because of the loss of the benzylthio group during the reaction. In another approach, the condensation of **13** with ethyl ortho(chloro)acetate[12] gave two products, **16** and **17**. The latter was identified by its uv spectrum and by conversion with dilute acid to the amide **18**. Apparently the air oxidation of **16** to **19** was prevented by the precipitation of **16** from the reaction mixture as its HCl salt. However, the oxidation of **16** to give **19** was effected with Ag_2O in dioxane.

We next determined the best sequence of reactions for the incorporation of the 4-amino group and the *p*-aminobenzoylglutamic acid side chain. As might be expected, treatment of **19** with ethyl *p*-aminobenzoate in refluxing dioxane gave a low yield of **20** as the only identifiable product. In contrast, under the same conditions, reaction of **19** with a hindered amine, methyl *p*-(methylamino)benzoate, replaced neither the benzylthio nor the chloro group.[10] Since previous observations indicated that 4-azido-7-azapteridines are converted by proton abstraction (from the solvent) to 4-amino-7-azapteridines,[5,9,13] treatment of **19** with NaN_3 was expected to give **21**. However, when this reaction was carried out in DMAC containing KI at room temperature, a good yield of the azidomethyl compound **22**

Table I

Compd	Uv absorption[a] spectra at pH 7, λ_{max}, nm ($\epsilon \times 10^{-3}$)	Ir absorption[b] spectra in KBr, selected bands, cm^{-1}	^1H NMR spectral assignments,[c] chemical shifts, δ (rel area)	Formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
3	268 (21.2), 412 (11.3)	1700, 1600		$C_{15}H_{13}ClN_6O_2$[d]	52.26	3.80	24.38	52.04	3.63	24.07
7	256 (13.5), 290 sh (2.48), 375 (5.47)	1620, 1560	5.26 (2, CH_2), 8.68 (1, CH), 8.88 (2, NH_2)	$C_6H_5ClN_6$[e]	36.66	2.56	42.75	36.66	2.49	42.38
9	256 (15.2), 297 (21.4), 374 (5.52)	1685, 1640 1600	1.28 t (3, CH_3), 4.22 q, 4.98 (2, 2, CH_2), 7.11 (1, NH), 7.29 (4, C_6H_4), 8.65 (1, CH), 8.88 br (2, NH_2)	$C_{15}H_{15}N_7O_2 \cdot H_2O$	52.47	4.99	28.56	52.58	5.17	28.36
11	258 (12.7), 295 sh (2.65), 383 (5.01)	2120, 1750 1645	1.21 (3, CH_3), 4.37 (2, CH_2), 8.70, 8.92 br (3, CH, NH_2)	$C_9H_8N_{12}O_2$	34.18	2.55	53.15	34.23	2.58	52.97
14	272 (9.46), 349 (2.68), 422 (5.20)	1725, 1635	1.18 t (3, CH_3), 4.15 q, 4.26 (4, OCH_2, CH_2), 4.53 (2, CH_2), 7.43 (5, C_6H_5), 7.95 (2, NH_2)	$C_{16}H_{16}N_6O_2S$	53.92	4.53	23.58	53.94	4.63	23.57
16	252 sh (13.2), 337 (5.84), 403 (2.40)[f]	1655, 1600	3.98, 4.31 (2, 2, CH_2), 7.37, 7.55 br (7, C_6H_5, NH_2), 8.88, 10.87 (1, 1, NH), ~11.5 (HCl)	$C_{13}H_{13}ClN_6S$[g]·HCl	43.71	3.95	23.51	43.73	3.93	23.53
17	252 sh (14.4), 318 (16.3)	1650, 1630		$C_{17}H_{18}Cl_2N_6OS$·HCl	44.22	4.15	18.20	44.15	4.18	18.64
18	252 sh (13.6), 317 (15.2)	1680, 1615	4.37, 4.54, 4.71 (6, CH_2), 6.04 (NH_2), 7.33 (5, C_6H_5), 11.87 (1, NH)	$C_{15}H_{14}Cl_2N_6OS$	45.35	3.55	21.15	45.73	3.66	21.22
19	277 (13.5), 377 (3.16), 420 (5.85)	1635, 1560	4.52, 5.08 (CH_2), 7.33 (C_6H_5), 8.00 (NH_2)	$C_{13}H_{11}ClN_6S$	48.98	3.48	26.36	49.14	3.46	25.72
20	256 sh (19.2), 277 (24.0), 428 (9.03)[h]	1700, 1660 1620	1.34 t (3, CH_3), 4.32 q (2, CH_2O), 5.14 (2, CH_2Cl), 7.61 (2, NH_2), 8.13 (4, C_6H_4), 10.55 (1, NH)	$C_{15}H_{14}ClN_7O_2 \cdot 1.33H_2O$	46.94	4.38	25.55	47.05	4.50	25.17
22	273 (14.5), 345 sh (3.37), 421 (6.35)	2100, 1635 1620	4.57, 4.90 (CH_2), 7.43 m (C_6H_5, C_6H_6[i]), 8.04 br (NH_2)	$C_{13}H_{11}N_9S \cdot 0.25C_6H_6 \cdot 0.44H_2O$	49.35	3.82	35.72	49.36	3.91	35.78
23	274 (27.8), 4.22 (8.02)	1720, 1620	2.04, 2.33 (CH_2-CH_2), 4.39 (NCH), 4.52, 4.82 (CH_2), 7.20 (C_6H_4), 7.45 (C_6H_5)[j]	$C_{25}H_{23}N_8O_5SK$	51.18	3.95	19.10	50.92	4.11	19.04
25	266 (20.0), 293 sh (14.3), 348 br (8.15)[f]	1715, 1600	2.05, 2.36 (CH_2-CH_2), 4.39 (NCH), 4.78 (CH_2), 7.20 (C_6H_4)[j]	$C_{18}H_{19}N_9O_5 \cdot 0.15DMAC \cdot 1.33HCl$	44.42	4.35	25.48	44.71	3.88	25.22

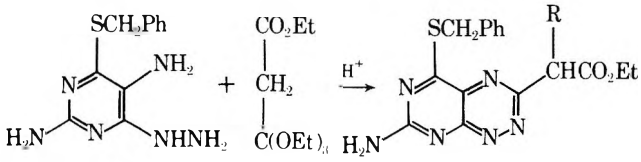
[a] Spectra were determined on solutions obtained by dissolving the samples in a mixture of 8% DMSO and 92% MeOH on a Cary Model 17 spectrophotometer. [b] Perkin-Elmer Model 621 spectrophotometer. [c] Spectra were determined on DMSO-d_6 solutions (2–10% w/v) on a Varian A-60A and XL-100-15 spectrometers with Me_4Si as an internal reference; peak positions quoted in the case of multiples are measured from the approximate center, and the relative peak areas are given to the nearest whole number. [d] Calcd: Cl, 10.28. Found: Cl, 10.22. [e] Calcd: Cl, 18.03. Found: Cl, 18.18. [f] Determined in 0.1 *N* HCl. [g] Calcd: Cl; 19.85. Found: Cl, 19.64. [h] Determined in a mixture of 8% DMSO and 92% MeOH. [i] Recrystallization solvent. [j] The assigned peaks shown were poorly resolved and are based on the position of the corresponding peaks in the diethyl ester derivative.



1, R_1 = Cl; R_2 = OMe
2, R_1 = 4-$NHC_6H_4CO_2Et$; R_2 = OMe
3, R_1 = Cl; R_2 = 4-$NHC_6H_4CO_2Et$
4, R_1 = H; R_2 = NH_2
5, R_1 = Br; R_2 = NH_2
6, R_1 = CO_2Et; R_2 = NH_2
7, R_1 = Cl; R_2 = NH_2
8, R_1 = R_2 = Cl
9, R_1 = 4-$NHC_6H_4CO_2Et$; R_2 = NH_2

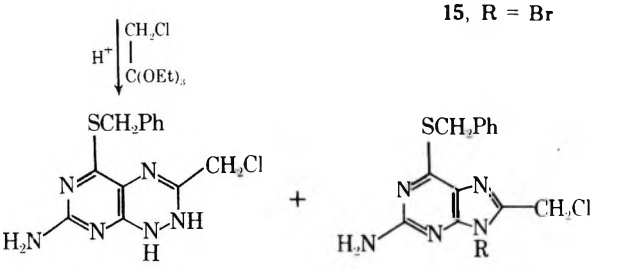
10, X = Br
11, X = N_3

12



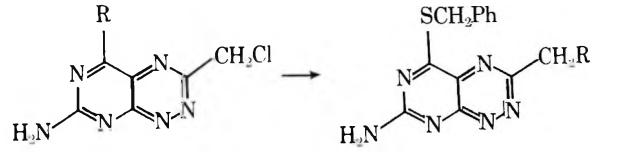
13

14, R = H
15, R = Br



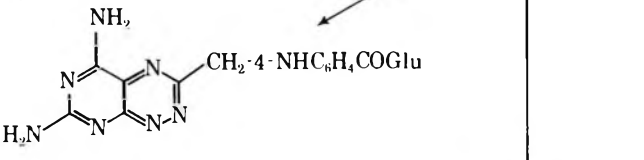
16

17, R = $NC(OEt)CH_2Cl$
18, R = $NHCOCH_2Cl$

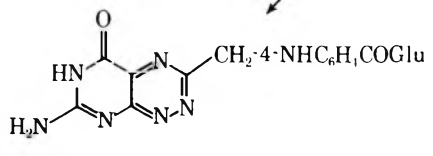


19, R = SCH_2Ph
20, R = 4-$NHC_6H_4CO_2Et$
21, R = NH_2

22, R = N_3
23, R = 4-NHC_6H_4COGlu



25



24

Glu = $NHCH(CO_2H)CH_2CH_2CO_2H$

was obtained. Presumably, in the presence of KI the chloro group of **19** underwent exchange with iodide, resulting in activation of this position. Under similar conditions, reaction of **19** with *p*-aminobenzoyl-L-glutamic acid gave **23** isolated as its monopotassium salt. The structure of this product was confirmed by treatment of **23** with base to give the known 7-azafolic acid (**24**).[5] Similarly, reaction of **23** with NaN_3 replaced the benzylthio group and resulted in the formation of 7-azaaminopterin (**25**).

The uv and ^1H NMR spectra and selected bands in the ir spectra for the new compounds are presented in Table I.

Against dihydrofolic reductase from pigeon liver, **25** (I_{50} 2.7×10^{-5} *M*) was less than one-thousandth as active as methotrexate (I_{50} 2×10^{-9} *M*).[14] Also, **25** was only slightly cytotoxic (ED_{50} 61 μg/ml) in the KB cell culture system.[15] Results similar to these were also observed with 7-azafolic acid, but surprisingly both **25** (ED_{50} 2.7×10^{-8} *M*) and **24** (ED_{50} 1.5×10^{-9} *M*) were good inhibitors of *Streptococcus faecium* ATCC 8043 (methotrexate, $ED_{50} < 10^{-10}$ *M*).[16] A possible explanation for the difference in activities observed in the *S. faecium* and KB tests is that the 7-azapteridines are reduced to hydro derivatives by the bacterium but not by mammalian cells.[7b]

Experimental Section[17]

Ethyl *p*-[[3-(Chloromethyl)pyrimido[5,4-*e*]-*as*-triazin-5-yl]amino]benzoate (3). A solution of **1** (500 mg)[9] and ethyl *p*-aminobenzoate (780 mg) in dioxane (25 ml) was refluxed for 4 hr. From the cooled reaction mixture, the precipitate was collected by filtration and extracted with $CHCl_3$; the residue obtained by evaporation of the extract was recrystallized from C_6H_6, yield 208 mg (26%), mp 245–246° dec.

5-Amino-3-(chloromethyl)pyrimido[5,4-*e*]-*as*-triazine (7). A mixture of **12** (500 mg)[9] and Ag_2O (1.35 g) in 3% anhydrous NH_3–dioxane (50 ml, v/v) was stirred at room temperature for 18 hr. The residue was removed by filtration, and the filtrate was evaporated to dryness in vacuo, yield 335 mg. For analyses a sample was recrystallized from THF, mp 212–213° dec.

Ethyl *p*-[[(5-Aminopyrimido[5,4-*e*]-*as*-triazin-3-yl)methyl]amino]benzoate (9). A solution of **7** (391 mg) and ethyl *p*-aminobenzoate (706 mg) in DMAC (25 ml) was heated at 120° for 4 hr and evaporated to dryness in vacuo. The resulting residue was washed with Et_2O, recrystallized from EtOH, and dried at 78° in vacuo over P_2O_5, yield 95 mg, mp 160° dec with presoftening.

The ethanol filtrate provided an additional 208 mg of crude **9**.

Ethyl 5-Amino-α,α-diazidopyrimido[5,4-*e*]-*as*-triazine-3-acetate (11). A solution of **6** (1.0 g)[9] in $CHCl_3$ (150 ml) containing Br_2 (0.25 ml) was heated at 55° for 6 hr. The cooled reaction mixture was filtered, and the resulting residue (0.96 g) was treated with NaN_3 (0.40 g) in 5:1 EtOH–H_2O (30 ml) at room temperature for 60 hr. This solution was evaporated to dryness, and the residue was washed with H_2O and recrystallized from C_6H_6, yield 0.11 g, mp 154°.

Ethyl 7-Amino-5-(benzylthio)pyrimido[5,4-*e*]-*as*-triazine-3-acetate (14). To a mixture of **13** (0.50 g)[3] and 1 *N* HCl (0.25 ml) in H_2O (25 ml) was added ethyl ortho(ethoxycarbonyl)acetate[11] (5.0 ml) with vigorous stirring. After 18 hr the orange product was collected by filtration, washed with H_2O, and dried in vacuo over P_2O_5, yield 0.31 g (46%), mp 201°.

7-Amino-5-(benzylthio)-3-(chloromethyl)-1,2-dihydropyrimido[5,4-*e*]-*as*-triazine (16). To a mixture of **13** (2.0 g)[3] and ethyl ortho(chloro)acetate (20 ml)[12] was added concentrated HCl (0.71 ml) with stirring. After 15 min the solid was collected by filtration and washed with Et_2O to give crude **16**, yield 1.5 g, mp 213° dec with presoftening. A portion of this solid (0.24 g) was recrystallized from MeOH and then MeCN to give pure **16**, yield 0.08 g, mp 219° dec.

The reaction filtrate from the first crop was stirred for an additional 15 min to deposit a second crop, which was collected by filtration and washed with Et_2O, yield 0.83 g, mp 139° dec with presoftening. The product was mainly the purine **17**, identified by its ultraviolet spectrum.

A portion of the above solid (0.5 g) was stirred in 0.1 *N* HCl for 18 hr, the solid was collected by filtration and recrystallized from EtOH–hexane to give **18**, yield 0.1 g, mp 217° dec with presoftening.

7-Amino-5-(benzylthio)-3-(chloromethyl)pyrimido[5,4-*e*]-*as*-triazine (19). A mixture of crude **16** HCl (0.50 g) and Ag_2O in dioxane was stirred at room temperature for 72 hr. After filtration the filtrate was evaporated to dryness, and the resulting residue was extracted with hot C_6H_6 (300 ml). Concentration of the extract deposited **19**, yield 0.03 g, mp 243° dec.

An additional amount of crude **19** was obtained by evaporation of the C_6H_6 filtrate to dryness in vacuo, yield 0.28 g, mp 215–217° dec.

Ethyl [*p*-[7-Amino-3-(chloromethyl)pyrimido[5,4-*e*]-*as*-

triazin-5-yl]amino]benzoate (20). A solution of **19** (150 mg) and ethyl *p*-aminobenzoate (155 mg) in dioxane (20 ml) was refluxed for 72 hr and evaporated to dryness in vacuo. The residue was triturated with Et_2O, and the resulting solid was reprecipitated from a DMSO solution by the addition of H_2O, yield 46 mg (22%), mp 157° dec taken rapidly. A sample was dried in vacuo over P_2O_5 at 78° for analysis. The ^1H NMR spectrum indicated that this sample was contaminated with a trace amount of an unidentified material.

7-Amino-3-(azidomethyl)-5-(benzylthio)pyrimido[5,4-*e*]-*as*-triazine (22). A mixture of **19** (100 mg), NaN_3 (25 mg), and KI (55 mg) in DMAC (2 ml) was stirred at room temperature for 18 hr and diluted with H_2O (10 ml), and the resulting precipitate was collected by filtration and recrystallized from C_6H_6: yield, 42 mg (60.5%); mp 210° dec; M^+ *m/e* 325. The ^1H NMR spectrum of this sample showed the presence of C_6H_6.

***N*-[*p*-[[[7-Amino-5-(benzylthio)pyrimido[5,4-*e*]-*as*-triazin-3-yl]methyl]amino]benzoyl]-L-glutamic Acid (23).** A mixture of **19** (500 mg, 1.57 mmol), *p*-aminobenzoyl-L-glutamic acid (425 mg, 1.59 mmol), and KI (250 mg) in DMAC (10 ml) was stirred at room temperature for 40 hr and diluted with H_2O (100 ml). The resulting precipitate was collected by filtration, washed with H_2O and Et_2O, and dried in vacuo over P_2O_5, yield 648 mg. This material appeared to decompose at 203°. A solution of this product in ethanolic HCl showed several spots on TLC (9:1 $CHCl_3$–MeOH), one of which was identical with that of the diethyl ester of **23**.[5]

When a portion of this sample was treated with 0.1 *N* HCl to obtain the free acid, elemental analyses indicated partial loss of the benzylthio group in the recovered material.

7-Azafolic Acid (24).[5] A mixture of **23** (50 mg) in oxygen-free 0.1 *N* NaOH (10 ml) was stirred at room temperature for 18 hr, neutralized with 1 *N* HCl, and centrifuged. The resulting residue was washed with Et_2O and identified as **24** by TLC [BuOH (5)–HOAc (2)–H_2O (3)] and by its uv and ir spectra, yield 19 mg.

Also, this compound was prepared by treatment of a solution of **23** (50 mg) in DMSO (2 ml) containing $KHCO_3$ (100 mg) and H_2O (1 ml) at 90° for 18 hr, yield 10 mg.

***N*-[*p*-[[(5,7-Diaminopyrimido[5,4-*e*]-*as*-triazin-3-yl)methyl]amino]benzoyl]-L-glutamic Acid (7-Azaaminopterin 25).** A mixture of **23** (200 mg) and NaN_3 (100 mg) in DMSO (2 ml) was heated with stirring at 90° for 4 hr and diluted with H_2O (20 ml), and the resulting solution was adjusted to pH 2 (paper) with 1 *N* HCl and centrifuged. The residue was washed successively with 0.1 *N* HCl, Et_2O, 10% aqueous DMAC, and H_2O and dried in vacuo over P_2O_5, yield 95 mg, mp >270°. A solution of this product in ethanolic HCl was shown to contain the diethyl ester of **25**[5] by TLC (EtOH). Another spot in the TLC of this solution was identified as the diethyl ester of **24**, presumably formed via acidic hydrolysis of the 5-amino group of **25** or its diethyl ester.

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Registry No.—**1**, 30855-45-9; **3**, 55428-87-0; **6**, 30855-48-2; **7**, 55428-88-1; **9**, 55428-89-2; **11**, 55428-90-5; **12**, 55428-91-6; **13**, 31736-47-7; **14**, 55428-92-7; **16**, 55428-93-8; **16** HCl, 55428-94-9; **17** HCl, 55428-95-0; **18**, 55428-96-1; **19**, 55428-97-2; **20**, 55428-98-3; **22**, 55428-99-4; **23** K salt, 55429-00-0; **24**, 51043-68-6; **25**, 55429-01-1; ethyl *p*-aminobenzoate, 94-09-7; *p*-aminobenzoyl-L-glutamic acid, 4271-30-1; ethyl ortho(ethoxycarbonyl)acetate, 32650-62-7.

References and Notes

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(17) Melting points were determined on a Kofler-Heizbank apparatus.

Synthesis of 3,3a-Dihydro-8*H*-pyrazolo[5,1-*a*]isoindol-8-ones and 8*H*-Pyrazolo[5,1-*a*]isoindol-8-ones

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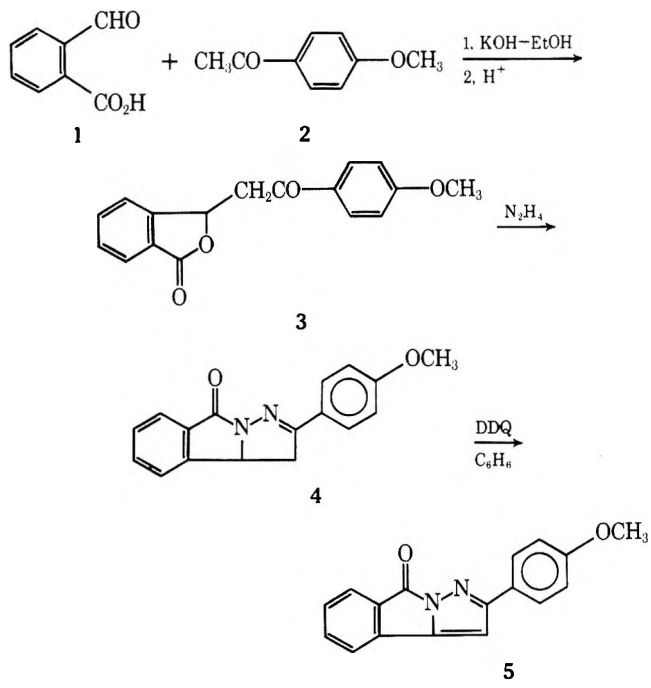
3-(4-Methoxyphenacyl)phthalide (**3**) arises from the base-catalyzed condensation of phthalaldehydic acid (**1**) with 4-methoxyacetophenone (**2**), and readily undergoes cyclization with hydrazine to form 2-(4-methoxyphenyl)-3,3a-dihydro-8*H*-pyrazolo[5,1-*a*]isoindol-8-one (**4**). Dehydrogenation of **4** produces 2-(4-methoxyphenyl)-8*H*-pyrazolo[5,1-*a*]isoindol-8-one (**5**). This synthetic sequence is completely general, and may be used to prepare numerous analogs of structures **3–5**.

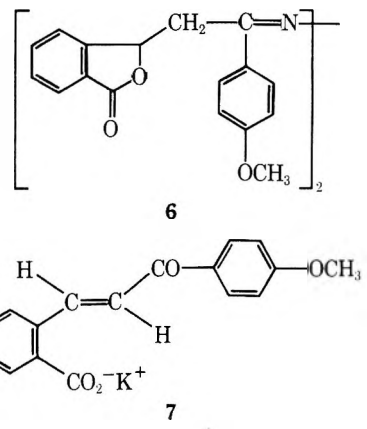
The condensation of 3,4-dimethoxyphthalaldehydic acid (opianic acid) with acetone and acetophenone under Claisen conditions to give 1:1 and 1:2 products was described in 1891 by Goldschmiedt,[1] elaborated by Hemmelmayr[2,3] shortly thereafter, and extended to phthalaldehydic acid (**1**) by Hamburger[4] in 1898. We have found their structural assignments of these reaction products as ketonic phthalide derivatives to be essentially correct,[5] and have investigated their further reaction products with hydrazine.[6,7] Hamburger[4] described the reaction products of 3-phenacylphthalide with hydroxylamine and phenylhydrazine, but his structural conclusions were uncertain, and the present work establishes the reaction course of carbonyl reagents with these interesting compounds.

Our exploratory work was done with the condensation product of **1** and 4-methoxyacetophenone (**2**) (Scheme I).

Scheme I



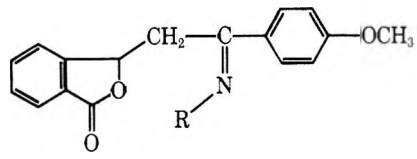
The product of this reaction, 3-(4-methoxyphenacyl)-phthalide (**3**), reacts normally at the ketonic carbonyl with hydroxylamine and semicarbazide, but undergoes a further cyclization with hydrazine to form pale yellow 2-(4-methoxyphenyl)-3,3a-dihydro-8*H*-pyrazolo[5,1-*a*]isoindol-8-one (**4**). Simple hydrazones of structure **3** have not been isolated, but small amounts of the azine **6** accompany **4**.



Dehydrogenation of **4** with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) gives 2-(4-methoxyphenyl)-8*H*-pyrazolo-[5,1-*a*]isoindol-8-one (**5**) as a bright yellow, crystalline solid. Our interest in structures **3–5** arises from their plant growth regulatory activity.[6–13] The synthetic procedures illustrated by the preparation of structures **3–5** are quite general, and some representative examples of their analogs (**8–10**) are listed in Table I.

Discussion

The initial condensation product of **1** and **2** in aqueous ethanolic KOH is the potassium salt **7**, which precipitates from the basic reaction mixture. The *trans*-chalcone structure is evident from its spectra [ν_{max} (Nujol) 1650, 1610, 1580 cm^{-1}; NMR (DMSO-d_6) two doublets (J = 16 Hz) at δ 8.70 and 7.57]; an intermediate ketol has not been seen in this reaction. In preparing the analogs **8** (Table I), the intermediate potassium salt does not always precipitate, but in all cases acidification precipitates the cyclized 3-phenacylphthalide derivative. The reaction of **3** with hydrazine or hydrazine salts in the presence of a tertiary base gives **4** as the major product; the yield of the minor product **6** may be enhanced by reducing the molar proportion of hydrazine used, but the ratio of **4**:**6** is always much larger than unity, indicating that cyclization is the strongly preferred pathway.[14] No simple hydrazone (**11**) of phthalide **3** has been isolated, but substitution of hydroxylamine for hydrazine gives the simple oxime (**12**), which was further characterized as its carbamate (**13**); similar substitution of semicarbazide for hydrazine gives the simple semicarbazone (**14**). Azine, oxime, and semicarbazone formation suggest that hydrazine also attacks first at the ketonic carbonyl, and the NH_2 group of the transient intermediate hydrazone **11** then attacks the lactone under the existing basic conditions to form **4**. This is supported by the observation that **3** does not react with hydrazine salts unless 1 equiv of tertiary base is present. Competition of a second molecule of **3** for the free NH_2 terminus of **11** (formation of **6**) is hindered both sterically and by the lower intrinsic reactivity of this moiety; the lactone ring is suitably placed for further nucleophilic attack, followed by ring opening, dehydration, and recyclization to **4**. No cyclic eight-membered intermediate has been isolated from this reaction, and this is not surprising in view of attempts to prepare analogous 1,4-diaza systems,[15,16] and the known propensity for intramolecular reactions to occur in eight-membered rings. Structure **4** and its analogs **9** are readily dehydrogenated to **5** and its analogs **10** in refluxing benzene with DDQ.



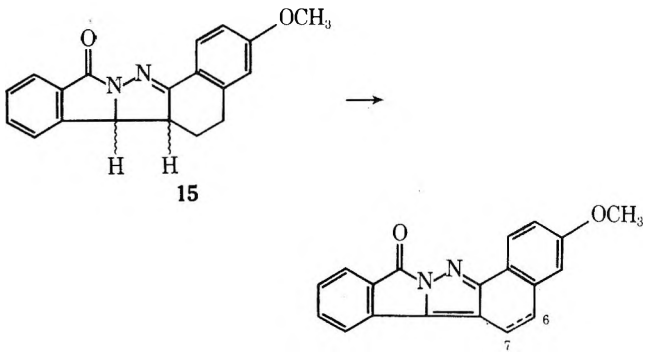
11, R = NH_2
12, R = OH
13, R = $OCONHCH_3$
14, R = $NHCONH_2$

The brief note published by Leclerc[17] concerning the preparation of the parent phenyl compound (**10**, entry 25, Table I) contains two serious errors in the spectral identification of this compound. The fused γ-lactam structure **5** is characterized by a weak band at 1780–1790 cm^{-1} and a strong band at 1760 cm^{-1} in the infrared, and by a pair of intense maxima at 346 nm (ϵ 12,100) and 331 (22,300) in the ultraviolet in an *unreactive solvent* such as THF. Corresponding values for **10** (R = C_6H_5) are λ_{max} (THF) 337 nm (ϵ 10,960) and 323 (10,880). Leclerc quotes ν_{max} 1790 and 1555 cm^{-1}, and λ_{max} (EtOH) 335 nm (ϵ 1480); the 1555-cm^{-1} value is an obvious misprint, but the low value of the extinction coefficient in the uv recorded by him is due to reaction with the solvent, a phenomenon which we shall discuss in a subsequent paper.

Two special examples which illustrate the ease of pyrazole formation are shown in the sequence **15–17** (Scheme II), in which the heterocyclic ring of **4** and **5** has been connected to the 2 substituent by a two-carbon bridge to restrict the rotation of the system. The mixture of geometric isomers (**15**) undergoes stepwise dehydrogenation to **16** and **17**. The use of 1 molar equiv of DDQ produces **16** exclusively; **16** can then be converted to **17** with a further 1 molar equiv of DDQ.

Spectra. The structures of **3–5** and their analogs are clearly assignable from their spectra. In the infrared, the phenacylphthalide **3** shows its lactone absorption at 1765 cm^{-1} and its ketone absorption at 1680 cm^{-1}; the fused γ-

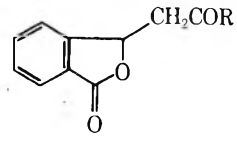
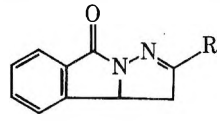
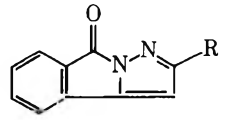
Scheme II



16, 6,7 single bond
17, 6,7 double bond

lactam carbonyl of **4** at 1700 cm^{-1} shifts to a weak band at 1780 cm^{-1} and a strong band at 1760 cm^{-1} on dehydrogenation to **5**. In the ultraviolet, colorless phthalide **3** has λ_{max} (CH_2Cl_2) 282 nm (ϵ 20,800) and 276 (20,200); pale yellow fused γ-lactam **4** has λ_{max} (CH_2Cl_2) 323 nm (ϵ 18,080), 277 (9080), and 268 (9150), while bright yellow **5** has λ_{max} (THF) 346 nm (ϵ 12,100), 331 (22,300), 285 (22,300), 260 (33,600), and 240 (32,000). In the NMR the $-CH_2CH-$ protons of **3** and **4** show a distinct ABX pattern; in **3** the tertiary proton (X) is centered at δ 6.13 ppm and the CH_2 protons (AB) at δ 3.75 ppm, while in **4** where the system is part of a five-membered ring, the X part is at δ 5.40 ppm, and the AB part is at δ 3.22 ppm. The coupling constants in the ABX pattern of **4**, obtained by decoupling its 100-MHz spectrum, are $J_{3a}J_{3\text{-trans}}$ = 10.64 Hz, $J_{3a}J_{3\text{-cis}}$ = 10.95 Hz, and $J_{3\text{-cis}3\text{-trans}}$ = −16.46 Hz. The pyrazole proton of **5** is

Table I
Synthesis of 8H-Pyrazolo[5,1-*a*]isoindol-8-ones[a]

Entry	R	Yield, %	Mp, °C	Recrystn solvent	Registry no.
	A. 3-Substituted Phthalides				
					
	8				
1	4-$CH_3OC_6H_4$ (3)	79	119.5–120	MeOH	
2	4-$C_2H_5OC_6H_4$	72.5	136.5–137.5	MeOH	55222-52-1
3	2,4-$(CH_3)_2C_6H_3$	68	112.5–113	EtOH	55222-53-2
4	2,4,6-$(CH_3)_3C_6H_2$	82	150–152	EtOH–$CHCl_3$	55222-54-3
5	3-$CH_3C_6H_4$	71	96–98	C_6H_6–C_6H_{12}	55222-55-4
6	4-$CF_3C_6H_4$	66	150–153	EtOH	55222-56-5
7	3-BrC_6H_4	73	124–127	CH_3CN	55222-57-6
8	3,4-$Cl_2C_6H_3$	98	184–186	CH_3CN	55222-58-7
9	4-FC_6H_4	62	130–133	C_6H_6	55222-59-8
10	$(CH_3)_3C$	8	72–73	MeOH	55222-60-1
	B. 2-Substituted 3,3a-dihydro-8*H*-pyrazolo[5,1-*a*]isoindol-8-ones				
					
	9				
11	4-$CH_3OC_6H_4$ (4)	88.5	177–178.5	MeOH	
12	4-$C_2H_5OC_6H_4$	58	157.8–159	MeOH	55222-61-2
13	2,4-$(CH_3)_2C_6H_3$	91	150.5–151.5	MeOH	55222-62-3
14	2,4,6-$(CH_3)_3C_6H_2$	38	129–131	MeOH	55222-63-4
15	3-$CH_3C_6H_4$	85	156–158	CH_3CN	55222-64-5
16	4-$CF_3C_6H_4$	82	239–241	CH_3CN	55222-65-6
17	3-BrC_6H_4	65	220–223	CH_3CN	55222-66-7
18	3,4-$Cl_2C_6H_3$	95	226–228	Dioxane	55222-67-8
19	4-FC_6H_4	75	171–173	MeOH	21138-14-7
20	$(CH_3)_3C$	7	118–119	C_6H_{12}	55222-68-9
	C. 2-Substituted 8*H*-pyrazolo[5,1-*a*]isoindol-8-ones				
					
	10				
21	4-$CH_3OC_6H_4$ (5)	83	186–187	Acetone	
22	4-$C_2H_5OC_6H_4$	70	171–172	Acetone	37564-19-5
23	2,4-$(CH_3)_2C_6H_3$	63	183–184	Acetone	37564-18-4
24	2,4,6-$(CH_3)_3C_6H_2$	20	153 dec	Acetone	55222-69-0
25	C_6H_5	29	146–147	Acetone	35564-20-8

[a] Satisfactory analyses (±0.3% for C, H) were reported for the compounds in part A of Table; analyses for C, H, N (±0.3%) were reported for compounds in parts B and C. Ed.

distinct from the benzenoid protons (δ 7.95–6.88 ppm) as a sharp singlet at δ 6.63 ppm. The spectra of analogs **8–10** follow the above patterns.

Experimental Section[18]

The general procedures described in detail for **3–5** were used to prepare the analogs listed in Table I.

3-(4-Methoxyphenacyl)phthalide (3). A solution of 85% KOH (66 g, 1.0 mol) in 50% EtOH (200 ml) was added dropwise to a vigorously stirred solution of phthalaldehydic acid (**1**, 75 g, 0.50 mol), 4-methoxyacetophenone (**2**, 75 g, 0.50 mol), and EtOH (300 ml) maintained at 25–30°. The mixture solidified after 75% of the KOH had been added, and it was necessary to add a further 600 ml of EtOH and continue the stirring for 30 min to complete the reaction. The potassium salt **7** was filtered, rinsed with EtOH, and air dried. This salt contained an indefinite amount of water and did not give satisfactory analysis, but its structure is clear from its spectra (see text). The crude salt **7** was dissolved in H_2O (500 ml), acidified with HCl, cooled, and filtered to give phthalide **3** (82 g). Concentration and acidification of the reaction mother liquors gave a further 29.8 g of **3**, total crude yield 111.8 g (0.396 mol, 79%), of material which was sufficiently pure for condensation with hydrazine. Recrystallization of a small sample (MeOH) gave pure 3-(4-methoxyphenacyl)phthalide as colorless crystals, mp 119.5–120°.

2-(4-Methoxyphenyl)-3,3a-dihydro-8*H*-pyrazolo[5,1-*a*]-isoindol-8-one (4). A stirred solution of phthalide **3** (14.0 g, 0.05 mol) in EtOH (400 ml) was heated to reflux and treated consecutively with a solution of hydrazine dihydrochloride (10.0 g, 0.10 mol) in H_2O (50 ml), and with triethylamine (20 g, 0.20 mol). The heating was continued for 2–3 hr, then the solution was cooled, acidified with HCl, concentrated to one-third its volume, diluted to turbidity with H_2O, and allowed to stand. The pale yellow, crystalline product **4** was filtered, yield 12.3 g (88.5%), mp 170–171°. Recrystallization (MeOH) gave 2-(4-methoxyphenyl)-3,3a-dihydro-8*H*-pyrazolo[5,1-*a*]isoindol-8-one, mp 177–178.5°. The use of hydrazine hydrate in place of the hydrochloride was equally satisfactory, either in the presence of Et_3N or with an extra 1 molar equiv of hydrazine hydrate.

3-(4-Methoxyphenacyl)phthalide azine (6) was obtained as a yellow, insoluble solid by filtering hot some of the reaction mixtures used to prepare **4**. Azine **6** has mp 185–185.5°; ν_{max} (Nujol) 1775, 1615, 1565 cm^{-1}; λ_{max} (CH_2Cl_2) 338 nm (ε 29,200), 282 (12,380), 275 (11,640); ^1H NMR ($CDCl_3$) δ 8.0–6.95 (m, 16 H, aromatic), 6.0 (X part, 2 H, tertiary protons), 3.75 (AB part, 4 H, CH_2), 3.95 ppm (s, 3 H, OCH_3). Anal. Calcd for $C_{34}H_{28}N_2O_6$: C, 72.84; H, 5.03; N, 5.00. Found: C, 72.90; H, 5.12; N, 4.98.

2-(4-Methoxyphenyl)-8*H*-pyrazolo[5,1-a]isoindol-8-one (5). A mixture of **4** (23.34 g, 0.084 mol), DDQ (9.95 g, 0.044 mol), and C_6H_6 (350 ml) was stirred at reflux for 2 hr and treated with another 9.95 g of DDQ, and the heating was continued for 3 hr longer. The insoluble dihydro-DDQ was filtered and rinsed with C_6H_6, and the filtrate was evaporated to leave an orange solid which was stirred at 25° for 1 hr with 1% KOH (500 ml) to remove residual quinone and by-products. The residue was rinsed with 5% $NaHCO_3$ and H_2O and air dried to a yellow powder which was recrystallized from acetone (1250 ml), yield 19.32 g (0.07 mol, 83%) of yellow needles of **5**, mp 180–181°. Further recrystallization raised the melting point to 186–187°. Anal. Calcd for $C_{17}H_{12}O_2N_2$: *m/e* 276.0899. Found: *m/e* 276.0878.

3-(4-Methoxyphenacyl)phthalide Oxime (12), Its Carbamate (13), and Semicarbazone (14). A mixture of **3** (2.82 g, 10 mmol), EtOH (170 ml), hydroxylamine hydrochloride (1.0 g, 14 mmol), and pyridine (2 ml) was stirred at reflux for 4 hr, then evaporated to dryness. The residue was extracted with H_2O and recrystallized from 90% MeOH (45 ml), yield 2.30 g (7.74 mmol, 77%) of oxime **12**, mp 116–117°. Anal. Calcd for $C_{17}H_{15}NO_4$: C, 68.67; H, 5.08; N, 4.71. Found: C, 68.53; H, 5.00; N, 4.62.

Treatment of oxime **12** (5.94 g, 20 mmol) with CH_3NCO (3 ml) in warm CH_3CN (200 ml) for 3 hr, followed by evaporation, gave a residue which was recrystallized from 60% MeOH (40 ml), yield 5.5 g (15.52 mmol, 78%) of carbamate **13**, mp 132–134°. Anal. Calcd for $C_{19}H_{18}N_2O_5$: C, 64.40; H, 5.12; N, 7.91. Found: C, 64.24; H, 5.23; N, 7.52.

Analogous treatment of **3** with semicarbazide hydrochloride gave semicarbazone **14** (24% yield), colorless crystals, mp 179–180° after recrystallization from *i*-PrOH. Anal. Calcd for $C_{18}H_{17}N_3O_4$: C, 63.71; H, 5.05; N, 12.38. Found: C, 63.39; H, 5.03; N, 12.65.

4-Methoxy-6,7,7a,13a-tetrahydronaphtho[2,3-*a*]-12*H*-pyrazolo[5,1-*a*]isoindol-8-one (15) was prepared in 33% yield by reaction of hydrazine with the condensation product of **1** and 6-methoxy-1-tetralone. It was recrystallized from CF_3CO_2H as a colorless solid: mp 256–259° dec; ν_{max} 1700 cm^{-1}; λ_{max} (CF_3CO_2H) 357 nm (ε 30,000), 298 (3950); ^1H NMR (CF_3CO_2H) δ 7.93–7.09 (m, 7 H, aromatic), 6.02 (d, J = 11 Hz) and 5.59 (d, J = 10 Hz) (2 H tertiary protons), 4.04 (s) and 3.97 (s) (3 H, OCH_3), 3.20–2.67 ppm (m, 4 H CH_2); the isomer ratio 3:2 was estimated from the OCH_3 peak integrals. Anal. Calcd for $C_{19}H_{16}N_2O_2$: C, 74.98; H, 5.30; N, 9.21. Found: C, 74.86; H, 5.36; N, 9.09.

4-Methoxy-6,7-dihydronaphtho[2,3-a]-12*H*-pyrazolo[5,1-*a*]-isoindol-12-one (16). A mixture of **15** (1.0 g, 3.29 mmol), C_6H_6 (50 ml), and DDQ (0.755 g, 3.29 mmol) was stirred at reflux for 6 hr and evaporated. The combined solids were washed with 0.5% KOH and with 5% $NaHCO_3$ to leave 0.96 g (3.18 mmol, 95%) of crude **14** as a yellow powder which was recrystallized from acetone (200 ml). Pure **15** has mp 239–242°; ν_{max} (KBr) 1790, 1740 cm^{-1}; λ_{max} (EtOH) 362 nm (ε 16,400), 348 (15,700), 288 (15,300), 268 (24,700), 258 (24,400), 241 (33,400); ^1H NMR (CF_3CO_2H) δ 7.90–7.20 (m, 7 H, aromatic), 4.05 (s, 3 H, OCH_3), 3.27 ppm (s, 4 H, CH_2). Anal. Calcd for $C_{19}H_{14}N_2O_2$: C, 75.48; H, 4.67; N, 9.27. Found: C, 75.35; H, 4.74; N, 9.26.

4-Methoxynaphtho[2,3-*a*]-12*H*-pyrazolo[5,1-a]isoindol-12-one (17). A. From 15. The above experiment was repeated using a 1:2 molar ratio of **15** to DDQ to give **17** as a red, crystalline solid (42% yield) after recrystallization from acetone. Pure **17** has mp 223–226°; ν_{max} (KBr) 1790, 1750 cm^{-1}; λ_{max} (EtOH) 395 nm (ε 5600), 365 (6250), 336 (4900), 311 (14,100), 298 (16,300), 254 (39,300). The only suitable NMR solvent, D_2SO_4, caused decomposition. Anal. Calcd for $C_{19}H_{12}N_2O_2$: C, 75.99; H, 4.03; N, 9.33. Found: C, 76.01; H, 4.26; N, 9.40.

B. From 16. Experiment A was repeated using a 1:1 molar ratio of **16** to DDQ to give **17** in 80% yield after recrystallization from acetone.

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Registry No.—**1**, 119-67-5; **2**, 100-06-1; **3**, 55222-45-2; **4**, 21138-13-6; **5**, 37564-17-3; **6**, 55222-46-3; **7**, 55222-47-4; **12**, 55254-61-0; **13**, 55222-48-5; **14**, 55222-49-6; *cis*-**15**, 55222-50-9; *trans*-**15**, 55222-51-0; **16**, 39785-30-3; **17**, 39785-31-4; hydrazine dihydrochloride, 5341-61-7; hydroxylamine hydrochloride, 5470-11-1; isocyanatomethane, 624-83-9; semicarbazide hydrochloride, 57-56-7; 6-methoxy-1-tetralone, 1078-19-9.

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Synthesis of Bicyclobutylidene, 1,3-Bis(trimethylene)propadiene, and 1,4-Bis(trimethylene)butatriene[1]

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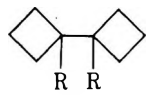
Two synthetic routes to bicyclobutylidene are described. Bicyclobutylidene can be readily epoxidized to 9-oxadispiro[3.0.3.1]nonane, and adds methylene to give dispiro[3.0.3.1]nonane and dibromocarbene to give the corresponding 9,9-dibromide. Reaction of the dibromide with methyllithium generated 1,3-bis(trimethylene)propadiene. This allene also reacted with dibromocarbene to give the mono- and bis adducts. Treatment of the monoadduct with methyllithium gave 1,4-bis(trimethylene)butatriene, and similar treatment of the bis adduct provided some evidence for the generation of 1,5-bis(trimethylene)pentatetraene.

Although bicyclobutyl (**1a**)[2] and 1,1′-bicyclobutyldiol (**1b**)[3] have been known for some time, bicyclobutylidene (**5**)

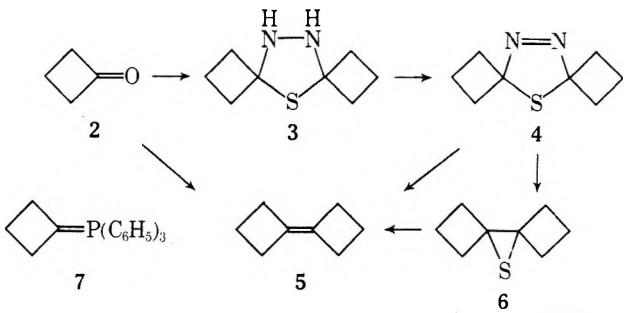


1a, R = H
b, R = OH

remained as one of the last simple ethylene derivatives which had not been prepared. The absence of a synthesis of **5** was probably due to the combination of the ease with which the cyclobutane ring rearranges,[4] together with the lack of a method of forming four-membered rings of comparable generality to that of carbene additions to olefins to give cyclopropanes.[5] We now report two synthetic routes to bicyclobutylidene, and describe some of its chemistry and its conversion into 1,3-bis(trimethylene)propadiene (**11**) and 1,4-bis(trimethylene)butatriene (**14**).[6]

The first synthetic route[1] to **5** utilized the olefin synthesis recently described by Barton[7] and Kellogg[8] and their respective coworkers. Reaction of cyclobutanone (**2**) with hydrazine hydrate and H_2S at −20° gave the thiadiazolidine **3**, mp 96–97°, in 82% yield. Oxidation of **3** with lead tetraacetate gave the thiadiazoline **4**, mp 72–73°, in 92% yield. Compound **4** was more stable than **3**, the latter compound decomposing with evolution of hydrogen sulfide. Reaction of **4** with triphenylphosphine gave bicyclobutylidene (**5**) as a colorless oil in 90% yield. The NMR spectrum had absorptions at τ 7.34–7.64 (allylic) and 7.88–8.28 (methylene) in the ratio 2:1, and the simple ir spectrum showed bands at 2930, 1425, 1035, and 915 cm^{-1}. The electronic spectra had its main maximum at 203 nm (see Figure 1).

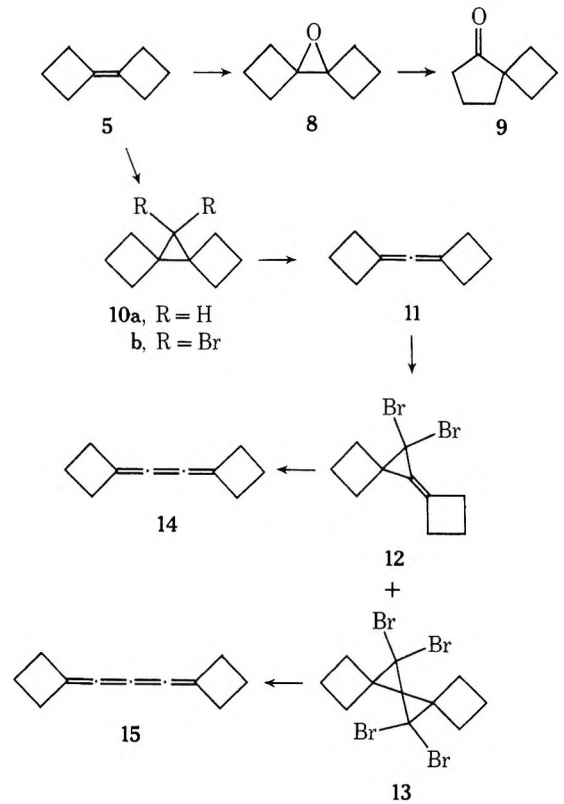
When **4** was heated in the absence of triphenylphosphine, **6**, mp 36–37°, was obtained in 98% yield. Reaction of **6** with triphenylphosphine at 85° again gave **5**.



The second route to **5** involved a Wittig reaction between the ylide **7** and cyclobutanone. Reaction of cyclobutyltriphenylphosphonium bromide with *n*-butyllithium generated the ylide **7**,[9] which on treatment with **2** gave **5** in 31% yield, identical in all observed respects with that obtained previously. The Wittig method appears to be the synthetic route of choice for the preparation of large amounts of **5** despite the somewhat lower yield.[10]

Compound **5** was oxidized by *m*-chloroperoxybenzoic acid to give the epoxide **8**, a colorless liquid, in 57% yield. When **8** was heated to 200° for 8 hr it was quantitatively rearranged to the known spiro[3.4]octan-5-one (**9**).[3]

Reaction of **5** with methylene iodide in the presence of a zinc–copper couple[11] gave **10a** as a colorless liquid in 35% yield. Similarly, reaction of **5** with bromoform and potassium *tert*-butoxide in pentane gave **10b**, mp 42–43°, in 84% yield. Treatment of **10b** with methyllithium gave 1,3-bis(trimethylene)propadiene (**11**) as a colorless liquid in 83% yield. The NMR spectrum ($CDCl_3$) showed a triplet at τ 6.9–7.6 and a multiplet at τ 7.8–8.45 in the ratio of 2:1.

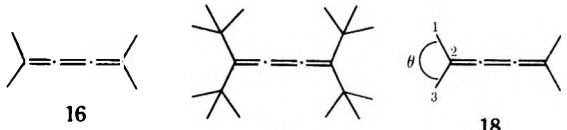


Reaction of **11** with 0.5 molar excess of bromoform and potassium *tert*-butoxide gave the dibromocyclopropane adduct **12** as a colorless liquid in 89% yield. Treatment of **12** with methyllithium at −10° gave 1,4-bis(trimethylene)butatriene (**14**). The cumulene **14** is relatively stable in solution at 0° and below, and it can be isolated as a crystalline compound. However, it rapidly forms an insoluble polymer in the latter state, probably by reaction with oxygen. The

NMR spectrum ($CDCl_3$, −50°) showed a triplet at τ 6.84–7.37 and a multiplet at τ 7.70–8.34, and the ir spectrum showed a weak cumulene band at 2230 cm^{-1}.

When **11** was treated with a five molar excess of bromoform and potassium *tert*-butoxide, a mixture of **12** and the bis(dibromocarbene) adduct **13** was obtained, from which **13** could be separated. Reaction of **13** with methyllithium at low temperature led to a very unstable material, solutions of which had an electronic spectrum consistent with the formation of 1,5-bis(trimethylene)pentatetraene (**15**), but this material could not be characterized.

The compounds **11**, **14**, and **15** show a progressive decrease in stability and a greater reactivity toward oxygen. The electronic spectra of **11** and **14**, together with that of bicyclobutyldiene (**5**), are shown in Figure 1. The virtual coincidence of the first absorption bands of **5** and **11** finds ample precedent in the literature for other pairs of substituted ethenes and allenes.[12] The allene **11** shows a maximum absorption at 199 nm, at a similar wavelength to that observed for tetramethylallene (195.5 nm),[13] while the cumulene **14** shows two absorption bands characteristic of a tetrasubstituted butatriene. However, in comparison to tetramethylbutatriene (**16**),[14] which shows a maximum at 230 nm, the short-wavelength band of **14** shows a bathochromic displacement to 248 nm. The extinction coefficient of the long-wavelength bands of **14**, **16**, and tetra-*tert*-butylbutatriene (**17**)[15] increase from 10,300 for **14**, through 17,000 for **16**, to 34,900 for **17**. This increase in extinction coefficient is probably associated with the change in the C^1–C^2–C^3 bond angle θ (see **18**). In the case of **11** the angle θ is the internal angle of the four-membered ring and consequently approximates to 90°, in **16** the angle is presumably 120°, and in **17** it is probably greater than 120°, owing to steric repulsion of the *tert*-butyl groups.



16 17 18

Compounds **5** and **11** are now readily available, and we are currently studying their elaboration to other new systems containing four-membered rings.

Experimental Section

NMR spectrum were obtained on either a Varian T-60 or HA-100 spectrometer and are recorded in τ units with Me_4Si as internal standard. Mass spectra were taken on either an AEI MS-12 or MS-9 spectrometer. Infrared spectra were recorded on a Unicam SP-200 spectrophotometer, only strong and medium bands being reported. Electronic spectra were recorded on a Unicam SP 800 recording spectrometer, except for the spectra of **5** and **11**, which were recorded on a Cary 17 spectrometer, flushed with nitrogen, by Dr. A. F. Drake, King's College London. Solvents were purified by standard methods.

Synthesis of 5-Thia-10,11-diazadispiro[3.1.3.2]undecane (3). Hydrogen sulfide was bubbled through vigorously stirred cyclobutanone (21 g, 0.30 mol) for 20 min, and then aqueous hydrazine (20 ml, 7.5 *M* solution, 0.15 mol) was added dropwise over 20 min with continued passage of H_2S. After completion of the addition of hydrazine, H_2S was passed for a further 20 min, a solid product having formed. The crude reaction mixture was then treated with dichloromethane (200 ml), the organic layer was separated, and the aqueous layer was reextracted with CH_2Cl_2 (2 × 50 ml). The combined organic layers were dried ($MgSO_4$) and the solvent was removed under reduced pressure to give **3**, 21 g (82%), white crystals [petroleum ether (bp 40–60°)]: mp 96–97°, MS *m/e* 170.0868 (calcd for $C_8H_{14}N_2S$, 170.0878), 170 (M^+, 1), 142 (M − N_2, 68), 136 (M − H_2S, 24), 114 (M − $C_2H_4N_2$, 46), 113 (16), 104 (100); NMR (CCl_4) τ 7.36–8.39 (m, 12 H), 6.47 (br s, 2 H); ir (KBr) 3200, 2910, 1425, 1245, 1170, 1140, 1075, 950, 860, and 820 cm^{-1}.

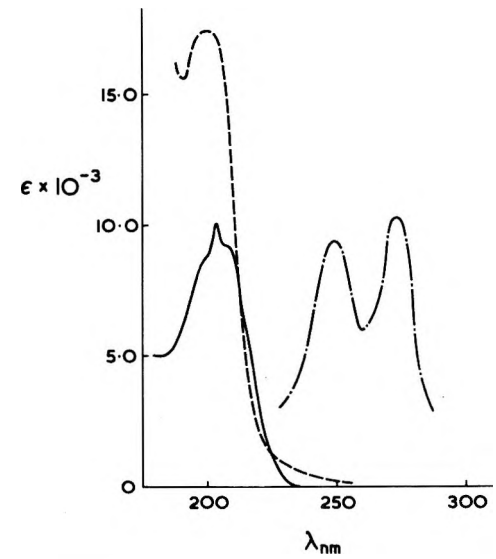


Figure 1. The electronic spectra of **5** (——) in isooctane, **11** (– – –) in isooctane, and **14** (– · –) in ether.

Oxidation of 3 to 5-Thia-10,11-diazadispiro[3.1.3.2]undecene-10 (4). Compound **3** (21 g, 0.12 mol) was dissolved in dry petroleum ether (800 ml), and the solution was then added slowly over 40 min to a vigorously stirred suspension of powdered lead tetraacetate (66 g, 0.15 mol) in dry petroleum ether (100 ml) at 0°. After completion of addition the reaction mixture was stirred for a further 40 min at 0°. The reaction mixture was filtered through Kieselguhr, and the precipitate was washed with petroleum ether (2 × 100 ml). The filtrates were combined, and the solvent was removed under reduced pressure to give **4**: 19.0 g (92%); white crystals (methanol); mp 72.5–73°; MS *m/e* 168 (M^+, 1), 140 (M − N_2, 48), 112 (M − $C_2H_4N_2$, 84), 111 (30), 97 (33), 91 (20), 80 (20), 79 (79), 77 (24), 61 (23), 58 (100); NMR (CCl_4) τ 7.04–7.76 (m, 10 H), 7.86–8.15 (m, 2 H); ir (KBr) 2950, 1565, 1425, 1250, 1090, 950, 880, and 800 cm^{-1}; λ_{max} (EtOH) 311 sh nm (ϵ 480), 292 (545), and 234 sh (370).

Anal. Calcd for $C_8H_{12}N_2S$: C, 57.11; H, 7.19; N, 16.65. Found: C, 56.67; H, 7.21; N, 17.06.

Conversion of 4 to Bicyclobutylidene (5). A mixture of powdered **4** (4.2 g, 0.025 mol) and dry triphenylphosphine (12.5 g, 0.075 mol) was heated at 85° for 1 hr under reduced pressure (100 mmHg). The voltatile liquid product was condensed from the evolved gases and purified by distillation over $MgSO_4$ to give bicyclobutylidene (**5**): 2.5 g (92%); bp ca 85° (100 mmHg); MS *m/e* 108 (M^+, 52), 93 (38), 80 (M − C_2H_4, 86), 79 (100); NMR, see discussion; ir, see discussion; λ_{max} (isooctane), see Figure 1.

Anal. Calcd for C_8H_{12}: C, 88.83; H, 11.18. Found: C, 88.86; H, 11.07.

Synthesis of Bicyclobutylidene (5) via the Wittig Reaction. Cyclobutyltriphenylphosphonium bromide (49.4 g, 0.12 mol) was suspended in dry tetrahydrofuran (600 ml). *n*-Butyllithium (55.5 ml, 2.2 *M* in *n*-hexane, 0.12 mol) was added to the stirred suspension and, after 15 min, all of the phosphonium bromide had dissolved. Cyclobutanone (7 g, 0.1 mol) in dry tetrahydrofuran (180 ml) was then added dropwise to the deep-red solution of the ylide over 45 min. The mixture was then stirred for a further 30 min at room temperature and then heated to 60–65° with stirring for 12 hr. The solution was allowed to cool, dichloromethane (240 ml) was added, and the mixture was extracted with water (5 × 100 ml). The organic layer was dried ($MgSO_4$) and distilled under reduced pressure, when triphenylphosphine oxide remained as the residue. Fractional distillation then gave **5**, 3.3 g (31%), identical in all observed respects with the previous sample.

Pyrolysis of 4. Synthesis of 9-Thiadispiro[3.0.3.1]nonane (6). Compound **4** (0.84 g, 5 mmol) was vigorously stirred and heated under dry nitrogen at 85° for 20 min. On cooling the melt solidified, and sublimation (40°, 50 mmHg) gave **6**: 0.68 g (98%); mp 36.5–37°; MS *m/e* 140 (M^+, 33), 112 (M − C_2H_4, 60), 111 (36), 107 (36), 97 (41), 91 (20), 84 (20), 80 (18), 79 (100); NMR (CCl_4) τ 7.30–8.28 (m); ir (film) 2950, 1440, 1390, 1235, 1195, 1075, 920, and 870 cm^{-1}; λ_{max} (EtOH) 263 nm (ϵ 37).

Oxidation of 5. Synthesis of 9-Oxadispiro[3.0.3.1]nonane (8). *m*-Chloroperoxybenzoic acid (2 g, 12 mmol) was dissolved in dry

ether (35 ml) and cooled to 0° under dry nitrogen and bicyclobutylidene (**5**) (1.08 g, 10 mmol) was added dropwise over 30 min. The solution was then stirred at 0° for a further 8 hr and the reaction mixture was filtered through Kieselguhr. The precipitate was washed with dry ether (2 × 10 ml), and the combined filtrates were washed with aqueous sodium hydroxide (2 × 20 ml, 0.1 *M* solution), water made alkaline with ammonia (20 ml), and basic aqueous ferrous sulfate (~0.1 *M* solution) until no further color change occurred in the aqueous layer. After a final wash with water made basic with ammonia, the organic solution was dried ($MgSO_4$) and the solvent was removed under reduced pressure to a volume of ca. 2 ml. Preparative TCL on alumina, eluting with petroleum ether–ether (95:5), gave **8**, 0.71 g (57%), as a colorless liquid: NMR (CCl_4) τ 7.47–8.44; ir (film) 2930, 1505, 1430, 1240, 1125, 1100, 1050, 910, and 820 cm^{-1}.

Anal. Calcd for $C_8H_{12}O$: C, 77.37; H, 9.74. Found: C, 77.67; H, 9.78.

Thermolysis of 8 to 9. Compound **8** (0.062 g, 0.5 mmol) was degassed, sealed in vacuo, and heated at 200° for 8 hr. Separation by TLC on alumina gave **9** (0.060 g), the structure being confirmed by the mass spectrum and comparison of the ir spectrum with that of an authentic sample.

Reaction of 5 with Methylene. Synthesis of Dispiro[3.0.3.1]nonane (10a). A suspension of zinc–copper couple, prepared from zinc dust (3.5 g, 0.06 g-atom) and cupric acetate (0.05 g), in ether (10 ml), was stirred and heated to reflux, and a mixture of **5** (1.08 g, 10 mmol) and dry, redistilled diiodomethane (6.70 g, 30 mmol) was added dropwise. Heating was continued for a further 24 hr, and the mixture was then filtered through Kieselguhr and the filtrate was concentrated under reduced pressure to give an oil. Distillation under reduced pressure (20°, 1 × 10^{-4} mmHg) followed by preparative GLC (6 ft × 0.25 in., Apiezon, 120°, He 40 psi) gave **10a**, 0.43 g (35%), as a colorless liquid: MS *m/e* 122 (M^+, 20), 121 (6), 119 (15), 117 (15), 107 (9), 95 (12), 94 ($M - C_2H_4$, 100); NMR (CCl_4) τ 7.79–8.27 (m, 12 H), 9.72 (s, 2 H); ir (film) 2950, 1435, 1110, 1005, and 920 cm^{-1}.

Anal. Calcd for C_9H_{14}: C, 88.45; H, 11.55. Found: C, 88.13; H, 11.43.

Reaction of 5 with Dibromocarbene. Synthesis of 9,9-Dibromodispiro[3.0.3.1]nonane (10b). A mixture of 5 (1.08 g, 10 mmol), potassium *tert*-butoxide (4.48 g, 40 mmol), and petroleum ether (150 ml) was stirred at 0° under dry nitrogen. Bromoform (3.86 g, 15 mmol) in petroleum ether (5 ml) was added dropwise over 35 min. The mixture was then allowed to warm to room temperature and was stirred for a further 12 hr. The insoluble material was then removed by filtration, and the precipitate was washed with petroleum ether. The solvent was then removed from the combined organic layers under reduced pressure at 0°, to give a brown, crystalline product (2.6 g). Chromatography on silica gel, eluting with petroleum ether, gave **10b:** 2.33 g (84%); mp 42–47°; MS *m/e* 280; NMR (CCl_4) τ 7.7–8.3 (m); ir (KBr) 2920, 1430, 1240, 1090, 810, and 750 cm^{-1}.

Anal. Calcd for $C_9H_{12}Br_2$: C, 38.60; H, 4.32; Br, 57.08. Found: C, 38.24; H, 4.35; Br, 56.73.

Reaction of 10b with Methyllithium. Synthesis of 1,3-Bis(trimethylene)propadiene (11). The dibromide **10b** (560 mg, 2.0 mmol) was dissolved in dry ether (30 ml), stirred, and cooled to −70° under dry N_2. Methyllithium (11 ml, 2.3 *M* in ether, 25 mmol) was added in one portion, and the reaction mixture was then allowed to warm to −10° and stirred for 1 hr. Degassed water (20 ml) was added, the ethereal layer was separated, and the aqueous layer was extracted with ether (50 ml). The combined organic layers were extracted with degassed water (2 × 20 ml) and dried ($MgSO_4$). Evaporation of the solvent gave a pale yellow liquid, which was purified by bulb-to-bulb distillation to give the allene **11** (200 mg, 83%) as a colorless liquid: MS *m/e* 120; NMR, see discussion; ir (liquid film) 2950, 1420, 1230, 1050, and 880 cm^{-1}; λ_{max}, see discussion.

Anal. Calcd for C_9H_{12}: C, 89.94; H, 10.06. Found: C, 89.55; H, 9.95.

Reaction of 11 with Dibromocarbene. The allene **11** (110 mg, 0.9 mmol) and potassium *tert*-butoxide (370 mg, 3.3 mmol) were added to petroleum ether (bp <40°, 15 ml) and the suspension was stirred and cooled at 0° under N_2. Bromoform (370 mg, 1.5 mmol) in petroleum ether (3 ml) was then added dropwise over 30 min with continuous stirring, the mixture was allowed to warm to room temperature, and stirring was continued for a further 18 hr. The insoluble material was removed by filtration, the precipitate was washed with petroleum ether (10 ml), and the solvent was then removed from the combined filtrates by evaporation to give **12** as an oil (240 mg, 89%): MS *m/e* 292; NMR ($CDCl_3$) τ 6.76–7.18 (q, 4 H), 7.22–8.20 (m, 8 H); ir (liquid film) 2930, 1760, 1414, 1406, 1106, 1080, 1038, 958, 804, 705, and 720 cm^{-1}.

Anal. Calcd for $C_{10}H_{12}Br_2$: C, 41.12; H, 4.14; Br, 54.73. Found: C, 40.81; H, 4.03; Br, 55.07.

Reaction of the allene **11** (100 mg, 0.83 mmol) with a large excess of potassium *tert*-butoxide (1.5 g, 13 mmol) and bromoform (1.0 g, 4 mmol) under similar conditions gave a mixture of **12** and 10,10,11,11-tetrabromotrispiro[3.0.0.3.1.1]undecane (**13**), which was separated by distillation. Compound **13** (120 mg, 21%) was a colorless liquid: MS *m/e* 463.7633 (calcd for $C_{11}H_{12}Br_4$, 463.7635); NMR ($CDCl_3$) τ 7.66–8.12 (m, 2 H), 8.16–9.12 (m, 10 H); ir (liquid film) 2930, 1460, 1380, 1125, 1090, 1050, 1000, 980, 920, 870, 830, 775, 738, and 650 cm^{-1}. Compound **12** (60 mg, 33%).

Reaction of 12 with Methyllithium. Synthesis of 1,4-Bis(trimethylene)butatriene (14). Compound **12** (160 mg, 0.5 mmol) was dissolved in dry ether (20 ml) and the solution was stirred and cooled to −70° under N_2. Methyllithium (2 ml, 2.3 *M* in ether, 4.6 mmol) was added and the reaction mixture was allowed to warm to −10° and stirred for 1 hr. Degassed water (5 ml) was added, and the ethereal layer was separated, washed with degassed water (5 ml), and dried ($MgSO_4$). Evaporation of the solvent gave the cumulene **14** (50 mg, 69%) as a white solid which decomposed on attempted melting point determination: MS *m/e* 132.0939 (calcd for $C_{10}H_{12}$, 132.0942); NMR, see discussion; ir (KBr) 2930, 2230, 1700, 1670, 1463, 1420, 1290, 1240, 1118, 945, and 898 cm^{-1}; λ_{max} (Et_2O) 248 nm (ϵ 9400), 273 (10,300).

Reaction of 13 with Methyllithium. Compound **13** (20 mg, 0.04 mmol) was treated with methyllithium (0.2 ml, 2.3 *M* in ether, 0.46 mmol) under the same conditions as described for the previous experiment. The solutions were washed rapidly with cold, degassed water, and the ethereal solution was dried at −78°. Examination of the electronic spectrum of the dried ethereal solution showed two absorption maxima at 248.5 and 272 nm, with a possible third, much smaller maximum at ca. 300 nm. Concentration of the solution led to rapid decomposition of the product.

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Registry No.—**2**, 1191-95-3; **3**, 37677-05-7; **4**, 37676-86-1; **5**, 6708-14-1; **6**, 37677-08-0; **8**, 37677-06-8; **9**, 10468-36-7; **10a**, 37677-07-9; **10b**, 55319-56-7; **11**, 55319-57-8; **12**, 55319-58-9; **13**, 55319-59-0; **14**, 55319-60-3; methylene, 2465-56-7; dibromocarbene, 74-95-3; methyllithium, 917-54-4; bromoform, 75-25-2.

References and Notes

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Transition-State Structure and Reactivity in the Acid–Base-Catalyzed Hydrolysis of a Model Intermediate for Corn-Plant Herbicide Resistance[1]

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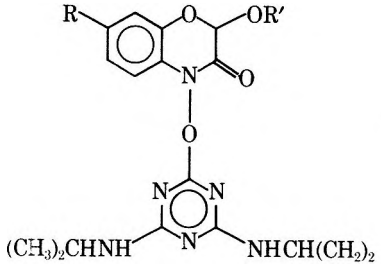
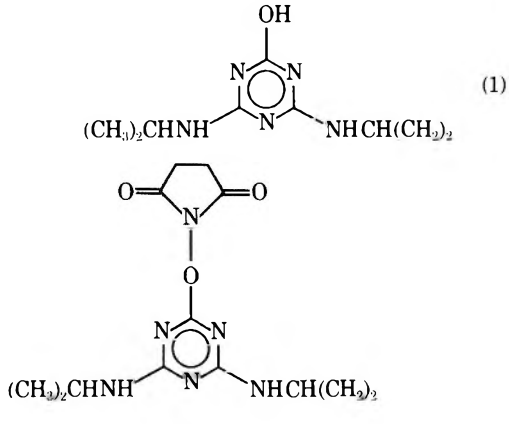
The intermediate formed by nucleophilic displacement of chloride from the herbicide Cyprazine (2-chloro-4-isopropylamino-6-cyclopropylamino-*s*-triazine) by *N*-hydroxysuccinimide undergoes hydrolysis with a complex pH dependence. The data are consistent with reactant, present in protonated, neutral, and anionic forms, undergoing addition of water to the aromatic ring to generate an intermediate compound which decomposes in acid-catalyzed, uncatalyzed, and base-catalyzed processes. Transition-state acidities and the absolute and relative activation parameters suggest activated complex structures which are highly aromatic. This is in contrast to the conventional expectation that these species should resemble the unstable intermediate. This apparent violation of Hammond's postulate may signal the intervention of kinetically significant solvent-reorganization processes.

The herbicide Cyprazine (2-chloro-4-isopropylamino-6-cyclopropylamino-*s*-triazine) is detoxified by the corn plant through a nonenzymatic nucleophilic displacement of chloride ion by a naturally present benzoxazinone hydroxamic acid glucoside to form compound 1H. This compound is then hydrolyzed to a water-soluble hydroxytriazine (eq 1) which is excreted.[4] We showed previously[4] that formation of the model compound 2H from Cyprazine and *N*-hydroxysuccinimide involved an extremely reactant-like transition state with catalytic proton bridging between substrate and nucleophile moieties. It was also demonstrated that the mechanistic principles uncovered could account quantitatively for observations on in vivo detoxification by corn plants.



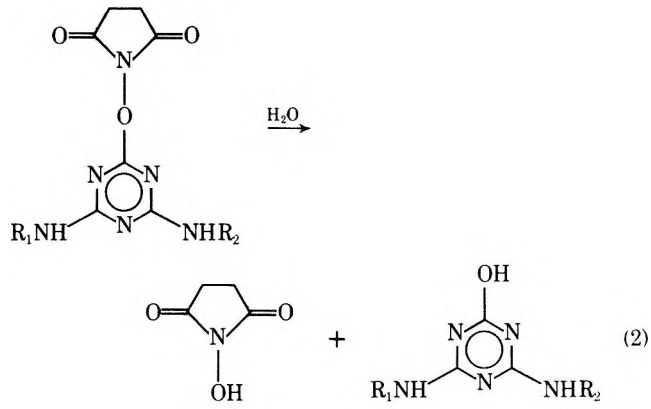
1H



(1)

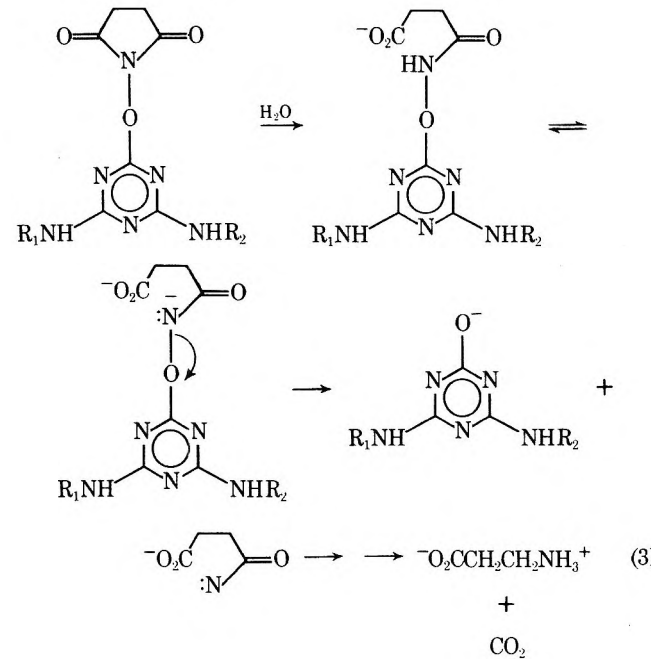
2H

We now turn our attention to the conversion of 2H to the hydroxytriazine through the agency of water, acids, and bases. 2H is a very highly functionalized molecule and it is not difficult to generate mechanisms for the hydrolysis reaction. Perhaps the simplest and most attractive from the viewpoint of biological economy is nucleophilic displacement by water or water-derived species (eq 2), which would regenerate the intact resistance factor in vivo. Another important possibility, however, is offered by the opening of the imide ring and a subsequent Lossen rearrangement (eq 3). This route would mean loss of the resistance factor in the course of herbicide destruction and would indicate that heavy application of herbicide might override the natural resistance of the corn plant.



3 4

(2)



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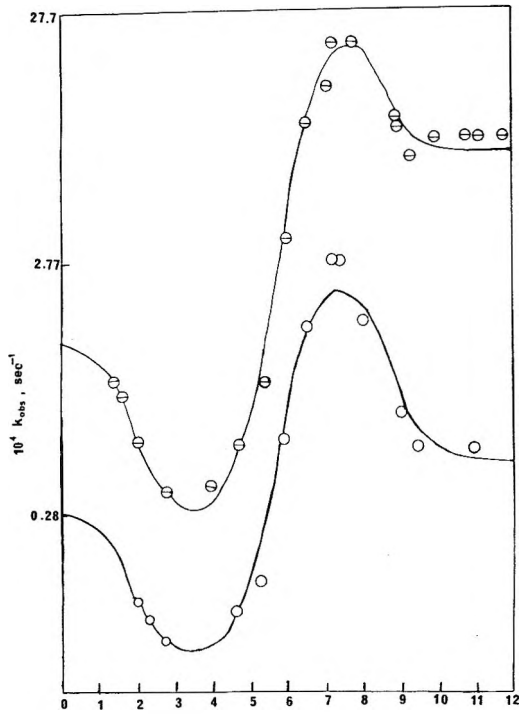


Figure 1. Dependence of the observed rate constant for hydrolysis of 2H on the pH of the solution at 70° (upper curve) and 50° (lower curve). Data are given in Table I.

This paper reports a characterization of the mechanistic routes from 2H to the hydroxytriazine and a discussion of their significance for transition-state structure in this reaction class.

Results

Reaction Products. Analysis of the reaction products as described in the Experimental Section showed only the hydroxytriazine 4 and *N*-hydroxysuccinimide (3) to be present at pH's of 2.50, 7.00, and 11.00. This excludes the mechanism of eq 3 and supports that of eq 2.

Kinetics. Table I shows first-order rate constants for the hydrolysis of 2H at various pH's at temperatures of 70 and 50°. These rate constants can be described by eq 4, the parameters of which will be discussed below. The calculated rate constants given in Table I are those from eq 4 with the parameters exhibited in Table II; graphical comparisons of the experimental and calculated pH dependences are presented in Figure 1. Although the curve fitting is unsophisticated, it produces data of sufficient reliability for the solution of the problems considered in this paper. Table II also contains the values of the enthalpies and entropies of activation calculated from the Eyring equation.[5]

$$k_{obsd} = \frac{k_1[H^+] + k_2K_a}{K_a + [H^+]} + \frac{k_ak_eK_w[H^+]}{(K_a' + [H^+])(k_a[H^+] + k_ek_w} + \frac{k_bK_a'}{K_a' + [H^+]} \quad (4)$$

Acidity of 2H. Spectrophotometric titration of 2H at 220 nm yielded a pK_a of 8.4 ± 0.1, presumably for loss of a proton from a side-chain NH function. This is in satisfactory agreement with pK_a' = 8.5, found from fitting eq 4 to the data of Table I.

Discussion

The mechanism of Scheme I is a reasonable manifold of processes and is consistent with eq 4 under the assumptions given below. Figure 2 shows a diagrammatic version

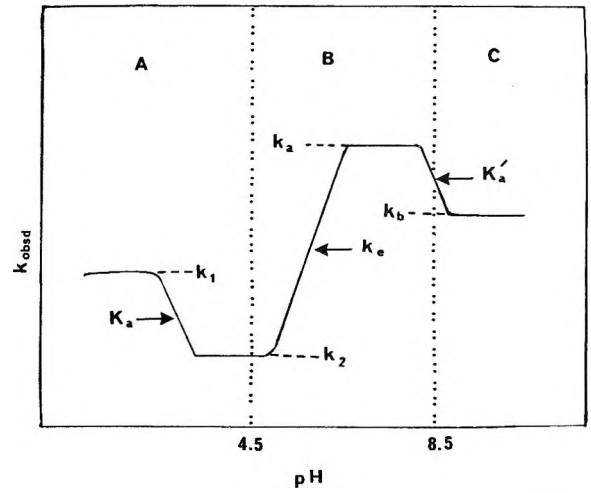
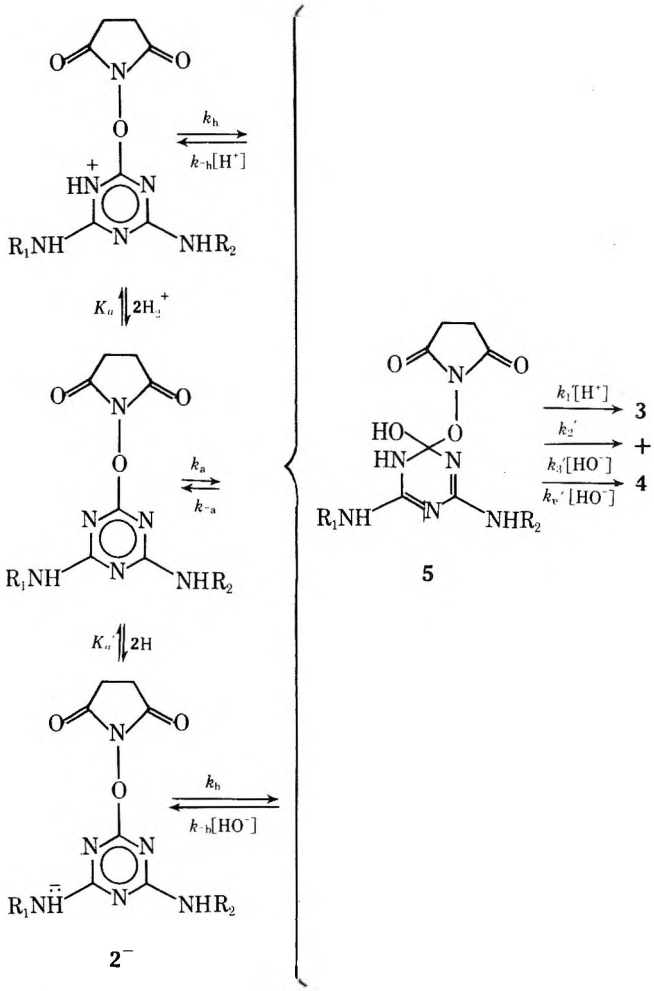


Figure 2. Schematic division of the pH dependence of Figure 1 into region A (below pH 4.5), region B (pH 4.5-8.5), and region C (above pH 8.5). Rate and equilibrium constants are those of eq 4.

of the pH–rate profiles of Figure 1, illustrating that they are divisible into three distinct regions, labeled A, B, and C. We consider these in turn.

Scheme I



Region A. Only $2H_2^+$ and 2H are present as reactants, interconnected by pK_a = 1.5. Both generate 5 in rapid, reversible processes (k_h and k_a). The slow decomposition of 5 by the k_1' and k_2' routes is then rate limiting. When reactant is primarily $2H_2^+$, only the k_1' decomposition path is important; when reactant is primarily 2H, only the k_2' path is observed. Then

Table I
First-Order Rate Constants for Hydrolysis of 3×10^{-4} *M* 2H in Water as a Function of pH at 70.00 ± 0.05° (μ = 0.50 *M*)[a]

$10^5 k_{obsd}$, sec^{-1} (pH) 70°	$10^5 k^b_{calcd}$, sec^{-1} 70°	$10^5 k_{obsd}$, sec^{-1} (pH) 50°	$10^5 k^b_{calcd}$, sec^{-1} 50°
9.77 (1.38)	9.75	1.31 (2.12)	1.33
8.44 (1.60)	8.31	1.08 (2.41)	1.10
5.50 (2.07)	5.55	0.92 (2.82)	0.94
3.50 (2.74)	3.50	1.18 (4.64)	1.10
3.72 (3.94)	3.25	1.53 (5.29)	2.15
5.42 (4.70)	4.94	5.55 (6.00)	6.44
9.56 (5.38)	12.8	16.2 (6.60)	14.4
35.2 (6.01)	39.4	29.7 (7.25)	20.9
99.7 (6.60)	102	29.2 (7.51)	21.7
140 (7.13)	167	17.0 (8.12)	19.1
212 (7.30)	181	6.97 (9.10)	8.86
208 (7.85)	195	5.19 (9.48)	6.67
103 (8.98)	114	4.97 (11.0)	4.75
96.9 (8.99)	114		
72.5 (9.35)	95.0		
83.6 (10.0)	80.0		
86.9 (10.8)	76.1		
86.9 (11.1)	76.1		
88.6 (11.8)	76.1		

[a] Ionic strength maintained by addition of KCl. pH's are correct at indicated temperatures and were maintained by acetate, phosphate, Tris, and carbonate buffers or adjusted by addition of hydrochloric acid or sodium hydroxide. Rate constants are reproducible to within ±5%.

$$k^A_{obsd} = \frac{[H^+]}{K_a + [H^+]} \frac{k_h}{k_{-h}} k_1' + \frac{K_a}{K_a + [H^+]} \frac{k_a}{k_{-a}} k_2' \quad (5)$$

Defining $k_h k_1'/k_{-h} = k_1$ and $k_a k_2'/k_{-a} = k_2$, we have eq 6. Note that this is the first term of eq 4.

$$k^A_{obsd} = \frac{k_1[H^+] + k_2 K_a}{K_a + [H^+]} \quad (6)$$

Region B. Only 2H is present through most of the region but begins to ionize to 2^- at higher pH. The k_e' route of elimination dominates all others and becomes so fast at about pH 7 that the rate-determining step changes to the k_a step. Including the correction for ionization of 2H, we have

$$k^B_{obsd} = \frac{[H^+] k_a k_e' [HO^-]}{(K_a' + [H^+])(k_{-a} + k_e'[HO^-])} \quad (7)$$

Multiplying numerator and denominator by k_a/k_{-a}, defining $k_a k_e'/k_{-a} = k_e$, and converting from hydroxide to hydrogen-ion concentrations yields eq 8, which is the second term of eq 4.

$$k^B_{obsd} = \frac{k_a k_e K_w [H^+]}{(K_a' + [H^+])(k_a[H^+] + k_e K_w)} \quad (8)$$

Region C. The conversion of 2H to 2^-, by the process of $pK_a' = 8.5$, is now completed and the rate finally levels off at high pH as water attack on 2^- becomes dominant. Thus

$$k^C_{obsd} = \frac{K_a' k_h}{K_a' + [H^+]} \quad (9)$$

Equation 9 is the third term of eq 4.

The mechanistic recapitulation is thus as follows. In region A, at pH < ~2, $2H_2^+$ rapidly and reversibly is converted to **5**, which then expels *N*-hydroxysuccinimide with acid catalysis. Since reactants and transition state are both uni-

Table II
Rate Constants in the Hydrolysis of 2H at 70.00 ± 0.05° and 50.00 ± 0.05° and Values of the Corresponding Activation Parameters

Constant,[a,b] dimensions	70°	50°	$\Delta H^\ddagger$, kcal/mol	$\Delta S^\ddagger$, eu
$10^4 k_1$, sec^{-1}	1.42	0.31	16 ± 1	−30 ± 3
$10^5 k_2$, sec^{-1}	2.78	0.78	14 ± 1	−40 ± 3
$10^3 k_a$, sec^{-1}	2.36	0.25	24 ± 1	0 ± 3
$10^4 k_b$, sec^{-1}	7.22	0.36	32 ± 1	+20 ± 3
$10^{-3} k_e$, M^{-1} sec^{-1}	2.71	1.47	6 ± 1	−25 ± 3

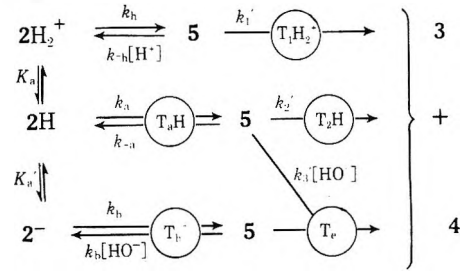
[a] Although errors in individual rate constants were not calculated, the root mean square deviation from the curves shown in Figure 1 is about 15% of the root mean square data point. [b] Equilibrium constants used with these rate constants to fit eq 4 were pK_a = 1.5 (70 and 50°), pK_a' = 8.5 (70 and 50°), and pK_w = 12.8 (70°), 13.3 (50°) ("Handbook of Chemistry and Physics", 54th ed, R. C. Weast, Ed., Chemical Rubber Publishing Co., Cleveland, Ohio, 1973, p D-131; the value for 70° was extrapolated).

positive, the rate is pH independent. As the pH is decreased, $2H_2^+$ goes over to 2H, which is also rapidly and reversibly converted to **5**. At the same time the acid-catalyzed route of elimination gives way to an uncatalyzed pathway. Now both reactants and transition state are electrically neutral and again the rate becomes pH independent (pH 3–4).

Beyond pH 4 the base-catalyzed decomposition of **5** comes into play and the rate rises with pH. Near pH 7, the decomposition rate surpasses the velocity of formation of **5** from 2H and the latter becomes rate determining. Again the rate loses its pH dependence. However, shortly beyond pH 8, the conversion of 2H to 2^- sets in and the rate begins to drop. This continues to around pH 9–10 when the reaction of water with 2^- to form **5** (which rapidly decomposes) becomes observable.

Accessibility of Transition States. Scheme II shows how we are able to study the properties of five different

Scheme II



transition states in this system. In pH region A, we can measure the rate constants k_1 and k_2, which contain information about the transition states $T_1H_2^+$, for acid-catalyzed breakdown of intermediate **5** to products, and T_2H, for uncatalyzed breakdown (eq 10 and 11). In pH region B,

$$H_2O + 2H_2^+ \xrightarrow{k_1} T_1H_2^+ \quad (10)$$

$$H_2O + 2H \xrightarrow{k_2} T_2H \quad (11)$$

we obtain values for k_e and k_a, illuminating transition states T_e^- for base-catalyzed breakdown of **5** and T_aH for addition of water to 2H to form **5**, respectively (eq 12 and

$$HO^- + 2H \xrightarrow{k_e} T_e^- \quad (12)$$

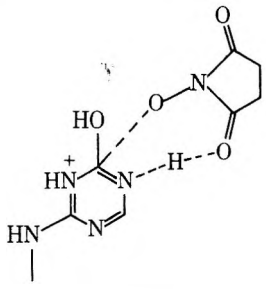
$$H_2O + 2H \xrightarrow{k_a} T_aH \quad (13)$$

13). Finally, in pH region C, k_b is measured allowing investigation of transition state T_b^- for addition of water to 2^- (eq 14).

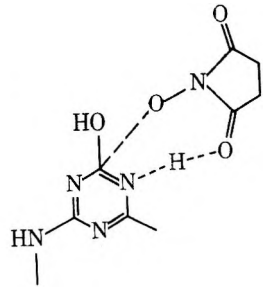
$$H_2O + 2^- \xrightarrow{k_b} T_b \qquad (14)$$

It should be kept in mind that the free energy of activation is a state function, so that the rate constants represent *overall* transformations from initial state to transition state and do not contain information about the *route* followed by reacting species between initial and transition states. Thus, for example, any number of rapid proton transfers or heavy-atom reorganizations may in principle intervene between the reactant structures on the left-hand sides and the transition-state structures on the right-hand sides of eq 10–14. We shall resist the temptation, at least initially, to speculate about the detailed routes of transition-state generation and concentrate on transition-state *structures* only.

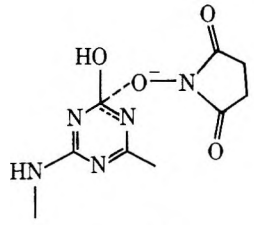
Transition-State Structural Proposals. We suggest that the structures of the five transition states investigated in this study are those shown in **6**–**10**. These structures are supported by (a) the transition-state acidities;[6] (b) the absolute values of the entropies of activation; and (c) the relative values of the enthalpies and entropies of activation. The arguments are given below; they have in common that fairly gross effects are involved so that precise rate-constant values are not needed.



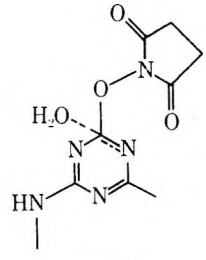
6($T_1H_2^+$)



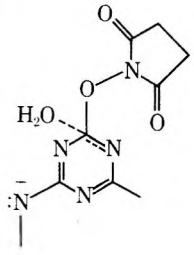
7(T_2H)



8(T_e^-)



9(T_aH)



10(T_b^-)

The feature possessed alike by all of these transition-state structures is that they do *not* resemble the intermediate adduct **5**. Rather the transition states between **5** and products (**6**, **7**, and 8) strongly resemble the products in having a nearly intact aromatic ring structure, with the bond to the leaving group nearly broken. Likewise, the transition states between reactants and **5** (**9** and **10**) closely favor the reactants, with nearly intact aromatic rings and entering-group bonds very weak. This runs counter to conventional thought about reactions involving unstable intermediates, where the Hammond postulate is usually taken to imply that transition states leading to and from such transient, unstable species as **5** should resemble it closely.[7]

Transition states $T_1H_2^+$ and T_2H are also postulated to contain the catalytic proton bridge between ring-nitrogen and leaving-group carbonyl which was found for the attack of *N*-hydroxysuccinimide on a chlorotriazine substrate.[4] This is reasonable since the steps in which these transition states are observed in this system are models for the microscopic reverse of nucleophilic attack on the chlorotriazine. Furthermore, the bridge is supported by the experimental observations in this case.

We now proceed to present the lines of evidence favoring structures **6**–**10**. First, we discuss transition-state acidities; second, the entropies of activation; and third, the relative activation parameters.

Transition-State Acidities. Because $\Delta G^\ddagger$ is a state function, we can define free energies of interconversion among different activated complexes (whether or not such interconversions occur under actual conditions). Kurz has used this idea to good avail.[6] For our present purpose, we use the thermodynamic cycles of eq 15–17, with data for 50°.

$$\begin{array}{ccc} 2H_2^+ & \xrightarrow{k_1 = 10^{-4.5}} & T_1H_2^+ \\ \Big\downarrow K_a = 10^{-1.5} & & \Big\downarrow K_{12}^* \\ 2H + H^+ & \xrightarrow[k_2 = 10^{-5.1}]{} & T_2H + H^+ \end{array} \qquad (15)$$

$$\begin{array}{ccc} 2H & \xrightarrow{k_a = 10^{-3.6}} & T_aH \\ \Big\downarrow K_{a'} = 10^{-8.5} & & \Big\downarrow K_{ab}^* \\ 2^- + H^+ & \xrightarrow[k_b = 10^{-4.4}]{} & T_b^- + H^+ \end{array} \qquad (16)$$

$$\begin{array}{ccc} HO^- + H^+ + 2H & \xrightarrow{k_2 = 10^{-5.1}} & T_2H + H^+ + HO^- \\ \Big\downarrow k_e = 10^{3.2} & & \Big\downarrow K = 10^{13.3} \\ H^+ + T_e^- & \xrightarrow[K_{2e}^*]{} & T_2H + H_2O \end{array} \qquad (17)$$

The cycle of eq 15 allows us to calculate K_{12}^*, the acidity constant for conversion of $T_1H_2^+$ to $T_2H + H^+$. If $T_1H_2^+$ closely resembles $2H_2^+$ and T_2H closely resembles 2H in having intact aromatic rings (the change of OH for the leaving group should have little effect), as suggested in structures **6** and **7**, then K_{12}^* should be nearly equal to K_a^*, the acidity constant for conversion of $2H_2^+$ to $2H + H^+$. On the other hand, if $T_1H_2^+$ resembled the protonated form of **5** and T_2H were structurally similar to **5** itself, then K_{12}^* should be near the ionization constant for the ring NH of **5**. This pK is probably[4] about 12. From eq 15, we find $pK_{12}^* = 1.5 + 5.1 - 4.5 = 2.9$. This value is far closer to 1.5 than to 12 and strongly supports the structural hypotheses of **6** and **7**.

Correspondingly, the value of K_{ab}^* from the cycle of eq

16 tests the postulate that T_aH and T_b^- structurally approximate 2H and 2^-, respectively, as advanced in structures **9** and **10**. pK_a' for ionization of 2H to 2^- is 8.5, while pK_{ab}^* is 9.3. These values are quite close, and pK_{ab}^* supports structures **9** and **10**. If the aromatic structure had been lost in T_aH and T_b, as it would have been had they resembled **5**, then pK_{ab}^* should have been much larger.

Finally, the cycle of eq 17 yields K_{2e}^* for ionization of T_2H to T_e^-. This provides information on the catalytic bridging proton in T_2H and $T_1H_2^+$, which is the proton released in this ionization. As we see from eq 17, $pK_{2e}^* = 5.0$. Now if this proton had been simply attached to the ring nitrogen and not in a bridging situation, we would have expected a pK a bit higher than that of $2H_2^+$ (1.5), perhaps about 2.9 as found for $T_1H_2^+$ above. Instead, the much lower acidity found shows that the proton is stabilized in place by the catalytic bridge.

In summary, the ionization of $T_1H_2^+$ to T_2H has about the same free-energy change as ionization of $2H_2^+$ to 2H. Also, the ionization of T_aH to T_b^- has about the same free-energy change as ionization of 2H to 2^-. These results show that the aromatic structure which is largely responsible for the acid–base properties of $2H_2^+$, 2H, and 2^- is essentially intact in $T_1H_2^+$, T_2H, T_aH, and T_b^-. Furthermore, the ionization of T_2H to T_e^- is relatively difficult, as expected from stabilization of the bridging proton in T_2H.

Entropies of Activation. Formation of $T_1H_2^+$ and T_2H from 2H involves large losses of entropy ($\Delta S^\ddagger = -30$ and -40 eu, respectively). This is consistent with structures **6** and **7** because (a) complete addition of a water molecule should have reduced the entropy, perhaps by 5–10 eu,[8] and (b) formation of the cyclic nucleophilic–protolytic bifunctional-catalytic bridge structure should have resulted in considerable further loss of internal rotational entropy. The bridging may also have prevented any effective gain of entropy from loosening of the leaving group oxygen–carbon bond.

Conversion of 2H to T_aH results in no change in entropy, fully consistent with the suggestion in **9** that only the loosest kind of association has formed with the nucleophilic water (thus little loss of translational and rotational entropy) and that no charges have developed, which would have reduced the entropy from electrostriction of solvent. The corresponding reaction of 2^- generating T_b^- actually produces an increase in entropy ($\Delta S^\ddagger = +20$ eu). This may indicate that the nucleophilic water (loosely bound as in **10**) was originally a member of the extensive solvation shell of the negative charge so that no entropy loss was associated with its weak binding to the substrate carbon. The entropy gain may be connected with a gain in rotational freedom of the leaving group as the nucleophile begins to prevent conjugation of its oxygen lone pairs into the ring, and with some disruption of the highly ordered reactant solvation shell. The same gain in leaving group rotational freedom in T_aH may also cancel some small entropy loss as the nucleophile begins to bind.

The production of T_e^- from 2H and HO^- is a second-order reaction and exhibits an apparently normal $\Delta S^\ddagger$ of -25 eu. However, as we shall see below, this actually is higher (more positive) than expected on the basis of the low $\Delta H^\ddagger$, and the discrepancy supports the loose bond to the leaving group shown in **8**.

Relative Activation Parameters. Enthalpy–Entropy Relation. Figure 3 shows a plot of $\Delta H^\ddagger$ vs. $\Delta S^\ddagger$ for each of the processes studied. For four of the five processes, the variations in $\Delta H^\ddagger$ are strongly correlated with the changes in $\Delta S^\ddagger$ as indicated by the line drawn through the points. The slope of the line, the isergonic ("isokinetic") temperature, is 300 K although the strict linearity of the relationship is unimportant for our purposes. Only the general fact that large decreases in $\Delta H^\ddagger$ are accompanied by large decreases in $\Delta S^\ddagger$ is relevant.

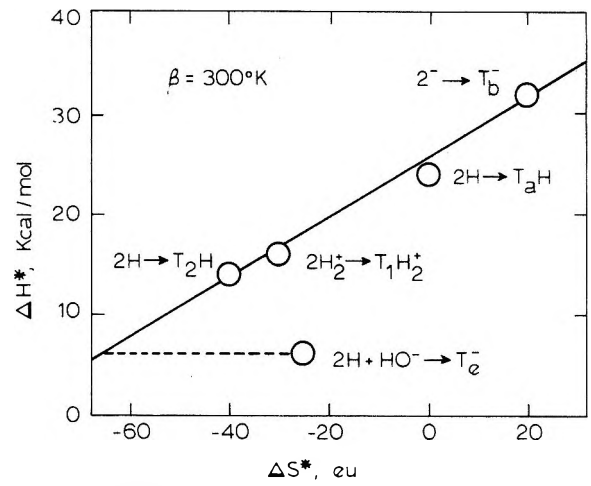


Figure 3. Relationship of the enthalpy of activation ($\Delta H^\ddagger$) to the entropy of activation ($\Delta S^\ddagger$) for the various activation processes.

The processes leading to transition states T_aH and T_b^- exhibit quite large $\Delta H^\ddagger$ with $\Delta S^\ddagger$ either zero or positive. It is these transition states which are proposed (in **9** and **10**) to involve incipient attack on the aromatic ring, possibly with some increased freedom of motion of the leaving group (as O lone-pair conjugation to the ring is interrupted) and possibly some solvent-shell disruption. No special stabilizing interactions are present.

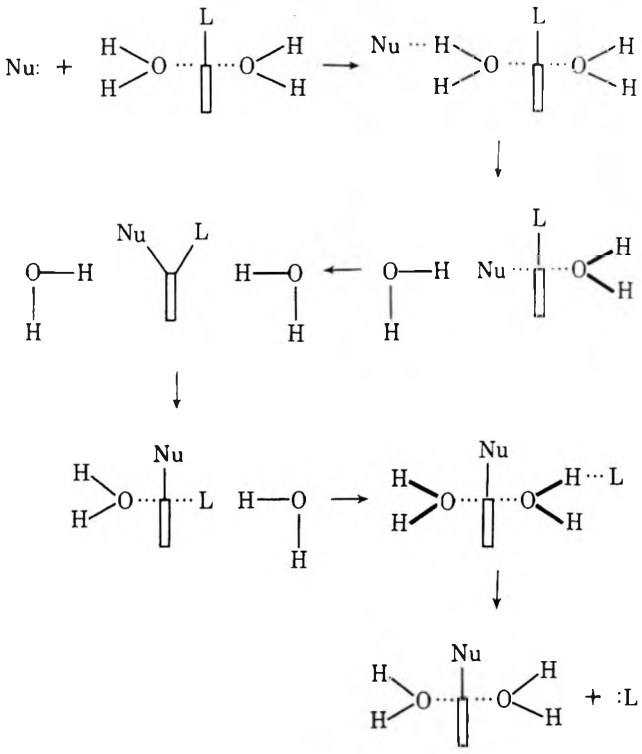
Formation of transition states $T_1H_2^+$ and T_2H, in which catalytic proton bridging is proposed (**6** and **7**), occurs with far less energy expenditure. Indeed, if the difference in $\Delta H^\ddagger$ between this pair of transition states and the T_aH–T_b^- pair represents the stabilization from catalytic bridging, the enthalpic contribution from this source is about 13 kcal/mol. This would produce a rate acceleration of around 10^{10}-fold if it were not offset by an unfavorable shift of about 55 eu in $\Delta S^\ddagger$. Presumably this arises from the loss of internal vibrational freedom as the leaving group is locked into the cyclic bridging structure. The large entropy loss suggests a reasonably rigid stereochemical requirement for the bifunctional interaction of the leaving group.

Finally we note that if formation of T_e^- had followed the tendency of the other processes, its very small $\Delta H^\ddagger$ of 6 kcal/mol would have produced a $\Delta S^\ddagger$ of less than -60 eu (see dashed line on Figure 3). This would not have been expected on the basis of structure **8**, however. The low $\Delta H^\ddagger$ here is not a reflection of catalytic bridging but of complete bond formation by the powerful nucleophile hydroxide ion. In fact, the leaving group is now presumably nearly broken free; the resultant freedom of internal motion presumably accounts for the relatively positive $\Delta S^\ddagger$.

Hammond's Postulate Violation. We noted above that the general experience of mechanisms science, as summarized in Hammond's postulate, is that transition states leading to and from unstable intermediates such as **5** should resemble the intermediates structurally, rather than reactants or products. We found the contrary here, with every accessible transition state having a nearly intact aromatic ring, like reactants or products but unlike the nonaromatic **5**. Several explanations are possible.

One ready explanation might seem to be that there is no intermediate and that the displacement is concerted. However, the interpretation offered above for the break in the pH–rate profile at pH 7 (region B) is that the rate-deter-

Scheme III



mining step changes at this pH. This constitutes kinetic evidence for an intermediate compound and thus casts doubt on this explanation.

A more likely view is that some other higher energy intermediates, having intact aromatic rings, intervene before and after **5**. For example, consider the sequence of Scheme III, which corresponds to the well-established course of events in the solvolysis reactions of alkyl derivatives.[9] In Scheme III, Nu: represents a nucleophile displacing the leaving group L: from an aromatic ring. Species which correspond to the intimate and solvent-separated ion pairs of solvolysis are shown. These are kinetically significant in solvolysis and their formation and decomposition are sometimes rate determining. If such is the case here, clearly the aromatic ring would remain intact in the transition state. However, even if the covalent-bond formation or fission steps are still rate limiting, conversion of a high-energy desolvated intermediate ("intimate ion pair") to the adduct **5** might well have a transition-state structure resembling the desolvated intermediate. Indeed, this would follow from Hammond's postulate.

Thus the apparent violation of Hammond's postulate may signal the intervention of kinetically significant solvent-reorganization processes along the main reaction path.

Experimental Section

Kinetics. Reaction rates were measured by following the first-order change in absorbance at 243 nm, as described previously.[4]

pK_a of Substrate. Starting material in methanol stock solution was diluted 50-fold with aqueous buffers to a final concentration of 1.5×10^{-5} *M*. Buffers controlled the pH at 6.32–9.58 and consisted of phosphate, Tris, carbonate, and sodium hydroxide solutions. The change in absorbance at 220 nm was used to determine a pK_a of 8.3–8.5.

Reaction Products. Reaction products were determined by thin layer chromatography. Samples were spotted on precoated silica gel F-254 plates (Brinkmann Instruments) and developed to a distance of 7 cm with two solvent systems: A [1-butanol–acetic acid–water (5:1:4)] and B [isopropyl alcohol–ammonia–water (80:5:15)]. These systems gave R_f values (A followed by B) of 0.74 and 0.44 for the starting material, 0.60 and 0.56 for 2-hydroxy-4-isopropylamino-6-cyclopropylamino-*s*-triazine ("hydroxy product"), and 0.41 and 0.11 for *N*-hydroxysuccinimide. Only these materials were detectable in reaction solutions after several days. Products were determined at pH 2.50 (solution of starting-material hydrochloride), 7.00, and 11.00 (adjusted with sodium hydroxide). Use of SilicAR TLC-7G (Mallinckrodt Chemical Works) plates resulted in the same findings.

Registry No.—2H, 54643-26-4.

References and Notes

(1) This research was supported by grants from the National Institutes of Health (NS 09399 and GM 18017) and the National Science Foundation. Data reduction was carried out in part in the Computation Center of the University of Kansas.
(2) On leave from the Nippon Shinyaku Co., Ltd., Kyoto, Japan.
(3) Dr. Smissman died on July 14, 1974.
(4) N. I. Nakano, E. E. Smissman, and R. L. Schowen, *J. Org. Chem.*, **38**, 4396 (1973), and references cited therein.
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Electrolytic Decarboxylation Reactions. II. Syntheses of Methyl Dihydrojasmonate and Methyl *dl*-Jasmonate from 3-Methoxycarbonyl-2-carboxynorbornane via Anodic Acetoxylation

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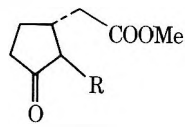
Methyl dihydrojasmonate (**1a**) and methyl *dl*-jasmonate (**1b**) were prepared from 3-methoxycarbonyl-2-carboxynorbornane (**2a**) via anodic acetoxylation. Electrolysis of **2a** in a mixed solvent of AcOH–*t*-BuOH–Et_3N gave a desired key intermediate, *exo*-2-acetoxy-*anti*-7-methoxycarbonylnorbornane (**3**), in 56% yield (GLC peak area) together with several minor products, **4** (12%), **5** (7%), **6** (11%), and **7** (4%). Hydrolysis of **3** followed by oxidation with chromic acid afforded 7-methoxycarbonyl-2-norbornanone (**9**) in good yield. The Baeyer–Villiger oxidation of **9** and subsequent hydrolysis and oxidation gave 2-methoxycarbonyl-3-methoxycarbonylmethylcyclopentanone (**12**) in 54% yield. Alkylation of **12** with pentyl and 2-pentynyl bromide and following cis hydrogenation and demethoxycarbonylation afforded **1a** and **1b**, efficiently.

In the preceding paper we reported the product-selective and chemically controlled electrolytic decarboxylation reaction involving the formation of either radical or carbonium ion intermediate.[1] We have now extended this electrochemical decarboxylation method to a novel acetoxylation reaction for the preparation of *exo*-2-acetoxy-*anti*-7-methoxycarbonylnorbornane (**3**), which is expected to be an intermediate for the methyl *dl*-jasmonate synthesis.[2]

Although electrolysis of *exo*- and *endo*-norbornane-2-carboxylic acid in Et_3N–MeOH has been shown to afford *exo*-2-methoxynorbornane in a sufficient yield via a carbonium intermediate,[3] instead of alkoxides acetoxy derivatives have been generally considered to be more useful intermediates for synthetic purposes. Indeed, one of the precursors for the preparation of methyl *dl*-jasmonate (**1b**) must be the acetoxy compound **3**, which may be derived from 2-methoxycarbonyl-3-carboxynorbornane (**2a**)[4] by electrolytic acetoxylation.

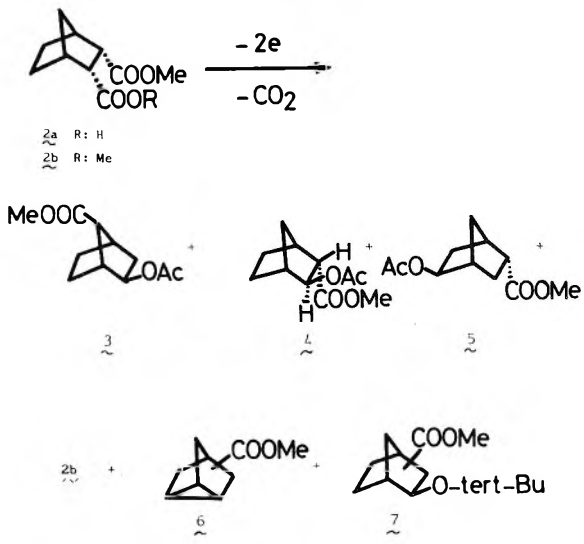


1a, R = n-C_5H_{11}
b, R = $CH_2CH{=}CHEt$-*cis*
c, R = $CH_2C{\equiv}CEt$

Results and Discussion

Electrolysis of the half-acid **2a** to the desired acetate **3** was carried out in a mixed solvent of AcOH–*t*-BuOH (2:1) using triethylamine as a supporting electrolyte on carbon rod electrodes (Table I, run 4). As shown in Scheme I, the electrolysis afforded **3** as a major product (56% yield based on GLC peak area) along with several minor products, **4**, **5**, **6**, and **7** (Table II). The structures of the products isolated by preparative GLC were elucidated by NMR, infrared, and mass spectral analyses together with elemental analysis.

Scheme I



The acetates **3**, **4**, and **5** (75% yield based on the neutral portion of the electrolysis product) isolated by column chromatography over silica gel from the reaction mixture were subjected to the ester exchange reaction[5] by stirring in dry methanol in the presence of sodium methoxide. The alcohol **8** (90% yield) isolated by column chromatography was homogeneous on GLC (3 m × 4 mm, SE-30 10% coated

Table I
Electrolytic Conditions and Results

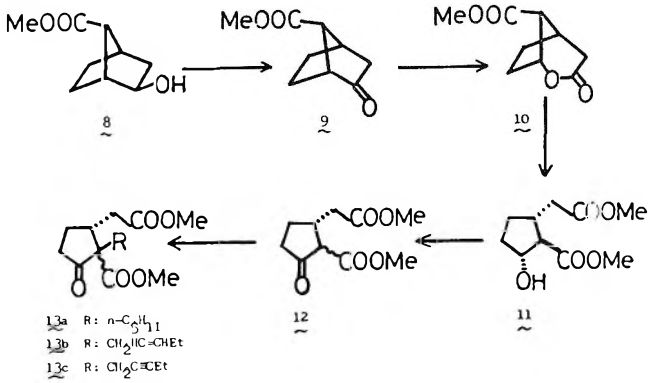
Run	Substrate 2a, g	Solvent (ml)	Supporting electrolyte (g)	Current, A	Applied voltage, V	Temp, °C	Time, hr	Product: Acetates (MeO), mg	Product: Others	Recovered 2a, mg
1	0.5	MeOH (30)	Et_3N (0.7)	0.5	20	30	6	(378)	66.2	10
2	1.0	AcOH (30)	AcONa (1.0)	0.14	50	32	20	286	143	300
3	1.0	AcOH (30)	Et_3N (0.7)	0.27	35	34	20	295	210	230
4	1.0	AcOH–*t*-BuOH (20) (10)	Et_3N (0.7)	0.18	35	30	20	353	117	340

Table II
Electrolytic Products (Table I, Run 4) from 2a

Products	6	7	4	3	5	Unknown	2b
Retention time,[a] min	4.4	9.4	23	26	28	30	31
Peak area, %	11	4	12	56	7	2	8

[a] GLC column, 3 m × 4 mm, 10% polyneopentyl glycol succinate coated on 80–100 mesh Chromosorb W, at 180°, carrier gas H_2, 30 ml/min.

column); however, the GLC analysis of the acetate regenerated from the alcohol still exhibited the presence of the minor peaks due to **4** and **5**. Without further purification the alcohols were oxidized with the Jones reagent[6] to the corresponding ketone in 90% yield. The difficulty was encountered in obtaining pure ketone **9** by simple column chromatography. By the above operation only the keto ester obtained from **4** could be stripped. The preparative route leading to methyl *dl*-jasmonate (**1b**) from **8** is shown in Scheme II. Thus, the ketone **9** contaminated with a small amount of the isomer derived from **5** was treated with monoperphthalic acid for 2 days at 17°. The reaction mixture was worked up in the usual manner and the product exhibited two spots on TLC, and was chromatographed over silica gel to give the pure Baeyer–Villiger product **10** in 71% yield. The ir, NMR, and mass spectral data fully support the structure **10**. Successful hydrolysis of **10** and following esterification with diazomethane afforded alcohol ester **11** in 92% yield. Further, the Jones oxidation of **11** gave the key intermediate **12**[7] in 82.6% yield.



Alkylation of the β-keto ester **12** with 2-pentynyl bromide using potassium *tert*-butoxide in dry dimethyl sulfoxide gave the corresponding C-alkylation product **13c** in 75% yield. In contrast, the reaction of **12** with *n*-pentyl bromide in the same base and solvent gave 39.5% of **13a** along with 17% of O-alkylation product. Cis hydrogenation of **13c** with Lindlar catalyst[8] gave **13b** in quantitative yield.

Recently, Krapcho and Lovey[9] have shown an efficient demethoxycarbonylation method of β-keto esters by heating in wet dimethyl sulfoxide containing sodium chloride. Thus, demethoxycarbonylation of **13b** with the solvent in a sealed tube at 180° for 3–4 hr yielded methyl *dl*-jasmonate (**1b**) in 56% yield. In a similar fashion, demethoxycarbonylation of **13c** and following hydrogenation could also lead to **1b** in 77.4% yield. Methyl dihydrojasmonate (**1a**) could be obtained in 70% yield from **13a**.

Electrolysis of 2a. Linstead[10] explored the electrolytic acetoxylation of diphenylacetic acid in AcOH–AcONa using platinum electrodes, giving the corresponding acetate in ca. 73% yield. On the other hand, electrolytic methoxylation of diphenylacetic acid in Et_3N–MeOH affords diphenylmethoxymethane in 80% yield.[11] These results demonstrate that attack of both nucleophiles to diphenylmethyl

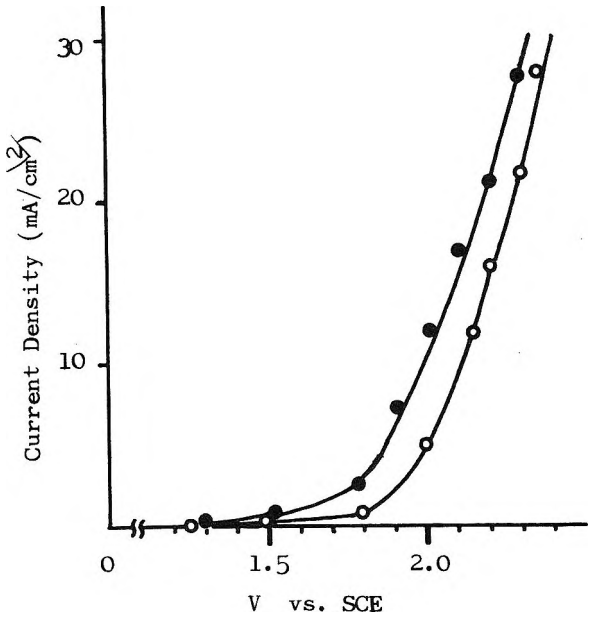


Figure 1. Current–potential curve of 2-carboxy-3-methoxycarbonylnorbornane (**2a**): ○, AcOH–*t*-BuOH–Et_3N (20:10:0.7) system; ●, AcOH–*t*-BuOH–Et_3N (20:10:0.7)–**2a** (0.6 *M*) system.

cation in the electrolytic solutions can proceed smoothly. The nucleophilic substitution of methanol, however, to *N*-acylaminomethyl cations derived from the electrolysis of *N*-acylaminoacetic acids has been shown to occur giving *N*-methoxymethylacylamides in 74–91% yields as compared with the reaction with acetic acid giving the corresponding acetate in ca. 38% yield.[12] These results are remarkable considering the problems involved in the electrolytic acetoxylation of complex carboxylic acids.

As shown in Table I, we examined the anodic acetoxylation of **2a** under several conditions (runs 1–4). Both routine electrolytic conditions (runs 1 and 2) provided the desired products in sufficient yield; however, the formation of acid anhydride[13] from **2a** (run 2) in addition to the low current efficiency prompted us to change the choice of the electrolytic solvent. In run 3, the improvement of the yield could be achieved but we experienced ease in producing the acid anhydride. However, the mixed solvent of AcOH–*t*-BuOH–Et_3N (run 4) afforded the more favorable result considering suppression of the formation of by-products, increase of the current efficiency, and facile isolation of the acetates.

The electrolysis of **2a** in run 4 (Table I) was carried out at the terminal voltage of ca. 35 V (cell voltages 2.2–2.3 V vs. SCE) under a constant current of ca. 0.18 A. The current–potential curve of the electrolysis of **2a** in AcOH–*t*-BuOH–Et_3N using platinum electrodes is shown in Figure 1, indicating that in this condition discharges of both **2a** and acetate anion occur competitively and the condition gives rise to the oxidation of **2a** favorably.

The analytical result of the product obtained in run 4 on GLC (Table II) indicates the presence of 75% of the acetates **3**, **4**, and **5** in the neutral portion. The product ratio of **3**, **4**, and **5** is well in accordance with the results from the solvolytic investigations on various norbornanes,[14] suggesting that the electrolytic reaction of **2a** would also proceed via nonclassical norbornyl cation.

Experimental Section

Melting points and boiling points are uncorrected. NMR spectra were determined with a Hitachi R-24 instrument. Ir spectra were recorded on a Hitachi EPI-S2, with only major absorptions being

cited. Mass spectral analyses were carried out with a Hitachi RMS-4 mass spectrometer at 70 eV, with molecular and major fragment ions being cited. Elemental analyses were performed by Mr. Tsutomu Okamoto of our Laboratory.

Electrolysis Apparatus. The electrolysis cell was a water-jacketed beaker, 3.5 cm in diameter and 10 cm high, fitted a gas-lead pipe, a thermometer, a magnetic stirrer, and two carbon rods (10 mm in diameter and 10 cm long) being placed parallel to each other 3 mm apart. Current was controlled by manually adjusting the applied voltage as required. The direction of current was changed every 30 sec by means of a commutator.

Electrolysis of 2-Carboxy-3-methoxycarbonylnorbornane (2a). The half-acid **2a**[4] (1 g, 5.05 mmol) was dissolved in a mixed solution of AcOH (20 ml), *t*-BuOH (10 ml), and Et_3N (700 mg). The mixture was electrolyzed at a constant current of 0.18 A (applied voltage ca. 35 V) at 30° for 20 hr. The solvent was rotoevaporated and the residue was taken up in benzene–ether (1:1). The organic layer was washed with water and saturated Na_2CO_3 and dried (Na_2SO_4). The starting material **2a** (340 mg) was recovered from the alkaline solution. The organic layer was concentrated to give a neutral oil (470 mg). The result from GLC analysis of the oil is shown in Table II. The components were separated by preparative GLC and the analytical results are as follows. *exo*-2-Acetoxy-*anti*-7-methoxycarbonylnorbornane (**3**): bp 62.0–63.0° (0.005 mm); ir 1739 and 1733 cm^{-1}; NMR ($CDCl_3$) δ 1.04–1.90 (m, 6 H), 2.00 (s, 3 H, CH_3CO), 2.54 (m, 2 H, bridgehead protons), 2.76 (s, 1 H, CHCO), 3.66 (s, 3 H, CH_3O), and 4.59 (double doublet, 1 H, CHO); mass spectrum *m/e* (rel intensity) 181 ($M^+ - CH_3O$, 13), 170 (14), 169 ($M^+ - CH_3CO$, 14), 153 (10), 152 (77), 142 (28), 138 (25), 137 (19), 124 (31), 121 (17), 110 (30), 109 (21), 100 (25), 93 (43), 92 (23), 87 (26), 81 (34), 74 (20), 67 (57), 66 (55), and 43 (100).

Anal. Calcd for $C_{11}H_{16}O_4$: C, 62.25; H, 7.60. Found: C, 62.27; H, 7.43.

exo-2-Acetoxy-*endo*-3-methoxycarbonylnorbornane (**4**): bp 62.0–63.0° (0.005 mm); ir (neat) 1738 and 1733 cm^{-1}; NMR ($CDCl_3$) δ 1.00–1.90 (m, 6 H), 2.00 (s, 3 H, CH_3CO), 2.37 (broad s, 1 H), 2.64 (broad s, 2 H), 3.70 (s, 3 H, CH_3O), and 4.88 (m, 1 H, CHO); mass spectrum *m/e* (rel intensity) 170 (24), 169 ($M^+ - CH_3CO$, 50), 153 (7), 152 (41), 143 (9), 142 (99), 138 (12), 137 (29), 124 (33), 121 (48), 110 (29), 109 (18), 103 (22), 100 (21), 93 (43), 87 (45), 82 (18), 81 (31), 79 (21), 77 (16), 74 (22), 68 (19), 67 (73), 66 (81), 65 (20), 59 (24), 55 (23), 53 (24), and 43 (100).

Anal. Calcd for $C_{11}H_{16}O_4$: C, 62.25; H, 7.60. Found: C, 62.43; H, 7.80.

exo-2-Acetoxy-*endo*-5-methoxycarbonylnorbornane (**5**): bp 62.0–63.0° (0.005 mm); ir (neat) 1744 and 1730 cm^{-1}; NMR ($CDCl_3$) δ 1.00–1.90 (m, 6 H), 1.92 (s, 3 H, CH_3CO), 2.44 (s, 1 H, CHCO), 2.67 (m, 2 H, bridgehead protons), 3.66 (s, 3 H, CH_3O), and 4.65 (double doublet, 1 H, CHO); mass spectrum *m/e* (rel intensity) 170 (69), 169 ($M^+ - CH_3CO$, 23), 153 (8), 152 (33), 142 (8), 141 (14), 139 (47), 138 (39), 137 (15), 127 (34), 126 (11), 111 (12), 110 (44), 109 (26), 100 (44), 93 (32), 92 (33), 91 (53), 87 (23), 81 (37), 79 (27), 67 (67), 66 (62), 59 (23), and 43 (100).

Anal. Calcd for $C_{11}H_{16}O_4$: C, 62.25; H, 7.60. Found: C, 62.06; H, 7.59.

Methoxycarbonyltricyclo[2.2.1.$0^{2,6}$]heptane (**6**): ir (neat) 1735 cm^{-1}; NMR ($CDCl_3$) δ 1.10–1.55 (m, 6 H), 1.60 (m, 1 H), 2.25 (m, 1 H), 2.45 (m, 1 H, CHCO), and 3.65 (s, 3 H, CH_3O); mass spectrum *m/e* (rel intensity) 152 (M^+, 5.7), 151 (64), 137 (11), 121 (17), 120 (22), 119 (13), 111 (22), 98 (17), 93 (100), 92 (70), and 91 (94).

Anal. Calcd for $C_9H_{12}O_2$: C, 71.03; H, 7.95. Found: C, 70.92; H, 7.97.

exo-2-*tert*-Butoxymethoxycarbonylnorbornane (**7**): ir (neat) 1734 cm^{-1}; NMR ($CDCl_3$) δ 1.15 (s, 9 H, 3 CH_3), 1.21–1.91 (m, 5 H), 2.37 (m, 3 H), 2.80 (m, 1 H), 3.53 (q, 1 H, CHO), and 3.65 (s, 3 H, CH_3O); mass spectrum *m/e* (rel intensity) 226 (M^+, 0.3), 195 (17), 171 (21), 170 (100), 152 (25), 151 (26), 142 (23), 141 (22), 139 (61), 138 (86), 127 (85), 110 (83), 100 (63), 93 (44), 92 (30), 91 (42), 90 (29), 87 (62), 81 (45), 67 (62), 66 (65), and 57 (93).

Anal. Calcd for $C_{13}H_{22}O_3$: C, 68.99; H, 9.80. Found: C, 68.93; H, 9.84.

cis-1,2-Dimethoxycarbonylnorbornane (**2b**), bp 153–155° (14.5 mm) [lit.[15] bp 152° (14 mm)], spectral data identical with those of an authentic sample.

The neutral oil (470 mg) obtained by the above work-up was chromatographed over silica gel using hexane–THF (15:1) and two fractions were collected. The first fraction gave an oil (117 mg) containing the compounds **6** and **7**. From the following fraction 353 mg of the acetates **3**, **4**, and **5** were obtained.

Ester Exchange Reaction of the Acetates 3, 4, and 5. Sodium metal (300 mg, 1.3 mg-atoms) was allowed to react with dry MeOH (6 ml) and cooled to 10°. To this solution the second elution (353 mg) obtained by the above chromatography dissolved in dry MeOH (0.5 ml) was added dropwise. The mixture was stirred for 12 hr at room temperature under nitrogen, quenched with ice–water (5–8 ml), extracted with $CHCl_3$, and dried (Na_2SO_4). The solvent was removed and the residue (280 mg) was carefully chromatographed over silica gel. Hexane–THF (10:1) elution gave 254 mg (90%) of the alcohol **8** containing a small amount of isomeric alcohols derived from **4** and **5**: bp 78.0–80.0° (0.01 mm); ir (neat) 3410 (broad, OH) and 1735 cm^{-1}; NMR ($CDCl_3$) δ 0.93–1.93 (m, 6 H), 2.49 (m, 2 H), 2.82 (broad, 1 H), 3.06 (broad, 1 H, OH), 3.62 (s, 3 H, CH_3O), and 3.68 (m, 1 H, HCO); mass spectrum *m/e* (rel intensity) 170 (M^+, 2), 153 (8), 152 (78), 151 (18), 142 (12), 141 (25), 139 (75), 138 (86), 127 (72), 124 (36), 120 (30), 111 (43), 110 (96), 109 (37), 100 (71), 97 (67), 95 (45), 93 (87), 92 (54), 91 (40), 87 (45), 81 (87), 79 (46), 77 (42), 74 (53), 69 (51), 68 (52), 67 (100), 66 (90), and 55 (68).

Anal. Calcd for $C_9H_{14}O_3$: C, 63.51; H, 8.29. Found: C, 63.31; H, 8.36.

7-Methoxycarbonyl-2-norbornanone (9). The alcohol **8** (120 mg, 0.706 mmol) contaminated with the isomeric alcohols derived from **4** and **5** was dissolved in CH_2Cl_2 (5 ml) and cooled to 0–4° in an ice bath. The Jones reagent (2.1 ml) prepared by dissolving $Na_2Cr_2O_7 \cdot 2H_2O$ (1 g, 3.3 mmol) in water (3 ml) and 97% of H_2SO_4 (1.36 g, 1.34 mmol), was added dropwise with vigorous stirring for 15 min and continued cooling and stirring for an additional 15 min. The ice bath was removed and the mixture was stirred for 3 hr at room temperature. The CH_2Cl_2 layer was separated and the aqueous layer was extracted with CH_2Cl_2. The combined extracts were washed with brine, dried (Na_2SO_4), and concentrated. The residue was chromatographed over silica gel using hexane–THF (6:1) to give **9** (107 mg, 90%) containing a small amount of isomeric ketones derived from **4** and **5**: bp 52.0–53.0° (0.01 mm); ir (neat) 1752 and 1741 cm^{-1} (ester and ketone carbonyls); NMR ($CDCl_3$) δ 1.23–2.23 (m, 6 H), 2.73 (broad s, 2 H), 2.82 (broad s, 1 H), and 3.66 (s, 3 H, CH_3O); mass spectrum *m/e* (rel intensity) 168 (M^+, 19), 152 (4), 140 (50), 137 (28), 136 (16), 121 (17), 108 (80), 81 (96), 80 (60), 79 (61), 74 (76), 67 (100), and 66 (59).

Anal. Calcd for $C_9H_{12}O_3$: C, 64.27; H, 7.19. Found: C, 64.57; H, 6.89.

8-Methoxycarbonyl-3-oxo-2-oxabicyclo[3.2.1]octane (10). 7-Carbomethoxy-2-norbornanone (**9**, 168 mg, 1 mmol) contaminated with a small amount of the isomeric ketones was dissolved in ether (3 ml) containing monoperphthalic acid[16] (364 mg, 2 mmol) and the mixture was allowed to stand for 2 days at 17°. The mixture was shaken with cooled saturated $NaHCO_3$ solution and dried (Na_2SO_4). The residue from rotoevaporation of the ether layer was extracted several times with hexane and the extracts were concentrated to give 160 mg of crude products. TLC of the residue on silica gel showed [Merck 60 PF_{254}, benzene–EtOAc (5:1)] showed two spots at R_f 0.45 and 0.37 (ca. 4:1). Repeated chromatography of the residue over silica gel using benzene–EtOAc (7:1) gave **10** (130 mg, 70.6%, R_f 0.45): bp 56.0–57.0° (0.015 mm); ir (neat) 1739 and 1724 cm^{-1}; NMR ($CDCl_3$) δ 1.50–2.47 (m, 4 H), 2.47–2.98 (m, 3 H), 3.06 (s, 1 H, CHCO), 3.65 (s, 3 H, CH_3O), and 4.90 (broad s, 1 H, CHO); mass spectrum *m/e* (rel intensity) 184 (M^+, 1), 156 (20), 153 (18), 140 (13), 126 (27), 124 (15), 113 (16), 111 (24), 102 (21), 96 (36), 83 (100), 82 (69), and 81 (64).

Anal. Calcd for $C_9H_{12}O_4$: C, 58.69; H, 6.57. Found: C, 58.70; H, 6.55.

2-Methoxycarbonyl-3-methoxycarbonylmethylcyclopentanol (11). The δ-lactone ester **10** (184 mg, 1 mmol) was dissolved in a solution of KOH (112 mg, 2 mmol) in MeOH (1 ml) containing 3 drops of water. The mixture was stirred for 12 hr at room temperature and then most of the solvent was rotoevaporated. The residue was neutralized with *l*-tartaric acid (83 mg) in MeOH (1.1 ml) and the white precipitate was deposited. The precipitate was filtered off and washed with ether. The combined organic phases were concentrated and the residue was dried azeotropically with benzene (3 ml). The residual oil was extracted several times with ether. The extracts were rotoevaporated and treated with excess diazomethane. Removal of the solvent and following column chromatography over silica gel [benzene–EtOAc (10:1)] gave the alcohol **11** (197 mg, 92%): bp 85–86° (0.02 mm); ir (neat) 3455 (OH), 1745, and 1732 cm^{-1}; NMR ($CDCl_3$) δ 1.39–2.79 (m, 9 H), 3.66 (s, 3 H, CH_3O), 3.71 (s, 3 H, CH_3O), and 4.38 (m, 1 H, HCO); mass spectrum *m/e* (rel intensity) 188 (7), 168 (4), 167 (48), 166 (8), 160 (7),

159 (18), 156 (81), 140 (31), 139 (48), 128 (53), 127 (90), 125 (48), 115 (65), 111 (57), 107 (27), 99 (66), 97 (24), 96 (32), 95 (44), 83 (100), 82 (61), 79 (57), 74 (44), and 59 (58).

Anal. Calcd for $C_{10}H_{16}O_5$: C, 55.55; H, 7.46. Found: C, 55.71; H, 7.56.

2-Methoxycarbonyl-3-methoxycarbonylmethylcyclopentanone (12). The cyclopentanol 11 (216 mg, 1 mmol) was dissolved in CH_2Cl_2 (5 ml) and cooled to 0–4° (ice bath). The Jones reagent (2.5 ml) was added dropwise with vigorous stirring for 15 min, then additional Jones reagent (2.5 ml) was added at 0–4° and the mixture was stirred at 15° for 3 hr. After work-up in a usual manner, the crude oil was distilled to give 12 (177 mg, 82.6%): bp 85.0° (0.01 mm); ir (neat) 1756, 1744, 1731, 1661, and 1626 cm^{-1}; NMR ($CDCl_3$) δ 1.00–2.73 (m, 7 H), 2.89 (broad s, 1 H, CH), 3.60 (s, 3 H, CH_3O), and 3.68 (s, 3 H, CH_3O); mass spectrum *m/e* (rel intensity) 214 (M^+, 2), 182 (36), 154 (78), 141 (100), 127 (82), 109 (99), 99 (81), 95 (56), 83 (97), 82 (78), and 74 (64).

Anal. Calcd for $C_{10}H_{14}O_5$: C, 56.07; H, 6.59. Found: C, 55.78; H, 6.62.

2-Methoxycarbonyl-2-(2′-pentynyl)-3-methoxycarbonylmethylcyclopentanone (13c). To a stirred solution of 12 (50 mg, 0.234 mmol) and *t*-BuOK (26 mg) in dry dimethyl sulfoxide (2 ml) was added 2-pentynyl bromide (34 mg, 0.233 mmol) at room temperature and the stirring was continued overnight. The mixture was poured into ice-cold brine. Extraction with hexane, washing with cold brine, drying (Na_2SO_4), and solvent removal in vacuo gave 60 mg of a crude oil. Column chromatography over silica gel using benzene–EtOAc (15:1) gave 49 mg (75%) of **13c**: bp 78.0–80.0° (0.02 mm); ir (neat) 1755 and 1740 cm^{-1}; NMR ($CDCl_3$) δ 1.08 (t, 3 H, CH_3), 1.53–2.63 (m, 9 H), 2.73 (m, 2 H), 3.68 (s, 3 H, CH_3O), and 3.70 (s, 3 H, CH_3O); mass spectrum *m/e* (rel intensity) 263 (10), 248 (16), 221 (34), 220 (50), 192 (23), 180 (50), 175 (35), 161 (37), 152 (41), 147 (66), 139 (30), 138 (33), 133 (34), 119 (41), 110 (41), 105 (49), 93 (43), 91 (67), 81 (42), 79 (49), 77 (54), 67 (100), 66 (62), 65 (40), 59 (80), and 55 (69).

Anal. Calcd for $C_{15}H_{20}O_5$: C, 64.27; H, 7.19. Found: C, 64.32; H, 6.99.

Similarly, 2-methoxycarbonyl-2-pentyl-3-methoxycarbonylmethylcyclopentanone (**13a**) was obtained in 39.5% yield together with 17% of O-alkylation product **14**: R_f [silica gel, benzene–EtOAc (40:1)] **13a**:**14** 0.58:0.53. The compound **13a** boiled at 77.0–80.0° (0.02 mm): ir (neat) 1756, 1745, and 1733 cm^{-1}; NMR ($CDCl_3$) δ 0.87 (t, 3 H, CH_3), 0.95–3.02 (m, 15 H), 3.68 (s, 3 H, CH_3O), and 3.70 (s, 3 H, CH_3O); mass spectrum *m/e* (rel intensity) 284 (M^+, 0.6), 254 (3), 253 (28), 252 (14), 225 (13), 224 (10), 214 (51), 197 (34), 196 (21), 195 (13), 183 (18), 182 (100), 179 (12), 169 (19), 168 (21), 167 (32), 166 (32), 165 (15), 154 (90), 151 (29), 141 (74), 138 (87), 125 (38), 124 (40), 122 (30), 109 (76), 107 (37), 95 (35), 93 (45), 81 (45), and 79 (79).

Anal. Calcd for $C_{15}H_{24}O_5$: C, 63.36; H, 8.51. Found: C, 63.35; H, 8.53.

2-(2′-Pentynyl)-3-methoxycarbonylmethylcyclopentanone, Methyl *dl*-Dehydrojasmonate (1c). A solution of **13c** (24 mg, 0.086 mmol) and NaCl (10 mg) in a mixed solution of dimethyl sulfoxide (1.5 ml) and water (20 mg) was heated for 3–4 hr at 180° in a sealed tube. After cooling the mixture was poured into ice-cold brine and extracted with hexane. The extracts were washed with brine, dried (Na_2SO_4), and rotoevaporated. Distillation of the residue gave 16.3 mg (86%) of **1c**: bp 102.0–103.0° (3 mm) [lit.[2b] bp 88° (0.001 mm)]; ir (neat) 2230 (C≡C), 1743 (shoulder), 1741, 1441, 1412, 1380, 1340, 1196, 1169, and 986 cm^{-1}; NMR ($CDCl_3$) δ 1.06 (t, J = 7.2 Hz, 3 H, CH_3), 1.44–3.02 (m, 12 H), and 3.70 (s, 3 H, CH_3O); mass spectrum *m/e* (rel intensity) 222 (M^+, 0.2), 205 (1), 194 (9), 193 (67), 162 (5), 161 (3), 149 (27), 148 (14), 147 (17), 133 (28), 123 (21), 122 (100), 119 (15), 107 (76), 105 (34), 91 (52), 79 (51), and 77 (31).

Similarly, demethoxycarbonylation of **13a** afforded methyl dihydrojasmonate (**1a**) in 70% yield: bp 92.0–94.0° (3 mm) [lit.[17] bp 133–135° (1 mm)]; ir (neat) 1742 (broad), 1465, 1442, 1381, 1338, 1261, 1197, 1172, 1098, 1013, and 988 cm^{-1}; NMR ($CDCl_3$) δ 0.88 (t, 3 H, CH_3), 1.05–1.90 (m, 11 H), 2.00–2.80 (m, 5 H), and 3.70 (s, 3 H, CH_3O); mass spectrum *m/e* (rel intensity) 226 (M^+, 2), 196 (2), 156 (33), 153 (32), 149 (5), 109 (4), 97 (8), 96 (11), 95 (7), 84 (8), 83 (100), 82 (36), and 55 (25).

Methyl *dl*-Jasmonate (1b) from 1c. A mixture of Lindlar catalyst (222 mg) and methyl *dl*-dehydrojasmonate (**1c**, 22 mg, 0.1 mmol) in hexane (1 ml) was stirred under 1 atm of hydrogen. After 20 min hydrogen uptake stopped and the mixture was filtered free of catalyst and concentrated to yield 20 mg (90%) of methyl *dl*-jasmonate (**1b**): bp 110.0–112.0° (5 mm) [lit.[2b] bp 81–84° (0.001 mm)]; ir (neat) 1742, 1462, 1440, 1412, 1379, 1339, 1262, 1197, 1164, 1095, 1072, 1018, 982, and 795 cm^{-1}; NMR ($CDCl_3$) δ 0.95 (t, 3 H, CH_3), 1.40–2.90 (m, 12 H, CH_2), 3.68 (s, 3 H, CH_3O), and 5.35 (m, 2 H, HC=C); mass spectrum *m/e* (rel intensity) 224 (M^+, 23), 206 (1), 195 (1), 193 (7), 177 (2), 156 (16), 151 (42), 150 (7), 149 (20), 135 (9), 133 (8), 121 (8), 109 (24), 95 (30), 93 (17), 91 (13), 83 (100), 82 (25), 79 (25), 67 (30), and 55 (30).

Similarly, hydrogenation of **13c** gave 2-methoxycarbonyl-2-(*cis*-2′-pentenyl)-3-methoxycarbonylmethylcyclopentanone (**13b**) in 91.2% yield: bp 84.0–85.0° (0.015 mm); ir 3020, 1752 (shoulder), 1740, 1442, 1227, and 1175 cm^{-1}; NMR ($CDCl_3$) δ 0.95 (t, 3 H, CH_3), 1.65–2.85 (m, 11 H), 3.66 (s, 3 H, CH_3O), and 4.85–5.75 (m, 2 H, HC=C); mass spectrum *m/e* (rel intensity) 282 (M^+, 4), 251 (16), 250 (19), 223 (17), 222 (40), 219 (25), 214 (21), 194 (45), 193 (100), 190 (15), 182 (33), 180 (17), 176 (15), 163 (18), 162 (18), 154 (45), 149 (46), 141 (49), 122 (30), 121 (33), 120 (20), 109 (52), 107 (44), 93 (38), 91 (43), 79 (54), 77 (43), 67 (40), and 55 (63).

Anal. Calcd for $C_{15}H_{22}O_5$: C, 63.81; H, 7.85. Found: C, 63.85; H, 7.84.

Demethoxycarbonylation of **13b** in aqueous dimethyl sulfoxide containing a small amount of NaCl at 180° afforded 56% of methyl *dl*-jasmonate (**1b**), whose spectral data (ir, NMR, and mass spectrum) were identical with those of an authentic sample.

Registry No.—**1a**, 2570-03-8; **1b**, 20073-13-6; **1c**, 29119-47-9; **2a**, 55298-06-1; **2b**, 4098-47-9; **3**, 55254-64-3; **4**, 55254-65-4; **5**, 55254-66-5; **6**, 55254-63-2; **7**, 55254-62-1; **8**, 55254-67-6; **9**, 55254-68-7; **10**, 55254-69-8; **11**, 55254-70-1; **12**, 55254-71-2; **13a**, 55254-72-3; **13b**, 55254-73-4; **13c**, 55254-74-5.

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Carbon-13 Nuclear Magnetic Resonance Spectroscopy. Substituted Vinyl Ethers and Acetates[1a]

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The ^{13}C NMR spectra of a number of substituted methyl vinyl ethers and vinyl acetates have been determined. In both series the polar substituent induces a large downfield shift of the directly bound olefinic carbon. This α shift varies in only a minor way with changes in the substitution pattern of alkyl groups on the double bond, except for bulky geminate substitution, which decreases the magnitude of this effect substantially. On the contrary, the substituent shift on the β-olefinic carbon is strongly shielding and depends significantly on the substitution pattern. Thus, alkyl groups cis to the methoxy function decrease this shielding in methyl vinyl ethers, whereas substitution at the geminate position causes a decrease in the β effect for vinyl acetates. The upfield shift of γ_{cis} and γ_{trans} carbons are also dependent on the structure of the molecule. These substituent effects are rationalized on the basis of steric and conjugative interactions in the substituted olefins.

The idea of substituent effects has proven to be an extremely useful tool in the study of organic molecules by ^{13}C NMR spectroscopy.[2] Substituent parameters have been derived for a number of functional groups on aliphatic and aromatic frameworks, but relatively little work has been done with olefinic compounds.[3] The effect of substitution at vinylic positions has been studied extensively only for simple alkenes, for which attention has been focused mainly on the unsaturated carbons.[4] In the present work, enol ethers and enol acetates are examined in order to probe the changes in chemical shifts in both the saturated and unsaturated portions of olefins provoked by substitution with the strongly interacting methoxy and acetoxy groups.

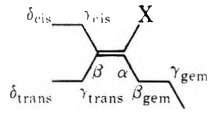
Experimental Section

Spectra. Carbon-13 NMR spectra were obtained using a modified high-resolution NMR spectrometer consisting of a Varian 14.1K Gauss electromagnet with an external ^{19}F lock, a Hewlett-Packard frequency synthesizer operating at 15.1 MHz, and an Ortec time-controlling device for gating the pulses. The free-induction decay signal was accumulated with a Fabri-Tek 1074 time-averaging computer. Fourier transformations were conducted with a Digital Electronics Corp. PDP 8/I computer. The limiting precision of the chemical shift data is ±0.12 ppm (4K data points in the time-domain spectra for a 250-ppm spectral window). Measurements were performed on ca. 10–30% (v/v) solutions in CCl_4. The solvent was used as an internal standard, and chemical shifts were converted to internal Me_4Si reference by the relation δ_{CCl_4} = 96.0 ppm. This relationship was verified in several instances.

Materials. Most of the enol acetates were prepared from the corresponding carbonyl compounds by reaction with acetic anhydride or isopropenyl acetate.[5,6] The enol ethers were prepared from the corresponding carbonyl compounds in the usual manner via the intermediate dimethoxy acetals and ketals.[6] Mixtures of isomers were separated by preparative GLC using a 20-ft column of 20% Carbowax 20M on Chromosorb W, or a 20-ft column of 30% SE-30 on Chromosorb W. Infrared and NMR spectra are consistent with the structures assigned. Proton NMR shifts for olefinic hydrogens were used to differentiate between *E* and *Z* isomers.[7] The structures assigned in this fashion are substantiated by the ^{13}C NMR data.

Results

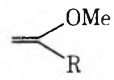
The chemical shifts for the series of vinyl ethers and vinyl acetates are listed in Tables I and II. The signals corresponding to the olefinic carbons are easily distinguished because of their low-field chemical shifts. In appropriate cases assignments were confirmed by single-frequency off-resonance spectra.[8] Assignments of signals to aliphatic carbons are more difficult and, in many cases, are based solely on analogy with the corresponding carbon in the parent alkane. However, possible ambiguities in these assignments are not of major significance for the conclusions given below. The validity of the concept of substituent effects for these compounds was confirmed by reasonable linear correlations (slopes approximating unity) for plots of the shifts of given carbons in the vinyl derivatives against the corresponding carbons of the parent olefins. The correlation for the β carbon for both types of compounds is improved by subdividing the data (see Figures 1 and 2). For vinyl ethers the two subgroups are compounds with alkyl substitution cis to the methoxy function and compounds without this feature. Vinyl acetates give a better correlation when separated into compounds possessing and compounds devoid of substituents geminate to the acetoxy-bearing carbon. The conventions indicated in I have been adopted to identify the different carbons.



I (X = H, OMe, OAc)

Discussion

I. Vinyl Ethers. α Effect. The α carbons of enol ethers (I, X = OMe) are shifted ca. 30 ppm downfield with respect to the corresponding carbon of the unsubstituted olefin (I, X = H). This shift is considerably larger than the ca. 17 ppm deshielding promoted by a similar substitution of the nonpolar ethyl group. Vinyl ethers without geminate substitution show substituent shifts in the range 31.4 ± 1.1 ppm. (Owing to the limited data available, *maximum* deviations from the average values are used throughout this paper.) However, geminate substitution causes a decrease in the α shift which is related to the size of this substituent as illustrated by the series **1** (30.6 ppm), **4** (27.4 ppm), **6** (23.8 ppm). The larger cyclic compounds **11** and **12** appear



1, R = H
4, R = CH_3
6, R = *i*-C_3H_7

to behave like other geminate-substituted examples, although five-membered compound **10** shows a larger α effect. This variance in substituent shift is probably related primarily to differences in the polarization of the double-bond electrons caused by the *gem*-alkyl group in the parent alkene,[9] and to nonbonded interactions between the methoxy group and the *gem*-alkyl moiety.[10]

Table I
^{13}C Chemical Shifts for Some Methyl Vinyl Ethers[a]

Compd	(No.)	C_1	C_2	C_3	C_4	C_5	C_6	C_7	C_8	OCH_3
Methyl vinyl ether[b]	(1)	153.2	84.1							52.5
		(30.6)[c]	(−38.5)							
(*E*)-1-Methoxypropene	(2)	147.5	96.0	12.5						54.9
		(31.8)	(−36.8)	(−6.8)						
(*Z*)-1-Methoxypropene	(3)	146.4	100.2	8.8						58.5
		(30.7)	(−32.6)	(−10.5)						
2-Methoxypropene	(4)	80.4	160.2	20.4						53.9
		(−35.3)	(27.4)	(1.1)						
1-Methoxy-2-methylpropene	(5)	141.4	109.0	14.3[d]	18.9[e]					58.0
		(30.9)	(−31.7)	(−9.0)	(−4.4)					
2-Methoxy-3-methyl-1-butene	(6)	76.8	168.9	33.1	20.2					53.5
		(−34.3)	(23.8)	(1.4)	(−1.5)					
(*E*)-1-Methoxy-1-heptene	(7)	147.0	101.8	27.7	30.5[f]	31.1[f]	22.4	13.7		54.6
		(32.5)	(−37.3)	(−6.8)	(1.1)	(1.1)	(−0.9)	(−0.7)		
(*Z*)-1-Methoxy-1-heptene	(8)	145.6	106.6	23.5	29.3	31.2	22.3	13.7		58.4
		(31.1)	(−32.5)	(−11.0)	(−0.1)	(−1.0)	(−1.0)	(−0.7)		
(*E*)-4-Methoxy-3-heptene	(9)	14.2[f]	18.3[f]	94.3	154.8	30.3	18.8[f]	12.0[f]		52.5
		(−0.1)	(−2.6)	(−37.6)	(25.6)	(0.7)	(−4.5)	(−1.6)		
1-Methoxycyclopentene	(10)	161.1	92.3	28.6	21.1	31.4				55.6
		(30.9)	(−37.9)	(−3.6)	(−1.5)	(−0.8)				
1-Methoxycyclohexene[g]	(11)	155.5	92.0	22.7	23.3	22.7	27.2			54.0
		(28.7)	(−34.8)	(−2.7)	(0.8)	(−1.5)	(1.8)			
1-Methoxycyclooctene[g]	(12)	158.3	93.5	24.3	31.0	25.8	25.8	29.5	28.3	53.3
		(28.6)	(−36.2)	(−2.3)	(−0.5)	(−0.1)	(−0.1)	(−0.3)	(1.7)	

[a] In parts per million downfield from Me_4Si. [b] Data from ref 21 (neat). Converted to the Me_4Si scale using δ_c (CS_2) = 193.7 ppm. [c] $\Delta\delta = \delta^1_{ROMe} - \delta^1_{RH}$, the difference between the chemical shift of the carbon in the vinyl ether and that of the corresponding carbon in the parent olefin. [d] Carbon cis to the methoxy function. [e] Carbon trans to the methoxy group. [f] Assignment not unambigously established. [g] Assignments are tentative both in the vinyl ether and in the corresponding cycloalkane.

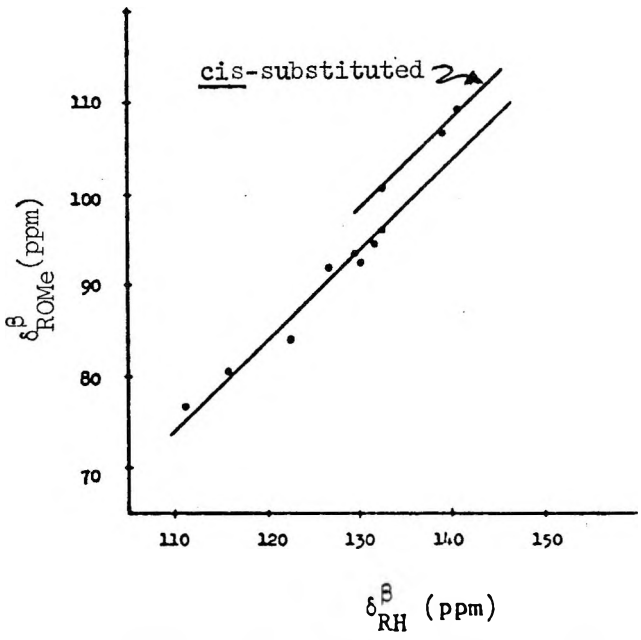


Figure 1. Correlation between ^{13}C chemical shifts of β carbons in methyl vinyl ethers (ROMe) and the corresponding alkenes (RH).

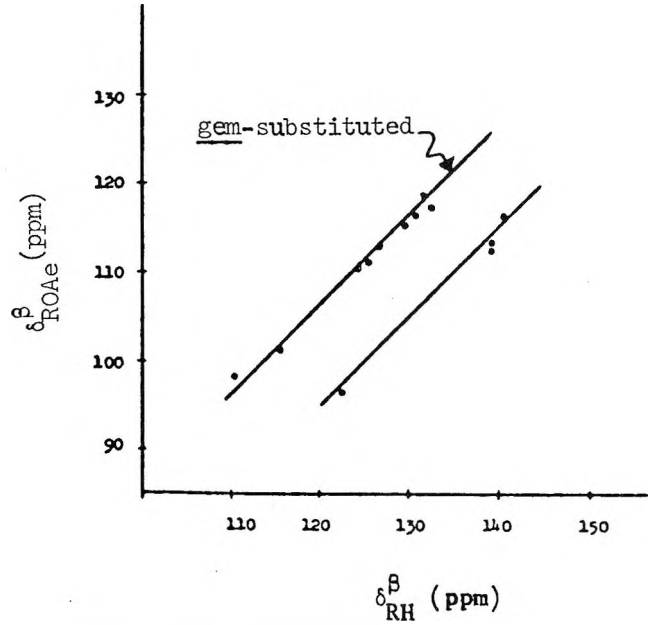


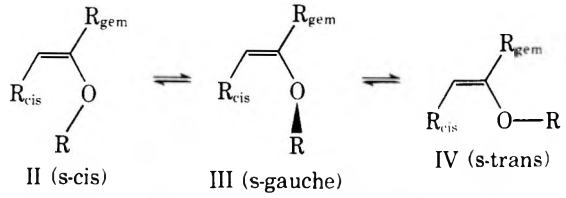
Figure 2. Correlation between the ^{13}C chemical shifts of β carbons in vinyl acetates (ROAc) and the corresponding alkenes (RH).

β Effect. An olefinic carbon β to the methoxy group suffers a large upfield shift. The magnitude of this effect appears to depend on substitution at the β carbon cis to the functional group (see Figure 1). Thus, cis-substituted compounds are shielded by -32.3 ± 0.6 ppm, whereas vinyl ethers without cis substituents show a β shift of -36.5 ± 2.2 ppm. (The scatter in these values appears to result from minor systematic differences with substitution patterns.) For comparison, an ethyl group introduces a β shift of only ca. -10 ppm.[4a] The large shielding effect on the β carbon is rationalized on basis of conjugative interaction between the double bond and the oxygen which increases electron density on the β carbon.[11,12] The difference between the two types of vinyl ethers may be attributed to a decrease in electron transfer in the cis-substituted compounds, since substituting at R_{cis} with an alkyl group modifies the conformational equilibrium II $\rightleftarrows$ III $\rightleftarrows$ IV so as to increase gauche conformation III which is not important for conju-

Table II
^{13}C Chemical Shifts for Some Vinyl Acetates[a]

Compd	(No.)	C_1	C_2	C_3	C_4	C_5	C_6	C_7	C_8	C=O	CH_3
Vinyl acetate	(13)	141.2	96.6							166.1	20.1
		(19.6)	(−25.0)[b]								
2-Acetoxypropene	(14)	101.2	152.8	19.3[c]						167.4	20.5[c]
		(−14.5)	(20.0)	(−0.2)							
2-Acetoxy-3-methyl-1-butene	(15)	98.6	160.9	32.1	20.1					167.0	20.5
		(−12.5)	(15.8)	(0.4)	(−1.6)						
1-Acetoxy-2-methylpropene	(16)	130.2	116.3	15.2[d]	19.2[c,e]					166.4	19.9[c]
		(19.7)	(−24.4)	(−8.1)	(−4.1)						
(*E*)-2-Acetoxy-2-butene	(17)	14.6	110.8	145.7	11.4					167.4	20.3
		(3.2)	(−12.5)	(21.5)	(0.0)						
(*Z*)-2-Acetoxy-2-butene	(18)	18.8	110.0	145.2	9.9					166.6	19.7
		(2.2)	(−15.2)	(20.0)	(−6.7)						
2-Acetoxy-3-methyl-2-butene	(19)	15.5	116.8	138.8	18.0[d]	16.8[e]				167.4	20.5
		(2.8)	(−14.0)	(20.7)	(−6.8)	(0.3)					
(*E*)-1-Acetoxy-1-heptene	(20)	135.5	113.5	27.1	29.1	31.1	22.3	13.8		166.0	20.1
		(21.0)	(−25.6)	(−7.4)	(−0.3)	(−1.2)	(−1.0)	(−0.6)			
(*Z*)-1-Acetoxy-1-heptene	(21)	134.0	112.8	24.3	28.8	31.3	22.3	14.0		165.8	20.3
		(19.5)	(−26.3)	(−10.2)	(−0.6)	(−0.9)	(−1.0)	(−0.4)			
(*E*)-4-Acetoxy-3-heptene	(22)	14.4	19.8[e]	119.0	147.9	30.7	19.8[e]	13.5		167.4	20.5[c]
		(0.1)	(−1.1)	(−12.9)	(18.7)	(1.1)	(−3.5)	(−0.1)			
(*Z*)-4-Acetoxy-3-heptene	(23)	13.4	18.6	117.2	147.5	35.3	19.6[e]	13.4		166.5	20.1[c]
		(−0.6)	(−7.4)	(−15.2)	(18.1)	(0.2)	(−3.6)	(−0.1)			
1-Acetoxycyclohexene[f]	(24)	148.4	113.0	21.5	23.5	22.5	27.0			167.4	20.5
		(21.6)	(−13.8)	(−3.5)	(1.0)	(0.0)	(2.0)				
1-Acetoxycyclooctene[f]	(25)	150.3	115.3	24.5	29.3	25.5	27.5	26.0	29.3	167.8	20.5
		(20.6)	(−14.4)	(−2.1)	(0.2)	(0.2)	(2.2)	(−3.1)	(3.2)		

[a] Chemical shifts reported in parts per million downfield from Me_4Si. [b] $\delta^1_{RX} - \delta^1_{RH}$, the difference between the chemical shift of the *i* carbon in the enol acetates and that of the corresponding carbon in the parent olefin. [c] The assignments are not unambigously established. [d] Carbon cis to the acetate function. [e] Carbon trans to the acetate function. [f] Except for C_1 and C_2, the assignments for the other carbons in both the acetate and the parent alkene are tentative.



gation.[13,21] In addition a shielding contribution for compounds without cis substituents may come from steric interaction between the methoxy function and the hydrogen at R_{cis}.[22] Support for the operation of this mechanism is derived from the chemical shift behavior of the methoxy group (vide infra).

γ_{cis} and γ_{trans} Effects. Generally, substitution of a vinylic hydrogen affects both cis and trans carbons attached to the other olefinic carbon. For instance, a methyl group shields a γ_{cis} carbon by ca. −5 ppm, whereas the effect at a γ_{trans} position is smaller and variable in sign.[23,24] In vinyl ethers both types of carbons experience an upfield shift suggestive of an increase in negative charge. The γ_{cis} carbon is shielded by −10.2 ± 1.2 ppm, considerably more than the −4.2 ± 2.6 ppm shift of the γ_{trans} carbon. These values vary appreciably with substitution pattern, especially γ_{trans}, which is smaller in the presence of a geminate substituent. The shielding at the γ carbons appears to reflect the β effect and, therefore, parallels the transfer of electron density to the β carbon. In addition, the γ_{cis} carbon is shielded by a through-space steric interaction with the added methoxy group. For simple cis–trans isomers, the through-bond contribution appears to predominate, as evidenced by shifts of ca. −11 and −7 ppm at the γ carbons of isomeric cis and trans compounds, respectively (e.g., compare **3** with **2**, and **8** with **7**).

Other Carbons. Carbons of the *gem*-alkyl chain appear to follow the general trends observed for straight-chain alkyl derivatives, namely, deshielding at β_{gem} (1.3 ± 0.6 ppm) and shielding at γ_{gem} (−1.6 ± 2.9 ppm).[4] Long-range effects, such as those at remote carbons in the alkyl chains of the isomeric 1-methoxy-1-heptenes (**7** and **8**), are noteworthy.

The Methoxy Carbon. The methyl carbon of the ether function falls in the chemical shift range of 52.5–58.5 ppm and depends on the structure of the molecule analogously to the β shifts. Thus, in compounds without cis substitution this carbon is found at higher field (52.5–55.6 ppm) than in cis-substituted ethers (58.0–58.5 ppm).[25] Steric interaction between the methyl and the β-vinylic hydrogen in s-cis conformation II (R_{cis} = H; R = CH_3) helps to account for the observed chemical shifts of both the methoxy carbon and the β carbon (vide supra).

II. Vinyl Acetates. α Effect. The acetate function deshields the α-olefinic carbon of enol acetates by ca. 20 ppm. The magnitude of the shift does not depend to a large extent on the alkyl substitution pattern of the double bond, although geminate substituents larger than methyl decrease the α effect as shown by the significantly smaller values for compounds **15**, **22**, and **23** (see Table II). The cyclic compounds do not show this behavior, suggesting that the decrease in the deshielding effect is caused by steric interactions between γ_{gem} carbons and the acetoxy group. For compounds differing only in the stereochemistry of the alkyl chain relative to the acetate function (i.e. pairs of *E* and *Z* isomers), the α carbon is consistently at ca. 1 ppm higher field for the isomer with cis-alkyl substitution. (Compare **17** vs. **18**, **20** vs. **21**, and **22** vs. **23**.)

β Effect. The dependence of the shielding of this carbon

on the structure of the molecule is evident from Figure 2, which shows a clean separation into groups of compounds *with* and *without* substitution at the geminate position. The β carbon of the double bond in geminate-substituted vinyl acetates (β shift of -14.0 ± 1.5 ppm) is less shielded by more than 10 ppm relative to compounds lacking this type of substitution (β shift of -25.6 ± 1.2 ppm). The general upfield shift at the β carbon is again ascribed to conjugation between the double bond and the attached oxygen.[26] The smaller shift for geminate-substituted vinyl acetates is associated with less conjugative transfer of electron density to the β carbon, alkyl substitution at the geminate position sterically hindering attainment of conformer IV (R = OAc) and forcing the molecule into the s-gauche conformation III. In both of the subgroups compounds with cis substituents are upfield of those with trans groups.

γ_{cis} and γ_{trans} Effects. As with vinyl ethers, both carbons bonded to the β-olefinic position show upfield substituent effects. The magnitudes of these shifts parallel those of the β shift. Both γ_{cis} and γ_{trans} carbons are strongly shielded in vinyl acetates that do not bear alkyl substitution at the geminate position (γ shifts of -9.2 ± 1.0 and -5.8 ± 1.7 ppm, respectively). However, a geminate substituent causes the shielding of the γ_{trans} carbon to drop considerably (ca. -1.0 ppm), whereas the shift of the γ_{cis} carbon (-7.0 ± 0.4 ppm) decreases only slightly. The *gem*-alkyl group decreases electron transfer to the β carbon and also retards charge relay to γ_{trans} by virture of its cis steric interaction with this carbon. However, steric interactions between the γ_{cis} carbon and the acetate group are increased by a butressing effect of the geminate substituent and presumably lead to a compensating shielding at γ_{cis}.

Other Effects. The β carbon in the *gem*-alkyl chain is, in general, deshielded and the magnitude of this effect appears to depend on the nature of the β-carbon moiety and on the substitution pattern of the double bond. Thus, methyl groups are deshielded relative to methylene groups in the β_{gem} position (compare **17** and **18** vs. **22** and **23**). Furthermore, in pairs of *Z* and *E* isomers, compounds with alkyl chains cis to each other show a larger downfield shift than those with a trans arrangement of these groups. Interestingly, remote carbons in the *cis*- and *trans*-alkyl chains of compounds **20** and **21** show upfield shifts.

The Acetate Group. Both carbonyl and methyl carbons fall into relatively narrow ranges (166.1–167.8 and 19.7–20.5 ppm, respectively). The failure of the carbonyl chemical shift to parallel the large changes of the β carbon is consistent with a lack of conjugative interaction between these two moieties. However, the chemical shifts of the carbonyl carbons in compounds without *gem*-alkyl substitution (166.1 ± 0.3) are consistently ca. 1 ppm upfield of compounds with *gem*-alkyl groups (167.2 ± 0.7 ppm), probably because of steric interactions in the latter.

Summary

The results of this study are in general accord with the correlations of ^{13}C chemical shifts with electron densities for monosubstituted ethylenes.[12] The large downfield α shift is attributed to inductive withdrawal by the highly electronegative substituents, the methoxy group being substantially more effective than the acetoxy function. The β shift is upfield and usually quite large also. The major factor here is undoubtedly conjugative transfer of electron density to the β carbon from the oxygen, although double-bond polarization[9] probably also plays a significant role. The larger shifts for methoxy relative to acetoxy are in agreement with the relative abilities of these functions to donate electron density by resonance.[27] Alkyl substituents which change the conformational situation of the methoxy or acetoxy group so as to decrease conjugation also lower the magnitude of the upfield β effect. This accounts for the smaller β shifts for cis-substituted enol ethers and geminate-substituted acetates. The much larger difference between the two subgroups of acetates reflects the greater difficulty the larger acetate group has in achieving a suitable alternative to conformation IV capable of conjugation, whereas methoxy can modify its conformational distribution toward form IV when the normally favored conformer II is destabilized. The γ carbons on the double bond also appear to be shielded by an increase in electron density at the β carbon suggesting a relay of charge to these centers. Other steric interactions (especially those involving geminate groups) can cause significant changes in substituent shifts, usually decreasing the magnitudes of these effects relative to those of molecules without such interactions. Thus, steric stress generally decreases the ability of a substituent to play its usual role, regardless of whether this is shielding or deshielding.

Registry No.—**1**, 107-25-5; **2**, 4188-69-6; **3**, 4188-68-5; **4**, 116-11-0; **5**, 17574-84-4; **6**, 51776-45-5; **7**, 55373-78-9; **8**, 55373-79-0; **9**, 55373-80-3; **10**, 1072-59-9; **11**, 931-57-7; **12**, 50438-51-2; **13**, 108-05-4; **14**, 108-22-5; **15**, 3814-40-2; **16**, 14478-14-9; **17**, 15984-02-8; **18**, 15984-03-9; **19**, 3814-41-3; **20**, 17574-85-5; **21**, 17574-86-6; **22**, 55373-81-4; **23**, 5780-51-8; **24**, 1424-22-2; **25**, 14478-13-8.

References and Notes

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Carbon-13 Nuclear Magnetic Resonance Spectra of the Vitamin B-6 Group

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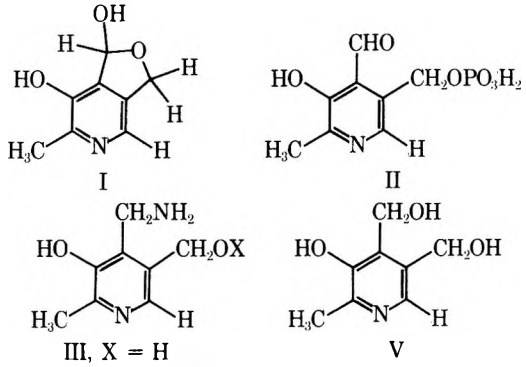
The Fourier transform natural abundance carbon-13 spectra of pyridoxal, pyridoxal 5′-phosphate, pyridoxamine, pyridoxamine 5′-phosphate, and pyridoxine are reported. Resonances are assigned by chemical shift analogies and by spin–spin coupling to adjacent protons. Chemical shifts are strongly pH dependent owing to the deprotonation of the various functional groups. Chemical shift analogies are interpreted as indicating a zwitterionic structure at neutrality. The detailed pH dependence of the carbon-13 chemical shifts of pyridoxal 5′-phosphate, pyridoxamine 5′-phosphate, and pyridoxine are reported. Long- and short-range proton-to-carbon coupling constants are also reported and are not found to be strongly pH dependent.

The vitamin B-6 group is comprised of pyridoxal (PL, I), pyridoxal 5′-phosphate (PLP, II), pyridoxamine (PM, III), pyridoxamine 5′-phosphate (PMP, IV), and pyridoxine (PN, V). These substituted pyridines are essential cofactors to a large number of enzymes involved in the metabolism of amino acids. The reactions they catalyze proceed through Schiff base formation of the amino acid with the substituted 4-pyridine aldehyde form of the vitamin. The Schiff base may undergo any one of a number of electron shifts transforming the amino acid moiety into the various observed products.[1] A particular type of enzyme apparently participates in the reaction by selectively catalyzing only the desired electron shift and by inhibiting all the other types of shifts. In order to understand the means by which enzymes can control the electron shifts in these Schiff bases, it is necessary to understand the factors which influence electron densities in the aromatic ring of the vitamin B-6 Schiff bases. The sensitivity of carbon-13 nuclear magnetic resonance (^{13}C NMR) to electronic structure is well known. We are in the process of carrying out a complete study of the ^{13}C NMR spectroscopy of the vitamin B-6 Schiff bases and their metal complexes, but, as a prelude, it has been necessary to study the vitamin B-6 group itself.



Herein we report the ^{13}C NMR spectral assignments, pH dependence, and coupling constants for the vitamin B-6 group and some related pyridine derivatives.

Experimental Section

Pyridoxal hydrochloride and pyridoxal-5′-phosphate were purchased from Sigma Chemical Co., and pyridoxamine dihydrochloride was obtained from Mann Research Laboratories. Picoline was from Reilly Tar and Chemical Corp. Pyridoxine, pyridoxamine 5′-phosphate, and the remaining monosubstituted pyridines were from Aldrich. Deuterium oxide was 99.8% from Thompson-Packard; NaOD (40% in D_2O) and DCl (20% in D_2O) were from Diaprep Inc.

Carbon-13 nuclear magnetic resonance spectra were obtained at 40° in Fourier transform mode with a Jeol PS/FFT-100 spectrometer and Jeol EC-100 data system. Chemical shifts were recorded in parts per million relative to an external capillary of dioxane; these values were adjusted to the tetramethylsilane (Me_4Si) scale by adding 67.4 ppm to the observed shift. This ignores a small (<0.2 ppm) correction due to diamagnetic susceptibility.[2] Typically a 6250-KHz range and 16K words of memory were used, giving a digital resolution of 0.76 Hz. The D_2O solvent was the source of an internal deuterium lock. Broad band decoupled (2 KHz), single frequency decoupled, and undecoupled spectra were recorded.

Solutions (1 *M*) of pyridoxal-related compounds (except pyridoxine) in D_2O were maintained at constant ionic strength with sodium chloride (3 *M*); in cases where 1 *M* solutions could not be prepared, saturated solutions were used. The pD (negative logarithm of deuterium ion activity) was recorded by adding 0.41 to the reading of a Brinkmann Model E512 pH meter standardized against aqueous buffers;[3] this method is valid only in the range $2 < pD < 9$, and values outside this range are approximate. No correction was made for sodium ion effects. Acidity was varied by the addition of DCl or NaOD. At these conditions of high salt and reagent concentration, observed pH becomes an ill-defined concept and reported pD values must be viewed as approximate measures of pH.

Results and Discussion

Resonance Assignments. Despite the structural similarity of compounds I–V, complete assignment of their resonances is an arduous task because many fall in a narrow

Table I
^{13}C Chemical Shifts of Pyridoxal and Related Compounds[a]

Compd	pD	CH_3	C-4'	C-5'	C-2	C-3	C-4	C-5	C-6
Pyridoxal (I)	2	15.8	99.6	71.2	144.9	149.9	140.8	139.2	127.0
Pyridoxal 5'-phosphate (II)	6.8	17.1	196.9	62.8	152.5	165.6	126.7	137.2	123.4
	8.7	18.3	197.2	63.1	154.4	166.7	125.9	135.8	125.5
Pyridoxamine (III)	2	16.9	36.1	60.0	144.1	154.3	137.3	139.4	132.6
	11	20.5	37.4	61.2	150.6	161.0	133.6	137.4	133.4
Pyridoxamine 5'-phosphate (IV)	7.1	16.6	37.6	63.0	145.6	163.6	133.6	135.6	124.7
	>11	20.7	37.5	63.9	150.9	161.0	138.2	131.8	134.2
Pyridoxine (V)	2.7	15.4	58.0	59.1	143.6	153.6	141.1	137.7	130.7
	9.9	18.6	58.0	60.3	148.8	161.2	135.5	134.1	130.6

[a] Shifts are in parts per million relative to tetramethylsilane (Me_4Si).

Table II
^{13}C Chemical Shifts for Some Substituted Pyridines in D_2O[a]

Substituent	Degree of protonation	C-2	C-3	C-4	C-5	C-6	Ref	Registry no.
H	0	150.4	124.1	136.1	124.1	150.4	*b*	
	100%	142.6	129.1	148.5	129.1	142.6	*b*	
2-CH_3	0	(159.9)	123.4	137.2	122.0	149.8	*c*	109-06-8
	0	(158.4)	124.7	138.4	122.1	148.4	*d*	
	50%	(156.7)	126.7	142.7	123.6	145.1	*d*	
	100%	(154.2)	129.0	147.6	125.3	141.2	*d*	
3-OH[e]	0	137.8	(153.5)	121.4	123.8	140.0	*f*	109-00-2
	0		(159.9)				*d*	
	100%		(157.4)				*d*	
4-CHO	0	151.5	122.8	(141.9)	122.8	151.5	*g*	872-85-5
	0	151.1	123.6	(142.6)	123.6	151.1	*d*	
4-$CH(OD)_2$	pD 1	142.5	125.6	(162.2)	125.6	142.5	*d*	55298-75-4
4-CH_2OH	pD 10	149.6	122.7	(152.0)	122.7	149.6	*d*	586-95-8
	pD 1	141.8	125.2	(164.3)	125.2	141.8	*d*	
3-CH_2OH[h]	0	148.4	(137.2)	137.4	125.2	148.8	*d*	100-55-0
	pD 5.9	144.9	(139.5)	141.1	126.6	145.6	*d*	
	pD 4.7	140.8	(142.0)	145.6	128.1	141.7	*d*	
	pD 1	140.1	(142.5)	146.3	128.4	141.0	*d*	

[a] δ_C, parts per million from Me_4Si. See ref 2. Data in parentheses are for the substituted carbon. [b] From R. J. Pugmire and D. M. Grant, *J. Am. Chem. Soc.*, **90**, 697 (1968). [c] From P. C. Lauterbur, *J. Chem. Phys.*, **43**, 360 (1968). [d] This work. [e] Only the assignment of C-3 could be made with certainty in aqueous solution because the resonances appeared in a narrow region and shifted with pH. [f] From ref 6. [g] From ref 11a. [h] The assignments of C-2 and C-6 are uncertain.

region of the spectrum and are substantially pD dependent. The following reasoning was used to arrive at the assignments in Table I. In all cases, a single resonance in the region of 15–21 ppm is clearly assignable to the 2'-methyl carbon atom. For pyridoxal and pyridoxal phosphate the remaining carbon atoms which are substituents of the aromatic ring are readily assignable by the multiplicity of their one-bond proton couplings. For pyridoxamine and pyridoxamine phosphate electronegativity arguments suggest that the upfield methylene resonance belongs to the 4' carbon atom while the downfield resonance belongs to the 5' carbon atom. For pyridoxamine phosphate this assignment is verified by the observation of $^2J_{CP} = 3$ Hz to the phosphate group. In all compounds the 5' carbon resonance shows $^3J_{CH} = 3$ Hz via coupling to 6-H. In pyridoxine this coupling was used to assign the resonance at 59–60 ppm to the 5' carbon atom, leaving the resonance at 58 ppm assigned to the 4' carbon atom.

The resonances of the pyrdine ring carbon atoms fall in a fairly narrow range. Here only the assignment of C-6 is straightforward by virtue of its large one-bond coupling to 6-H. In DMSO the 3-carbon atom of 3-hydroxypyridine is found at much lower field than the other carbon resonances.[4] We verified this in D_2O and studied the dependence of chemical shift on pH during deprotonation of the 3-OH group (Table II). The similar chemical shift of the lowest field resonance of all the vitamin B-6 group leads to its assignment as the 3-carbon atom.

Extensive use was made of long-range coupling constants and of single frequency decoupling experiments to arrive at the remaining assignments. In pyridoxal phosphate and pyridoxamine phosphate the 5-C resonance is readily assigned by the observation of three-bond carbon–phosphorus couplings[5] in proton-decoupled spectra. For pyridoxal phosphate, C-4 is also distinctive by virtue of its large (27 Hz) coupling to the aldehyde proton.[6] The remaining unassigned aromatic resonance in pyridoxal phosphate is then C-2 and this must be the resonance at 152–154 ppm which appears as a doublet of quartets via its two-bond coupling to the methyl protons ($J = 4$ Hz) and its three-bond coupling to 6-H ($J = 7$ Hz). For all the vitamin B-6 compounds a resonance of similar structure was observed in a similar region and therefore could be assigned confidently to C-2. These arguments leave all resonances assigned except C-4 and C-5 in the nonphosphorylated compounds. In these compounds, the two resonances are observed within 5 ppm of one another and are observed to cross over upon varying pH in some cases. Assignments of the resonances are difficult and are based on the general observation that two-bond proton–carbon-13 coupling constants are in the range of 1–4 Hz while three-bond couplings are somewhat larger, usually 4–7 Hz.[7] For pyridoxal, the decoupler was set at a

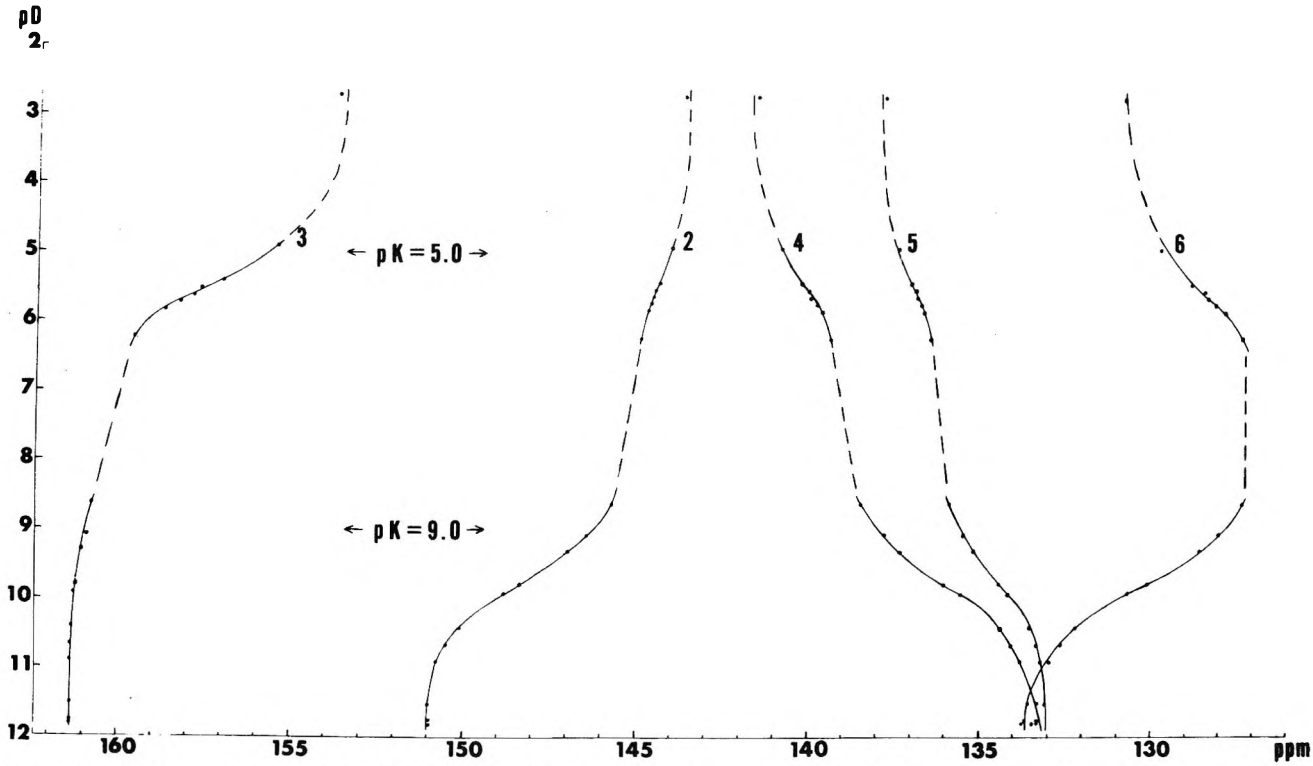


Figure 1. The pD dependence of chemical shifts for the carbon-13 resonances of pyridoxine. The reference is Me_4Si. Arrows refer to reported pK's, determined in H_2O.

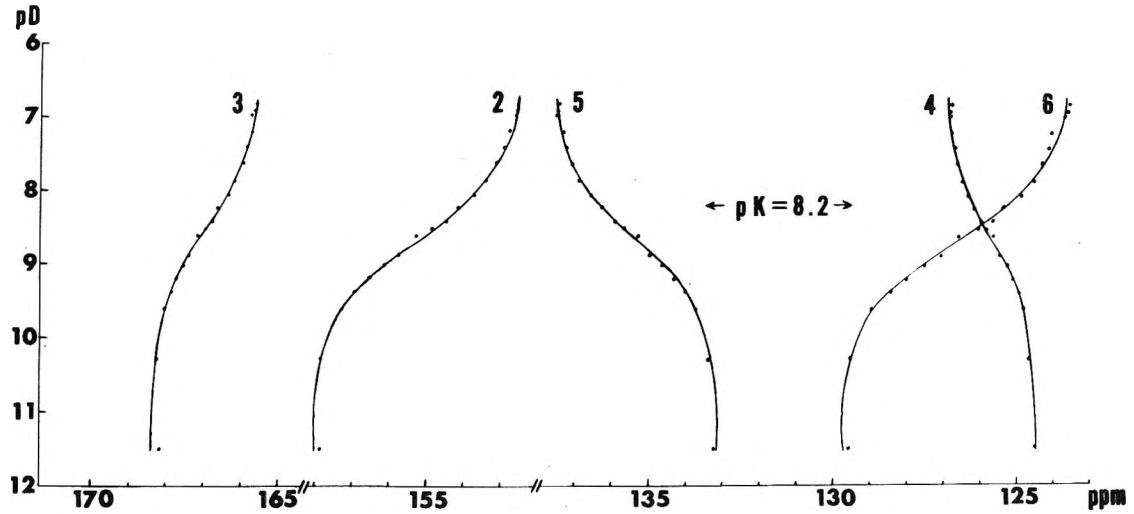


Figure 2. The pD dependence of chemical shifts for the carbon-13 resonances of pyridoxal phosphate. The reference is Me_4Si. Arrows refer to reported pK's, determined in H_2O.

frequency between those of 4′-CH and 5′-CH_2 in the proton spectrum. The decoupling power was adjusted so that 6-C was observed to be nearly completely coupled to 6-H but 4′-C and 5′-C were entirely decoupled from their protons. Under these conditions the resonance at 140.8 ppm is a doublet with J = 5.8 Hz and assigned to 4-C while the resonance at 139.2 ppm is a doublet split by about 2 Hz and is assigned to 5-C. On moving the decoupling frequency toward the 5′-CH_2 resonance, small additional splittings are observed at 4-C while larger ones develop at 5-C. This is indicative of the larger coupling of 5-C to 4′-CH as it becomes inefficiently decoupled. In pyridoxamine, a similar experiment reveals that 4-C and 5-C are reversed and that the resonance at 137.3 ppm belongs to 4-C while that at 139.4 belongs to 5-C. In pyridoxine, the resonances are in the same order as for pyridoxal with 4-C at 141.1 ppm and 5-C at 137.7 Hz.

pH Dependence of Chemical Shifts. Ionization of the pyridinium nitrogen and of the several substituents on the vitamin B-6 ring occurs as the pH of an acidic solution is increased. As expected, this results in a pH dependence of chemical shifts. For the aliphalic carbon nuclei chemical shifts on deprotonation are small—of the order of 1 ppm. Shifts are observed in both upfield and downfield directions with, for example, the 2′-carbon resonance of pyridoxine shifting downfield by 1 ppm while the 4′-carbon resonance shifts upfield by the same amount between pD 2 and pD 9. These and other data for substituent atoms appear in Table I.

The carbon resonances of the pyridine rings are much more profoundly influenced by pH change. Here shifts are as much as 10 ppm over a deprotonation, they occur in either the upfield or downfield directions, and some resonances first shift upfield and then downfield. The data are reported in Figures 1–3. The small differences between the inflection points of these NMR titration curves and the re-

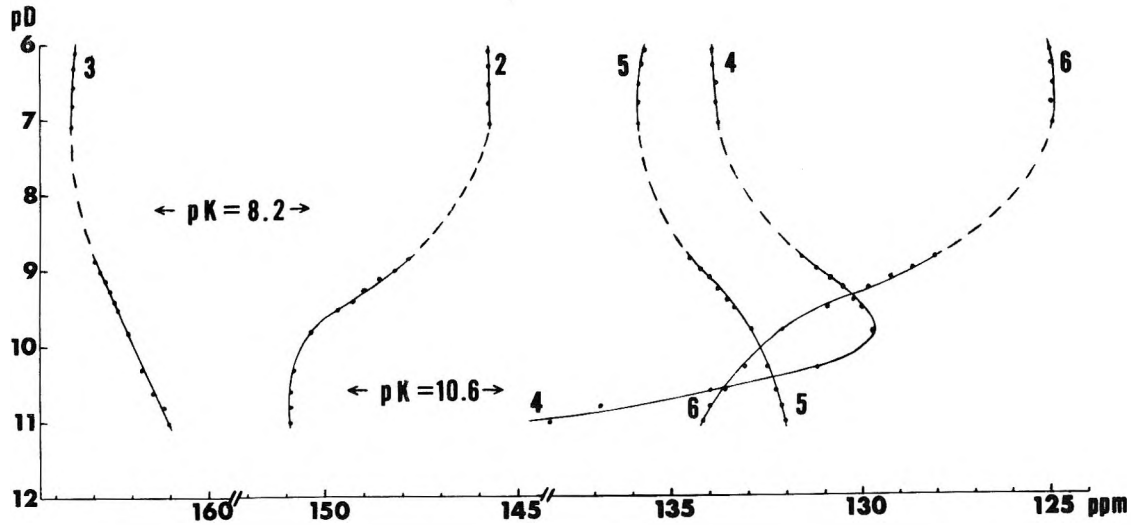
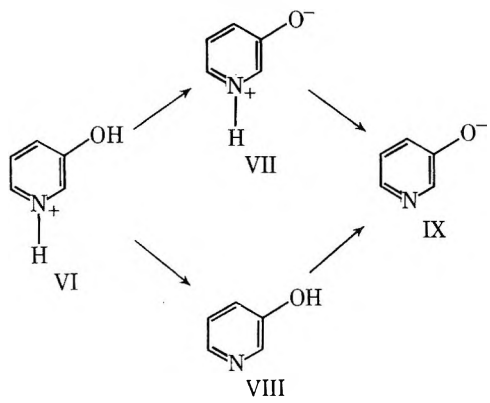


Figure 3. The pD dependence of chemical shifts for the carbon-13 resonances of pyridoxamine phosphate. The reference is Me_4Si. Arrows refer to reported pK's, determined in H_2O for pyridoxamine.

Chart I



ported pK's are due to the fact the pK's were determined at much lower ionic strength and in H_2O rather than D_2O.[8]

For 3-hydroxypyridine derivatives two general pathways for deprotonation are possible. They are represented as VI–IX in Chart I. In neutral solution either the zwitterionic species VII or the neutral species VIII is anticipated. In polar media such as water, VII predominates, although significant amounts of VIII are in equilibrium with it.[9] Therefore, the first deprotonation (pK_a = 4) of the vitamin B-6 group largely corresponds to the deprotonation of the phenolic group while the second corresponds to the deprotonation of the pyridinium nitrogen atom.

In pyridine, deprotonation results in downfield shifts of 2-C and upfield shifts for 3-C and 4-C. The theoretical interpretation for this has been discussed from several points of view.[10] Table II shows that pyridines with individual substituents similar to those of the vitamin B-6 group behave virtually identically to pyridine itself. Figures 1–3 illustrate that fairly similar trends are observed for all but C-3 of the vitamin B-6 group. This resonance shifts to higher field in the high pH deprotonation of pyridoxamine phosphate, to low field with pyridoxal phosphate, and is virtually unchanged for pyridoxine. A possible explanation would be that the different behaviors of 3-C reflect greater or lesser mixing of the 3-OH microscopic deprotonation into the high pK macroscopic deprotonation.

The directions and magnitudes of the pH dependence of chemical shift reflect such important physical effects as changes of electron density and changes in the difference between the energies of the ground and excited states. Since an important way that the enzyme can influence the reactivity of the coenzyme is through selective protonation or deprotonation of the various functional groups, it is particularly important to understand these effects in the vitamin B-6 group. Unfortunately, a detailed rationalization requires an extensive theoretical treatment of the electronic structure and is further complicated by the large and variable solvation energies involved. At the present time, it will suffice to point out that Figure 1 shows that the effect of two deprotonations on 2-C, 4-C, and 6-C is to make their pH dependences distinctive. In the low pH deprotonation 6-C and 4-C shift upfield while 2-C shifts downfield. In the second deprotonation 6-C and 2-C shift downfield while 4-C shifts upfield. Since all three sites are either ortho or para to the deprotonation, such behavior is not explicable by simple arguments; however, it shows that the effect of the substituents is to make the three sites each very different at different pH's. Selective protonation of the two sites can be expected to optimize these differences.

Beyond the effects of deprotonation of the phenolic and pyridinium sites, several other interesting effects are noted. The largest pH dependence of chemical shift is that of the pyridoxamine phosphate's 4-C near the pK for deprotonation of the 4′-$CH_2NH_3^+$. Interestingly, the effects of this deprotonation show up only at this carbon atom and all other adjacent atom are virtually unaffected by it. Also, in the phosphorylated compounds, deprotonations occuring at the phosphate group have almost no influence on the chemical shift of any aromatic carbon atoms in the compounds. Apparently the phosphate deprotonation produces minimal electronic changes in the aromatic system, in contrast to the ammonium deprotonation.

A recent ^{13}C NMR study of 3-hydroxypyridine and related compounds showed great differences between the spectra of the O-methylated and N-methylated isomers.[4] As these correspond to the neutral (VIII) and zwitterionic (VII) forms of the vitamin B-6 group in neutral solution, it is of interest to compare the shifts of these compounds with our data. Table III compares observed shifts for pyridoxal phosphate and for pyridoxine with calculated values predicted from the two methylated 3-hydroxypyridines, using substituent effects observed with monosubstituted pyridines.[11] These substituent shifts were taken from the literature and from the data in Table II. Shifts relative to pyridine were tabulated for each carbon nucleus of the appropriate monosubstituted pyridine. These were added together for all the substituents. Values obtained were added

Table III
Comparison of Observed Carbon-13 Shifts with Values Calculated from Neutral and Zwitterionic Models

	2-C	3-C	4-C	5-C	6-C
Pyridoxal Phosphate					
Observed, pD 6.9	151.5	165.6	126.7	137.2	124.0
Calculated from the neutral model[a]	144.9	152.1	124.8	134.3	141.2
Calculated from the zwitterionic model[b]	142.0	165.7	136.5	136.8	121.2
Pyridoxine					
Observed, pD 6.2	144.8	159.5	139.3	136.3	127.3
Calculated from the neutral model[a]	143.2	152.3	135.7	133.8	139.5
Calculated from the zwitterionic model[b]	140.3	165.8	146.7	136.8	119.5

[a] Calculated by adding substituent effects for monosubstituted pyridines to the chemical shifts of 3-OCH_3 pyridine. [4,b] Calculated by adding substituent effects for monosubstituted pyridines to the chemical shifts of the zwitterion derived by deprotonation of 1-methyl-3-hydroxypyridinium ion.

Table IV
One-Bond Coupling Constants (J_{C-H}) for Pyridoxal and Related Compounds[a]

Compd	pD	C-2'	C-4'	C-5'	C-6
PL	2	131.7	177.8	152.2	194.6
PLP	6.8	129.7	184.6	149.1	193
	8.3	128.2	181.6	148.0	186.9
PM	2	131.5	146.5	146.5	191.5
	11	126.1	136.6	144.6	177
PMP	7.1	130.3	145.0	145.7	188
	>11	126.6	136.2	145.0	177.4
PN	2.7	131.2	146.8	145.7	190.0
	9.9	127.7	144.2	144.2	180.0

[a] In hertz; signs were not determined.

to the reported chemical shifts for the zwitterion resulting from deprotonation of 1-methyl-3-hydroxypyridinium ion and to shifts observed for 3-methoxypyridine, respectively. The CH_2OH group was used as a model for the CH_2OX group.

As discussed above, the vitamin B-6 derivatives are thought to exist in the N-protonated zwitterionic form in neutral solution. The chemical shifts in Table IV generally support this assertion. Observed values are found to be generally quite close to those predicted from the simple model. Some of the discrepancies may be attributed to substantial amounts of the neutral tautomers in equilibrium with the zwitterion, particularly in the case of pyridoxine, where the equilibrium is more important.[9] However, the generally poor agreement for 2-C and 4-C must be attributed to the nonadditivity of substituent effects for these sites.

Coupling Constants. One-bond coupling constants for compounds I–V are listed in Table IV. These coupling constants are controlled by hybridization of the carbon atom. All values of these constants are within reported ranges of related compounds except those of the phosphorylated derivatives. Observed one-bond coupling for methylene carbon atoms uniformly are about 25 Hz less than those reported for the methylene groups of organic phosphates. Evidently, this reflects the interaction of the aromatic ring

Table V
Selected Two- and Three-Bond Coupling Constants for Pyridoxal and Related Compounds[a]

Compd	pD	J^b	
Pyridoxal (I)	2	$^2J_{CCH}$ (methyl to C-2)	6.1
		$^3J_{CNCH}$ (6-H to C-2)	6.1
		$^2J_{CCH}$ (6-H to C-5)	2.3
		$^3J_{CCCH}$ (6-H to C-4)	5.8
Pyridoxal 5'-phosphate (II)	6.8	$^2J_{CCH}$ (methyl to C-2)	6.9
		$^3J_{CNCH}$ (6-H to C-2)	6.9
		$^3J_{CCH}$ (6-H to C-4)	3.6
		$^2J_{CCH}$ (CHO to C-4)	19.2
	8.7	$^2J_{CCH}$ (methyl to C-2)	6.1
		$^3J_{CCCH}$ (6-H to C-4)	6.1
		$^2J_{CCH}$ (CHO to C-4)	21.4
Pyridoxamine (III)	2	$^2J_{CCH}$ (methyl to C-2)	6.5
		$^3J_{CNCH}$ (6-H to C-2)	6.5
		$^3J_{CCCH}$ (5'-methylene to C-6)	4.6
		$^2J_{CCH}$ (6-H to C-5)	2.9
		$^3J_{CCCH}$ (6-H to C-4)	5.0
	11	$^2J_{CCH}$ (methyl to C-2)	6.1
		$^3J_{CNCH}$ (6-H to C-2)	9.9
		$^3J_{CCCH}$ (5'-methylene to C-6)	5.3
Pyridoxamine 5'-phosphate (IV)	7.1	$^2J_{CCH}$ (methyl to C-2)	6.9
		$^3J_{CNCH}$ (6-H to C-2)	6.9
		$^3J_{CCCH}$ (5'-methylene to C-6)	4.6
	>11	$^2J_{CCH}$ (methyl to C-2)	6.1
		$^3J_{CNCH}$ (6-H to C-2)	9.9
		$^3J_{CCCH}$ (5'-methylene to C-6)	4.6
Pyridoxine (V)	2.7	$^2J_{CCH}$ (methyl to C-2)	6.1
		$^3J_{CNCH}$ (6-H to C-2)	6.1
		$^3J_{CCCH}$ (5'-methylene to C-6)	4.2
		$^2J_{CCH}$ (6-H to C-5)	4.9
	9.9	$^2J_{CCH}$ (methyl to C-2)	6.1
		$^3J_{CNCH}$ (6-H to C-2)	9.2
		$^3J_{CCCH}$ (5'-methylene to C-6)	5.3

[a] ±0.8 Hz; signs were not determined.

with the phosphorylated methylene group. In all cases coupling constants decreased upon deprotonation of the compound; however, the changes are not sufficiently great to indicate a strikingly different electronic structure for the pyridine ring upon deprotonation. No correlation of these changes in coupling constant is observed with the pH dependence of chemical shift. Evidently s orbital changes are small compared to p orbital changes during deprotonation in the compounds.

As an aid to the assignment of the various resonances, two- and three-bond proton–carbon coupling constants were also determined. These are reported in Table V.

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Registry No.—I, 17281-92-4; II, 54-47-7; III, 85-87-0, IV, 529-96-4; V, 65-23-6.

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The Chemistry of 2-Alkoxy-3,4-dihydro-2*H*-pyrans. III. Synthesis and Solvolysis of the Dichlorocarbene Adducts 3-Alkoxy-2-oxa-7,7-dichloronorcaranes

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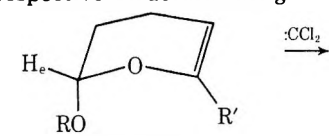
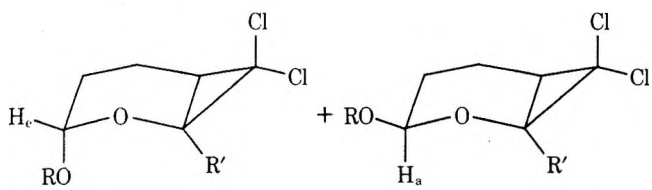
trans- and *cis*-3-alkoxy-2-oxa-7,7-dichloronorcaranes (**2a,b**) and *trans*- and *cis*-3-alkoxy-1-methyl-2-oxa-7,7-dichloronorcaranes (**2c,d**) were prepared by the addition of dichlorocarbene to 2-alkoxy-3,4-dihydro-2*H*-pyrans (**1a,b**) and 2-alkoxy-6-methyl-3,4-dihydro-2*H*-pyrans (**1c,d**), respectively. The addition, which is rather stereoselective owing primarily to the steric interactions of the axial 2-alkoxy group on the 3,4-dihydro-2*H*-pyran ring, yields predominantly the trans product. Subsequent solvolysis of the trans–*cis* mixtures **2a** and **2b** in alcoholic silver nitrate yielded 2-chloro-1,1,6,6-tetramethoxy-*cis*-2-hexene (**3a**) and 2-chloro-1,1,6,6-tetraethoxy-*cis*-2-hexene (**3b**), respectively. Similar treatment of **2c** and **2d** resulted in the formation of 3-chloro-7,7-dimethoxy-*cis*-3-hepten-2-one (**4a**) and 3-chloro-7,7-diethoxy-*cis*-3-hepten-2-one (**4b**), respectively. Evidence is presented that the electrocyclic ring opening requires the synchronous assistance of the equatorial 3-alkoxy substituent.

For some time we have been interested in the rather unusual effect of ring substituents on the chemistry of 3,4-dihydro-2*H*-pyrans.[2] In particular, an alkoxy group at the C-2 position seems to play a significant role in the outcome of electrophilic additions to the dihydropyran **1**.[2,3] We now describe the influence of the 2-alkoxy group on the addition of dichlorocarbene to the title compounds **1a–d**, and the subsequent solvolytic rearrangement studies of the dichlorocarbene adducts **2a–d** in alcoholic silver nitrate solutions.

Addition of dichlorocarbene, generated by the decomposition of ethyl trichloroacetate with sodium methoxide,[4] to 2-alkoxy-3,4-dihydro-2*H*-pyrans (**1a,b**)[5] and 2-alkoxy-6-methyl-3,4-dihydro-2*H*-pyrans (**1c,d**)[5] yielded a trans–cis mixture of the corresponding 3-alkoxy-2-oxa-7,7-dichloronorcaranes (**2a,b**) and 3-alkoxy-1-methyl-2-oxa-7,7-dichloronorcaranes (**2c,d**), respectively. The trans–cis mixtures were separated by careful column chromatography, and the respective structural assignments were based on spectral data and composition analyses. The stereochemical and conformational assignments of the adducts **2a–d** were made by analyzing the 100-MHz NMR spectra of the products (see Table I) and are consistent with the assigned conformation of the substituted dihydropyrans **1a–d.**

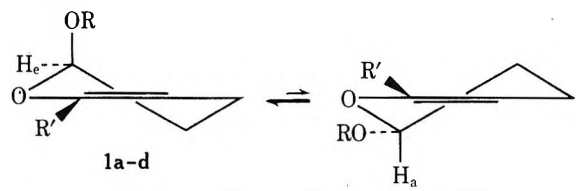


1a, R = CH_3; R′ = H
b, R = C_2H_5; R′ = H
c, R = CH_3; R′ = CH_3
d, R = C_2H_5; R′ = CH_3



trans-**2a–d** *cis*-**2a–d**

The conformations of the 2-alkoxy-3,4-dihydro-2*H*-pyrans (**1a–d**) were assigned by inspection of the 100-MHz NMR spectra. Two conformations for the 2-alkoxy-3,4-dihydro-2*H*-pyrans (**1a–d**) are possible, one with an equatorial anomeric proton (H_e) and another with an axial anomeric proton (H_a). The NMR spectrum of **1a** and **1c** each



1a-d

contains only one methoxy signal, indicating that only one conformation is present. Similarly, **1b** and **1d** each contain only one ethoxy triplet (see Table II). Since the anomeric proton of each 2-alkoxy-3,4-dihydro-2*H*-pyran (**1a–d**) is clearly a triplet, where $J_{ae} = J_{ee}$, the dihydropyrans **1a–d** exist predominantly (greater than 90%) in the conformation where the anomeric proton (H_e) is equatorial. Such a conformation is also predicted by the anomeric effect (Edward–Lemieux effect)[6] and makes the rather stereoselective addition of the dichlorocarbene to the olefins **1a–d** understandable.

The presence of a bulky axial group (the alkoxy substituent of the C-2 position) would result in a preferential trans addition to the dihydropyran **1**, yielding *trans*-**2** as the predominant product containing an anomeric equatorial proton (see Table I). Addition to the less favored sterically hindered side of the molecule would yield the minor product *cis*-**2**, which would assume a conformation containing

Table I

Adduct	R	R	Trans:cis	Trans H_e proton, δ	Cis H_a proton, δ
2a	CH_3	H	73:27	4.54 (t, J = 3 Hz)[a]	4.32 (dd, J = 4, 7 Hz)[a]
2b	C_2H_5	H	74:26	4.64 (t, J = 3 Hz)[a]	4.38 (dd, J = 4, 7 Hz)[a]
2c	CH_3	CH_3	80:20	4.70 (t, J = 3 Hz)[b]	4.36 (dd, J = 5, 7 Hz)[b]
2d	C_2H_5	CH_3	95:5	4.78 (t, J = 3 Hz)[b]	4.43 (dd, J = 5, 7 Hz)[b]

[a] 100 MHz, CCl_4. [b] 100 MHz, $CDCl_3$.

Table II[a]

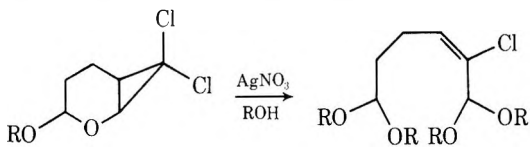
Dihydropyran	R	R	H_e anomeric proton, δ	CH_3O–, δ	CH_3CH_2O–, δ
1a	CH_3	H	4.77 (t, J = 3 Hz)	3.37 (s)	
1b	C_2H_5	H	4.86 (t, J = 3 Hz)		1.16 (t)
1c	CH_3	CH_3	4.82 (t, J = 3 Hz)[b]	3.37 (s)	
1d	C_2H_5	CH_3	4.93 (t, J = 3 Hz)[b,c]		1.18 (t)

[a] 100 MHz, CCl_4. [b] Similar results in CD_3CN. [c] Similar results in $CDCl_3$.

an anomeric axial proton (see Table I) to minimize steric interactions.

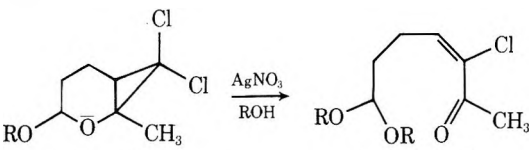
The successful preparation of the *trans*- and *cis*-3-alkoxy-2-oxa-7,7-dichloronorcaranes (**2a–d**) gave us an excellent opportunity to study the effect of the 3-alkoxy group on the electrocyclic ring opening of this system, which should proceed in a stereospecific disrotatory fashion.[7] Some previous ring openings of dihalocarbene adducts which have led to interesting results include thermolysis of 2-oxa-7,7-dichloronorcarane (**5**) with quinoline at reduced pressure,[4b] thermal rearrangement of 6,6-dichloro-2-oxabicyclo[3.1.0]hexane and its 3,3-dimethyl derivative,[8] and the silver ion assisted methanolysis of 11,11-dibromotricyclo[4.4.1.$0^{1,6}$]undecane.[9] We chose the latter less drastic conditions for our present study of the rather labile compounds **2a–d.**

Solvolysis of the trans–cis mixtures **2a** and **2b** in alcoholic silver nitrate yielded 2-chloro-1,1,6,6-tetramethoxy-*cis*-2-hexene (**3a**) and 2-chloro-1,1,6,6-tetraethoxy-*cis*-2-hexene (**3b**), respectively. Similar treatment of **2c** and **2d** re-



2a, R = CH_3 **3a**, R = CH_3
b, R = C_2H_5 **b**, R = C_2H_5

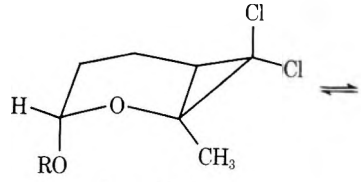
sulted in the formation of 3-chloro-7,7-dimethoxy-*cis*-3-hepten-2-one (**4a**) and 3-chloro-7,7-diethoxy-*cis*-3-hepten-2-one (**4b**), respectively. The isolated yield of each product



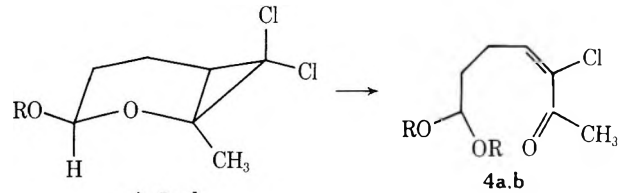
2c, R = CH_3 **4a**, R = CH_3
d, R = C_2H_5 **b**, R = C_2H_5

was respectable (78–86%). The assigned structures for the solvolysis products **3a, 3b, 4a,** and **4b** are all consistent with the spectral data and composition analyses.

Solvolysis of the pure *cis*-**2d** and *trans*-**2d** dichlorocarbene adducts turned out to be extremely important in understanding the mechanism of this rearrangement. Treatment of *cis*-3-ethoxy-1-methyl-2-oxa-7,7-dichloronorcarane (*cis*-**2d**) with ethanolic silver nitrate at 25° immediately produced the silver chloride precipitate, indicating a rather fast reaction. On the other hand, no precipitate was detected for several hours when *trans*-3-ethoxy-1-methyl-2-oxa-7,7-dichloronorcarane (*trans*-**2d**) was subjected to these conditions, suggesting a very slow reaction. The rate could be enhanced by gently warming the reaction mixture. Premature quenching of a solvolytic experiment using *trans*-**2d,** where trace amounts of silver nitrate were used in a very dilute system, yielded a mixture composed of *trans*-**2d,** product **4b,** and trace quantities of *cis*-**2d** which were isolated and identified. The presence of small amounts of *cis*-**2d** implies that *trans*-**2d** epimerizes to *cis*-**2d** and that it is the latter which undergoes electrocyclic ring opening. Similar empirical rate observations were evi-



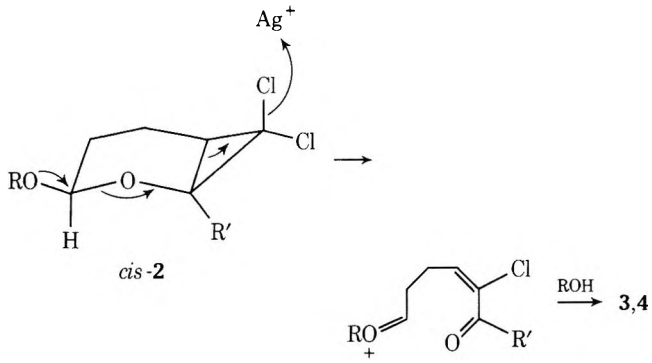
trans-**2c,d**



cis-**2c,d** **4a,b**

dent with *cis*- and *trans*-3-methoxy-1-methyl-2-oxa-7,7-dichloronorcarane (**2c**), although not quite as dramatic; which probably mean that the trans to cis epimerization is somewhat faster in this system.[10]

Consequently, it appears that the solvolysis of the syn substituent,[8,11] which results in a concerted disrotatory ring opening of the dichloroadducts **2** yielding the cis double bond[7,12] products **3** and **4,** requires the synchronous as-



cis-**2**

sistance[13] of the equatorial 3-alkoxy substituent. It was thus not surprising to find that the parent 2-oxa-7,7-dichloronorcarane (5), the dichlorocarbene adduct of 3,4-dihydro-2*H*-pyran,[4b,c] was inert to these and even more vigorous conditions.

Experimental Section[15]

The 2-alkoxy-3,4-dihydro-2*H*-pyrans (**1a, 1b**) and the 2-alkoxy-6-methyl-3,4-dihydro-2*H*-pyrans (**1c, 1d**) were prepared by a method previously described.[5a,b] Pyran **1b** is also available from Aldrich Chemical Co. Two of the commercial reagents require some special attention: the ethyl trichloroacetate must be distilled just prior to use and the sodium methoxide should be a freshly opened sample. Both solvents, methanol and the olefin-free pentane, were reagent grade. The pentane was passed through a Woelm neutral aluminum oxide (activity grade I) column just prior to use. All reactions were performed in dry glassware under a static nitrogen atmosphere. Gas chromatography (GLC) was performed on a Hewlett-Packard Model 7610A high-efficiency chromatograph (flame detector) using a 4 ft × 6 mm (all glass) 5% Carbowax 20M on 60–80 Chromosorb W column. Distillations were accomplished with short-path or Büchi Kugelrohr bulb-to-bulb apparatus. All boiling points are uncorrected. Column chromatography was performed on Woelm neutral aluminum oxide (activity grade III), Matheson Coleman and Bell activated alumina (chromatographic grade, 80–325 mesh), and Floridin magnesium silicate (Florisil, 60–100 mesh) columns by eluting with petroleum ether and petroleum ether–Et_2O.

3-Methoxy-2-oxa-7,7-dichloronorcarane (2a). To a stirred and cooled (0°) slurry of 2-methoxy-3,4-dihydro-2*H*-pyran (**1a,** 7.22 g, 0.063 mol) and sodium methoxide (5.0 g, 0.088 mol) in pentane (40 ml) was slowly added (ca. 10 min) 16.5 g (0.086 mol) of ethyl trichloroacetate. The mixture was stirred for 6 hr at 0° and then for 16 hr at 25°, after which the reaction mixture was partitioned between water and petroleum ether. The organic layer was separated and dried ($MgSO_4$), and the solvent was removed in vacuo affording a yellow oil (13.2 g). Analysis (GLC) of the yellow oil indicated a 73:27 mixture of trans and cis isomers of **2a,** which distilled together yielding a colorless oil (6.38 g, 52%): bp 105–107° (10 mm); ir (film) 2936, 1450, 1365, 1216, 1142, 1116, 1083, 1039, 1022, 905, 835, 711 cm^{-1}; mass spectrum *m/e* (rel intensity) 169 (8), 167 (23), 165 (19), 161 (8), 138 (10), 136 (10), 133 (13), 131 (10), 111 (37), 109 (62), 101 (27), 97 (19), 71 (100), 65 (29), 58 (65), 45 (29), 43 (21), 41 (27), 39 (27).

Anal. Calcd for $C_7H_{10}Cl_2O_2$: C, 42.67; H, 5.11; Cl, 35.98. Found: C, 42.73; H, 5.02; Cl, 36.03.

Column chromatography of distillate **2a** on alumina (Matheson Coleman and Bell) yielded 4.85 g (39%) of *trans*-**2a** (colorless oil), NMR (100 MHz, CCl_4) δ 4.54 (1 H, t, J = 3 Hz, equatorial anomeric proton), 3.50 (1 H, d, J = 8 Hz), 3.39 (3 H, s), 2.26–1.23 (5 H, m); a mixture which contained 415 mg (3%) of *trans*- and *cis*-**2a;** and 479 mg (4%) of *cis*-**2a** (colorless oil), NMR (100 MHz, CCl_4) δ 4.32 (1 H, d of d, J = 4 and 7 Hz, axial anomeric proton), 3.71 (1 H, d, J = 8 Hz), 3.41 (3 H, s), 2.22–1.99 (2 H, m), 1.80–1.40 (3 H, m).

3-Ethoxy-2-oxa-7,7-dichloronorcarane (2b). To a stirred and cooled (0°) slurry of 2-ethoxy-3,4-dihydro-2*H*-pyran (**1b,** 12.8 g, 0.10 mol) and sodium methoxide (7.4 g, 0.13 mol) in pentane (75 ml) was slowly added (*ca.* 15 min) 22.7 g (0.12 mol) of ethyl trichloroacetate. The mixture was stirred for 6 hr at 0° and then for 16 hr at 25°. Normal work-up, as described above for **2a,** afforded a yellow oil (11.8 g). Analysis (GLC) of the yellow oil indicated a 74:26 mixture of trans and cis isomers of **2b,** which distilled together yielding a colorless oil (9.7 g, 46%): bp 64–66° (12 mm); ir (film) 2975, 2930, 1445, 1370, 1228, 1210, 1145, 1114, 1085, 1046, 1024, 952, 876, 836, 814, 717 cm^{-1}; mass spectrum *m/e* (rel intensity) 185 (1), 183 (5), 181 (10), 177 (2), 175 (8), 169 (5), 167 (14), 165 (22), 149 (9), 147 (32), 145 (12), 138 (10), 136 (12), 129 (8), 128 (13), 125 (11), 111 (33), 109 (53), 101 (36), 85 (100), 83 (33), 72 (81), 65 (28), 57 (58), 44 (71), 39 (32).

Anal. Calcd for $C_8H_{12}Cl_2O_2$: C, 45.52; H, 5.73; Cl, 33.59. Found: C, 45.81; H, 5.91; Cl, 33.38.

Column chromatography of distillate **2b** on alumina (Matheson Coleman and Bell) yielded 5.72 g (27%) of *trans*-**2b** (colorless oil), NMR (100 MHz, CCl_4) δ 4.64 (1 H, t, J = 3 Hz, equatorial anomeric proton), 3.46 (1 H, d, J = 8 Hz) superimposed on four overlapping quartets centered at 3.76 (1 H, two overlapping quartets, J = 7 and 10 Hz) and 3.45 (1 H, two overlapping quartets, J = 7 and 10 Hz), 2.34–1.29 (5 H, complex m), 1.19 (3 H, t, J = 7 Hz); a mixture which contained 2.23 g (11%) of *trans*- and *cis*-**2b;** and 291 mg (1.5%) of *cis*-**2b** (colorless oil), NMR (100 MHz, CCl_4) δ 4.38 (1 H, d of d, J = 4 and 7 Hz, axial anomeric proton), 3.88 (1 H, two overlapping quartets, J = 7 and 9 Hz) on which is superimposed a doublet at 3.68 (1 H, d, J = 8 Hz), 3.40 (1 H, two overlapping quartets, J = 7 and 9 Hz), 2.34–1.93 (2 H, m), 1.92–1 25 (3 H, m), 1.17 (3 H, t, J = 7 Hz).

3-Methoxy-1-methyl-2-oxa-7,7-dichloronorcarane (2c). To a stirred and cooled (0°) slurry of 2-methoxy-6-methyl-3,4-dihydro-2*H*-pyran (**1c,** 19.2 g, 0.12 mol) and sodium methoxide (9.7 g, 0.18 mol) in pentane (100 ml) was slowly added (*ca.* 20 min) 32.5 g (0.17 mol) of ethyl trichloracetate. The mixture was stirred for 6 hr at 0° and then for 16 hr at 25°. Normal work-up, as described above for **2a,** afforded a yellow oil (35 g). Analysis (GLC) of the yellow oil indicated a 80:20 mixture of trans and cis isomers of **2c,** which distilled together yielding a colorless oil (19.0 g, 60%): bp 73–75° (1 mm); ir (film) 2925, 2830, 1440, 1375, 1220, 1112, 1055, 1030, 920, 895, 845, 700 cm^{-1}.

Anal. Calcd for $C_8H_{12}Cl_2O_2$: C, 45.52; H, 5.73; Cl, 33.59. Found: C, 45.78; H, 5.88; Cl, 33.51.

Column chromatography of distillate **2c** on aluminum oxide (Woelm) yielded 13.68 g (43%) of *trans*-**2c** (colorless oil), NMR (100 MHz, $CDCl_3$) δ 4.70 (1 H, t, J = 3 Hz, equatorial anomeric proton), 3.48 (3 H, s), 1.64 (3 H, s) superimposed on a multiplet at 2.40–1.35 (5 H, m), mass spectrum *m/e* (rel intensity) 183 (0.2), 181 (1), 179 (1), 177 (0.3), 175 (1), 169 (0.6), 167 (1), 143 (1), 141 (3), 139 (7), 111 (23), 109 (38), 97 (12), 79 (19), 72 (17), 71 (85), 58 (40), 43 (100); a mixture which contained 2.66 g (8%) of *trans*- and *cis*-**2c;** and 2.09 g (7%) of *cis*-**2c** (colorless oil), NMR (100 MHz, $CDCl_3$) δ 4.36 (1 H, d of d, J = 5 and 7 Hz, axial anomeric proton), 3.50 (3 H, s), 2.30–2.04 (2 H, m), 1.63 (3 H, s) superimposed on a multiplet at 1.70–1.37 (3 H, m), mass spectrum *m/e* (rel intensity) 181 (0.3), 179 (0.4), 177 (0.4), 175 (1), 171 (0.2), 169 (1), 167 (1), 143 (1), 141 (4), 139 (8), 111 (28), 109 (44), 97 (12), 79 (17), 72 (22), 71 (84), 58 (45), 43 (100).

3-Ethoxy-1-methyl-2-oxa-7,7-dichloronorcarane (2d). To a stirred and cooled (0°) slurry of 2-ethoxy-6-methyl-3,4-dihydro-2-*H*-pyran (**1d,** 15.0 g, 0.105 mol) and sodium methoxide (7.2 g, 0.13 mol) in pentane (75 ml) was slowly added (ca. 15 min) 23.0 g (0.116 mol) of ethyl trichloroacetate. The mixture was stirred for 6 hr at 0° and then for 16 hr at 25°. Normal work-up, as described above for **2a,** afforded a yellow oil (15.8 g). Analysis (GLC) of the yellow oil indicated a 95:5 mixture of trans and cis isomers of **2d,** which distilled together yielding a colorless oil (12 g, 51%): bp 76–78° (1 mm); ir (film) 2980, 2935, 1445, 1375, 1245, 1212, 1110, 1060, 1030, 960, 895, 880, 845, 700 cm^{-1}.

Anal. Calcd for $C_9H_{14}Cl_2O_2$: C, 48.02; H, 6.27; Cl, 31.50. Found: C, 48.31; H, 6.28; Cl, 30.59.

Column chromatography of distillate **2d** on alumina (Matheson Coleman and Bell) yielded 9.0 g (38%) of *trans*-**2d** (colorless oil), NMR (100 MHz, $CDCl_3$) δ 4.78 (1 H, t, J = 3 Hz, equatorial anomeric proton), 3.89 (1 H, two overlapping quartets, J = 7 and 10 Hz), 3.52 (1 H, two overlapping quartets, J = 7 and 10 Hz), 1.59 (3 H, s) superimposed on a complex multiplet at 2.28–1.32 (5 H, m), 1.20 (3 H, t, J = 7 Hz), mass spectrum *m/e* (rel intensity) 193 (0.1), 191 (0.6), 189 (2), 183 (2), 181 (3), 179 (3), 145 (7), 141 (10), 139 (7), 117 (13), 115 (14), 111 (28), 109 (38), 89 (27), 85 (74), 57 (66), 53 (27), 43 (100); a mixture which contained 360 mg (1.5%) of *trans*- and *cis*-**2d;** and 360 mg (1.5%) of *cis*-**2d** (colorless oil), NMR (100 MHz, $CDCl_3$) δ 4.43 (1 H, d of d, J = 5 and 7 Hz, axial anomeric proton), 3.99 (1 H, two overlapping quartets, J = 7 and 10 Hz), 3.52 (1 H, two overlapping quartets, J = 7 and 10 Hz), 2.28–1.94 (2 H, m), a singlet at 1.61 (3 H, s) and a triplet at 1.21 (3 H, t, J = 7 Hz) superimposed on a complex multiplet at 1.92–1.20 (3 H, m), mass spectrum *m/e* (rel intensity) 191 (0.3), 189 (0.8), 183 (0.9), 181 (2), 179 (0.4), 145 (3), 141 (6), 139 (4), 117 (6), 115 (5), 111 (17), 109 (24), 89 (12), 85 (30), 57 (38), 53 (13), 43 (100).

2-Chloro-1,1,6,6-tetramethoxy-*cis*-2-hexene (3a). A solution of 3-methoxy-2-oxa-7,7-dichloronorcarane (**2a,** trans and cis mixture, 262 mg, 1.33 mmol) in 2 ml of methanol was added to a stirred solution of silver nitrate (249 mg, 1.46 mmol) in 5 ml of methanol; subsequently a white precipitate gradually appeared. After 24 hr the mixture was partitioned between petroleum ether and water; then the organic phase was separated, washed with brine, dried ($MgSO_4$), and concentrated in vacuo, affording a pale yellow oil (ca. 320 mg). Analysis (GLC) indicated one product. Further purification of the oil by column chromatography on Florisil yielded 2-chloro-1,1,6,6-tetramethoxy-*cis*-2-hexene (**3a**) as a colorless oil (247 mg, 78%): ir (film) 2970, 2915, 2810, 1660, 1450,

1360, 1190, 1130, 1060, 975, 915, 735 cm^{-1}; NMR (60 MHz, $CDCl_3$) δ 6.10 (1 H, t, J = 7 Hz with further fine splitting), 4.75 (1 H, perturbed s), 4.40 (1 H, t, J = 6 Hz), 3.39 (12 H, s), 2.36 (2 H, q, J = 7 Hz), 1.98–1.52 (2 H, m); mass spectrum m/e (rel intensity) 209 (3), 207 (8), 177 (2), 175 (4), 149 (9), 148 (9), 139 (5), 101 (4), 88 (5), 75 (100), 71 (4), 47 (5).

Anal. Calcd $C_{10}H_{19}ClO_4$: C, 50.32; H, 8.02; Cl, 14.85. Found: C, 50.61; H, 8.19; Cl, 14.99.

2-Chloro-1,1,6,6-tetraethoxy-*cis*-2-hexene (3b). A solution of 3-ethoxy-2-oxa-7,7-dichloronorcarane (**2b**, trans and cis mixture, 492 mg, 2.33 mmol) in 5 ml of ethanol was added to a stirred solution of silver nitrate (420 mg, 2.47 mmol) in 10 ml of ethanol; subsequently a white precipitate gradually appeared. Normal work-up, as described above for **3a**, after 24 hr afforded a pale yellow oil (ca. 670 mg). Analysis (GLC) indicated one product. Further purification of the oil by column chromatography on Florisil yielded 2-chloro-1,1,6,6-tetraethoxy-*cis*-2-hexene (**3b**) as a colorless oil (585 mg, 85%): ir (film) 2985, 2940, 2890, 1662, 1442, 1370, 1270, 1120, 1050 cm^{-1}; NMR (60 MHz, CCl_4) δ 5.98 (1 H, t, J = 7 Hz with further fine splitting), 4.72 (1 H, perturbed s), 4.57 (1 H, t, J = 6 Hz), 3.85–3.11 (8 H, complex m which appears to be a series of overlapping quartets, J = 7 Hz), 2.24 (2 H, q, J = 7 Hz), 1.88–1.41 (2 H, m), and two overlapping triplets at 1.18 (6 H, t J = 7 Hz) and 1.15 (6 H, t, J = 7 Hz); mass spectrum m/e (rel intensity) 251 (4), 249 (12), 205 (2), 203 (3), 178 (3), 177 (4), 176 (10), 175 (6), 111 (9), 103 (100), 83 (12), 75 (38), 47 (32).

Anal. Calcd $C_{14}H_{27}ClO_4$: C, 57.04; H, 9.23; Cl, 12.03. Found: C, 56.88; H, 9.03; Cl, 12.34.

3-Chloro-7,7-dimethoxy-*cis*-3-hepten-2-one (4a). A solution of 3-methoxy-1-methyl-2-oxa-7,7-dichloronorcarane (**2a**, trans and cis mixture, 615 mg, 2.91 mmol) in 12 ml of methanol was added to a stirred solution of silver nitrate (551 mg, 3.24 mmol) in 30 ml of methanol; subsequently a white precipitate gradually appeared. Normal work-up, as described above for **3a**, after 24 hr afforded a pale yellow oil (581 mg). Analysis (GLC) indicated a major component (**4a**, 94%) and minor component (**6**, 6%).[14] Purification of the oil by column chromatography on Florisil yielded a mixture which contained 77 mg of **6** and **4a** and 518 mg (86%) of 3-chloro-7,7-dimethoxy-*cis*-3-hepten-2-one (**4a**) as a colorless oil: ir (film) 2930, 2820, 1685, 1615, 1435, 1355, 1245, 1220, 1125, 1065, 895 cm^{-1}; NMR (60 MHz, CCl_4) δ 6.85 (1 H, t, J = 7 Hz), 4.28 (1 H, t, J = 5.5 Hz), 3.26 (6 H, s), 2.34 (3 H, s) superimposed on 2.30 (2 H, q, J = 7 Hz), 1.93–1.50 (2 H, m); mass spectrum m/e (rel intensity) 177 (5), 175 (16), 162 (2), 160 (6), 137 (6), 135 (28), 133 (3), 131 (14), 101 (14), 89 (15), 75 (89), 58 (26), 53 (43), 43 (100).

Anal. Calcd for $C_9H_{15}ClO_3$: C, 52.31; H, 7.32; Cl, 17.15. Found: C, 52.10; H, 7.61; Cl, 16.85.

3-Chloro-7,7-diethoxy-*cis*-3-hepten-2-one (4b). A solution of 3-ethoxy-1-methyl-2-oxa-7,7-dichloronorcarane (**2d**, trans and cis mixture, 1.20 g, 5.33 mmol) in 5 ml of ethanol was added to a stirred solution of silver nitrate (1.02 g, 6.00 mmol) in 75 ml of ethanol; after some time a white precipitate gradually appeared. After 24 hr the mixture was filtered and the supernate was concentrated in vacuo to ca. 20 ml and then partitioned between hexane and water. The organic phase was separated, washed with brine, dried (Na_2SO_4), and concentrated in vacuo, affording a pale yellow oil (1.10 g). Analysis (GLC) indicated one product. Further purification of the oil by column chromatography on Florisil yielded 3-chloro-7,7-diethoxy-*cis*-3-hepten-2-one (**4b**) as a colorless oil (1.08 g, 86%): ir (film) 2965, 2920, 2870, 1685, 1613, 1355, 1365, 1240, 1220, 1120, 1060 cm^{-1}; NMR (100 MHz, $CDCl_3$) δ 7.02 (1 H, t, J = 7 Hz), 4.52 (1 H, t, J = 5.3 Hz), 3.68 (2 H, two overlapping quartets, J = 7 and 9.5 Hz), 3.49 (2 H, two overlapping quartets, J = 7 and 9.5 Hz), 2.40 (3 H, s) superimposed on 2.49 (2 H, q, J = 7 Hz), 1.82 (2 H, two overlapping triplets, J = 5.3 and 7 Hz), 1.20 (6 H, t, J = 7 Hz); mass spectrum m/e (rel intensity) 236 (M^+, 0.2), 234 (M^+, 0.7), 191 (15), 189 (47), 161 (2), 159 (6), 151 (13), 149 (40), 125 (10), 115 (24), 103 (100), 85 (13), 75 (40), 47 (33), 43 (74).

Anal. Calcd for $C_{11}H_{19}ClO_3$: C, 56.29; H, 8.16; Cl, 15.10. Found: C, 56.55; H, 8.43; Cl, 14.82.

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Registry No.—**1a**, 4454-05-1; **1b**, 103-75-3; **1c**, 28194-35-6; **1d**, 52438-71-8; *cis*-**2a**, 30823-16-6; *trans*-**2a**, 30823-17-7; *cis*-**2b**, 30823-18-8; *trans*-**2b**, 30823-19-9; *cis*-**2c**, 55089-06-0; *trans*-**2c**, 55123-04-1; *cis*-**2d**, 55089-07-1; *trans*-**2d**, 55123-05-2; **3a**, 55089-08-2; **3b**, 55124-44-2; **4a**, 55089-09-3; **4b**, 55089-10-6; dichlorocarbene, 1605-72-7.

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(14) 3-Chloro-2,2,7,7-tetramethoxy-*cis*-3-heptene (**6**): ir (film) 2990, 2950, 2830, 1650, 1450, 1370, 1275, 1240, 1185, 1125, 1050, 875, 805, 670 cm^{-1}; NMR (60 MHz, $CDCl_3$) δ 6.10 (1 H, t, J = 7 Hz), 4.22 (1 H, t, J = 5.5 Hz), 3.28 (6 H, s), 3.14 (6 H, s), 2.28 (2 H, q, J = 7 Hz), 1.93–1.50 (2 H, m), 1.44 (3 H, s); mass spectrum m/e (rel intensity) 223 (8), 222 (6), 221 (24), 220 (10), 191 (2), 189 (6), 165 (5), 163 (13), 95 (14), 93 (19), 89 (62), 75 (100), 43 (24).
Anal. Calcd for $C_{11}H_{21}ClO_4$: C, 52.28; H, 8.38; Cl, 14.03. Found: C, 52.58; H, 8.11; Cl, 13.91.
(15) The ir spectra were determined with a Perkin-Elmer Model 237B infrared recording spectrophotometer and a Beckman Model IR-10 infrared recording spectrophotometer. The NMR spectra were determined at 60 MHz with a Varian Associates Model T-60 NMR spectrometer and at 100 MHz with a Varian Associates Model HA-100 NMR spectrometer. The chemical shifts are expressed in δ values (parts per million) relative to a Me_4Si internal standard. The mass spectra were obtained with a Consolidated Electronics Corp. Model 110-21B mass spectrometer.

3-Alkoxy-2-oxanorcaranes. Synthesis of Labile Cyclopropanes from Labile Olefins Using an Improved Lithium–Ammonia Reduction Procedure on the Dichlorocarbene Adducts[1]

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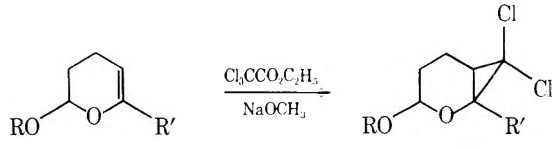
The most serious limitation of the Simmons–Smith cyclopropane synthesis procedure is that labile olefins, which can be polymerized by the strong Lewis acid zinc iodide, sometimes give poor yields.[3] Consequently, it was not too surprising for us to find *no* cyclopropane adducts when the extremely sensitive 2-alkoxy-3,4-dihydro-2*H*-pyrans (**1a–d**)[4] were subjected to these conditions. Evidently the major problem with attempts to convert **1a–d** to the corresponding 3-alkoxy-2-oxanorcaranes (**3a–d**) is that both the starting olefins **1a–d** and the cyclopropane products **3a–d** are very acid sensitive. This obstacle was circumvented by first adding dichlorocarbene, generated from ethyl trichloroacetate with sodium methoxide,[5] to the olefins **1a–d,** and then reducing the adducts **2a–d** using an improved metal–ammonia procedure.

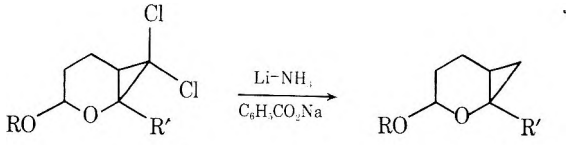
Trans–cis mixtures of 3-alkoxy-2-oxa-7,7-dichlorononorcarane (**2a,b**) and 3-alkoxy-1-methyl-2-oxa-7,7-dichlorononorcarane (**2c,d**) were prepared by the addition of dichlorocarbene to 2-alkoxy-3,4-dihydro-2*H*-pyran (**1a,b**) and 2-alkoxy-6-methyl-3,4-dihydro-2*H*-pyran (**1c,d**), respectively.[1] Subsequent reduction of the adducts **2a–d** in lithium–



1a, R = CH_3; R′ = H
b, R = C_2H_5; R′ = H
c, R = CH_3; R′ = CH_3
d, R = C_2H_5; R′ = CH_3

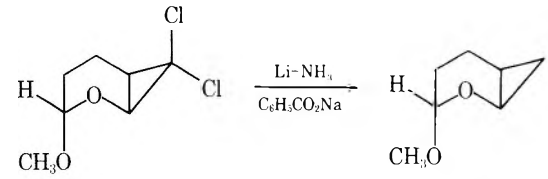
trans- and *cis*-**2a–d**

ammonia, followed by a sodium benzoate quench,[6] gave reasonable isolated yields (62–78%, distilled) of the corresponding trans–cis mixtures of 3-alkoxy-2-oxanorcaranes (**3a,b**) and 3-alkoxy-1-methyl-2-oxanorcaranes (**3c,d**).[7]



trans- and *cis*-**2a–d** *trans*- and *cis*-**3a–d**

The trans to cis ratios did not change during the reduction of the dichlorocarbene adducts **2a–d;** and when a pure isomer, obtained by careful column chromatography, was reduced the configuration was retained. For example, *trans*-3-methoxy-2-oxa-7,7-dichlorononorcarane (*trans*-**2a**) yielded *trans*-3-methoxy-2-oxanorcarane (*trans*-**3a**), exclusively.



trans-**2a** *trans*-**3a**

Quenching the lithium–ammonia reduction step with sodium benzoate[6] is essential. When protonic quenches, such as ammonium chloride or alcohol, were used additional products were detected (GLC) and the isolated yields were substantially lower. In addition, the result obtained with the sodium benzoate quench indicates that the reduction of 1,1-dichlorocyclopropane to cyclopropane is complete in lithium–ammonia and does not require an added proton source.

Experimental Section[8]

The 3-alkoxy-2-oxa-7,7-dichlorononorcaranes (**2a,b**) and 3-alkoxy-1-methyl-2-oxa-7,7-dichlorononorcaranes (**2c,d**) were prepared by a method previously described.[1] All reactions were performed in dry glassware under a static prepurified nitrogen atmosphere which was connected by a T tube to the assembly and to a soda lime drying trap. Anhydrous ammonia was distilled, through a KOH column, directly into the reaction vessel and anhydrous ethyl ether was used directly from freshly opened containers. The lithium wire (0.125 in., 0.01% Na, Ventron Corp.) was wiped free of oil, rinsed in petroleum ether, and cut into small pieces (0.5 cm) just prior to use. Gas chromatography (GLC) was performed on a Hewlett-Packard Model 7610A high-efficiency chromatograph (flame detector) using a 4 ft × 6 mm (all glass) 5% Carbowax 20M on 60–80 Chromosorb W column. Distillations were accomplished with a short-path distillation apparatus at atmospheric pressure. All boiling points are uncorrected.

***trans*-3-Methoxy-2-oxanorcarane (*trans*-3a).** A solution of 4.13 g (21 mmol) of *trans*-3-methoxy-2-oxa-7,7-dichlorononorcarane (*trans*-**2a**) in 25 ml of Et_2O was added dropwise (ca. 5 min) to a stirred solution of 882 mg (126 mg-atoms) of lithium in 25 ml of Et_2O and 125 ml of ammonia. After 30 min the dark-blue color of the solution was discharged by the cautious addition of ca. 4 g of sodium benzoate (ca. 5 min). Pentane (50 ml) was added and the ammonia was allowed to evaporate. The residue was partitioned between pentane and water; then the organic phase was separated, washed with 5% $NaHCO_3$, and dried ($MgSO_4$). Analysis (GLC) indicated one product (*trans*-**3a**), which after distillation yielded 1.80 g (70%) of a colorless oil: bp 125–130° (760 mm); ir (film) 3080, 3010, 2940, 2835, 1455, 1440, 1370, 1210, 1150, 1100, 1045, 940, 900, 810, 720 cm^{-1}; NMR (100 MHz, CCl_4) δ 4.32 (1 H, t, J = 3 Hz, equatorial anomeric proton), 3.31 (3 H, s), 3.27–3.08 (1 H, m), 2.28–1.88 (1 H, m), 1.68–1.35 (3 H, m), 1.11–0.76 (1 H, m), 0.66–0.22 (2 H, m); mass spectrum *m/e* (rel intensity) 100 (8), 97 (15), 72 (10), 71 (10), 68 (14), 67 (14), 59 (16), 58 (100), 45 (12), 43 (10), 41 (34), 39 (13).

Anal. Calcd for $C_7H_{12}O_2$: C, 65.60; H, 9.44. Found: C, 65.59; H, 9.42.

***trans*- and *cis*-3-Ethoxy-2-oxanorcarane (*trans*- and *cis*-3b).** Treatment of 4.36 g (20.6 mmol) of a 78:22 mixture of *trans*- and *cis*-3-ethoxy-2-oxa-7,7-dichlorononorcarane (*trans*- and *cis*-**2b**) as described above for *trans*-**2a** afforded a 78:22 mixture (analyzed by GLC) of *trans*- and *cis*-**3b** which distilled together, yielding 2.16 g (74%) of a colorless oil: bp 130–135° (760 mm); ir (film) 3080, 3010, 2940, 1440, 1370, 1210, 1150, 1105, 1050, 960, 910, 815, 720 cm^{-1}; NMR (100 MHz, CCl_4) δ 4.44 (0.78 H, t, J = 3 Hz, equatorial anomeric proton), 4.32 (0.22 H, d of d, J = 2.5 and 7.5 Hz, axial anomeric proton), two overlapping quartets centered at 3.73 (1 H, d of q, J = 7 and 10 Hz), and two overlapping quartets centered at 3.39 (1 H, d of q, J = 7 and 10 Hz) superimposed on 3.28–

3.06 (1 H, m), 2.39–1.75 (1 H, m), 1.67–1.34 (3 H, m), two overlapping triplets centered at 1.19 (2.34 H, t, J = 7 Hz) and 1.13 (0.66 H, t, J = 7 Hz), 1.06–0.72 (1 H, m), 0.66–0.21 (2 H, m); mass spectrum m/e (rel intensity) 114 (6), 97 (19), 86 (14), 79 (6), 73 (12), 72 (100), 68 (15), 67 (17), 57 (14), 44 (59), 43 (51), 41 (41).

Anal. Calcd for $C_8H_{14}O_2$: C, 67.58; H, 9.92. Found: C, 67.66; H, 9.90.

***trans*- and *cis*-3-Methoxy-1-methyl-2-oxanorcarane (*trans*- and *cis*-3c).** Treatment of 5.05 g (24 mmol) of a 80:20 mixture of *trans*- and *cis*-3-methoxy-1-methyl-2-oxa-7,7-dichloronorcarane (*trans*- and *cis*-**2c**) as described above for *trans*-**2a**, except that 945 mg (135 mg-atoms) of lithium was used, afforded a 80:20 mixture (analyzed by GLC) of *trans*- and *cis*-**3c** which distilled together, yielding 2.10 g (62%) of a colorless oil: bp 145–155° (760 mm); ir (film) 3080, 3010, 2960, 2880, 2840, 1450, 1365, 1240, 1210, 1120, 1100, 1040, 1010, 970, 920, 900, 880, 855 cm^{-1}; NMR (100 MHz, CCl_4) δ 4.31 (0.8 H, t, J = 3 Hz, equatorial anomeric proton), which overlaps slightly with 4.23 (0.2 H, d of d, J = 2.5 and 7 Hz, axial anomeric proton), 3.31 (2.4 H, s), 3.28 (0.6 H, s), 2.25–1.76 (1 H, m), 1.75–1.32 (3 H, m), 1.29 (3 H, s), 1.00–0.52 (1 H, m), 0.51–0.25 (2 H, m); mass spectrum m/e (rel intensity) 142 (M^+, 0.7), 114 (8), 112 (5), 111 (12), 72 (20), 71 (18), 67 (14), 58 (100), 55 (8), 45 (15), 43 (55), 41 (24).

Anal. Calcd for $C_8H_{14}O_2$: C, 67.58; H, 9.92. Found: C, 67.31; H, 9.87.

***trans*- and *cis*-3-Ethoxy-1-methyl-2-oxanorcarane (*trans*- and *cis*-3d).** Treatment of 3.32 g (14.8 mmol) of a 95:5 mixture of *trans*- and *cis*-3-ethoxy-1-methyl-2-oxa-7,7-dichloronorcarane (*trans*- and *cis*-**2d**) as described above for *trans*-**2a**, except that 640 mg (91 mg-atoms) of lithium was used, afforded a 95:5 mixture (analyzed by GLC) of *trans*- and *cis*-**3d** which distilled together, yielding 1.80 g (78%) of a colorless oil: bp 170–175° (760 mm); ir (film) 3080, 3010, 2970, 2880, 1460, 1380, 1250, 1120, 1105, 1055, 1030, 965, 930, 890, 860, 840 cm^{-1}; NMR (100 MHz, CCl_4) δ 4.45 (ca. 0.95 H, t, J = 3 Hz, equatorial anomeric proton), slightly detectable apparent quartet at ca. 4.34 (ca. 0.05 H, axial anomeric proton), two overlapping quartets centered at 3.78 (1 H, d of q, J = 7 and 10 Hz), two overlapping quartets centered at 3.38 (1 H, d of q, J = 7 and 10 Hz), 2.33–1.76 (1 H, m), 1.70–1.35 (3 H, m), 1.30 (3 H, s), 1.19 (ca. 2.85 H, t, J = 7 Hz) superimposed on 1.15 (ca. 0.15 H, t, J = 7 Hz), 1.03–0.60 (1 H, m), 0.54–0.27 (2 H, m); mass spectrum m/e (rel intensity) 156 (M^+, 2), 141 (1), 128 (25), 112 (17), 111 (28), 99 (8), 95 (8), 93 (15), 86 (39), 72 (100), 67 (24), 57 (23), 55 (25), 44 (46), 43 (79), 41 (24), 39 (14).

Anal. Calcd for $C_9H_{16}O_2$: C, 69.20; H, 10.32. Found: C, 68.90; H, 10.29.

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Registry No.—*trans*-**2a**, 30823-17-7; *trans*-**2b**, 30823-19-9; *cis*-**2b**, 30823-18-8; *trans*-**2c**, 55123-04-1; *cis*-**2c**, 55089-06-0; *trans*-**2d**, 55123-05-2; *cis*-**2d**, 55089-07-1; *trans*-**3a**, 55298-07-2; *trans*-**3b**, 55298-08-3; *cis*-**3b**, 55332-71-3; *trans*-**3c**, 55255-15-7; *cis*-**3c**, 55298-09-4; *trans*-**3d**, 55255-16-8; *cis*-**3d**, 55298-10-7; lithium, 7439-93-2.

References and Notes

(1) Part IV in a series "The Chemistry of 2-Alkoxy-3,4-dihydro-2*H*-pyrans". Part III: A. J. Duggan and S. S. Hall, *J. Org. Chem.*, in this issue.

(2) Taken in part from the Ph.D. Thesis of A.J.D. which was submitted to the Graduate Faculty, Rutgers University, Oct 1974.

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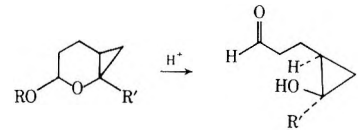
(6) The potential advantages of using sodium benzoate as a quenching agent for metal–ammonia reductions was first suggested by (a) M. Smith in R. L. Augustine, Ed., "Reduction", Marcel Dekker, New York, N.Y., 1968, p 105; and successfully applied in (b) S. S. Hall, S. D. Lipsky, and G. H. Small, *Tetrahedron Lett.*, 1853 (1971); (c) S. S. Hall, *J. Org. Chem.*, **38**, 1738 (1973).

(7) Hydrolysis of these compounds, using the method described in ref 4a, would yield the corresponding cyclopropanol. The overall sequence, then, should provide a selective procedure to synthesize these unique structures.



(8) The ir spectra were determined with a Beckman Model IR-10 infrared recording spectrophctometer. The NMR spectra were determined at 100 MHz with Varian Associates Model XL-100 and Model HA-100 NMR spectrometers. The chemical shifts are expressed in δ values (parts per million) relative to a Me_4Si internal standard. The mass spectra were obtained with a Consolidated Electronics Corp. Model 110-21B mass spectrometer.

An Improved Synthesis of Dicyclohexylidene Diperoxide

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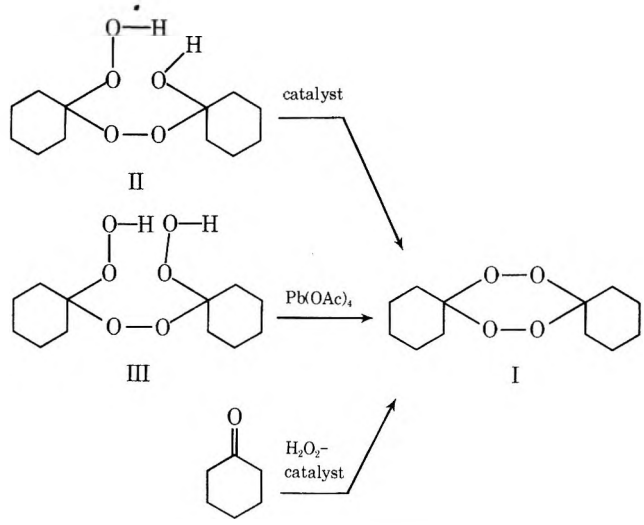
Dicyclohexylidene diperoxide (I) has been prepared by the "dehydration" of 1-hydroxy-1′-hydroperoxydicyclohexyl peroxide (II)[1,2] and by reaction of 1,1′-dihydroperoxydicyclohexyl peroxide (III) with lead tetraacetate.[3–5] Dicyclohexylidene diperoxide (I) has also been prepared "directly" from cyclohexanone and hydrogen peroxide[6] (Scheme I).

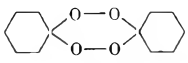
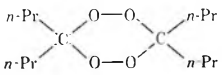
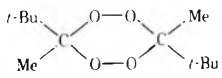
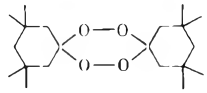
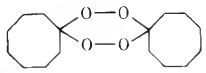
Scheme I



The disadvantages of preparing diperoxides such as I from the "open" peroxides such as II and III follow. For optimum results, the intermediate open peroxides should be purified by recrystallization before use. In general, "open" peroxides are more hazardous to work with owing to the shock sensitivity of these materials. The yields of the diperoxides prepared using this procedure are generally low.[1–5]

The former procedures for the direct conversion of cyclohexanone to the diperoxide also give low yields. Furthermore, the procedures often give mixtures of I, the triperoxide (IV), and "open" peroxides such as II and III that can be difficult to purify.[6]

Table I
Preparation of Some Alkylidene Diperoxides

Peroxide	Registry no.	Mp (lit.), °C	Yield, %
	183-84-6	128–130 (128–130)[a]	87[b] (84)[c]
	55208-76-9	52–54 (47–48)[d-f]	(89)[c]
	20732-35-8	122–125 (124–125)[e, g, h]	(26)[c]
	55208-77-0	184–186[e, i]	(48)[c]
	5681-37-8	97–98 (98)[e, j, k]	(20)[c]

[a] Reference 6. [b] VPC yield. [c] Isolated yield. [d] Reference 9. [e] Satisfactory combustion analytical data for C, H (±0.35%) were provided. Ed. [f] Mol wt calcd 260, found 270. [g] Mol wt calcd 232, found 200. [h] Reference 10. [i] Mol wt calcd 340, found 373. [j] Mol wt calcd 284, found 293. [k] Reference 11.

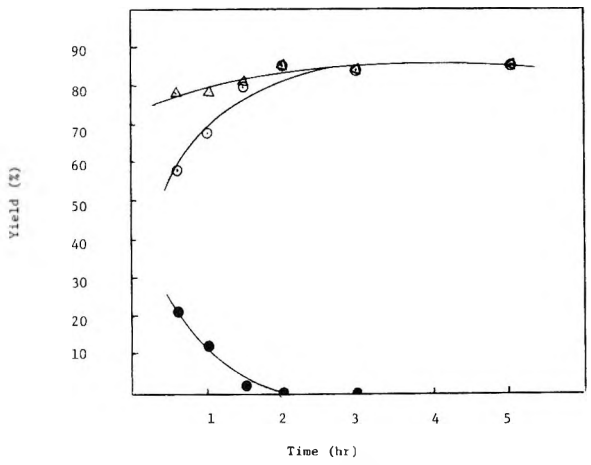
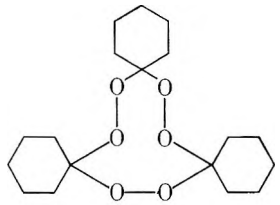


Figure 1. Plot of percent yield of cyclohexanone peroxides vs. time (hours): ●, cyclohexanone triperoxide; ⊙, cyclohexanone diperoxide; △, sum of diperoxide plus triperoxide.



IV

Since dicycloalkylidene diperoxides are useful for the preparation of macrocyclic compounds,[7] an investigation of this synthesis was conducted. After a rather extensive series of experiments in which we varied acids, solvents, temperature, mole ratio, etc., we found that high yields of the diperoxide (I) could be obtained by the reaction of cyclohexanone with hydrogen peroxide in the presence of anhydrous methanesulfonic acid (MSA) using an acetonitrile–methylene chloride solvent system.

Under optimum conditions (given in the Experimental Section), an 87% yield of the diperoxide I has been observed along with only trace amounts of the trimeric peroxide IV and the "open" peroxides II and III. The product can be conveniently isolated to afford pure dicyclohexylidene diperoxide (I) without recrystallization. It should be noted that this procedure greatly simplifies the work-up of the subsequent thermolysis mixture, since the number of components is reduced.

Story and coworkers have shown that, under a variety of conditions, the diperoxide I is formed from the triperoxide IV rather than the dehydration of the "open" peroxide II.[7] The following scheme was proposed (Scheme II).

Scheme II

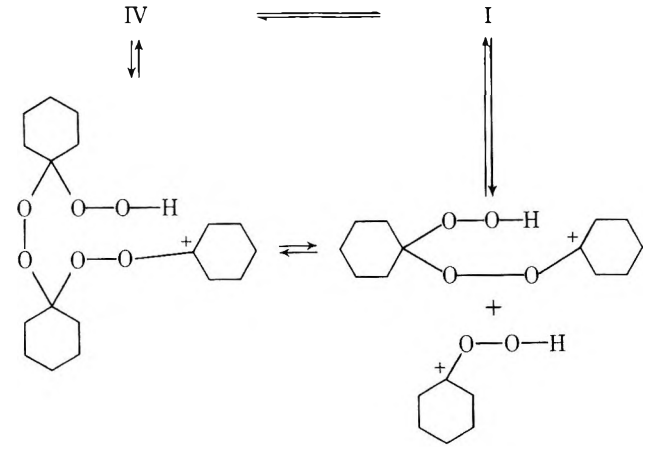
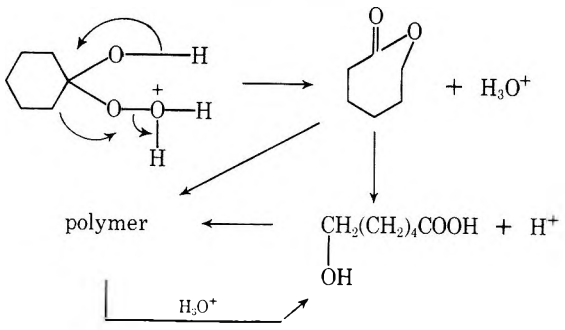


Figure 1 is a plot of the yield of cyclohexanone diperoxide (I) and triperoxide (IV) vs. time. (The initial conditions are given in the Experimental Section.) One notes immediately the high yields of the triperoxide in the early stages of the reaction. It is also very evident that the diperoxide is formed at about the same rate that the triperoxide is destroyed. Furthermore, the diperoxide is much more stable than the triperoxide under the conditions of this series of experiments. This is in agreement with the results previously reported by Story and coworkers.[6] These workers found that, under a variety of conditions, tricyclohexylidene triperoxide (IV) was the kinetic product and dicyclohexylidene diperoxide (I) was the thermodynamic product.

The major by-product from the diperoxide synthesis was caprolactone or products derived from caprolactone (i.e., polycaprolactone or the hydroxy acid). A Baeyer–Villiger-like reaction[8] would account for these products (Scheme III).

Since the procedure was so successful for the preparation of cyclohexanone diperoxide, a few representative ketones

Scheme III



were chosen and an attempt was made to synthesize the diperoxides under essentially the same conditions. The results are shown in Table I. No attempt was made to maximize the yields of any but the first entry in Table I.

In conclusion and summary, the procedure given in this paper is useful for the preparation of high-purity cyclohexanone diperoxide in high yield. Furthermore, there is an indication that the diperoxide I is formed from the triperoxide IV, although one cannot discard the possibility that some of I is formed from the "open" peroxide II. The procedure is also useful for the preparation of peroxides derived from noncyclic ketones as well as cyclic ketones.

Experimental Section

Preparation of Diperoxide. Typical Procedure. Acetonitrile (25 ml) and methylene chloride (25 ml) were placed in a 300-ml round-bottom flask equipped with a stirrer and thermometer. Cyclohexanone (9.8 g, 0.1 mol) was placed in the flask. The mixture was cooled to about 5° and 8 ml of anhydrous methanesulfonic acid was added slowly (small exotherm). Hydrogen peroxide (90%, 3 ml, 0.11 mol) was then added dropwise over about a 10-min period (exothermic). The temperature was maintained at 5° during the addition and during the hold period. At the end of the hold time, 100 ml of water and 100 ml of methylene chloride were added to the reaction mixture. The contents of the flask were transferred to a separatory funnel and the organic and water layers were separated. The water layer was washed with 25 ml of methylene chloride. The methylene chloride was then separated and combined with the first cut. The methylene chloride solution was washed once more with an equal volume of water, dried over anhydrous sodium sulfate, and analyzed for percent cyclohexanone diperoxide and triperoxide by VPC using an internal standard. In some cases an aliquot of the methylene chloride was removed from the sample before it was submitted for VPC analysis and a crude yield of peroxide was obtained. In most cases the crude yield was within a few percent of the yields determined by VPC. The solid peroxide was isolated by removing most of the methylene chloride on a rotary evaporator, adding methanol, and collecting the solid by filtration.

Material Balance Experiment. Methylene chloride (250 ml) was placed in a 1-l. flask along with 250 ml of acetonitrile and cooled to about 5° in a methanol–water–ice bath. Anhydrous methanesulfonic acid (80 ml) was then added slowly (mild exotherm) such that the temperature did not rise above 10°. Hydrogen peroxide (90%, 30 ml, 1.1 mol) and cyclohexanone (98.1 ml, 1.0 mol) were then added simultaneously (slowly) to the stirred mixture by means of two addition funnels. The temperature was maintained within ±2° of 5°. Addition of cyclohexanone required about 45 min. Addition of hydrogen peroxide required about 25 min. The mixture was kept at about 5° and checked for "open" peroxide by TLC. Only a trace of "open" peroxide remained after 2 hr.

Methylene chloride (300 ml) was then added along with 200 ml of water. The mixture was transferred to a separatory funnel and shaken, and the organic and water layers were separated. The water layer was washed with 50 ml of methylene chloride and this was combined with the first cut. The methylene chloride was washed with 300 ml of saturated bicarbonate solution and dried over magnesium sulfate. An aliquot was withdrawn for VPC analysis. The crude yield of isolated dimer was 84%. By VPC the yield was 87.1% dimer and 0.1% trimer.

After filtration of the dimer, an oil was isolated (16 g, 14 wt %) which still contained some dimer–trimer (TLC). By ir, this oil appeared to be mainly a polymer of hexanolactone. (Some 6-hydroxyhexanoic acid was also present). VPC indicated that there was less than 1% cyclohexanone remaining.

VPC Assay for Dicyclohexylidene Diperoxide and Tricyclohexylidene Triperoxide. Although the peroxides are thermally unstable, they can be successfully chromatographed at temperatures below 150° using on-column injection into glass columns that have been silynized. The yields for dicyclohexylidene diperoxide and tricyclohexylidene triperoxide reported in this paper were determined on a 10 ft × 0.375 in. glass column packed with 0.1% OV-17 on glass beads 60–80 mesh. Methyl stearate was used as an internal standard.

Acknowledgment. We would like to thank Story Chemical Corp. for permission to publish this work.

Registry No.—Cyclohexanone, 108-94-1; 4-heptanone, 123-19-3; 3,3-dimethyl-2-butanone, 75-97-3; 3,3,5,5-tetramethylcyclohexanone, 14376-79-5; cyclooctanone, 502-49-8; hydrogen peroxide, 7722-84-1; acetonitrile, 75-05-8; methylene chloride, 75-09-2; methanesulfonic acid, 75-75-2.

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Synthesis and Identification by Shift Reagents of Isomeric 2-Methyl-2-*n*-propylcyclopentane-1,3-diols

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Received February 19, 1975

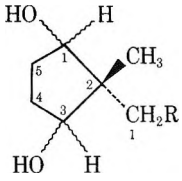
During research aimed at pinpointing the relationships between configuration and activity in meprobamate-type substances, it was necessary to obtain, as starting products, the three 2-methyl-2-*n*-propylcyclopentane-1,3-diol isomers (**4–6**). Their synthesis and structure determined by NMR spectra in the presence of $Eu(DPM)_3$ are reported here.

Chemistry. Sodium borohydride reduction of 2-methyl-2-allylcyclopentane-1,3-dione[1] gave the expected mixture of three isomeric diols, **1**, **2**, and **3**, that were separated by column chromatography. Further catalytic reduction with hydrogen afforded, in nearly quantitative yield, **4**, **5**, and **6** (Scheme I). This method was preferred to the one involving a previous reduction of the allyl group as it gave better yields and easier chromatographic separations.

To obtain the corresponding 4,5-unsaturated compounds, 2-methyl-2-*n*-propyl-4-cyclopentene-1,3-dione (**8**) was synthesized. Yet reduction of **8** with sodium borohydride or lithium aluminum hydride afforded the known mixture of saturated diols **4–6** because of the prevalence of 1,4 over 1,2 addition (Scheme I).

Structure Determination. No compound of the **1–3** and **4–6** series gives the characteristic reactions of the cis diols, probably owing to the considerable steric hindrance

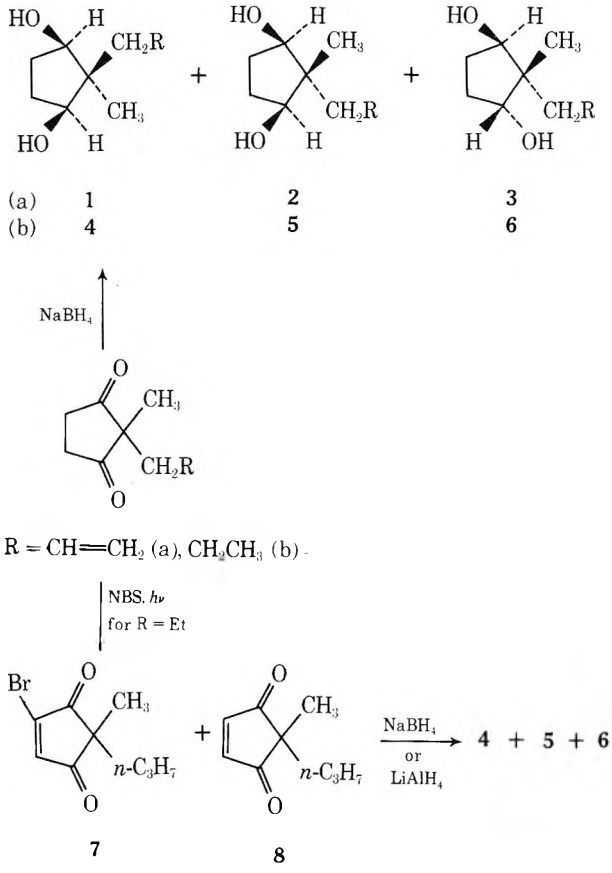
Table I
Paramagnetic Induced Shift (ΔEu)[a]



Compd	R	2-CH_3	$H_{1,3}$	$OH_{1,3}$	2-(1-CH_2)	$H_{4,5}$	2-(2-CH_2)	2-(3-CH_3)
1	$CH{=}CH_2$	−7.94	−15.51	−44.45	−14.36	−8.94 −13.29		
2	$CH{=}CH_2$	−12.66	−15.51	−46.05	−8.43	−9.06 −13.38		
3	$CH{=}CH_2$	−10.20	−16.59 −19.99	−44.63 −52.54	−10.46	*b*		
4	CH_2CH_3	−8.96	−16.12	−38.17	−10.21	−14.66	−6.93	−0.03
5	CH_2CH_3	−12.27	−15.27	−44.99	−7.09	−10.75 −13.12	−5.37	−2.51
6	CH_2CH_3	−13.61	−22.41 −26.86	−59.89 −68.37	−15.11	*b*	−8.33	−2.59

[a] $\Delta Eu = \delta_{CDCl_3} - \delta_{Eu}$ ($n = 1$). Extrapolated from least-squares lines for each protons. [b] Could not be determined.

Scheme I



of the molecule. On the other hand, NMR spectra, which are in good agreement with the general structure of compounds **1–6**, cannot be reliably used for detailed stereostructural assignments because of the impossibility of evaluating the contribution of the inductive and anisotropic effects of the hydroxyl group to the chemical shift of 2-CH_3 and 2-(1-CH_2).[2] The ir spectra in solution suggest a trans structure for the hydroxyls of compounds **3** and **6** but **2** and **5**, being solids, seem to contradict such an attribution, indicating for these last two a greater disposition to the intermolecular hydrogen bonding.

Therefore it was impossible, on these bases, to assign the structures with confidence.

Definitive evidence for the structural assignments was obtained by studying the pseudocontact shift in the NMR spectra of both series of compounds **1–3** and **4–6** by addition of $Eu(DPM)_3$. The induced paramagnetic shifts (ΔEu values), obtained from the slopes of the linear relations of the induced shift vs. $Eu(DPM)_3$/ligand molar ratios, are reported in Table I. ΔEu values were obtained according to Demarco[3] by simple extrapolation of the least-squares lines to $n = 1$ and $n = 0$. As a slight deviation[3] from linearity occurs at low $Eu(DPM)_3$ concentration, there are some differences between observed and extrapolated δ_{CDCl_3}.

As expected, the 2-methyl groups of compounds **2** and **5** are more strongly affected by the complex than the corresponding groups of compounds **1** and **4** and the reverse is true for 2-(1-CH_2) groups of the same compounds. As to products **3** and **6**, both groups are simultaneously influenced by europium action with consequential high ΔEu for both. Characteristic of these last two isomers and further confirmation of their structure is the differentiation of the 1,3 hydroxyls and 1,3 proton signals as the europium concentration increases.

It is interesting to note, in light of the results obtained with the shift reagents, that the 2-CH_3 [and that of 2-(1-CH_2) equivalently] appears at lower fields when the two hydroxyls are on the same side (δ_{CH_3} 1.06 and 1.05 for **2** and **5**, respectively), rather than on the opposite side (δ_{CH_3} 0.78 and 0.75 for **1** and **4** respectively). With trans hydroxyls, the situation is intermediate (δ_{CH_3} 0.88 and 0.83 for **3** and **6**, respectively). The values obtained show that the inductive effect of the hydroxyl groups[2,4–7] is dominated by the anisotropy effect of the C–OH bonding,[8] possibly because such molecules result sterically congested.[9–11]

Registry No.—**1**, 55319-49-8; **2**, 55319-50-1; **3**, 55319-51-2; **4**, 55399-41-2; **5**, 55399-42-3; **6**, 55399-43-4; **7**, 55319-52-3; **8**, 55319-53-4; NBS, 128-08-5; 2-methyl-2-*n*-propylcyclopentane-1,3-dione, 25112-79-2.

Supplementary Material Available. The Experimental Section containing preparation methods for compounds **1–8** as well as their spectroscopic characteristics will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 24 × reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 16th St., N.W., Washington, D.C. 20036. Remit check or money order for $4.00 for photocopy or $2.50 for microfiche, referring to code number JOC-75-2241.

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Synthesis and Spectral Properties of a Series of New α,ω-Diphenylpolyenes

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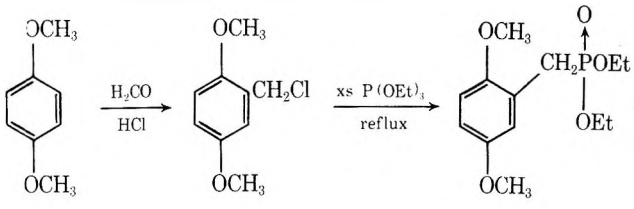
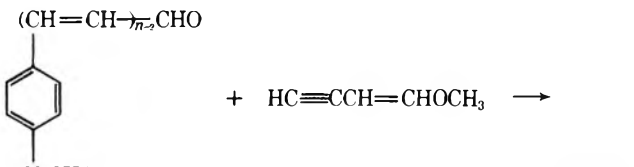
Received January 15, 1975

It has been determined that substituted *trans*-stilbenes act as sensitizers for the photochemical decomposition of arenesulfonyl azides.[1] A series of new α,ω-diphenylpolyenes has been synthesized which extend the spectral sensitivity of the azide-sensitizer system into the visible region of the electromagnetic spectrum. The study of energy transfer and quantum yield determination will be the topic of a forthcoming paper.

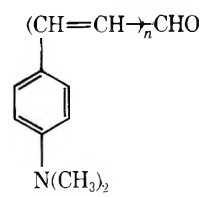
The synthesis involves formation of aromatic polyenals (IV → VII) which are subsequently converted to α,ω-diphenylpolyenes (VIII → XI) via a phosphonate carbanion reaction with 2,5-dimethoxybenzyl phosphonate (III). Several methods are available for the extension of double bond conjugation in systems containing an aldehyde function: multiple aldol condensations with paraldehyde;[2] aldol condensation with crotonaldehyde[3] or acetaldehyde;[4] reaction of 1-methylaniline penta-1,3-dienal (Zincke aldehyde) with dimethylaniline in the presence of $POCl_3$[5] and condensation of methoxybutenyne with either benzaldehyde or cinnamaldehyde followed by reduction with $LiAlH_4$.[6] The last method is a stepwise approach and was selected as being the most appropriate for the current work.



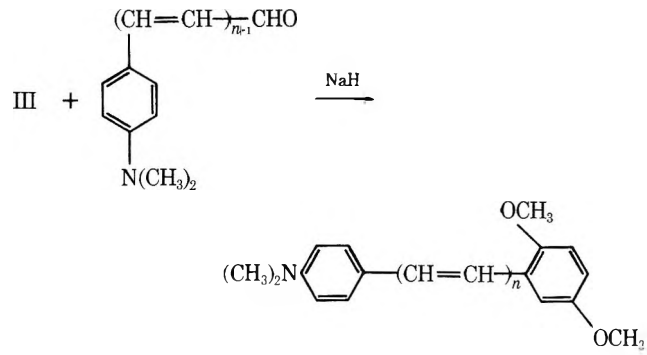
I II III



IV, $n = 2$
V, $n = 3$



VI, $n = 2$
VII, $n = 3$



VIII, $n = 1$
IX, $n = 2$
X, $n = 3$
XI, $n = 4$

It was desired to obtain the α,ω-diphenylpolyenes in the all-trans configuration to ensure the highest extinction coefficients and the longest wavelength absorption maxima. Several criteria were utilized in assigning the all-trans stereochemical configuration to the compounds synthesized: known stereochemistry of the chemical reactions involved; comparison of physical properties to those of similar compounds with known stereochemistry; analysis of the ultraviolet absorption spectra and analysis of the infrared spectra.

The reaction of the benzyl phosphonate III with an aldehyde produces an exclusively trans double bond.[9] The intermediate step in which $LiAlH_4$ is used to reduce the acetylenic bond of methoxybutenyne also results in formation of an exclusively trans double bond.[8] Finally, the *p*-dimethylaminocinnamaldehyde (V) was known to be the trans isomer. From these considerations we can assign the trans configuration to the stilbene VIII, both olefinic bonds in the butadiene IX, two of the three olefinic bonds in the hexatriene X, and three of the four olefinic bonds in the octatetraiene XI. The double bonds remaining unassigned are due to the methoxybutenyne for which the configuration of the double bond is not certain.

Table I compares some physical properties of known isomers with those of the first two members of the α,ω-diphenylpolyene series. Only the all-trans isomers are crystalline, high melting point solids.

In a review by Lewis and Calvin[7] it is reported that for a series of all-trans diphenylpolyenes the square of the ultraviolet absorbance maximum (λ^2_{max}) is related in a linear fashion to the number of olefinic bonds separating the aromatic rings (n). Plotting λ^2_{max} vs. n for the current series of diphenylpolyenes (Figure 1) gives the linear relationship expected if the members of the homologous series are in the all-trans configuration.

The 650–1050-cm^{-1} region of the infrared spectrum has been used by some researchers[6,11] to distinguish the out-of-plane vinyl C–H bonding of cis olefins (650–850 cm^{-1}) from that of trans olefins (950–1050 cm^{-1}). The presence of aromatic C–H bonding absorbances in the 700–800-cm^{-1} range[12] in the infrared spectra of the compounds under discussion, however, precludes the unambiguous assignment of any cis bond. The infrared spectrum of each α,ω-diphenylpolyene does contain a strong absorbance in the 950–1050-cm^{-1} region which could be assigned to a trans vinyl C–H bond.

In the present homologous α,ω-diphenylpolyene series each successive olefinic bond introduced into the system resulted in a bathochromic shift in the position of the ultraviolet absorbance maximum by about 17 nm and in an increase in the intensity of the absorption maximum.

Table I
Comparison of Physical Properties between α,ω-Diphenylpolyenes and Known Cis,Trans Isomers

Compd	Isomer	Mp (bp), °C	λ_{max}, nm	ϵ_{max}
4-Methoxystilbene[9]	Trans	136	306[a]	29,000
	Cis	(98–100, 2 mm)	270[a]	11,700
Diphenylbutadiene[10,16]	Trans,trans	152–153	328[b]	56,200
	Trans,cis	Oil	312[b]	31,600
	Cis,cis	70.5	299[b]	29,500
2,5-Dimethoxy-4′-dimethylamino-stilbene (VIII)	Trans	120–121	363[b]	32,350
1-(2,5-Dimethoxyphenyl)-4(4′-dimethylaminophenyl)buta-1,3-diene (IX)	Trans,trans	121–121.5	380[c]	49,500
1-(2,5-Dimethoxyphenyl)-6(4′-dimethylaminophenyl)hexa-1,3,5-triene (X)	All-trans	123–123.5	397[c]	54,600
1-(2,5-Dimethoxyphenyl)-8-(4′-dimethylaminophenyl)octa-1,3,5,7-tetraene (XI)	All-trans	146–147	413[c]	70,150

[a] 95% ethanol. [b] Hexane. [c] Acetonitrile.

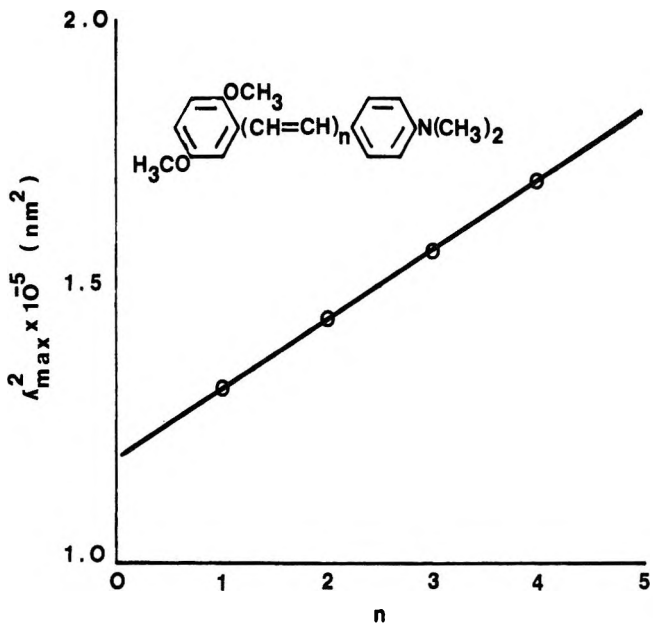


Figure 1. Linear relationship between λ^2_{max} and n for the trans polyene series.

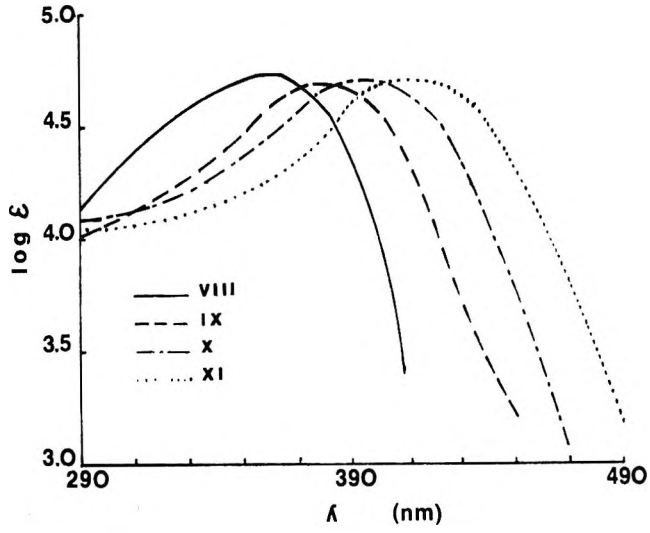


Figure 2. Ultraviolet absorbtion curves for the homologous polyene series.

These shifts were accompanied by a decrease in the energy of the lowest lying excited state singlet ($E_{0\rightarrow0}$) energy levels. A comparison of the ultraviolet absorbance spectra of these α,ω-diphenylpolyenes is shown in Figure 2.

Experimental Section

General. Melting points were measured on a Thomas-Hoover capillary apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 621 spectrophotometer using KBr pellets. NMR spectra were measured on a Varian T-60 spectrometer. Ultraviolet absorption spectra were recorded on a Cary Model 14 spectrophotometer. Emission–excitation spectra were determined on an Aminco-Bowman spectrophotofluorometer. The NaH (50% in mineral oil) was washed with *n*-hexane prior to use. The elemental analyses were performed in these laboratories.

Starting Materials. The 2,5-dimethoxybenzyl phosphonate (III) was prepared by the Michaelis–Arbuzov reaction.[13] The 2,5-dimethoxybenzyl chloride (II) was prepared by chloromethylation of hydroquinone dimethyl ether (I) according to the method of Mel'nikov and Prilutskaya.[14]

5-(*p*-Dimethylaminophenyl)penta-2,4-dienal (VI). Using the method of Marshall and Whiting,[6] 1.6 g (66.6 mmol) of magnesium turnings plus 45 ml of tetrahydrofuran (THF) (dried over tosyl isocyanate and distilled) together with a crystal of iodine were placed in a 250-ml three-neck flask fitted with a thermometer, reflux condenser, and addition funnel both topped with $CaCl_2$ drying tubes. To this mixture was added dropwise 7.2 g (66.0 mmol) of ethyl bromide in 10 ml of THF at a rate fast enough to ensure continued refluxing.[15] The water-white reaction mixture was allowed to cool to 34–45°, then 7.3 g (89.0 mmol) of freshly distilled 1-methoxybut-1-en-3-yne in 10 ml of THF was added dropwise maintaining a temperature of 40–45°. Upon completion of this addition, the reaction mixture was stirred at room temperature for 1 hr followed by cooling on an ice–salt bath and dropwise addition of 10 g (67.1 mmol) of *p*-dimethylaminobenzaldehyde in 10 ml of THF. A temperature of 0–5° was maintained during the aldehyde addition, then the mixture was allowed to warm to room temperature and was stirred for an additional 2 hr. After this time the mixture was cooled to 0° and 5 ml of absolute ethanol was added followed by stirring for 20 min. Then 2.0 g (52.6 mmol) of $LiAlH_4$ powder was added to the cold solution over a 30-min period followed by stirring at room temperature for 3 hr. The mixture was again cooled to 0° and the following were added consecutively: 3 ml of ethyl acetate, 15 ml of H_2O, 75 ml of 4 *N* H_2SO_4, and 100 ml of benzene. After stirring for 5–10 min the red benzene layer was separated, dried (sodium sulfate), and evaporated in vacuo to yield

a reddish-brown solid which after recrystallization from isopropyl alcohol afforded 6.7 g (50%) of yellow plates of VI: mp 153–155°; NMR ($CDCl_3$) 3.0 (s, W = 1.0 Hz, 2 CH_3), 9.58 (d, J = 8 Hz, 1 CHO), 6.0–7.5 ppm (m, 8 H); uv (acetonitrile) λ_{max} 405 nm (ϵ 24,500); ir ($CHCl_3$) 3025, 1665, 1590 cm^{-1}.

Anal. Calcd for $C_{13}H_{15}NO$: C, 77.58; H, 7.51; N, 6.96. Found: C, 77.40; H, 7.44; N, 6.81.

7-(*p*-Dimethylaminophenyl)hepta-2,4,6-trienal (VII) was prepared similarly to IV from *p*-dimethylaminocinnamaldehyde. Recrystallization from ligroin (bp 90–120°) gave VII (2%) as a red powder: mp 177–179°; NMR ($CDCl_3$) 3.0 (s, W = 1.0 Hz, 2 CH_3), 5.9–7.4 (m, 10 H), 9.56 ppm (d, J = 8 Hz, 1 CHO); uv (acetonitrile) λ_{max} 425 nm (ϵ 36,260); ir ($CHCl_3$) 3020, 1665, 1560 cm^{-1}.

Anal. Calcd for $C_{15}H_{17}NO$: C, 79.26; H, 7.54; N, 6.16. Found: C, 79.17; H, 7.49; N, 6.03.

General Procedure for Synthesis of α,ω-Diphenylpolyenes (VIII → XI).[13] Into the reaction vessel were charged 7 mmol of 2,5-dimethoxybenzyl phosphonate (III), 7 mmol of the appropriate aldehyde (IV → VII), and 25 ml of 1,2-dimethoxyethane (dried over Na). To this stirred solution was added in several portions 7 mmol of NaH followed by refluxing of the mixture for 0.5–1.5 hr. The reaction mixture was then cooled to room temperature and drowned in 150 ml of cold water followed by filtration (in the case of VIII) or extraction with benzene (in the case of IX, X, and XI) of the α,ω-diphenylpolyene.

2,5-Dimethoxy-4′-dimethylaminostilbene (VIII): yield 70%; yellow hexagonal crystals (acetone), mp 120–121°; NMR ($CDCl_3$) 2.90 (s, 2 NCH_3), 3.73 (s, $-OCH_3$), 3.77 (s, $-OCH_3$), 6.6–7.5 ppm (m, 9 H); ir 705 (m), 800 (s), 840 (m), 1045 cm^{-1} (s); $E_{o\to o}$ = 70.6 ± 0.6 kcal/mol.

Anal. Calcd for $C_{18}H_{21}NO_2$: C, 76.28; H, 7.48; N, 4.94. Found: C, 76.50; H, 7.36; N, 4.84.

1-(2,5-Dimethoxyphenyl)-4-(4′-dimethylaminophenyl)buta-1,3-diene (IX): yield 52%; yellow needles (ethanol), mp 121–121.5°; NMR ($CDCl_3$) 2.93 (s, 2 NCH_3), 3.73 (s, $-OCH_3$), 3.78 (s, $-OCH_3$), 6.6–7.4 ppm (m, 11 H); ir 715 (m), 810 (m), 860 (m), 985 cm^{-1} (s); $E_{o\to o}$ = 66.0 ± 0.6 kcal/mol.

Anal. Calcd for $C_{20}H_{23}NO_2$: C, 77.62; H, 7.51; N, 4.53. Found: C, 77.80; H, 7.67; N, 4.45.

1-(2,5-Dimethoxyphenyl)-6-(4′-dimethylaminophenyl)hexa-1,3,5-triene (X): yield 40%; orange needles (isopropyl alcohol), mp 123–123.5°; NMR ($CDCl_3$) 2.90 (s, 2 NCH_3), 3.77 (s, OCH_3), 3.80 (s, OCH_3), 6.6–7.4 ppm (m 13 H); ir 800 (s), 820 (s), 995 (s), 1045 cm^{-1} (s); $E_{o\to o}$ = 61.2 ± 0.6 kcal/mol.

Anal. Calcd for $C_{22}H_{25}NO_2$: C, 78.76; H, 7.53; N, 4.18. Found: C, 79.08; H, 7.78; N, 4.08.

1-(2,5-Dimethoxyphenyl)-8-(4′-dimethylaminophenyl)octa-1,3,5,7-tetraene (XI): yield 25%; shiny copper plates (acetone), mp 146–147°; NMR ($CDCl_3$) 2.95 (s, 2 NCH_3), 3.78 (s, OCH_3), 3.80 (s, OCH_3), 6.4–7.4 ppm (m, 15 H); ir 810 (s), 1000 cm^{-1} (vs); $E_{o\to o}$ = 58.0 ± 0.6 kcal/mol.

Anal. Calcd for $C_{24}H_{27}NO_2$: C, 79.73; H, 7.54; N, 3.88. Found: C, 79.61; H, 7.72; N, 3.73.

Registry No.—**III,** 55298-76-5; **IV,** 100-10-7; **V,** 20432-35-3; **VI,** 20432-36-4; **VII,** 55298-77-6; **VIII,** 55298-78-7; **IX,** 55298-79-8; **X,** 55298-80-1; **XI,** 55298-81-2; 1-methoxybut-1-en-3-yne, 2798-73-4.

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(15) It may be necessary to heat the reaction mixture until the orange iodine color disappears in order to initiate the reflux.
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Carbon-13 Nuclear Magnetic Resonance Spectra of 4-Phosphorinanones. Carbonyl Hydration in Oxides, Sulfides, and Quaternary Salts[1]

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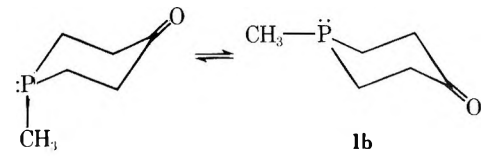
We recently reported on the ^{13}C NMR spectra of phosphorinanes[2] and their 4-hydroxy derivatives,[2,3] pointing out especially the value of the technique for gaining information on conformational aspects of this ring system. The effect of a covalence change (addition of sulfur) at the phosphorus atom was also considered.[2,4] We have extended our study to include some 4-keto derivatives of this series. On conducting ^{13}C NMR measurements on the tetracovalent species in water solution, we noted an important effect: extensive covalent hydration occurred at the carbonyl group. The present paper summarizes our observations on these compounds.

^{13}C NMR Spectra of Keto Derivatives. The ^{13}C NMR spectra of a family of *P*-methyl 4-phosphorinanone derivatives are given in Table I. In the trivalent compound **1**, assignment of the ring carbons was easily made, since their signals were separated by 12.5 ppm through the shielding effect of the phosphino group on attached carbons,[2] and the deshielding effect of carbonyl on carbons attached to it.[5] The carbonyl carbon was located in the same far-downfield position as seen for 4-methylcyclohexanone (δ 209[6]). The PCH_3 signal was in its expected high-field position. This carbon is particularly sensitive to conformational properties; the chemical shift observed is determined by the relative amounts at equilibrium of the conformer with axial (upfield) and with equatorial (downfield) methyl. Previous studies[7] on this 4-phosphorinanone have indicat-



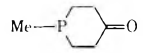
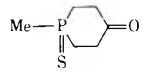
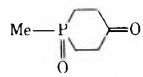
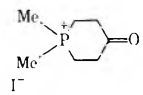
1a **1b**

ed that the equilibrium lacks the very strong bias to the equatorial side that is so well known for 4-methylcyclohexanone. Indeed, there seems to be a small excess of the axial conformer, a property that has been recently confirmed for the 1-methylphosphorinane system.[8] The sterically dependent $^2J_{P-C}$ value for $C_{3,5}$ in ketophosphine **1** is quite small (<2 Hz); for the corresponding phosphorinane it is 3 Hz. Rigid models in the latter series (*cis*- and *trans*-1-methyl-4-*tert*-butyl-4-phosphorinanols) have provided[3] values for the axial methyl case of 1 Hz, and for the equatorial of 7 Hz. The small $^2J_{PC}$ value for **1** therefore is qualitatively consistent with some excess of **1a** over **1b**.

When sulfur or oxygen are added to phosphorus of **1**, it is likely that these substituents adopt the axial position in preference to methyl, as has been demonstrated for the phosphorinane compounds.[2] These atoms generally cause downfield shifts at α carbons;[2,9] this is seen in the spectrum for the sulfide (**2**) at both CH_3 and $C_{2,6}$, and in that of the oxide (**3**) at CH_3. On the other hand, quaternization of phosphines causes upfield shifts of attached carbons, and this is noted on comparing the data for the methiodide (**4**) to those for the phosphine (**1**).

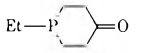
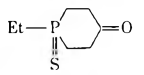
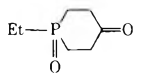
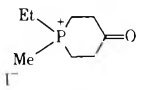
We detect a small but significant upfield shift at C_4 on converting 1-methyl-4-phosphorinanone to any of its tetra-

Table I
^{13}C NMR Spectra of 1-Methyl-4-phosphorinanone and Derivatives[a]

	Compd	Solvent	$C_{2,6}$	$C_{3,5}$	C_4	PCH_3
1		$CHCl_3$	23.8 (14)	36.3 (<2)	209 (<2)	7.9 (18)
2		$CHCl_3$	30.9 (51)	36.2 (6)	206.8 (5)	19.6 (56)
		H_2O	31.1 (52)	37.9 (8)	215.2 (7)	19.8 (55)
3		$CHCl_3$	23.3 (65)	32.8 (7)	204.9 (7)	11.5 (68)
		H_2O	26.8 (64)	37.5 (6)	214.6 (8)	15.3 (68)
4		DMSO	15.1 (51)	32.0 (6)	203.6 (11)	4.6 (52)
		H_2O	19.6 (50)	36.3 (8)	210.7 (7)	8.4 (54)

[a] Shifts were measured at ambient temperatures from the internal standards Me_4Si in $CHCl_3$, CH_3OH in H_2O, and $CHCl_3$ in DMSO. The H_2O solutions were run immediately after preparation before hydration was extensive. Values in parentheses are P–C coupling constants, in hertz.

Table II
^{13}C NMR Spectra of 1-Ethyl-4-phosphorinanone and Derivatives[a]

	Compd	Solvent	$C_{2,6}$	$C_{3,5}$	C_4	PCH_3	PCH_2	CCH_3
5		$CHCl_3$	21.9 (15)	37.1 (<2)	210.1 (<2)		17.3 (13)	9.3 (18)
6		$CHCl_3$	29.0 (50)	36.2 (4)	207.4 (5)		25.4 (53)	6.1 (4)
		H_2O	39.1 (50)	37.8 (7)	214.0 (6)		26.0 (53)	7.6[b]
7		$CHCl_3$	24.2 (60)	35.9 (5)	207.9 (7)		21.6 (70)	5.4 (5)
		H_2O	24.7 (63)	37.3 (8)	214.1 (6)		22.5 (66)	6.7 (<2)
8		DMSO	13.4 (49)	35.3 (7)	203.0 (7)	2.7 (54)	12.3 (50)	3.4 (5)
		H_2O	17.1 (49)	36.3 (7)	211.0 (6)	6.6 (53)	16.7 (50)	6.9 (5)

[a] See footnote *a*, Table I. [b] Coupling not clearly observed.

covalent derivatives **2**, **3**, or **4**. The shift is most pronounced in the salt **4** (5.4 ppm) but it is clearly present in both the sulfide (2.2 ppm) and the oxide (4.1 ppm). We have observed[2] the same upfield shift in the parent phosphorinane ring as well as in the 4-phosphorinanols, and it is therefore independent of both the hybridization of C_4 and the presence of substituents on C_4. It is also independent of the size of the substituent on phosphorus, and hence on the position of the conformational equilibrium for mobile systems in this series.[2] Furthermore, it can be determined from examination of published X-ray structural data that conversion of a phosphine to its sulfide has essentially no effect on the geometry of the ring in the vicinity of C_4. Thus, the C_3–C_4–C_5 angle in *r*-1-methyl-*c*-4-*tert*-butyl-*t*-4-phosphorinanol[10] is 111°, while that for the sulfide of the corresponding 4-methyl derivative[4] is 112°. The same values apply to the corresponding cis isomers.[11] Torsion angles about the rings are also not changed appreciably on sulfurization. We believe that the best explanation available at this time for the long-range shielding of C_4 is the operation of an electric field associated with the polar phosphorus functions. This effect has been postulated by others to explain a similar upfield shift at C_4 on S-alkylation of thianes[12] and on quaternization of piperidines.[5c] The field effect is receiving current attention in noncyclic structures as well,[13] where examples of its operation from nonionic polar groups have been presented.

In Table II are included ^{13}C NMR data for the same series of 4-phosphorinanones (**5**–**8**) but with a *P*-ethyl substituent. The features discussed for the *P*-methyl series are clearly evident in these data also. The effect of lengthening the exocyclic chain has been discussed previously,[2] and no new features are seen here.

Table III
Infrared and Ultraviolet Spectra for 1-Ethyl-4-phosphorinanone (5) and Its Oxide (6) and Sulfide (7)

Compd	$\nu_{C=O}$, cm^{-1}[a]	λ_{max}, nm (ϵ)[b]
5	1714	286 (4)
6	1717	287 (10)
7	1716	287 (14)

[a] Taken on 0.02 *M* solutions in tetrahydrofuran. [b] For the n → π^* transition, using THF solutions.

Some correlation has been noted in other systems between ^{13}C NMR shifts of the carbonyl group and the wavelength of its n → π^* transition in the ultraviolet spectrum.[14] We note no such effect in the present series of compounds; it can be seen from the data in Table III that no significant change in the uv maximum occurred when a phosphine (**5**) is converted to either the sulfide (**6**) or oxide (**7**), yet as noted changes in the ^{13}C shift do take place. Similarly, we observe no change in the carbonyl stretching frequency in the infrared spectra of these compounds (Table III), and we must assume that the electric field effect, if indeed operative in these compounds from the polar phosphorus functions, does not influence these important spectral properties of the carbonyl group.[15]

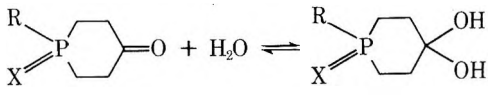
Table IV
^{13}C NMR Spectra[a] of 4,4-Phosphorinanediols in Water at 30°

Compd	$C_{2,6}$	$C_{3,5}$	C_4	PCH_3	PCH_2	CCH_3
9	26.1 (64)	35.2 (6)	95.7 (7)	14.4 (66)		
10	23.4 (64)	35.3[b]	96.0 (8)		21.9 (64)	6.5 (<2)
11	30.0 (49)	35.1 (6)	95.8 (6)	18.9 (55)		
12	27.8 (49)	34.7 (8)	95.7 (6)		25.0 (53)	7.6[b]
13	19.6 (50)	33.5 (7)	94.3 (8)	8.2 (56)		
14	17.5 (50)	33.5 (8)	94.4 (6)	5.1 (55)	15.5 (51)	6.9 (5)

[a] Shifts were determined from the signal of internal CH_3OH. Values in parentheses are C–P coupling constants, in hertz. [b] Coupling not readily measurable.

When the ^{13}C NMR spectra of the ketone oxides **3** or **7** are determined in water solution, pronounced downfield shifts relative to the signals for chloroform solutions are noted at all carbons. The same is true for salts **4** and **8** for water vs. dimethyl sulfoxide solution. For all compounds, the effect is strongest at the carbonyl carbon, where it amounts to some 7–10 ppm. These shifts are not unexpected and are clearly to be associated with the occurrence of hydrogen bonding at the carbonyl oxygen.[5b]

Hydration of the Carbonyl Group. The ^{13}C NMR spectra of freshly prepared water solutions of 4-phosphorinanone oxides **3** or **7** changed rapidly on standing, and an entirely new set of peaks appeared. This set (Table IV) lacked any signal for carbonyl carbon, but a new signal at about δ 96.0 provided the clue to the event taking place. This signal is in the characteristic region of *gem*-dioxy groups[16] and suggests that **3** and **7** are undergoing reversible covalent hydration to **9** and **10**, respectively. The ^{31}P

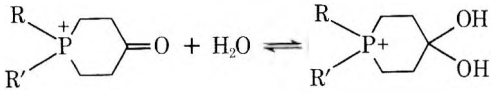


9, R = CH_3; X = O
10, R = C_2H_5; X = O
11, R = CH_3; X = S
12, R = C_2H_5; X = S

NMR signal for each compound in the equilibrium mixtures was also different; the signals were very sharp and useful for analysis of the mixtures even though they were separated by less than 1 ppm. The equilibrium compositions of Table V were obtained by this method. Signals were assigned to the keto or diol form on the basis of the similarity of peak intensities to those seen in the ^{13}C spectra.

The position of the hydration equilibrium was quite sensitive to temperature; at 70°, the ketone spectrum was in great predominance (80–90%), while at 10° only the diol spectrum was obtained.

Similar hydration effects were observed for the salts **4** and **8**, which formed **13** and **14**, respectively, and even for



13, R = R′ = CH_3
14, R = CH_3; R′ = C_2H_5

the sulfides **2** and **6** (Tables IV and V); the latter were less soluble in water, but gave readily observable signals attributable to diols **11** and **12**, respectively, in 5–10% methanol.

Contrary to the behavior of the phosphorinanes with tetracoordinate phosphorus, phosphines in this family (**1** and **5**) failed to undergo the hydration reaction to a detectable extent. They were insoluble in water, and it was necessary to test for hydration in the presence of dioxane (1:1).

Table V
^{31}P NMR Spectra and Equilibrium Compositions for the Hydration of 4-Phosphorinanones[a]

	$\delta^{31}P$[b]		Composition, %	
	Keto	Diol	Keto	Diol
3 ⇌ 9	−42.0	−41.6	35	65
7 ⇌ 10	−51.1	−51.8	47	53
4 ⇌ 13	−20.0	−17.2	40	60
8 ⇌ 14	−25.0	−21.7	42	58

[a] Spectral measurements were made on water solutions containing 5–10% of CH_3OH as ^{13}C reference. [b] Parts per million downfield from 85% H_3PO_4. Measured at 30°.

Similar hydration effects are known in other cyclic ketones with polar substituents; the methiodide of *N*-methyl-4-piperidone behaves very much like its phosphorus counterpart **4** and is extensively hydrated at room temperature,[16,17] while the free base, which is water soluble, shows about 16% hydration.[17]

It is thus seen that for both the P and the N compounds there is unusually great reactivity toward the nucleophile water in the same carbonyl groups that have the most upfield ^{13}C signals. It is possible that these effects result from similar through-space influences of the polar function on the carbonyl group; they seem less readily explained by transmission through the σ-bond structure. However, there is a change in stereochemistry about C_4 accompanying the hydration reaction and it is not known if this change has more influence on the reaction energetics for hydration of phosphorinanones with tetracoordinate phosphorus than with trivalent phosphorus. Any correlation between ^{13}C shifts and chemical reactivity for these ketones must remain speculative at this time.

Another unusual effect noted among these compounds is that oxide **3** underwent extensive proton–deuterium exchange at $C_{3,5}$ in neutral D_2O. Thus, after 24-hr exposure to D_2O at 75°, only 3% of the oxide remained undeuterated, and about 50% had achieved the d_4 stage. Such ready exchange would be more likely for the phosphine, since its basic center could promote the reaction, as has been suggested[17] to explain the rapid exchange of *N*-methyl-4-piperidone in D_2O. While the phosphine (**1**) did undergo some exchange in D_2O–dioxane (1:1), the extent was much less then that seen for the oxide. The manner in which remote phosphoryl influences the exchangeability of protons remains to be clarified.

Experimental Section

General. All manipulations of phosphines were conducted in a nitrogen atmosphere in a glove bag. Melting points are corrected.

Proton-decoupled Fourier transform ^{13}C spectra were taken with a Bruker HFX-10 system at 22.62 MHz utilizing C_6F_6 in a 3-mm coaxial capillary as external heteronuclear lock. Chemical shifts were measured from internal Me_4Si for $CHCl_3$ solutions, and from internal CH_3OH for water solutions (δ CH_3OH = 141.2; δ CS_2 = 192.5 ppm). C–P coupling constants are ±1.2 Hz. Proton-decoupled ^{31}P NMR spectra (CW mode) were obtained at 36.43 MHz again with a C_6F_6 lock; offsets relative to prerun 85% H_3PO_4 were used to determine δ values. Ir spectra were obtained with a Perkin-Elmer 621 spectrophotometer, and uv spectra with a Cary 15 spectrophotometer.

1-Methyl-4-phosphorinanone Derivatives. The parent ketone 1 was prepared as described previously.[18] Its conversion to sulfide 2 has also been reported.[2] Phosphine 1 readily gave the salt 4 with CH_3I, which was used directly for the NMR study.

Oxidation of 1 was accomplished by stirring 3.0 g (23.1 mmol) in 50 ml of benzene with 1.98 ml (23.1 mmol) of 30% H_2O_2 in an ice bath for 1 hr. Stripping of solvents left a white solid residue of 3 which was recrystallized from a mixture of methylene chloride and petroleum ether: mp 138–142°; ir ($CHCl_3$) ν 1730 cm^{-1} (C=O); NMR ($CDCl_3$) δ 1.70 (d, $^2J_{PH}$ = 13 Hz, PCH_3); NMR (D_2O, 30°) δ 2.12 and 2.25 (1:1, each d, $^2J_{PH}$ = 13.5 Hz, PCH_3 for diol and keto forms, respectively, as seen from temperature effects). The compound is extremely hygroscopic and gave only partly satisfactory analyses.

Anal. Calcd for $C_6H_{11}O_2P$: C, 49.32; H, 7.54; P, 21.21. Found: C, 48.92; H, 7.97; P, 20.87.

Oxide 3, previously characterized as the oxime,[19] underwent exchange in D_2O at 75°. After 24 hr, a sample recovered by $CHCl_3$ extraction was found by mass spectral analysis to contain 50% d_4, 25% d_3, 12% d_2, and 7% d_1 derivative; only 3% remained undeuterated.

1-Ethyl-4-phosphorinanone Derivatives. The parent phosphine 5 has been reported previously.[20] Conversion to sulfide 6 was accomplished by a general procedure.[2] The sulfide after vacuum sublimation had mp 60–61.5°.

Anal. Calcd for $C_7H_{13}OPS$: C, 47.71; H, 7.44; P, 17.58. Found: C, 47.83; H, 7.50; P, 17.48.

Phosphine 5 was also oxidized to form compound 7, which had previously been characterized as the oxime.[19] Quaternization of 5 with CH_3I gave salt 8 for the NMR studies.

Registry No.—1, 16327-48-3; 2, 55298-82-3; 3, 54662-09-8; 4, 55298-83-4; 5, 55298-84-5; 6, 55298-85-6; 7, 51805-19-7; 8, 1194-42-9; 9, 55298-86-7; 10, 55298-87-8; 11, 55298-88-9; 12, 55298-89-0; 13, 55298-90-3; 14, 55298-91-4.

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Preparation of (*E,E*)- and (*Z,Z*)-1,4-Dibromo-1,4-diphenylbutadienes and Conversion to Mono- and Dilithio Derivatives

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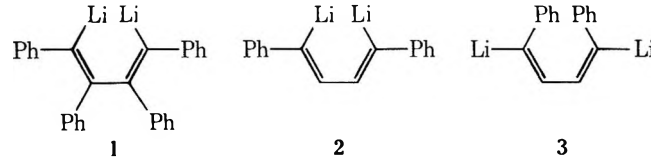
The ready availability of the dilithium reagent 1 by reduction of tolane[1,2] has resulted in its widespread use for the preparation of metallocycles (heterocyclopentadienes).[1a-c,3] The 1,4-diphenyl dilithio compound 2 should be equally and perhaps even more useful than 1. The published synthesis[4] of the precursor dibromide 4a is a five-step sequence, however, so that 2 and 4a have been used infrequently.[5]



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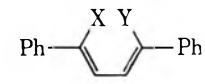
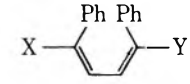
We required dibromides 4a and 5a, as well as the mono- and dilithium reagents derived from them, in connection with studies on the preparation of chlorolium ions.[6] The



4

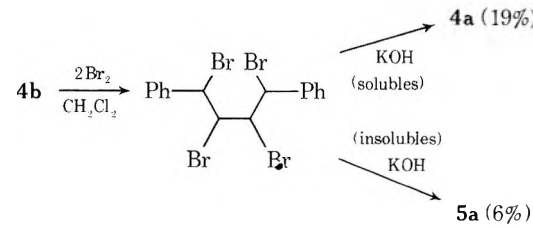
	a	b	c	d	e	f	g
X	Br	H	Cl	SCH_3	Br	Br	Br
Y	Br	H	Cl	SCH_3	H	Cl	SCH_3



5

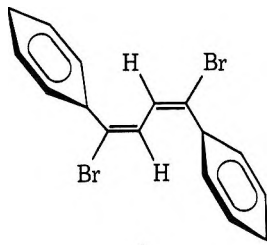
	a	b	c
X	Br	H	Br
Y	Br	H	Li

most convenient synthesis of 4a and 5a would appear to be by bromination–dehydrobromination of the readily available 1,4-diphenylbutadiene.[7] We have developed procedures for the preparation of 4a and 5a in pure form by this route. The yields are low, but the procedures are simple, and the products are obtained in pure form by a single crystallization. The principal separation is performed at the tetrabromide stage; the precursor for 5a is extremely insoluble and is filtered off after the bromine addition. Dehydrohalogenation (KOH–EtOH) of crystals and mother liquor gives the dibromides 5a and 4a, respectively.

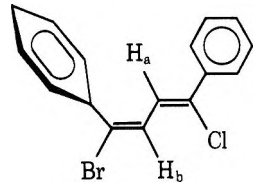


(*E,Z*)-1,4-Dibromo-1,4-diphenyl-1,3-butadiene appeared to be formed as well (see Experimental Section), but it could not be isolated in pure form.

Stereochemical assignments were made on the basis of several arguments. The chemical shifts of the vinyl protons in 4a and 5a are δ 7.30 and 6.63. The pronounced upfield shift in the *E,E* isomer (5a) can be in part ascribed to the operation of a phenyl ring current effect. Apparently steric interactions of the ortho protons with the bromine and cis vinyl group result in the phenyl ring being turned out of the diene plane, so that the vinyl hydrogen is located in the shielding region of the phenyl ring current (see conformation 6). An upfield shift of H_a (δ 6.64) in 7 was attributed to



6



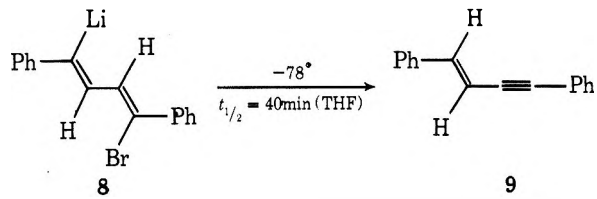
7

the same effect[6] (assignments were unambiguous in **7** since both monodeuterated compounds were also prepared). Proton H_b in **7** appears at δ 7.32, indicating that simply being on an *E* double bond does not result in an upfield shift. Further stereochemical evidence is found in the facile elimination of **4a** to 1,4-diphenylbutadiyne, whereas **5a** is resistant to dehydrohalogenation by KOH in refluxing ethanol.

Compound **4a** was identical in physical and chemical properties with the dibromide prepared by Gilman and coworkers.[4] These workers called this compound the trans,trans isomer, but a figure showed the *E,E* configuration. Their compound undoubtedly has the *Z,Z* structure (**4a**), since the derived dilithium reagent was converted to dimethyl-2,5-diphenylsilole or (*E,E*)-1,4-diphenylbutadiene (**4b**) by reaction with dimethyl dichlorosilane or water. We have confirmed the conversion of **2** to **4b** by protonation and have also shown that protonation of **3** gives (*Z,Z*)-1,4-diphenyl-1,3-butadiene (**5b**). The stereochemistry of the 1,4-diphenyl-1,3-butadienes has been previously assigned.[8] The formation and reactions of vinyllithium reagents, when stereospecific, invariably occur with retention of configuration.[9] Only a small amount of isomerization is observed when the presumably thermodynamically less stable dilithium compound **3** is converted back to dibromide **5a** by reaction with 1,2-dibromoethane.

The dilithio derivative **2** has also been converted to the dichloro (**4c**, reaction with hexachloroethane) and the bismethylthio (**4d**, reaction with dimethyl disulfide) compounds.

Treatment of **4a** with only 1 equiv of *n*-butyllithium gives the monolithio compound **8**, with only a few percent of **2** and **4a** as contaminants. When **8** is prepared in THF, extreme care must be taken to avoid warming the solution above −78° (the *n*-BuLi solution must be cooled to −78° before addition), and the anion must be derivatized promptly to avoid decomposition to **9**. This reaction proba-



8 9

bly occurs by intramolecular dehydrohalogenation, again consistent with the assigned stereochemistry. In ether solution, however, the anion can be prepared and utilized at 0°, with little formation of **9** even after several hours at this temperature. Huge solvent effects on the rate of reaction of organolithiums on going from THF to ether have been observed previously.[2a,9c,10] We have prepared **4e**, **4f**, and **4g** by protonation, chlorination (C_2Cl_6), and methylsulfenylation (Me_2S_2) of **8**. The NMR spectrum of the monobromo compound **4e** provides further stereochemical evidence. The proton at C-4 is a doublet with J = 16 Hz, characteristic of a trans vinyl coupling.

The monolithio derivative of **5a** (**5c**) can also be prepared by metal–halogen interchange in ether (0°). This anion does not decompose to **9** in THF at −78°, but it appears to react slowly with the butyl bromide present.

Experimental Section

Nuclear magnetic resonance spectra were measured in carbon tetrachloride using a Jeol MH-100 spectrometer. A 5 ft × 0.125 in. column of 3% SE-30 on 100/120 Varaport 30 was used for analytical GLC. Tetrahydrofuran (THF) was freshly distilled from $LiAlH_4$; ether was Mallinckrodt reagent grade. All reactions involving organometallics were carried out in an atmosphere of nitrogen.

In the standard work-up for the organometallic reactions, the reaction mixture was poured into 1:1 ether–pentane and saturated $NaHCO_3$ solution and shaken. The aqueous layer was removed and the organic layer was washed with NaCl solution, dried (Na_2SO_4), and evaporated.

All of the dienes prepared here were configurationally stable when crystalline. Most of the compounds also showed little tendency to isomerize during normal laboratory manipulations, but solutions of the methylthio compounds **4d** and **4g** isomerized over a period of hours during exposure to fluorescent room lights.

(*Z,Z*)-1,4-Dibromo-1,4-diphenyl-1,3-butadiene (4a) and (*E,E*)-1,4-Dibromo-1,4-diphenyl-1,3-butadiene (5a). A solution of 8 ml (0.149 mol) of Br_2 in 25 ml of dichloromethane was added dropwise over about 45 min to a solution of 16 g (0.078 mol) of **4b** in 300 ml of dichloromethane which was stirred magnetically. After the addition stirring was continued for an additional 15 min. The white insoluble tetrabromide which was formed was removed by vacuum filtration. It was transferred to a flask, heated with 50 ml of dichloromethane, filtered and washed thoroughly with dichloromethane, giving 7.47 g. A sample of the tetrabromide was recrystallized by soxhlet extraction with dichloromethane to give material with mp 263° dec.

Anal. Calcd for $C_{16}H_{14}Br_4$: C, 36.54; H, 2.68. Found: C, 36.64; H, 2.78.

The total filtrate was evaporated, 250 ml of absolute ethanol was added, and the mixture was cooled in an ice bath. While the mixture was stirred mechanically 16 g (0.24 mol) of KOH pellets was added in portions at such a rate that the temperature of the reaction mixture was kept below 15°. After 45 min, when all the KOH had dissolved, the ice bath was removed, stirring was continued for 3.5 hr at 25°, $NaHCO_3$ (16 g, 0.19 mol) was added to the slurry, and the ethanol was evaporated. Ether (150 ml), pentane (100 ml), and water (150 ml) were added to the residue. After stirring for 10 min the mixture was filtered, giving a further 1.18 g of insoluble tetrabromide which was washed with ether and water. The organic layer of the filtrate was washed with NaCl solution, dried (Na_2SO_4), and evaporated. The resulting semisolid was crystallized from 20 ml of hexane at 4°, yielding 5.30 g (19%) of **4a**, mp 117–120°, which was 97% pure by analytical GLC. A second crystallization from hexane gave material with mp 122–123° (lit.[4] mp 121–123°); NMR δ 7.2–7.4 (m, including a sharp singlet at 7.30, 8 H), 7.5–7.7 (m, 4 H). The mother liquor from the above crystallization was dissolved in pentane (20 ml) and allowed to crystallize, giving mainly 1,4-diphenylbutadiyne (1.1 g). The filtrate (13.0 g) showed a doublet at δ 6.73 (J = 11 Hz), which was assigned to (*E,Z*)-1,4-dibromo-1.4-diphenyl-1,3-butadiene (about 25% of the sample by NMR integration). The chemical shift is as expected on the basis of data for **7**.

The combined insoluble tetrabromide obtained above (8.65 g, 0.016 mol) was refluxed with 4.2 g (0.064 mol) of KOH in 125 ml of absolute ethanol for 4 hr, $NaHCO_3$ (4.2 g, 0.05 mol) was added, and the ethanol was evaporated. Ether (100 ml) and water (100 ml) were added with swirling. Work-up as above followed by crystallization from 10 ml of hexane at 25° (cooling below 25° may result in cocrystallization of 1,4-diphenylbutadiyne) gave 1.56 g (6%) of **5a**, mp 135–138° [NMR δ 6.63 (s, 2 H), 7.2–7.6 (m, 10 H)] which had less than 1% of volatile impurities by analytical GLC and was >90% pure by NMR integration. Further crystallization from ether, hexane, or ethanol gave lower melting material of variable melting point. This erratic behavior could be caused by the change in concentration of an unidentified nonvolatile impurity.

Anal. Calcd for $C_{16}H_{12}Br_2$: C, 52.78; H, 3.32. Found: C, 52.81; H, 3.31.

(*Z,Z*)-1,4-Dichloro-1,4-diphenyl-1,3-butadiene (4c). To a magnetically stirred solution of 3.3 ml of *n*-butyllithium (1.19 *M* in hexane, 4.0 mmol) in 6 ml of THF at −78° was added 0.364 g (1.0 mmol) of **4a**. After stirring for 15 min at −78°, 1.23 g (5.0 mmol) of hexachloroethane (crystallized from hexane) was added, the cool-

ing bath was removed, and after 10 min the reaction mixture was worked up. The resulting solid was crystallized from ethanol, yielding 0.247 g (90%) of **4c**, mp 117–118°, NMR δ 7.1–7.4 (m, including a sharp singlet at 7.27, 8 H), 7.5–7.8 (m, 4 H).

Anal. Calcd for $C_{16}H_{12}Cl_2$: *m/e* 274.03160. Found: *m/e* 274.03202.

(*Z,Z*)-1,4-Bis(methylthio)-1,4-diphenyl-1,3-butadiene (4d). To a magnetically stirred solution of 2.5 ml of *n*-butyllithium (1.19 *M* in hexane, 3.0 mmol) in 6 ml of THF at −78° was added 0.366 g (1.0 mmol) of **4a**. After stirring for 15 min at −78° 0.40 ml (5.0 mmol) of dimethyl disulfide was added, the cooling bath was removed, and after 10 min the reaction mixture was worked up in the usual way including a 5% NaOH wash. The resulting solid was crystallized from ethanol to yield 0.203 g (68%) of **4d**, mp 123–130°. Recrystallization from hexane yielded a sample with mp 131–133°; NMR δ 2.00 (s, 6 H), 7.0–7.4 (m, including a sharp singlet at 7.14, 8 H), 7.4–7.7 (m, 4 H).

Anal. Calcd for $C_{18}H_{18}S_2$: *m/e* 298.08499. Found: *m/e* 298.08474.

(*Z,E*)-1-Bromo-1,4-diphenyl-1,3-butadiene (4e). An ether solution (15 ml) of 0.366 g (1.0 mmol) of **4a** was cooled to 0° with stirring, resulting in a fine suspension, and 0.80 ml of *n*-butyllithium (1.19 *M* in hexane, 1.0 mmol) was added dropwise. After 3 min 0.2 ml of methanol was added to the reaction mixture followed by the usual work-up. GLC analysis showed 95% monolithiation accompanied by 2.6% dilithiation and 2.5% unreacted starting material. Crystallization from pentane yielded 0.246 g (86%) of solid: mp 78–79°; NMR δ 6.84 (d, *J* = 16 Hz, 1 H), 7.02 (d, *J* = 10 Hz, 1 H), 7.1–7.8 (m, 11 H). An analytical sample was collected by preparative GLC on a 0.25 × 8 in. column of 20% SE-30 on 60/80 Chromosorb W, AW-DMCS, mp 79–80°.

Anal. Calcd for $C_{16}H_{13}Br$: C, 67.38; H, 4.59. Found: C, 67.36; H, 4.62.

(*Z,Z*)-1-Bromo-4-chloro-1,4-diphenyl-1,3-butadiene (4f). To 4.5 ml of THF was added 0.02 ml of *n*-butyllithium (1.19 *M* in hexane) followed by 0.185 g (0.50 mmol) of **4a**. After the solid had dissolved, the solution was cooled to −78° and 0.44 ml (0.52 mmol) of *n*-butyllithium which had been cooled to −78° was added. After stirring for 3 min, hexachloroethane (0.149 g, 0.63 mmol) was added, the cooling bath was removed, and after 10 min the reaction was worked up. The solid was crystallized from ethanol, yielding 0.135 g (84%) of **4f**, mp 107–108°, identical with authentic material.[6]

(*Z,Z*)-1-Bromo-4-methylthio-1,4-diphenyl-1,3-butadiene (4g). To 15 ml of ether was added 0.04 ml of *n*-butyllithium (1.19 *M* in hexane) followed by 0.364 g (1.0 mmol) of **4a**. After the solid had dissolved, the solution was cooled to 0° and 0.86 ml (1.0 mmol) of *n*-butyllithium was added dropwise with magnetic stirring. After 3 min dimethyl disulfide (0.11 ml, 1.4 mmol) was added and the reaction mixture was worked up as usual (5% NaOH wash). The product was crystallized from hexane, yielding 0.255 g (77%) of **4g**, mp 80–81°. Another crystallization gave material with mp 83–84°; NMR δ 2.02(s, 3 H), 6.87 (d, *J* = 10 Hz, 1 H), 7.1–7.4 (m, 6 H), 7.4–7.7 (m, 5 H).

Anal. Calcd for $C_{17}H_{15}SBr$: *m/e* 330.00775. Found: *m/e* 330.01078.

(*Z,Z*)-1,4-Diphenyl-1,3-butadiene (5b). An ether solution (15 ml) of 0.364 g (1.0 mmol) of **5a** was cooled to 0° and 2.5 ml of *n*-butyllithium (1.19 *M* in hexane, 3.0 mmol) was added. Methanol (0.2 ml) was added and the reaction mixture was worked up. The product was crystallized from methanol to give 0.134 g (65%) of **5b**, mp 66–68°. A second crystallization from pentane gave material with mp 69–70° (lit.[8] mp 70–70.5°); NMR δ 6.46 (closely spaced AA′BB′, 4 H), 6.9–7.4 (m, 10 H).

Bromination of 3. The dianion **3** was prepared as above and quenched with dibromoethane. NMR showed the product to be **5a**, about 80% pure. GLC analysis indicated that **5a** was 83% pure (retention time 3.6 min at 195°); the impurities, identified by GLC retention times, being 2% of **5b** (0.9 min), 10% of (*E,Z*)-1-bromo-1,4-diphenyl-1,3-butadiene (1.8 min), 0.2% of **4a** (6.6 min), and 5% of a peak tentatively identified as (*E,Z*)-1,4-dibromo-1,4-diphenyl-1,3-butadiene (4.3 min). Thus the formation and reaction of **3** appears to give 94% isomerically pure product with retention of configuration.

Preparation and Decomposition of Monoanion 5c. To a solution of 0.364 g (1.0 mmol) of **4a** in 4.5 ml of THF at −78° was added 0.84 ml of *n*-butyllithium (1.19 *M* in hexane, 1.0 mmol) diluted with 1.5 ml of THF, which had been cooled to −78°. The reaction mixture was stirred at −78° and aliquots were removed and quenched with methanol at −78°. GLC determination of the ratio of **9** to **4e** at four intervals showed **9** increasing with a first-order rate constant of 3.1 ± 0.1 × 10^{-4} sec^{-1}. The retention times of **9** and **4e** were 1.3 and 3.5 min at 195°. After 3 hr GLC analysis showed 93% **9** and the reaction mixture was worked up. (*E*)-1,4-Diphenyl-3-buten-1-yne (*9*) was identified from its NMR spectrum and GLC retention time: NMR δ 6.30, 6.95 (AB q, *J* = 16.3 Hz, 2 H), 7.1–7.5 (m, 10 H).

Acknowledgment. We thank the Research Corporation and the National Science Foundation for support of this work.

Registry No.—**2**, 55373-67-6; **4a**, 55373-68-7; **4b**, 538-81-8; **4c**, 55373-69-8; **4d**, 55373-70-1; **4e**, 55373-71-2; **4f**, 52516-76-4; **4g**, 55373-72-3; **5a**, 7641-45-4; **5b**, 5807-76-1; **9**, 13343-79-8; bromine, 7726-95-6; 1,2,3,4-tetrabromo-1,4-diphenylbutane, 53446-15-4; hexachloroethane, 67-72-1; dimethyl disulfide, 624-92-0.

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Preparation of Monolithium Acetylide in Tetrahydrofuran. Reaction with Aldehydes and Ketones

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We wish to report a highly convenient and simple method for the preparation of amine-free monolithium acetylide in tetrahydrofuran. This monolithium acetylide reacts with a variety of aldehydes and ketones under exceptionally mild conditions to give high yields of the corresponding ethynyl carbinols.

Monolithium acetylide is a valuable reagent for the preparation of ethynyl carbinols and terminal acetylenes.[1] One disadvantage of this reagent is that it readily disproportionates into dilithium acetylide and acetylene in the absence of a complexing agent.[2] Therefore the reagent is usually prepared in liquid ammonia, which presumably serves

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Table I
Addition of Monolithium Acetylide to Aldehydes and Ketones

RCOR'	Registry no.	% yield[a] of $RR'C(OH)-C\equiv CH$	Registry no.	$n^{20}D$ or mp, °C
Acetone	67-64-1	94	115-19-5	
Hexanal	66-25-1	98	818-72-4	1.4420
2-Hexanone	591-78-6	92	17356-17-1	1.4366
Diisobutyl ketone	108-83-8	75, 86[b]	10562-68-2	1.4419
Di-*sec*-butyl ketone	19549-84-9	89	55373-73-4	1.4542
Di-*tert*-butyl ketone	815-24-7	66, 98[b]	33420-19-8	1.4584
Phenylacetone	103-79-7	94	55373-74-5	1.5289
Acetophenone	98-86-2	75	127-66-2	48–50
Benzaldehyde	100-52-7	93	4187-87-5	1.5466
Benzophenone	119-61-9	(85)	3923-52-2	47–48
Cinnamaldehyde	104-55-2	96	14604-31-0	65–66
Mesityl oxide	141-79-7	86 (77)	20109-03-9	1.4625
β-Ionone	14901-07-6	93	17075-53-5	1.5124
Cyclopentanone	120-92-3	94	17356-19-3	1.4725
Cyclohexanone	108-94-1	95	78-27-3	31–33
Cycloheptanone	502-42-1	90 (83)	2809-78-1	1.4896
Cyclooctanone	502-49-8	86	55373-76-7	43–44
Norcamphor	497-38-1	97 (92)[c]	55373-77-8	46–47
Cyclohexanecarboxaldehyde	2043-61-0	98	4187-88-6	1.4830

[a] By VPC based on RCOR'. Isolated yields are in parentheses. [b] 100% excess monolithium acetylide was used. [c] The product was >99% 2-ethynyl-*endo*-2-norbornanol by VPC and ^{13}C NMR examination.

$$2LiC\equiv CH \longrightarrow LiC\equiv CLi + HC\equiv CH$$

as an appropriate complexing agent. An amine, such as ethylenediamine, may similarly be used to stabilize the monolithium acetylide.[3] However, the addition of an amine complexing agent may greatly diminish the reactivity of the monolithium acetylide.

For certain reactions it may be desirable to have the amine-free monolithium acetylide in a solvent, such as tetrahydrofuran. It has been reported that monolithium acetylide may be prepared from acetylene and lithium dispersion in tetrahydrofuran,[4] but Beumel and Harris were unable to reproduce this work.[3] It has also been reported that monolithium acetylide may be prepared from acetylene and lithium napthalide in tetrahydrofuran.[5] However, addition of this lithium acetylide to aldehydes or ketones gives only low yields of ethynyl carbinols. In light of the shortcomings of these preparative methods, we have investigated the preparation of amine-free monolithium acetylide and have developed a convenient procedure based on the reaction of *n*-butyllithium with acetylene.

Addition of *n*-butyllithium to acetylene in tetrahydrofuran at 0° produces a heavy white precipitate. The use of excess acetylene does not suppress the formation of the precipitate. Addition of acetone to this suspension gives only a low yield (32%) of the desired carbinol. If monolithium acetylide is formed under these conditions, it rapidly disproportionates into the more stable dilithium acetylide, which is insoluble.

However, addition of *n*-butyllithium to acetylene at −78° results in a clear solution. Addition of hexanal to this solution, followed by warming to room temperature, produces an essentially quantitative yield of 1-octyn-3-ol.

$$HC\equiv CH + n\text{-}C_4H_9Li \xrightarrow[THF]{-78^\circ} LiC\equiv CH + C_4H_{10}$$

$$n\text{-}C_5H_{11}CHO + LiC\equiv CH \xrightarrow[THF]{-78^\circ} \xrightarrow[H_2O]{25^\circ}$$

$$n\text{-}C_5H_{11}\underset{\displaystyle OH}{\underset{|}{C}}HC\equiv CH \quad 98\%$$

The monolithium acetylide is fairly stable when maintained at low temperatures. The solution remains clear for several hours at −78°. Use of such a solution, maintained at −78° for 6 hr, results in a small decrease in the yield of 1-octyn-3-ol to 87%. Warming the solution of monolithium acetylide to 0° results in the irreversible formation of a white solid, presumably dilithium acetylide. Cooling this solution to −78°, followed by addition of hexanal, produces only 39% of the carbinol. Tetrahydrofuran apparently forms a complex which stabilizes the monolithium acetylide at the lower temperatures, but not at the higher temperatures. This unusual stability makes amine-free monolithium acetylide exceptionally suitable for ethynylation reactions.

The monolithium acetylide was added to a number of aldehydes and ketones (Table I). As a standard procedure, the reactants were stirred at −78° for 20 min and then brought to room temperature. In all cases, the reactions appeared to be essentially complete under these conditions. Thus, this monolithium acetylide appears to be far more reactive than lithium acetylide–ethylenediamine. The latter reagent requires longer reaction times and, in some cases, forcing conditions.[6] The milder conditions of the present reagent minimize the occurrence of side reactions, such as diol formation.

Optimum yields are obtained with an approximately 0.5 *M* concentration of monolithium acetylide. At 1.0 *M* the solution becomes slightly cloudy and yields are 10–15% lower.

Most compounds give satisfactory results with a 1:1 ratio of acetylide to carbonyl compounds. As a standard practice, a 10% excess of acetylide is recommended. Certain hindered ketones, such as diisobutyl or di-*tert*-butyl ketone, give somewhat lower yields unless excess monolithium acetylide is used.

This process allows one for the first time to prepare an amine-free tetrahydrofuran solution of monolithium acetylide. The ready availability and high reactivity under exceptionally mild conditions should make it a valuable synthetic reagent.

Experimental Section

Tetrahydrofuran was distilled from lithium aluminum hydride and stored under nitrogen. Acetylene (welding grade) was purified by passage through a −78° trap, then a sulfuric acid trap, and finally through soda lime. The acetylene was transferred to the reaction flask with a gas syringe.[7] *n*-Butyllithium in hexane (Alfa) was standardized by the method of Watson and Eastham.[8]

All ketones were obtained commercially and were used without further purification. All aldehydes were obtained commercially and were distilled under nitrogen prior to use.

All glassware was dried in an oven at 130° for several hours, then assembled hot and flushed with nitrogen while cooling. Liquids were transferred using syringe and double-ended needle techniques.[9,10] Solids were dissolved in tetrahydrofuran and transferred as the solution.

Melting points were determined with a Thomas-Hoover melting point apparatus and are uncorrected. Infrared spectra were taken on a Perkin-Elmer 700 spectrometer. ^1H and ^{13}C NMR spectra were recorded on a Varian T-60 and Varian CFT-20 spectrometer, respectively, using tetramethylsilane as an internal standard. High-resolution mass spectra were obtained on a CEC 21-110 instrument. A Hewlett-Packard 5750 gas chromatograph was used for VPC analysis using either a 6 ft × 0.25 in. 10% SE-30 or 10% XE-60 column with Chromosorb W as a stationary phase. Decane (Philips 99%) was used as an internal standard.

General Procedure for Monolithium Acetylide Preparation. 2-Ethynyl-*endo*-2-norbornanol. A dry 500-ml flask equipped with a magnetic stirring bar and septum-capped inlet was connected to a mercury bubbler and flushed with nitrogen. Tetrahydrofuran (200 ml) was placed in the flask and the flask was cooled in a Dry Ice–acetone bath. Acetylene (110 mmol) was added by means of a large gas syringe. *n*-Butyllithium (110 mmol, 49 ml of a 2.24 *M* solution in hexane) was measured into a graduated cylinder[10] by double-ended needle and then transferred dropwise into the reaction flask over a 15-min period. The solution was stirred for 10 min. Norcamphor (100 mmol, 11.1 g) was placed in a graduated cylinder and dissolved in 30 ml of tetrahydrofuran. The solution was added over a 5-min period to the monolithium acetylide. An additional 5 ml of tetrahydrofuran was used to wash the last of the norcamphor into the reaction flask. The solution was stirred for 20 min at −78° and then warmed to room temperature. Water (40 ml) was added followed by anhydrous potassium carbonate until the aqueous phase became pasty. The organic phase was decanted and the aqueous layer was washed with 2 × 30 ml of ether. The combined organic phase was dried (magnesium sulfate) and distilled through a short-path distillation head. There was obtained 12.5 g (92%), bp 84–86° (15 mm). The product solidified upon cooling on Dry Ice: mp 46–47° (lit.[11] mp 45–46°); ^1H NMR ($CDCl_3$) δ 2.47 (s, C≡CH), 2.43–1.2 (complex m, ring H and OH); proton-decoupled ^{13}C NMR δ C_1, 49.6; C_2, 73.1; C_3, 47.6; C_4, 36.8; C_5, 26.7; C_6, 21.0; C_7, 38.7; terminal acetylene, 90.1; internal acetylene, 71.1; exact mass (P − 1) 135.083 (calcd, 135.081).

VPC analyses were obtained from 5-mmol scale reactions. All products were isolated from these reactions by Kugelrohr distillation or preparative VPC. All products exhibited consistent ir, NMR, and mass spectra. Satisfactory exact mass measurements (±0.003 mass units) were obtained for all compounds.

Stability. In a dry 50-ml flask was prepared 5 mmol of monolithium acetylide in 10 ml of tetrahydrofuran. The solution was stirred for 6 hr in a Dry Ice–acetone bath. Then 5 mmol of hexanal was added. After 20 min the flask was warmed to room temperature and 2 ml of water was added. The solution was saturated with potassium carbonate and 5 mmol of decane was added. Analysis by VPC revealed 4.35 mmol (87%) of 1-octyn-3-ol.

In a similar manner, 5 mmol of monolithium acetylide was prepared and after 10 min it was warmed to 0° for 15 min, then cooled to −78°. A white precipitate had formed at 0°. Hexanal was added and the reaction was worked up as above. Analysis revealed 1.95 mmol (39%) of 1-octyn-3-ol.

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Registry No.—Monolithium acetylide, 1111-64-4; acetylene, 74-86-2; *n*-butyllithium, 109-72-8.

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A Facile Synthesis of 1-(Carbethoxyethoxymethyl)camphene

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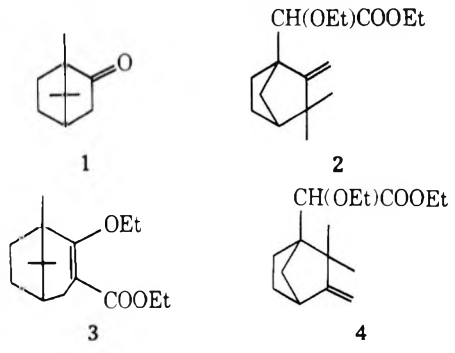
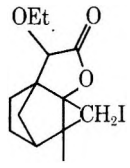
The potential of camphene derivatives possessing a functionalized C-1 side chain as synthetic precursors of natural products and related compounds has been realized in the recent syntheses of isolongifolene[1] and zizaane-type sesquiterpenoids.[2,3] The methods available for their preparation[1-7] were, however, limited to multistep transformations of camphor (**1**) and often gave the desired products in unsatisfactory yields. In connection with our studies on the regioselectivity of boron trifluoride catalyzed ring enlargement of unsymmetrically substituted cycloalkanones,[8] we have discovered an efficient conversion of *dl*-camphor (**1**) to the title compound (**2**) which should prove synthetically useful, particularly in constructing naturally occurring compounds of the zizaane family.[9]

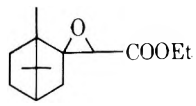


1 2 3 4

Prolonged treatment of *dl*-camphor (**1**) with an excess of boron trifluoride etherate and ethyl diazoacetate in ether afforded, in addition to a minor amount of 3-carbethoxy-2-ethoxy-1,8,8-trimethylbicyclo[3.2.1]oct-2-ene (**3**),[8] a mixture of 1-(carbethoxyethoxymethyl)camphene (**2**) and its positional isomer **4** (2:1) in 63% yield.[10] Subsequent treatment of the mixture with zinc dust and glacial acetic acid at reflux for 24 hr resulted in an essentially quantitative and clean rearrangement of **4** to **2**. The structure of **2** was readily assigned on the basis of its spectral data (see Experimental Section) and was further confirmed by its conversion to crystalline iodo lactone **5**. The sharp spectral peaks and thin layer chromatographic behavior of **2** and **5** coupled with the sharp melting point of **5** are suggestive of single stereoisomers of both **2** and **5**. The data presently available, however, do not permit unambiguous definition of their stereochemistry.



5



6

The formation of **2** and **4** from *dl*-camphor (**1**) might be rationalized by invoking Wagner–Meerwein rearrangements[11] of an intermediate of glycidic ester[12] **6**.

Experimental Section[13]

1- (2) and 4-(Carbethoxyethoxymethyl)camphene (4). To a chilled solution (0°) of 3.04 g (0.02 mol) of *dl*-camphor (**1**) and 4.26 g (0.03 mol) of boron trifluoride etherate in 25 ml of ether under a nitrogen atmosphere was added dropwise, over a period of 15 min, a solution of 3.42 g (0.03 mol) of ethyl diazoacetate in 5 ml of ether. The resulting solution was stirred in the dark at room temperature for 120 hr; at the end of each 24-hr period, a further 1.42 g (0.01 mol) of boron trifluoride etherate and 1.14 g (0.01 mol) of ethyl diazoacetate were added. The reaction mixture was cautiously made basic at 0° with saturated aqueous sodium bicarbonate and extracted with chloroform. The organic solution was washed with 1 *N* aqueous hydrochloric acid and water, dried ($MgSO_4$), filtered, and concentrated. Column chromatography of the oily product on silica gel with benzene elution gave 1.275 g (24% yield) of **3**[8] (slower moving) and 3.36 g (63% yield) of a mixture of **2** and **4**. The ir and mass spectra of the mixture were similar to those of pure **2** (see below). Its NMR spectrum (CCl_4) displayed two partly superimposed sets of signals integrated in a ratio of 2:1. The bands of the major set were found to coincide with those of **2** (see below) and the minor set contained the following diagnostic signals of **4**:[14] δ_{TMS} 4.64 (s, 1 H, vinylic), 4.46 (s, 1 H, vinylic), 4.12 (q, 2 H, J = 7.2 Hz, $COOCH_2CH_3$), 4.05 (s, 1 H, OCH), 3.54 [q of d, 1 H, J = 8.5, J' = 7 Hz, $OCH(H)CH_3$], 3.35 [q of d, 1 H, J = 8.5, J' = 7 Hz, $OCH(H)CH_3$], 2.55 (br s, 1 H, allylic), 1.25 (t, 3 H, J = 7.2 Hz, $COOCH_2CH_3$), 1.16 (t, 3 H, J = 7 Hz, OCH_2CH_3), 1.05 (s, 3 H, methyl), and 0.99 (s, 3 H, methyl).

Isomerization of 4 to 2. A stirred mixture of 0.5 g (0.0019 mol) of the above mixture of **2** and **4** and 2.5 g (0.038 g-atom) of zinc dust in 20 ml of glacial acetic acid was heated at gentle reflux under an atmosphere of nitrogen for 24 hr. After cooling to room temperature, the reaction mixture was filtered and the filtrate was concentrated. Bulb-to-bulb distillation of the residue at 75° (oven temperature) (1.5 mm) gave 0.482 g (96% yield) of **2**: ir (film) 1740 (C=O) and 1650 cm^{-1} (C=C); NMR (CCl_4) δ_{TMS} 4.79 (s, 1 H, vinylic), 4.55 (s, 1 H, vinylic), 4.12 (t, 2 H, J = 7.2 Hz, $COOCH_2CH_3$), 4.01 (s, 1 H, OCH), 3.54 [q of d, 1 H, J = 8.5, J' = 7 Hz, $OCH(H)CH_3$], 3.35 [q of d, 1 H, J = 8.5, J' = 7 Hz, $OCH(H)CH_3$], 1.25 (t, 3 H, J = 7.2 Hz, $COOCH_2CH_3$), 1.20 (t, 3 H, J = 7 Hz, OCH_2CH_3), 1.05 (s, 3 H, methyl), and 0.99 (s, 3 H, methyl); mass spectrum *m/e* 266.1888 (M^+, calcd for $C_{16}H_{26}O_3$, 266.1882) and 193 (base peak).

Anal. Calcd for $C_{16}H_{26}O_3$: C, 72.14; H, 9.84. Found: C, 72.18, 72.42; H, 10.06, 9.88.

Under other applied conditions (boiling acetic acid; *p*-toluenesulfonic acid in benzene at room temperature or at reflux), the isomerization was found to proceed less effectively.

2-Ethoxy-5-(iodomethyl)-6,6-dimethyl-4-oxatricyclo-[5.2.1.0^{1,5}]decan-3-one (5). A solution of 0.42 g (0.0016 mol) of **2** and 10 ml of 4 *N* aqueous sodium hydroxide in 10 ml of methanol was refluxed with stirring under a nitrogen atmosphere for 16 hr. After cooling to room temperature, the reaction mixture was diluted with 20 ml of water and washed twice with ether. The aqueous solution was then acidified with 1 *N* aqueous hydrochloric acid and extracted with chloroform. Work-up of the chloroform solution in the usual manner afforded 0.36 g of acidic product which, without purification, was dissolved in 20 ml of 0.5 *N* aqueous sodium bicarbonate. To this solution, 1.59 g (0.0096 mol) of potassium iodide and 0.81 g (0.0064 mol) of iodine were added.[15] After stirring at room temperature in the dark for 20 hr, the mixture was poured into a slurry of 40 ml of 1 *N* aqueous sodium hydroxide and ice. Extraction with methylene chloride followed by the usual work-up of the organic solution gave 0.471 g (82% yield based on **2**) of **5**: mp 137–138° (ether); ir ($CHCl_3$) 1775 cm^{-1} (C=O); NMR ($CDCl_3$) δ_{TMS} 4.57 (s, 1 H, OCH), 4.11 [q of d, 1 H, J = 9, J' = 7 Hz, $OCH(H)CH_3$], 3.66 [q of d, 1 H, J = 9, J' = 7 Hz, $OCH(H)CH_3$], 3.51 [d, 1 H, J = 11 Hz, $CH(H)I$], 3.30 [d, 1 H, J = 11 Hz, $CH(H)I$], 1.22 (t, 3 H, J = 7 Hz, OCH_2CH_3), 1.19 (s, 3 H, methyl), and 1.10 (s, 3 H, methyl); mass spectrum *m/e* 364.0527 (M^+, calcd for $C_{14}H_{21}O_3I^{127}$, 364.0536) and 193 (base peak).

Acknowledgments. This work was generously supported by the National Research Council of Canada and the University of Alberta.

Registry No.—**1**, 21368-68-3; **2**, 55319-46-5; **4**, 55319-47-6; **5**, 55319-48-7; ethyl diazoacetate, 623-73-4.

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(10) Separation of **2** and **4** was attempted without much success by means of column and gas chromatography and by distillation. The structural assignment of **4** follows from its rearrangement to **2** (vide infra) and from the spectral data of the mixture (see Experimental Section).
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(12) The reported isolation of ethyl β,β-dimethylglycidate in large quantity from the boron trifluoride catalyzed reaction of acetone and ethyl diazoacetate [W. T. Tai and E. W. Warnhoff, *Can. J. Chem.*, **42**, 1333 (1964)] serves as a precedent.
(13) The following spectrometers were used: ir, Perkin-Elmer Model 457; NMR, Varian HA-100; mass spectra, AEI MS-9. The melting point was determined on a Kofler hot stage apparatus and is uncorrected. Elemental analyses were performed by the microanalytical laboratory of this department.
(14) Three signlets at δ 4.64, 4.46, and 2.55 were most significant in assigning its structure; the corresponding hydrogen atoms of camphene appeared in the NMR spectrum taken under the same conditions at δ 4.68 (s), 4.47 (s), and 2.65 (br s).
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Activated Metals. IX. A New Reformatsky Reagent Involving Activated Indium for the Preparation of β-Hydroxy Esters[1]

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Until recently, synthesis using the direct reaction of indium metal was at best limited. Use was restricted to the preparation of triaryl- and trialkylindium compounds from the reaction of indium metal and diorganomercury compounds[3–5] and the preparation of alkylindium halides[6] from alkyl halides. We have recently reported a new procedure for the preparation of activated metals[1,7] and we have shown that by using this procedure highly reactive indium metal powders are generated.[8,9] In this paper, we would like to report that this highly reactive indium metal reacts readily with α-halo esters to give a Reformatsky-type reagent which will add to ketones and aldehydes to give β-hydroxy esters. The Reformatsky reaction using zinc metal has been used in the preparation of β-hydroxy esters for many years. Recent improvements have made this reaction a fairly reliable reaction.[7,10,11]

The activated indium powder was prepared by reducing anhydrous $InCl_3$ (Alfa ultrapure) with freshly cut potassium metal in dry, freshly distilled xylene. The mixture is

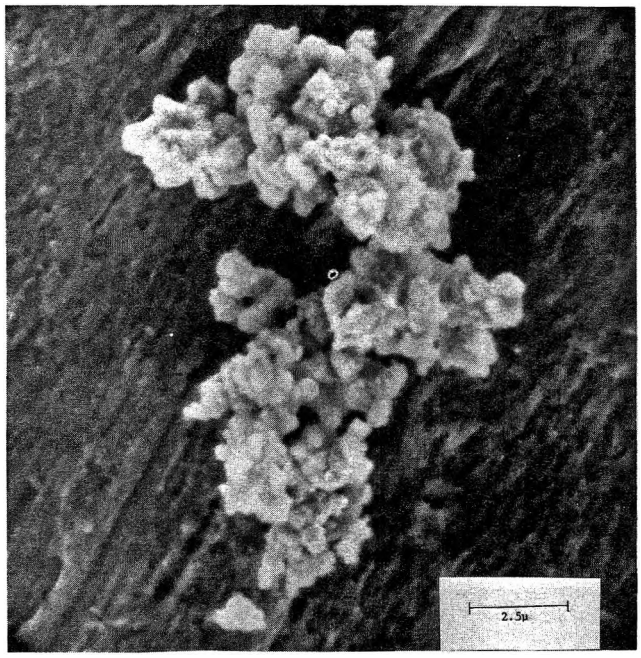


Figure 1. Activated indium prepared by reduction of $InCl_3$ with potassium in xylene.

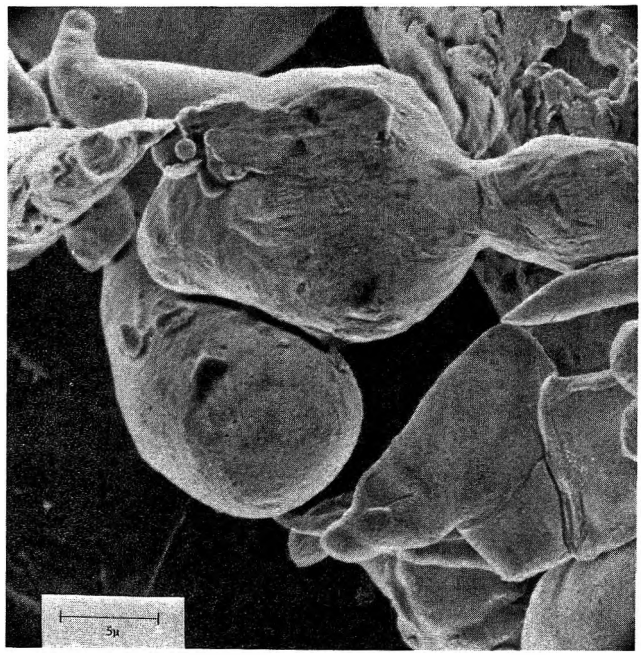


Figure 2. Commercial atomized 325-mesh indium metal.

heated to reflux and stirred with a magnetic stirrer under argon for 4–6 hr, yielding a light black powder. Particle size

$$InCl_3 + 3K \longrightarrow In^* + 3KCl$$

determination on this material indicated a range of 10–0.2 μm with the average particle size being 4.0 μm. This is much smaller than that of commercially available indium powder (325 mesh). The activated indium shows a normal powder pattern of both indium metal and also the KCl. Scanning electron microscope photographs of both the activated indium (Figure 1) and commercial indium (atomized 325 mesh, Figure 2) are shown. The photographs clearly show the high surface area of the activated indium and appear to be conglomerates of even smaller crystals. Until we can get X-ray fluorescence studies done on these crystals, we cannot single out the individual crystallites of KCl or In. The material appears uniform and thus we are assuming that the conglomerates are mixtures of KCl and In crystals.

Table I
Solvent Effect on the Yield of the Reactions with Activated Indium[a]

Carbonyl compd	Solvent	Reaction temp, °C	Reaction time, hr	% yield[b]
Cyclohexanone	Xylene	55	2	100
Cyclohexanone	Et_2O	34	12	100
Cyclohexanone	THF	66	4.5	39–71[c]
Benzaldehyde	Xylene	55	2	83–100
Benzaldehyde	Et_2O	34	6	81
Benzaldehyde	THF	66	4	67

[a] All reactions were carried out in the ratio of In*:$BrCH_2CO_2Et$:>=O = 1.0:0.95:0.95. [b] Yield was measured by GC based on $BrCH_2CO_2Et/2$ = 100% yield.[d] [c] Unreacted cyclohexanone was not completely recovered. [d] The factor of ½ is necessary because only one $-CH_2CO_2Et$ group of $BrIn(CH_2CO_2Et)_2$ adds to a ketone or aldehyde.

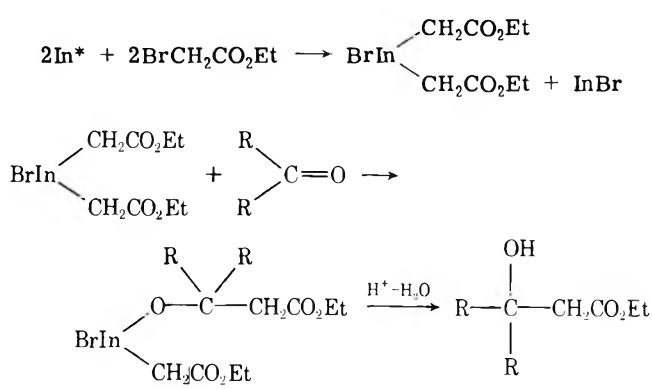
Table II
Effect of Stoichiometric Ratio of Ethyl Bromoacetate to Carbonyl Compounds on the Yield of the Reaction with Activated Indium[a]

Carbonyl compd	In*:$BrCH_2CO_2Et$:>=O	% yield
Cyclohexanone	1.0:0.95:0.95	100
Cyclohexanone	2.1:2.0:1.0	18
Benzaldehyde	1.0:0.95:0.95	83–100
Benzaldehyde	2.1:2.0:1.0	54

[a] All reactions were carried out in xylene at 55° for 2 hr.

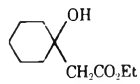
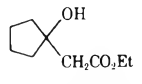
Reaction of this activated indium metal with α-halo esters is rapid. For example, reaction of a mixture of ethyl α-bromoacetate and cyclohexanone in xylene at 55° for 2 hr gives an almost quantitative yield of the corresponding β-hydroxy ester. The activated indium will also react with ethyl α-chloroacetate. In this case reaction for 7 hr at 55° in xylene gave a 42% yield of the β-hydroxy ester. In contrast, commercial indium metal (325 mesh) was treated with ethyl α-bromoacetate for periods of time up to 18 hr with a maximum yield of only 17%.

The reaction of the black indium powder with the α-bromoacetate can be readily observed by the rapid disappearance of the black powder and the formation of a brownish-yellow material. The proposed structure for the intermediate indium compounds is $(EtOCOCH_2)_2InBr$. This is based on an analysis of the material which was xylene soluble and showed an In/halide ratio of 1.05–1.00. The overall reaction scheme is shown below.



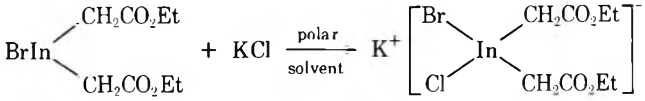
When we extracted the brownish-yellow solid with THF, in which it is much more soluble, we obtained different analysis results. In this case it was found that the K:In:ha-

Table III
Summary of Reformatsky Reaction of Carbonyl Compounds with Activated Indium and Ethyl Bromoacetate[a]

Carbonyl compd	Product	Registry no.	Solvent	Reaction temp, °C	% yield[b]
Cyclohexanone		5326-50-1	Xylene	55	100
Cyclopentanone		3197-76-0	Xylene	55	80
Benzaldehyde	$C_6H_5CH(OH)CH_2CO_2Et$	5764-85-2	Xylene	55	83–100
p-Methylacetophone	$CH_3C_6H_4C(OH)(CH_3)CH_2CO_2Et$	55319-45-4	Et_2O	34	59

[a] All reactions were carried out for 2 hr. [b] Based upon GLC analysis using internal standard, $BrCH_2CO_2Et/2 = 100\%$.[c] [c] The factor of ½ is necessary because only one $-CH_2CO_2Et$ group of $BrIn(CH_2CO_2Et)_2$ adds to a ketone or aldehyde.

lide ratio was 0.85:1.00:2.02 and it contained 25.6% of In. This fits the structure of the ate complex of $(EtOCOCH_2)_2InBr$ with KCl. Thus it appears that the composition



of this Reformatsky reagent is quite solvent dependent, with the ate complex being favored in polar solvents. We examined the effect of the solvent on the yield of the β-hydroxy ester and the results are summarized in Table I. It is readily apparent that the reactions in polar solvents gave lower yields and more side products. We attribute these results to the formation of the ate complex in polar solvents.

In order to obtain good yields of β-hydroxy esters, several reaction conditions must be carefully controlled. In the preparation of the activated indium it is very important that the molar ratio of $InCl_3$ to K be exactly 1:3. If there is an excess of either $InCl_3$ or K, side reaction products become considerable. The ratio of the carbonyl compound to the α-bromoacetate is also very critical. In order to obtain high yields, a onefold excess of the carbonyl compound is necessary; the excess carbonyl compound can be recovered later. The reason for the necessity of the excess carbonyl compound is not readily obvious. Some of the results with varying ratios of bromoacetate to ketone are summarized in Table II.

Finally, the results of reactions of a variety of carbonyl compounds with the activated indium and ethyl α-bromoacetate are summarized in Table III. In general, the yields of β-hydroxy esters are good with ketones and also with benzaldehyde in xylene and diethyl ether. However, alkyl aldehydes give relatively low yields.

Experimental Section

Materials. Cyclohexanone, cyclopentanone, benzaldehyde, *p*-methylacetophenone, ethyl bromoacetate, and ethyl chloroacetate were obtained from commercial sources. They were used without further purification. Xylene (ortho, 99%) was obtained from Aldrich and distilled over $NaAlH_4$. Diethyl ether (Fisher Anhydrous) and THF (MCB) were distilled over $LiAlH_4$ under argon. Commercial indium (325 mesh, 99.9%) and anhydrous indium trichloride were obtained from Alfa. Potassium (Baker purified) was cleaned under heptane prior to use. Activated indium metal was prepared by reducing indium trichloride with potassium in xylene by refluxing for 4–6 hr under an argon atmosphere.

Reactions Using Activated Indium. The following procedure for the conversion of cyclohexanone to ethyl (1-hydroxycyclohexyl)acetate is representative. Activated indium metal (10 mmol) was prepared from the reduction of $InCl_3$ (2.21 g, 10 mmol) and K (1.17 g, 30 g-atoms) in 25 ml of xylene in a 100-ml round-bottom flask with a side arm equipped with a septum cap under an argon atmosphere. After refluxing for 4.5 hr the mixtures were cooled down to 2° with ice–water, 1.0 g of biphenyl was added as an internal standard, and then two loaded syringes with cyclohexanone (0.93 g, 9.5 mmol) and ethyl bromoacetate (1.5 g, 9.5 mmol) were inserted into the flask via a septum cap. Both components were added simultaneously and stirred at 2° for 10 min; then the mixtures were heated to 55°. One 2-ml sample was withdrawn periodically and hydrolyzed with 2 *N* HCl solution. The organic layer was subjected to GLC. GLC analyses were carried out with an HP Model 5750 research gas chromatograph equipped with 6 ft × 0.125 in. stainless steel columns packed with 10% SE-30 on Chromosorb W. The product was identified by comparing GLC retention time with that of the authentic sample obtained from the regular zinc Reformatsky reaction.

Acknowledgment. Support of this research by the U.S. Army Research Office is gratefully acknowledged.

Registry No.—Cyclohexanone, 108-94-1; cyclopentanone, 120-92-3; benzaldehyde, 100-52-7; *p*-methylacetophenone, 122-00-9; ethyl bromoacetate, 105-36-2; ethyl chloroacetate, 105-39-5; indium, 7440-74-6; $InCl_3$, 10025-82-8; K, 7440-09-7.

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Long Range Electron Paramagnetic Resonance Coupling Interactions in Spiro Derivatives of Bicyclo[2.2.1]heptyl Semiquinone

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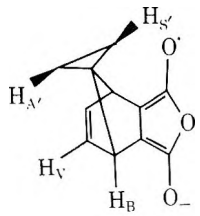
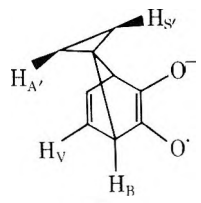
Nelsen,[1] Blankespoor,[2] and Russell[3] and their associates have investigated long range δ coupling constants in the semifuraquinone (1) and semidione (2) series. The observations for 1 and 2 illustrate that the interactions between



1

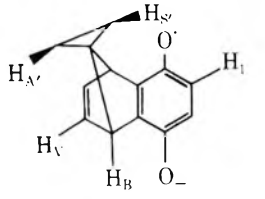
a = 1.07 (2 H), $H_{A'}$
0.81 (2 H), H_V
0.52 (2 H), $H_{S'}$ or H_B
0.46 (2 H), H_B or $H_{S'}$



2

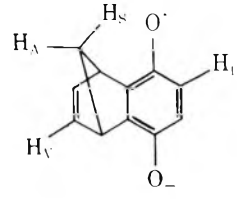
a = 0.95 (2 H), H_B
0.68 (2 H), H_V
0.20 (2 H), $H_{A'}$

the δ hydrogen atoms and the spin label can, indeed, be large as we previously noted for the related semiquinone **3-S**.[4,5] Comparison of these values with the data for **4-S** and **5-S** indicate that the spin population at the anti′ and syn′ hydrogen atoms of the cyclopropane ring is quite large. This finding prompted us to examine the less strained saturated semiquinone, **6-S**, and the related cyclopentane derivatives, **7-S** and **8-S**, in which the δ hydrogen atoms occupy essentially the same positions in space in molecules with more normal carbon–carbon bond hybridization.



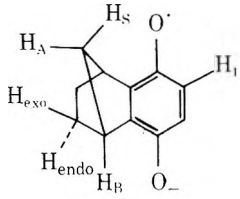
3-S

a = 2.40 (2 H), H_1
0.47 (2 H), H_V
0.38 (2 H), $H_{A'}$
0.18 (2 H), $H_{S'}$ or H_B
0.10 (2 H), H_B or $H_{S'}$



4-S

a = 2.36 G (2 H), H_1
0.80 G (1 H), H_A
0.40 G (3 H), H_V, H_8

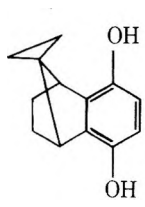


5-S

a = 2.50 G (2 H), H_1
0.70 G (3 H), H_{exo}, H_A

Results

Spiro[2.4]hepta-2,4-diene and spiro[4.4]nona-2,4-diene were prepared from cyclopentadiene and the appropriate dibromoalkane using sodium hydride in diglyme. This procedure is more convenient than methods using sodamide and ammonia.[6] Adduct formation with benzoquinone, tautomerization to the hydroquinone, and reduction of the isolated double bond proceeded smoothly.[4]



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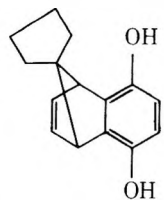

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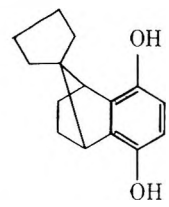


8

Semiquinones **3-S**, **6-S**, and **7-S** were generated by air oxidation of the hydroquinone (10^{-3} M) in acetonitrile containing sodium hydroxide. Semiquinone **8-S** (10^{-3} M) was prepared from the corresponding diacetate in dimethyl sulfoxide containing potassium *tert*-butoxide. Experience indicates that the important features of the spectra are unaltered by this variation in the procedure.[4] The coupling constants are presented in Table I.

Table I
Coupling Constants for Semiquinones[a]

Nucleus	Coupling constant, G			
	3-S	6-S	7-S	8-S
H_1	2.40	2.55	2.40	2.60
H_V	0.47		0.40	
H_{EXO}		0.81		0.85
H_{ENDO}		0.10		*b*
H_B	0.10 (0.18)	*b* (0.10)	*b* (0.08)	*b*
$H_{A'}$	0.38	0.23	0.40	0.25
$H_{S'}$	0.18 (0.10)	0.10 (*b*)	0.08 (*b*)	*b*

[a] Alternative assignments, where appropriate, are presented in parentheses. [b] Undetectably small.

Discussion

The constants for the aryl, vinyl, and exo hydrogen atoms of **3-S**, and **6-S**–**8-S** can be assigned on the basis of prior data for the many derivatives of **4-S** and **5-S**.[4] For **8-S**, there is only one additional coupling constant which is reasonably assigned to the anti′ hydrogen atoms of the cyclopentane ring.[7a] For **7-S** there are two additional constants which must be assigned. We reported previously that the introduction of unsaturation increases the magnitude of the anti and syn coupling constants.[4] Consequently, the larger constant may be assigned to $H_{A'}$ and the smaller constant to $H_{S'}$. Prior work on both the semiquinones and semifuraquinones indicates that the bridgehead hydrogen atoms exhibit the smallest coupling constants.[1,4] However, an alternate, less likely assignment for **7-S** is shown in Table I.

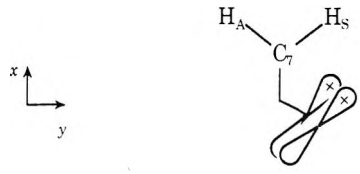
Semiquinones **6-S** and **8-S** exhibit essentially the same spectrum except that four additional hydrogen atoms of **6-S** exhibit small coupling constants. It is likely that the bridgehead hydrogen atoms remain uncoupled. The alternative assignment is, however, noted in Table I. All the hydrogen atoms of **3-S** are coupled. The larger constants are assigned to the vinyl and anti′ hydrogen atoms with the smaller pair assigned to the bridgehead and syn′ groups.

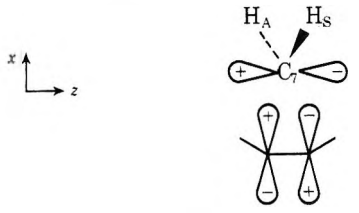
The results (Table I) reveal that spin density appears at remote sites in **3-S** and **6-S**–**8-S**. The coupling constants for the vinyl and exo hydrogen atoms in these four radicals are comparable to the constants for **4-S** and **5-S**. The coupling constants of the syn′ and anti′ methylene groups of the cyclopropane and cyclopentane fragments are quite large. These constants are nearly equal for the heptadienes, **3-S** and **7-S**, with $a_{H_{A'}}$ = 0.38 and 0.40 G, respectively, and for the heptenes, **6-S** and **8-S**, with $a_{H_{A'}}$ = 0.25 and 0.23 G, respectively.[7b] Thus, the additional strain in the cyclopropane derivatives does not have an important impact on the magnitude of the coupling interaction. The near equality of the constants suggests that simple geometric relationships rather than bond hybridization factors play a dominant role in the determination of spin density at the δ hydrogen atoms. The constants for the anti′ hydrogen atoms of **3-S** and **7-S** are about 50% of the value of a_{H_A} for **4-S**. Similar results have been reported for the semifuraquinone.[1] On

the other hand, the constant for the anti′ hydrogen atom of the semidione **2** is only about 2% of the value of a_{H_A} in bicyclo[2.2.1]hepta-5-ene-2,3-semidione.[2,3]

Several interactions require consideration in the interpretation of these constants. Spin density is distributed in molecules by direct and indirect interactions involving the delocalization and polarization of electrons. The spin density measured at a particular nucleus may, therefore, result from four distinct contributions. Indeed, only relatively advanced theories such as the INDO model or configuration interaction formulations which focus on spin polarization can adequately estimate spin distributions.[8,9] Nevertheless, simple concepts such as hyperconjugation, homohyperconjugation, the W plan arrangement, and the symmetry properties of the orbitals of the spin label have proved valuable for the qualitative discussion of the factors governing long range coupling constants.[1-4]

In the absence of confident information concerning the signs of the long range coupling constants, all explanations are somewhat speculative. However, the INDO model can be used to guide these interpretations. Homohyperconjugation, the INDO model, and a CI approach have been employed to account for the stereospecific coupling interaction of the H_A nucleus in bicyclo[2.2.1]heptane-2,3-semidione.[3,9,10] Because the highest occupied molecular orbital of the semidione is symmetric, the orbitals of the spin label can mix with the s, p_x, and p_y orbitals of the C_7 group directly to delocalize the spin density and place large, apparently positive, spin at H_A. This explanation is not applicable for spin labels such as the semiquinone or semifuraquinone with antisymmetric highest occupied molecular orbitals, in these cases the orbital of the spin label can only mix with the p_Z orbital to place spin density in a 2p orbital at C_7. The syn and anti protons then couple via an indirect spin polarization interaction. The constants for these nuclei should be negative as predicted by the INDO model.[3] Nelsen, Travecedo, and Seppanen adopted this viewpoint in their analysis of the coupling interactions in bicyclo[2.2.1]hept-5-ene-2,3-semifuraquinone.[1]





These qualitative ideas can account for the coupling behavior of the syn′ and anti′ methylene groups in the spirocyclopropyl and spirocyclopentyl derivatives of the semidione, semifuraquinone, and semiquinone. For the semiquinones and the semifuraquinones, spin density may be propagated to the methylene groups, in part, through an interaction between the spin in the p_z orbital centered at C_7 and the C–H bonding orbitals. Consequently, the spin populations at $H_{A'}$ is quite large. In this case, a negative constant for the methylene groups is expected. For the semidione **2**, there is no spin in an orbital with a geometry favorable for the coupling of the syn′ and anti′ methylene groups; only a rather small coupling is observed. Thus, this model adequately portrays the principal features of the spectra. We note, however, that the spin density at these remote nuclei are, in fact, determined by the spin populations in many nearby orbitals and that more subtle mechanisms must also play a role.

Experimental Section

3′,6′-Dihydroxybenzobicyclo[2.2.1]hepta-2,5-diene-7-spirocyclopropane (3). Spiro[2.4]hepta-2,4-diene was prepared from cyclopentadiene and 1,2-dibromoethane. Sodium hydride (48%, 34.0 g, 0.67 mol) was suspended in diglyme (175 ml, freshly distilled from lithium aluminum hydride) in a flask equipped with a mechanical stirrer, dropping funnel, and a condenser fitted with a nitrogen inlet tube. This flask was cooled to 0° and cyclopentadiene (22.0 g, 0.33 mol) in diglyme (25 ml) was added slowly with very vigorous stirring. After 0.5 hr, 1,2-dibromoethane (63.0 g, 0.34 mol) in diglyme (25 ml) was added over 0.5 hr. Additional solvent (50 ml) was added. After 3 hr, water (25 ml) was added cautiously, then pentane (100 ml), and the entire mixture was poured into ice–water (500 ml). The layers were separated, the aqueous phase was extracted with pentane (3 × 50 ml), and the combined organic layers were washed with cold, saturated sodium chloride solution (3 × 50 ml). After drying over sodium sulfate, the pentane was removed by distillation, then the product was distilled at reduced pressure. The first fraction [bp 40–44° (75 mm), 4.95 g] was a 1:1 mixture of the product and diglyme; the second fraction [bp 53° (75 mm), 9.4 g] contained 95% spiro[2.4]hepta-2,4-diene. The total yield was 11.8 g (38% based on cyclopentadiene).

Spiro[2.4]hepta-2,4-diene (11.8 g, 0.13 mol) in methanol (10 ml) was added to benzoquinone (13.8 g, 0.13 mol) suspended in methanol (50 ml) in a flask cooled in an ice–water bath. The bath was removed and the solution was stirred magnetically for 1 hr. The product was filtered cold, washed with cold methanol, and dried in vacuo. This adduct (21.0 g, mp 109.5–110.0°) was recrystallized from methanol. The adduct then was converted to the diacetate (mp 96.5–96.8° from methanol) by base-catalyzed tautomerization and acetylation as described previously.[4] The diacetate was hydrolyzed as described previously to yield 3′,6′-dihydroxybenzobicyclo[2.2.1]hepta-2,5-diene-7-spirocyclopropane (**3**) (mp 171.0–172.5° from benzene).

Anal. Calcd for $C_{13}H_{12}O_2$: C, 78.00; H, 6.00. Found: C, 77.94; H, 6.08.

3′,6′-Dihydroxybenzobicyclo[2.2.1]hept-2-ene-7-spirocyclopropane (6). This compound (mp 193.0–194.0° from benzene) was prepared from **3** via platinum-catalyzed low-pressure hydrogenation.

Anal. Calcd for $C_{13}H_{14}O_2$: C, 77.25; H, 6.94. Found: C, 77.18; H, 6.99.

3′,6′-Dihydroxybenzobicyclo[2.2.1]hepta-2,5-diene-7-spirocyclopentane (7). Spiro[4.4]nona-2,4-diene, bp 48° (15 mm), was prepared from cyclopentadiene and 1,4-dibromobutane in 22% yield by the method used for the synthesis of spiro[2.4]hepta-2,4-diene.

The adduct (mp 98.0–98.5° from methanol) of spiro[4.4]nona-2,4-diene and benzoquinone was prepared in 89% yield as described above. The diacetate (mp 72.0–73.0° after sublimation) was prepared as described previously and hydrolyzed to 3′,6′-dihydroxybenzobicyclo[2.2.1]hepta-2,5-diene-7-spirocyclopentane (**7**) (mp 167.0–168.0° from benzene) under acidic conditions.

Anal. Calcd for $C_{15}H_{16}O_2$: C, 79.00; H, 7.02. Found: C, 79.11; H, 7.07.

3′,6′-Diacetoxybenzobicyclo[2.2.1]hept-2-ene-7-spiropentane (8-D). The diacetate prepared in the synthesis of **7** was hydrogenated at low pressure with platinum to yield 3′,6′-diacetoxybenzobicyclo[2.2.1]hept2-ene-7-spiropentane (**8-D**) (mp 97.5–99.0° after sublimation).

Spectroscopic Results. The semiquinone derived from **8** was prepared by the hydrolysis of the related diacetate (10^{-3} *M*) in dimethyl sulfoxide containing potassium *tert*-butoxide. The other semiquinones were prepared by air oxidation of the hydroquinones (10^{-3} *M*) in acetonitrile. All the spectra were recorded on a Varian E3 spectrometer. The field sweep was calibrated by the study of perylene cation radical. All the spectra were simulated with a Jeolco JRA5 system.

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Registry No.—**3,** 55373-45-0; **3-D,** 55373-46-1; **3-S,** 55428-86-9; **6,** 55373-47-2; **6-S,** 55373-48-3; **7,** 55373-49-4; **7-D,** 55373-50-7; **7-S,** 55373-51-8; **8,** 55373-52-9; **8-D,** 55373-53-0; **8-S,** 55373-54-1; spiro[2.4]hepta-2,4-diene, 765-46-8; cyclopentadiene, 542-92-7; 1,2-dibromoethane, 106-93-4; benzoquinone, 106-51-4; 3′,6′-dioxobenzobicyclo[2.2.1]heptadiene-7-spirocyclopropane, 55373-55-2; spiro[4.4]nona-2,4-diene, 766-29-0; 1,4-dibromobutane, 110-52-1; 3′,6′-dioxobenzobicyclo[2.2.1]hepta-2,5-diene-7-spirocyclopentane, 55373-56-3.

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Sensitized Photooxygenation of Linear Monoterpenes Bearing Conjugated Double Bonds

Summary: Sensitized photooxygenation of linear monoterpenes bearing conjugated double bonds, such as α-myrcene, epoxymyrcene, and epoxyhymenthrene was found to afford the corresponding 1,4-endoperoxides, i.e., 3,6-dihydro-1,2-dioxins.

Sir: It has recently been reported that 1,4 cycloaddition of singlet oxygen ($^1O_2$) to acyclic conjugated dienes occurs readily, even if an allylic hydrogen exists in the same molecule.[1] This fact seems to show that the dienophilic reactivity of $^1O_2$ surpasses the other two modes of reaction affording hydroperoxides and 1,2-dioxetanes. Contrary to this expectation, however, β-myrcene (**1**), which has both isolated and conjugated double bonds, is known to give a mixture of hydroperoxides **2** and **3** and thus no reaction occurs on the 1,3-diene moiety of **1**.[2] To shed light on the reactivities of various double bonds toward $^1O_2$, we have now reinvestigated the sensitized photooxygenation of the monoterpene **1** and have found that the conjugated double bond in **1** is also reactive to $^1O_2$, although the isolated one is far more reactive.

A solution of **1** (0.03 mol) and Rose Bengal (2×10^{-4} mol) in dichloromethane containing 5% methanol was irradiated under an oxygen atmosphere with a halogen lamp (Toshiba JD 100V 500W) for 1.5 hr.[3] After removal of the solvent under reduced pressure, the residual liquid was fractionated by column chromatography on silica gel with *n*-hexane. The first eluate contained unreacted **1** (3%). The hydroperoxides **2** (36%) and **3** (56%) were then eluted in this order. Further elution of the column with benzene afforded a mixture of new hydroperoxides **4** and **5** (0.3%).[4] Prolonged irradiation (4.5 hr) of a solution of **1** gave a mixture of **2** and **3** in 44% total yield and a mixture of **4** and **5** in 20% total yield (Figure 1). These results clearly demonstrate that **4** and **5** are produced by further photooxygenation of **2** and **3** respectively. This conclusion was now confirmed by the following experiments. When a solution of the hydroperoxides **2** in carbon tetrachloride was irradiated for 4 hr using tetraphenylporphine as a sensitizer, the 3,6-dihydro-1,2-dioxin **4** was obtained in 35% yield.[5] Similar photooxygenation of **3** for 3 hr also afforded the cyclic peroxide **5** in 45% yield. The physical properties of these hydroperoxy 1,2-dioxins, as well as the other dioxins (vide infra), are collected in Table I (microfilm edition).

One of the other possible products from **1** would be the dioxin **8** resulting from the selective oxygenation of the diene moiety in **1**. An authentic sample of **8** was prepared by dehydration of **7** with P_2O_5 in dichloromethane at room temperature in 53% yield. The dioxin **7** was synthesized from myrcenol **6**[6] in 81% yield by the sensitized photooxygenation under conditions similar to those described above. The presence of **8** could not be proved, although the NMR spectrum of the crude product obtained by the oxygenation of **1** was carefully compared with that of the authentic sample of **8**.

The observed result shows that, under the reaction conditions, the conjugated double bond in **1** is significantly less reactive to $^1O_2$ than is the isolated one. Consequently,

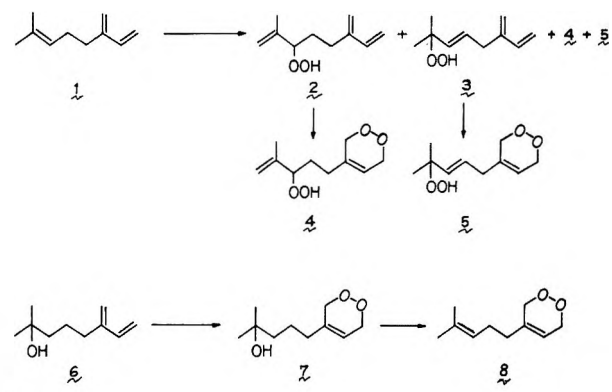

Figure 1.

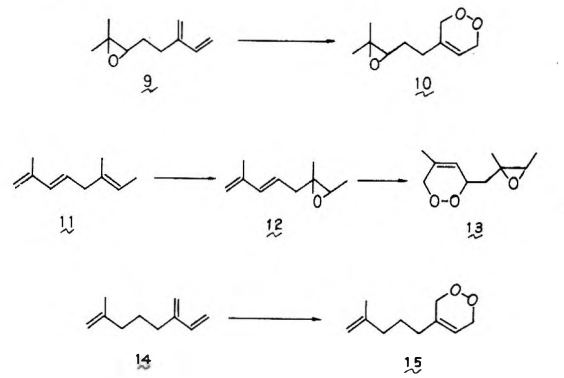

Figure 2.

when the isolated double bond in **1** is protected by epoxidation, as in epoxymyrcene (**9**),[7] the oxygenation now occurs smoothly on the conjugated diene to afford the epoxy 1,2-dioxin **10** in 41% yield (Figure 2). The protection of the reactive double bond by epoxidation was also successful in the case of hymenthrene (**11**);[3] epoxyhymenthrene (**12**)[8] underwent 1,4 cycloaddition to $^1O_2$ to give the 1,2-dioxin **13**, mp 57–58° (colorless needles from *n*-hexane), in 59% yield, while **11** itself afforded a mixture of hydroperoxides.[9]

The selective formation of **4** and **5** from **2** and **3**, respectively, suggested that the isolated double bond with two alkyl substituents appeared to be less reactive to $^1O_2$ than the conjugated 1,3-diene. On the basis of this assumption, we then examined the oxygenation of α-myrcene (**14**).[10] Irradiation of **14** under similar conditions now produced selectively the expected 1,2-dioxin **15** in 79% yield. In conclusion, the reactivity of carbon–carbon double bonds toward $^1O_2$ follows roughly the order shown: trisubstituted monoolefin > 1,3-diene with an alkyl substituent on the 2 position > 1,1-disubstituted monoolefin.[11]

The observed selectivity as well as the oxygenation products obtained by these experiments are useful tools for the synthesis of naturally occurring furanoterpenes. These results will be presented in forthcoming communications.

Supplementary Material Available. Table I will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 24× reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Journals Department, American

Chemical Society, 1155 16th St., N.W., Washington, D.C. 20036. Remit check or money order for $4.00 for photocopy or $2.50 for microfiche, referring to code number JOC-75-2259.

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(3) Monoterpenes **1** and **11** were commercially available.
(4) All the peroxides obtained in this work were colorless oils, unless otherwise stated, and gave satisfactory analytical data.
(5) When the sensitized photooxygenation of **2** and **3** were carried out in dichloromethane–methanol mixed solvent, the peroxides **4** and **5** were also obtained, although the reaction was slow and the yield was low.
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(8) The epoxide **12** was prepared from **11** by oxidation with *m*-chloroperbenzoic acid in dichloromethane in 48% yield: bp 78–81° (11 mm); NMR (CCl_4) δ 6.26 (d, J = 17.0 Hz, 1 H), 5.62 (d of t, J = 17.0 and 6.0 Hz, 1 H), 2.88 (q, J = 5.8 Hz, 1 H), 2.34 (br d, J = 6.0 Hz, 2 H), 1.83 (s with fine coupling, 3 H), 1.31 (d, J = 5.8 Hz, 3 H), and 1.17 (s, 3 H).
(9) The mixture (68% yield) was comprised of at least two hydroperoxides which could be assigned as 2,6-dimethyl-6-hydroperoxy-1,3,7-octatriene and 7-hydroperoxy-2-methyl-6-methylene-1,3-octadiene based on the NMR spectrum.
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1,3-Dipolar Cycloadditions of Azomethine Imines and Sulfenes

Summary: The first examples of a new heterocyclic ring system (**2**) have been prepared by the 1,3-dipolar cycloaddition of azomethine imines **1** and sulfenes.

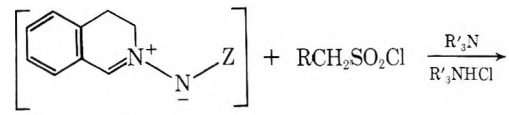
Sir: Although numerous examples of 1,2 and 1,4 cycloaddition reactions of sulfenes to yield four- and six-membered-ring heterocycles, respectively, are known,[1] only two examples of the formation of five-membered rings by cycloaddition reactions of sulfenes have been reported.[2,3] Reactions of other 1,3 dipoles under sulfene-generating conditions have led to products other than those expected from 1,3-dipolar cycloaddition reactions.[1] To further define the reactivity of sulfenes and dipolarophiles, the reactions of sulfenes with highly reactive azomethine imines of the 3,4-dihydroisoquinoline type (**1**)[4] have been explored.

The brightly-colored dipoles **1** were prepared in situ by the thermal dissociation of their respective dimers[4-6] in aromatic hydrocarbon solvents. Dropwise addition of a solution of the alkanesulfonyl chloride to the hot mixture containing the azomethine imine and an excess of trialkylamine led to the formation of adducts **2** (Table I; also, see supplementary material). Derivatives of this ring system have not previously been described. The structural assignments of **2** were based primarily on spectral and elemental analysis data. Further support for these assignments was obtained through the dehydrogenation of three of the adducts (**2a, 2b,** and **2i**) to compounds **3** by 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ).

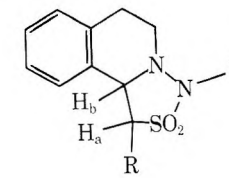
Table I
Preparation of 1,2,3-Thiadiazolidine Derivatives

2[a]	Z	R	R′	Conditions[b]	Yield,[c] %
a	C_6H_5	H	Et	A	92
b	C_6H_5	C_6H_5	Et	A	77
c	C_6H_5	Cl	Et	A	29
d	C_6H_5	C_6H_5CO	Et	A	31
e	*p*-$NO_2C_6H_4$	H	*n*-Pr	B	86
f	*p*-$NO_2C_6H_4$	C_6H_5	*n*-Pr	B	88
g	EtO_2C	H	*n*-Pr	C	51
h	EtO_2C	C_6H_5	*n*-Pr	C	61
i	C_6H_5CO	H	Et	D	43
j	C_6H_5CO	C_6H_5	Et	D	57
k	*p*-$CH_3C_6H_4SO_2$	H	*n*-Pr	B	29
l	*p*-$CH_3C_6H_4SO_2$	C_6H_5	*n*-Pr	B	58

[a] Satisfactory elemental analysis data were obtained for compounds **2a** through **2l** (see supplementary material). [b] (A) In benzene at 70°; (B) in toluene at 100°; (C) in mesitylene at 155°; (D) in benzene at 80°. [c] Isolated yields of purified product.



1



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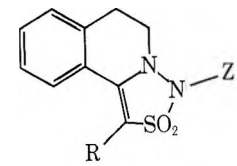
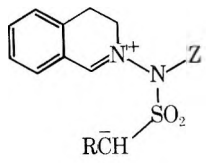


3

The reactions of substituted sulfenes with the dipoles **1** could lead to the formation of two possible stereoisomers of **2** (i.e., H_a and H_b may be cis or trans). The stereoselectivity with which adducts **2b, 2h, 2j,** and **2l** were formed was studied in some detail by observing the splitting patterns of H_a and H_b in the δ 6.5–4.5 region of their NMR spectra.[7] The NMR spectrum of the crude product isolated from the reaction in which **2b** was formed indicated that the two possible isomers were present in approximately equal amounts.[8] These two isomers were separated by column chromatography and were shown to be noninterconvertible under the conditions leading to their formation.

In contrast to **2b,** adduct **2f** was formed with a high degree of stereoselectivity. Within the limits of detection of the NMR spectrometer, only one isomer of **2f** was observed in the crude product. The NMR spectra of crude adducts **2j** and **2l** showed a great preponderance of one isomer, although small amounts (<10% and <20%, respectively) of the second isomers may have been formed.[10] Purification of crude adducts **2f, 2j,** and **2l** led to the isolation of a single isomer of each adduct.

The most likely mechanisms for the formation of products **2** are either (a) a concerted $[_{\pi}4_s + _{\pi}2_s]$ cycloaddition process or (b) a stepwise addition of sulfene to **1**, leading to **2** by the ring closure of zwitterion **4**. Since it was observed



4

that under identical conditions of temperature (80°) and concentration (8 mmol of the dipole in 60 ml of benzene) adduct **2b** was produced with a complete lack of stereoselectivity, while **2j** was formed with a high degree of stereoselectivity, the intermediacy of zwitterion **4** in these reactions seems unlikely; the effect of the "Z" group on the stereochemical outcome of the ring closure of **4** is expected to be minimal. On the other hand, if it is assumed that the azomethine imines and sulfenes undergo a concerted $[_{\pi}2_s + _{\pi}4_s]$ cycloaddition,[11] the differences in the stereoselectivities with which **2b** and **2j** were formed may be rationalized by considering the reactivity of the dipoles **1**. Those azomethine imines in which the charge on the anionic nitrogen is stabilized by a carbonyl or a sulfonyl group may be less reactive and more selective than those in which the anionic charge is stabilized by a phenyl group. The more selective dipoles may discriminate between the two possible orientations of phenyl sulfene leading to the transition state and therefore may lead stereoselectively to the observed product.[14] The more reactive, less selective dipole **1** ($Z = C_6H_5$) may react indiscriminantly with phenyl sulfene to yield a mixture of two isomers.

A more complete evaluation of the scope and utility of these reactions is underway and will be reported at a later date.

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Supplementary Material Available. Procedures for the preparation of all compounds **2** and **3**, along with spectral data for each, will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 24× reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 16th Street N.W., Washington, D.C. 20036. Remit check or money order for $4.50 for photocopy or $2.50 for microfiche, referring to code number JOC-75-2260.

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(4) (a) R. Huisgen, R. Grashey, P. Laur, and H. Leitermann, *Angew. Chem.*, **72**, 416 (1960); (b) R. Huisgen, *Proc. Chem. Soc. (London)*, 363 (1961); (c) R. Grashey and K. Adelsberger, *Angew. Chem., Int. Ed. Engl.*, **1**, 267 (1962); (d) R. Grashey, H. Leitermann, R. Schmidt, and K. Adelsberger, *ibid.*, **1**, 406 (1962); (e) R. Huisgen, *ibid.*, **2**, 581 (1963).
(5) We wish to thank Professor R. Huisgen and Dr. R. Grashey for providing directions for the preparation of certain of the dimers of dipoles **1**.
(6) D. Walker and J. D. Hiebert, *Chem. Rev.*, **67**, 153 (1967).
(7) The NMR spectra of the crude products **2c** and **2d** indicated that both isomers had been formed in each case. Owing to the low yield of these reactions, detailed stereochemical investigations were not carried out. The low solubility of **2f** in organic solvents precluded the use of NMR spectroscopy as a means of determining the stereoselectivity with which it was formed.
(8) Because J_{ab} was 9.5 Hz for one isomer of **2b** and 10.5 Hz for the other, it was not possible to use the Karplus relationship[9] to assign absolute stereochemistries to these adducts.
(9) M. Karplus, *J. Chem. Phys.*, **30**, 11 (1959); *J. Am. Chem. Soc.*, **85**, 2870 (1963).
(10) Peaks which may have been due to a small amount of a second isomer may also have been caused by impurities in the crude products.
(11) Recent molecular orbital calculations on the frontier orbitals of azomethine imine **1** ($Z = C_6H_5$)[12] and of sulfene[13] suggest that the orbital symmetries of these two species are compatible with a $[_{\pi}4_s + _{\pi}2_s]$ cycloaddition.
(12) K. N. Houk et al., *J. Am. Chem. Soc.*, **95**, 7287, 7301 (1973).
(13) J. P. Snyder, *J. Org. Chem.*, **37**, 3965 (1972).
(14) This argument suggests that the isolated isomers of **2h, 2j**, and **2l** are those in which H_a and H_b are trans. However, the absolute stereochemistry of these adducts has not yet been determined.

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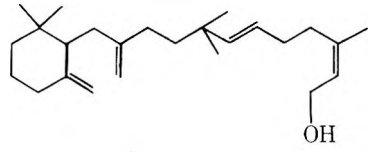
The Total Synthesis of (±)-Diumycinol

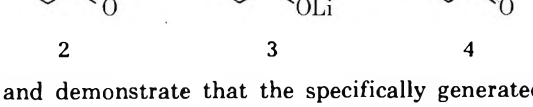
Summary: The first synthesis of the sesterterpene (±)-diumycinol (**1**) is reported featuring the reductive opening of a cyclopropyl ketone (**2**) which regiospecifically generates the β,β-disubstituted lithium enolate **3** and undergoes alkylation exclusively at C-2 with no loss of regiospecificity.

Sir: Diumycinol, the nonisoprenoid C_{25} lipid obtained by acid hydrolysis of the antibiotic diumycin, has been shown to possess structure **1**.[1] Diumycinol became of interest to



1

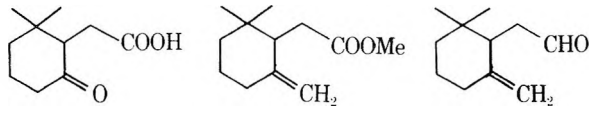
us, not only because of its polyolefinic nonisoprenoid nature, but also because it allowed us the opportunity to generate regiospecifically an enolate ion (e.g., from a cyclopropyl ketone[2]) which in principle should be capable of being alkylated without loss of structural integrity (cf. **2** → **3** → **4**).[2-5] We wish to report the first synthesis of (±)-diumycinol and demonstrate that the specifically generated β,β-disubstituted lithium enolate **3** undergoes alkylation as the exclusive process with no loss of regiospecificity.[5]



2 3 4

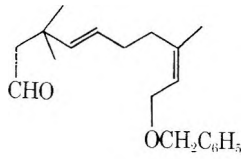
The synthesis of diumycinol outlined below involves the combination of two synthetic pieces, the six-membered-ring building block **7** and the sulfone moiety **12**.[7] The required intermediate **7**[8] was prepared from cyclopropyl ketone **2**[10] in the following manner. The β,β-disubstituted lithium enolate **3** formed during the metal–ammonia cleavage of cyclopropyl ketone **2** underwent exclusive C-2 alkylation (70%) with allyl bromide in 1,2-dimethoxyethane (glyme).[11] Oxidative cleavage of the double bond of **4** (R = allyl) in a two-phase system [benzene–water (1:1)] contain-

ing potassium permanganate and tetra-*n*-butylammonium bromide[12] resulted in a 42% yield of pure keto acid **5**. Methylenation[13] (methylenetriphenylphosphorane, DMSO, 60°, 96 hr) followed by esterification (ethereal diazomethane) provided a 76% yield of ester **6** which was smoothly converted to aldehyde **7** (58%)with diisobutylaluminum hydride in hexane (−70°).



5 **6** **7**

The synthesis of sulfone **12** from the previously described[14] aldehyde **8** is detailed below. Reduction of aldehyde **8** (sodium borohydride, ethanol, room temperature, 1.5 hr) generated alcohol **9** which upon mesylation (methanesulfonyl chloride, pyridine, 0°, 1 hr) and exchange with iodide (sodium iodide, acetone, reflux, 15 hr) afforded a 90% overall yield (from **8**) of iodide **11** (*m/e* 412.1267). Treatment of iodide **11** with sodium *p*-toluenesulfinate in anhydrous DMF at 135° (15 hr) resulted in an 80% yield of chromatographically pure sulfone **12** (*m/e* 440.2385). The NMR spectrum of **12** exhibited peaks at 0.92 [s, 6 H, $C(CH_3)_2$], 1.68 (br s, 3 H, olefinic methyl), 2.41 (s, 3 H, $ArCH_3$), 2.85 (m, 2 H, $-CH_2SO_2$), 3.85 (d, 2 H, CH_2O), 4.38 (s, 2H, OCH_2Ar), 5.12 (m, 2 H, −CH=CH−), 5.30 (t, 1 H, =CH−), 7.18 (s, 5 H, $-C_6H_5$), and an AB quartet (4 H) centered at 7.42.



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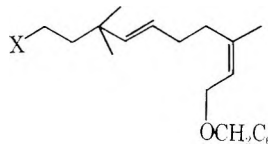


9. X = OH
10. X = OMs
11, X = I
12, X = $SO_2C_6H_4CH_3$

Metalation of sulfone **12** at −20° with *n*-butyllithium in tetrahydrofuran followed by addition of aldehyde **7** (−20°) afforded an adduct which was immediately oxidized (Jones reagent) to keto sulfone **13** in ~40% overall yield. The carbon-sulfur bond of **13** was readily cleaved (3% Na–Hg, ethanol, room temperature, 1 hr) in 77% yield producing intermediate **14** (*m/e* 450.3501).[15] Methylenation[13] of **14** (methylenetriphenylphosphorane, DMSO, 65°, 48 hr) afforded benzyl ether **15** (80%) (*m/e* 448.3692) which upon debenzylation (lithium, liquid ammonia, −78°, 30 min) resulted in an 83% yield of chromatographically pure (±)-diumycinol (**1**). The NMR and ir spectra of synthetic (±)-**1** were in agreement with reference spectra of natural diumycinol kindly provided by Dr. W. A. Slusarchyk. The NMR spectrum (60 MHz, $CDCl_3$) of synthetic **1** displayed three sharp singlets at 0.87 (3 H), 0.95 (3 H), and 0.98 (6 H), a broad singlet at 1.73 (3 H), a doublet centered at 4.12 (2 H), and multiplets located at 4.80–4.45 (4 H) and 5.40 (3 H). The 250-MHz NMR spectrum (CCl_4) of synthetic **1** cleanly separates the four terminal methylene protons from each other as well as the trisubstituted olefinic proton from the trans-disubstituted olefinic protons (Figure 1).

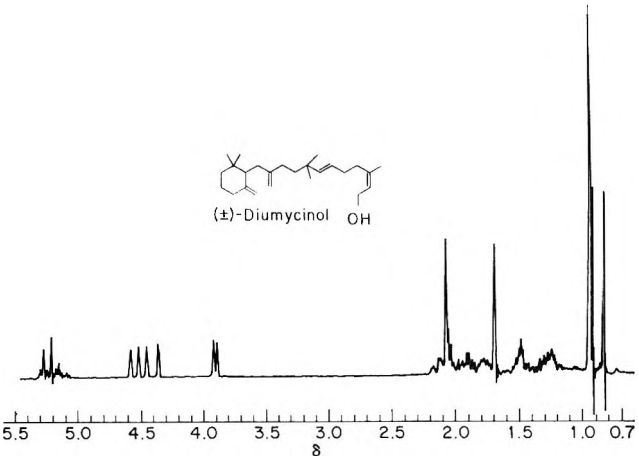
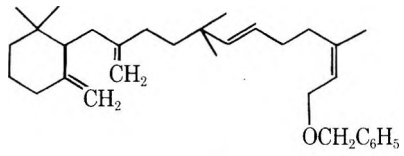


Figure 1. 250-MHz ^1H NMR spectrum of synthetic (±)-diumycinol in CCl_4 with TMS as internal standard.



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Acknowledgment. This investigation was supported in part by a Public Health Service Research Grant from the National Cancer Institute (CA 13689) and Eli Lilly and Co. NMR spectra were obtained on facilities (250 MHz) partially supported by Public Health Service Grant RR 00297. We thank Dr. W. A. Slusarchyk (The Squibb Institute for Medical Research) for supplying us with reference spectra of natural diumycinol and Mr. Bernard Kane (Glidden Organics) for generous gifts of nerol.

Supplementary Material Available. The Experiment Section will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 24× reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 16th St., N.W., Washington, D.C. 20036. Remit check or money order for $4.00 for photocopy or $2.50 for microfiche, referring to code number JOC-75-2261.

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(2) For the use and extension of enolate trapping[3] to a cyclopropyl ketone, see G. Stork, S. Uyeo, T. Wakamatsu, P. A. Grieco, and J. Labovitz, *J. Am. Chem. Soc.*, **93**, 4945 (1971); also see W. G. Dauben and E. J. Deviny, *J. Org. Chem.*, **31**, 3794 (1966).
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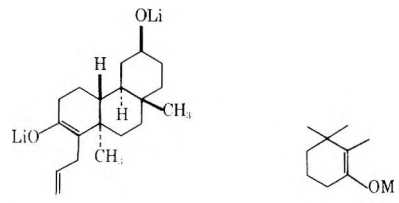
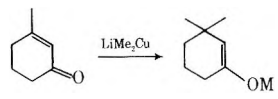
(5) It has recently been suggested[4e] that, when β substitution is present, enolate equilibration, resulting in loss of regiospecificity, will be a major, if not exclusive, process. With reference to enolate **3**, we have found this not to be the case (vide supra).[6] To our knowledge two examples exist (cf. i[2] and ii[4f]) in which α,β,β,β-tetrasubstituted enolates undergo regiospecific alkylation with no enolate equilibration.



i ii

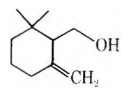
(6) S. Danishefsky and J. Eggler have regiospecifically generated enolate iii from 3-methylcyclohexenone and alkylated exclusively with methyl iodide at C-2 (private communication).



iii

(7) NMR spectra (CCl_4, 60 MHz) and ir spectra were obtained for all intermediates and were in every instance in accord with the assigned structure. Chemical shifts are expressed in parts per million downfield from TMS and coupling constants are expressed in hertz. Satisfactory C, H data and/or high resolution mass spectral data were obtained for all intermediates. Yields are for chromatographically pure substances unless indicated otherwise.

(8) Compound 7 was identical in all respects with a sample prepared from the homoallylic alcohol iv[9] via mesylation, displacement by cyanide ion, and reduction (DIBAL).



iv

(9) We thank Bernard Kane, Glidden Organics, Jacksonville, Fla., for a generous gift of iv.

(10) Treatment of 3-methylcyclohexenone with dimethyloxosulfonium methylide in DMSO afforded cyclopropyl ketone **2** in ~90% yield according to the procedure of E. J. Corey and M. Chaykovsky, *J. Am. Chem. Soc.*, **37**, 1353 (1965).

(11) Reductive alkylation of 2 provided exclusively the C-2 allylated ketone **4** (R = allyl). A solution of 372 mg (3 mmol) of **2** in 12 ml of dry glyme and 0.28 ml (3 mmol) of *tert*-butyl alcohol was added to 63 mg (9 mmol) of lithium in 125 ml of anhydrous liquid ammonia. After 40 min, allyl bromide (2 ml) was added all at once. Evaporation of the ammonia gave the desired ketone **4** (R = allyl) in ~70% yield after chromatography. Similarly, methyl iodide (73%) and methallyl bromide (35%) underwent exclusive C-2 alkylation. No products resulting from enolate equilibration or polyalkylation could be detected by GPC analysis.[5] Attempts to alkylate **3** with methyl bromoacetate resulted in a disappointingly low yield (<10%) of C-2 alkylated product. It is apparent from the above that reductive alkylations can be accomplished regiospecifically, albeit in low yield in some instances, under mild conditions with β-substituted cyclopropyl ketones.

(12) A. W. Herriott and D. Picker, *Tetrahedron Lett.*, 1511 (1974).

(13) R. Greenwald, M. Chaykovsky, and E. J. Corey, *J. Org. Chem.*, **28**, 1128 (1963).

(14) P. A. Grieco, Y. Masaki, and D. Boxler, *J. Am. Chem. Soc.*, **97**, 1597 (1975).

(15) Attempts to prepare **14** directly via the Grignard reagent derived from iodide **11** followed by oxidation were thwarted by our inability to prepare the required Grignard reagent. Presumably this was due to traces of water or peroxides which we were not able to get rid of.

(16) Fellow of the Alfred P. Sloan Foundation, 1974–1976.

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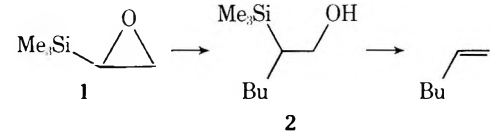
Received March 27, 1975

Reactions of α,β-Epoxysilanes with Organocuprate Reagents. A New Stereospecific Olefin Synthesis[1]

Summary: α,β-Epoxysilanes react with organocuprate reagents in a regio- and stereospecific manner to give good yields of β-hydroxyalkylsilanes, which can be stereospecifically converted to olefins in high yield under mild conditions.

Sir: Olefin-forming elimination reactions of β-hydroxyalkylsilanes have recently been used for the synthesis of a wide variety of compounds;[2] usually isomeric mixtures of cis and trans olefins have been formed. Using a diastereomerically enriched β-hydroxyalkylsilane, we have recently shown that these elimination reactions are stereospecific, and that the acid- and base-induced reactions take opposite stereochemical courses.[3] We now report the first method for the regio- and stereospecific synthesis of β-hydroxyalkylsilanes.[4] This method, coupled with the facile elimination reactions, provides a new, highly stereospecific olefin synthesis of potential generality, and in addition constitutes a definitive proof of the stereochemical course of the elimination reactions of β-hydroxyalkylsilanes.

We have found that the reactions of α,β-epoxysilanes[5] with organocuprate reagents[8] result in regiospecific opening of the epoxide ring to form β-hydroxyalkylsilanes in good yields.[9] Thus, treatment of trimethylsilylethylene oxide (**1**)[10] with lithium di-*n*-butyl cuprate[11] (2 equiv, ether, −25°, 5 hr) produced, in 88% yield, 2-trimethylsilyl-1-hexanol (**2**).[12,13] A similar reaction with epoxide **3**[12] (prepared from isobutenyltrimethylsilane[14] in 79% yield by treatment with *m*-chloroperbenzoic acid in CH_2Cl_2) yielded the alcohol **4**[12,15] in 75% yield.



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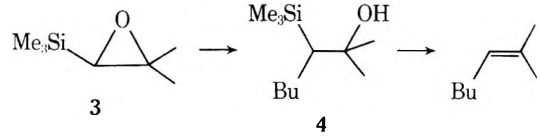


3 4

Both silyl alcohols underwent facile β elimination reactions to the corresponding olefins. Treatment of alcohol **2** with potassium hydride (THF, room temperature, 1 hr) produced 1-hexene in 95% yield by VPC; treatment of alcohol **4** with sodium acetate in acetic acid (room temperature, 1 hr) gave 2-methyl-2-heptene in quantitative yield (by NMR; isolated yield 81%).

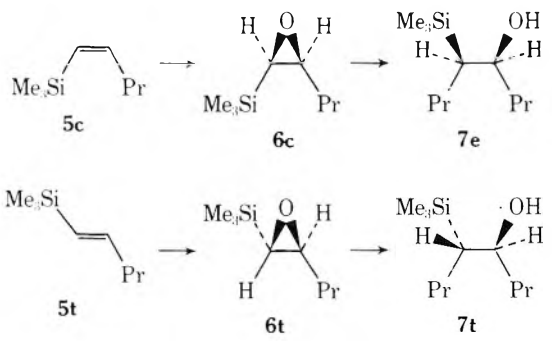
To determine the stereospecificity of these reactions, we have treated both cis and trans epoxysilanes **6c** and **6t** with an organocuprate reagent and have subjected the resulting β-hydroxyalkylsilanes to the conditions which we have previously shown to cause stereospecific β elimination.[3] The epoxides were synthesized in the following manner. *cis*-1-Pentenyltrimethylsilane (**5c**)[12,16,17] (98% cis by VPC) [ir (film) 6.23, 13.1 μm; NMR (CCl_4) δ 5.32 (d, 1 H, J = 14 Hz), 6.16 (m, 1 H)] was treated with *m*-chloroperbenzoic acid in CH_2Cl_2 to give, in 65% yield, the cis epoxide **6c**[12] [NMR (CCl_4) δ 1.90 (d, 1 H, J = 5 Hz), 2.83 (m, 1 H); mass spectrum *m/e* 158.1115 (calcd for $C_8H_{18}OSi$: 158.1126)]. An analogous sequence served to convert *trans*-1-pentenyltrimethylsilane (**5t**)[12,16b,19] [ir (film) 6.20, 10.1 μm; NMR (CCl_4) δ 5.52 (d, 1 H, J = 19 Hz), 6.02 (m, 1 H)] to the trans epoxide **6t**[12] [NMR ($CHCl_3$) δ 1.91 (d, 1 H, J = 4 Hz), 2.73

Table I
Elimination Reactions of the Alcohols 7e (Erythro) and 7t (Threo)

Precursor	Elimination conditions	4-Octene [a] % yield	% cis	% trans
7e	KH/THF, room temp, 1 hr	98	98	2
7e	BF_3·Et_2O/CH_2Cl_2, 0°, 1 hr	102	2	98
7e	H_2SO_4/THF, room temp, 18 hr	96	1	99
7t	KH/THF, room temp, 1 hr	93	*b*	100
7t	BF_3·Et_2O/CH_2Cl_2, 0°, 1 hr	98	99.5	0.5
7t	H_2SO_4/THF, room temp, 18 hr	94	99.5	0.5

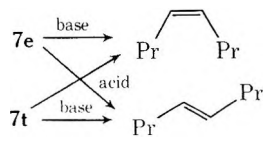
[a] Yields and isomer ratios were determined by VPC using an internal standard. [b] Undetectable; about 0.5% would have been detectable.

(m, 1 H); mass spectrum *m/e* 158.1091 (calcd for $C_8H_{18}OSi$: 158.1126)] in 87% yield.



Treatment of the cis epoxide **6c** with lithium di-*n*-propyl cuprate (ether, −78° warmed to 5° over 4 hr) yielded the erythro alcohol **7e**[20] in 70% yield.[21] In a similar reaction, the trans epoxide **6t** gave the threo alcohol **7t**[20] in 82% yield.

Both alcohols **7e** and **7t** could be converted into either *cis*- or *trans*-4-octene in virtually quantitative yields by proper choice of the conditions used for the elimination reaction. The results are shown in Table I.



This work demonstrates that the opening of α,β-epoxysilanes with organocuprate reagents is both regiospecific and stereospecific, and also proves unequivocally that the stereochemistry of the base-induced β elimination reactions is syn,[22] while that of the acid-catalyzed eliminations is anti. The high stereospecificity of this olefin synthesis and its applicability to mono-, di-, and trisubstituted olefins indicate its synthetic promise. Applications to the stereospecific synthesis of trisubstituted olefins and to the synthesis of insect hormones and pheromones are in progress.

Acknowledgments. We are grateful to Johnson and Johnson for a Fellowship to D.P., and we thank the National Science Foundation, the donors of the Petroleum Research Fund, administered by the American Chemical Society, the Rutgers Research Council, and Research Corporation for partial support of this work. We thank Mr. John C. Hogan for some of the preparations.

References and Notes

(1) Presented in part at the 168th National Meeting of the American Chemical Society, Atlantic City, N.J., Sept 1974, Abstracts, ORGN 99.
(2) (a) D. J. Peterson, *J. Org. Chem.*, **33**, 780 (1968); (b) T. H. Chan and E. Chang, *ibid.*, **39**, 3264 (1974); (c) I. Ojima, M. Kumagai, and Y. Nagai, *Tetrahedron Lett.*, 4005 (1974). For additional examples, see the references cited in ref 3.
(3) P. F. Hudrlik and D. Peterson, *J. Am. Chem. Soc.*, **97**, 1464 (1975).
(4) The few reported stereospecific methods for the preparation of β-hydroxyalkylsilanes are not regiospecific. See (a) H. Gilman, D. Aoki, and D. Wittenberg, *J. Am. Chem. Soc.*, **81**, 1107 (1959); (b) G. J. D. Peddle, *J. Organomet. Chem.*, **14**, 115 (1968); (c) W. K. Musker and G. L. Larson, *Tetrahedron Lett.*, 3481 (1968).
(5) Stork has recently shown that α,β-epoxysilanes are versatile precursors to carbonyl compounds.[6] Reductions of α,β-epoxysilanes by lithium aluminum hydride to give β-hydroxyalkylsilanes are known,[7] but no analogous reactions with organometallic reagents have been reported.
(6) (a) G. Stork and E. Colvin, *J. Am. Chem. Soc.*, **93**, 2080 (1971); (b) G. Stork and M. E. Jung, *J. Am. Chem. Soc.*, **96**, 3682 (1974); see also (c) B.-T. Gröbel and D. Seebach, *Angew. Chem., Int. Ed. Engl.*, **13**, 83 (1974); (d) R. K. Boeckman, Jr., and K. J. Bruza, *Tetrahedron Lett.*, 3365 (1974).
(7) J. J. Eisch and J. T. Trainor, *J. Org. Chem.*, **28**, 2870 (1963).
(8) For previous studies of the reactions of epoxides with organocuprate reagents, see C. R. Johnson, R. W. Herr, and D. M. Wieland, *J. Org. Chem.*, **38**, 4263 (1973), and references cited therein.
(9) Reactions with Grignard and organolithium reagents did not give products of simple ring opening; thus, treatment of epoxide **1** with *n*-butylmagnesium bromide (ether, reflux 15 hr) gave 1-trimethylsilyl-2-hexanol in 65% yield, while *tert*-butyllithium (THF, −78°, 4 hr) gave 1-trimethylsilyl-1-*tert*-butylethylene in 53% yield. The scope and mechanisms of these reactions are under investigation. (P. F. Hudrlik, D. Peterson, and R. Misra, unpublished results.)
(10) (a) V. Bažant and V. Matoušek, *Collect. Czech. Chem. Commun.*, **24**, 3758 (1959); (b) J. W. Wilt, O. Kolewe, and J. F. Kraemer, *J. Am. Chem. Soc.*, **91**, 2624 (1969).
(11) The reagent was prepared from n-BuLi and CuI. The reaction could also be effected using catalytic quantities (10%) of CuI.
(12) Satisfactory ir, NMR, and mass spectra were obtained for this compound. For epoxides **3**, **6c**, and **6t**, precise molecular weights obtained by high resolution mass spectroscopy confirmed the expected molecular formulas. We have so far had difficulty in obtaining satisfactory combustion analyses for these compounds.
(13) This compound was identical with a sample of **2** prepared independently from vinyltrimethylsilane, by treatment with *n*-PrLi (THF, −20°), followed by paraformaldehyde (80% yield).
(14) A. D. Petrov and G. I. Nikishin, *Dokl. Akad. Nauk SSSR*, **93**, 1049 (1953); *Chem. Abstr.*, **49**, 841c (1955).
(15) This compound was identical with a sample of **4** prepared independently from vinyltrimethylsilane, by treatment with *n*-PrLi (THF, −25°), followed by acetone (40% yield).
(16) (a) K. C. Frisch and R. B. Young, *J. Am. Chem. Soc.*, **74**, 4853 (1952); (b) R. A. Benkeser, M. L. Burrous, L. E. Nelson, and J. V. Swisher, *ibid.*, **83**, 4385 (1961).
(17) The cis vinylsilane **5c** was prepared from 1-pentynyltrimethylsilane[16] by treatment with dicyclohexylborane followed by protonolysis with acetic acid.[18]
(18) R. B. Miller and T. Reichenbach, *Tetrahedron Lett.*, 543 (1974).
(19) The trans vinylsilane **5t** was prepared by chloroplatinic acid catalyzed hydrosilylation (compare ref 6a and 16b) of 1-pentyne with Me_2HSiCl, followed by treatment with MeMgBr, and (on three occasions) by hydroboration–protonolysis of 1-pentynyltrimethylsilane by a procedure similar to that used for the preparation of the cis vinylsilane **5c**.[17,18] The reasons for the abnormal stereochemistry in these hydroboration experiments are not known.
(20) The diastereomeric alcohols **7e** and **7t** had ir, NMR, and mass spectra which were nearly identical with each other and with those of the mixtures of **7e** and **7t** which were prepared earlier,[3] and could not be separated by VPC. The assignment of erythro and threo configurations to these compounds is based on the previously reported reactions of epoxides with organocuprate reagents,[8] in which ring opening with predominant back-side attack was observed.
(21) The stereospecific conversion of **6c** to **7e** could also be effected with di-*n*-propyimagnesium in ether (P. F. Hudrlik and A. M. Hudrlik, unpublished results).
(22) Professor P. Dervan (California Institute of Technology) has independently demonstrated that the stereochemistry of the base-induced elimination reactions is syn, using β-hydroxyalkylsilanes prepared by a different route. We thank Professor Dervan for communicating his results to us prior to publication.

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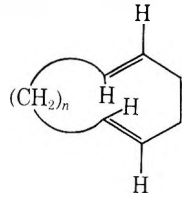
Useful New Organometallic Reagents for the Synthesis of Allylic Alcohols by Nucleophilic Vinylation

Summary: *trans*-1-Tri-*n*-butylstannyl-1-propene-3-tetrahydropyranyl ether (**1**), available in one step from propargyl tetrahydropyranyl ether, allows the generation of the vinylic nucleophiles **2** and **5**; these reagents can be used for the extension of chains, the addition of a vinylic appendage by conjugate addition to an enone, or for ring formation.

Sir: For some time it has been clear that a method for the nucleophilic introduction of the *trans*-$CH{=}CHCH_2OH$ unit would be of considerable utility in synthesis. For example, such a process could allow the expeditious synthesis of medium–large rings from 1,*n*-dihalides by sequence A

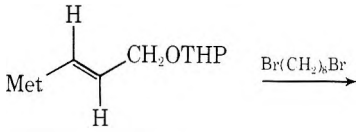
$$Br(CH_2)_nBr \longrightarrow HOCH_2CH\overset{t}{=}CH(CH_2)_nCH\overset{t}{=}CHCH_2OH \longrightarrow$$



(A)

using the previously discovered cyclization of bis allylic halides under the influence of nickel carbonyl,[1] or the introduction of a highly functionalized appendage by conjugate addition to α,β-enones.[2,3] We report here on a readily available organometallic reagent, *trans*-1-tri-*n*-butylstannyl-1-propene-3-tetrahydropyranyl ether (**1**),[4] which allows the realization of this methodology. Applications are presented to chain extension, ring appendage introduction, and ring formation operations, including a new synthetic route to the biologically interesting 11-deoxyprostaglandins.

The vinyltin reagent **1** was readily prepared from propargyl tetrahydropyranyl ether.[5,6] Reaction of **1** with 1 equiv of *n*-butyllithium in tetrahydrofuran (THF) at −78° for 1 hr resulted in complete formation of the lithium reagent **2**.



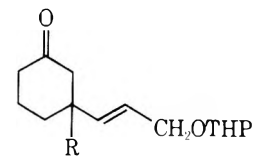
1, Met = *n*-Bu_3Sn
2, Met = Li
5, Met = Cu—C≡CC_3H_7

$$ROCH_2CH\overset{t}{=}CH(CH_2)_8CH\overset{t}{=}CHCH_2OR$$

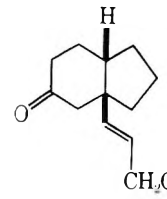
3, R = THP
4, R = H

The effectiveness of **2** as a nucleophilic vinylating agent was demonstrated by reaction with 1,8-dibromooctane to afford the THP ether **3** in 85% isolated yield. From **3** the diol **4** and cyclotetradeca-1,5-diene (trans,trans) can be obtained in high yield according to scheme A.[1]

Reaction of the lithio derivative **2** in THF with 1 equiv of 1-pentynylcopper[7] (−78°, 60 min; −50°, 10 min) afforded a red-orange, soluble mixed Gilman (cuprate) reagent **5** which has proven to be a highly reactive and useful intermediate for synthesis. Using only 1.05–1.1 equiv of this reagent, the conjugate adducts **6**–**8** were obtained from the corresponding α,β-enones as indicated (conditions, yield). In addition, the vinylated product **9** was prepared from 2-cyclopentenone (reaction at −78 to −50° for ~2 hr, isolated

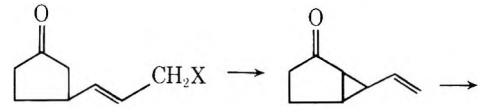


6, R = H (−78° for 75 min, 85%)
7, R = CH_3 (−78 to −20° for 2 hr, 84%)



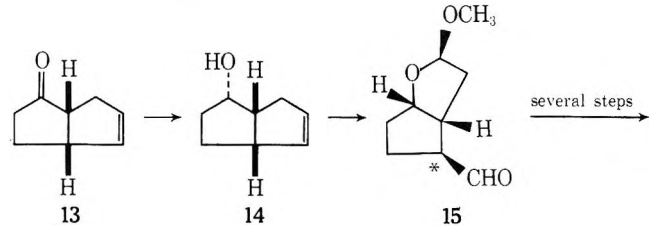
8. (−78 to −20° for 1.5hr, 71%)

yield 80%). These intermediates have been converted in a variety of ways to useful and otherwise less accessible compounds. An illustration of such utility is provided herein for the adduct **9** which can be converted to 11-deoxyprostaglandin E_2 (**16**) as shown in sequence B. The allylic alcohol

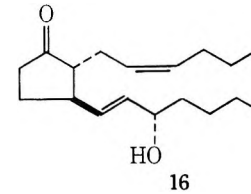


9, X = OTHP
10, X = OH
11, X = OSO_2CH_3

12



13 14 15



16

(B)

10, obtained by hydrolysis of the tetrahydropyranyl ether **9**, was converted to the allylic mesylate **11**. Reaction of **11** at 0° for 5 min with potassium *tert*-butoxide in THF gave the vinylcyclopropane **12** in nearly quantitative yield (carbonyl, 1730 cm^{-1}). Thermolysis of **12** by evaporation at 0.2-mm pressure through a 33-cm column heated to 600° (packed with chips of leaded potash glass) afforded ketone **13**.[8] Reduction of this bicyclic ketone with sodium borohydride in methanol at −40° afforded alcohol **14** stereospecifically. Treatment of **14** with osmium tetroxide–sodium metaperiodate effected fission of the double bond. The resulting material when treated with methanol containing a catalytic amount of boron trifluoride etherate afforded the aldehyde **15** and the epimer at C* (65% yield from **14**). Exposure of the mixture of epimeric aldehydes [^1H NMR peaks ($CDCl_3$) due to CHO at δ 9.68 and 9.58] to 1,5-diazabicyclo[5.4.0]undec-5-ene (1 equiv) in methylene chloride (12 hr at 25°) converted it to a single isomer (δ 9.58), the more stable **15**.[9] The transformation of **15** to 11-deoxyprostaglandin E_2 is readily effected as described previously.[10]

The simple preparation of reagent **1** and its use for both direct displacement (via the lithium derivative) and conju-

gate addition (via the copper derivative) under very mild conditions makes this the method of choice for the introduction of a trans allylic alcohol group to a wide variety of molecules.[11]

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(2) (a) Although metallic acetylides derived from propargyl tetrahydropyranyl ether have been used for such processes (e.g., ref 1c), they suffer from the disadvantage of giving only moderate to poor yields in SN2 alkylation [see E. J. Corey, J. A. Katzenellenbogen, N. W. Gilman, S. A. Roman, and B. W. Erickson, *J. Am. Chem. Soc.*, **90**, 5618 (1968), and also J. A. Katzenellenbogen, Ph.D. thesis, Harvard University]. Further, such acetylenic derivatives are not suitable for cuprate mediated conjugated addition to α,β-enones (see ref 2b). (b) E. J. Corey and D. J. Beames, *J. Am. Chem. Soc.*, **94**, 7210 (1972).

(3) For conjugate addition of unsubstituted vinyl, see E. J. Corey and R. L. Carney, *J. Am. Chem. Soc.*, **93**, 7318 (1971).

(4) For a related previous study in the organotin field, see E. J. Corey and R. H. Wollenberg, *J. Am. Chem. Soc.*, **96**, 5581 (1974).

(5) The following procedure was used. A neat mixture of 42.5 g (71.3 mmol) of bis(tri-*n*-butyltin) oxide (Alfa Products, Ventron Corp.) and 9.50 g of polymethylhydrogen siloxane (Aldrich Chemical Co.) was stirred at room temperature under argon for 30 min and then treated with 14.0 g (100 mmol) of propargyl tetrahydropyranyl ether and 100 mg of azobisisobutyronitrile. The mixture was stirred at 80° for 2 hr and distilled directly from the reaction vessel to afford **38** g (89%) of **1** (bp 140–142° at 0.1 mm) as a colorless oil. NMR studies showed that the hydrostannation reaction occurs only by terminal addition to the acetylenic bond and that the reaction mixture consists of mostly the cis isomer of **1** below 80°, consistent with previous results [see A. J. Leusink, H. A. Budding, and J. W. Marsman, *J. Organomet. Chem.*, **9**, 285 (1967)]. However, at temperatures above 80° (e.g., during distillation) isomerization to the trans isomer takes place. All organometallic reactions were carried out under an inert (argon) atmosphere.

(6) Satisfactory ir, ^{1}H NMR, and mass spectral data were obtained on all products cited herein.

(7) See ref 2b for a description of selective transfer from such alkynyl-containing Gilman reagents.

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(11) This work was assisted financially by a grant from the National Science Foundation.

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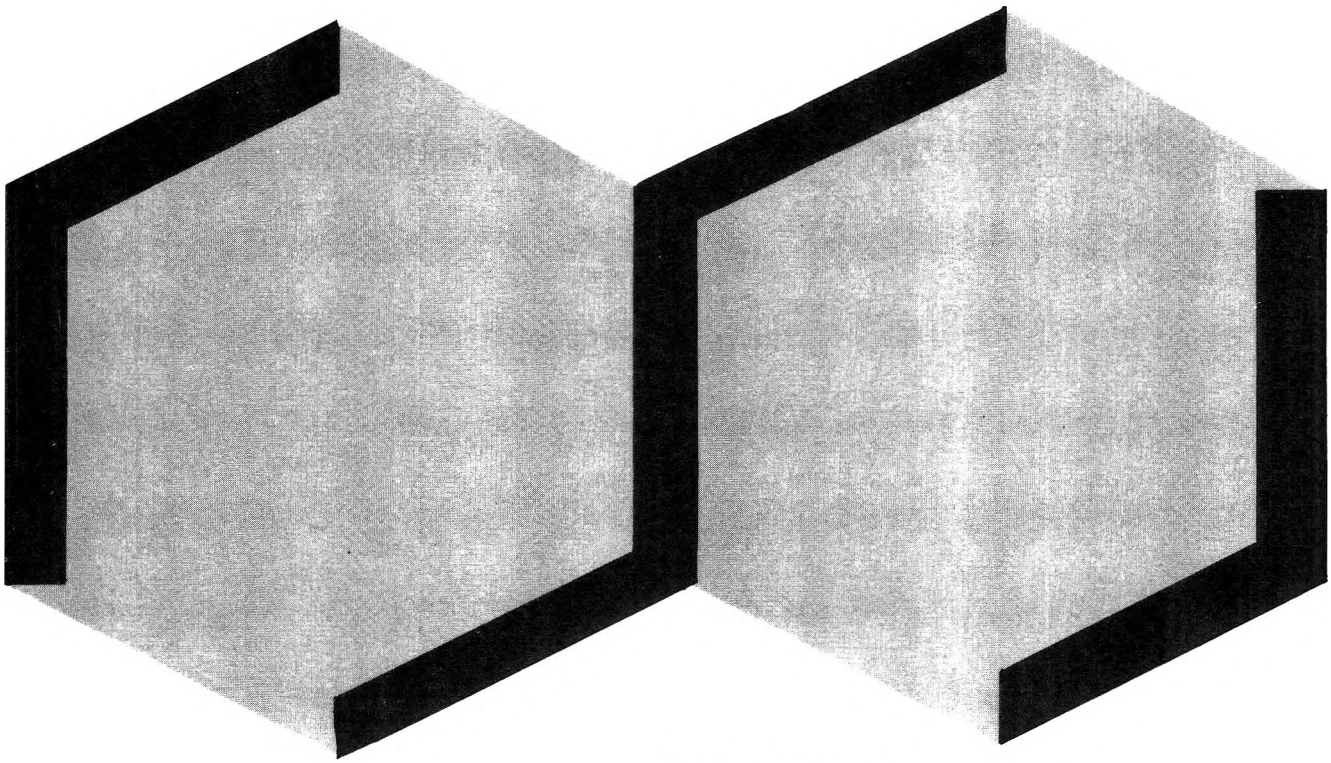

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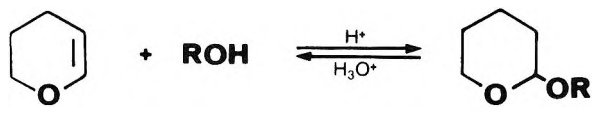
Dihydropyrans

For the protection of chiral and achiral alcohols

2,3-DIHYDROPYRAN

for the protection of hydroxyl functions

The formation of tetrahydropyranyl (THP) ethers by the reaction of **2,3-dihydropyran** with alcohols under mild acid catalysis[1,2] is a very useful method for protecting alcohols because THP ethers are stable to bases, Grignard reagents, metal hydrides, lithium alkyls, chromic acid oxidation, and epoxidation with alkaline hydrogen peroxide,[1] yet are easily cleaved by dilute acids.



2,3-Dihydropyran has also been used to protect carboxyl and sulfhydryl groups, the 9-nitrogen of purines, and propargylic[3] and steroidal[4] alcohols. Typical applications include the total syntheses of prostaglandins[5] and humulene.[6] Recently, it was used in the penicillin field for trapping a sulfenic acid[7] and in the syntheses of sulfur-free penicillin derivatives.[8]

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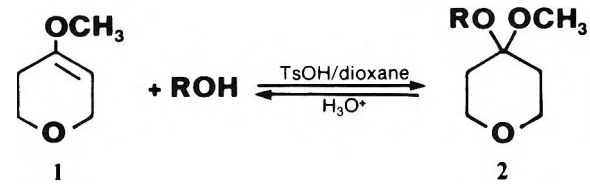
for the protection of chiral alcohols

The use of the tetrahydropyranyl group for protection of hydroxyls of chiral alcohols leads to the introduction of another chiral center, and undesirable mixtures of diastereoisomeric products are obtained, *e.g.*, in steroids,[1] carbohydrates,[2] and nucleosides.[3]



1 2

Reese, van Boom and coworkers[4] have demonstrated that **5,6-dihydro-4-methoxy-2*H*-pyran (1)** is an excellent reagent for the protection of optically active alcohols because the 4,4-disubstituted tetrahydropyran moiety of the products (**2**) is symmetrical, and its introduction does not therefore lead to an additional chiral center. The derivatives, which are usually crystalline, are formed in high yields by *p*-toluenesulfonic acid-catalyzed reactions in anhydrous dioxane; they are base-stable, yet are easily hydrolyzed by dilute acids.[4,5] **5,6-Dihydro-4-methoxy-2*H*-pyran** has been employed mainly in the syntheses of nucleotides and oligonucleotides;[6] it has also been used for steroidal alcohol protection.[5]

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