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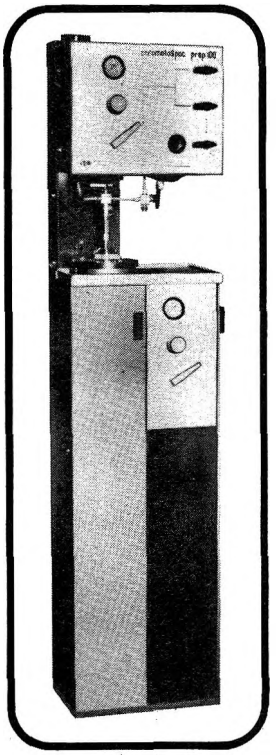

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Pteridines. XXXIX. Synthesis of 2,4-Diamino-7-alkenylpteridines and Their 8-Oxides[1,2]

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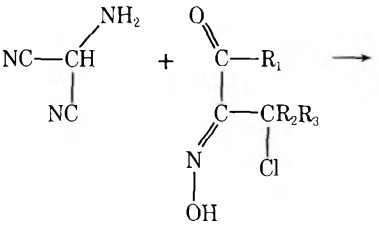
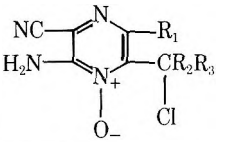
Received November 19, 1975

A versatile and flexible route to a variety of 2,4-diamino-7-alkenylpteridines is described. Condensation of aminomalononitrile with α-oximino-β-chloro aldehydes (prepared by the addition of nitrosyl chloride to α,β-unsaturated aldehydes) gives 2-amino-3-cyano-6-(1-chloroalkyl)pyrazine 1-oxides (**1**–**4**). The 6-chloromethyl compound (**1**) was converted to the stable phosphorane **10** which was condensed with aldehydes to give a series of 2-amino-3-cyano-6-alkenylpyrazine 1-oxides (**16**) which were cyclized with guanidine to 2,4-diamino-7-alkenylpteridine 8-oxides (**17**). Deoxygenation of **1** with phosphorus trichloride in THF gave 2-amino-3-cyano-6-chloromethylpyrazine (**5**), which was carried through an analogous sequence of steps to give a series of 2,4-diamino-7-alkenylpteridines (**15**). *These pteridines are potential intermediates for the synthesis of derivatives carrying multifunctional* substituents at position 7 which would be isomeric with the naturally occurring 6-substituted cofactors biopterin and neopterin.

We have recently described a new and general approach to the unequivocal synthesis of pteridines bearing olefinic substituents at position 6, suitable for eventual elaboration into the family of 6-substituted pterins represented by biopterin, neopterin, and related compounds.[3] The key steps in this synthetic sequence involved the initial condensation of aminomalononitrile with β-chloropyruvaldoxime to give 2-amino-3-cyano-5-chloromethylpyrazine 1-oxide and the subsequent elaboration of the olefinic side chains via the Wittig synthesis. Final cyclization with guanidine gave the desired 6-substituted pteridines, which were readily hydrolyzed with dilute acid or base to pterins. The present paper describes the unequivocal synthesis of a series of isomeric 2,4-diaminopteridines substituted at position 7 with olefinic groups suitable for final elaboration into structural analogues of the naturally occurring 6-substituted pterins.

Application of the same oxime cyclization principle to the preparation of pyrazine intermediates suitable for cyclization to 7-substituted pteridines would require that aminomalononitrile tosylate be condensed with an α-oximino-β-chloro aldehyde. Fortunately, such intermediates are readily accessible by addition of nitrosyl chloride to α,β-unsaturated aldehydes.[4] Thus, reaction of aminomalononitrile with α-oximino-β-chloropropionaldehyde (from the addition of nitrosyl chloride to acrolein) gave 2-amino-3-cyano-6-chloromethylpyrazine 1-oxide (**1**). This condensation is apparently completely general; condensation of aminomalononitrile with the α-oximinocarbonyl compounds derived by addition of nitrosyl chloride to crotonaldehyde, 2-pentenal, and 2-cyclohexenone gave the corresponding pyrazine 1-oxides **2**, **3**, and **4**. All of the subsequent reactions described in this paper were carried out with the parent chloromethylpyrazine **1**, but we would anticipate that these various derivatization reactions would be equally effective with other 6-(α-chloroalkyl)pyrazines such as **2**, **3**, and **4**.

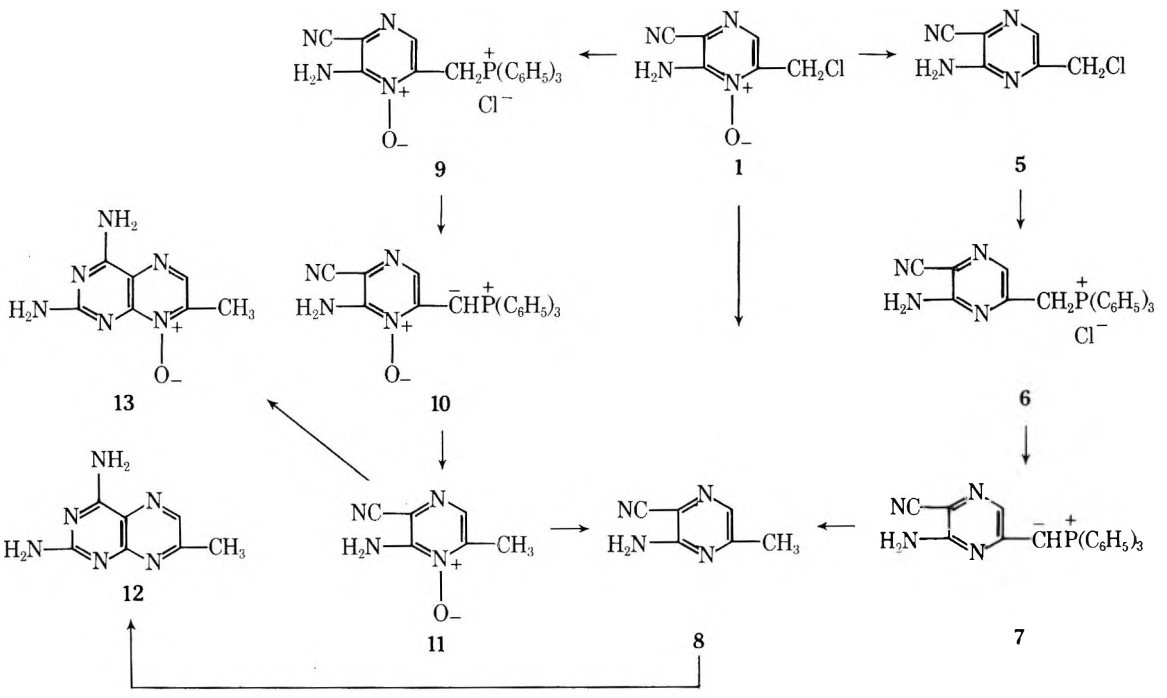




1, $R_1 = R_2 = R_3 = H$
2, $R_1 = R_2 = H$; $R_3 = CH_3$
3, $R_1 = R_2 = H$; $R_3 = C_3H_7$
4, $R_1, R_2 = -CH_2CH_2CH_2-$; $R_3 = H$

We first examined the deoxygenation of **1** to 2-amino-3-cyano-6-chloromethylpyrazine (**5**). Although many methods are available for reductive deoxygenation of aromatic *N*-oxides,[5] the conversion of **1** to **5** is at least potentially complicated by the presence of three reactive substituents, of which two (the cyano and chloromethyl groups) would be expected to be extremely susceptible to reduction. The best conditions appeared to involve heating **1** with phosphorus trichloride in tetrahydrofuran as solvent. Use of the more customary solvents for such deoxygenation reactions

Scheme I



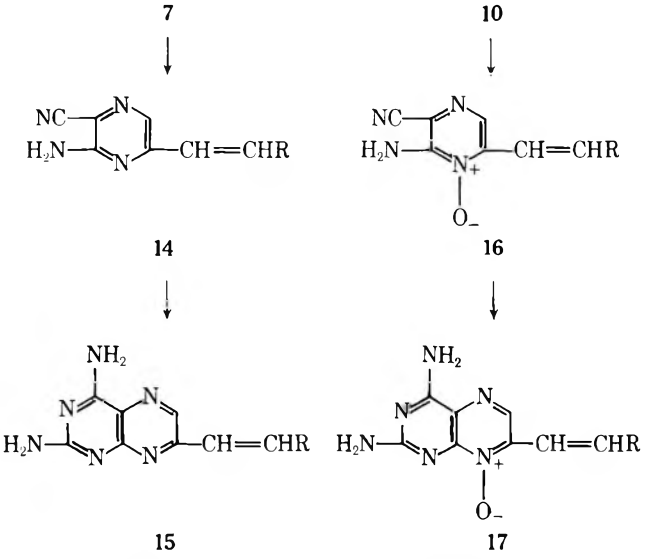
(chloroform, dioxane) led to slow reactions which were accompanied by the formation of numerous unidentified byproducts. The optimum reaction conditions (see Experimental Section) were determined by TLC monitoring of the reaction mixture; refluxing was discontinued at the moment of complete disappearance of starting material.

Treatment of **5** with triphenylphosphine in dimethylformamide resulted in smooth conversion to the corresponding triphenylphosphonium salt **6**, which was converted to the stable methylenetriphenylphosphorane (Wittig reagent) **7** by treatment with aqueous sodium bicarbonate. The structure of this phosphorane was confirmed by hydrolysis in boiling 30% aqueous ethanol to 2-amino-3-cyano-6-methylpyrazine (**8**), identical with the compound prepared by sodium hydrosulfite reduction of the initial 2-amino-3-cyano-6-chloromethylpyrazine 1-oxide (**1**).

Treatment of **1** with triphenylphosphine in dimethylformamide solution analogously led to the triphenylphosphonium salt **9**, which was likewise converted with aqueous sodium bicarbonate into the methylenetriphenylphosphorane (Wittig reagent) **10**. The structure of this latter compound was confirmed by hydrolysis in 30% aqueous ethanol to 2-amino-3-cyano-6-methylpyrazine 1-oxide (**11**), which could be readily deoxygenated with sodium hydrosulfite to **8**, identical with the compound prepared by reduction of **1**, or by hydrolysis of **7**, as described above. Finally, cyclization of **8** and **11** with guanidine in methanol solution in the presence of sodium methoxide resulted in the formation of 2,4-diamino-7-methylpteridine (**12**) and its corresponding *N*-oxide (**13**). Compound **12** was identical with a sample of 2,4-diamino-7-methylpteridine prepared by the method of Seeger.[6] The above reactions are schematically summarized in Scheme I.

The phosphoranes **7** and **10** were converted to olefins by reaction with aldehydes in refluxing tetrahydrofuran (see Scheme II). Long reaction periods (1–5 days) were required, as expected for highly stabilized Wittig reagents. The phosphorane **10** was less reactive than its deoxygenated counterpart **7**. For example, condensation of **7** with benzaldehyde was complete in 1 day, but 5 days were required for the comparable condensation with **10**. In no instance was anil formation observed between the aldehyde

Scheme II

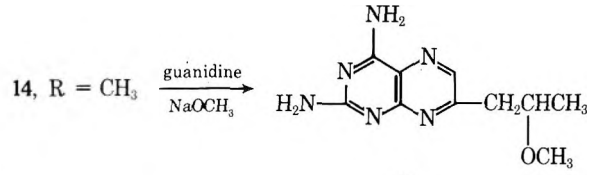


R = CH_3, CH_2OH, COOH, C_6H_5, 3,4-diClC_6H_3, 3,4-$(OCH_2O)C_6H_3$, 2-thienyl, 3-pyridyl

and the 2-amino group of either **7** or **10**. This side reaction, which might have been expected to complicate the above Wittig syntheses, is undoubtedly inhibited by the very weak basicity of the pyrazine amino groups in **7** and **10**. With the single exception of the product arising from the condensation of **10** with glyoxylic acid (**16**, R = COOH), all of the olefins prepared from **7** and **10** (i.e., **14** and **16**) had the trans configuration, as judged by careful analysis of the NMR spectra of the crude (as well as recrystallized) reaction products. Infrared spectral data also confirmed the trans configuration for these olefins. The condensation of **10** with glyoxylic acid proceeded exceptionally rapidly in boiling tetrahydrofuran (20 min) and gave a 50:50 mixture of the cis and trans isomers of **16**, R = COOH. No attempt was made to devise reaction conditions which would provide exclusively trans product. It should be noted that the formation of trans olefins in the above Wittig syntheses

significantly simplifies the subsequent projected utilization of these olefinic intermediates for the preparation of pteridines isomeric with biopterin, neopterin, etc., all of which possess the erythro configuration of the 6-substituted polyhydroxypropyl side chains.

The olefinic pyrazine precursors **14** and **16** were converted to 2,4-diaminopteridines and the corresponding 8-oxides (**15** and **17**, respectively) by condensation with guanidine in the presence of sodium methoxide. This procedure for the conversion of *o*-aminonitriles to fused 2,4-diaminopyrimidines has been thoroughly documented and needs no further discussion here.[7] In all of the pteridines prepared in this fashion (see Experimental Section), the trans configuration of the olefinic side chain was retained, as judged by NMR. The only abnormal reaction course observed was in the cyclization of **14** (R = CH_3), which resulted in the formation of 2,4-diamino-7-(2-methoxypropyl)pteridine (**18**) by Michael addition of methanol to the C=C bond. At-



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tempted condensation of the corresponding *N*-oxide (**16**, R = CH_3) with guanidine under the same reaction conditions failed to give the desired product (**17**, R = CH_3); the complex mixture of compounds resulting from this condensation is still under investigation. It should be noted that similar complications do not arise in the guanidine cyclization of the isomeric 2-amino-3-cyano-5-(1-propenyl)pyrazine and its corresponding *N*-oxide.[3]

It is apparent that the condensation of aminomalononitrile with α-oximino-β-chloropropionaldehyde to give **1**, followed by the series of simple conversions discussed above leading ultimately to the pteridines **15** and **17**, constitutes a versatile synthetic route to precursors of the 7-substituted isomers of the biopterin and neopterin series of pteridine natural products. These extensions of the present work will be discussed in future papers in this series.

Experimental Section

2-Amino-3-cyano-6-chloromethylpyrazine 1-Oxide (1). A mixture of 20.2 g (0.08 mol) of aminomalononitrile tosylate and 9.7 g (0.08 mol) of α-oximino-β-chloropropionaldehyde[4] in 250 ml of 2-propanol was stirred overnight at room temperature. The precipitate which had formed was collected by filtration, suspended in 100 ml of methanol, and filtered again to give 6.0 g (41%) of **1**, mp 245 °C dec. The analytical sample, mp 250 °C dec, was obtained as pale yellow flakes by recrystallization from methanol.

Anal. Calcd for $C_6H_5ClN_4O$: C, 39.01; H, 2.71; N, 30.38; Cl, 19.25. Found: C, 39.20; H, 2.75; N, 30.64; Cl, 19.55.

2-Amino-3-cyano-6-(1-chloroethyl)pyrazine 1-Oxide (2). A mixture of 7.6 g (0.03 mol) of aminomalononitrile tosylate and 4.1 g (0.03 mol) of α-oximino-β-chlorobutyraldehyde[4] in 100 ml of 2-propanol was treated as described above to give 2.2 g (37%) of **2**, mp 222 °C dec. The analytical sample was obtained as pale yellow needles, but without change in the melting point, by recrystallization from methanol.

Anal. Calcd for $C_7H_7N_4OCl$: C, 42.33; H, 3.55; N, 28.21; Cl, 17.85. Found: C, 42.36; H, 3.37; N, 28.50; Cl, 17.79.

2-Amino-3-cyano-6-(1-chlorobutyl)pyrazine 1-Oxide (3). In the same manner as described above, condensation of 13.1 g (0.052 mol) of aminomalononitrile tosylate and 8.5 g (0.052 mol) of α-oximino-β-chlorocapraldehyde[4] in 100 ml of 2-propanol gave 0.7 g (6%) of **3**, mp 155–157 °C dec. The analytical sample was prepared by vacuum sublimation at 100 °C (0.1 mm).

Anal. Calcd for $C_9H_{11}N_4OCl$: C, 47.68; H, 4.86; N, 24.72; Cl, 15.67. Found: C, 47.96; H, 4.91; N, 25.00; Cl, 15.46.

2-Amino-3-cyano-8-chloro-5,6,7,8-tetrahydroquinoxaline 1-Oxide (4). Nitrosyl chloride was passed into a stirred solution of 6.45 g (0.067 mol) of 2-cyclohexenone in 45 ml of diethyl ether, held at approximately −40 °C, until 4.4 g (0.067 mol) had been absorbed. Stirring was continued for a further 2 h while the reaction mixture was allowed to warm to room temperature. The white solid which had separated was collected by filtration and washed with methanol followed by diethyl ether to give 5.3 g (72%) of the dimer of 2-nitroso-3-chlorocyclohexanone, mp 93–94 °C dec. Since microanalysis of the crude dimer indicated that it was pure (Anal. Calcd for $C_6H_8NO_2Cl$: C, 44.51; H, 4.95; N, 8.67; Cl, 21.98. Found: C, 44.94; H, 4.95; N, 8.77; Cl, 22.20), and attempted recrystallization resulted in decomposition, it was used directly in the next step. Conversion to the monomer was effected by suspension of 1.61 g of the above dimer in 20 ml of Me_2SO and heating at 50 °C for 10 min. The resulting solution was poured into 50 ml of ice water, the monomeric 2-oximino-3-chlorocyclohexanone was extracted with ether and dried over anhydrous $MgSO_4$, and the ether was evaporated. Addition of 0.76 g (3 mmol) of aminomalononitrile tosylate to the resulting 0.76 g (3 mmol) of crude 2-oximino-3-chlorocyclohexanone in 3 ml of 2-propanol and stirring overnight at room temperature gave a solid which was collected by filtration and recrystallized from methanol to give 0.23 g (13%) of **4**, mp 186–187 °C dec.

Anal. Calcd for $C_9H_9N_4OCl$: C, 48.11; H, 4.04; N, 24.94; Cl, 15.78. Found: C, 48.38; H, 4.25; N, 25.46; Cl, 15.42.

2-Amino-3-cyano-6-methylpyrazine (8). To a solution of 1.85 g (0.01 mol) of 2-amino-3-cyano-6-chloromethylpyrazine 1-oxide in 50 ml of boiling water was added, in small portions and with stirring, 6.0 g (0.03 mol) of sodium hydrosulfite. The reaction mixture was boiled for an additional 5 min and then cooled to give 0.87 g (65%) of pure **8**, mp 212–213 °C dec, as light tan needles.

Anal. Calcd for $C_6H_6N_4$: C, 53.72; H, 4.51; N, 41.77. Found: C, 53.90; H, 4.64; N, 41.74.

2-Amino-3-cyano-6-chloromethylpyrazine (5). A mixture of 9.3 g of 2-amino-3-cyano-6-chloromethylpyrazine 1-oxide, 30 ml of phosphorus trichloride, and 500 ml of THF was heated under reflux for 1 h. A homogeneous solution resulted after the first 15 min of heating. The resulting dark brown solution was poured over ice, neutralized with sodium bicarbonate, and extracted with three 200-ml portions of ethyl acetate. The combined extracts were dried over anhydrous $MgSO_4$ and evaporated to dryness, and the resulting dark brown solid (6.9 g, 82%) dissolved in 100 ml of methanol, decolorized with Norit, concentrated, and cooled. Filtration then gave 4.8 g (56%) of **5** as a light brown powder, mp 174 °C dec. The analytical sample was prepared in the form of a pale yellow, microcrystalline solid by sublimation at 100 °C (0.1 mm).

Anal. Calcd for $C_6H_5N_4Cl$: C, 42.73; H, 2.97; N, 33.22; Cl, 21.07. Found: C, 42.69; H, 3.19; N, 32.94; Cl, 21.38.

(1-Oxy-2-amino-3-cyano-6-pyrazinyl)methyltriphenylphosphonium Chloride (9). A solution of 5.54 g (0.03 mol) of 2-amino-3-cyano-6-chloromethylpyrazine 1-oxide, 8.8 g (0.03 mol) of triphenylphosphine, and 60 ml of DMF was stirred at 80–90 °C for 40 min. The reaction mixture was then cooled, 600 ml of diethyl ether added, and the resulting precipitate collected by filtration and washed with ether–methanol (1:1) to give 12.3 g (92%) of **9** as pale yellow flakes, mp 239–240 °C dec.

Anal. Calcd for $C_{24}H_{20}N_4OClP$: Cl, 7.95. Found: Cl, 7.84.

(2-Amino-3-cyano-6-pyrazinyl)methyltriphenylphosphonium Chloride (6). In the same manner as described above, 2-amino-3-cyano-6-chloromethylpyrazine (1.0 g, 6 mmol) was converted to **6** by stirring with 1.57 g (6 mmol) of triphenylphosphine in 12 ml of DMF, yield 2.16 g (85%) of **6**, mp 271 °C dec (from methanol–ether).

Anal. Calcd for $C_{24}H_{20}N_4ClP$: Cl, 8.25. Found: Cl, 8.38.

(1-Oxy-2-amino-3-cyano-6-pyrazinyl)methylenetriphenylphosphorane (10). To a solution of 5.0 g (11.3 mmol) of (1-oxy-2-amino-3-cyano-6-pyrazinyl)methyltriphenylphosphonium chloride in 150 ml of water was added 1.26 g (15.0 mmol) of sodium bicarbonate, and the resulting slurry was stirred at room temperature for 1 h. The precipitated deep yellow solid was collected by filtration and washed with water to give 4.3 g (98%) of **10**, mp 240–241 °C dec, which was used directly for subsequent Wittig condensations with aldehydes. The analytical sample was prepared in the form of deep yellow platelets, mp 243–244 °C dec, by recrystallization from ethanol.

Anal. Calcd for $C_{24}H_{19}N_4OP$: C, 70.20; H, 4.64; N, 13.66. Found: C, 69.99; H, 4.84; N, 13.58.

(2-Amino-3-cyano-6-pyrazinyl)methylenetriphenylphosphorane (7). In the same manner as described above, treatment of 1.0 g (2.3 mmol) of (2-amino-3-cyano-6-pyrazinyl)methyltriphenylphosphonium chloride with 0.3 g (3.5 mmol) of sodium bi-

carbonate gave 0.85 g (93%) of **7**, mp 243–244 °C dec. Recrystallization from DMF–methanol gave deep yellow prisms, mp 249–250 °C dec.

Anal. Calcd for $C_{24}H_{19}N_4P$: C, 73.10; H, 4.82; N, 14.21. Found: C, 72.86; H, 5.02; N, 14.10.

Hydrolysis of 7 to 2-Amino-3-cyano-6-methylpyrazine (8). A solution of 0.1 g of the phosphorane **7** in 10 ml of 30% aqueous ethanol was heated under reflux for 5 h. The resulting solution was concentrated to a small volume by evaporation under reduced pressure, and the precipitated solid was collected by filtration, triturated with benzene, and then recrystallized from methanol to give 0.03 g (88%) of 2-amino-3-cyano-6-methylpyrazine, mp 212–213 °C dec. The product was identical with an authentic sample of **8** prepared as described above by reduction of 2-amino-3-cyano-6-chloromethylpyrazine 1-oxide with sodium hydrosulfite.

Hydrolysis of 10 to 2-Amino-3-cyano-6-methylpyrazine 1-Oxide (11). A solution of 2.0 g of the phosphorane **10** in 150 ml of 30% aqueous ethanol was heated under reflux for 2.5 h and concentrated under reduced pressure and the resulting precipitate was collected by filtration, dried, and triturated for 30 min in 50 ml of benzene. Filtration then gave 0.69 g (95%) of **11** as light brown needles, mp 244–245 °C dec. The analytical sample was prepared in the form of pale yellow needles, mp 246–247 °C dec, by sublimation at 180 °C (0.1 mm).

Anal. Calcd for $C_6H_6N_4O$: C, 48.00; H, 4.03; N, 37.32. Found: C, 47.77; H, 4.13; N, 37.43.

Reduction of 11 to 2-Amino-3-cyano-6-methylpyrazine (8). To a solution of 50 mg (0.33 mmol) of 2-amino-3-cyano-6-methylpyrazine 1-oxide in 1.5 ml of boiling water was added slowly and with stirring 104 mg (0.6 mmol) of sodium hydrosulfite. The resulting reaction mixture was boiled for an additional 10 min and cooled, and the fine crystalline precipitate was collected by filtration and recrystallized from methanol, yield 20 mg (45%), mp 212–213 °C dec. The product was identical in all respects with an authentic sample of **8** prepared as described above by hydrolysis of the phosphorane **7**, or by reduction of **1**.

2-Amino-3-cyano-6-styrylpyrazine 1-Oxide (16, R = C_6H_5). A solution of 2.0 g (4.9 mmol) of **10** and 2.0 g (18.8 mmol) of benzaldehyde in 100 ml of dry THF was heated under reflux for 5 days and evaporated to dryness under reduced pressure, and the residual solid was triturated with benzene for 30 min. Filtration then gave 1.0 g (86%) of **16**, R = C_6H_5, as fine yellow needles, mp 270–271 °C dec. The analytical sample, mp 280–281 °C dec, was prepared by sublimation at 180 °C (0.1 mm).

Anal. Calcd for $C_{13}H_{10}N_4O$: C, 65.53; H, 4.23; N, 23.52. Found: C, 65.49; H, 4.41; N, 23.39.

2-Amino-3-cyano-6-styrylpyrazine (14, R = C_6H_5). A solution of 2.0 g (5.1 mmol) of **7** and 2.0 g (18.8 mmol) of benzaldehyde in 100 ml of dry THF was heated under reflux overnight and then evaporated to dryness under reduced pressure. The residue was triturated for 30 min in 50 ml of benzene and then filtered to give 0.95 g (84%) of a bright yellow solid, mp 218–219 °C. The analytical sample, mp 222–223 °C, was prepared by sublimation at 180 °C (0.1 mm).

Anal. Calcd for $C_{13}H_{10}N_4$: C, 70.25; H, 4.54; N, 25.21. Found: C, 70.01; H, 4.53; N, 25.25.

2-Amino-3-cyano-6-(1-propenyl)pyrazine 1-Oxide (16, R = CH_3). A solution of 2.05 g (5 mmol) of the phosphorane **10** and 2.2 g (50 mmol) of acetaldehyde in 50 ml of dry THF was stirred at 60 °C in a pressure bottle for 3 days and then evaporated to dryness under reduced pressure. The residue was triturated with 50 ml of benzene at room temperature for 30 min and then filtered to give 0.70 g (80%) of yellow crystals of **16**, R = CH_3, mp 185–186 °C dec. The analytical sample, mp 187–188 °C dec, was prepared by sublimation at 120 °C (0.1 mm).

Anal. Calcd for $C_8H_8N_4O$: C, 54.54; H, 4.58; N, 31.80. Found: C, 54.56; H, 4.74; N, 32.09.

2-Amino-3-cyano-6-(1-propenyl)pyrazine (14, R = CH_3). A solution of 3.0 g of the phosphorane **7** and 2.4 g of acetaldehyde in 60 ml of dry DMF was stirred at room temperature for 24 h in a pressure bottle and then poured into ice water. The precipitate which formed was collected by filtration, dried, and triturated with benzene for 30 min. Filtration then gave 0.85 g (75%) of **14**, R = CH_3, as a light brown powder, mp 184–185 °C. The analytical sample was obtained as a pale yellow powder, mp 189–190 °C, by sublimation at 120 °C (0.1 mm).

Anal. Calcd for $C_8H_8N_4$: C, 59.98; H, 5.03; N, 34.98. Found: C, 59.85; H, 5.16; N, 34.83.

2-Amino-3-cyano-6-(3-hydroxy-1-propenyl)pyrazine 1-Oxide (16, R = CH_2OH). A solution of 1.95 g (4.7 mmol) of the phosphorane **10** and 1.5 g (25 mmol) of glycolaldehyde in 50 ml of dry THF was heated under reflux for 18 h and then evaporated to dryness. The residue was washed thoroughly with water, dried, and then triturated for 30 min at room temperature with 50 ml of benzene. Filtration gave 0.73 g (80%) of **16**, R = CH_2OH, as a yellow, microcrystalline solid, mp 114–115 °C dec. The product was obtained in the form of light yellow needles, mp 117 °C dec, by recrystallization from methanol.

Anal. Calcd for $C_8H_8N_4O_2$: C, 49.99; H, 4.20; N, 29.16. Found: C, 50.18; H, 4.43; N, 29.32.

2-Amino-3-cyano-6-[2-(2-thienyl)vinyl]pyrazine 1-Oxide (16, R = 2-Thienyl). A solution of 2.05 g (5 mmol) of the phosphorane **10** and 2.2 g (20 mmol) of thiophene-2-carboxaldehyde in 50 ml of THF was heated under reflux for 2 days and then evaporated to dryness under reduced pressure. The residue was triturated for 1 h at room temperature with 50 ml of benzene and then filtered to give 1.1 g (89%) of **16**, R = 2-thienyl, as a light brown solid, mp 229–230 °C dec. Recrystallization from THF gave light tan crystals, mp 232–233 °C dec.

Anal. Calcd for $C_{11}H_8N_4OS$: C, 54.10; H, 3.28; N, 22.95; S, 13.11. Found: C, 53.93; H, 3.46; N, 22.66; S, 12.89.

2-Amino-3-cyano-6-(2-carboxyvinyl)pyrazine 1-Oxide (16, R = COOH). A solution of 2.05 g (5 mmol) of the phosphorane **10** and 1.1 g (15 mmol) of glyoxylic acid in 50 ml of dry THF was heated under reflux for 20 min and then evaporated to dryness. The residue was treated as described above to give 0.99 g (96%) of a bright yellow solid, mp >234 °C dec, which appeared to be a mixture of approximately 50% trans and 50% cis isomers.

Anal. Calcd for $C_8H_6N_4O_3$: C, 46.60; H, 2.93; N, 27.18. Found: C, 46.34; H, 3.18; N, 27.28.

2-Amino-3-cyano-6-[2-(3-pyridyl)vinyl]pyrazine 1-Oxide (16, R = 3-Pyridyl). In the same manner as described above, a solution of 2.05 g of the phosphorane **10** and 1.61 g of nicotinaldehyde was condensed in THF to give 1.04 g (87%) of **16**, R = 3-pyridyl, as fine yellow crystals, mp 258 °C dec. The product could be recrystallized from tetrahydrofuran–benzene without change in the melting point.

Anal. Calcd for $C_{12}H_9N_5O$: C, 60.24; H, 3.79; N, 29.28. Found: C, 59.97; H, 4.02; N, 29.12.

2-Amino-3-cyano-6-(3,4-dichlorostyryl)pyrazine (14, R = 3,4-$Cl_2C_6H_3$). A solution of 10.0 g of the phosphorane **7** and 8.8 g of 3,4-dichlorobenzaldehyde in 300 ml of THF was stirred at room temperature for 24 h and then worked up as described above, yield, 5.9 g (80%), mp 249–250 °C.

Anal. Calcd for $C_{13}H_8N_4Cl_2$: C, 53.64; H, 2.75; N, 19.24; Cl, 24.39. Found: C, 53.73; H, 3.03; N, 19.14; Cl, 24.06.

2-Amino-3-cyano-6-(3,4-methylenedioxystyryl)pyrazine [14, R = 3,4-$(OCH_2O)C_6H_3$]. Condensation of 10.0 g of the phosphorane **7** with 11.4 g of piperonal, under the conditions described above, gave 5.82 g (86%) of **14**, R = 3,4-$(OCH_2O)C_6H_3$, as a bright yellow powder, mp 273–274 °C. The analytical sample was obtained by recrystallization from DMF without change in the melting point.

Anal. Calcd for $C_{14}H_{10}N_4O_2$: C, 63.15; H, 3.79; N, 21.04. Found: C, 63.09; H, 4.01; N, 21.00.

2,4-Diamino-7-methylpteridine 8-Oxide (13). Guanidine hydrochloride (0.48 g, 5 mmol) was added to a solution of 0.665 g (12.3 mmol) of sodium methoxide in 30 ml of absolute methanol, and the precipitated sodium chloride was removed by filtration. To the filtrate was added 0.50 g (3.34 mmol) of 2-amino-3-cyano-6-methylpyrazine 1-oxide and the reaction mixture was heated under reflux for 18 h. It was then cooled to room temperature, and the precipitated solid was collected by filtration, washed with methanol, and recrystallized from DMF to give 0.53 g (83%) of a bright yellow solid, mp 295–296 °C dec.

Anal. Calcd for $C_7H_8N_6O$: C, 43.75; H, 4.20; N, 43.73. Found: C, 43.84; H, 4.20; N, 43.47.

The following pteridines were prepared in the same manner from guanidine and the appropriate 2-amino-3-cyano-6-substituted pyrazine (or its 1-oxide).

2,4-Diamino-7-methylpteridine (12): 81% yield, mp (from DMF) 347 °C dec. This compound was identical in all respects (ir, uv, NMR, and TLC) with an authentic sample of 2,4-diamino-7-methylpteridine prepared by the method of Seeger.[6]

Anal. Calcd for $C_7H_8N_6$: C, 47.42; H, 4.58; N, 47.71. Found: C, 47.75; H, 4.75; N, 47.69.

2,4-Diamino-7-styrylpteridine 8-Oxide (17, R = C_6H_5): 88% yield, mp (from DMF) 273–274 °C dec.

Anal. Calcd for $C_{14}H_{12}N_6O$: C, 59.99; H, 4.32; N, 29.99. Found: C, 59.76; H, 4.29; N, 29.80.

2,4-Diamino-7-styrylpteridine (15, R = C_6H_5): 89% yield, mp (from DMF) 303 °C dec.

Anal. Calcd for $C_{14}H_{12}N_6$: C, 63.62; H, 4.58; N, 31.80. Found: C, 63.43; H, 4.77; N, 31.86.

2,4-Diamino-7-(2-methoxypropyl)pteridine (18): 60% yield, mp (from methanol) 223–224 °C dec.

Anal. Calcd for $C_{10}H_{14}N_6O$: C, 51.27; H, 6.02; N, 35.88. Found: C, 51.26; H, 6.05; N, 35.73.

2,4-Diamino-7-(3,4-dichlorostyryl)pteridine (15, R = 3,4-$Cl_2C_6H_3$): 79.5% yield, mp (from trituration with hot DMF) 338–339 °C dec.

Anal. Calcd for $C_{14}H_{10}N_6Cl_2$: C, 50.45; H, 3.00; N, 25.22; Cl, 21.32. Found: C, 50.36; H, 3.25; N, 25.24; Cl, 21.47.

2,4-Diamino-7-(3,4-methylenedioxystyryl)pteridine [15, R = 3,4-$(OCH_2O)C_6H_3$]: 91% yield, mp (from trituration with hot methanol) 334–335 °C dec.

Anal. Calcd for $C_{15}H_{12}N_6O_2$: C, 58.44; H, 3.92, N, 27.26. Found: C, 58.47; H, 3.94; N, 27.51.

Registry No.—**1**, 58091-59-1; **2**, 58091-60-4; **3**, 58091-61-5; **4**, 58091-62-6; **5**, 58091-63-7; **6**, 58091-64-8; **7**, 58091-65-9; **8**, 58091-66-0; **9**, 58091-67-1; **10**, 58091-68-2; **11**, 58091-69-3; **12**, 4215-07-0; **13**, 58091-70-6; **14** (R = Me), 58091-71-7; **14** (R = Ph), 58091-72-8; **14** (R = 3,4-diClC_6H_3), 58091-73-9; **14** [R = 3,4-$(OCH_2O)C_6H_3$], 58091-74-0; **15** (R = Ph), 58091-75-1; **15** (R = 3,4-diClC_6H_3), 58091-76-2; **15** [R = 3,4-$(OCH_2O)C_6H_3$], 58091-77-3; **16** (R = Me), 58091-78-4; **16** (R = Ph), 58091-79-5; **16** (R = CH_2OH), 58091-80-8; **16** (R = 2-thienyl), 58091-81-9; *cis*-**16** (R = CO_2H), 58091-82-0; **16** (R = CO_2H), 58091-83-1; **16** (R = 3-pyridyl), 58091-84-2; **17** (R = Ph), 58091-85-3; **18**, 58091-86-4; aminomalonitrile tosylate, 5098-14-6; α-oximino-β-chloropropionaldehyde, 4815-01-4; α-oximino-β-chlorobutyraldehyde, 4749-21-7; α-oximino-β-chlorocaproaldehyde, 58091-87-5; 2-nitroso-3-chlorocyclohexanone dimer, 58091-89-7; 2-oximino-3-chlorocyclohexanone, 58091-90-0; triphenylphosphine, 603-35-0; benzaldehyde, 100-52-7; acetaldehyde, 75-07-0; glycolaldehyde, 141-46-8; thiophene-2-carboxaldehyde, 98-03-3; glyoxylic acid, 298-12-4; nicotinaldehyde, 500-22-1; 3,4-dichlorobenzaldehyde, 6287-38-3; piperonal, 120-57-0; guanidine HCl, 15827-40-4.

References and Notes

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(2) This work was supported by a grant (CA-12876) to Princeton University from the National Cancer Institute, National Institutes of Health, Public Health Service.
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Covalent Amination. Substituent Effects on the Site of Addition of Ammonia to Quaternized Pyridines and Pyrazines

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1,3-Disubstituted pyridinium ions react completely at about −40 °C with ammonia to give covalent amination products. Addition occurs at C-6 when the C-3 group is $CONH_2$, CO_2CH_3, CF_3, or $COCH_3$. Addition at C-2 results when the 3 substituent is Cl or I, and a mixture is found for the 3-CN compound. Parent 1-methyl- and 1-benzylpyridinium ions do not yield 2 adducts unless powdered KOH is added to neutralize ammonium ion. 1-Methoxypyridinium ions at −50 °C give adducts which open to 5-amino-2(*cis*),4(*trans*)-pentadienal oxime *O*-methyl ether. 1-Methyl-3-substituted pyrazinium ions react at the 2 position when the substituent is Cl or CH_3O and at the 6 position in the $CONH_2$ case. 1-Methylpyrazinium ion first forms a 2 adduct and then a 2,3 diadduct.

Many heteroaromatic molecules are known to undergo "covalent hydration" reactions in aqueous solution.[1] In the presence of acid or base, solvent adds to an annular carbon atom to form a covalently bonded hydrate. Quaternization of an annular nitrogen atom greatly promotes such a reaction with water; the product, a "pseudobase", may be in equilibrium with its ring-opened carbonyl tautomer.[2,3] The influence of structure on the position of hydration as well as on rates and equilibria involving aromatic material, its hydroxy adduct, and ring-opened isomer has long intrigued chemists.[4] Recognition of the existence of covalent hydrates in solution has allowed otherwise puzzling chemistry to become understandable.

Covalent amination involving ammonia as solvent has been a largely overlooked counterpart to hydration. No doubt this primarily is a consequence of the greater difficulty in handling ammonia with its low boiling point, −33 °C. However, NMR now makes examination of ammonia reaction mixtures at a variety of temperatures easy, if not routine, and provides access to an area of investigation which is likely to be as rewarding as that involving aqueous solutions.

Already, recognition of the covalent amination process is providing new insight into reactions of heteroaromatic molecules in ammonia. Many simple heteroaromatic molecules such as quinoline,[5] isoquinoline,[5] the three diazines,[6] and their halogenated derivatives[7] react rapidly and completely with ammonia containing amide ion to give anionic σ complexes in which an amino group is bonded to an annular carbon atom. This discovery makes understandable the surprising rearrangement reactions involving amide ion in ammonia and the halogenated derivatives of the heteroaromatic compounds.[8–10]

We now report the results of reactions involving quaternized heteroaromatic molecules and ammonia free of amide ion. Adducts having an amino group bonded to an annular carbon atom are produced in a reaction which is the amination counterpart to pseudobase formation in aqueous solution. Two ring systems, quaternized pyridines and pyrazines, are extensively studied. The site of amination is found to depend on substituents bonded to carbon. In some cases a single adduct is observed, in others, mixtures of adducts. Even diadducts are formed. Ring-opened isomers may be observed as well. The present study supplements our preliminary communication which revealed that many kinds of heterocyclic rings containing a quaternized nitrogen atom undergo covalent amination in ammonia.[11] The accompanying article shows that sulfur and carbon nucleo-

Table I. Chemical Shifts (τ) and Coupling Constants (Hz) for 1,5-Disubstituted 2-Amino-1,2-dihydropyridines (I)

Compd	1-Subst	5-Subst	H-2	H-3	H-4	H-6	Other	$J_{2,3}$	$J_{3,4}$	$J_{4,6}$	J_{CH_2}
Ia	CH_3	$CONH_2$	5.19	4.80	3.34	2.58	CH_3, 6.78	4.5	10	2	
b	CH_3	CO_2CH_3	5.10	4.79	3.51	2.48	NCH_3, 6.72; OCH_3, 6.33	4.5	10	1.5	
c	CH_3	CF_3	5.19	4.69	3.84	3.01	CH_3, 6.80	5	9.5	2	
d	$CH_2C_6H_5$	$CONH_2$	5.46	4.92	3.36	2.36	CH_2, 4.97, 5.48; C_6H_5, 2.58	4.5	10	1.5	15
e	$CH_2C_6H_4$-NO_2-*p*	$CONH_2$	5.31	4.74	3.31	2.36	CH_2, 4.72, 5.27; C_6H_4, 1.70, 2.28	4.5	9.5	1.5	16.5
f	$CH_2C_6H_5$	$COCH_3$	5.22	4.74	3.35	2.18	CH_2, 4.92, 5.32; C_6H_5, 2.59; CH_3, 7.87	4	10	2	15
g	CH_3	CN	5.13	4.72	3.81	2.52	CH_3, 6.76	4.5	9.5	1.5	
h	$CH_2C_6H_5$	CN	~5.2	~4.8	3.83	2.32	CH_2, 4.9, 5.4; C_6H_5, 2.55	4.5	9.5	1.5	15
i	$CH_2C_6H_4$-NO_2-*p*	CN	5.36	4.71	3.84	2.23	CH_2, 4.8, 5.2; C_6H_4, 1.8, 2.3	4.5	10	1.5	~16

Table II. Chemical Shifts (τ) and Coupling Constants (Hz) for 1,3-Disubstituted 2-Amino-1,2-dihydropyridines (II)[a] and for 1-Substituted 2-Amino-1,2-dihydropyridines (III)[a]

Compd	1-Subst	3-Subst	H-2	H-4	H-5	H-6	Other	$J_{4,5}$	$J_{5,6}$	Other
IIa	CH_3	Cl	5.25	3.75	5.21	3.67	CH_3, 6.95	6.5	6.5	
b	CH_3	I	5.39	3.59	5.29	3.42	CH_3, 6.97	7	6.5	
c	$CH_2C_6H_5$	I	5.26	3.39	5.18	3.35	CH_2, 5.19, 5.59; C_6H_5, 2.55	6.5	6.5	J_{CH_2} = 15
d	CH_3	CN	~5	3.09	~5	2.97	CH_3, 6.76	7	6	
e	$CH_2C_6H_5$	CN	5.33	3.01	~4.9	2.90	CH_2, 4.9, 5.4; C_6H_5, 2.55	~6	~6	J_{CH_2} ~ 15
f	$CH_2C_6H_4$-NO_2-*p*	CN	5.23	2.99	4.87	2.86	CH_2, 4.8, 5.2; C_6H_4, 1.8, 2.3	7	6.5	J_{CH_2} ~ 16
g	OCH_3	$CONH_2$	4.56	3.02	4.89	3.02	CH_3, 6.25	6.5	6.5	
IIIa	CH_3[b]	H	~5.4	3.80	5.19	3.72	CH_3, 6.95	5.5	7	$J_{2,3}$ = 5.0; $J_{3,4}$ = 9.5; $J_{3,5}$ = 1.5; $J_{3,6}$ = 1
b	$CH_2C_6H_5$[c]	H	5.34	3.90	4.96	3.61	CH_2, 5.19, 5.64; C_6H_5, 2.59	5.5	7	$J_{2,3}$ = 5.0; $J_{3,4}$ = 9.5; J_{CH_2} = 15.5
c	OCH_3[d]	H	5.12	3.97	5.03	3.45	CH_3, 6.30	5.2	7.5	$J_{2,3}$ = 5.0; $J_{3,4}$ = 9.8; $J_{3,5}$ = 1.8; $J_{3,6}$ = 0.8

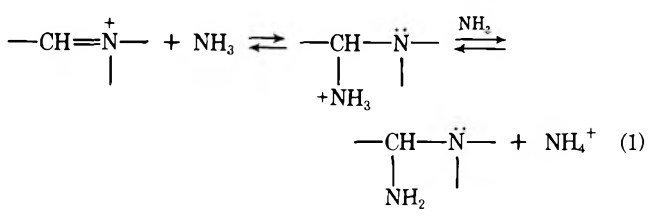
[a] $J_{2,4} \leq 1$ Hz. [b] H-3, τ 4.79; $J_{2,4}$ = 1.5 Hz. [c] H-3, τ 4.81. [d] H-3, τ 4.35; $J_{2,4}$ = 1.3 Hz.

philes can successfully compete with ammonia to produce new adducts.[12] Another investigation involves kinetic studies.[13]

Results and Discussion

Addition of a nucleophile to an aromatic ring to form a covalent, nonaromatic adduct can easily be detected by NMR. The adduct spectrum is characterized by upfield shifts; shieldings as large as 3–4 ppm are observed for the newly formed tetrahedral center. In many instances spectra were recorded over a range of temperatures; generally, good quality spectra were obtained over the interval −40 to 0 °C.

The nucleophile in the addition reactions must be ammonia and not the anion of quaternized compound, since halide and perchlorate salts give rise to the same spectrum. Spin coupling between the amino group of adduct and an adjacent proton usually was not observed. Ammonium ion is liberated in the addition reaction, eq 1; this acid catalyzes signal averaging between the protons of the amino group and solvent.[14]



(1)

When a prochiral benzyl or *p*-nitrobenzyl group was bonded to the annular nitrogen atom in place of a methyl group, the methylene protons became diastereotopic on adduct formation. Addition of ammonia to the ring produces a chiral carbon atom which maintains its chirality long enough to make the methylene protons diastereotopic. That is, a reaction leading to the loss of chirality, for example, by the reverse of addition, must be slow. The pseudo-first-order rate constant for such a dissociation must be less than about 10^2 s^{-1}.[15] Such amino group turnover has been shown in the case of adducts formed by the addition of ammonia to 2-benzylisoquinolinium ions to be accelerated by temperature and by ammonium ion.[13]

The main features of NMR spectra of adducts are given in tables; analyses of these spectra and those of by-products will be found in the supplement (see paragraph at end of paper regarding supplementary material).

Pyridinium Ions. Ammonia can add to positions 2, 4, or 6 of a 1,3-disubstituted pyridinium ion to form a carbon–nitrogen σ bond and give adducts which are amino dihydro compounds.[16] Addition to either the 2 or 6 position of the ion was observed, the site of addition being dependent upon the identity of the substituent at the 3 position of the ion. Heretofore, only addition of ammonia to the 6 position

Table III. Chemical Shifts (τ) and Coupling Constants (Hz) for 5-Amino-2,4-pentadienal Oxime *O*-Methyl Ether (IV) and Derivatives (V)

Compd	Subst	H-1	H-2	H-3	H-4	H-5	$NOCH_3$	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$
IV	H	1.74	4.66	3.56	4.29	3.22	6.20	11	10.5	12	12.5
Va	2-$CONH_2$	1.64		2.29	4.04	2.67	6.15			13	12
b	2-CO_2^-	1.63		2.62	3.50	2.94	6.17			12	12.5
c	3-CO_2CH_3[c]	1.79	3.91	(CH_3O) (6.13)[a,b]	4.43	2.91	6.19[b]	10.5			12.5

[a] Ester group. [b] Assignments may be interchanged. [c] $J_{1,3}$ = 1.5 Hz.

Table IV. Chemical Shifts (τ) and Coupling Constants (Hz) for 1-Methyl-2-amino 3-Substituted 1,2-Dihydropyrazines (VI) and 1-Methyl-2-amino-1,2-dihydropyrazine (VIII)

Compd	3-Subst	H-2	H-5	H-6	NCH_3	Other	$J_{2,6}$	$J_{5,6}$	Other
VIa	CH_3	5.58	4.20	*a*	7.00	CH_3, 7.95, 8.10			
b	Cl	5.21	4.16	3.55	6.93		1	4.5	
c	CH_3O	5.53	4.28	4.00	7.06	CH_3O, 6.28	1.5	4.5	
VIII[b]	H	5.46	4.04	3.70	6.93	H-3, 3.08	1	5	$J_{2,3}$ = 4 $J_{3,6}$ < 1

[a] A methyl group is bonded to position 6.

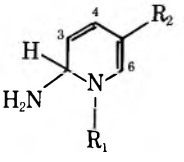
Table V. Chemical Shifts (τ) and Coupling Constants (Hz) for 1-Methyl-2-amino-5-carbamoyl-1,2-dihydropyrazine (VII) and 1-Methyl-2,3-diamino 5-Substituted 1,2,3,4-Tetrahydropyrazines (IX)

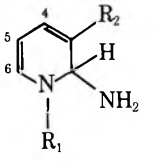
Compd	5-Subst	H-2	H-3	H-6	NCH_3	$J_{2,3}$	$J_{2,6}$	Other
VII	$CONH_2$	5.32	3.10	2.76	6.77	3.5	1.5	$J_{3,6}$ = 1
IXa[a]	H[b]	6.44	6.19	5.16	7.39	3	1.5	$J_{5,6}$ = 6; $J_{3,5}$ = 1
b[c]	$CONH_2$	6.21	6.05	3.45	7.03	~3	~1.5	

[a] Assignments for positions 2 and 3 may be interchanged as well as those for 5 and 6. [b] H-5, τ 4.67. [c] Low intensity prevents accurate analysis.

of such ions was observed; 3 substituents employed in the earlier study included SO_2CH_3, NO_2, or $COCH_3$.[11]

Numbering of annular positions of adduct I is different from that of the corresponding starting material. Positions





	R_1	R_2
Ia	CH_3	$CONH_2$
b	CH_3	CO_2CH_3
c	CH_3	CF_3
d	$CH_2C_6H_5$	$CONH_2$
e	$CH_2C_6H_4NO_2$-*p*	$CONH_2$
f	$CH_2C_6H_5$	$COCH_3$
g	CH_3	CN
h	$CH_2C_6H_5$	CN
i	$CH_2C_6H_4NO_2$-*p*	CN

	R_1	R_2
IIa	CH_3	Cl
b	CH_3	I
c	$CH_2C_6H_5$	I
d	CH_3	CN
e	$CH_2C_6H_5$	CN
f	$CH_2C_6H_4NO_2$-*p*	CN
g	OCH_3	$CONH_2$

	R_1	R_2
IIIa	CH_3	H
b	$CH_2C_6H_5$	H
c	OCH_3	H

in starting material and product are numbered in opposite sequences so that the substituent at position 3 in starting material corresponds to position 5 in adduct. Thus, when ammonia adds to the 6 position of aromatic ion, the amino group is located at position 2 of product. This confusing numbering arises in the case of pyridine adducts I and also pyrazine adduct VII.

When the substituent at position 3 of the ion was a strongly electron-attracting group such as $CONH_2$, CO_2CH_3, CF_3, or $COCH_3$, ammonia added to the 6 position of the ion to give a single adduct which is a 1,5-disubstituted 2-amino-1,2-dihydropyridine (Ia–f), Table I. Two observations support the structural assignment for I. (a) The ring proton at highest field, likely to be that associated with the newly formed tetrahedral site, shows an approximately 4.5 Hz coupling constant. A constant of this magnitude must be associated with coupling to an adjacent proton. Addition to the 2 position of the ion would give a proton bonded to a tetrahedral center with a much smaller coupling constant, since there is no adjacent proton. (b) The large 9.5–10 Hz coupling constant eliminates the possibility that the nucleophile added to position 4 of the ion. Known 4 adducts do not show coupling constants this large.[16,17]

Ammonia added to the 2 position of 1-substituted 3-chloro- or 3-iodopyridinium ion to give a new group of adducts, IIa–c, Table II. Characterizing such adducts are two moderately large coupling constants, each about 6.5 Hz. The ring proton at highest field shows only a small coupling, <1 Hz, indicating addition to position 2. A minor byproduct observed in the 1-benzyl-3-iodopyridinium ion reaction may be the 6 adduct.

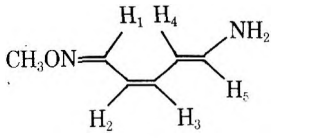
The 3-cyanopyridinium ion is especially interesting because it is converted to at least two adducts at about −40 °C. The major product (Ig, Ih, or Ii) results from the addition of ammonia to position 6 of the ion; some nucleophile also adds to position 2 (IId, IIe, or IIf). Careful analysis at 100 MHz of the mixture produced from the 1-*p*-nitrobenzyl substrate revealed the presence of a third component, perhaps the 4 adduct, but signal overlap precludes firm identification.

Neither 1-methyl- nor 1-benzylpyridinium ion underwent detectable covalent amination in neutral ammonia. However, when powdered KOH was added, adducts IIIa and IIIb, Table II, resulting from reaction of the heteroaromatic cation at the 2 position were observed. The presence of five nonequivalent protons indicates that addition to a 2 and not to a 4 position took place. The added strong base[18]

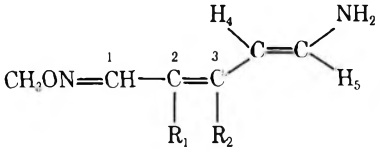
neutralized the ammonium ion acid formed by the addition reaction, eq 1, driving addition to apparent completion.

1-Methoxypyridinium ion is completely converted to adduct IIIc on addition to ammonia at −50 °C. Addition of KOH to promote adduct formation is unnecessary. Evidently, the *N*-methoxy group exerts an electron-withdrawing effect[19] which destabilizes the cation and thereby facilitates addition to the ring.

Allowing the adduct of 1-methoxypyridinium ion to stand at −50 °C or to warm resulted in the formation of a new product. Ring opening gives 5-amino-2(*cis*),4(*trans*)-pentadienal oxime *O*-methyl ether (IV), Table III. At −50 °C the half-life for this conversion is roughly 2 h. Strong evidence for a ring-opened structure is found in the presence of an aldoxime signal at τ 1.74 and in the large coupling constants. Although signals for an NH_2 group are observed, they are broad and their shifts are highly temperature dependent. Since the signals of the amino group are broad we are unable to determine coupling constants for this ABX system[20] and so we are unable to decide whether amino group rotation is "free" or restricted.[21] The cis–trans stereochemistry is suggested by the 10.5 and 12.5 Hz coupling constants, respectively. The other large coupling constants suggest s-trans conformations.[22] The stereochemistry is likely to be that given by IV.



IV



Va, $R_1 = CONH_2$; $R_2 = H$
b, $R_1 = CO_2^-$; $R_2 = H$
c, $R_1 = H$; $R_2 = CO_2CH_3$

Results for a 1-methoxy 3-substituted pyridinium ion are especially interesting. Ammonia could add to either a 2 or 6 position of the ion and either adduct could ring open by undergoing cleavage of the bond between the annular nitrogen and the tetrahedral carbon atoms. The results for 1-methoxy-3-carbamoylpyridinium ion are intriguing. At −60 °C adduct and ring-cleaved materials clearly are present; at −45 °C essentially only cleaved compound is found. However, the observed adduct is not the precursor of ring-opened material. Observed adduct must rearrange to a second isomer which is not present in detectable quantity; the second adduct must ring cleave faster than the first.

The observable adduct from 1-methoxy-3-carbamoylpyridinium ion is produced by the addition of ammonia to the 2 position of the ion to give IIg. The coupling constants of IIg, Table II, are similar to those of other adducts having structure II and different from those of I. This similarity is the basis for the structural assignment. Addition to the 2 position stands in marked contrast to addition to 6 which is observed for all the other 3-carbamoyl compounds considered here.

The ring-cleaved product from 1-methoxy-3-carbamoylpyridinium ion is likely to have structure Va, Table III, which results from an adduct formed by addition of ammonia to the 6 position of the ion. The proposed structure is based on the belief that the aldoxime proton is more deshielded than any olefinic proton[22,23] and that the magnitude of spin coupling to this proton allows isomeric structures to be distinguished. The most deshielded proton in the ring cleaved material is a sharp singlet; its chemical shift is very similar to that for IV and similar oximes.[22,24,25] The singlet results because a carbamoyl group rather than a proton is bonded to the adjacent carbon atom. If observed adduct IIg were the precursor to cleaved material, then the oxime proton of the isomeric structure would be a doublet having a large coupling constant due to the presence of a proton on the adjacent carbon; the substituent would be bonded to position 4 of V. That end of Va bearing the amino group has a trans double bond; the coupling constant is 12 Hz. Stereochemistry about the other carbon–carbon double bond cannot be assigned, spin coupling is not possible due to the presence of the carbamoyl group. Although some small signals of another component were present in the spectrum they were so low in intensity that they could not be identified as being due to the adduct giving rise to Va. From these results it appears that ring opening, like nucleophilic addition, is strongly substituent dependent.

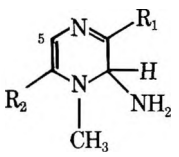
Ring-opened materials arising from two other substituted 1-methoxypyridinium ions were observed. In one, the substituted ion contained a carboxylate ion group at position 3, the other a 4-carbomethoxy substituent. In neither case was the intensity and quality of the spectrum of the precursor adduct sufficient for conclusive identification. Again, the 3-substituted ion gave rise to a ring-cleaved product (Vb) which resulted from the adduct produced by the addition of ammonia to position 6 of the ion. Only one ring-cleavage product is possible from the 4-substituted ion since the 2 and 6 positions are equivalent. The double bond about carbon atoms 4 and 5 of both Vb and Vc must be trans as in the case of IV. The propensity of 1-alkoxypyridinium ion adducts to ring open[24-27] is said to be due to the stability of the oxime functional group.[24]

Adducts having structure I after standing at room temperature were converted to the corresponding 3-substituted pyridine. Although dealkylation by nucleophilic attack on the side chain is a possible route to such products, it seems likely that a less direct pathway is followed. This involves ring opening of an adduct followed by ring closure so as to incorporate the nitrogen atom of the primary amino group into the ring; this is followed by expulsion of an alkylamine. Such a sequence has been demonstrated for other covalent adducts using isotopically labeled nitrogen.[28]

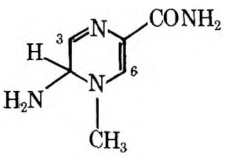
Pyrazinium Ions. Ammonia was observed to add either to the 2 position of a 3-substituted 1-methylpyrazinium ion to give a 1-methyl-2-amino 3-substituted 1,2-dihydropyrazine (VI) or to the 6 position of the ion to yield a 1-methyl-2-amino 5-substituted 1,2-dihydropyrazine (VII). Structural assignments are more difficult with pyrazine than with pyridine adducts, owing to smaller and fewer coupling constants associated with the presence of a second annular nitrogen atom. Model compounds were employed to aid assignments; one had a methyl group bonded to position 6, another a deuterium atom at position 2. A detailed analysis is found in the supplement.

Ammonia added to the 2 position of those ions having at the 3 position a CH_3, Cl, or CH_3O substituent to give VIa, VIb, or VIc. However, addition to the 6 position of the ion took place when the 3 substituent was $CONH_2$ (VII). Adducts VI having two adjacent sp^2-hybridized protons have a larger coupling constant (4.5 Hz) than VII (3.5 Hz) where the adjacent protons are sp^2 and sp^3. Moreover, the high-field proton which is associated with the tetrahedral ring site is highly spin coupled in VII but not in VI.

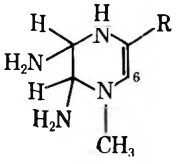
Interestingly, 1-methylpyrazinium ion is completely con-



VIa, $R_1 = R_2 = CH_3$
b, $R_1 = Cl$; $R_2 = H$
c, $R_1 = CH_3O$; $R_2 = H$
VIII, $R_1 = R_2 = H$



VII



IXa, R = H
b, R = $CONH_2$

verted to adduct VIII at −50 °C. Comparison of this result with that for 1-methylpyridinium ion which does not give an adduct[11] emphasizes the conclusion that electron-withdrawing groups or atoms facilitate adduct formation. The assignment placing the signal of H-3 at lower field than H-6 is based on coupling constants, Table IV. The minor component in this sample becomes the major product at higher temperatures; it has diadduct structure IXa.

At −28 °C a diadduct spectrum was found for 1-methylpyrazinium ion; none of the monoadduct VIII appeared to be present. Relative to VIII, all signals for IXa are shifted upfield; two, instead of the usual one, annular proton signals undergo large shieldings, Table V. No change in the spectrum was observed on warming the sample to −10 °C. Since IXa has two chiral carbon atoms, diastereomers are possible. However, we are unable to decide whether the sample consists of a single pair of enantiomers or whether rapidly equilibrating diastereomers are present. Therefore, no stereochemistry is to be implied by structure IXa.

A diadduct of 1-methyl-3-carbamoylpyrazinium ion probably is present at about 20 °C. However, this diadduct, IXb, is a minor component and the quality of the signal at τ 6.21 was not good enough to yield coupling constants and so the assignment in Table V is tentative.

Diaddition to a pyrazine ring is not unprecedented.[29,30] Under similar conditions the benzolog of diadduct IXa is produced.[11] Moreover, diaddition to a series of pteridines in ammonia has been reported.[31]

General. Significantly, repetition of reactions which gave rise to mixed products produced essentially the same product distributions. Reversibility of the amination reactions for several pyridines and pyrazines was demonstrated by regeneration of starting materials in high yields. Details are given in the Experimental Section. Preliminary experiments reveal that isolation of amino adducts in high yields will not be easy.

Our situation dealing with amino adduct formation is reminiscent of that a few years ago regarding the generation of anionic ("Meisenheimer") σ complexes just prior to the application of fast reaction techniques.[32] It is not unlikely that others who employ faster mixing–measuring methods will see other adducts before they rearrange to those observed by us. Interpretation of our results in terms of kinetic and thermodynamic control of addition is premature.

Covalent amination studies have considerable potential. Many more adducts will be found. The wide array of adduct structures and the ease with which their formation may be studied offer a new dimension to investigations involving the addition of nucleophiles to aromatic rings.

Experimental Section

Most compounds (perchlorate and/or iodide salts) were available from other studies.[33] A Varian A-60A spectrometer equipped with a V-6040 variable temperature controller or an XL-100 was employed. The spectra of IIIc and IV were simulated using a computer program (LAMP 2) kindly supplied by Dr. R. W. King. Spin decoupling of H-1 and H-2 of IV was carried out on the XL-100 to check signal assignments. Deuterated derivatives of IIIc and IV were prepared from 1-methoxypyridinium-2,6-d_2 ion. The general method of preparing samples for NMR analysis has been described.[11]

Preparation of 1-*p*-Nitrobenzyl-3-cyanopyridinium Bromide. A mixture of 2.6 g (25 mmol) of 3-cyanopyridine and 5.4 g (25 mmol) of *p*-nitrobenzyl bromide dissolved in 20 ml of acetonitrile was heated at reflux for 1 h. Crystalline product was removed from the cooled mixture and recrystallized from 95% ethanol to give 3.6 g (11.3 mmol, 45%) of product: mp 227–228 °C; NMR (D_2O) τ 0.32 (H-2), 0.62 (H-6), 0.85 (H-4), 1.52 (H-5), 1.9 (phenylene), 3.80 (CH_2), $J_{2,4} \sim 1.5$, $J_{2,6} \sim 1.5$, $J_{4,5} = 8$, $J_{4,6} \sim 1.5$, $J_{5,6} = 6$ Hz.

Anal. Calcd for $C_{13}H_{10}N_3O_2Br$: C, 48.77; H, 3.15; N, 13.13. Found: C, 48.73; H, 3.21; N, 13.20.

Preparation of 1-Methyl-3-chloropyrazinium-2-*d* Iodide. To 1.5 g (5.8 mmol) of 1-methyl-3-chloropyrazinium iodide dissolved in 4 ml of D_2O was added 0.20 ml of 1.0 M CH_3COOD and 0.20 ml of 1.0 M sodium acetate in D_2O. The solution was heated at 75 °C for 160 min; during this time five additional 1-ml aliquots of the acetate solution were added to keep the acidity of the solution approximately constant. The cooled sample then was acidified with concentrated HI, filtered, and freeze dried. The resultant solid was recrystallized from 95% ethanol to afford 1.05 g (4.1 mmol, 70%) of product containing 80% D (NMR) at the 2 position.

Recovery of Starting Materials from Amination Reaction Mixtures. A. Pyridinium Salts. To 0.20 g of either 1-methyl-3-carbamoyl- or 1-methyl-3-carbomethoxypyridinium iodide cooled in an acetone–dry ice bath was added 2 ml of ammonia. The sample was allowed to warm to −33 °C and held at this temperature for 5 min and then recooled with the dry ice mixture. After adding 5 ml of ether to the cold mixture, the sample was allowed to warm to room temperature. Crystalline amide (99%) was removed by filtration and compared with authentic starting material. Recovery in the case of ester amounted to approximately 86%; NMR analysis of the sample in D_2O showed the sample to consist of 30% starting material and 70% of amide solvolysis product, H-2 (τ 0.57, ester, and τ 0.71, amide) and OCH_3 (τ 5.92) serving to indicate composition.

B. Pyrazinium Salts. To 0.060 g of 1-methyl-, 1-methyl-3-chloro-, or 1-methyl-3-carbamoylpyrazinium iodide cooled in an acetone–dry ice bath was added about 0.5 ml of ammonia; the mixture was allowed to warm to −33 °C. After recooling to −78 °C, solvent was removed under vacuum. To the first two samples 0.5 ml of 4 M CF_3CO_2H in methanol and 0.10 ml of 1.0 M CH_3CO_2H in methanol (internal standard) were added to the residue at −78 °C; D_2O was the solvent in the case of the amide. Room-temperature NMR spectra indicated that at least 70% of the starting material had been regenerated. Comparison of the NMR spectra of the chloro sample with that of 1-methyl-3-aminopyrazinium ion indicated that no significant aminodechlorination had taken place.

Registry No.—Ia, 58219-05-9; Ib, 58219-06-0; Ic, 58219-07-1; Id, 58219-08-2; Ie, 58219-09-3; If, 58219-10-6; Ig, 58219-11-7; Ih, 58219-12-8; Ii, 58219-13-9; IIa, 58219-14-0; IIb, 58219-15-1; IIc, 58219-16-2; IId, 58219-17-3; IIe, 58219-18-4; IIf, 58219-19-5; IIg, 58219-20-8; IIIa, 58219-21-9; IIIb, 58219-22-0; IIIc, 58219-23-1; IV, 58219-24-2; Va, 58219-25-3; Vb, 58219-26-4; Vc, 58219-27-5; VIa, 58219-28-6; VIb, 58219-29-7; VIc, 58219-30-0; VII, 58219-31-1; VIII, 58219-32-2; IXa, 58219-33-3; IXb, 58219-34-4; 1-*p*-nitrobenzyl-3-cyanopyridinium bromide, 58219-35-5; 3-cyanopyridine, 100-54-9; *p*-nitrobenzyl bromide, 100-11-8; 1-methyl-3-carbamoylpyridinium iodide, 6456-44-6; 1-methyl-3-carbomethoxypyridinium iodide, 58219-36-6; ammonia, 7664-41-7; 1-methylpyrazinium iodide, 6277-35-6; 1-methyl-3-chloropyrazinium iodide, 34260-02-1; 1-methyl-3-carbamoylpyrazinium iodide, 58219-37-7; 1-methyl-3-carbamoylpyridinium ion, 3106-60-3; 1-methyl-3-carbomethoxypyridinium ion, 18899-18-8; 1-methyl-3-trifluoromethylpyridinium ion, 58091-56-8; 1-benzyl-3-carbamoylpyridinium ion, 16183-83-8; 1-*p*-nitrobenzyl-3-carbamoylpyridinium ion, 58219-38-8; 1-benzyl-3-acetylpyridinium ion, 16183-85-0; 1-methyl-3-cyanopyridinium ion, 15923-33-8; 1-benzyl-3-cyanopyridinium ion, 16183-87-2; 1-*p*-nitrobenzyl-3-cyanopyridinium ion, 58219-39-9; 1-methyl-3-chlo-

ropyridinium ion, 54560-55-3; 1-methyl-3-iodopyridinium ion, 54560-56-4; 1-benzyl-3-iodopyridinium ion, 58219-40-2; 1-methoxy-3-carbamoylpyridinium ion, 54212-29-2; 1-methylpyridinium ion, 694-56-4; 1-benzylpyridinium ion, 15519-25-2; 1-methoxypyridinium ion, 30718-14-0; 1,2,5-trimethylpyrazinium ion, 58091-57-9; 1-methyl-3-chloropyrazinium ion, 58219-41-3; 1-methyl-3-methoxypyrazinium ion, 58219-42-4; 1-methyl-3-carbamoylpyrazinium ion, 58091-58-0; 1-methylpyrazinium ion, 17066-96-5.

Supplementary Material Available. Additional information on side reactions and NMR interpretation (2 pages). Ordering information is given on any current masthead page.

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Competitive Addition of Carbon, Sulfur, and Nitrogen Nucleophiles to Quaternized Heteroaromatic Compounds in Liquid Ammonia

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Nitromethide and ethanethiolate ions when present as ammonium salts in liquid ammonia add to the 4 position of 1-methylpyridinium ion. Each anion adds to the 4 positions of 3-iodo- and 3-cyano-1-methylpyridinium ions, to the 6 position of 1,2,5-trimethylpyrazinium ion, and to the 1 positions of 2-benzylisoquinolinium and 2-benzylphthalazinium ions. Carbanion addition to the 4 position of 3-substituted 1-methylpyridinium ions having CH_3, $CONH_2$, $COCH_3$, CO_2CH_3, and CF_3 substituents and to the 2 position of 3-methoxy-1-methylpyridinium ion also was observed. Carbanion addition is complete except with the 1-methyl-, 1,3-dimethyl-, and 1-methyl-3-methoxypyridinium and 2-benzylphthalazinium ions; aromatic starting material is present in the case of the pyridinium ions while 1-amino adduct is present in the phthalazinium ion case. Amino and not carbon adducts are detected for 3-chloro- and 3-carbamoyl-1-methylpyrazinium ions. Thiolate ion adds to the 4 and 6 positions of 3-acetyl- and 3-carbomethoxy-1-methylpyridinium ions to give mixtures. 3-Carbamoyl-1-methylpyridinium ion adds thiolate ion at the 4 and 6 positions; interconversion is fast enough to make the mixture appear by NMR as a single adduct. Thiolate ion addition is complete except in the cases of 1-methyl- and 1-methyl-3-methoxypyridinium ions.

Many quaternized heteroaromatic molecules on addition to liquid ammonia rapidly and quantitatively add solvent at an annular carbon atom to yield amino dihydro derivatives.[1-4] We now report that nitromethide and ethanethiolate ions dissolved in ammonia successfully compete with solvent to give carbon and sulfur addition products. In these competition reactions aromatic substrates often are completely transformed to a carbon or sulfur addition product. However, the site of addition of the carbon and sulfur nucleophiles may be different from that of ammonia. Nitromethide ion was selected for study because it is readily formed from nitromethane in ammonia[5] and it seemed likely that successful competition with ammonia might result. Many quaternized heteroaromatic molecules are known to add nitromethide ion in hydroxylic solvent.[6-8] The high carbon affinity of sulfur nucleophiles[9] prompted the selection of ethanethiolate ion, which is known to add to aromatic compounds to form anionic σ complexes.[10]

Results and Discussion

Addition of Nitromethide Ion. Deprotonation of nitroalkanes by liquid ammonia is unusual. The extent of proton transfer from the carbon acid to ammonia increases with decreasing temperatures,[5] in contrast to deprotona-

Table I. Chemical Shifts (τ) and Coupling Constants (Hz) for Compounds Produced by the Addition of Nitromethide Ion[a]

Compd	H-α	H-2	H-4	H-5	H-6	Other	$J_{4,5}$	$J_{5,6}$	$J_{4,\alpha}$	Other
Ia	4.29	4.01	5.8[b]	5.6[b]	4.01	NCH_3, 7.15		7		
b	4.27	3.45	5.63	5.54	3.95	NCH_3, 7.10	4	7	7.5	
c	4.34	4.24	5.90	5.67	4.06	NCH_3, 7.19 CCH_3, 8.47	3.5	7.5	7.5	
d	4.24	2.95	5.56	5.25	3.79	NCH_3, 6.91	5	7.5	8	
e	4.51	2.51	5.69	4.86	3.85	NCH_3, 6.90 $COCH_3$, 7.87	4.5	7.5	6.5	
f	4.39	2.73	5.68	4.92	3.95	NCH_3, 6.92 OCH_3, 6.36	4.5	8	6.5	
g	4.26	3.19	5.63	5.19	3.91	NCH_3, 6.96	4.5	7.5	7	
h	4.17	2.90	5.62	5.18	3.95	NCH_3, 6.95	4	8	7.5	
II	3.99	5.08	4.86	5.34	4.21	NCH_3, 7.26 OCH_3, 6.43	6	7		$J_{2,\alpha}$ = 8.5
III	3.97	5.16		4.36		NCH_3, 7.18 CCH_3, 8.03; 8.18				$J_{2,\alpha}$ = 8.5
IV	3.74[b]	4.42[b,c]	4.80	3.69[d]		H-5–8, 2.8–3.3 C_6H_5, 2.67 CH_2, 5.55; 5.73				$J_{3,4}$ = 7.5 $J_{1,\alpha}$ = 8 J_{CH_3} = 15.7
V	3.79[b]	4.44[b,c]				H-4–H-8 and C_6H_5 2.5–2.9				$J_{1,\alpha}$ = 8.5

[a] $J_{2,6}$ for pyridine derivatives ≤1.5 Hz. [b] Assignments may be interchanged. [c] H-1. [d] H-3.

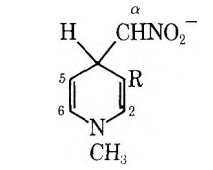
tion by hydroxide ion or water in aqueous solution.[11] Ionization of nitromethane in ammonia becomes detectable by NMR at about −10°C.[5]

Addition of nitromethide ion to the annular position of an aromatic electrophile is easily recognized by NMR. Spectra of the carbon adducts, shielded with respect to aromatic starting material, show a sharp doublet with coupling constant about 7–8 Hz. A doublet results because the nitromethyl side chain formed in the addition step undergoes deprotonation by the solvent. The remaining single proton of the side chain is spin coupled to the annular proton at the site of addition.

The presence of this doublet confirms that the nucleophilic atom of the ambident nitromethide ion is carbon and not oxygen and indicates that turnover of the side chain must be slow. A likely mechanism of turnover first involves protonation of the side chain prior to elimination. An upper limit of $J\,\pi/\sqrt{2}$ or about 17 s^{-1} can be set for protonation and ligand loss by a pseudo-first-order reaction. Supporting this conclusion is the observation that separate signals always were observed for bound ligand and methide ion in solution.

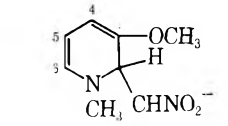
The greater affinity of the carbon nucleophile over ammonia is readily seen in the results for 1-methylpyidinium ion. Reaction of this electrophile with ammonia is not apparent by NMR analysis over a wide temperature range. By contrast, addition of the carbon nucleophile is extensive but incomplete. Substrate and a slight excess of nitromethide ion were allowed to warm to 10 °C in order to achieve solution and then cooled. Spectra recorded over the interval −50 to −20 °C clearly showed the presence of both adduct and starting material; at −50 °C about 90% of the material was present as adduct. The simplicity of the adduct spectrum and the integrated areas clearly indicate that the major adduct is Ia, which results from addition to the 4 position of the ion, Table I. No attempt was made to extract coupling constants from the second-order spectrum involving the five annular protons.[12] Previous attempts to achieve addition between nitromethane and 1-alkylpyridinium ions have failed.[6]

A series of 3-substituted 1-methylpyridinium ions was examined. Included are the 3-methyl ion, which does not give detectable addition with ammonia, and the 3-methoxy compound, which shows only a trace of reaction with solvent. Also considered are ions which quantitatively add

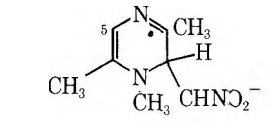


R

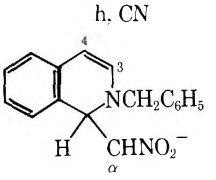
Ia, H
b, I
c, CH_3
d, $CONH_2$
e, $COCH_3$
f, CO_2CH_3
g, CF_3
h, CN



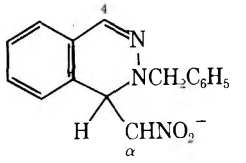
II



III



IV



V

ammonia, the 6 position of the ion being favored except in the case of the 3-iodo compound where the 2 position is the site of addition of ammonia. All these ions underwent addition with nitromethide ion. Addition of the carbon nucleophile to position 4 was observed for all except the 3-methoxy compound, which reacts at position 2.

Coupling constants of 4-position adducts are similar to those of known structure.[7,13] The known adducts do not, however, have an ionized nitromethyl side chain.[7] A deuterium-labeling experiment was utilized to show that the carbon nucleophile added to position 4 of the 3-iodo compound to give the 4-deuterio derivative of Ib. Details are given in the supplementary material.

At −5 °C a little protonated 3-iodo adduct was produced; essentially complete conversion to the adduct having a nitromethyl chain was observed on raising the temperature to 20 °C. Relative to the anion, H-2 and H-6 of the carbon protonated adduct are deshielded by about 14 Hz while H-4 and H-5 are shielded by about 21 and 7 Hz, respectively.

Interestingly, the presence of an electron-donating meth-

Table II. Chemical Shifts (τ) and Coupling Constants for Compounds Produced by the Addition of Ethanethiolate Ion[a]

Compd	H-2	H-4	H-5	H-6	Other	J, Hz
VIb[b]	3.30	5.30	5.45	3.62	NCH_3, 6.98	$J_{4,5} = 4.5$; $J_{5,6} = 7$
c	2.69	5.49	5.07	3.63	NCH_3, 6.86	$J_{4,5} = 5$; $J_{5,6} = 7.5$
d	2.19	5.33	4.90	3.51	NCH_3, 6.74; CH_3, 7.85	$J_{4,5} = 5.5$; $J_{5,6} = 7.5$
e	2.52	5.40	4.96	3.50	NCH_3, 6.79; CH_3, 6.32	$J_{4,5} = 5.5$; $J_{5,6} = 7$
VIf and VIIc[f]	2.59	4.40	4.96	3.80	NCH_3, 6.83	$J_{4,5} = 7$; $J_{5,6} = 6.5$
VIIa[c]	4.24	3.21	4.71[d]	2.04	NCH_3, 6.67	$J_{2,3} = 4.5$;
					CH_3, 7.72	$J_{3,4} = 10$
b	4.18	3.35	4.78[d]	2.39	NCH_3, 6.71	$J_{2,3} = 4.5$;
					CH_3, 6.28	$J_{3,4} = 9.5$
VIII	4.46		4.18		NCH_3, 7.01	
					CH_3, 7.92, 8.12	
IX	4.33		3.00[d]	2.75	NCH_3, 6.79	$J_{2,3} = 3.5$;
						$J_{3,6} = 1$; $J_{2,6} < 1$
X	4.10[e]	4.57	3.52[d]		CH_2, 5.41	$J_{1,3} = 1.5$;
					band, 2.6–3.1	$J_{3,4} = 7.5$
XI	4.18[e]				CH_2, 5.22	
					band, 2.4–2.9	

[a] Free and bonded ethanethiolate ions undergo rapid averaging in all cases except VIc, IX, and XI, where separate but overlapping signals are found; $CH_2 \sim \tau$ 7.6 and $CH_3 \sim \tau$ 8.8. [b] $J_{2,6}$ and $J_{2,4} \leq 1.5$ Hz. [c] $J_{2,6} < 1$ Hz; $J_{4,6} = 1.5$ Hz. [d] H-3. [e] H-1. [f] Positions are numbered according to VIf.

yl group at the 3 position of 1-methylpyridinium ion does not prevent adduct Ic from being formed. However, conversion to adduct was only about one-half complete in the presence of a slight excess of nucleophile over the range −65 to −25 °C. The 3-carbamoylpyridinium ion formed adduct Id; good spectra were recorded at −45 and at −25 °C, although solubility was a problem. Similarly, the 3-acetyl ion gave adduct Ie at −31 °C; a minor component (~20%) was not identified.

Amino adduct formed by the addition of ammonia to the 6 position of a pyridinium ion was present along with carbanion adducts If–h when the substituent at position 3 was CO_2CH_3, CF_3, or CN. Some 2-amino adduct also was present in the case of cyano substrate. Initial spectra recorded at about −60 °C showed the presence of multiple adducts. Raising the temperature at about −25 °C caused the formation of more carbon adduct to take place at the expense of amino compound.

Reaction of 1-methyl-3-methoxypyridinium ion with nitromethide ion constitutes an exception to the pattern of addition to position 4. The nucleophile adds to position 2 to give II. All the annular proton signals of adduct show major couplings; the largest involves the side chain, being 8.5 Hz. The splitting pattern is different from those observed for the other 3-substituted pyridinium ion adducts and indicates another site of addition which can only be position 2. The presence of starting material signifies that conversion to adduct is incomplete over the range −65 to 25 °C but the adduct is the major component. Adduct formation again demonstrates the greater affinity of the carbon nucleophile over that of ammonia. Essentially no adduct is detected in the presence of the latter nucleophile alone.

Failure to undergo the carbon addition reaction was found with some pyrazinium ions. Neither the 3-chloro- nor the 3-carbamoyl-1-methylpyrazinium ion gave carbon adduct. Only the known amino adducts[4] were detected over the range −60 to 0 °C. Observation time was about 0.5 h; no attempt was made to determine whether carbon adduct slowly forms over longer periods. By contrast, addition of nitromethide ion to 1,2,5-trimethylpyrazinium ion to give III was complete at −60 °C. The spectrum did not change on raising the temperature to 0 °C; no other component was detected.

Comparison of the results for 2-benzylisoquinolinium ion and its 3-aza derivative, 2-benzylphthalazinium ion, provides a striking contrast. Only carbon adduct IV formed by the addition of nitromethide ion to position 1 of the isoquinolinium ion was observed over the temperature range −51 to 0 °C. However, the phthalazinium ion only formed amino adduct at low temperatures; a very small amount of carbon adduct V was finally observed at 0 °C, as evidenced by the presence of a pair of doublets resulting from coupling of H-1 with the ionized nitromethyl side chain. Signal overlap with the main component prevents full characterization of the carbon adduct, however.

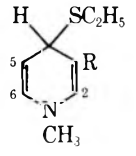
Addition of Ethanethiolate Ion. Results for a mixture of 1-methylpyridinium iodide and ethanethiolate ion are understandable if it is assumed that starting material and thiolate ion adduct both are present and that the resultant spectrum is an average of the two forms. Thiol ligand turnover is rapid enough to give rise to signal averaging, leading to a single spectrum. Lack of separate signals for free and bonded thiolate ions supports this assumption.

As a mixture of 1-methylpyridinium ion and the thiolate ion was warmed from −60 °C signals for the annular protons and those of the methyl group shifted upfield as more of the ammonium thiolate salt dissolved and reacted. Above about −10 °C the spectrum began to shift in the opposite direction, probably owing to dissociation of the adduct. The spectrum consists of an apparent doublet at low field due to H-2 and -6 and overlapped multiplets for the remaining annular protons. The extent of overlap increases as more adduct is formed. The spectrum is qualitatively similar to that for Ia, resulting from the addition of nitromethide ion to the 4 position of the same heterocycle. The simplicity of the spectrum indicates that the thiolate ion adds largely to position 4 to give VIa. Chemical shifts taken from the most shielded spectrum employing a large excess of thiolate ion in order to shift the equilibrium position to favor adduct are τ 2.41 (H-2, -6), 3.48 (H-4), 3.75 (H-3, -5), and 6.34 (NCH_3). Comparison of these values with those reported in Table II for other 4 adducts shows that conversion to adduct is incomplete.

Similar results were observed for 3-methoxy-1-methylpyridinium ion and ethanethiolate ion. Again, on raising the temperature from −50 to −10 °C the spectrum shifted upfield as more of the thiolate salt dissolved and added. At 10 °C the spectrum shifted downfield, apparently as a result of dissociation of an adduct or adducts. Cooling the mixture to −10 °C caused the signals to shift back upfield, indicating reversibility. The most shielded spectrum has

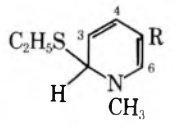
the following characteristics: τ 2.36 (J = 6 Hz, H-4, or H-6), 2.41 (J = 1 Hz, H-2), 2.97 (J = 1 and 7.5 Hz, H-6 or H-4), and 3.32 (J = 6 and 7.5 Hz, H-5), 6.08 and 6.14 (CH_3 groups). Insufficient adduct is present to assign a structure. Interestingly, both 1-methyl- and 3-methoxy-1-methylpyridinium ion undergo less addition with ethanethiolate ion than with nitromethide ion. However, addition of the thiolate ion proceeds to a greater degree than ammonia.

1-Methyl-3-iodopyridinium ion in the presence of ethanethiolate ion does not give the known amino adduct.[4] Adduct VIb results from addition of thiolate ion to position 4 of the ion. Supporting this conclusion is the observation that a signal at high field (τ 5.30) disappeared on deuteration of position 4. At 20 °C signals due to another ethylthio group appeared slightly downfield from those due to adduct and thiolate ion. The new signals probably result from displacement of the iodo group to form a 3-ethylthio substitution product.



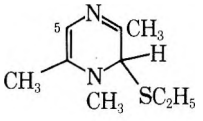
R

VIa, H
b, I
c, CN
d, $COCH_3$
e, CO_2CH_3
f, $CONH_2$

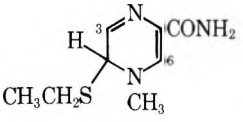


R

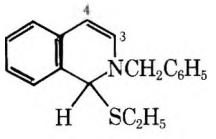
VIIa, $COCH_3$
b, CO_2CH_3
c, $CONH_2$



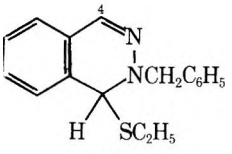
VIII



IX



X



XI

3-Cyano-1-methylpyridinium ion in the presence of ethanethiolate ion first forms the known adduct resulting from the addition of solvent to the 6 position of the ion.[4] This amino adduct was the major product at −65 °C but at −25 °C appreciable amounts of thiol adduct were present. At −10 °C only the new product was observable; cooling the sample to −35 °C did not regenerate the spectrum of amino adduct. At −10 °C separate but overlapping signals were found for the methylene protons of free and bonded thiolate ion, indicating that ligand turnover is slow. However, signal overlap prevents determination of coupling constants of bonded thiolate ion. The shielded position of H-4 in the spectrum requires the adduct to have structure VIc resulting from the addition of the nucleophile to position 4 of the ion.

Broadening was clearly evident in the spectrum of a sample of 1-methyl-3-acetylpyridinium ion and ethanethiolate ion in ammonia. At 35 °C the spectrum consisted of a sharp peak at τ 2.5 (H-2), a very broad signal at τ 4.1, and a sharp apparent triplet at τ 4.8 (H-5) along with sharp singlets at τ 6.8 (NCH_3) and 7.8 ($COCH_3$). Raising the temperature to 70 °C produced no significant change. Cooling to −40 °C, however, resulted in a dramatic increase in resolution. An approximately equimolar mixture of two adducts clearly was present. Cycles of broadening and resolving of spectra were observed on repeated warming and cooling, indicating reversibility. Both adducts are due to the addition of thiolate ion to the pyridinium ion, one to position 4 to give VId and the other to position 6 of the ion to yield VIIa,[14] Table II. Assignments are supported, for example, by the fact that each adduct shows a signal for H-2 at the lowest field portion of the spectrum, eliminating a 2 adduct from consideration. The known amino adduct[4] can be eliminated as a possibility; see supplementary material.

The pattern of signal averaging at high temperatures is understandable when the spectra of the two adducts are considered. The two annular protons which show sharp signals at higher temperatures have chemical shifts which are very similar in both adducts. However, the two broadened signals are associated with adducts in which there is a large separation between signals for equivalent protons. Consider, for example, H-4, which shows a signal at τ 3.21 in one adduct and at τ 5.33 in the other, a separation of 127 Hz. Interconversion of these widely separated signals requires a much faster rate (higher temperature) than that, say, for H-2 where the separation of the signals in the two adducts is only 10 Hz. The protons with similar shifts coalesce at a much lower temperature than the more widely spaced ones as the adducts interconvert.

Spectra for a mixture of 1-methyl-3-carbomethoxypyridinium ion and ethanethiolate ion are similar to those for the 3-acetyl ion. At −10 °C broad peaks were observed but cooling to −40 °C resulted in an increase in resolution. Again, two adducts present to approximately the same degree clearly were observed. As in the 3-acetyl case, products VIe and VIIb[14] are likely to be the result of addition of thiolate ion to positions 4 and 6 of the pyridinium ion, respectively, Table II.

At 35 °C the spectrum of 1-methyl-3-carbamoylpyridinium ion and ethanethiolate ion was much like those for the 3-acetyl and 3-carbomethoxy ions under similar conditions. A sharp peak at τ 2.5, broad bands at τ 3.8 and 4.1, and an apparent triplet at τ 4.7 were observed for the annular protons. Cooling, however, led to a completely different result. The two broad bands resolved into two multiplets. Superficial examination suggests that one, rather than two, adducts appears to be present.

In an effort to obtain more information about the reaction of the 3-carbamoyl ion, the 1-benzyl derivative was examined. Although the benzyl methylene protons of an adduct are diastereotopic and therefore can give rise to separate signals, they appeared as a singlet even at −25 °C. Moreover, separate signals for the diastereotopic ethylthio protons were not observed. Hence, ligand turnover seems to be rapid, causing diastereotopic protons to appear enantiotopic.

Careful consideration of the spectrum for the carbamoyl substrate leads to a most interesting conclusion. A rapidly equilibrating mixture of adducts resulting from thiolate ion addition to the 4 (VIf) and 6 (VIIc) positions of the ion is being observed. Equilibration is so fast that the spectrum appears to be that of a single substance. There is strong support for this conclusion. If the spectra of the two adducts of the 3-acetyl or 3-carbomethoxy compound are assumed to be models of those for similar adducts of the 3-carbamoyl compound and if it also is assumed that an equimolar mixture of the two adducts is present, then the observed spectrum, chemical shifts and coupling constants, is essentially that calculated using parameters for these known adducts. In making this calculation appropriate shifts and coupling constants were averaged. Those proton

signals which undergo the largest changes in shift and therefore constitute the most sensitive test of the hypothesis concerning averaging may be used to illustrate the method of calculation. The average of τ 5.40 for H-4 of VIe and τ 3.35 for H-4 of VIIb is 4.38. This is to be compared with the observed value τ 4.40 for the carbamoyl substrate. Although the difference between observed and calculated values is slightly larger (0.13 ppm) using the acetyl adducts as models, the difference again is insignificant. Moreover, the rate constant for the interconversion of the two adducts may be estimated. Thus, at coalescence, $k = \Delta\pi/\sqrt{2} = 265^{-1}$, where Δ is the difference in hertz between the signals being averaged. Since the spectra showing sharp signals are recorded above the coalescence temperature, the lifetime of an adduct under these conditions is less than $1/k$ or 3.8 ms. Turnover of adducts indeed is rapid.

Interconversion of the two adducts formed from carbamoyl substrate is so facile that we have not been able to "freeze out" the individual adducts by lowering the temperature. By contrast, with acetyl and carbomethoxy substrates it is possible to see the spectra of two adducts at low temperatures. However, we have not been able to interconvert them rapidly enough on raising the temperature to get a single, averaged spectrum, as in the case of the carbamoyl compound. The reason for broad signals at probe temperature in the carbamoyl case is unknown; raising the temperature of the sample led to uninformative results. It should be noted that although adduct structures are written with a neutral carbamoyl group, ionization of this group may take place. We have no independent evidence concerning the extent of such deprotonation for these or any other adducts containing a "carbamoyl" group.

Both 1,2,5-trimethylpyrazinium and 1-methyl-3-carbamoylpyrazinium ions react at probe temperature with ethanethiolate ion to give adducts VIII and IX,[14] respectively. In the first case the product structure can be assigned easily because the two CH_3 groups bonded to carbon have similar chemical shifts, indicating nucleophilic addition to a site unoccupied by a methyl group. In the second example the 3.5-Hz coupling constant suggests that the thiolate ion adds to the 6 position of the pyrazinium ion; addition to position 2, the other possibility, would result in an adduct with a larger coupling constant.[4] The methylene protons of IX clearly are diastereotopic, indicating slow ligand turnover. However, partial overlap with those of the free ion prevents us from determining coupling constants.

Both 2-benzylisoquinolinium and 2-benzylphthalazinium ions in the presence of a slight excess of thiolate ion are completely converted at 30 °C to sulfur adducts. Addition to position 1 led to the formation of X and XI, respectively. The *N*-methylene protons of both adducts show a singlet rather than a multiplet signal. Separate signals were not observed at 30 °C for free and bonded thiolate ion in the case of X, suggesting that ligand turnover may be rapid enough to make the diastereotopic protons of X appear enantiotopic. However, with XI separate but largely overlapping signals were observed at 30 °C for free and bonded thiolate ions, suggesting that the presence of the second annular nitrogen atom in XI causes a reduced rate of turnover. The reason for the singlet signal for the benzyl methylene protons of XI is unclear. The singlet may be due to accidental degeneracy of the diastereotopic protons[15] or to ligand exchange.

Successful formation of adducts IX and XI involving thiolate ion and 3-carbamoyl-1-methylpyrazinium and 2-benzylphthalazinium ions, respectively, is especially interesting. By contrast, the first heterocyclic ion did not give rise to an adduct with nitromethide ion while the second yielded only a minor amount of product. In the presence of the carbon nucleophile, amino adduct is the major product in both cases. Reaction temperatures were very different in experiments involving the carbon and sulfur nucleophiles, however. The thiolate ion reactions were examined at about 30 °C, while those with nitromethide ion were conducted below about 0 °C. Higher temperatures were avoided with the carbanion because it is largely converted to nonnucleophilic nitromethane under such conditions. It would be worthwhile to examine the thiolate ion and the two quaternized compounds at low temperatures; perhaps thiolate ion adduct formation would be slow because starting material is converted largely to amino adduct.

General. Reversibility of the addition of the carbon and sulfur nucleophiles was demonstrated by recovering aromatic starting material from addition reactions. Details are found in the Experimental Section. Attempts were not made to isolate adducts or to broaden the scope of the investigation by studying other nucleophiles. Certainly, other carbon nucleophiles are likely to undergo addition reactions similar to those of nitromethide ion.[13,16]

A solid foundation has been laid for the addition of various nucleophiles to quaternized heteroaromatic electrophiles in ammonia. Possibilities for extensive studies dealing with kinetic and thermodynamic control of addition reactions and their relationships to structural effects are obvious. Methods utilizing the nitrogen, carbon, and sulfur adducts as intermediates in synthetic sequences await exploitation.

Experimental Section

All compounds with the exception of 1-methyl-3-iodopyridinium-*4-d* iodide were available from previous studies.[17] 3-Iodopyridine-*4-d*[18] (55–60% D) was quaternized with methyl iodide.[19] Reaction mixtures were prepared in NMR tubes as previously indicated.[1] Ethanethiol or nitromethane (1–2 equiv) was added by syringe to cooled mixtures. Spectra were recorded on a Varian A-60A spectrometer equipped with a V-6040 variable temperature controller.

Recovery of Heteroaromatic Starting Material Following Adduct Formation. After NMR spectra of a mixture of 1-methylpyridinium iodide and nitromethane were recorded, the sample was cooled in an acetone–dry ice bath, and then poured into 5 ml of ether cooled in the same bath. The yellow resultant precipitate was removed by filtration and dissolved in D_2O containing sodium acetate internal standard. The NMR spectrum was identical with that of starting material; integration with reference to the standard indicated that recovery was 91%. The same procedure was employed for a mixture of ethanethiol and 1-methyl-3-carbamoylpyrazinium iodide which had stood at room temperature for 1 week; recovery of starting material was 40%.

A mixture of 100 mg (0.426 mmol) of 1-methyl-3-acetylpyridinium perchlorate and 100 μl (1.35 mmol) of ethanethiol in 5 ml of ammonia was held at −33 °C for 5 min. After 5 ml of cold ether was added, the mixture was allowed to warm slowly to evaporate the ammonia. The ether was decanted and the crystalline material was washed once with ether; 59 mg (59%) of compound having an NMR spectrum identical with that of starting material was recovered. The same procedure was employed with the same substrate and nitromethane (100 μl, 1.87 mmol) and afforded 75 mg (75%) of starting material.

Registry No.—Ia, 58091-32-0; Ib, 58091-33-1; Ic, 58091-34-2; Id, 58091-35-3; Ie, 58091-36-4; If, 58091-37-5; Ig, 58091-38-6; Ih, 58091-39-7; II, 58091-40-0; III, 58091-41-1; IV, 58091-42-2; V, 58091-43-3; VIb, 58091-44-4; VIc, 58091-45-5; VId, 58091-46-6; VIe, 58091-47-7; VIf, 58091-48-8; VIIa, 58091-49-9; VIIb, 58091-50-2; VIIc, 58091-51-3; VIII, 58091-52-4; IX, 58091-53-5; X, 58091-54-6; XI, 58091-55-7; 1-methylpyridinium ion, 694-56-4; 3-iodo-1-methylpyridinium ion, 54560-56-4; 1,3-dimethylpyridinium ion, 18241-34-4; 3-carbamoyl-1-methylpyridinium ion, 3106-60-3; 3-acetyl-1-methylpyridinium ion, 51061-43-9; 3-carbomethoxy-1-methylpyridinium ion, 18899-18-8; 3-trifluoromethyl-1-methylpyridinium ion, 58091-56-8; 3-cyano-1-methylpyridinium ion, 15923-

33-8; 3-methoxy-1-methylpyridinium ion, 54560-57-5; 1,2,5-trimethylpyrazinium ion, 58091-57-9; 2-benzylisoquinolinium ion, 38602-73-2; 2-benzylphthalazinium ion, 46818-75-1; 3-carbamoyl-1-methylpyrazinium ion, 58091-58-0; nitromethide ion, 18137-96-7; ethanethiolate ion, 20733-13-5.

Supplementary Material Available. Additional NMR data and interpretation (2 pages). Ordering information is given on any current masthead page.

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The Nature of the Carbonium Ion. XII. The *N*-*p*-Toluenesulfonyl-2-aza-5-norbornyl Cation[1a]

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The syntheses of several C_5-substituted *N*-*p*-toluenesulfonyl-2-azabicyclo[2.2.1]heptanes are described. Solvolytic studies carried out on the *exo*- and *endo*-*p*-bromobenzenesulfonates **13** and **16**, respectively, in buffered acetic acid indicate a 10^{-4}–10^{-5}-fold rate retardation for either isomer as compared with the acetolysis rate of its corresponding 2-norbornyl analogue. The **13**:**16** (exo/endo) rate ratio is 5. The endo acetate **15**, formed in a relatively high proportion, and the anticipated exo acetate **9** were primary acetolysis products from both **13** and **16**. A mechanistic interpretation of the results is presented.

In connection with our interest in heterocyclic analogues of the norbornyl skeleton, we commenced a synthetic sequence leading to the incorporation of a nitrogen atom into a two-carbon bridge of the bicyclo[2.2.1]heptane skeleton. We elected to investigate those derivatives which possess functional groups attached to the opposite bridge such that they are separated from the nitrogen atom by a minimum of three carbons. The strong structural resemblance of these derivatives to the analgetic agents meperidine and prodine suggested a potential for physiological activity in a manner originally suggested by Portoghese.[4] In addition, for most dissociation reactions of secondary 2-norbornyl derivatives which lead to carbonium ions, it is uncertain whether the C_6–C_1 σ bond is directly involved in ionization, affording a delocalized cation, or only involved in a subsequent Wagner–Meerwein shift interconverting two localized cations.[5,6] In the case of the 2-sulfonyl-2-aza 5-substituted compound, the proximity of the electron-withdrawing sulfonamide function to the C_3–C_4 ethylene bond (analogous to the C_6–C_1 bond in the 2-substituted carbocyclic compounds) promised to shed light on the electronic requirements for involvement of this bond in cation forming reactions on the opposite two-carbon bridge.

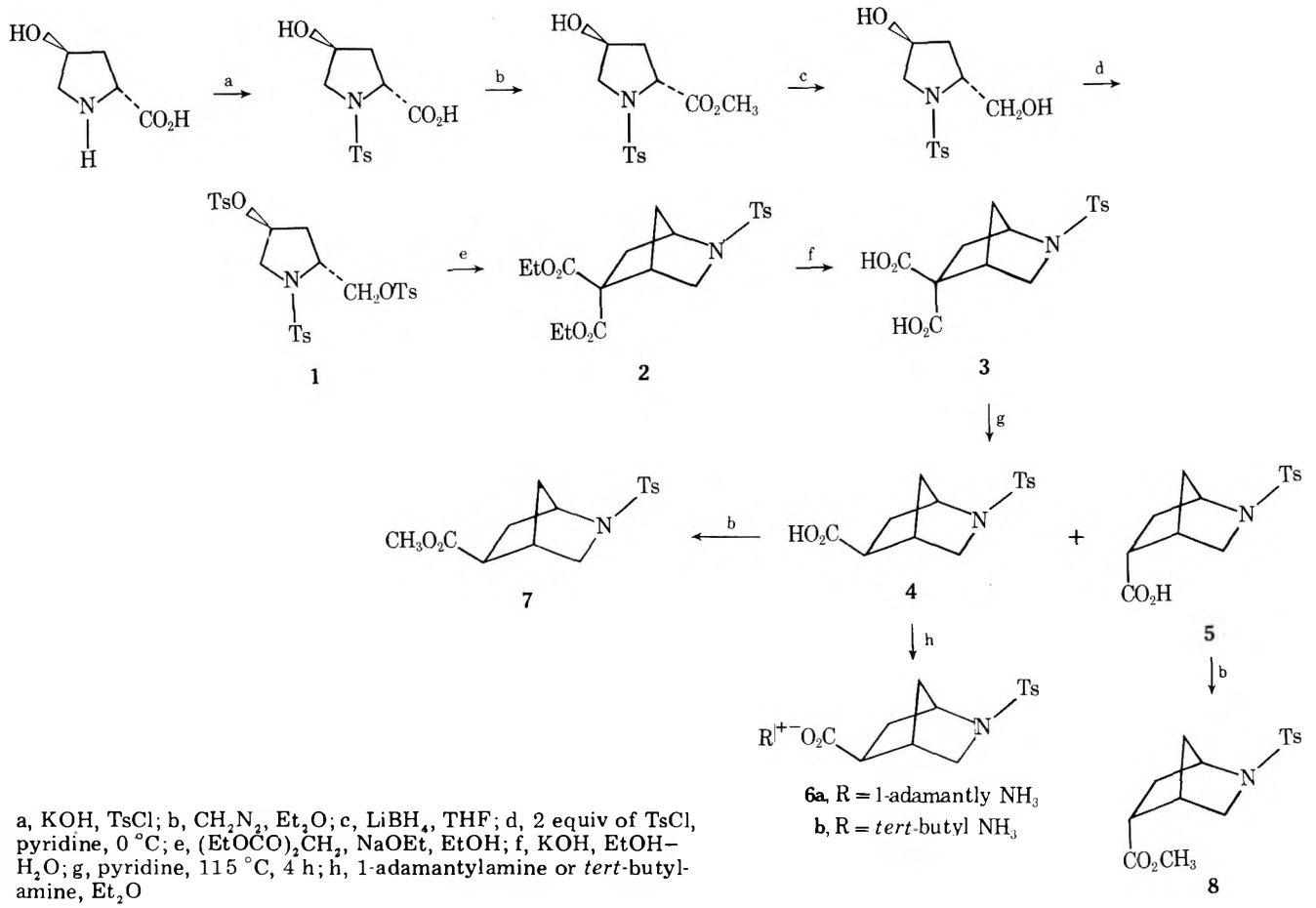
As the syntheses of C_5-substituted 2-azanorbornyl systems are rather complex, only a few derivatives with this substitution pattern have been reported.[4,7]

Results

The *N*,*O*,*O*′-tri-*p*-toluenesulfonate ester of hydroxy-L-prolinol (**1**) was prepared by the method of Portoghese[4] and employed as the chief precursor to the 2-azabicyclo-[2.2.1]hept-5-yl derivatives.[8] (See Scheme I.) Reaction of the triarenesulfonate ester **1** with sodiomalonic ester in ethanol or in diglyme effected ring closure to bicyclic diester **2**. Hydrolysis in ethanol or in diglyme afforded the corresponding geminal diacid **3**. The crude diacid was effectively decarboxylated in pyridine at reflux to yield a mixture of the epimeric monoacids **4** and **5**. The acids were shown to be in an endo/exo ratio of 80:20 by GC analysis of their methyl esters. As the endo acid **5** was substantially more hindered than its epimer, a partial purification was achieved by preferential reaction of exo acid **4** with *tert*-butylamine, generating the acid salt **6**. Regeneration of the acid and crystallization from benzene gave pure exo acid **4**. The endo acid **5** was recovered from the mother liquors of the salt forming reaction.

In an attempt to further verify the stereochemical assignments about C_5, the methyl esters **7** and **8** were pre-

Scheme I[a]



a, KOH, TsCl; b, CH_2N_2, Et_2O; c, $LiBH_4$, THF; d, 2 equiv of TsCl, pyridine, 0 °C; e, $(EtOCO)_2CH_2$, NaOEt, EtOH; f, KOH, EtOH–H_2O; g, pyridine, 115 °C, 4 h; h, 1-adamantylamine or *tert*-butylamine, Et_2O

[a] For the sake of clarity in this and subsequent schemes, the structural formulas represent the configuration corresponding to *trans*-hydroxy-D-proline. The compounds actually prepared were derived from hydroxy-L-proline.

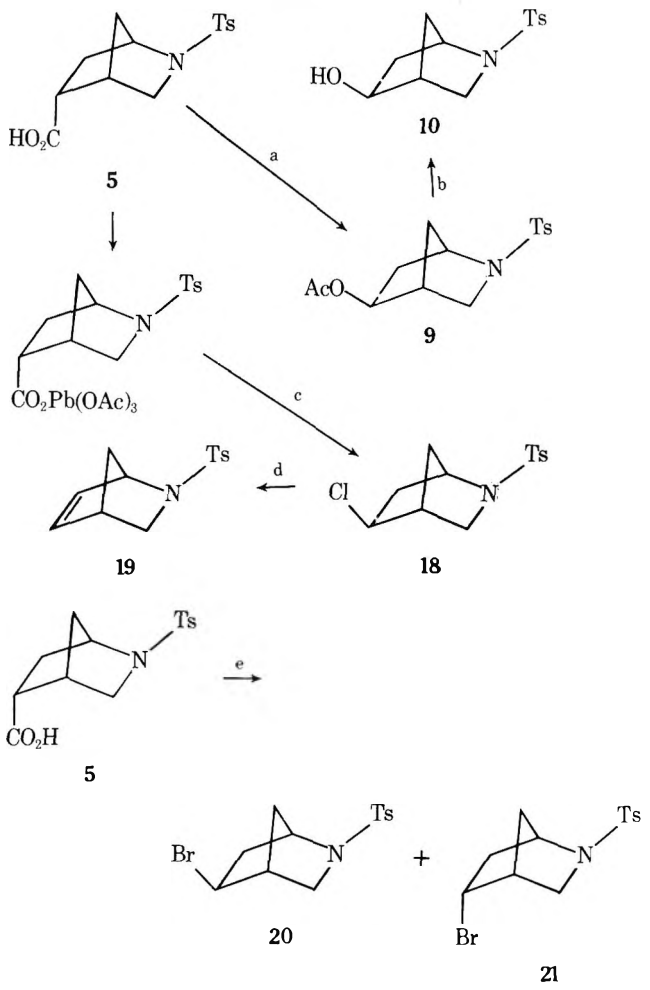
pared from the acid mixture by treatment with diazomethane. By analogy with the documented geometry of the norbornyl skeleton, we felt that steric hindrance by the endo hydrogen atom at C_3 would lead to a predominance of the exo ester upon base-catalyzed equilibration. In actuality, the exclusive formation of exo acid **4** on treatment of the endo methyl ester **8** with aqueous ethanolic potassium hydroxide proved the best support for the epimerization-based deductions leading to stereochemical assignment.

As our interests centered on placing a suitable leaving group at C_5, a pathway leading to replacement of the carboxyl group by a hydroxyl function was begun. Treatment of the endo carboxylic acid **5** with lead tetraacetate in pyridine–benzene solution afforded a mixture of the epimeric acetates **9** and **15.** Although these epimeric acetates possessed identical retention times on GC analysis, a NMR spectrum indicated that less than 10% of endo acetate had formed in the conversion of the endo acid **5** (see Scheme II). Supporting this finding was the observation that when the reaction was run for time periods less than 1 h and rapidly decanted into a 40% hydrochloric acid solution, the exo chloride **18** was the predominant product. No endo chloride was observed within the detection limits of the NMR spectrometer, or of GC analysis.

Elution of the acetate mixture from neutral alumina produced a fraction containing pure exo acetate **9.** Reduction of **9** with lithium aluminum hydride gave the exo alcohol **10** which was ultimately characterized as its *p*-bromobenzenesulfonate ester **13.** (See Scheme III.) Oxidation of exo alcohol **10** with a chromium(VI) oxide–pyridine complex[9] generated the analogous ketone **11.** The endo alcohol **12** was efficiently synthesized by reduction of ketone **11** with lithium aluminum hydride or lithium aluminum tri-*tert*-butoxyhydride. The alcohol was characterized as its acetate and *p*-bromobenzenesulfonate esters, **15** and **16,** respectively. Isotopic labeling, accomplished by reduction of ketone **11** with 99.9% lithium aluminum deuteride, afforded deuterioalcohol **14,** and allowed unequivocal assignment of the exo-C_5 proton signal in the NMR spectrum of endo alcohol **12.**

As an alternative pathway toward generation of a hydroxyl function from the original carboxyl group at C_5, we attempted a synthetic sequence beginning with the stereochemically pure exo carboxylic acid **4.** (See Scheme IV.) This acid was treated with an ethereal solution of methyllithium to give stereospecifically the exo methyl ketone **17,** which was contaminated with some exo *tert*-carbinol. Fractional crystallization from ether gave the pure methyl ketone. Treatment of methyl ketone **17** with *m*-chloroperbenzoic acid in 1,2-dichloroethane afforded only exo acetate **9.** The stereochemical integrity of this ester was established by its reduction with lithium aluminum hydride, or hydrolysis with 1 N ethanolic potassium hydroxide, exclusively to the previously characterized exo alcohol **10.** The exo alcohol obtained in this fashion was homogeneous to GC analysis. Conversion of **10** to its *p*-bromobenzenesulfonate ester **13** was accomplished by teatment with *n*-butyllithium followed by *p*-bromobenzenesulfonyl chloride. Crystallization of this exo ester, and its epimer **16,** from methylene chloride–ether produced the analytically pure samples employed in the acetolysis product studies and kinetic rate determinations subsequently described.

Scheme II



a, $Pb(OAc)_4$, pyridine, benzene; b, $LiAlH_4$, Et_2O; c, 40% HCl; d, K, *t*-BuOH; e, HgO, CCl_4, Br_2

In a further investigation of the stereoselectivity of various functional transformations at C_5, the pure endo acid **5** was treated with mercuric oxide and molecular bromine to give a mixture of epimeric bromides, **20** and **21**.

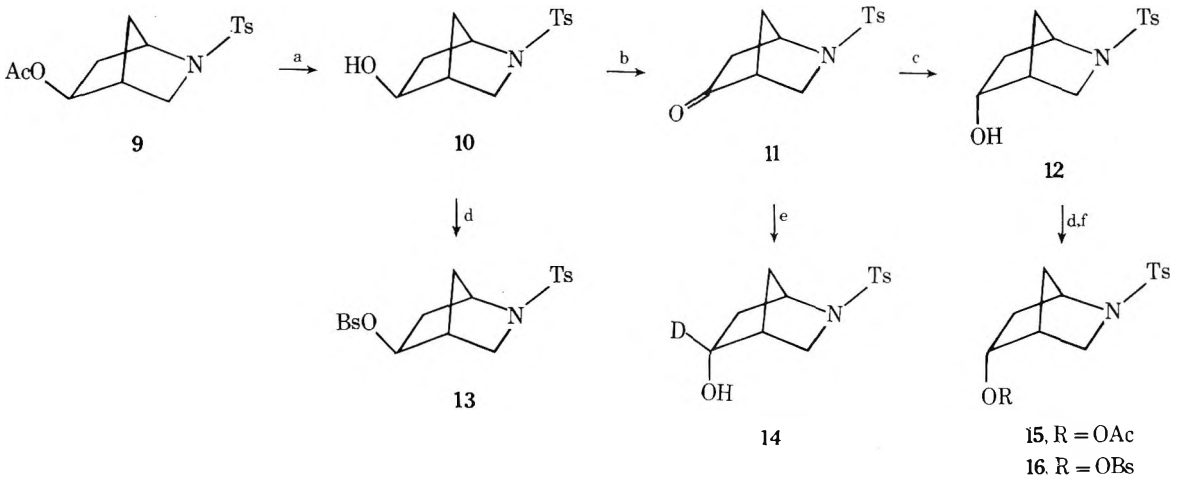
Fractional crystallization from ether separated the isomers. The ether insoluble component failed to react with alcoholic silver nitrate, whereas the isomer obtained from the ethereal mother liquor gave a silver bromide precipitate after several minutes. Similar observations of the epimeric 2-norbornyl bromides had shown that the exo isomer reacted with alcoholic silver nitrate more rapidly than the endo bromide. Our ether soluble bromide was therefore assumed to be the exo isomer **20**. As the ether insoluble bromide failed to react with silver acetate in aqueous acetone even when heated at reflux for 24 h, we assigned it the endo configuration, **21**.

Supporting these assignments were the analyses of the NMR spectra of the two isomers. The bromine in **21** induces a much greater chemical shift differentiation between the endo and exo hydrogen atoms at C_3 than is observed for the exo bromide of **20**. Furthermore, reaction of exo bromide **20** (or exo chloride **18**) with potassium *tert*-butoxide effected a slow dehydrohalogenation to generate olefin **19**. Similar treatment of the endo bromide **21** afforded only uncharacterizable products resulting from fragmentation of the bicyclic ring.

The solvolytic behaviors of the isomeric *p*-bromobenzenesulfonate esters **13** and **16** were studied in sodium acetate buffered acetic acid. Similar studies in unbuffered medium were considered and rejected on the grounds that generation of the strong acid, *p*-bromobenzenesulfonic acid, would tremendously complicate the product and kinetic studies by allowing an unknown amount of protonation of the ring nitrogen during solvolysis. Product studies were carried out at 150 °C for a minimum of 7 half-lives with 0.042 M solutions of the sulfonate esters in the buffered medium. GC analysis of the products derived from acetolysis of the endo ester **16** indicated one major component as 97% of the mixture. The minor component possessed a considerably shorter retention time. By analogy with the preferred 1,3-elimination mode of the norbornyl system, and with consideration for the probable enhanced acidity of the C_3 protons, the minor compound was tentatively assigned an azanortricyclene ring structure.

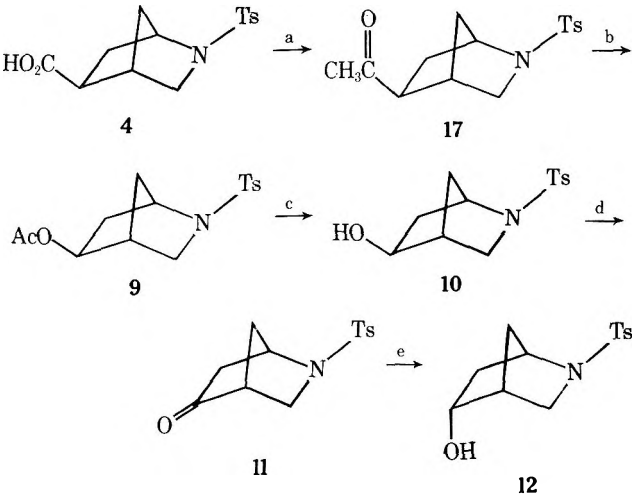
As the retention time of the major component was identical with that of both epimeric exo and endo acetates **9** and **15**, the acetolysis mixture was reduced with lithium aluminum hydride to the corresponding alcohols. GC analysis clearly showed the predominance of the exo alcohol **10** but also indicated a minor incompletely resolved peak with retention time identical with that of authentic endo alcohol **12**. Full resolution of the components was ultimately obtained by conversion of the alcoholic product mixture to

Scheme III



a, $LiAlH_4$, Et_2O; b, CrO_3–2 pyridine, CH_2Cl_2; c, $LiAlH(O\text{-}t\text{-}Bu)_3$, Et_2O; d, BsCl, pyridine, 0 °C; e, $LiAlD_4$, Et_2O; f, Ac_2O, pyridine

Scheme IV



a, CH_3Li, Et_2O, 0 °C; b, *m*-chloroperoxybenzoic acid, CH_2Cl_2; c, $LiAlH_4$, Et_2O; d, CrO_3–2 pyridine, CH_2Cl_2; e, $LiAlH(O\text{-}t\text{-}Bu)_3$

Table I. Rate Data for Sodium Acetate Buffered Acetolyses of Norbornyl *p*-Bromobenzenesulfonates

ROBS	Temp, °C	k, $s^{-1} \times 10^5$	$\Delta H^{\ddagger}$, kcal/mol	$\Delta S^{\ddagger}$, eu
13	102	0.14	27.2	−13.2
	146	6.65		
16	146	1.39	24.0	−24.2
	176	8.90		
exo-2-Norbornyl	146	2.2×10^5 [a]	25	
endo-2-Norbornyl	146	1×10^a	26	

[a] Extrapolated from rates at 25 °C.

the trimethylsilyl ethers. The major constituent (80%) of the ether mixture was shown to have the exo configuration by comparison with an authentic sample. The remaining 20% was confirmed as the endo ether.

Acetolysis of *exo*-*p*-bromobenzenesulfonate **13** followed by a similar isolation and analysis procedure indicated the acetate fraction of acetolysis to be composed of 84% exo and 16% endo acetate. The minor nonacetate component (3%) was shown to have a retention time different from that of authentic olefin **19** and so was also assumed to have the azanortricyclene structure. In a control experiment the acetate esters **9** and **15** were shown to be stable to the solvolytic conditions at 150 and 180 °C for 96 h (0.042 M solutions).

Kinetic rates for the acetolyses were determined at 102, 146, and 176 °C. The reactions exhibited linear first-order kinetics over the indicated temperature range. Reaction rates were determined from plots of ln [ROB] vs. time and represent the averages of duplicate experiments. A summary of the averaged kinetic rate data may be found in Table I.

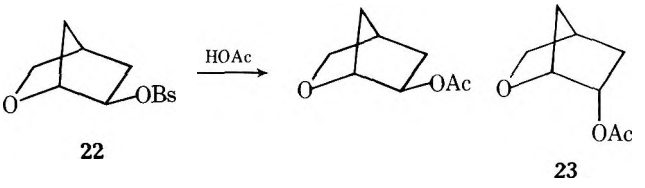
Discussion

In their investigation of the reactions of the optically active 2-norbornylcarboxylic acids with lead tetraacetate, Corey and Casanova[10] suggested that "the most obvious possibilities for the intermediate species are either the radical or the cation or both. However, rearrangement of the norbornyl radical by homolytic scission of the C_6–C_1 bond has been shown to occur only at high temperature (300 °C)"[11] The responsibility for the retention of optical activity observed in production of the exo acetate was thereby relegated to a cationic species. If this is so, the conclusion is significant: all of the norbornyl acetate is derived from a cation, which at least in the case of the optically active product must be nonsymmetrical. The absence of symmetry in this case was attributed to the rapid collapse of an initially formed intimate ion pair, resulting in a greatly shortened ion lifetime.

The oxidative decarboxylation of the 2-aza-endo acid **4** yielded both endo and exo **9** and **15**. This result suggests the presence of a symmetrical intermediate,[12] and in this case a localized cation is at least implicated in part. The most interesting feature of this ion is its unusual ability to accept nucleophilic attack at the endo face of the norbornyl skeleton.

This unusual quality of the *N*-*p*-toluenesulfonyl-2-azanorbornyl cation(s) was further shown in the acetolyses of the *p*-bromobenzenesulfonate esters **13** and **16** where both esters yielded a mixture of acetate epimers as the chief product. Interestingly, the endo acetate **15** was found to be present as 16% of the product acetates from **13** and 20% of the acetates from **16**. The formation of these relatively large amounts of endo acetate must be contrasted with the acetolyses of the 2-norbornyl *p*-bromobenzenesulfonates in which essentially no endo acetate was observed.

Nevertheless the observation of endo product from acetolyses of norbornyl esters is not without precedent. In an acetolysis study of *exo*-2-oxabicyclo[2.2.1]hept-6-yl *p*-bromobenzenesulfonate (**22**), Fayter and Spurlock[3] reported the formation of endo acetate **23** as 0.4% of the acetate products. The epimeric endo sulfonate ester afforded a slightly higher propotion of **23**. The authors have suggested that coordination of the oxygen atom in the ring with the solvent facilitates delivery of acetate to the endo face.



22 **23**

More recently, Gassman et al.[13] have described the syntheses and solvolytic properties of the epimeric 7,7′-dimethoxybicyclo[2.2.1]hept-2-yl *p*-toluenesulfonates. Their observation of endo product from solvolysis of the exo ester, in addition to a rate retardation of this compound as compared with its unsubstituted analogue, suggests an inefficient assistance to ionization and formation of an ion with the charge localized at C_2. On the basis of these observations the authors conclude that "substituents in the 1 or 7 positions with electron withdrawing power greater than two methoxy groups will not yield ions in which the charge will be localized in the 1 position in the transition state for ionization . . ." As we will presently reconfirm, substituents on the 6 position may be added to this statement.

Clearly, a major difference between the *N*-toluenesulfonyl-2-azabicyclo[2.2.1]heptyl skeleton and the carbocyclic 2-norbornyl one is the lessened electron density at C_3 brought on by the presence of the sulfonamide group. A rough approximation of the rate differential caused by introduction of a sulfonamide function γ to a solvolytic center in a carbocyclic molecule is 7.5.[14] Whether the inductive effect of the sulfonamide is sufficient in the case of *exo*-*p*-bromobenzenesulfonate **13** to completely quench C_3–C_4 σ-bond assistance to ionization is not clear, but the rate difference of 3×10^5 between **13** and its *exo*-2-norbornyl counterpart strongly suggests this possibility. It is at least

certain that the effect transmitted from the γ substituent to C_5 does not lead to an appreciable exo/endo rate ratio.

The ground state energy for *endo*-2-norbornanol is known to exceed that observed fo *exo*-2-norbornanol by approximately 1 kcal/mol.[15] A similar energy barrier assumed for the related sulfonate esters would allow the prediction that ionization of the endo ester should occur more rapidly than that of its exo isomer by about sixfold. In light of the actual exo/endo rate ratio at 25 °C of ~350 it has been speculated that to some degree decelerative effects must therefore operate more effectively on the transition state for solvolysis of the endo sulfonate ester than on that of the exo. To explain part of the discrepancy between prediction and observation, Sargent has argued that either steric factors more effectively inhibit dissociation of the endo ester or that solvolysis of the endo material is hindered by torsional interactions which lead to a transition state of higher energy than that from the exo ester, or that a combination of effects is operative.

Similar arguments can be advanced, in a somewhat less ambiguous example, to explain the exo/endo rate ratio of approximately 5 observed for the acetolyses of the *N*-*p*-toluenesulfonyl-2-azabicyclo[2.2.1]hept-5-yl *p*-bromobenzenesulfonates, **13** and **16.** In this case, apparent means by which the solvolytic rate for exo ester **13** can be accelerated are absent, other than the distinct possibility of solvent assisted ionization.[17] This fact and the observation of a 7×10^3 fold rate retardation of **16** when compared to its *endo*-2-norbornyl analogue lead to the conclusion that a greater increase in nonbonded strain during passage from the endo ground state to its transition state must be at least partially responsible for the observed small, but positive, exo/endo rate ratio.

In summary, several facts are obtainable from the synthetic and solvolytic results. First, based on the results of equilibration studies, substituents at the exo position of C_5 are thermodynamically favored over their endo counterparts; second, removal of a carboxyl group from C_5 by either a carbonium ion generating reaction (lead tetraacetate) or radical reaction (mercuric oxide, bromine) gives a mixture of exo and endo products; third, the formation of relatively large quantities of endo acetate **15** from acetolyses of either *p*-bromobenzenesulfonate **13** or **16** suggests a localized ion at C_5 as the major product forming species; fourth, the large rate retardation (10^{-5}–10^{-4}) for acetolysis of either sulfonate ester, relative to its carbocyclic norbornyl analogue, indicates a profound detrimental inductive influence on ionization by the γ-sulfonamide group and in the endo case suggests detrimental influences of nonbonded interactions on ionization of **16**; fifth, the relatively small, but not inverse, exo/endo rate ratio for acetolyses of **13** and **16** indicates that while assistance to ionization may be mainly responsible for large exo/endo rate ratios observed in other norbornyl acetolyses, it is not the only reason for more rapid reactions by the exo compounds; sixth, and finally, the large negative entropies of activation for acetolyses of **13** and **16** imply much demand for solvent participation in the transition states to ionization of both esters.

Experimental Section[18]

***N,O,O'*-Tri-*p*-toluenesulfonylhydroxy-L-prolinol (1).** The tri-*p*-toluenesulfonate **1** was prepared from hydroxy-L-proline according to the procedure of Portoghese[4] in 85% yield, mp 132–135 °C (lit.[4] mp 134.5–136 °C).

***N*-*p*-Toluenesulfonyl-2-azabicyclo[2.2.1]heptane-5,5-dioic Acid (3).** To 100 ml of absolute ethanol at reflux was added 4.14 g (0.18 g-atom) of sodium metal under an atmosphere of nitrogen. Upon complete reaction of the sodium, 36 g (0.225 mol) of diethyl malonate in 75 ml of ethanol was added dropwise. After 0.5 h this sodiomalonic ester was transferred to a dropping funnel and added to 25.8 g (0.045 mol) of **1** in 650 ml of ethanol at reflux. The reaction mixture was stirred for 7 h at reflux and then for 13 h at room temperature. The precipitate of sodium *p*-toluenesulfonate was removed by filtration and the filtrate diluted with 400 ml of water and concentrated under vacuum. The concentrate was saturated with sodium chloride and continuously extracted with ether to yield 15.5 g (88%) of crude diester. This material was employed without further purification. To 15.5 g (0.039 mol) of the diester in 350 ml of 80% ethanol was added 13.4 g (0.236 mol) of potassium hydroxide. The reaction mixture was heated at reflux for 10.5 h and continuously extracted with ether to yield 9.5 g of reddish oil which could be induced to crystallize after trituration with 30–60 °C petroleum ether. Recrystallization of the solid from the same solvent afforded colorless crystals: mp 168.5–170.5 °C; ir (mull) 2900–2500, 1720, 1350, 1250, 1160, 1080, 1030, 820, and 665 cm^{-1}.

***N*-*p*-Toluenesulfonyl-2-azabicyclo[2.2.1]heptane-5-carboxylic Acids (4 and 5).** A 9.5-g (0.028 mol) sample of crude diacid **3** was heated at reflux in 40 ml of pyridine. Evolution of carbon dioxide was observed by trapping the escaping gas in an aqueous barium hydroxide solution. After 3 h gas evolution had ceased and the reaction mixture was basified with 1 N sodium hydroxide and extracted with ether. Separation of the aqueous layer was followed by its acidification with 10% hydrochloric acid solution and subsequent extraction with ether. The extracts were dried with magnesium sulfate, filtered, and concentrated to give 4.2 g (51%) of the crude epimeric monoacids. The oily mixture was redissolved in ether and reacted with an ethereal solution of *tert*-butylamine. The precipitated salt was separated by filtration. The firtrate was acidified with 10% hydrochloric acid and extracted with ether, producing a yellow oil whose infrared spectrum suggested the predominant presence of one isomer. This was tentatively assigned the endo configuration **5.** The oil subsequently solidified and several recrystallizations from benzene afforded pure endo acid **5** as white crystals: mp 189.5–191.0 °C (lit.[8] mp 188–190 °C); NMR ($CDCl_3$) τ 1.0 (1 H, br s), 2.45 (4 H, A_2B_2), 5.70 (1 H, m), 6.75–7.30 (4 H, complex m), 7.55 (3 H, s), 7.80–8.90 (4 H, complex m).

The *tert*-butylamine salt was dissolved in water and acidified with 10% hydrochloric acid. Extraction with ether followed by drying and concentration of the solution afforded 0.9 g of a light brown solid whose infrared spectrum was different from that of the solid obtained previously. Four recrystallizations of this exo acid **4** from benzene–ether gave white needles, mp 138.5–140 °C. The exo epimer was characterized as its 1-adamantylamine salt **6,** a white solid with mp 212–215 °C dec. The pure exo acid could be regenerated from the adamantyl salt with concentrated acid: ir (mull) 3600–3000, 3050, 2900–2300, 1695, 1340, 1155, 820, and 685 cm^{-1}; NMR ($CDCl_3$) τ 1.50 (1 H, br s), 2.50 (4 H, A_2B_2), 5.7 (1 H, br m), 6.75–6.90 (2 H, m), 7.20 (1 H, br m), 7.40–7.60 (1 H, m), 7.60 (3 H, s), 7.80–9.19 (4 H, br m).

Anal. Calcd for $C_{14}H_{17}NO_4S$: C, 56.93; H, 5.80; N, 4.74. Found: C, 56.87; H, 5.93; N, 4.48.

Methyl *N*-*p*-Toluenesulfonyl-2-azabicyclo[2.2.1]heptane-*exo*-5-carboxylate (7). To 10 mg (0.03 mmol) of the exo acid **4** in 2 ml of methylene chloride was added an ethereal solution of diazomethane (generated from Diazald) until the evolution of nitrogen ceased and the pale yellow color of diazomethane persisted. On concentration of the solution a fluffy white solid resulted: mp 148.5–149 °C; ir (CH_2Cl_2) 3060, 2950, 2900, 1740, 1600, 1440, 1350, 1220, 1100, 810, and 660 cm^{-1}; NMR ($CDCl_3$) τ 2.20–2.80 (4 H, A_2B_2), 5.70–5.90 (1 H, br m), 6.40 (3 H, s), 6.85–6.95 (2 H, m), 7.15–7.50 (2 H, m), 7.60 (3 H, s), 7.80–8.20 (2 H, m), 8.40–9.15 (2 H, complex m).

Methyl *N*-*p*-Toluenesulfonyl-2-azabicyclo[2.2.1]heptane-*endo*-5-carboxylate (8). A 10-mg (0.03 mmol) sample of the pure endo acid **5** was treated with diazomethane as described previously, affording the endo ester **8** as a pale yellow oil which could not be induced to solidify: ir (CH_2Cl_2) 3060, 2950, 2900, 1740, 1600, 1440, 1350, 1220, 1160, 1100, 2950, 2900, 1740, 1600, 1440, 1350, 1220, 1160, 1100, 810, and 660 cm^{-1}; NMR ($CDCl_3$) τ 2.15–2.70 (4 H, A_2B_2), 5.50–5.85 (1 H, br m), 6.35 (3 H, s), 6.70–6.85 (2 H, m), 6.90–7.30 (2 H, m), 7.60 (3 H, s), 7.80–8.10 (2 H, br m), 8.45–9.0 (3 H, m).

***exo*- and *endo*-*N*-*p*-Toluenesulfonyl-2-azabicyclo[2.2.1]-hept-5-yl Acetates (9 and 15).** To 17.5 g (0.05 mol) of endo acid **5** in a mixture of 300 ml of anhydrous benzene and 60 ml of pyridine under nitrogen was added 60 g (130 mmol) of lead tetraacetate which had been recrystallized from acetic acid and stored under vacuum. The solution was heated at reflux for 9 h. Work-up was accomplished by filtration through a bed of Celite 503 and succes-

sive washings of the filtrate with 500 ml of a 10% hydrochloric acid solution, 250 ml of 10% sodium hydroxide solution, and 500 ml of water. The solution was dried with magnesium sulfate, filtered, and concentrated to yield 5.5 g (35%) of a bicyclic acetate mixture contaminated with an unidentified material. The acetate mixture was triturated with *n*-pentane to remove the contaminant and used directly in the succeeding reaction: ir (film) 2950, 1740, 1600, 1500, 1340, 1160, 1100, 820, and 680 cm^{-1}; NMR ($CDCl_3$) τ 2.20–3.10 (4 H, A_2B_2), 5.20–5.35 (1 H, br m), 5.90 (1 H, br s), 6.70–7.10 (2 H, br m), 7.10 (4 H, m), 8.10 (3 H, s), 8.50–9.20 (2 H, m).

***exo*-*N*-*p*-Toluenesulfonyl-2-azabicyclo[2.2.1]heptan-5-ol (10).** To 0.8 g (21 mmol) of lithium aluminum hydride in 30 ml of anhydrous ether was added 5.5 g (17 mmol) of the crude exo acetate mixture (from above) in 20 ml of anhydrous ether. The reaction mixture was stirred at room temperatue for 3 h. Work-up was accomplished by addition of 0.5 ml of water, followed by 2.5 ml of 15% potassium hydroxide solution and an additional 1 ml of water. The white salts were removed by filtration and the filtrate dried with magnesium sulfate and concentrated to yield 2.5 g (55%) of a yellow oil. A 750-mg sample of the crude alcohol mixture was chromatographed on 8 g of neutral alumina. Elution with ether gave pure exo alcohol **10** as a white, waxy solid: mp 120.5–122.5 ° C (lit.[8] mp 120–122 °C); ir (film) 3600–3450, 2950, 1600, 1500, 1340, 1300, 1160, 1090, 1040, and 820 cm^{-1}; NMR ($CDCl_3$) τ 2.30–2.80 (4 H, A_2B_2), 5.95 (1 H, br m), 6.50 (3 H, m), 6.80–7.20 (2 H, m), 7.70 (3 H, s), 8.00–9.20 (4 H, m).

***N*-*p*-Toluenesulfonyl-2-azabicyclo[2.2.1]heptan-5-one (11).** To the complex formed from the reaction of 2.69 g (0.027 mol) of chromium trioxide and 6 ml of pyridine in 60 ml of methylene chloride was added 1.2 g (4.5 mmol) of the exo alcohol **10** in 6 ml of methylene chloride. The reaction mixture was stirred overnight at room temperature and then terminated with successive washes of 250 ml of 10% hydrochloric acid solution, 250 ml of 10% sodium hydroxide solution, and 200 ml of water. The methylene chloride solution was dried with magnesium sulfate and concentrated to yield 0.91 g (83%) of the ketone as a pale oil which failed to solidify on standing: ir (film) 2950, 1750, 1600, 1500, 1340, 1160, 1100, 820, and 700 cm^{-1}; NMR ($CDCl_3$) τ 2.20–2.80 (4 H, A_2B_2), 5.50 (1 H, br m), 6.75–7.20 (3 H, m), 7.60 (3 H, s), 7.80–9.20 (4 H, br m).

***exo*-*N*-*p*-Toluenesulfonyl-2-azabicyclo[2.2.1]hept-5-yl *p*-Bromobenzenesulfonate (13).** To 1.0 g (3.7 mmol) of the exo alcohol **10** in 15 ml of anhydrous ether at 0 °C was added 2.5 ml of a 1.6 M *n*-butyllithium solution in hexane. After stirring for 0.5 h, the alkoxide salt had precipitated. A solution of 1.1 g (4.1 mmol) of *p*-bromobenzenesulfonyl chloride in 10 ml of tetrahydrofuran was then added. The reaction mixture was maintained at 6 °C for 10 h and then decanted into 50 ml of water. The organic phase was collected, dried with magnesium sulfate, and concentrated to yield 1.82 g of yellow oil. The crude residue was chromatographed on 15 g of Florisil and eluted with 90:10 ether–chloroform. Crystallization from ether afforded a white solid: mp 156–158 °C dec; ir (mull) 3100, 2960, 1600, 1570, 1500, 1380, 1340, 1200, 1160, and 820 cm^{-1}; NMR ($CDCl_3$) τ 2.10–2.80 (4 H, A_2B_2), 2.25 (4 H, s), 4.70–5.50 (1 H, br m), 5.85 (1 H, br m), 6.30–6.50 (1 H, d), 6.70–7.40 (2 H, m), 7.60 (3 H, s), 7.85–9.20 (4 H, m).

Anal. Calcd for $C_{19}H_{20}S_2O_5NBr$: C, 46.93; H, 4.11; N, 2.97. Found: C, 46.84; H, 4.39; N, 2.72.

***endo*-*N*-*p*-Toluenesulfonyl-2-azabicyclo[2.2.1]heptan-5-ol (12).** To 50 mg (1.3 mmol) of lithium aluminum hydride stirring in 10 ml of ether was added 30 mg (1.14 mmol) of ketone **11** in 4 ml of ether. The reaction mixture was stirred at room temperature for 10 h. Treatment with 4 drops of water and 6 drops of 15% potassium hydroxide solution gave a white precipitate which was removed by filtration. The filtrate was dried and concentrated, producing endo alcohol **12** as a white solid: mp 144–148 °C (lit.[8] mp 146–149 °C); ir (film) 3600, 3450, 2950, 1600, 1500, 1340, 1160, 920, 820, and 680 cm^{-1}; NMR ($CDCl_3$) τ 2.20–2.80 (4 H, A_2B_2), 5.55–6.10 (2 H, br m), 6.25–6.40 (1 H, d), 6.70–7.20 (3 H, br m), 7.60 (3 H, s), 7.80–9.20 (4 H, br m).

***exo*-*N*-*p*-Toluenesulfonyl-2-azabicyclo[2.2.1]hept-5-yl *p*-Bromobenzenesulfonate (16).** To 1.42 g (5.3 mmol) of endo alcohol **12** in 10 ml of ether at 0 °C was added 4.3 ml (6.9 mmol) of a 1.6 M *n*-butyllithium solution. A white precipitate developed after 15 min and the reaction was maintained at 0 °C for 0.5 h. A solution of 1.48 g (5.0 mmol) of *p*-bromobenzenesulfonyl chloride in 10 ml of ether was then added. The reaction mixture was stored at 6 °C overnight and then decanted into 50 ml of ice water. The organic phase was separated, dried, and concentrated to give 1.9 g (73%) of **16** as a white solid: mp 142–144.5 °C; ir (mull) 3100, 2950, 1600, 1570, 1500, 1470, 1360, 1340, 1200, and 820 cm^{-1}; NMR ($CDCl_3$) τ 2.15–2.75 (4 H, A_2B_2), 2.25 (4 H, s), 4.90–5.25 (1 H, br m), 5.80 (1 H, br m), 6.20–7.00 (2 H, m), 7.25 (1 H, br m), 7.60 (3 H, s), 7.80–9.10 (4 H, br m).

Anal. Calcd for $C_{19}H_{20}S_2O_5NBr$: C, 46.93; H, 4.11; N, 2.87. Found: C, 46.76; H, 4.13; N, 2.89.

***exo*- and *endo*-*N*-*p*-Toluenesulfonyl-2-azabicyclo[2.2.1]-hept-5-yl Bromides (20 and 21).** To 460 mg (1.55 mmol) of endo acid **5** and 760 mg (3.50 mmol) of red mercuric oxide in 30 ml of carbon tetrachloride at reflux was added 610 mg (3.8 mmol) of molecular bromine. After stirring for 24 h in the dark, the solution was decanted into an iced 10% potassium hydroxide solution. The organic layer was separated and dried. Concentration in vacuo gave a yellow oil which on trituration with ether proved to be partially soluble. The solid insoluble material was recrystallized from methylene chloride to give 210 mg (42%) of endo bromide **21** as a white solid: mp 170.5–171.5 °C; ir (CH_2Cl_2) 2950, 1600, 1500, 1340, 1300, 1150, 1160, 1100, 820, and 680 cm^{-1}; NMR ($CDCl_3$) τ 2.20–2.75 (4 H, A_2B_2), 5.50–6.00 (2 H, m), 6.15–6.35 (2 H, d), 6.65–7.95 (1 H, d), 7.30 (1 H, br m), 7.60 (3 H, s), 7.80–8.85 (3 H, m). The ether-soluble component was isolated by concentration of the solution to give 10 mg of exo bromide **20** as a colorless oil which could not be induced to crystallize: ir (film) 2980, 1600, 1500, 1340, 1160, 1100, 810, 705, and 680 cm^{-1}; NMR ($CDCl_3$) τ 2.20–2.75 (4 H, A_2B_2), 5.60–6.15 (2 H, br m), 6.70–6.85 (2 H, m), 7.10–7.30 (1 H, br m), 7.60 (3 H, s), 7.70–9.10 (4 H, m).

***N*-*p*-Toluenesulfonyl-2-azabicyclo[2.2.1]hept-5-ene (19).** To 420 mg (1.3 mmol) of exo bromide **20** in 4 ml of *tert*-butyl alcohol at reflux was added 430 mg (3.8 mmol) of potassium *tert*-butoxide in 5 ml of *tert*-butyl alcohol. After 24 h, the reaction mixture was decanted into ice water and extracted with two 20-ml portions of ether. The combined extracts were dried and concentrated to give 110 mg (36%) of pure olefin **19** as a colorless oil: ir (film) 3050, 2900, 1600, 1340, 1160, 1100, 820, and 680 cm^{-1}; NMR ($CDCl_3$) τ 2.15–2.75 (4 H, A_2B_2), 3.80–4.10 (2 H, m), 5.20–5.35 (1 H, br m), 6.55–6.75 (1 H, dd), 6.75–6.85 (1 H, br m), 7.35–7.55 (1 H, d), 7.60 (3 H, s), 8.55–8.70 (1 H, br s), 8.70 (1 H, br s).

***exo*-*N*-*p*-Toluenesulfonyl-2-azabicyclo[2.2.1]hept-5-yl Chloride (18).** To 5.1 g (17 mmol) of an 80:20 mixture of acids **5** and **4**, respectively, in 10 ml of pyridine and 75 ml of benzene was added 17.1 g (3.8 mmol) of lead tetraacetate. The solution was heated at reflux for 2 h and then decanted into a 40% hydrochloric acid solution. The benzene fraction was washed with saturated sodium bicarbonate solution until neutral and dried with magnesium sulfate. Concentration of the extract afforded 1.9 g (39%) of **18** as a white solid: mp 93.5–95.5 °C; ir (CH_2Cl_2) 3000, 2950, 1600, 1500, 1350, 1160, 1100, and 820 cm^{-1}; NMR ($CDCl_3$) τ 2.20–2.75 (4 H, A_2B_2), 5.8–5.95 (1 H, br m), 5.80–6.10 (1 H, br m), 6.80–7.00 (2 H, m), 7.25–7.55 (1 H, br m), 7.60 (3 H, s), 7.70–9.30 (4 H, br m).

***exo*-*N*-*p*-Toluenesulfonyl-2-azabicyclo[2.2.1]heptane-5-carboxylic Acid (4) via Epimerization.** To a solution of 17.8 g (0.33 mol) of sodium methoxide in anhydrous methanol was added 10 g (33 mmol) of an 80:20 mixture of endo and exo methyl esters **8** and **7**. The solution was heated at reflux for 48 h, quenched with water, and concentrated in vacuo. The residue was treated with ether to remove residual ester (1.1 g). The ether-insoluble fraction was acidified with 10% hydrochloric acid solution and extracted with ether. The organic fraction was dried and concentrated to give 7.5 g (84%) of a white solid which was spectroscopically identical with the authentic exo carboxylic acid **4**, mp 138.5–140 °C.

***exo*-*N*-*p*-Toluenesulfonyl-2-azabicyclo[2.2.1]hept-5-yl Methyl Ketone (17).** To a vigorously stirred solution of 2.62 g (8.8 mmol) of pure exo acid **4** in 150 ml of anhydrous ether under nitrogen at 0 °C was added 9.7 ml (17.6 mmol) of a solution of methyllithium (1.8 M) in ether. During addition the reaction mixture was allowed to slowly warm to room temperature. After 2 h the reaction was quenched with 5 ml of water and 20 ml of 15% hydrochloric acid solution. The ether layer was separated, dried, and concentrated in vacuo to yield 1.85 g of exo methyl ketone **17** contaminated with the *tert*-carbinol. The residue was taken up in ether and *n*-pentane added until a yellow oil was completely deposited. This insoluble material was isolated and shown to be the exo *tert*-carbinol: ir (film) 3600–3300, 2950, 2880, 1600, 1500, 1340, 1160, 1100, 1060, and 690 cm^{-1}. The ether–pentane solution was concentrated to produce the exo methyl ketone **17** as a colorless oil which solidified on standing: mp 158–162 °C (GC analysis suggested that the ketone was 99% pure; therefore no further purification was attempted); ir (film) 2950, 2880, 1710, 1600, 1500, 1340, 1160, 1100, 760, and 680 cm^{-1}; NMR ($CDCl_3$) τ 2.20–2.75 (4 H, A_2B_2), 5.80 (1 H, m), 6.90 (2 H, m), 7.30 (2 H, br m), 7.60 (3 H, s), 7.85 (3 H, s), 8.00–8.30 (2 H, m), 7.80–9.20 (2 H, m).

***exo*-*N*-*p*-Toluenesulfonyl-2-azabicyclo[2.2.1]hept-5-yl Acetate (9).** To 6.0 g (29 mmol) of *m*-chloroperbenzoic acid in 200 ml of methylene chloride was added 1.60 g (5.4 mmol) of **17** in 20 ml of methylene chloride. The reaction was heated at reflux for 24 h, cooled to room temperature, and terminated by addition of 40 ml of 20% sodium sulfite solution. After 2 h a test for the peracid with starch–iodide paper proved negative. The reaction mixture was then concentrated in vacuo. The residue was twice extracted with 50-ml portions of ether, and the combined extracts were dried with magnesium sulfate. Concentration of the solution yielded 1.3 g of crude exo acetate **9** which solidified on standing. Crystallization from ether–pentane afforded **9** as a white solid, mp 122–123.5 °C. This acetate was converted to its corresponding alcohol **10** by treatment with lithium aluminum hydride. The exo alcohol **10** obtained in this fashion appeared to be free of its endo epimer **12** when subjected to GC analysis.

Trimethylsilylation of Alcohols 10 and 12. To approximately 10 mg of either alcohol in a one-dram vial fitted with a micro magnetic stirring bar was added 1 ml of a silylating mixture composed of 10 parts pyridine, 2 parts hexamethyldisilazane, and 1 part trimethylsilyl chloride. The mixture was capped and stirred for 12 h, decanted into 30 ml of ice water, and extracted with 30 ml of ether. The ether extract was successively washed with cold 10% hydrochloric acid solution, saturated sodium bicarbonate solution, and water. The solution was then dried and concentrated to give the silyl ether samples employed for GC comparison. The authentic exo silyl ether exhibited a retention time of 3.6 min, whereas the endo epimer possessed a retention time of 4.2 min at 285 °C, 32 psi.

***endo*-*N*-*p*-Toluenesulfonyl-2-azabicyclo[2.2.1]hept-5-yl Acetate (15).** To 29 g (1 mmol) of **12** stirring in 5 ml of pyridine (63 mmol) was added 12 ml (130 mmol) of acetic anhydride. The reaction mixture was stirred at 115 °C for 4 h, cooled, and decanted into 100 ml of iced 10% hydrochloric acid solution and extracted with ether. The organic solution was neutralized with sodium bicarbonate solution, dried, and concentrated to give 150 mg of **15** as a pale yellow oil: NMR analysis of the product revealed no epimeric exo acetate **9** accompanying **15**; ir (film) 2950, 1740, 1600, 1500, 1340, 1160, 1100, 820, and 680 cm^{-1}; NMR ($CDCl_3$) τ 2.20–2.80 (4 H, A_2B_2), 4.80–5.20 (1 H, complex m), 5.90 (1 H, broad m), 6.30–6.50 (1 H, m), 6.80–7.10 (1 H, dq), 7.30 (1 H, broad m), 7.65 (3 H, s), 7.70–8.10 (2 H, complex m), 8.10 (3 H, s), 8.40–9.30 (2 H, m).

***endo*-*N*-*p*-Toluenesulfonyl-2-azabicyclo[2.2.1]heptan-5-ol-*exo*-5-*d* (14).** To 100 mg (2.6 mmol) of lithium aluminum deuteride in 10 ml of anhydrous ether was added 60 mg (0.22 mmol) of ketone **11** in 1 ml of anhydrous ether The reaction mixture was stirred overnight at room temperature and reaction was terminated with 5 drops of water and 0.5 ml of a 15% potassium hydroxide solution. After 1 h the white salts were separated by filtration and washed twice with 10-ml portions of ether. The combined extracts were dried and concentrated to yield 45 mg (70%) of the deuterated alcohol **14**: ir (film) 3600–3200, 2950, 1600, 1500, 1340, 1160, 1100, 820, and 680 cm^{-1}; NMR ($CDCl_3$) τ 2.20–2.95 (4 H, A_2B_2), 5.90–6.10 (1 H, broad m), 6.25–6.45 (1 H, m), 6.90–7.25 (1 H, m), 7.10 (1 H, s), 7.30 (1 H, m), 7.60–9.10 (4 H, complex m).

Acetolysis Product Studies. A 230-mg sample (0.47 mmol) of the analytically pure *endo*-*p*-bromobenzenesulfonate ester **16** and a 85-mg sample (0.17 mmol) of pure exo ester **13** were dissolved in 11 and 4 ml, respectively, of 0.085 N sodium acetate in acetic acid containing 1% by weight acetic anhydride. The solutions were sealed under nitrogen in Carius combustion tubes and heated at 150 °C for approximately 8 half-lives in an isothermal bath. The tubes were then cooled and opened and the contents decanted into 100 ml of ice water. The solutions were extracted with three 30-ml portions of ether, and the combined extracts neutralized with a saturated solution of sodium bicarbonate. The solutions were then dried and concentrated to give the samples of crude acetolysate.

A sample of the acetolysis mixture from **16** was subjected to GC analysis at 285 °C and 32 psi. One major component (97%) was noted in the product mixture. The retention time (5 min) was identical with that of both acetates **9** and **15**. A 50-mg (0.1 mmol) sample of the acetolysis residue was therefore added to 0.2 g (5.2 mmol) of lithium aluminum hydride in 30 ml of ethyl ether. The reaction mixture was stirred for 2 h and subsequently worked up with aqueous 15% sodium hydroxide solution. Concentration of the resulting ether solution afforded 35 mg of alcohol mixture. GC analysis under the aforementioned conditions indicated the predominant presence of the exo alcohol **10** along with an incompletely resolved peak having a retention time (4.7 min) similar to that of the epimeric endo alcohol **12**. Trimethylsilylation of the alcohol mixture in the manner previously described afforded 30 mg of the trimethylsilyl ethers. GC analysis of the silyl ethers indicated a product mixture consisting of 20.4% of endo ether and 79.6% of the exo ether.

GC analysis of the acetate produce mixture from exo ester **13** likewise indicated only one component with retention time identical with that of **9** and **15**. Reduction of a 30-mg portion of this acetolysate with lithium aluminum hydride, in a manner identical with that described previously, gave 20 mg of alcohol mixture. Trimethylsilylation of this mixture followed by GC analysis indicated a product composition of 83.5% exo ether and 16.5% endo ether.

Kinetic Studies. Kinetic rates for **13** and **16** were measured in buffered solutions of sodium acetate in acetic acid to which 1% acetic anhydride by weight had been added. Determination of the acetate concentration at various time intervals was accomplished by titration with standardized solutions of perchloric acid in acetic acid. All titrations were made with a 5-ml Fisher microburet, precise to 0.01 ml. An approximate 0.2% solution of crystal violet in glacial acetic acid was used as the indicator, with the end point of each titrimetric determination being taken at blue. The constant temperatures for each kinetic run were maintained with a Neslab TEX9-H isothermal bath filled with Dow Corning 200 silicone fluid. Temperatures were measured with a National Bureau of Standards thermometer calibrated to 0.1 °C.

The kinetic determinations were made by the following general procedure. A sample of the *p*-bromobenzenesulfonate was weighed into a 10-ml volumetric flask and diluted to volume with standardized sodium acetate solution. Aliquots (0.5 ml) of this solution were sealed in ampules (Kimble Neutraglas no. 12012-L) and placed in an isothermal bath.

As the acetolysis rates were sufficiently slow, zero time was taken as the time of immersion. At appropriate time intervals the tubes were withdrawn, cooled in ice water, and opened and the contents titrated with a standard perchloric acid solution. The reactions were followed through approximately 3 half-lives.

All first-order rate constants were determined using PLSTSQR, a computer program in APL language, which plots the graph of ln [ROBS] vs. time and determines a best-fit straight line to the valid points by the method of least squares.

Registry No.—**1**, 5234-75-3; **3**, 58267-19-9; **4**, 58267-20-2; **5**, 35320-35-5; **6a**, 58310-78-4; **6b**, 58310-79-5; **7**, 58267-21-3; **8**, 58267-22-4; **9**, 58229-30-4; **10**, 35299-52-6; **11**, 58267-23-5; **12**, 58267-24-6; **13**, 58229-31-5; **14**, 58310-80-8; **15**, 58267-25-7; **16**, 58267-26-8; **17**, 58267-27-9; **18**, 58229-32-6; **19**, 58229-33-7; **20**, 58229-34-8; **21**, 58267-28-0; diethyl malonate, 105-53-3; diazomethane, 334-88-3; lead tetraacetate, 546-67-8; *p*-bromobenzenesulfonyl chloride, 98-58-8; hexamethyldisilazane, 999-97-3; trimethylsilyl chloride, 75-77-4; lithium aluminum deuteride, 14128-54-2.

References and Notes

(1) (a) Presented in part at the 162d National Meeting of the American Chemical Society, Washington, D.C., Sept 1971, Abstracts, No. ORGN-133. (b) Taken in part from the Ph.D. Thesis of R.D. Gleim, Brown University, 1973.
(2) Alfred P. Sloan Fellow, 1973–1975.
(3) See, for example, (a) L. A. Spurlock and R. G. Fayter, *J. Am. Chem. Soc.*, **94**, 2707 (1972); (b) R. J. Schultz, W. H. Staas, and L. A. Spurlock, *J. Org. Chem.*, **38**, 3091 (1973).
(4) See P. S. Portoghese and A. A. Mikhail, *J. Org. Chem.*, **31**, 1059 (1966); P. S. Portoghese, A. A. Mikhail, and H. J. Kupferberg, *J. Med. Chem.*, **11**, 219 (1968); P. S. Portoghese, *ibid.*, **8**, 609 (1965), and references cited therein.
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(11) J. A. Berson, D. J. Olsen, and J. S. Walia, *J. Am. Chem. Soc.*, **82**, 5000 (1960).
(12) The observation of exo chloride **18** as the only short-term reaction product is explained by a nucleophilic attack of chloride ion on the initially formed lead carboxylate salt during work-up of the reaction.
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(14) C. A. Grob, H. R. Kiefer, H. Lutz, and H. Wilkings, *Tetrahedron Lett.*, 2901 (1964).
(15) C. F. Wilcox, Jr., M. Sexton, and M. F. Wilcox, *J. Org. Chem.*, **28**, 1079 (1963).
(16) G. D. Sargent, "Carbonium Ions", Wiley-Interscience, New York, N.Y., 1972, Chapter 24, p 1099.
(17) The relatively large amount of endo acetate **15** formed in acetolysis of *exo-p*-bromobenzenesulfonate **13** suggests that a cationic product forming intermediate does not possess sufficient steric hindrance to preclude approach from the endo face. It is therefore probable that the starting ester **13** is likewise subject, in some measure, to endo-face solvent assistance. Based on simple steric observations, the endo ester **16** should be at least equally, if not more, subject to this type of assistance.
(18) Infrared spectra were determined utilizing a Perkin-Elmer 247 grating infrared spectrometer with sodium chloride optics. Nuclear magnetic resonance spectra were obtained via a Varian Associates A-60A spectrometer; approximately 20% solutions in $CDCl_3$, acetone-d_6, or Me_2SO-d_6 were employed with teramethylsilane as the internal standard. A Perkin-Elmer 881 flame ionization gas chromatograph or a Perkin-Elmer F-11 gas chromatograph employing 20 ft × 0.125 in. columns of 3% OV-210 on Chromosorb W were used in product analyses. Elemental analyses were performed by either the Baron Consulting Co., Orange, Conn., or by Micro-Analysis, Inc., Wilmington, Del.

Synthesis of the Three Isomeric Ortho-Substituted Phenylthienyl Benzoic Acids

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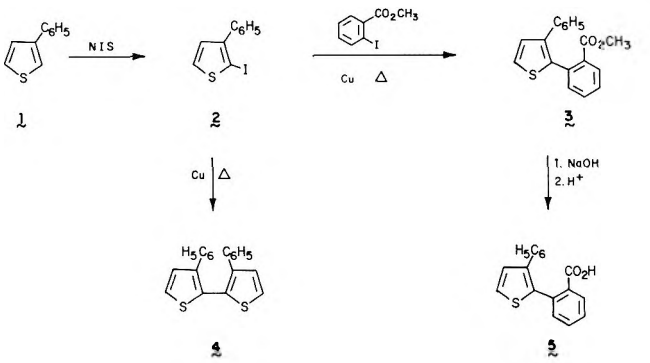
The syntheses of the three isomeric 2-(phenyl-2-thienyl)benzoic acids (**5, 19b, 19d**) are described. 2-(3-Phenyl-2-thienyl)benzoic acid (**5**) was prepared via the Ullmann biaryl synthesis from 2-iodo-3-phenylthiophene (**2**) and methyl 2-iodobenzoate. The 4- and 5-phenyl isomers (**19b, 19d**) were prepared by constructing the benzoic acid moiety by Diels–Alder reaction of butadiene with the acrylate esters (**15b, 15d**), derived from the Knoevenagel reaction of 4- and 5-phenylthiophene-2-carboxaldehydes (**14a, 14b**) with malonic acid. A cyclohexenyl group which is conjugated to the thiophene ring, as in **12a** and **12b**, was dehydrogenated rapidly to a phenyl group with 2,3-dichloro-4,5-dicyanobenzoquinone (DDQ) whereas an unconjugated cyclohexenyl group, as in **17a** and **17b** was difficult to aromatize by this procedure.

Over the past several years, I have been interested in the synthesis of benzoic acid derivatives which have a heterocyclic substituent in the ortho position and the heteroatom γ to the carboxyl group.[1-4] This paper describes the syntheses of the hitherto unknown 2-(3-, 4-, and 5-phenyl-2-thienyl)benzoic acids (**5, 19b, 19d**) shown in Schemes I and II. The literature syntheses[5-7] of the parent compound, 2-(2-thienyl)benzoic acid, and its methyl ester suggest the Ullmann method as being applicable to the phenyl compounds.

The bromination or iodination of 2- and 3-phenylthiophene[8-10] was the starting point for the new compounds. The synthesis and electrophilic substitutions of these thiophenes has been extensively studied by Gronowitz[10-13] and Wynberg[11,14] and their collaborators. 2-Bromo-5-phenyl- and 2-bromo-3-phenylthiophene are readily obtained in high yield by treating 2- and 3-phenylthiophene, respectively, with NBS,[11,14] and they appeared to be good candidates with which to start the synthesis of **5** and **19d.** Bromination of 3-phenylthiophene in acetic acid[11] gives a difficultly separable mixture of 2-bromo-3-phenyl- and 2-bromo-4-phenylthiophene, in which the former predominates. In acetic acid, 2-bromo-3-phenylthiophene equilibrates with its isomer, and undergoes disproportionation to 3-phenylthiophene and 2,5-dibromo-3-phenylthiophene.[11-14] This did not appear to be a promising method of preparing quantities of 2-bromo-4-phenylthiophene to use as starting material for **19b.**

In Scheme I, attempts to condense 2-bromo-3-phenylthiophene with methyl 2-iodobenzoate using copper powder at 200 °C were unsuccessful. 2-Iodo-3-phenylthiophene (**2**), prepared from 3-phenylthiophene and *N*-iodosuccinimide in 80% yield, was successfully used to give a 45% yield of the desired ester **3** as a distillable oil. As expected in a mixed Ullmann reaction,[15,16] bibenzoic acid ester was

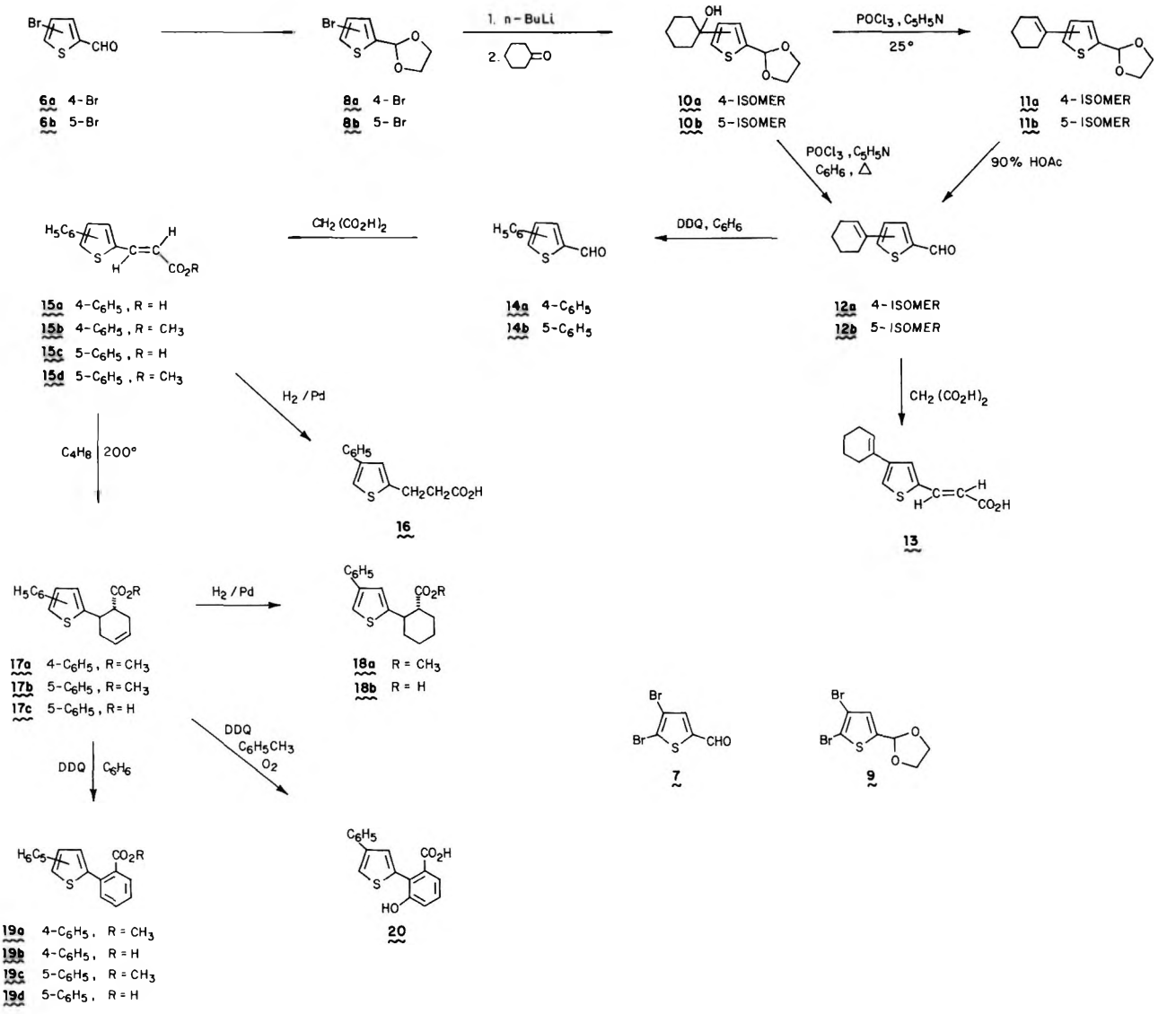
Scheme I



present in the reaction mixture, but 3,3′-diphenyl-2,2′-bithiophene (**4**) was not detected. Structure **4**, a new compound,[17] was prepared separately in 13% yield from **2** by the Ullmann reaction. 2-(3-Phenyl-2-thienyl)benzoic acid (**5**) was obtained in good yield by saponification of ester **3.**

The problems discussed above in preparing sufficient quantities of pure 2-bromo-4-phenylthiophene by the direct bromination of 3-phenylthiophene[11-14] required a different approach to the synthesis of 2-(4-phenyl-2-thienyl)benzoic acid (**19b**). In Scheme II, 4-bromothiophene-2-carboxaldehyde (**6a**), the aluminum chloride catalyzed bromination product of thiophene-2-carboxaldehyde,[18,19] was chosen because it was readily prepared in quantity and had the necessary orientation of functional groups which could be modified to produce **19b** in a sequence of eight steps. The product distribution in this bromination depends upon how well the reaction mixture, which has the consistency of heavy grease, is stirred. In tenth-mole runs good conversion to **6a** was observed, the minor amounts of 4,5-dibromothiophene-2-carboxaldehyde (**7**) being readily

Scheme II



separable by fractional distillation. In 0.5–1.0-mol runs, the inhomogeneity of the reaction mixture gave higher proportions both of unreacted thiophene-2-carboxaldehyde and **7**. A more convenient separation procedure, which also provided the next compound in the sequence, 4-bromothiophene-2-carboxaldehyde ethylene acetal (**8a**), was to separate the ethylene acetals of the aldehyde mixture by fractional distillation. The two aromatic subtituents were then introduced in sequence as shown in Scheme II.

The 4-phenyl substituent was introduced into **8a** by sequential treatment with *n*-BuLi and cyclohexanone, followed by dehydration and deacetalization of the hydroxy acetal (**10a**) to 4-(1-cyclohexenyl)thiophene-2-carboxaldehyde (**12a**), and dehydrogenation of **12a** to 4-phenylthiophene-2-carboxaldehyde (**14a**). I isolated the previously unreported[10] 3-(1-hydroxycyclohexyl)thiophene and 3-(1-hydroxycyclohexyl)thiophene-2-carboxaldehyde ethylene acetal (**10a**), respectively, from 3-bromothiophene and **6a**. They are crystalline solids which are readily dehydrated to the corresponding 3-(1-cyclohexenyl)thiophenes with phosphorus oxychloride and pyridine. Direct conversion of **10a** to **12a** occurs when **10a** is stirred briefly at reflux with a benzene solution of phosphorus oxychloride and benzene. The product thus obtained is difficult to purify, and decomposes on storage within a few days, because of the presence of unknown by-products. A two-step room temperature procedure (**10a** → **11a** → **12a**) with phosphorus oxychloride and pyridine, followed by 90% acetic acid, eliminates this problem. The dehydrogenation of cyclohexene **12a** to **14a** and of 3-(1-cyclohexenyl)thiophene to 3-phenylthiophene is accomplished more rapidly and in higher yield with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) than with chloranil.[10] This dehydrogenation occurs so readily that each portion of DDQ changes color almost as soon as it is added, and the benzene solvent goes from 25 °C to reflux during the course of the addition. 4-Phenylthiophene-2-carboxaldehyde is a known compound which was previously prepared[13] in 60% yield by treating the difficultly accessible 2-bromo-4-phenylthiophene with EtLi and DMF. My synthesis of this intermediate aldehyde is free of isomer ambiguities, may be carried through from **6a** to **14a** without purification of intermediates, and is applicable to the preparation of large quantities of **14a**.

The intermediate 3-(1-cyclohexenyl)thiophene-2-carboxaldehyde (**12a**) was characterized as the crystalline 3-[4-(1-cyclohexenyl)-2-thienyl]acrylic acid (**13**) using the Knoevenagel reaction. Similar treatment of **14a** gave 3-(4-phenyl-2-thienyl)acrylic acid (**15a**); both **13** and **15a** had a trans double bond,[20] shown conclusively by the proton NMR coupling constant of 16 Hz for the vinyl protons. Product **15a** was also characterized by catalytic reduction to 3-(4-phenyl-2-thienyl)propionic acid (**16**). The necessary

number of carbon atoms of the benzoic acid moiety was completed by Diels–Alder addition of butadiene to the methyl ester **15b**. The ester was chosen because (1) preliminary experiments with 2-thienylacrylic acid[21] showed that while addition was complete, it was difficult to isolate the free acid in the pure state; (2) dehydrogenation of the resulting cyclohexene with DDQ gives a more tractable product from the ester than from the acid. Reaction of ester **15b** with butadiene at 200 °C for 20 h gave the expected trans adduct[22] (**17a**). This was characterized by catalytic reduction to methyl *trans*-2-(4-phenyl-2-thienyl)cyclohexanecarboxylate (**18a**), and saponification of the latter to its parent acid (**18b**).

In sharp contrast to **12a**, the dehydrogenation of unconjugated methyl *trans*-2-(4-phenyl-2-thienyl)-4-cyclohexenylcarboxylate (**17a**) to the completely aromatic ester **19a** occurred very slowly with DDQ. This method gave more tractable results than attempts to use sulfur or palladium on carbon. The progress of the reaction was monitored by the disappearance of the aliphatic proton signals in the NMR, and required 2 days for completion in refluxing benzene. Saponification of **19a** gave the desired final product 2-(4-phenyl-2-thienyl)benzoic acid (**19b**). An attempt to accelerate the rate of dehydrogenation by using refluxing toluene as the solvent gave a 4% yield of hydroxy acid **20** as the only recognizable product after saponification. This product presumably arises by allylic oxidation of **17a** at the higher reaction temperature.

In considering a synthesis of the third isomer, **19d**, both Schemes I and II appeared to be equally difficult. Scheme II was chosen for the following reasons. (1) The experience in making **19b** encouraged the belief that a parallel sequence would work for **19d**. (2) 5-Bromothiophene-2-carboxaldehyde (**6b**) is commercially available in large amounts. (3) The Ullmann reaction route would require the preparation of 2-phenylthiophene. (4) The literature[17,23] indicates that a mixed Ullmann reaction with 5-phenyl-2-iodothiophene would produce a fairly high proportion of 5,5′-diphenyl-2,2′-bithienyl, the formation of which is less sterically hindered than that of its isomer **4**. Accordingly, Scheme II was also used to prepare **19d**, and pure isolated samples of the intermediate products **8b**, **10b**, **12b**, **14b**, **15c**, **15d**, **17b**, **19c**, and **19d** were obtained in an analogous manner to their 4-phenyl isomers in the **a** series. The same marked difference in reactivity of the conjugated and unconjugated cyclohexenes **12b** and **17b** toward DDQ dehydrogenation was noted as in the **a** series. Completely conjugated **17b** did appear to be more reactive than its cross-conjugated isomer **17a**. The saponification of esters **17b** and **19c** was normal, and good recoveries of parent acids were obtained.

Experimental Section[24]

2-Iodo-3-phenylthiophene (2) was prepared from *N*-iodosuccinimide and 3-phenylthiophene[10–14,25] in 79–81% yield, using the procedure described for the bromo compound.[14] Pure **2** is a liquid: bp 126–130 °C (0.90 mm); ν_{max} 1600, 1480, 955, 860, and 680 cm^{-1}; λ_{max} (C_8H_{18}) 258 nm (ϵ 10 300) and 233 (16 100); ^{1}H NMR δ 7.52–7.12 (m) 6 H (C_6H_5, thiophene), and 6.88 ppm (d, J = 6 Hz) 1 H (thiophene). Anal. Calcd for $C_{10}H_7SI$: C, 41.97; H, 2.47. Found: C, 42.24; H, 2.50.

Methyl 2-(3-Phenyl-2-thienyl)benzoate (3). A preheated mixture (180 °C) of **2** (14.44 g, 50.5 mmol) and methyl 2-iodobenzoate (13.20 g, 50.5 mmol) was treated in small portions with Cu powder (Venus No. 44, fine, 15.90 g, 0.25 g-atom). The temperature rose spontaneously to 230 °C, and it was held at 210 °C for 30 min. The cooled mixture was extracted with C_6H_6 to give a brown oil which was short-path distilled at 150° (0.2 mm) to remove ~1 g of **2**. The residue was chromatographed on 330 g of Woelm activity III neutral Al_2O_3 (50-ml fractions). Fractions 1–8 (hexane) and 9–12 (C_6H_6) gave 2.15 g of **2**; fractions 13–15 (C_6H_6) gave 6.19 g (22.7 mmol, 45%) of product **3**; and fractions 16–20 (C_6H_6) gave 2.54 g of bibenzoic ester and other substances. Pure **3**, sublimed at 110 °C (0.25 mm), had mp 61–65 °C; ν_{max} 1725, 690, and 650 cm^{-1}; λ_{max} (MeOH) 225 nm (ϵ 20 500); ^{1}H NMR δ 7.83–7.08 (m) 6 H (C_6H_4, thiophene), 7.15 (s) 5 H (C_6H_5), and 3.52 ppm (s) 3 H (CO_2CH_3). Anal. Calcd for $C_{18}H_{14}SO_2$: C, 73.46; H, 4.80; *m/e* 294.0714. Found: C, 73.59; H, 4.64; *m/e* 294.0746.

The above product appeared to be free of 3,3′-diphenyl-2,2′-bithienyl (**4**), which was not identified in any of the fractions. 2-Bromo-3-phenylthiophene[14] was unsatisfactory in this Ullmann condensation, and no coupling product was found.

3,3′-Diphenyl-2,2′-bithiophene (4) was prepared by heating **2** (5.0 g, 18.5 mmol) and Cu powder (6.35 g, 0.1 g-atom) at 200 °C for 30 min. Extraction of the cooled residue with C_6H_6 gave a brown oil from which 0.7076 g (2.22 mmol, 13%) of colorless prisms of **4** sublimed at 130 °C (0.1 mm). Pure **4** has mp 107–109°; ν_{max} (KBr) 1600, 865, 685, and 645 cm^{-1}; λ_{max} (C_8H_{18}) 300 nm (ϵ 6650), 251 (21 000), and 232 (22 100); ^{1}H NMR δ 7.70–7.22 (m) 10 H and 7.12 ppm (s) 4 H. Anal. Calcd for $C_{20}H_{14}S_2$: C, 75.46; H, 4.43; *m/e* 318.0536. Found: C, 75.99; H, 4.64; *m/e* 318.0531.

2-(3-Phenyl-2-thienyl)benzoic Acid (5). A mixture of ester **3** (6.68 g, 22.7 mmol), H_2O (25 ml), MeOH (25 ml), and NaOH (8.0 g, 0.20 mol) was stirred at reflux for 5 h. The brown solid which precipitated after acidification (pH 3, HCl) was recrystallized (75% MeOH, 105 ml): yield 3.66 g (13.0 mmol, 55%); mp 173–175°. The analytical sample formed colorless crystals with mp 176 °C dec; ν_{max} (KBr) 1675 and 1295 cm^{-1}; λ_{max} (MeOH) 225 nm (ϵ 19 300); ^{1}H NMR (Me_2SO-d_6) δ 7.80–7.22 (m) 6 H (C_6H_4, thiophene) and 7.13 ppm (s) 5 H (C_6H_5). Anal. Calcd for $C_{17}H_{12}SO_2$: C, 72.85; H, 4.32. Found: C, 72.94; H, 4.42.

4-Bromothiophene-2-carboxaldehyde (6a) was prepared by the literature procedure[18] from thiophene-2-carboxaldehyde, Br_2, and $AlCl_3$. In large-scale runs, the thick reaction mixture is difficult to stir, and this reduces the yield of **6a**, and increases the proportions of starting aldehyde and 4,5-dibromothiophene-2-aldehyde (**7**). Small proportions of these impurities are readily separated by distillation, but for larger samples conversion of the crude aldehyde mixture to the corresponding acetals is more effective for purification.

4-Bromothiophene-2-carboxaldehyde Ethylene Acetal (8a).
A. A mixture of pure **6a** (76.0 g, 0.397 mol), ethylene glycol (62 g, 1.0 mol), C_6H_6 (400 ml), and *p*-TsOH (1.0 g) was stirred at reflux under H_2O separation for 5 h. Distillation at 87–88 °C (0.4 mm) gave 83.5 g (0.355 mol, 90%) of **8a** with ν_{max} 1170, 1080 cm^{-1}; λ_{max} (C_8H_{18}) 247 nm (ϵ 4380) and 229 (5750); ^{1}H NMR δ 7.22 (s) 1 H (H_3), 7.08 (s) 1 H (H_5), 6.03 (s) 1 H (OCHO), and 6.00 ppm (m) 4 H (OCH_2). Anal. Calcd for $C_7H_7BrO_2S$: C, 35.76; H, 3.00. Found: C, 35.64; H, 2.82. Its properties are similar to those of the diethyl acetal described by Goldfarb.[18]

B. The crude bromination mixture (186 g) was similarly converted to a mixture of acetals which was separated on a 16-in. spinning band column to give thiophene-2-carboxaldehyde ethylene acetal (15 g), bp 74 °C (0.2 mm), **8a** (85.4 g), bp 92 °C (0.1 mm), and 4,5-dibromothiophene-2-carboxaldehyde ethylene acetal (**9**) (56.1 g), bp 108 °C (0.2 mm).

C. Aldehyde **6a** was regenerated from **8a** in 78% yield by stirring a mixture of **8a** (19.6 g, 84 mmol), $POCl_3$ (20 ml), C_6H_6 (50 ml), and C_5H_5N (20 ml) at reflux for 30 min, followed by adding the mixture to water, separation, extraction with dilute HCl, and distillation of the residue from the dried C_6H_6 layer at 60° (0.1 mm).

4,5-Dibromothiophene-2-carboxaldehyde ethylene acetal (9) was prepared in 91% yield from solid aldehyde **7** as described above. It is a colorless liquid with λ_{max} (C_8H_{18}) 298 nm (ϵ 234) and 241 (8800); ^{1}H NMR δ 6.86 (s) 1 H (H_3), 5.90 (s) 1 H (OCHO), and 3.95 ppm (s) 4 H (OCH_2). Anal. Calcd for $C_7H_6Br_2O_2S$: C, 26.77; H, 1.92. Found: C, 27.06; H, 1.98.

4-(1-Hydroxycyclohexyl)thiophene-2-carboxaldehyde Ethylene Acetal (10a). A solution of *n*-BuLi in hexane (1.6 M, 45 ml, 72 mmol) was stirred at −70 °C and treated in sequence with a solution of **8a** (15.25 g, 65 mmol) in Et_2O (45 ml) and with cyclohexanone (6.36 g, 65 mmol). The mixture was stirred at 25 °C overnight, decomposed with 10 ml of HOAc, and the volatile materials were removed by vacuum distillation to leave 7.5 g of brown residue which solidified overnight. The impurities were rinsed away with hexane, and the residue recrystallized (C_6H_6–C_6H_{14}) as colorless needles (6.9 g, 27.1 mmol, 42%), mp 76–77 °C. Sublimation at 150 °C (0.1 mm) causes decomposition. The pure tertiary alcohol **10a** has ν_{max} 3560 and 3440 cm^{-1}; λ_{max} (dioxane) 293 nm (ϵ 118) and 232 (7350); ^{1}H NMR δ 7.13 (s), 2 H (H_3, H_5), 6.00 (s) 1 H (OCHO), 4.00 (m) 4 H (OCH_2), 2.12 (s) 1 H (OH), and 1.76 ppm

(m) 10 H (cyclohexyl). Anal. Calcd for $C_{13}H_{18}SO_3$: C, 61.40; H, 7.14. Found: C, 61.59; H, 7.11.

4-(1-Cyclohexenyl)thiophene-2-carboxaldehyde (12a). A. A mixture of **10a** (27.78 g, 0.109 mol), $POCl_3$ (38.4 g, 0.25 mol), C_5H_5N (50 ml), and C_6H_6 (150 ml) was left overnight at 25 °C. The clear solution became warm within 15 min, and deposited a crystalline solid. The mixture was poured onto 250 g of ice and separated, and the C_6H_6 layer was washed with 2 × 250 ml of H_2O, dried, and evaporated to leave 15.8 g (67 mmol, 62%) of crude 4-(1-cyclohexenyl)thiophene-2-carboxaldehyde ethylene acetal (**11a**) identified by ^1H NMR δ 6.25 (m) (vinyl), 6.12 (s) (OCHO), and 4.05 ppm (m) (OCH_2).

B. The crude acetal **11a** was stirred with 90% HOAc (75 ml) for 2 h at 25 °C to effect deacetalization. The mixture was poured into 300 ml of H_2O and extracted with 3 × 75 ml of $CHCl_3$, the extracts were rinsed with 5% $NaHCO_3$, dried, and evaporated, and the residue was distilled at 123 °C (0.1 mm), yield 7.10 g (37 mmol, 34% overall) of **12a**. Pure aldehyde **12a** was a yellow solid with mp 38–39°; ν_{max} 1670 cm^{-1}; λ_{max} (C_8H_{18}) 318 nm (ε 6100) and 245 (21 500); ^1H NMR δ 9.88 (s) 1 H (CHO), 7.87 (s) and 7.47 (s) 2 H (H_3, H_5), 6.25 (m) 1 H (vinyl), 2.27 (m) 2 H (allylic), and 1.70 ppm (m) 6 H (CH_2). Anal. Calcd for $C_{11}H_{12}SO$: C, 68.73; H, 6.29. Found: C, 68.75; H, 6.25.

C. Tertiary alcohol **10a** can be converted to **12a** in one step (67% yield) by the hot $POCl_3$–C_5H_5N procedure, but the product so obtained is impure, and decomposes fairly quickly on storage.

***trans*-3-[4-(1-Cyclohexenyl)-2-thienyl]acrylic Acid (13).** A mixture of aldehyde **12a** (4.20 g, 21.9 mmol), malonic acid (2.3 g, 22 mmol), C_5H_5N (20 ml), and piperidine (2 ml) was stirred at reflux for 5 h,[20] then poured into H_2O. The solution was acidifed (HCl, pH 4), cooled, and filtered to give crude acid **13**. Recrystallization (EtOH, 50 ml) gave 3.63 g (15.5 mmol, 71%) of yellow needles of **13** with mp 158–160 °C dec; ν_{max} (KBr) 1675 and 1615 cm^{-1}; λ_{max} (EtOH) 330 nm (ε 7600), 287 (15 600), and 252 (18 900); ^1H NMR δ 10.23 (broad) 1 H (CO_2H), 8.00 (d, J = 16 Hz) and 6.32 (d, J = 16 Hz) 2 H (trans CH=CH), 7.52 (d, J = 2 Hz) 1 H (H_3), 7.28 (d, J = 2 Hz) 1 H (H_5), 6.28 (m) 1 H (vinyl) 2.50–2.16 (m) 4 H (allylic), and 1.83–1.58 (m) 4 H (CH_2). Anal. Calcd for $C_{13}H_{14}SO_2$: C, 66.65; H, 6.02. Found: C, 66.45; H, 6.02.

4-Phenylthiophene-2-carboxaldehyde (14a). A mixture of aldehyde **12a** (8.50 g, 44 mmol), C_6H_6 (75 ml), and DDQ (20.4 g, 90 mmol) was stirred at reflux for 1 h, cooled, and filtered. The filtrate was extracted with 5% $NaHCO_3$, dried, and evaporated, and the residue was sublimed at 80 °C (0.1 mm), yield 5.37 g (29 mmol, 65%) of **14a** as a yellow solid with mp 56–57 °C (lit.[13] 67–68 °C); ν_{max} 1690 cm^{-1}; λ_{max} (EtOH) 314 nm (ε 2900) and 252 (28 400); ^1H NMR δ 9.88 (s), 1 H (CHO), 7.93 (s) and 7.78 (s) 2 H (H_3, H_5), and 7.45 ppm (s) 5 H (C_6H_5), identical with material prepared by treatment of 2-lithio-4-phenylthiophene with DMF.[13] The steps from **6a** may be done without purification of intermediate products.

***trans*-3-(4-Phenyl-2-thienyl)acrylic Acid (15a).** A mixture of **14a** (1.43 g, 7.60 mmol), malonic acid (0.79 g, 7.60 mmol), C_5H_5N (5 ml), and piperidine (1 ml) was stirred at 120 °C for 5 h, and the product was then isolated as described for **13** above, yield 1.45 g (6.31 mmol, 83%) of yellow solid acid **15a** with mp 190–192 °C dec; ν_{max} (KBr) 1680 cm^{-1}; λ_{max} (CH_3OH) 322 nm (ε 9900) and 263 (30 200); ^1H NMR δ 12.33 (broad) 1 H (CO_2H), 7.92–7.35 (m) 8 H (C_6H_5, thiophene, vinyl), and 6.30 ppm (d, J = 16 Hz) 1 H (vinyl). Anal. Calcd for $C_{13}H_{10}SO_2$: C, 67.82; H, 4.38. Found: C, 67.73; H, 4.73.

Methyl *trans*-3-(4-phenyl-2-thienyl)acrylate (15b) was prepared from acid **15a** (10.41 g, 45 mmol) by converting it to its acid chloride with $SOCl_2$ (30 ml) (30 min reflux), and then treating the crude acid chloride with MeOH (75 ml) under reflux for 2 h. Sublimation at 95 °C (0.5 mm) gave 6.87 g (28 mmol, 63%) of yellow solid ester **15b** with mp 85–87 °C; ν_{max} 1720 cm^{-1}; λ_{max} (EtOH) 362 nm (ε 10 450) and 265 (24 200); ^1H NMR δ 7.83 (d, J = 16 Hz) 1 H and 6.20 (d, J = 16 Hz) 1 H (trans CH=CH), 7.67–7.20 (m) 7 H (C_6H_5, thiophene), and 3.78 ppm (s), 3 H (OCH_3). Anal. Calcd for $C_{14}H_{12}SO_2$: C, 68.84; H, 4.95. Found: C, 64.45; H, 4.36.

3-(4-Phenyl-2-thienyl)propionic Acid (16). A mixture of **15a** (6.9 g, 30 mmol), 10% Pd/C (0.5 g), and HOAc (200 ml) was hydrogenated in a Parr shaker at 25 °C for 96 h. The catalyst was filtered, and the product was precipitated from the filtrate by dilution with H_2O (300 ml), yield 6.34 g of almost colorless solid. Recrystallization (EtOH, 50 ml) gave 4.89 g (21 mmol, 70%) of acid **16** with mp 159–161 °C; ν_{max} (KBr) 1680 cm^{-1}; λ_{max} (EtOH) 264 nm (ε 21 800) and 232 (15 500); ^1H NMR (Me_2SO-d_6) δ 7.98 (m), 7.82–7.53 (m), and 7.47–7.30 (m) 7 H (C_6H_5, thiophene), 3.08 (t, J = 7 Hz), 2 H (CH_2), and 2.63 ppm (t, J = 7 Hz) 2 H (CH_2). Anal. Calcd for $C_{13}H_{12}SO_2$: C, 67.23; H, 5.21. Found: C, 67.47; H, 4.78.

Methyl *trans*-2-(4-Phenyl-2-thienyl)-4-cyclohexenecarboxylate (17a). A mixture of ester **15b** (18.79 g, 77 mmol), butadiene (20 g), and C_6H_6 (35 ml) was held at 200 °C for 20 h in an autoclave. The crude product, isolated by evaporation, was recrystallized (MeOH, 100 ml), yield 19.57 g (66 mmol, 86%). Pure **17a** formed pale yellow prisms with mp 105–106 °C; ν_{max} (KBr) 1720 and 1300 cm^{-1}; λ_{max} (MeOH) 330 nm (ε 195), 263 (12 400), and 232 (22 000); ^1H NMR δ 7.57–7.03 (m) 7 H (C_6H_5, thiophene), 5.70 (m) 2 H (vinyl), 3.45 (s) 3 H (OCH_3), and 3.50–2.16 ppm (m) 6 H (cyclohexyl). Anal. Calcd for $C_{18}H_{18}SO_2$: C, 72.46; H, 6.08. Found: C, 72.21; H, 6.39.

Methyl *trans*-2-(4-Phenyl-2-thienyl)cyclohexanecarboxylate (18a). A mixture of ester **17a** (4.46 g, 15.0 mmol), MeOH (100 ml), and 5% Pd/C (1.0 g) was hydrogenated in a Parr shaker at 25 °C for 15 h. The catalyst was filtered, and the filtrate evaporated to give a residue which was recrystallized (MeOH, 10 ml), yield 3.66 g (12.2 mmol, 82%) of ester **18a** with mp 58–59 °C; ν_{max} 1720 cm^{-1}; λ_{max} (MeOH) 262 nm (ε 12 600) and 232 (23 000); ^1H NMR δ 7.60–7.03 (m) 7 H (C_6H_5, thiophene), 3.45 (s) 3 H (OCH_3), and 3.17–1.17 ppm (m) 10 H (cyclohexyl). Anal. Calcd for $C_{18}H_{20}SO_2$: C, 71.98; H, 6.71. Found: C, 71.81; H, 6.86.

***trans*-2-(4-Phenyl-2-thienyl)cyclohexanecarboxylic Acid (18b).** A mixture of ester **18a** (3.34 g, 11.1 mmol) and 20% NaOH (20 ml) was stirred at reflux for 4 h, then it was cooled, acidified (HCl), and filtered. The precipitate of **18b** was filtered and sublimed at 160 °C (0.1 mm) as a glassy solid with indefinite melting point: ν_{max} 1700 cm^{-1}; λ_{max} (MeOH) 263 nm (ε 12 600) and 233 (21 200); ^1H NMR δ 9.87 (broad) 1 H (CO_2H), 7.55–7.00 (m) 7 H (aromatic), 3.17–2.33 (m) 2 H and 2.17–1.17 (m) 8 H (cyclohexyl). Anal. Calcd for $C_{17}H_{18}SO_2$: C, 71.31; H, 6.34. Found: C, 71.05; H, 6.41.

2-(4-Phenyl-2-thienyl)benzoic Acid (19b). A. A mixture of ester **17a** (2.81 g, 9.45 mmol), C_6H_6 (50 ml), and DDQ (4.55 g, 20 mmol) was stirred at reflux for 44 h. Isolation of the product as described for **14a** gave 1.87 g (6.35 mmol, 67%) of methyl 2-(4-phenyl-2-thienyl)benzoate (**19a**) as a brown syrup, characterized by ^1H NMR, δ 7.95–7.33 (m) 11 H (aromatic) and 3.75 ppm (s) 3 H (OCH_3).

B. Crude ester **19a** (1.87 g) was stirred at reflux with 20% NaOH (10 ml) for 3 h. The mixture was cooled and acidified (HCl) and crude **19b** (0.75 g, 29% from **17a**) was extracted ($CHCl_3$). Recrystallization (EtOH, 3 ml) gave yellow needles of **19b** with mp 130–132 °C; ν_{max} (KBr) 1680 cm^{-1}; λ_{max} (MeOH) 257 nm (ε 30 000); ^1H NMR δ 9.26 (broad) 1 H (CO_2H), 8.07 (m) 1 H (H_5), and 7.72–7.38 (m) 10 H (aromatic). Anal. Calcd for $C_{17}H_{12}SO_2$: C, 72.85; H, 4.32; *m/e* 280.0577. Found: C, 72.31; H, 4.42; *m/e* 280.0564.

3-Hydroxy-2-(4-phenyl-2-thienyl)benzoic Acid (20). When 12.0 g (40.3 mmol) of **17a** was stirred with refluxing toluene (100 ml) and DDQ (18.4 g, 81.0 mmol) the only recognizable product obtained by the usual isolation procedure was 1.69 g of syrupy ester which was saponified with 20% NaOH (10 ml). The resulting tan solid was recrystallized (40% MeOH), yield 0.4772 g (1.71 mmol, 4% overall) of colorless, crystalline **20** with mp 181–185 °C dec; ν_{max} (KBr) 1685, 1600, and 1575 cm^{-1}; λ_{max} (MeOH) 253 nm (ε 29 600); ^1H NMR (Me_2SO-d_6) δ 7.78–7.57 (m) 5 H, 7.43–7.23 (m) 4 H, and 6.88 ppm (m) 2 H (aromatic). Anal. Calcd for $C_{17}H_{12}SO_3$: C, 68.91; H, 4.08; *m/e* 296.0506. Found: C, 68.69; H, 3.99; *m/e* 296.0499. Silylation showed two OH groups, *m/e* 440 corresponding to $C_{23}H_{28}SO_3Si_2$.

5-Bromothiophene-2-carboxaldehyde Ethylene Acetal (8b). 5-Bromothiophene-2-carboxaldehyde (**6b**, 100.5 g, 0.525 mol) (Aldrich) was converted to its ethylene acetal (**8b**) in 95% yield by the procedure described for **8a**. Acetal **8b** is a colorless liquid with bp 68–72 °C (0.025 mm); λ_{max} (C_8H_{18}) 289 nm (ε 392) and 242 (9900); ^1H NMR δ 6.82 (s) 2 H (H_3, H_4), 5.92 (s) 1 H (OCHO), and 3.95 ppm (m) 4 H (OCH_2). Anal. Calcd for $C_7H_7BrO_2S$: C, 35.76; H, 3.00. Found: C, 35.66; H, 2.83.

5-(1-Hydroxycyclohexyl)thiophene-2-carboxaldehyde Ethylene Acetal (10b). The *n*-BuLi–cyclohexanone method described for **10a** using 89.25 g (0.38 mol) of **8b** gave, on allowing the crude product to stand overnight at 25 °C, 46.4 g of crystalline **10b** and 26.9 g of oily supernatant material, total yield 73.3 g (0.284 mol, 75%). Recrystallization of 5 g of the solid fraction (1:2 C_6H_6–C_6H_{14}, 31 ml) gave 3.41 g of colorless plates of **10b** with mp 43–44 °C; ν_{max} 3580 and 3400 cm^{-1}; λ_{max} (THF) 291 nm (ε 12 300) and 266 (11 400); ^1H NMR δ 6.97 (d, J = 4 Hz) and 6.80 (d, J = 4 Hz) 2 H (H_3, H_4), 5.98 (s) 1 H (OCHO), 4.00 (m) 4 H (OCH_2), 2.63 (s) 1 H (OH), and 2.00–1.33 ppm (m) 10 H (cyclohexyl). Anal. Calcd for $C_{13}H_{18}O_3S$: C, 61.40; H, 7.14. Found: C, 61.52; H, 7.18.

5-(1-Cyclohexenyl)thiophene-2-carboxaldehyde (12b). The two-step procedure described for **12a** gave (0.29-mol scale) with **10b** and **11b** a 33–45% yield of **12b**, bp 127–130 °C (0.2 mm). Aldehyde **12b** is a pale yellow solid which darkens on storage, with mp 57–59 °C; ν_{max} (KBr) 1640 cm^{-1}; λ_{max} (CH_3CN) 331 nm (ϵ 16 350) and 226 (7360); ^1H NMR δ 9.78 (s), 1 H (CHO), 7.60 (d, J = 4 Hz) and 7.00 (d, J = 4 Hz) 2 H (H_3, H_4), 6.40 (m) 1 H (vinyl), 2.33 (m) 4 H (allylic), and 1.68 ppm (m) 4 H (CH_2). Anal. Calcd for $C_{11}H_{12}OS$: C, 68.73; H, 6.29. Found: C, 68.73; H, 6.17.

5-Phenylthiophene-2-carboxaldehyde (14b). The DDQ procedure described for **14a** gave with **12b** (0.17-mol scale) and 3-h reflux time a 66–71% yield of pale yellow crystalline **14b**, purified by sublimation at 105 °C (0.25 mm). Pure **14b** has mp 80–81 °C; ν_{max} (KBr) 1640 cm^{-1}; λ_{max} (C_8H_{18}) 320 nm (ϵ 16 400) and 228 (8750); ^1H NMR δ 9.87 (s) 1 H (CHO), 7.72 (d, J = 4 Hz) and 7.40 (d, J = 4 Hz) 2 H (H_3, H_4), 7.62 (m) and 7.45–7.25 ppm (m) 5 H (C_6H_5). Anal. Calcd for $C_{11}H_8SO$: C, 70.21; H, 4.29. Found: C, 70.28; H, 4.69.

***trans*-3-(5-Phenyl-2-thienyl)acrylic Acid (15c).** The Knoevenagel procedure described for **15a** gave, with **14b** (58.5-mmol scale), after recrystallization (EtOH, 150 ml), 12.28 g (53.3 mmol, 91%) of **15c**, mp 173–175 °C dec. The analytical sample was a pale yellow crystalline solid with mp 183–189 °C dec; ν_{max} (KBr) 1660 cm^{-1}; λ_{max} (EtOH) 346 nm (ϵ 27 600) and 243 (10 000); ^1H NMR (Me_2SO-d_6) δ 7.80 (d, J = 16 Hz) and 6.23 (d, J = 16 Hz) 2 H (trans CH=CH), 7.83–7.33 (m) 7 H (aromatic), and 6.50 ppm (broad) 1 H (CO_2H). Anal. Calcd for $C_{13}H_{10}SO_2$: C, 67.82; H, 4.38. Found: C, 67.73; H, 4.65.

Methyl *trans*-3-(5-Phenyl-2-thienyl)acrylate (15d). Esterification of acid **15c** (27.0 g, 0.117 mol) in DMF with CH_3I and Na_2CO_3 (Newman procedure[26]) gave 29.65 g of crude ester **15d** upon dilution of the cooled reaction mixture with H_2O. Recrystallization (MeOH, 300 ml) gave 18.84 g (77 mmol, 65%) of pure **15d**, a yellow, crystalline solid with mp 137–138 °C; ν_{max} (KBr) 1710, 1620, 1295, and 1280 cm^{-1}; λ_{max} (MeOH) 351 nm (ϵ 29 800) and 245 (9800); ^1H NMR δ 7.74 (d, J = 16 Hz) and 6.19 (d, J = 16 Hz) 2 H (trans CH=CH), 7.58–7.17 (m) 7 H (aromatic), and 3.75 ppm (s) 3 H (OCH_3). Anal. Calcd for $C_{14}H_{12}SO_2$: C, 68.84; H, 4.95. Found: C, 68.75; H, 4.95.

Methyl *trans*-2-(5-Phenyl-2-thienyl)-4-cyclohexenecarboxylate (17b). A mixture of **15d** (18.8 g, 77 mmol), C_6H_6 (50 ml), and butadiene (25 g) was held at 200 °C for 20 h. The crude product was chromatographed on 450 g of Woelm activity III Al_2O_3 (50-ml fractions), to give butadiene oligomers (fractions 1–8, C_6H_{14}; fractions 9, 10, C_6H_6) and **17b** (12.13 g, 40.7 mmol, 53%) (fractions 11–22, C_6H_6). The analytical sample, purified by sublimation at 100 °C (0.1 mm), had mp 57–58 °C; ν_{max} 1720 cm^{-1}; λ_{max} (MeOH) 347 nm (ϵ 238) and 290 (17 500); ^1H NMR δ 7.72–7.27 (m) 5 H (C_6H_5), 7.14 (d, J = 4 Hz) and 6.84 (d, J = 4 Hz) 2 H (H_3, H_4), 5.78 (m) 2 H (vinyl), 3.53 (s) 3 H (OCH_3), and 3.67–2.33 ppm (m) 6 H (cyclohexyl). Anal. Calcd for $C_{18}H_{18}SO_2$: C, 72.46; H, 6.08. Found: C, 72.42; H, 5.95.

***trans*-2-(5-Phenyl-2-thienyl)-4-cyclohexenecarboxylic Acid (17c).** Saponification of 4.0 g (13.4 mmol) of **17b** in 15% aqueous methanolic NaOH gave, after $CHCl_3$ extraction, 2.99 g (10 mmol, 75%) of acid **17c**, mp 104–106 °C. The analytical sample after sublimation at 170 °C (0.1 mm) had ν_{max} 1700 cm^{-1}; λ_{max} (MeOH) 345 nm (ϵ 217) and 292 (16 800); ^1H NMR δ 11.03 (s) 1 H (CO_2H), 7.65–7.25 (m) (C_6H_5), 7.09 (d, J = 4 Hz) and 6.84 (d, J = 4 Hz) 2 H (H_3, H_4), 5.77 (m) 2 H (vinyl), and 3.33–1.83 ppm (m) 6 H (cyclohexyl). Anal. Calcd for $C_{17}H_{16}SO_2$: C, 71.82; H, 5.07. Found: C, 71.61; H, 5.30.

Methyl 2-(5-Phenyl-2-thienyl)benzoate (19c). Ester **17b** (7.28 g, 24.4 mmol) was dehydrogenated by the DDQ procedure (24-h reflux). The crude product was filtered through 110 g of Woelm activity III Al_2O_3 to give 4.62 g (15.7 mmol, 65%) of **19c** which was short-path distilled at 135 °C (0.25 mm) as a syrupy liquid with ν_{max} 1710 and 1280 cm^{-1}; λ_{max} (MeOH) 313 nm (ϵ 16 200); ^1H NMR δ 7.82–7.27 (m) 6 H (C_6H_5, thiophene), 7.04 (d, J = 4 Hz) 1 H (thiophene), and 3.75 ppm (s) 3 H (OCH_3). Anal. Calcd for $C_{18}H_{14}SO_2$: C, 73.46; H, 4.80. Found: C, 73.34; H, 4.97.

2-(5-Phenyl-2-thienyl)benzoic Acid (19d) was prepared by saponifying 4.10 g (14.0 mmol) of ester **19c** with 15% aqueous methanolic NaOH. $CHCl_3$ extraction gave 3.55 g (12.7 mmol, 91%) of crude acid, which was recrystallized (MeOH, 20 ml), recovery 2.43 g of yellow crystals with mp 138–189 °C; ν_{max} ($CHCl_3$) 1680 cm^{-1}; λ_{max} (MeOH) 315 nm (ϵ 21 000); ^1H NMR δ 11.32 (s) 1 H (CO_2H) and 7.90–7.08 ppm (m) 11 H (aromatic). Anal. Calcd for $C_{17}H_{12}SO_2$: C, 72.85; H, 4.32. Found: C, 72.68; H, 4.37.

Registry No.—**1**, 2404-87-7; **2**, 58267-81-5; **3**, 58267-82-6; **4**, 58267-83-7; **5**, 58267-84-8; **6a**, 18791-75-8; **6b**, 4701-17-1; **7**, 38071-22-6; **8a**, 58267-85-9; **8b**, 52157-62-7; **9**, 58267-86-0; **10a**, 58267-87-1; **10b**, 58267-88-2; **11a**, 58267-89-3; **12a**, 58267-90-6; **12b**, 58267-91-7; **13**, 58267-92-8; **14a**, 26170-87-6; **14b**, 9163-21-4; **15a**, 58267-93-9; **15b**, 58267-94-0; **15c**, 58267-95-1, **15d**, 58267-96-2; **16**, 58267-97-3; **17a**, 58267-98-4; **17b**, 58267-99-5; **17c**, 58268-00-1; **18a**, 58268-01-2; **18b**, 58268-02-3; **19a**, 58268-03-4; **19b**, 58268-04-5; **19c**, 58268-05-6; **19d**, 58268-06-7; **20**, 58268-07-8; *N*-iodosuccinimide, 516-12-1; methyl 2-iodobenzoate, 610-97-9; thiophene-2-carboxaldehyde ethylene acetal, 58268-08-9; malonic acid, 141-82-2.

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(25) The initial adduct of 3-lithiothiophene and cyclohexanone, 1-(3-thienyl)cyclohexanol, was not reported in the original literature;[10-14] it may be obtained as a crystalline solid by allowing the crude product to stand at 25 °C for a few days and filtering the mixture. It has mp 33–35°; ν_{max} 3580 cm^{-1}; λ_{max} (EtOH) 234 nm (ϵ 5730); ^1H NMR δ 7.22 (m) 3 H (thiophene), 1.87 (broad) 1 H (OH), and 1.67 ppm (m) 10 H (cyclohexyl). Anal. Calcd for $C_{10}H_{14}OS$: C, 65.91; H, 7.74. Found: C, 66.03; H, 6.89. This product is readily dehydrated to 3-(1-cyclohexenyl)thiophene by 30-min reflux in a mixture of $POCl_3$, C_6H_6, and C_5H_5N.
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Rearrangement of 2-Phenacyl-1,2-benzisothiazolin-3-one to 2-Benzoyl-2*H*-1,3-benzothiazin-4(3*H*)-one

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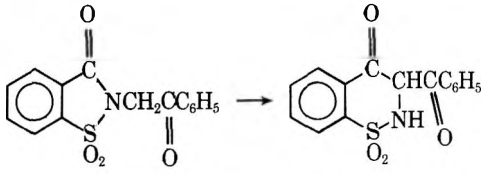
2-Phenacyl-1,2-benzisothiazolin-3-one (**4**) rearranges to 2-benzoyl-2*H*-1,3-benzothiazin-4(3*H*)-one (**6**) in good yield under mild basic conditions. Evidence supports a general-base-catalyzed mechanism initiated by abstraction of a proton from the α carbon atom, followed by attack on the sulfur atom, and opening of the S–N bond. Compound **6** rearranges to a yellow isomer which was not identified. Reaction of 2-mercaptobenzamide with phenylglyoxal gave 2-benzoyl-4*H*-3,1-benzoxathiin-4-one (**13**) instead of the expected **6**.

The presence of an active hydrogen adjacent to nitrogen in 2-phenacylsaccharin (**1**) presents the opportunity for a base-catalyzed ring expansion and the formation[1-3] of 1,2-benzothiazine dioxide **2**. In contrast, 2-(α-phenylethoxycarbonylmethyl)saccharin has been reported[4] to give a 1,3-benzothiazine. In this report the rearrangement of 2-phenacyl-1,2-benzisothiazolin-3-one (**4**) to 2-benzoyl-2*H*-1,3-benzothiazin-4(3*H*)-one (**6**) under mild base-catalyzed conditions is presented.



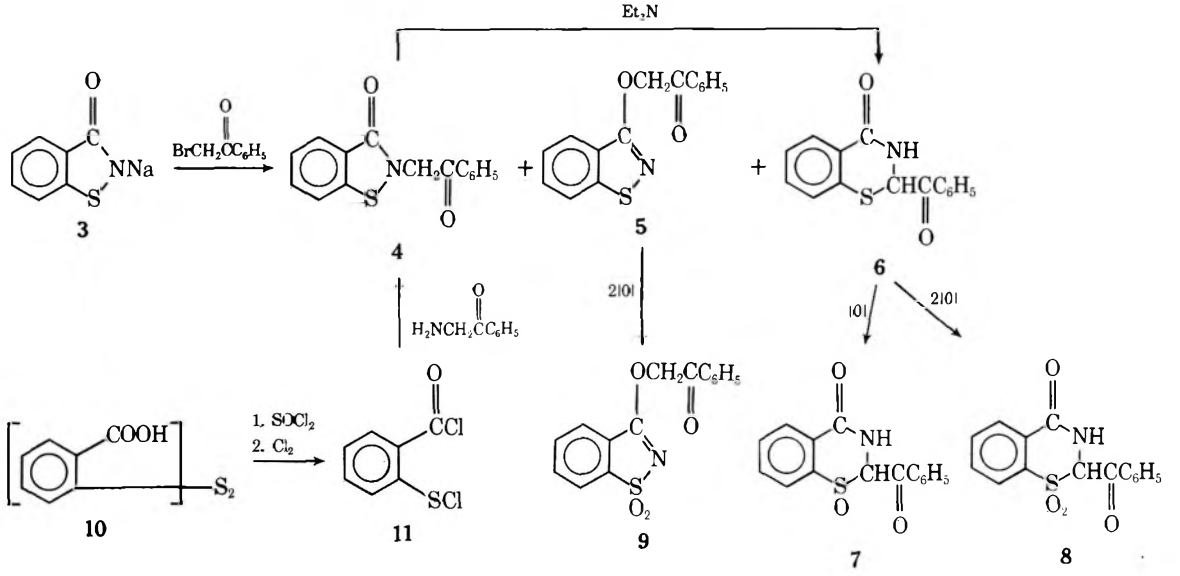
1 **2**

Results and Discussion

The rearrangement was first observed during a brief study of the alkylation of **3** by α-bromoacetophenone. Unexpectedly, this reaction yielded **6**, in addition to products **4** and **5** from N- and O-alkylation of **3** (Scheme I). The isolation of pure **4**, **5**, and **6** was greatly facilitated by good separation on TLC silica gel plates with chloroform–methanol (99:1). Structure **4** was proven unequivocally by oxidation to the known dioxide **1** and synthesis (**10** → **11** → **4**). Oxidation of **5** gave dioxide **9**, both **5** and **9** exhibiting ir and NMR spectra consistent with their assigned structures. The ketone absorption[5] appeared near 1700 cm^{-1}, while the characteristic amide band[6] of 2-substituted 1,2-benzisothiazolin-3-ones near 1660 cm^{-1} was absent. It is on this basis that the 1705- and 1660-cm^{-1} absorptions of **4** were assigned to the ketone and amide vibrations, respectively.

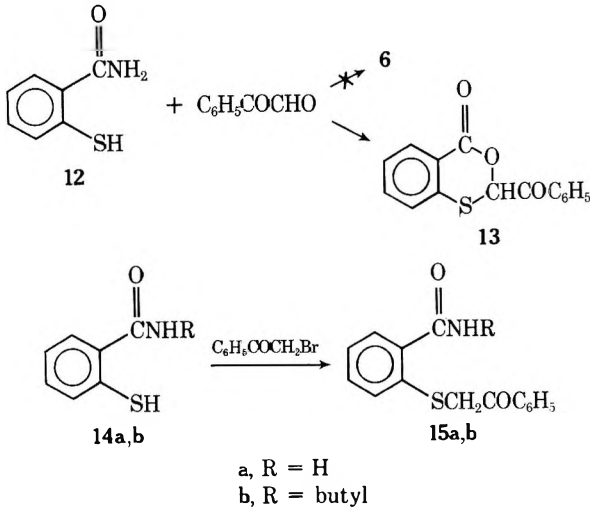
The ir spectrum of **6** showed the ν(NH) absorption at 3200 cm^{-1} in Nujol mull, in addition to the strong ketone and amide absorptions at 1688 and 1656 cm^{-1}, respectively. In chloroform solution the NH vibration appeared as a very sharp band of medium intensity at 3340 cm^{-1} definitely indicating a secondary amino grouping. Additional evidence for **6** was provided by the NMR spectra in DMF-d_6, which showed two doublets at 8.44 and 6.62 ppm for the NH and CH groups, respectively. Upon deuteration, the NH proton exchanged and the 6.62-ppm CH doublet collapsed into a singlet indicating coupling between the two groups and, thus, firmly establishing the existence of the –CHNH– moiety. Oxidation of **6** by hydrogen peroxide gave oxide **7**, but attempts to effect conversion to dioxide **8** resulted in overoxidation. On the other hand, oxidation of **6** with *m*-chloroperbenzoic acid provided **8** (mp 217–218 °C), and not the known **2** (mp 163–164.5 °C). The spectral behavior of **8** and **2** is also substantially different. The latter is actually a completely enolized β-diketone[2,7] showing a positive ferric chloride test, an enolic hydroxy group, and no carbonyl absorption. In contrast, compounds **6** and **8** exhibited none of those properties. Subsequently, evidence to substantiate the possibility that **6** was formed by ring expansion of pre-

Scheme I



cursor **4** and not by any other plausible route was sought. When pure **4** was treated with 1–2 equiv of sodium methoxide in methanol a fast rearrangement (**4** → **6**) occurred accompanied by substantial decomposition (TLC). Compound **4** remained unchanged after 10-h reflux in toluene, but in the presence of 1 equiv of triethylamine, a smooth, nearly quantitative (TLC) rearrangement took place which yielded pure **6**, identical in all respects with the alkylation product. Therefore, on the basis of the aforementioned results, structure **6** was assigned to the rearrangement product of **4**.

In an attempt to synthesize **6**, the procedure[8] for the preparation of 2-substituted 1,3-benzothiazin-4-ones by passing hydrogen chloride into an ethanolic solution of 2-mercaptobenzamide (**12**) and an aldehyde was tested. Surprisingly, treatment of **12** with phenylglyoxal hydrate under the same conditions yielded 2-benzoyl-4*H*-3,1-benzoxathiin-4-one (**13**) in 28% yield but none of the expected **6** (TLC).



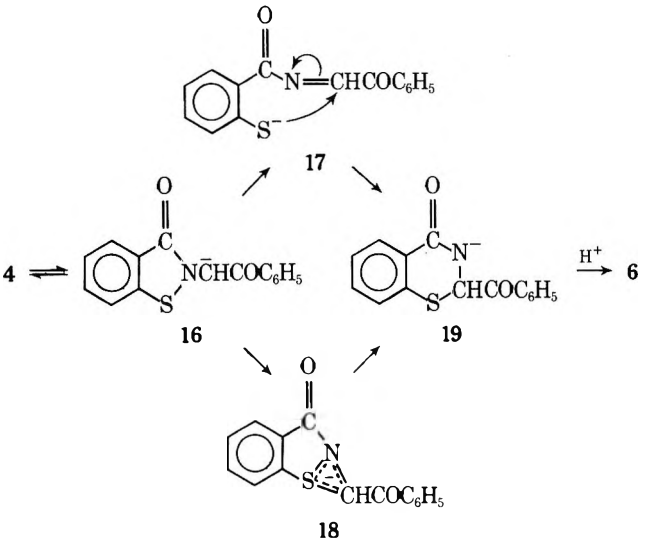
The assignment of structure **13** was based on the lack of nitrogen (microanalysis) and ir spectra, which showed the absence of ν(NH) and amide I bands as in **6**, and the presence of ketone (1697 cm^{-1}) and δ-lactone (1743 cm^{-1}) stretching vibrations in carbon disulfide solution. Possibly, this difference in behavior between an aldehyde and phenylglyoxal is due to the highly acidic hydroxyl group of the intermediate hemiacetal formed which attacks the amide carbonyl group with the expulsion of ammonia.

In another attempt to synthesize the 1,3-thiazinone ring compounds **15** were prepared by alkylation of **14**. Bromination of the phenacyl moiety of **15** followed by heating in the presence of triethylamine failed to effect cyclization.

From a mechanistic point of view, the ring expansion of **4** must be initiated by abstraction of a proton and the formation of carbanion **16**, which may rearrange by means of species **17**.

In view of the ability of the S atom to utilize its empty d orbitals and accommodate the negative charge in the p orbitals of the carbon atom, a second path through **18** is also possible. Both paths involve the severance of the sulfenamide and not the amide bond, since the former is weaker than the latter. In contrast, the rearrangement of 2-phenacylsaccharin (**1**) gives[2] 1,2-benzothiazinone **2** because the amide bond is weaker than the sulfonamide bond and split preferentially.

The formation of a number of compounds during the rearrangement of **4** under strongly basic conditions has already been mentioned. In fact, such solutions turn yellow-red, mainly because of the formation of a yellow substance, which was proven to be the rearrangement product of **6**. Thus, the yellow substance was isolated in 37% yield by subjecting **6** to slightly more severe conditions. It was found to be an isomer of **6**, devoid of NH, enolic OH, and



ketone groups, but retaining the amide moiety (strong absorption at 1665 cm^{-1}). No additional work to identify this compound was carried out.

Experimental Section[9]

Alkylation of the Sodium Salt of 1,2-Benzisothiazolin-3-one with α-Bromoacetophenone. Isolation of 4, 5, and 6. A mixture of the sodium salt of 1,2-benzisothiazolin-3-one (**3**, 17.3 g, 0.1 mol) and α-bromoacetophenone (19.9 g, 0.1 mol) in benzene was refluxed with stirring for 3 h, filtered from a solid, and evaporated to dryness. The sticky residue obtained was stirred in water (200 ml), and then in acetone (300 ml) for 30 min to yield a solid, which was filtered off, taken up in boiling benzene (150 ml), and filtered hot. Upon cooling the benzene filtrate deposited almost pure **2-phenacyl-1,2-benzisothiazolin-3-one (4).** One recrystallization from benzene gave the analytical sample: mp 156–157 °C; yield 4.7 g (17.5%); ir ($CHCl_3$) 1705 (ketone) and 1660 cm^{-1} (amide); NMR ($CDCl_3$) δ 5.25 (s, 2, CH_2), 7.20–7.70 (m, 6, aromatic H), 7.90–8.10 (m, 3, aromatic H).

Anal. Calcd for $C_{15}H_{11}NO_2S$: C, 66.89; H, 4.12; N, 5.20; S, 11.90. Found: C, 66.91; H, 4.29; N, 5.14; S, 12.13.

The above acetone mother liquor was evaporated to dryness, and the residue was dissolved in hot benzene (50 ml), diluted with cyclohexane (30 ml) until a slight precipitation occurred, made clear by addition of acetone (2 ml), and allowed to stand at room temperature. The crystallized crude product (7.8 g, mp 128–160 °C) was found (TLC) to be a mixture of **4** (40%) and **6** (60%). The crude product was recrystallized six times from benzene to yield pure **2-benzoyl-2*H*-1,3-benzothiazin-4(3*H*)-one (6)** free of **4** (TLC): mp 190–192 °C; yield 2.1 g (8%); ir (Nujol mull) 3200 (NH), 1688 (ketone), and 1656 cm^{-1} (amide); NMR (DMF-d_6) δ 6.62 (d, 1, CH), 7.10–7.80 (m, 6, aromatic H), 8.00–8.30 (m, 3, aromatic H), 8.44 (d, 1, NH).

Anal. Calcd for $C_{15}H_{11}NO_2S$: C, 66.89; H, 4.12; N, 5.20; S, 11.90. Found: C, 66.92; H, 3.96; N, 5.25; S, 11.61.

All mother liquors were combined and brought to dryness and the residue was dissolved in benzene and chromatographed through silica gel. Elutions with benzene–chloroform mixtures yielded crude **3-phenacyloxy-1,2-benzisothiazole (5)** which was purified by two recrystallizations from acetone–hexane: mp 146.5–147.5 °C; yield 1.1 g (4%); ir (KBr) 1700 cm^{-1} (ketone); NMR ($CDCl_3$) δ 5.78 (s, 2, CH_2), 7.20–7.80 (m, 6, aromatic H), 7.80–8.20 (m, 3, aromatic H).

Anal. Calcd for $C_{15}H_{11}NO_2S$: C, 66.89; H, 4.12, N, 5.20; S, 11.90. Found: C, 66.92; H, 3.96; N, 5.25; S, 11.61.

Additional elutions with $CHCl_3$ and $CHCl_3$–MeOH gave several fractions of crude **4** and **6** which were purified by crystallization to give additional **4** (3.1 g, 11.5%) and **6** (1.3 g, 4.8%).

2-Phenacyl-1,2-benzisothiazolin-3-one (10 → 11 → 4). To a stirred solution of 2,2′-dithiodibenzoic acid (23 g, 0.075 mol) and

dimethylformamide (4 drops) in 1,2-dichlorobenzene (125 ml) at 110–115 °C, a solution of thionyl chloride (14 ml, 0.19 mol) in the same solvent (20 ml) was added dropwise over a period of 1 h. The reaction mixture was cooled and chlorine gas (~11 g) was bubbled through at 10–15 °C for 25 min. The clear solution of sulfenyl halide 11 obtained was kept at 10–15 °C for an additional 20 min and at 60 °C under reduced pressure for 10 min, cooled, and added dropwise at 20–40 °C to a vigorously stirred mixture of α-aminoacetophenone hydrochloride (26 g, 0.15 mol), water (50 ml), and 1,2-dichlorobenzene (50 ml). During the addition, simultaneously and through a separate addition funnel, triethylamine (65 ml, 0.46 mol) was added at such a rate that a slight excess of triethylamine was present in the reaction mixture. After the additions had been completed (15 min) the mixture was heated to 60 °C, cooled, and filtered from a solid. This solid was stirred in water (100 ml), filtered off, and purified by two crystallizations from methylene chloride–benzene to yield 9.3 g (23%) of pure **4**, mp 157–158 °C.

The water layer from the filtrate of the reaction mixture was separated, and the organic layer was diluted with petroleum ether (1000 ml), cooled overnight, and filtered to give a second crop of **4**, which was purified by three crystallizations from methylene chloride–benzene; mp 155–157 °C, yield 13.2 g (32%). Total yield was 55%. The product was identical with the sample isolated from the aforementioned alkylation reaction as shown by mixture melting point, ir, NMR, and TLC.

2-Phenacyl-1,2-benzisothiazolin-3-one 1,1-Dioxide (4 → 1). A solution of **4** (0.54 g, 2 mmol) and *m*-chloroperbenzoic acid (85%, 0.9 g, 4.4 mmol) in chloroform was allowed to stand at room temperature for 4 days, extracted with aqueous $NaHCO_3$ and water, and evaporated to dryness under reduced pressure. The crude 1 obtained was purified by two recrystallizations from ethanol; mp 193–195 °C (lit.[1] mp 193–194 °C); ir (Nujol) 1735 (amide), 1697 (ketone), 1335 and 1182 cm^{-1} ($-SO_2-$); NMR (DMF-d_6) δ 8–8.5 and 7.5–7.8 (aromatic H), 5.52 (s, 2, CH_2).

3-Phenacyloxy-1,2-benzisothiazoline 1,1-Dioxide (9). A solution of **5** (0.27 g, 1 mmol) and *m*-chloroperbenzoic acid (0.45 g, 2.2 mmol) in chloroform (15 ml) was stirred at room temperature for 4 days and the crystallized product (mp 190–191 °C, 70 mg) was filtered off. The filtrate was extracted with aqueous $NaHCO_3$, then water, and the chloroform layer was evaporated to dryness to yield a second crop of crude **9**. The two crops were combined and recrystallized twice from ethanol to give pure **9**: mp 190–191 °C; yield 0.24 g (80%); ir (Nujol) 1700 (ketone), 1325 and 1173 cm^{-1} ($-SO_2-$); NMR (DMF-d_6) δ 6.25 (s, 2, CH_2), 7.50–7.90 (m, 3, aromatic H), 7.95–8.30 (m, 6, aromatic H).

Anal. Calcd for $C_{15}H_{11}NO_4S$: C, 59.79, H, 3.68; N, 4.65; O, 21.24; S, 10.65. Found: C, 59.96; H, 3.57; N, 4.54; O, 21.09; S, 10.51.

Preparation of 6 by Rearrangement of 4. To a stirred solution of **4** (1.08 g, 4 mmol) in toluene (50 ml) at 80 °C, triethylamine (0.55 ml, 4 mmol) was added and the reaction mixture was refluxed for 1 h. The solution was then concentrated to 30 ml, further concentrated in vacuo to 10 ml, cooled, and filtered to yield crude **6** (0.9 g, mp 184–189 °C). The crude product was purified by two recrystallizations from ethanol to give 0.7 g (65%) of pure **6**. This sample was identical in all respects (ir, NMR, TLC, and mixture melting point) with the sample isolated from the alkylation of **3**.

2-Benzoyl-2*H*-1,3-benzothiazin-4(3*H*)-one 1-Oxide (7). To a solution of **6** (2.7 g, 10 mmol) in glacial acetic acid, H_2O_2 (30%, 1.8 ml, 0.15 mmol) was added and the mixture was allowed to stand at room temperature for 5 days. The crystallized product (1.1 g, mp 222–227 °C) was recrystallized twice from ethanol to give the analytical sample; mp 235–236 °C (gas evolution); yield 1 g (33%); ir (Nujol) 3340, 3220 (NH), 1695 (ketone), 1665 (amide), 1100 cm^{-1} (S=O); NMR (DMF-d_6) δ 8.24 (s, 1, NH), 7.47 (d, 1, CH), 7.3–8.1 (m, 9, aromatic H).

Anal. Calcd for $C_{15}H_{11}NO_3S$: C, 63.14; H, 3.89; N, 4.91; O, 16.82; S, 11.24. Found: C, 62.96; H, 3.64; N, 4.78; O, 16.91; S, 11.44.

2-Benzoyl-2*H*-1,3-benzothiazin-4(3*H*)-one 1,1-Dioxide (8). To a stirred cold solution of **6** (0.54 g, 2 mmol) in chloroform, *m*-chloroperbenzoic acid (85%, 0.9 g, 4.4 mmol) was added. The solution obtained was allowed to stand at room temperature for 3 days and evaporated to dryness under reduced pressure to give a solid, which was stirred in ether (30 ml), filtered off, and purified by two recrystallizations from ethanol: mp 217–218 °C (when placed at 170 °C, it melted, resolidified, and remelted at 212–214 °C); yield 0.2 g (33%); ir (Nujol) 3230, 3100 (NH), 1690 (ketone), 1670 (amide), 1336 and 1187 cm^{-1} ($-SO_2-$); NMR (DMF-d_6) δ 9.1 (s, 1, NH), 7.25–8.40 (m, 10, aromatic H + CH).

Anal. Calcd for $C_{15}H_{11}NO_4S$: C, 59.79; H, 3.68; N, 4.65; O, 21.24; S, 10.64. Found: C, 59.79: H, 3.59; N, 4.62; O, 21.09; S, 10.62.

2-Phenacylthiobenzamide (15a). A solution of 2-mercaptobenzamide (0.77 g, 5 mmol) and α-bromoacetophenone (1 g, 5 mmol) in pyridine (10 ml) was stirred at ambient temperature for 15 min, heated under reflux for 15 min, and evaporated in vacuo to dryness. The crystalline residue was stirred in water (100 ml), filtered off, and recrystallized from methanol to yield crude **15a** (1.15 g, mp 150–152 °C), which was purified by two recrystallizations from methanol; mp 154.5–155 °C; yield 0.95 g (70%); ir (KBr) 3350 and 3180 (NH_2), 1680 (ketone), and 1633 cm^{-1} (amide); NMR (DMF-d_6) δ 8.12 (d of d, 2, aromatic H), 7.86 (broad, 2, NH_2), 7.1–7.8 (m, 7, aromatic H), 4.65 (s, 2, CH_2).

Anal. Calcd for $C_{15}H_{13}NO_2S$: C, 66.40; H, 4.83; N, 5.16; S, 11.82. Found: C, 66.67; H, 4.66; N, 5.03; S, 11.60.

***N*-Butyl-2-phenacylthiobenzamide (15b).** A solution of *N*-butyl-2-mercaptobenzamide (2.1 g, 10 mmol) and α-bromoacetophenone (2 g, 10 mmol) in pyridine (20 ml) was stirred at ambient temperature for 15 min, heated under reflux for 15 min, and evaporated to dryness. The residue was extracted with hot benzene (100 ml), diluted with cyclohexane (20 ml), concentrated, and cooled to yield 2.4 g (73%) of crude **15b**, mp 73–75 °C. A small sample was recrystallized from aqueous methanol; mp 76–78 °C; ir (KBr) 3300 (NH), 1680 (ketone), and 1625 cm^{-1} (amide); NMR (DMF-d_6) δ 8–8.25 (d of d, 3, aromatic H + NH), 7.1–7.8 (m, 7, aromatic H), 4.66 (s, 2, SCH_2) 3.33 (q, 2, NCH_2) 1.2–1.8 (m, 4, CH_2CH_2), 0.89 (t, 3, CH_3).

Anal. Calcd for $C_{19}H_{21}NO_2S$; C, 69.69; H, 6.46; N, 4.28; S, 9.79. Found: C, 69.90; H, 6.56; N, 4.38; S, 9.64.

2-Benzoyl-4*H*-3,1-benzoxathiin-4-one (13). Dry hydrogen chloride was passed through a solution of 2-mercaptobenzamide (1.5 g, 10 mmol) and phenylglyoxal monohydrate (1.5 g, 10 mmol) in ethanol (4 ml) at 50 °C for 15 min to yield a crystalline precipitate. The mixture was cooled, and the crude product was filtered off and purified by two recrystallizations from ethanol: mp 126.5–127.5 °C; yield 0.75 g (28%); ir (CS_2) 1743 (lactone), 1697 cm^{-1} (ketone); NMR (DMF-d_6) δ 8.0–8.4 and 7.3–7.9 (m, 10, aromatic H + CH); mol wt 270 ($CHCl_3$).

Anal. Calcd for $C_{15}H_{10}O_3S$: C, 66.65; H, 3.73; S, 11.86. Found: C, 66.41; H, 3.65; S, 11.61.

Yellow Product by Rearrangement of 6. 1,3-Benzothiazine **6** (1.08 g, 4 mmol) was dissolved in toluene (50 ml) by brief heating under reflux. The solution was cooled to ca. 70 °C, triethylamine (1.1 ml, 8 mmol) was added, and heating at 70 °C was continued for a total of 16 h. The yellow-red solution was evaporated to dryness, the residue was stirred in acetone (3 ml), and the yellow solid was filtered off, mp 150–156 °C, yield 0.55 g (51%). The crude product was purified by two recrystallizations from methylene chloride–petroleum ether (bp 30–60 °C): mp 160–160.5 °C; yield 0.4 g (37%); ir (Nujol) 1665 cm^{-1} (amide); NMR (DMF-d_6) δ 7.50–8.10 (m, 6, aromatic H), 8.10–8.60 (m, 3, aromatic H). Mol wt: calcd, 269; found, 272 ($CHCl_3$).

Anal. Calcd for $C_{15}H_{11}NO_2S$: C, 66.89; H, 4.12; N, 5.20; O, 11.89; S, 11.90. Found: C, 67.09; H, 4.04; N, 5.19; O, 12.12; S, 11.93.

Registry No.—**1**, 15246-95-4; **3**, 58249-25-5; **4**, 49549-92-0; **5**, 58249-26-6; **6**, 58249-27-7; **7**, 58249-28-8; **8**, 58249-29-9; **9**, 58249-30-2; **10**, 119-80-2; **11**, 3950-02-5; **12**, 5697-20-1; **13**, 58249-31-3; **14b**, 58249-32-4; **15a**, 58249-33-5; **15b**, 58249-34-6; α-bromoacetophenone, 70-11-1.

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Reaction of Benzothiazole and Substituted Benzothiazoles with Dimethyl Acetylenedicarboxylate. A Novel Heterocyclic Ring Transformation[1]

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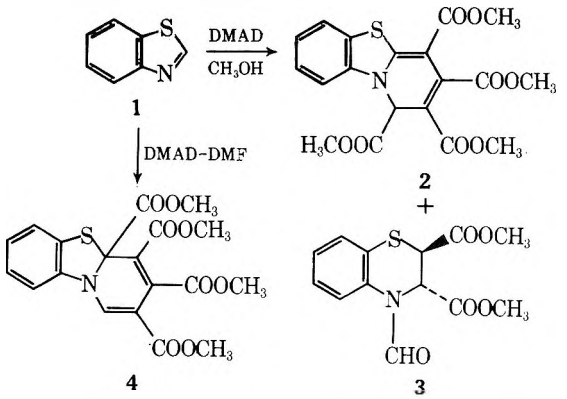
Reaction of benzothiazole with dimethyl acetylenedicarboxylate in aqueous methanol gives *trans*-dimethyl 4-formyl-2,3-dihydro-1,4-benzothiazine-2,3-dicarboxylate in high yield, and a mechanism is proposed for this novel transformation. The scope and limitations of the process have been defined by examination of the reactions of a wide range of substituted benzothiazoles with dimethyl acetylenedicarboxylate in aqueous methanol; the results are fully consistent with the postulated mechanism.

The reactions of benzothiazole 1 with dimethyl acetylenedicarboxylate (DMAD) have been studied by various groups of workers during the last 12 years, but only recently have the structures of the various products been unambiguously assigned by Ogura and his colleagues.[2] At least three products can be obtained, depending on the nature of the solvent used; thus, 2 and 3 are formed in 5 and 8% yield, respectively, when methanol is employed, whereas 4 is produced in 10% yield when DMF is used.



1 → 2 + 3 (DMAD, CH_3OH); 1 → 4 (DMAD-DMF)

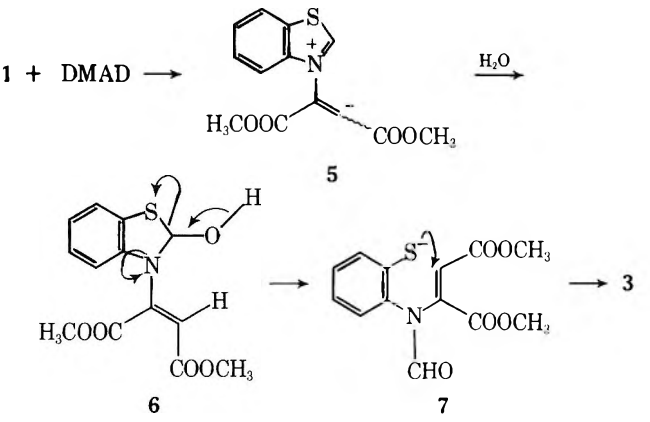
We have recently investigated the unusual transformation involved in the formation of 3 and demonstrated that (a) this product is *only* formed when the methanol contains water, and (b) it is produced in virtually quantitative yield when aqueous methanol is used in excess as solvent.[1] Moreover, the cleanness with which this ring transformation takes place is remarkable. Addition of benzothiazole to DMAD gives a deep red colored solution, and reaction to produce 2 proceeds with formation of considerable amounts of tarry, polymeric materials. Reactions carried out in absolute methanol or in methanol containing small amounts of water similarly give rise to deep red colored solutions and formation of polymeric products. In the presence of a large excess of water, however, the reaction mixture is pale yellow in color throughout and 3 crystallizes from it as a colorless solid. TLC examination of the crude product thus obtained showed that the only impurities present were trace amounts of benzothiazole and DMAD.

These results are fully consistent with the mechanism outlined in Scheme I for the conversion of 1 into 3. That is, the initial addition product 5 formed from benzothiazole and DMAD can be trapped very effectively with water rather than DMAD, and the overall course of reaction is thus diverted to production of 3.

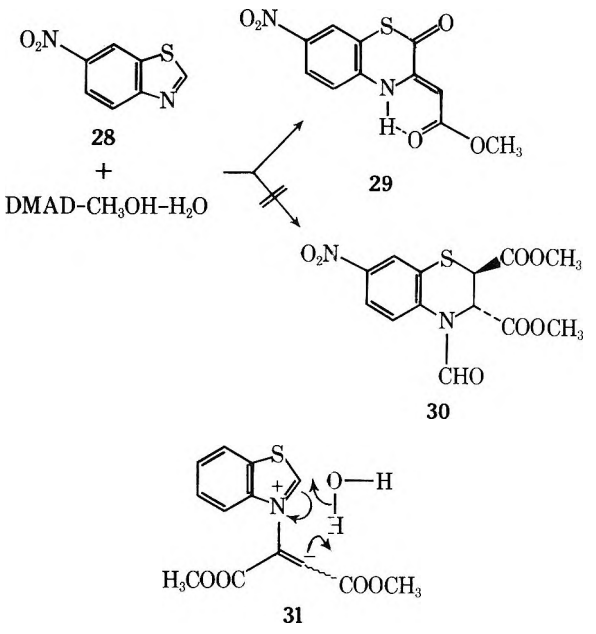
Discussion

The nature of the reaction of benzothiazole with DMAD to produce 3 having been clarified, it remained to determine the generality of this ring transformation. A wide range of substituted benzothiazoles was therefore prepared and treated with DMAD in aqueous methanol; the scope and limitations of the process were then readily deduced from the results obtained. Thus, with the exceptions of 6-nitro-, 5-acetoxy-, and 5,6-dimethoxybenzothiazole, benzothiazoles substituted in the 5, 6, and 7 positions with either electron-donating or electron-withdrawing groups were smoothly converted into the corresponding substituted *trans*-dimethyl 4-formyl-2,3-dihydro-1,4-benzothiazine-2,3-dicarboxylates; yield and experimental data for the various conversions are summarized in Table I.

Scheme I



Reaction of 5-acetoxy- (26) and 5,6-dimethoxybenzothiazole (27) with DMAD in aqueous methanol resulted only in formation of deep colored, polymeric tars. Neither of the starting benzothiazoles, however, is particularly stable; the dimethoxy compound, for example, rapidly discolored and decomposed on storage at room temperature, and decomposition was extremely rapid if the compound was exposed to light. Consequently, the failure of these compounds to react with DMAD to give identifiable products is almost certainly merely a result of their inherent instability. Reaction of 6-nitrobenzothiazole 28 with DMAD in aqueous methanol proceeded smoothly; the product, however, which was obtained in 60% yield, was easily shown by analytical and spectroscopic means (Experimental Section) to be the thiolactone 29, and not the *N*-formyl-1,4-benzothiazine 30. As is indicated below, formation of 29 is not entirely unexpected; moreover, consideration of the probable mechanism for this transformation provides further information on the relative stereochemistry of the two ester groups, both in this case and in the conversion of 1 into 3. Thus, in the latter case, protonation of the intermediate 5 would be expected to be rapid, and may possibly occur in an intra-



molecular fashion as shown in 31. Consequently, the ester groups in the subsequent intermediates 6 and 7 would be expected to be cis. Examination of molecular models clearly reveals that this stereochemistry *must* pertain for ring closure to occur in the observed manner; when the ester groups are trans there is severe steric hindrance to conjugate addition of the thiolate anion to the α,β-unsaturated ester system and some steric hindrance to nucleophilic attack of the thiolate anion at the nearer of the two ester carbonyl functions. There is, however, very little steric hindrance to conjugate addition when the two ester groups are cis.

A plausible mechanism for the conversion of 28 into 29 is outlined in Scheme II. In this case, decomposition of the intermediate ortho ester 32 occurs by C–N bond cleavage, and not by C–S bond cleavage as was observed with benzothiazole and the substituted benzothiazoles listed in

Scheme II

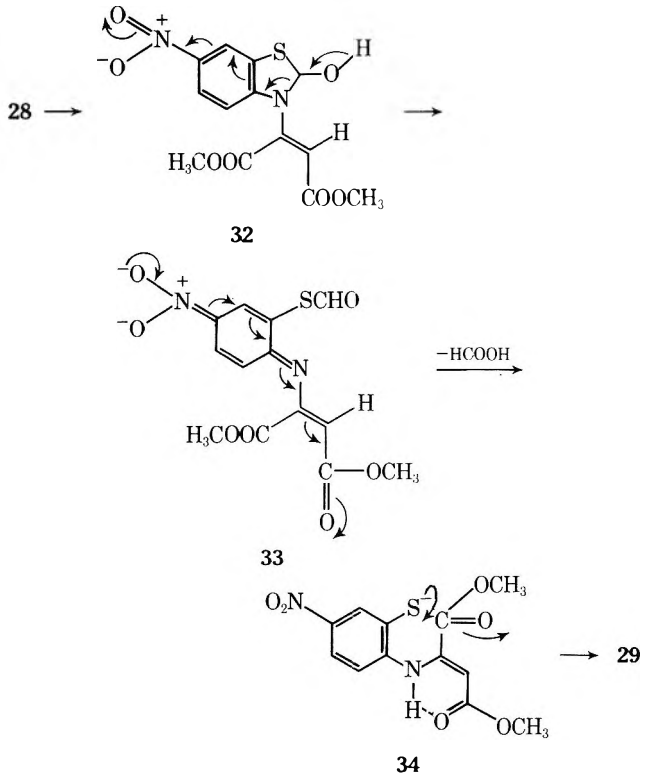
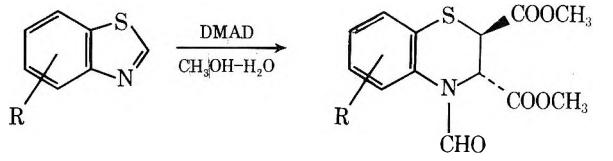


Table I. Conversion of Benzothiazoles into *trans*-Dimethyl 4-Formyl-2,3-dihydro-1,4-benzothiazine-2,3-dicarboxylates[a]

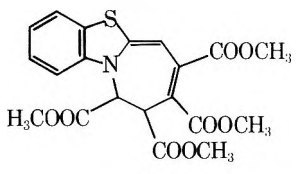


Benzothiazole		Benzothiazine		
Compd	R	Compd	Yield, %[b]	Mp, °C
1	H	3	85	135–136
8	5-CN	9	60	122–123
10	5-CH_3CONH	11	76	155–156
12	5-NO_2	13	80	135–136
14	5-Br	15	70	123–124
16	6-CN	17	60	123–124
18	6-CH_3CONH	19	82	129–130
20	6-CH_3O	21	72	124–125
22	6-Br	23	70	145–146
24	6-CH_3O-7-NO_2	25	70	163–165

[a] Full analytical and spectroscopic data (ir, NMR) for the benzothiazines are listed in Tables II and III (see paragraph at end of paper regarding supplementary material). [b] Refers to pure, recrystallized material.

Table I. That is, the mesomeric effect of the 6-nitro substituent is sufficiently powerful to render the C–N bond in the intermediate 32 weaker than the C–S bond (normal bond energies are C–N 69–75 kcal/mol[3] and C–S 66 kcal/mol[4]). Conversion of 32 into 34 via the resonance stabilized intermediate 33 would be expected to result in formation of the thermodynamically more stable trans diester,[5] lactonization of which leads to the observed product.[6]

The reactions of a variety of 4- and 2-substituted benzothiazoles were then examined. 4-Nitro-6-methoxy-, 4-acetamido-6-methoxy-, 4,6-dichloro-, 4,6-dichloro-7-nitro-, and 4,6-dichloro-7-acetamidobenzothiazole **35–39** were treated with DMAD in aqueous methanol; even after reflux periods of up to 25 h, however, no reaction had taken place, and the starting materials were recovered in virtually quantitative yield in every case. A similar situation was encountered with respect to 2-substituted benzothiazoles. Thus, 2-chloro-, 2-fluoro-, 2-methoxy-, 2-phenyl-, and 2-*p*-methoxyphenylbenzothiazole **40–44** were recovered unchanged even after prolonged reaction times; 2-benzothiazolone **45** also failed to react, even in the presence of sodium hydroxide. 2-Methylbenzothiazole **46** did react, but the product was the known azepine **47**, which has been obtained previously from the reaction of **46** with DMAD.[7]



The above unsuccessful reactions clearly indicate that the ring transformation summarized in Scheme I is subject to fairly fine control by both steric and electronic effects. The major factor which contributes to lack of reaction in the case of the 4-substituted derivatives **35–39** is almost certainly steric inhibition of the condensation between the heterocyclic ring nitrogen atom and DMAD, although in the case of **35** and **37–39** inductive electron withdrawal by the nitro and chloro substituents might also reduce slightly the basicity of the benzothiazole nitrogen atom. This latter effect is almost certainly the dominant reason for the failure of compounds **40–42** to react, i.e., the benzothiazole ni-

trogen atom is no longer sufficiently basic to participate in the initial conjugate addition to DMAD. Unfortunately pK_a values for the compounds in question are not available, but on a purely qualitative basis comparison with the corresponding pyridine derivatives gives some indication of the magnitude of the effect which might be operative. Thus, relative to pyridine (pK_a = 5.25) the pK_a values for 2-chloro-, 2-fluoro-, and 2-methoxypyridine are 0.49, −0.44, and 3.25, respectively. Steric effects alone are most probably responsible for inhibition of the reaction of DMAD with **43** and **44**, especially as in the latter case the basicity of the ring nitrogen atom would be expected to be greater than that of benzothiazole owing to the mesomeric effect of the *p*-methoxyphenyl group.

Experimental Section

Melting points were determined on a Kofler hot-stage microscope melting point apparatus and are uncorrected. Microanalyses were performed by Mr. A. R. Saunders and Mr. J. Robinson of the University of East Anglia. Infrared spectra were recorded on a Perkin-Elmer Model 257 grating infrared spectrophotometer using the standard Nujol mull, sodium chloride plate, and liquid film techniques. Nuclear magnetic resonance spectra were determined as solutions in either $CDCl_3$ or Me_2SO-d_6 on a Perkin-Elmer Model R-12 60-MHz nuclear magnetic resonance spectrometer using tetramethylsilane as internal standard.

Starting Materials. Crude benzothiazole (BDH) was first purified by vacuum distillation. It was then converted into the sulfate salt which, after crystallization from alcohol, was neutralized with sodium hydroxide solution. The benzothiazole was then extracted and distilled, and the fraction bp 125–128 °C (18 mm) was collected.

The following substituted benzothiazoles were synthesized by literature procedures: **10**,[8] **12**,[8] **16**,[9] **20**,[10,11] **22**,[9] **24**,[11] **28**,[9] **35**,[11] **37**,[12] **38**,[12] **40**,[13] **41**,[14,15] **42**,[16] **43**,[17,13] **45**,[19] **46**.[18]

5-Cyanobenzothiazole (8). This compound was prepared from 5-aminobenzothiazole[8] by exactly the same procedure as has been described for the preparation of 6-cyanobenzothiazole,[9] and was obtained in 61% yield as long, colorless, glistening needles, mp 138–140 °C from aqueous ethanol.

Anal. Calcd for $C_8H_4N_2S$: C, 60.00; H, 2.50; N, 17.50; S, 20.00. Found: C, 59.94; H, 2.60; N, 17.54; S, 19.94.

5-Bromobenzothiazole (14). This compound was prepared from 5-aminobenzothiazole[8] by exactly the same procedure as has been described for the preparation of 6-bromobenzothiazole,[9] and was obtained in 62% yield as colorless, glistening plates, mp 100–102 °C from aqueous ethanol.

Anal. Calcd for C_7H_4BrNS: C, 39.26; H, 1.87; Br, 37.39; N, 6.54; S, 14.95. Found: C, 39.39; H, 1.90; Br, 37.28; N, 6.50; S, 14.91.

6-Acetamidobenzothiazole (18). A solution of 6-aminobenzothiazole[9] (1.5 g, 0.01 mol) in a mixture of acetic acid (5 ml) and acetic anhydride (5 ml) was heated gently under reflux for 1 h. The cooled reaction mixture was then poured onto crushed ice (50 g) and the solid which separated was collected by filtration, washed with cold water, dried, and recrystallized from ethyl acetate–hexane. This gave 1.65 g (86%) of pure **18** as colorless needles, mp 170–171 °C.

Anal. Calcd for $C_9H_8N_2OS$: C, 56.25; H, 4.17; N, 14.58; S, 16.67. Found: C, 56.27; H, 4.12; N, 14.64; S, 16.71.

5-Acetoxybenzothiazole (26). A solution of 5-aminobenzothiazole[9] (6 g, 0.04 mol) in a mixture of concentrated hydrochloric acid (15 ml) and water (35 ml) was cooled to 0 °C and carefully diazotized by the dropwise addition of a cold (0 °C) solution of sodium nitrite (3 g) in water (10 ml). The resulting clear, bright orange solution was stirred at 0 °C for 5 min and then added to a cold (0 °C) solution of 9.35 M hydrofluoroboric acid (42.8 ml). The mixture turned deep orange in color and the diazonium fluoroborate began to precipitate. After 1 h at 0 °C the fluoroborate salt was collected by vacuum filtration, washed with ice–water (2 × 20 ml), and dried over phosphorus pentoxide at room temperature, yield 5.9 g (65%).

The fluoroborate salt thus prepared (5.4 g, 0.024 mol) was suspended in glacial acetic acid (100 ml) and the mixture was stirred and heated under reflux for 1 h. The solvent was then removed by evaporation under reduced pressure and the residual red oil diluted with water (200 ml). The resulting solution was extracted with ether (5 × 40 ml) and the combined extracts were washed with aqueous sodium bicarbonate solution and then dried (Na_2SO_4). The ether was removed by evaporation under reduced pressure and the residual yellow oil distilled to give 1.5 g (32%) of **26** as a colorless oil, bp 129–131 °C (0.2 mm), which slowly solidified on standing to colorless needles, mp 61–62 °C.

Anal. Calcd for $C_9H_7NO_2S$: C, 55.96; H, 3.63; N, 7.25; S, 16.58. Found: C, 55.94; H, 3.57; N, 7.17; S, 16.64.

5,6-Dimethoxybenzothiazole (27). The starting material, 6,6′-dinitro-3,3′,4,4′-tetramethoxydiphenyl disulfide, was prepared from 4,5-dinitroveratrole[20] according to the procedure of Ast and Bogert.[10]

Finely powdered 6,6′-dinitro-3,3′,4,4′-tetramethoxydiphenyl disulfide (4.3 g, 0.01 mol) was slurried with glacial acetic acid (40 ml) and the mixture heated to reflux. Zinc dust was then added carefully until a colorless solution was obtained; the solution was heated under reflux for 15 min, the excess zinc dust was removed by filtration under reduced pressure, and the resulting clear green solution was cooled to room temperature. Anhydrous formic acid (200 ml) and granulated zinc (3 g) were added with stirring to this solution of the zinc mercaptide and the resulting blue-green solution was heated under reflux for 28 h. The mixture was then cooled to room temperature, excess formic acid was removed by distillation under reduced pressure, and the residual blue oil was basified with solid sodium hydroxide (30 g). This gave a colorless emulsion containing a purple-blue oil which was extracted with ether (4 × 25 ml). The combined ether extracts were dried (Na_2SO_4) and evaporated under reduced pressure to give a thick purple oil. This was dissolved in chloroform (100 ml) and the solution treated with charcoal; evaporation of the solvent under reduced pressure gave a colorless, crystalline solid which was recrystallized from hexane to give 1.1 g (30%) of pure **27** as colorless, glistening plates, mp 74–75 °C. This compound discolors rapidly on storage at room temperature and very rapidly on exposure to light.

Anal. Calcd for $C_9H_9NO_2S$: C, 55.38; H, 4.62; N, 7.18; S, 16.41. Found: C, 55.30; H, 4.71; N, 7.15; S, 16.38.

4-Acetamido-6-methoxybenzothiazole (36). This compound was prepared by acetylation of 4-amino-6-methoxybenzothiazole[11] in exactly the same manner as is described above for the preparation of 6-acetamidobenzothiazole, and was obtained in 95% yield as colorless needles, mp 157–158 °C from ethyl acetate–hexane.

Anal. Calcd for $C_{10}H_{10}N_2O_2S$: C, 54.05; H, 4.50; N, 12.61; S, 14.41. Found: C, 53.76; H, 4.66; N, 12.53; S, 14.43.

4,6-Dichloro-7-acetamidobenzothiazole (39). This compound was prepared by acetylation of 4,6-dichloro-7-aminobenzothiazole[12] in exactly the same manner as is described above for the preparation of 6-acetamidobenzothiazole, and was obtained in 98% yield as long, colorless needles, mp 270–271 °C from glacial acetic acid.

Anal. Calcd for $C_9H_6Cl_2N_2OS$: C, 41.38; H, 2.30; Cl, 27.20; N, 10.73; S, 12.26. Found: C, 41.14; H, 2.47; Cl, 27.09; N, 10.75; S, 12.39.

2-*p*-Methoxyphenylbenzothiazole (44). This compound was prepared from 2,2′-bis(4-methoxybenzoylamino)diphenyl disulfide by exactly the same procedure as has been described for the preparation of 2-phenylbenzothiazole,[17,18] and was obtained in 75% yield as long, colorless needles, mp 117–118 °C from methanol.

Anal. Calcd for $C_{14}H_{11}NOS$: C, 69.70; H, 4.66; N, 5.80; S, 13.28. Found: C, 69.68; H, 4.67; N, 5.72; S, 13.29.

2,2′-Bis(4-methoxybenzoylamino)diphenyl disulfide was prepared from 2,2′-diaminodiphenyl by the same procedure as has been described for the preparation of 2,2′-diaminodiphenyl disulfide,[17,18] and was obtained in 70% yield as colorless microneedles, mp 110–111 °C.

Anal. Calcd for $C_{28}H_{24}N_2O_4S_2$: C, 65.12; H, 4.65; N, 5.43; S, 12.40. Found: C, 65.02; H, 4.61; N, 5.40; S, 12.50.

***trans*-Dimethyl 4-Formyl-2,3-dihydro-1,4-benzothiazine-2,3-dicarboxylate (3).** A solution of DMAD (1.5 g, 0.0105 mol, redistilled prior to use) in AnalaR methanol (5 ml) was added in one portion to a stirred solution of benzothiazole (1.3 g, 0.01 mol) in a mixture of AnalaR methanol (25 ml) and water (5 ml). The solution immediately turned pale yellow in color and was either heated under reflux for 5 h or stirred at room temperature for 3 days. The resulting mixture, from which some of the product had crystallized, was evaporated to dryness and the semisolid mass thus obtained triturated with a little ethanol at 0 °C. The solid was collected by filtration, washed with a small quantity of ice-cold ethanol, and recrystallized from ethanol. This gave 2.5 g (85%) of pure **3** as colorless rhombohedrons, mp 135–136 °C.

The other 1,4-benzothiazines listed in Table I were prepared in

an analogous fashion. Full analytical and spectroscopic data (ir, NMR) for these compounds are listed in Tables II and III (see paragraph at end of paper regarding supplementary material).

3-Carbomethoxymethylene-3,4-dihydro-7-nitro-2-oxo-2*H*-1,4-benzothiazine (29). A solution of DMAD (1.5 g, 0.0105 mol) in AnalaR methanol (5 ml) was added in one portion to a stirred suspension of 6-nitrobenzothiazole (1.8 g, 0.01 mol) in a mixture of AnalaR methanol (55 ml) and water (10 ml). The mixture was heated under reflux for 5 h, during which time the 6-nitrobenzothiazole gradually dissolved and a bright yellow solid precipitated. The reaction mixture was cooled and the solid collected by filtration, washed with ether, and dried This gave 1.7 g (60%) of **29** as bright yellow needles: mp 305–310 °C dec; ir (Nujol) ν_{N-H} 3225 cm^{-1}, $\nu_{C=O}$ 1690 (lactone), and 1670 cm^{-1} (unsaturated ester). The NMR spectrum could not be recorded as the solid is completely insoluble in all common solvents.

Anal. Calcd for $C_{11}H_{18}N_2O_5S$: C, 47.14; H, 2.86; N, 10.00; S, 11.43. Found: C, 47.23; H, 2.81; N, 10.12; S, 11.48.

Acknowledgments. Two of us (T.S.B.S. and G.C.A.B.) acknowledge the receipt of Science Research Council Scholarships.

Supplementary Material Available. Full analytical and spectroscopic (ir, NMR) data for compounds **3, 9, 11, 13, 15, 17, 19, 21, 23,** and **25** are listed in Tables II and III (2 pages). Ordering information is given on any current masthead page.

Registry No.—**1,** 95-16-9; **3,** 55052-31-8; **8,** 58249-57-3; **9,** 58249-58-4; **10,** 36894-61-8; **11,** 58249-59-5; **12,** 2942-07-6; **13,** 58268-61-4; **14,** 768-11-6; **15,** 58249-60-8; **16,** 58249-61-9; **17,** 58249-62-0; **18,** 58249-63-1; **19,** 58249-64-2; **20,** 19989-66-3; **21,** 58249-65-3; **22,** 53218-26-1; **23,** 58249-66-4; **24,** 30132-83-3; **25,** 58249-67-5; **26,** 58249-68-6; **27,** 58249-69-7; **28,** 2942-06-5; **29,** 58249-70-0; **36,** 58249-71-1; **39,** 58249-72-2; **44,** 6265-92-5; DMAD, 503-17-3; 5-aminobenzothiazole, 1123-93-9; 6,6′-dinitro-3,3′,4,4′-tetramethoxydiphenyl disulfide, 58249-73-3; 4-amino-6-methoxybenzothiazole, 58249-74-4; 4,6-dichloro-7-aminobenzothiazole, 58249-75-5; 2,2′-bis(4-methoxybenzoylamino)diphenyl disulfide, 58249-76-6; 6-aminobenzothiazole, 533-30-2.

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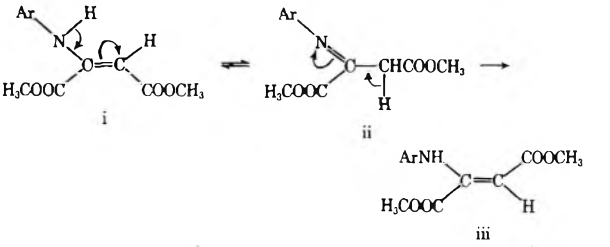

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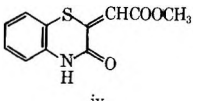

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Reaction of 1,2,3-Benzothiadiazole with Arylthio Radicals†

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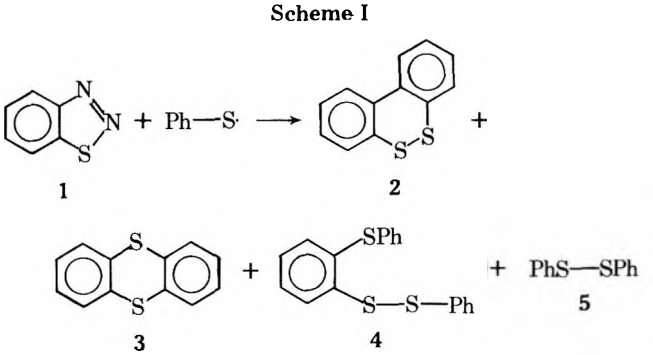
The reaction of 1,2,3-benzothiadiazole (1) with phenylthio radicals afforded dibenzo[c,*e*]-o-dithiin, thianthrene, and 2-(phenylthio)diphenyl disulfide. A mechanism is proposed which assumes initial attack of phenylthio radical at the sulfur atom of 1 to give radical 6, a key intermediate in this reaction.

Homolytic aromatic thioarylations have been achieved in a very limited number of cases and only if certain conditions are satisfied. High homolytic reactivity of the substrate and a strongly oxidizing medium allow direct substitution to occur on furan[1] and thiophene[2] rings. Indirect substitution has been observed at high temperatures with halobenzenes,[3] while intramolecular indirect substitutions occur easily when arylthio radical displaces an arylthio, phenoxy, and mercapto group to give a stable product such as dibenzothiophene or thianthrene.[4]

We now have found what is, to the best of our knowledge, the first example of an aromatic SH2 reaction effected by thiyl radicals at heterocyclic sulfur atom. In Scheme I are reported the products obtained from reaction between 1,2,3-benzothiadiazole (1) and phenylthio radicals

Scheme I



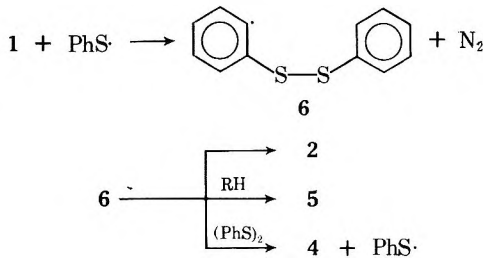
generated both by hydrogen abstraction from thiophenol with 2-cyanopropyl radicals[5] and by thermal decomposition of diphenyl disulfide (at 165 °C).[6] Under the latter

† Dedicated to Professor Martino Colonna on his 70th birthday.

more vigorous conditions part of the asymmetric disulfide (4) disproportionates giving rise to the 2,2′-bis(phenylthio)diphenyl disulfide. Traces of dibenzothiophene, probably derived from radical attack on 2, are also present in the high-temperature reaction.[4] Thermal unassisted decomposition of 1[7] has been proved, by independent experiments, to be unimportant at this temperature.

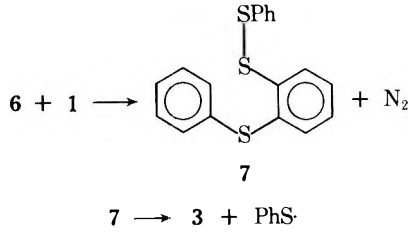
We believe that the attack of thioaryl radicals at the sulfur atom of benzothiadiazole (1), leading to the radical intermediate 6 by fission of the heteroaromatic ring and nitrogen loss, represents the first step of the reaction. Radical 6 may be considered as the key intermediate since all reaction products can be easily rationalized in terms of the following reactions (Scheme II). Thus 6 can lead to dibenzo[c,e]-o-dithiin (2) by intramolecular cyclization, to diphenyl disulfide (5) by hydrogen abstraction from the solvent, and to 2-(phenylthio)diphenyl disulfide (4) by an SH2 reaction on the sulfur atom of the disulfide present in the reaction mixture (Scheme II).

Scheme II



The ortho-substituted phenyl radical (6) can in addition react with 1 to afford the aryl radical 7,[8] which then leads to thianthrene (3) by homolytic intramolecular substitution on the sulfur atom of the S–S bond linked to the adjacent benzene ring (Scheme III).

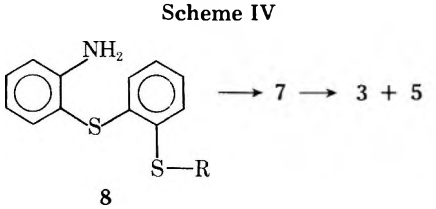
Scheme III



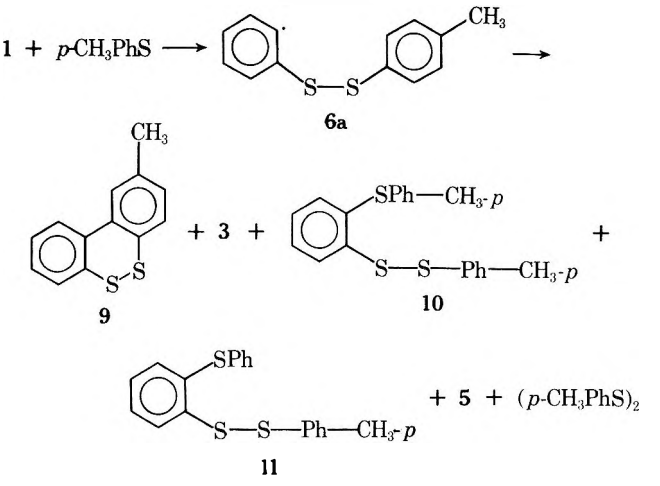
The foregoing mechanism assumes the intermediacy of the two substituted aryl radicals 6 and 7; moreover, the radical 7 should be formed from 6. Several independent experiments have been carried out in order to gain indirect support for this interpretation. By aprotic diazotization of 8 with *n*-pentyl nitrite thianthrene (3) and diphenyl disulfide (5) were obtained. The radical pathway of this reaction, which leads to intermediate 7, was demonstrated on analogous compounds where R = Ph, CH_3.[9]

It is interesting to note that, as indicated in Scheme IV, the intramolecular SH2 reaction at the sulfur atom leading to 3 with phenylthio radical as leaving group appears to be much faster than the intramolecular homolytic substitution on the adjacent benzene ring and the hydrogen abstraction reaction. The intermediacy of 6 was demonstrated as follows. When the 1,2,3-benzothiadiazole (1) was allowed to react with *p*-tolylthio radicals, generated from the parent thiophenol and AIBN, 2-methyldibenzo[c,e]-o-dithiin (9), thianthrene (3), and a mixture of asymmetric disulfides (10, 11) were obtained (Scheme V).

Scheme IV

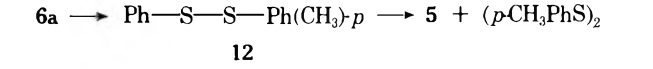


Scheme V



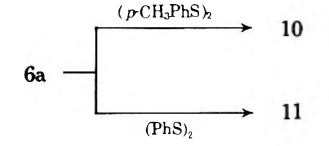
The formation of 9, in this case, shows clearly that 6a, analogous to 6, is the key intermediate of the reaction, from which 9 arises by intramolecular cyclization.

Unsubstituted diphenyl disulfide was also separated; this product can derive from the asymmetric disulfide 12 generated by the hydrogen abstraction reaction of 6a. It is



actually well known that asymmetrical disulfides easily "disproportionate" in organic solvent giving mixtures of the symmetrical ones.[10]

Reaction of 6a with the disulfides present in the reaction mixture could account for the formation of 10 and 11.



Experimental Section

The reaction products were identified, when possible, by mixture melting points with prepared authentic specimens, and by comparison of their ir (Perkin-Elmer 257) and NMR (JEOL 60 MHz) spectra, or by low-resolution mass spectral analysis (JEOL JMS D100).

2-(phenylthio)diphenyl disulfide (4) was obtained from 2-mercaptodiphenyl sulfide[11] and benzenesulfenyl chloride[12] in ethanol-free chloroform. To the solution was added a small quantity of copper bronze, and the mixture was stirred for 3 h. Column chromatography of the reaction mixture on silica gel gave the disulfide as an oil, yield 60%. Anal. Calcd for $C_{18}H_{14}S_3$: C, 66.21; H, 4.32; S, 29.46. Found: C, 66.07; H, 4.34; S, 29.62. Mass spectrum *m/e* (rel intensity) 326 (55) M^+, 294 (8), 292 (13), 252 (7), 250 (6), 217 (87), 185 (39), 184 (100), 110 (34), 109 (31).

2-(*o*-Aminophenylthio)diphenyl Disulfide (8). The crude 2-amino-2′-mercaptodiphenyl sulfide obtained from 2-nitro-2′-aminodiphenyl sulfide[13] under the conditions of the modified Leuckart reaction as described by Campaigne[14] was allowed to react with benzenesulfenyl chloride[12] as described above. Column chromatography of the reaction mixture on silica gel gave the title product as

a colorless oil which is easily decomposed by light, yield 50%. Anal. Calcd for $C_{18}H_{15}NS_3$: C, 63.3; H, 4.43; N, 4.10; S, 28.17. Found: C, 63.38; H, 4.53; N, 4.02; S, 27.89. Mass spectrum: *m/e* (rel intensity) 341 (56) M^+, 309 (34), 276 (15), 232 (91), 199 (100).

Anal. Calcd for $C_{18}H_{15}NS_3$·HCl (mp 150 °C): C, 57.19; H, 4.27; N, 3.71; S, 25.45; Cl, 9.38. Found: C, 57.19; H, 4.22; N, 3.82; S, 25.25; Cl, 9.45.

Reaction of 1,2,3-Benzothiadiazole (1) with Thiophenol and AIBN. A solution of 1,2,3-benzothiadiazole (**1**,[7] 1.36 g, 1×10^{-2} mol), thiophenol (1.10 g, 1×10^{-2} mol), and AIBN (1.6 g) in ethyl acetate was refluxed for 1 h. Column chromatography of the reaction mixture on silica gel with light petroleum (bp 40–70 °C) as eluent gave diphenyl disulfide (**5**,[15] 1.37 g 6.3×10^{-3} mol), thianthrene (**3**, 0.19 g, 0.9×10^{-3} mol), dibenzo[*c,e*]-o-dithiin (**2**,[16] 0.06 g, 0.3×10^{-3} mol), and 2-(phenylthio)diphenyl disulfide (**4**, 0.33 g, 1×10^{-3} mol).

Reaction of 1,2,3-Benzothiadiazole (1) with Diphenyl Disulfide. A solution of 1,2,3-benzothiadiazole (**1**,[7] 2.04 g, 1.5×10^{-2} mol) and diphenyl disulfide[15] (1.64 g, 0.75×10^{-2} mol) in methyl benzoate (28 ml) was warmed at 165 °C for 20 h. The solvent was distilled under vacuum (17 mmHg) and the residue was chromatographed on silica gel with light petroleum as eluent. The following products were separated: diphenyl disulfide (**5**,[15] 0.9 g, 4.13×10^{-3} mol), dibenzothiophene (0.05 g, 0.27×10^{-3} mol), thianthrene (**3**, 0.35 g, 1.62×10^{-3} mol), dibenzo[*c,e*]-*o*-dithiin (**2**,[16] 0.45 g, 2.08×10^{-3} mol), 2-(phenylthio)diphenyl disulfide (**4**, 0.45 g, 1.38×10^{-3} mol), and 2,2′-bis(phenylthio)diphenyl disulfide (0.20 g, 0.46×10^{-3} mol), identified by mixture melting point with an authentic specimen obtained from 2-mercaptodiphenyl sulfide[11] by oxidation with bromine in chloroform, mp 124–125 °C. Mass spectrum: *m/e* (rel intensity) 434 (38) M^+, 217 (100), 184 (49). GLC analysis of a solution of **1** (0.136 g, 1×10^{-3} mol) in methyl benzoate, heated at 165 °C for 20 h, showed unchanged **1** (94%). Thianthrene (**3**) and dibenzo[*c,e*]-*o*-dithiin (**2**) were not present.

Reaction of 1,2,3-Benzothiadiazole (1) with *p*-Methylthiophenol and AIBN. A solution of 1,2,3-benzothiadiazole (1.77 g, 1.3×10^{-2} mol), *p*-methylthiophenol (1.62 g, 1.3×10^{-2} mol), and AIBN (2.40 g) in ethyl acetate (23 ml) was refluxed for 1 h. The solvent was evaporated and the residue was chromatographed on silica gel with light petroleum as eluent. The following products were eluted in the order cited: a mixture of diphenyl and *p,p′*-ditolyl disulfide[17] (0.63 g), thianthrene (**3**, 0.31 g, 1.43×10^{-3} mol), and 2-methyldibenzo[*c,e*]-*o*-dithiin (**9**, 0.08 g, 0.34×10^{-3} mol), mp 95 °C. Anal. Calcd for $C_{13}H_{10}S_2$: C, 67.75; H, 4.4; S, 27.85. Found: C, 67.7; H, 4.65; S, 27.45. **9**, by desulfuration with Raney nickel in boiling ethanol, gave 3-methylbiphenyl.

A mixture of 2-(*p*-tolylthio)phenyl-*p*-tolyl disulfide (**10**) and 2-(phenylthio)phenyl-*p*-tolyl disulfide (**11**, 0.4 g) was also separated. The ratio of **10** to **11**, determined by NMR spectra, was 65:35.

Aprotic Diazotization of 2-(*o*-Aminophenylthio)diphenyl Disulfide (8). A. To a solution of **8** in boiling ethyl acetate an equimolecular amount of *n*-pentyl nitrite was added carefully. After nitrogen evolution was finished (~5 min) the solvent was evaporated and the residue chromatographed on silica gel. Thianthrene (**3**) and diphenyl disulfide (**5**) was separated in 90% yields.

B. The diazotization of **8** in methyl benzoate at 165 °C yields **3**, **5**, and thianthrene *S*-oxide,[18] mp 143–144 °C.

Acknowledgment. We thank Consiglio Nazionale delle Ricerche (Rome) for financial support.

Registry No.—**1**, 273-77-8; **4**, 58074-42-3; **8**, 58074-43-4; **8** HCl, 58074-44-5; **9**, 58074-45-6; 2-mercaptodiphenyl sulfide, 53691-60-4; benzenesulfonyl chloride, 931-59-9; 2-amino-2′-mercaptodiphenyl sulfide, 58074-46-7; thiophenol, 108-98-5; diphenyl disulfide, 882-33-7; 2,2′-bis(phenylthio)diphenyl disulfide, 58074-47-8; *p*-methylthiophenol, 1073-72-9.

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Chemistry of the Sulfur–Nitrogen Bond. XI. Synthesis and Thermal Decomposition of *N,N′*-Thiodiamines

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The synthesis and thermal decomposition of *N,N′*-thiodiamines (**1**) and *N,N′*-thioareneaminopiperidines (**5**) were investigated. Series **1** was prepared by addition of piperidine-1-sulfenyl chloride to the aryl amine at −20 °C. An intermediate in the formation of **1** is **5** which is obtained in good yield when the addition of the sulfenyl chloride to the aryl amine is carried out at −78 °C. Azobenzene (**6**), aryl amine, and sulfur are the principal products in the thermal decomposition of **1**. A mechanism involving the initial formation of thionitrosobenzene (ArN=S) was proposed. The thermal decomposition of **5** yields aryl amine and lower amounts of azobenzene. Homolytic cleavage of the S–N bond in **5** followed by recombination of the intermediate radicals yields **1** which is believed to account for the formation of **6**. Oxidation of **1** under anhydrous conditions yields *N*-sulfinylaniline.

N,N′-Thiodianilines (**1**) are a class of important sulfur–nitrogen compounds that have received relatively little attention. Their importance stems from the fact that they are at present the only known source of thionitrosobenzene (**2**).[2,3] The existence of **2** was demonstrated in the thermal decomposition of **1** by trapping with 2,3-dimethyl-1,3-butadiene to yield the 1,2-thiazine **3**.[2] An unstable *N*-thionitrosoamine (R_2N–N=S) has been reported.[4] Attempts to pre-

Table I. Properties of *N,N'*-Thiodiamines

Compd	Yield, %	Mp, °C	Ir, cm^{-1} (NH)	NMR ($CDCl_3$), δ
1a	55	102–103[a]	3310	3.8 (s, 6 H, OMe), 6.2–3 (broad, 2 H, NH), 7.0 (m, 8 H)
b	75 (90, oil)[b]	73–74[c]	*b*	5.9–6.2 (broad, 2 H, NH), 7.5–6.7 (m, 10 H)
c	67 (55)[b]	106–108	*b*	5.8–6.1 (broad, 2 H, NH), 6.8–7.4 (m, 8 H)
d	70 (53)[b]	102–103	*b*	5.8–6.1 (broad, 2 H, NH), 6.8–7.3 (m, 8 H)
e	64	190–195	3350	5.8–6.4 (broad, 2 H, NH), 7.0–7.6 (m, 8 H)
5a	42	Oil	3330	1.2–1.8 (m, 6 H), 3.0 (m, 4 H), 3 (s, 3 H, OMe), 5.8 (broad, 1 H, NH), 6.9–7.5 (q, 4 H)
b	46	Oil	3320	1.2–1.9 (m, 6 H), 2.9–3.3 (m, 4 H), 5.9 (broad, 1 H, NH), 7.0–7.5 (s, 5 H)
c	60	81–82[a]	3455	1.0–1.9 (m, 6 H), 3.0–3.3 (m, 4 H), 5.9 (broad, 1 H, NH), 6.9–7.5 (q, 4 H)
d	70	53–54[a]	3220	1.0–1.9 (m, 6 H), 2.9–3.3 (m, 4 H), 5.9 (broad, 1 H, NH), 7.0–7.5 (q, 4 H)
e	65	125–126[a]	3360	1.3–1.7 (m, 6 H), 2.8 (m, 4 H), 5.8 (broad, 1 H, NH), 7.0–7.5 (m, 4 H)

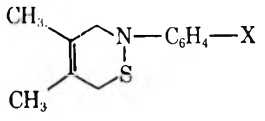
[a] A satisfactory elemental analysis was obtained. [b] See ref 2. [c] This compound was reported as an oil.

pare **2** (X = 4-NMe_2) by treatment of the nitrosobenzene with phosphorus pentasulfide gave an *N*-thiosulfinylaniline (ArN=S=S).[5]

$$(X—C_6H_4NH)_2S \longrightarrow X—C_6H_4—N{=}S + X—C_6H_4—NH_2$$

1 **2** **4**

X = **a**, 4-OMe
b, H
c, 4-Br
d, 4-Cl
e, 3-NO_2



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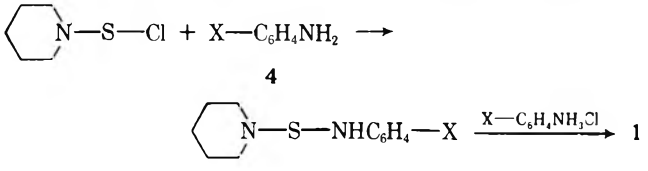
Our interest in the chemistry of the sulfur–nitrogen bond[6] and the thionitroso group prompted a study of the synthesis and thermal decomposition of *N,N'*-thiodiamines and we report here the results of that investigation.

Synthesis. Compounds **1a–d** were prepared by addition of piperidine-1-sulfenyl chloride to a twofold excess of the appropriate aryl amine at −20 °C. When the addition of the sulfenyl chloride to **4** was carried out at −78 °C *N,N'*-thioareneaminopiperidines (**5**) were obtained in good yield.



4 **5**

An NMR spectrum of the crude reaction mixture indicated the presence of both **1** and **5**. These results suggest that **5** is an intermediate in the formation of **1**. This is supported by the isolation of **1b** in greater than 80% yield when **5b** was treated with aniline hydrochloride. All attempts to prepare unsymmetrical thiodianilines by allowing aniline hydrochloride to react with **5e** gave only the symmetrical thiodianiline, **1e**. Compound **1e** was prepared by dropwise addition of sulfur dichloride to 3-nitroaniline and triethylamine. Thiodiamines **1** and **5** are moderately stable compounds that can be stored for short periods of time without noticeable decomposition. Electron-attracting groups appear to increase the stability of both **1** and **5** since **1e** and **5e** were stable for more than 2 years.

Structural proof for **1** and **5** is supported by their elemental analyses, where stability of the compound permitted, ir, and NMR (Table I).

Thermal Decomposition of 1 and 5. When **1a–e** were heated in benzene at 50 °C for 72 h in the absence of trapping agent, azobenzene (**6**), aryl amine, **4**, and sulfur were obtained (eq 1).

$$1 \longrightarrow X—C_6H_4N{=}NC_6H_4—X + X—C_6H_4NH_2 + S \quad (1)$$

6 **4**

Table II. Thermal Decomposition of *N,N'*-Thiodiamines at 50 °C for 72 h

Compd	Solvent	Products (% yield)[a]
1a	Benzene	**6a** (99), **4a** (91), S (47)
b	Benzene	**6b** (83), **4b** (66), S (60)
	Benzene, 2,3-dimethyl-1,3-butadiene	**4b** (82), **9** (56)
c	Benzene	**6c** (90), **4c** (92), S (89)
d	Benzene	**6d** (89), **4d** (93), S (92)
e	Benzene	No reaction
e[b,c]	Bromobenzene	**6e** (83), **4e** (74), S (10)
5a	Benzene	**6a** (21), **4a** (75)
b	Benzene	**6b** (11), **4b** (78)
	Benzene, 2,3-dimethyl-1,3-butadiene	**4b** (60), **9** (10)
c	Benzene	**4c** (84)
d	Benzene	**6d** (25), **4d** (75)

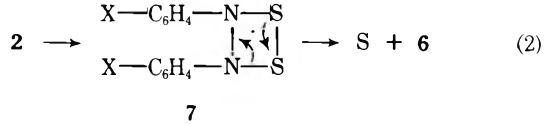
[a] Yields calculated assuming that **1** and **5** yield 1 mol of **4** and 0.5 mol of **6**. [b] Heated at 120 °C for 96 h. [c] Isolated by chromatography on Florisil.

The composition of the reaction mixture was determined by comparison of GLC analysis with authentic samples. These results are summarized in Table II.

At least two mechanisms may be considered for the formation of **4** and **6** in the thermal decomposition of **1**. The first mechanism involved a sulfur extrusion from **1** to yield a hydrazobenzene which disproportionates to **4** and **6**. The thermal instability of the S–N bond in sulfenamides is well known.[6] Arenesulfenanilides when heated at 150–190 °C give among other products azobenzene and aniline.[7] A mechanism involving homolytic cleavage of the S–N bond and formation of hydrazobenzene was proposed.

The formation of hydrazobenzene in the decomposition of **1**, however, can be eliminated as a major mechanistic pathway for the formation of azobenzene since under the reaction conditions hydrazobenzene was converted to less than 4% azobenzene. Furthermore, when the reaction of **1b** was monitored by NMR, absorption due to the NH protons of hydrazobenzene was not detected.

A second and more likely mechanism for the formation of **4** and **6** from **1** involves the formation of **2**. Dimerization of two thionitroso units may give **7** which disproportionates to azobenzene and sulfur (eq 2). The formation of alkenes

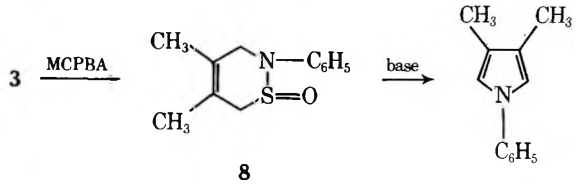


7

from thiocarbonyl compounds under the influence of heat,[8] the isolation of benzophenone anil from thiobenzophenone and nitrosobenzene,[9] and the formation of mixed thioketones and imines in the photolytic decomposition of thio-

benzophenone and imines[10] have been suggested to involve intermediates similar to 7.

The trapping of **2** with 2,3-dimethyl-1,3-butadiene under our reaction conditions to give **3b** further supports the proposed mechanism. Since **3** is unstable toward analysis by GLC it was necessary to devise an alternate procedure for its analysis. The procedure develcped for the GLC analysis of **3** involved the oxidation of **3** with *m*-chloroperbenzoic acid (MCPBA) to give the 1,2-thiazine 1-oxide (**8**) followed by alkaline hydrolysis to yield the pyrrole[11] which could be analyzed by GLC techniques. In a separate experiment oxidation of **3b** followed by alkaline hydrolysis gave an 82% yield of **9**.



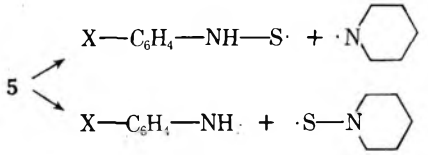
8 **9**

A quite different product distribution is observed in the thermal decomposition of **5a–d** (Table II). Only low yields of azobenzene **6** were found with the major product being the amine **4**. Monitoring the decomposition of **5a–d** by NMR indicated a slow decrease in the NH absorption due to **5** with buildup and slow decrease of a new NH absorption. This new absorption in the NMR, which was not hydrazobenzene, was established to be the symmetrical *N,N'*-thiodiamine **1** by addition of authentic samples of **1** to the reaction mixture. When **5b** was heated in the presence of 2,3-dimethyl-1,3-butadiene followed by oxidation and alkaline hydrolysis, a 10% yield of **9** (1,2-thiazine **3**) was obtained. A TLC of the dark reaction residue indicated the presence of *N,N'*-piperidinyl disulfide (**10**)[12a] and *N,N'*-piperidinyl sulfide (**11**).[12b]

10 **11**

The formation of **4** and **6** and the detection of **1**, **10**, and **11** in the thermal decomposition of **5** is best accounted for in terms of a mechanism which involves homolytic cleavage of the S–N bond in **5** (Scheme I).

Scheme I



Recombination of the radical intermediates (Scheme I) would lead to **1**, **10**, and **11**. Abstraction of a hydrogen atom by the aryl amino radical yields **4**. The hydrogen atom apparently is abstracted from the piperidine unit since an NMR of the polymeric-like residue shows absorption characteristic of piperdine ring protons.

The major source of azobenzene **6** appears to result from the intermediate thionitrosobenzene (eq 2) since **2b** was trapped and **1** was detected by NMR in the decomposition of **5** (eq (eq 3).

$$5 \longrightarrow (X\text{—}C_5H_4NH)_2S \longrightarrow 6 + 4 \qquad (3)$$

1

The possibility that some of **2** is formed directly from **5**, however, cannot be excluded.

Oxidation of *N,N'*-Thiodiamines. The oxidation of *N,N'*-thiodiamine **1b** was briefly explored. When **1b** was allowed to react with 1 equiv of MCPBA in chloroform–sodium bicarbonate–water mixture an 81% yield of aniline (**4b**) was obtained. When the oxidation was carried out under anhydrous conditions followed by reaction of the dark oil with 2,3-dimethyl-1,3-butadiene a 55% yield of **9** was obtained. These results may be interpreted in terms of the intermediate formation of **12** which rapidly eliminates aniline to give *N*-sulfinylaniline (**13**). *N*-Sulfinylaniline is known

$$\mathbf{1b} \xrightarrow{\text{MCPBA}} (C_6H_5NH)_2SO \xrightarrow{-C_6H_5NH_2} C_6H_5N{=}S{=}O$$

12 **13**

to react with 2,3-dimethyl-1,3-butadiene to give **8** and to be hydrolyzed to aniline and sulfur dioxide.[13]

Experimental Section

Solvents and aromatic amines were purified by standard methods. Melting points are uncorrected. Infrared spectra were taken on a Perkin-Elmer 457 spectrometer. Proton NMR spectra were performed on a Varian A-60A spectrometer. Elemental analyses were obtained from Chemalytics, Inc., Tempe, Ariz. Gas chromatography was performed on a Perkin-Elmer 900 gas chromatograph using a 12 ft, 15% silicone grease on 60/80 mesh Chromosorb W (regular) and on a 6 ft 3% OV-1 on 60/80 mesh Chromosorb W (regular) columns.

Preparation of *N,N'*-Thiodianilines (1). The preparation of **1** is a modified version of that reported by Tavs.[2] In a 250-ml three-necked flask equipped with nitrogen inlet, magnetic stirrer, and dropping funnel was placed 0.025 mol of the appropriate amine in 50 ml of ether. The reaction mixture was cooled to 10 °C in an ice–salt bath and 1.9 g (0.0125 mol) of piperidine-1-sulfenyl chloride[14] (*Caution:* an explosion occurred on distillation of piperidine-1-sulfenyl chloride when the flask temperature exceeded 80 °C) in 50 ml of ether was added dropwise within 5 min. The reaction mixture was allowed to stir under N_2 for 1 h at room temperature and the precipitate removed by filtration. The reaction can be tested for completeness at this point by dissolving a small amount of the precipitate in 1 N NaOH solution. If the precipitate fails to dissolve the collected precipitate and filtrate are recombined. When the reaction was complete the ether solution was washed with water (3 × 50 ml) and dried over $MgSO_4$. Removal of the solvent gave crude **1** which may be crystallized from pentane–ether.

***N,N'*-Thiobis-3-nitroaniline (1e).** In a 250-ml three-necked flask equipped with dropping funnel, condenser, nitrogen inlet, and magnetic stirrer was placed 7.3 g (0.053 mol) of 3-nitroaniline in 100 ml of ether. The reaction mixture was cooled in an ice bath and 1.5 g (0.014 mol) of sulfur dichloride in 50 ml of ether added dropwise. After refluxing for 0.5 h the precipitate was removed by filtration and the solution was washed with water and dried over $MgSO_4$. Removal of solvent gave a yellow powder which was dissolved in dimethylacetamide and water to give **1e**.

***N,N'*-Thioarylaminopiperidine (5).** Compound **5** was prepared as described above for the synthesis of **1** except that the reaction was carried out at −78 °C using a dry ice–acetone bath and the reaction mixture filtered while still cold. Alternatively **5** can be prepared by addition of 1 equiv of the sulfenyl chloride to 1 equiv of the appropriate amine in ether containing triethylamine.

Thermal Decomposition of 1 and 5. Compound **1** or **5** (usually 0.007 mol) was dissolved in 25 ml of dry benzene and placed in a sealed tube. The reaction mixture was heated in an oil bath at 50 °C for 72 h at which time the solution was filtered to remove the precipitated sulfur. The solvent was removed and redissolved in CH_2Cl_2 and a known amount of undecane was added. The reaction mixture was analyzed by GLC by comparison of peak areas with standard solutions of the reaction products. Analyses were performed at least twice and the results averaged.

Detection of Thionitrosobenzene (2) [1-Phenyl-3,4-dimethylpyrrole (9)]. Thionitrosobenzene **2b** was analyzed by GLC as **9** by the following procedure. Compound **1b** (0.5 g, 0.0023 mol) was placed in 25 ml of benzene containing 2 ml of 2,3-dimethyl-1,3-butadiene. The reaction mixture was heated in a sealed tube at 50 °C for 72 h and diluted with 50 ml of CH_2Cl_2. This solution was placed in a 250-ml three-necked flask equipped with dropping funnel and magnetic stirrer and containing 0.2 g of $NaHCO_3$ in 100 ml of water. The solution was cooled in an ice bath and 0.51 g (0.0025

mol) of 85% MCPBA in 50 ml of CH_2Cl_2 was added dropwise. Following the addition, the reaction mixture was refluxed for 15 min and dried over $MgSO_4$. The removal of the solvent gave a dark oil which was dissolved in 50 ml of alcohol containing 0.38 g of KOH. After refluxing for 1.5 h the solution was diluted with water and extracted with CH_2Cl_2. The dried CH_2Cl_2 solution was analyzed as described above by GLC.

Oxidation of 1b. In a 250-ml three-necked flask equipped with dropping funnel and magnetic stirrer and containing 0.8 g of $NaCO_3$ in 50 ml of water was placed 1.43 g (0.0066 mol) of **1b** in 50 ml of CH_2Cl_2. The reaction mixture was cooled in an ice bath and 1.43 g (0.0066 mol) of 85% MCPBA in 50 ml of CH_2Cl_2 added dropwise. The solution was stirred for 15 min, washed with water, and dried over $MgSO_4$. Removal of the solvent gave 1.0 g (81%) of an oil identified as aniline (**4b**) by comparison of its ir and NMR spectra with those of an authentic sample.

Oxidation of 1b Followed by Reaction with 2,3-Dimethyl-1,3-butadiene. In a 250-ml three-necked flask equipped with dropping funnel and magnetic stirrer was placed 3.0 g (0.0131 mol) of **1b** in 50 ml of $CHCl_3$. The solution was cooled in an ice bath and 2.8 g (0.014 mol) of 85% MCPBA in 50 ml of $CHCl_3$ was added dropwise. After stirring for 15 min the precipitate was removed and 3 ml of 2,3-dimethyl-1,3-butadiene added. After stirring for 3 days the solution was washed with 10% $NaHCO_3$ solution and dried over $MgSO_4$. Removal of the solvent gave an oil which contained **4b** and **8** by TLC (silica gel). Removal of the aniline by molecular distillation gave a solid which was crystallized from cyclohexane to give 1.5 g (52%) of white crystals, mp 78–80 °C (lit.[15] mp 79–80 °C).

Registry No.—**1a**, 58241-34-2; **1b**, 13628-09-6; **1c**, 13616-64-3; **1d**, 13616-65-4; **1e**, 19552-05-7; **4a**, 104-94-9; **4b**, 62-53-3; **4c**, 106-40-1; **4d**, 106-47-8; **4e**, 100-01-6; **5a**, 58241-35-3; **5b**, 58241-36-4; **5c**, 58241-37-5; **5d**, 58267-78-0; **5e**, 58241-38-6; sulfur dichloride, 10545-99-0; piperidine-1-sulfenyl chloride, 16005-90-6.

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Thioasparagine and Derivatives for Peptide Synthesis. A Trifluoroacetic Acid Catalyzed Anisyl Transfer to Sulfur

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Thioamidation of *N*-*p*-methoxybenzyloxycarbonyl-L-β-cyanoalanine with H_2S–NH_3 furnished *N*-*p*-methoxybenzyloxy-L-thioasparagine. Deprotection of the latter with trifluoroacetic acid or HF yielded the asparagine analogue, thioasparagine (L-aspartic acid β-thioamide). *tert*-Butyloxycarbonyl-L-thioasparagine and benzyloxycarbonyl-L-thioasparagine were prepared from the corresponding β-cyanoalanine derivatives by similar treatment, and these likewise gave thioasparagine. During the deprotection of Meoz-L-thioasparagine in TFA a major side reaction (anisyl transfer) ensued that led to the formation of aspartic *p*-methoxybenzyl β-imidothiolic ester and, from this, β-*S*-*p*-methoxybenzyl aspartic thioester. This transfer reaction has been extended to the synthesis of a thioether, *S*-*p*-methoxybenzylcysteine. Anisyl transfer can therefore be a source of decreased yield in peptide synthesis when the *N*-p-methoxybenzyloxycarbonyl group is deprotected in the presence of a preformed or newly generated thiol group. *N*-Meoz-L-alanine and *p*-methoxybenzyl carbazate in TFA under very mild conditions are convenient alternate sources of the *p*-methoxybenzyl carbonium ion. *N*-*p*-Methoxybenzyl thioacetamide was synthesized for ^1H NMR reference.

Intramolecular hydrogen bonding between the carbonyl oxygen of specific carboxamide or peptide linkages and the amide hydrogen of other peptide or amide linkages in polypeptides is considered to be one of the key features in determining and stabilizing conformation. For example, in oxytocin and vasopressin[1] the asparagine residue participates in forming the characteristic "β turn" of the ring moiety by means of hydrogen bonding. These thoughts have led us to consider the effect on biological activity of subtle structural changes that might alter chiefly the degree of intramolecular hydrogen bonding. Replacement of a carboxamide by a thiocarboxamide might be expected to introduce electronic effects suitable for such a purpose.[2] Accordingly, the desire to replace asparagine in oxytocin with thioasparagine prompted synthesis of the latter. Thioasparagine had added interest as a possible antimetabolite of asparagine since asparagine holds an important position as a nutritional requirement in the metabolism of certain neoplastic cells lacking asparagine synthetase.[3] This report deals with the synthesis and chemical properties of thioasparagine and makes available a variety of derivatives expected to be suitable for its introduction into peptides. During the deprotection of *N*-*p*-methoxybenzyloxycarbonyl-L-thioasparagine to thioasparagine with trifluoroacetic acid an unexpected alkylating side reaction was encountered that led predominantly to the formation of the *S*-anisyl ester of β-thioaspartic acid. The reaction has preparative value also for the synthesis of an *S*-anisyl thioether, *S*-anisyl-L-cysteine. Possible implication of this side reaction for peptide synthesis has been pointed out.

General methods for the synthesis of thioamides include thiolysis of nitriles, amidines, or imidic esters with H_2S and the thionation of amides with phosphorus pentasulfide.[4] The base-catalyzed addition of H_2S to the nitrile was chosen for the synthesis of thioasparagine, with the amino nitrogen group being protected by the *p*-methoxybenzyloxy-

carbonyl group, inasmuch as Meoz-β-cyanoalanine was available in the laboratory from previous work.[5] In addition this route had recently proved suitable for preparing a series of amino acid thioamides corresponding to alanine, phenylalanine, dihydrophenylalanine, tyrosine, Dopa, and histidine from the *N*-Meoz-cyanoamine.[6]

Treatment of Meoz-β-cyanoalanine (**1a**) with H_2S and concentrated NH_3 furnished a solid product that when deprotected and examined on the amino acid analyzer showed incomplete thioamidation. Separation of Meoz-L-thioasparagine (**2a**) from the starting material was accomplished through crystallization of the dicyclohexylamine salt. After liberation from the DCHA salt, purified **2a** melted sharply some 37 °C below the corresponding asparagine derivative. Properties and yields are listed in Table I. Deprotection of **2a** with trifluoroacetic acid in the usual manner (TFA containing 3 equiv of anisole at 0 °C)[7] afforded crystalline thioasparagine (**3**). Thioasparagine showed the expected elemental analysis, infrared absorption, and chromatographic and electrophoretic behavior. However, the yield of **3** in the deprotection step was only 25%. Deprotection of **2a** in the presence of a large excess of anisole (43 equiv) raised the yield of **3** to 64%. Deprotection with HF in the absence and the presence of anisole gave **3** in 85 and 100% yield, respectively.

For comparison *tert*-butyloxycarbonyl (Boc) and benzyloxycarbonyl (Z) were also examined for suitability as N-protecting groups for the synthesis of thioasparagine. Boc-β-cyanoalanine (**1b**), known previously as its DCHA salt,[8] was obtained in the free state as a crude solid melting at 92–94 °C and was used directly. The thioamidation of **1b** and of **1c**[9] was accomplished with H_2S and NH_3 in the same manner as for **1a**. In each case a single recrystallization of the DCHA salt, with the precaution of not cooling below room temperature, was usually sufficient to remove the unreacted β-cyanoalanine derivative. Properties and yields of these derivatives of **3** are included in Table I. Deprotection of **2b** with TFA gave **3** in high yield in the presence or absence of anisole. Deprotection of **2c** with 30% HBr–acetic acid at 25 °C likewise was satisfactory. This latter reaction, however, tended to be susceptible to hydrolysis to give asparagine which was observed when a long reaction time or a large excess of reagent was used. In each of the three preparations of **3** the limiting step was thioamidation, the yields being 20–40%. The Meoz derivative is generally preferred on the basis of ease of recrystallization. For incorporating thioasparagine into peptides *N*-Boc-, *N*-Z-, and *N*-Meoz-L-thioasparagine should all be suitable providing appropriate care is taken in subsequent deprotection.

When the deprotection of **2a** was carried out in TFA in the presence of 2 equiv of anisole, in addition to **3**, 32% of another ninhydrin-positive compound was obtained that was less water soluble and higher melting. In the absence of anisole the yield of this by-product rose to 81%. The ^1H NMR spectrum of this material (two aromatic doublets) suggested the presence of an anisyl group. Strong absorption at 1675 cm^{-1} in the infrared is characteristic of thiolic esters.[10] Treatment with several equivalents of alkali at 25 °C or dilute acid at 100 °C afforded aspartic acid in close to quantitative yield. In the acid-treated material a nitroprusside-positive compound was present that was identified as anisyl mercaptan by oxidation to the well-characterized anisyl disulfide.[11] Alkaline hydrolysis yielded the disulfide directly. On this basis as well as elemental analysis the isolated by-product was considered to be β-*S*-anisyl aspartic thioester (**5**).

Alkylating side reactions involving a protecting group have been encountered occasionally before on deprotection

Table I. Syntheses and Properties of Thioasparagine and Derivatives

Starting compd RNHCHCOOH $CH_2C{\equiv}N$ (1)	Thioasparagine derivative[a] RNHCHCOOH CH_2CSNH_2 (2)								Thioasparagine (3)	
	DCHA salt		Carboxylic acid							
	Mp, °C	Crystn solvent	Mp, °C	Crystn solvent	Formula	Anal, %			Rotation $[\alpha]_D$, deg	Yield,[b] %
R = $CH_3OC_6H_4CH_2OCO$–, Meoz	155–165									
	174–176 (38)	EtOH	122–123 (87)	H_2O–EtOH	$C_{13}H_{16}N_2O_5S$	C, 50.0	H, 5.16	N, 8.97	S, 10.3	68[c]
						50.2	5.17	8.77	10.2	
R = $C_6H_5CH_2OCO$–, Z	155–160		120–122							
	167–169 (39)	EtOH	123–125 (82)	H_2O	$C_{12}H_{14}N_2O_4S$	51.1	5.00	9.92	11.3	90 + 4.3 asn
		Et_2O				50.9	5.01	9.80	11.2	+ 1.3 asp[d]
R = $(CH_3)_3COCO$–, Boc	174–178		65–68							
	183–184[e] (21)	EtOH	69–71 (70)	H_2O	$C_9H_{16}N_2O_4S{\cdot}H_2O$	40.6	6.81	10.5	12.1	−35.7
						40.9	6.58	10.4	12.1	85 + 1.4 asn[f]

[a] Melting points of crude products are given first, those of purified products are below. Yields of **2** are given within parentheses. For analyses calculated values are given first; found values are below. Optical rotations are at 24–25 °C in methanol, c 1. [b] Deprotection yields as determined on the amino acid analyzer. [c] TFA and anisole for 20 min at 0 °C. [d] 8 equiv HBr–HOAc for 2 h at 25 °C; 4 equiv for 1 h gave 53% 3; 300 equiv for 35 min gave 19% 3 and 61% asn. [e] Anal. Calcd for $C_{21}H_{39}N_3O_4S$: C, 58.7; H, 9.15; N, 9.78; S, 7.45. Found: C, 59.0; H, 9.27; N, 9.68; S, 7.47. [f] TFA for 1 h at 25 °C.

Table II. ^{1}H NMR Chemical Shifts of Various *S*- and *N*-Anisyl and Benzyl Derivatives[a]

Registry no.	Compd	Solvent[b]	$ArCH_2$	$ArOCH_3$
2544-31-2	*S*-*p*-Methoxybenzyl-L-cysteine	1	3.4	3.55
16741-80-3	*S*-Benzyl-L-cysteine OMe·HCl	1	3.4	
		3	3.83	
17004-42-1	*p*-Methoxybenzyl disulfide	2	3.7	3.85
		3	3.69	3.72
6436-90-4	*N*-Benzylglycine OEt	1	4.18	
		3	3.73	
103-46-8	*S*-Benzylthioglycolic acid	1	3.39	
		3	3.82	
2393-23-9	*p*-Methoxybenzylamine	1	4.45	4.03
		3	3.62	3.70
6258-60-2	*p*-Methoxybenzyl mercaptan	1[c]	3.87	3.52
		3	3.70 (d)	3.72
58208-17-6	β-S-*p*-Methoxybenzyl aspartic thioester (5)	1	3.78	3.51
		3	3.68	3.76
		4[c]	3.55	3.76
58208-18-7	β-*p*-Methoxybenzyl aspartic imidothiolic ester (4a)	1	4.10	3.45
		3	3.71	3.73
58208-19-8	*N*-*p*-Methoxybenzyl thioacetamide[d]	1[c]	4.73	4.05
		2	4.73	3.83
		3	4.71 (d)	3.73

[a] Tetramethylsilane served as internal reference for spectra in Me_2SO-d_6. In other solvents Me_4Si generally served as external reference. [b] 1, TFA-*d*; 2, $CDCl_3$; 3, Me_2SO-d_6; 4, NaOD. [c] Some decomposition was apparent in this solvent. [d] Prepared from thioacetamide and *p*-methoxybenzylamine as described for *N*-benzyl thioacetamide [M. J. Schlatter, *J. Am. Chem. Soc.*, **64**, 2722 (1942)]; long needles, mp 82–84 °C. Anal. Calcd for $C_{10}H_{13}NOS$: C, 61.5; H, 6.71; N, 7.17; S, 16.4. Found: C, 61.7; H, 6.87; N, 7.19; S, 16.3.

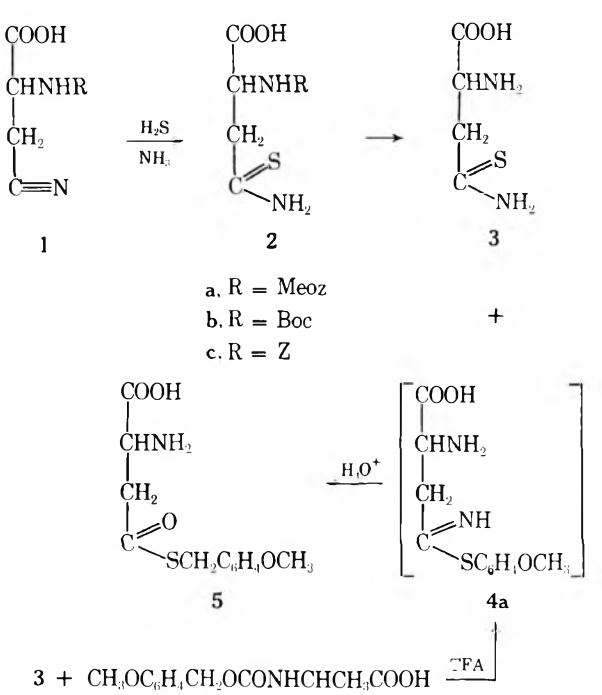
of certain amino acid derivatives under acidic conditions. Thus, C-alkylation of the tyrosine ring results when *O*-benzyltyrosine or *N*-carbobenzoxytyrosine is hydrolyzed in 6 N HCl at 100 °C[12] or solvolyzed with 50% TFA–CH_2Cl_2 or 50% HF–anisole,[13] or when *O*-benzyl 2-fluorophenyl ether is treated with TFA.[14] S-Alkylation to give *S*-benzylhomocysteine takes place when *N*-carbobenzoxy-L-methionine anilide is refluxed in concentrated HCl.[15] S-Alkylation of thioamides by alkyl halides is considered to be a very suitable preparative route to imidothiolic esters.[4] Therefore, it seemed likely that the thioasparagine β-thioamide had been alkylated by the *p*-methoxybenzyl (Meb) carbonium ion formed on deprotection of **1a** thereby giving the imidothiolic ester (**4a**). Consistent with an imidothiolic ester structure was the liberation of 0.7 mol of NH_3 after brief treatment of **4a** with dilute acid at 100 °C, as well as the formation of 0.2 mol of β-cyanoalanine and 0.4 mol each of aspartic acid and anisyl disulfide on treatment of **4a** with 1 N NaOH for 18 h at 25 °C.

Instances of N- and S-alkylation have been noted on treatment of thioamides with alcohols or halides under acidic conditions although N-alkylation appears to be less common.[16] That S-alkylation had resulted in forming the imidothiolic ester (**4a**) was suggested chiefly by the chemical shift of the anisyl methylene protons in Me_2SO-d_6 when ^{1}H NMR spectra were compared with those of various available *S*- and *N*-anisyl and benzyl compounds (Table II). ^{1}H NMR spectroscopy in TFA-*d* was less informative, the downfield shift of the *S*-anisyl methylene of **4a** probably being the result of protonation of the neighboring iminium nitrogen.

Conversion of imidothiolic esters to thiolic esters is known to be facile.[17] Owing to limited solubility crude **4a** had been recrystallized under mildly hydrolytic conditions during which presumably deimidation ensued to give the *S*-anisyl ester of β-thioaspartic acid (**5**). Consistent with this was the appearance of the carbonyl absorption band at 1675 cm^{-1} only after crude **4a** had been recrystallized. The likely sequence of reactions leading from **2a** to **5** is given in Scheme I.

The finding that the Meoz group of the *N*-Meoz thioamides of five monocarboxylic amino acids could be removed

Scheme I



1 2 3 5 4a 8

with TFA with no detectable S-anisylation raises a question whether the S-anisylation observed with aspartic acid derivative **2a** is intramolecularly facilitated by the α-carboxyl group. That the sulfur is an important participant in the reaction is supported by the fact that under the same conditions *N*-Meoz-L-asparagine is deprotected to asparagine in over 90% yield. That the transfer of the anisyl group from the *N*-methoxybenzyloxycarbonyl group to the thioamide group of **2a** is probably intermolecular is indicated by the observation that **4a** results also when **3** and *N*-Meoz-alanine (**8**) are placed in TFA.

The facility with which the thioamide of **3** was alkylated by a *p*-methoxybenzyl cation generated on deprotection of an *N*-Meoz amino acid in TFA prompted us to examine the

reactivity of cysteinethiol under deprotection conditions in order to assess S-anisylation as a possible side reaction in the synthesis of cysteine containing peptides. An equimolar mixture of cysteine (**9**) and Meoz-alanine (**8**) in TFA at −20 °C afforded in 85% yield *S*-*p*-methoxybenzyl-L-cysteine (S-Meb-cys, **10**) that agreed in properties with a reference sample. Although the yield of **10** dropped to 6% when

$$\underset{\mathbf{9}}{HSCH_2CHNH_2COOH} + 8 \xrightarrow[-20°C]{TFA} CH_3OC_6H_4CH_2SCH_2CHNH_2COOH \quad (\mathbf{10})$$

the reaction was carried out in the presence of anisole S-anisylation merits consideration as a potential side reaction when in the course of peptide synthesis the *N*-Meoz group and an S-protecting group are to be removed simultaneously. In HF the transfer reaction to give **10** from **8** and **9** was not significant.

The commercially available *p*-methoxybenzyl carbazate ($CH_3OC_6H_4CH_2OCONHNH_2$) proved to be as effective as Meoz-ala as a source of the *p*-methoxybenzyl carbonium ion as it led to a 91% yield of **10** from **9**. Conversion of **9** to **10** with *p*-methoxybenzyl alcohol in acetic–sulfuric acids proceeded in 53% yield; treatment of **9** with *p*-methoxybenzyl chloride in liquid NH_3 gives a 78% yield of **10**.[18] The anisyl transfer reaction would therefore appear to offer an attractive alternative to the two latter routes to alkylate sulfur since yields are promising and conditions are milder, and it may be worth examination as a general route for anisylation of mercaptans and acylthiols. In addition, the possibility of extending the scope of this transfer reaction to the in situ generation and utilization of certain other carbonium ions remains to be examined.

Experimental Section

Elemental analyses were carried out by Micro-Tech Laboratories, Skokie, Ill. Proton magnetic resonance spectra were obtained on a Varian EM-360 spectrometer. Infrared spectra, melting points, and optical rotations were determined as described elsewhere.[19] Amino acid analyses were performed on a Beckman-Spinco automatic amino acid analyzer, Model 120.[20] System 1 refers to the 150-cm column, 30 °C, pH 3.25; system 2 to the 15-cm column, 30 °C, pH 4.26. *S*-*p*-Methoxybenzyl-L-cysteine was purchased from Peninsula Labs, San Carlos, Calif.; *p*-methoxybenzyl carbazate from the Protein Research Co., Institute for Protein Research, Osaka City, Japan; trifluoroacetic acid from Matheson Co., N.J.; *p*-methoxybenzylamine, *S*-benzylthioglycolic acid, and *N*-benzylglycine ethyl ester from Aldrich Chemical Co., Inc., Milwaukee, Wis.

Meoz-L-β-cyanoalanine (1a) was prepared essentially as described[5] except that a preparative scale (16 g of Meoz-L-asparagine in 110 ml of pyridine) and only a 4% excess of DCCI (11.5 g in 86 ml of pyridine) were used. Crude **1a** (13 g, mp 84–86 °C) was recrystallized from ether–benzene (50:150) with a few drops of petroleum ether added to induce turbidity. Cooling overnight at 0 °C furnished **1a** (12 g, 80%), mp 91–92 °C.

Meoz-L-thioasparagine (2a). A solution of **1a** (2.8 g, 10 mmol) in 280 ml of MeOH and 60 ml of concentrated NH_3 was saturated with a stream of H_2S at 0 °C. The solution was sealed and kept at room temperature for 4 days. It was then concentrated to one-sixth its volume, diluted with H_2O, and extracted with ether. The alkaline solution was cooled to 0 °C, adjusted to pH 2, and extracted with EtOAc. The organic extract was washed with H_2O and dried ($MgSO_4$) and the solvent was removed. The residue was taken up in 30 ml of EtOH and 9 ml of dicyclohexylamine was added. After 1 h at 0 °C the precipitated DCHA salt was filtered off (3.6 g), mp 155–156 °C. The DCHA salt was dissolved in 45 ml of boiling EtOH and the solution was allowed to stand at room temperature for 3.5 h to give **2a** DCHA salt (1.9 g, 38%), mp 174–176 °C. This material (4 g, 8.7 mmol) was dissolved in 150 ml of MeOH–H_2O (2:1) and stirred with Dowex 50 (H^+) resin (8% cross-link, 50–100 mesh, 80 g) for 2 h at 5–10 °C. The resin was filtered off and washed well with MeOH, and the solution was concentrated to incipient crystallization and then cooled to give **2a** (2.2 g, 87%), mp 122–123 °C. Recrystallization from EtOH–H_2O resulted in no change in melting point.

Boc-L-thioasparagine Hydrate (2b). Boc-L-β-CNala, like **1a** and **1c**, was prepared by carbodiimide dehydration of the asn derivative.[5,9] Prepared for reference, its DCHA salt melted at 166–168 °C (lit.[8] 166–167 °C). The crude **1b** melted at 92–94 °C and was converted to **2b** as described for **2a**. However, the DCHA salt of **2b** was prepared in EtOAc. Further, after treatment of the DCHA salt with the resin and evaporation of the methanol, the aqueous solution was diluted with a small amount of H_2O, saturated with NaCl, and extracted well with EtOAc. The extract was dried ($MgSO_4$) and concentrated. The residue crystallized on trituration with a little H_2O. After three recrystallizations the air-dried product analyzed as the hydrate.

Z-L-Thioasparagine (2c) was prepared as described for **2a** except that the aqueous MeOH solution obtained after treatment of the DCHA salt with resin was concentrated to turbidity, then diluted with H_2O and cooled to furnish the crystalline product.

Thioasparagine (3). A. A mixture of **2a** (3 g, 9.6 mmol) and anisole (45 ml, 414 mmol) was treated with TFA (150 ml) at 0 °C for 30 min. TFA was removed in vacuo and the residue was triturated with ether and collected on a filter. It was then treated with 2 ml of water, and the solution was adjusted to pH 5 with a few drops of pyridine. Any solid present was removed by filtration affording **4a** (0.2 g, 7%), mp 214–215 °C dec. The filtrate was taken to dryness and the solid was collected with the aid of EtOH affording **3** (920 mg, 64%), mp 195–198 °C dec. **3** was recrystallized in 93% yield by dissolution in the minimal volume of water with gentle warming and concentrating the solution to 0.3 ml and cooling: mp 195 °C dec; $[\alpha]^{26}D$ −49.8° (c 1, 1 N acetic acid); ir 3330–3030 (NH_3^+), 1625 (COO^-), 1470, 1208 (C=S), 869 cm^{-1}.

Anal. Calcd for $C_4H_8N_2O_2S$: C, 32.4; H, 5.44; N, 18.9; S, 21.6. Found: C, 32.3; H, 5.40; N, 19.1; S, 21.9.

On amino acid analysis in system 1, **3** eluted at 241 ml, 60 ml after asn and 64 ml before ala. Its ninhydrin color constant was 17.5 compared to 22.1 for leu. The 440/570 nm ninhydrin absorption ratio was 7.4. In 0.1 M solution at 25 °C for 24 h in 0.04 M NaOAc, pH 5.0, the stability of **3** was 97%; in 0.05 M Tris·HCl, pH 9.0, its stability was 86%.

B. A mixture of **2a** (0.5 g, 1.7 mmol), anisole (0.4 ml, 3.7 mmol), and TFA (5 ml) was treated as described under A furnishing **3** (60 mg, 25%), mp 195–198 °C, and **4a** that gave 32% **5** upon recrystallization in the manner described under **5** (A).

β-*S*-*p*-Methoxybenzyl Aspartic Thioester (5) and β-*p*-Methoxybenzyl Aspartic Imidothiolic Ester (4a). A. The crystalline **4a** appearing during the preparation of **3** was dissolved in hot H_2O by addition of a few drops of 3 N HCl. The solution was cooled directly and adjusted to pH 5 with pyridine to give **5** (140 mg, 32%), mp 213–215 °C dec. For analysis **5** was recrystallized three times: mp 214–215 °C dec; NMR (NaOD) δ 2.2–2.8 (2 H, m, β-CH_2), 3.2–3.6 (3 H, m, SCH_2 + α-CH), 3.77 (3 H, s, OCH_3), 6.75–7.40 (4 H, m, C_6H_4); ir 3030 (NH_3^+), 1686 (O=C–SR), 1620 cm^{-1} (COO^-).

Anal. Calcd for $C_{12}H_{15}NO_4S$: C, 53.5; H, 5.61; N, 5.20; S, 11.9. Found: C, 53.4; H, 5.63; N, 5.05; S, 11.9.

B. A mixture of **2a** (250 mg) and TFA (4 ml) was treated as described under **3** (A). All subsequent treatments were at 5 °C. The solid present after neutralization was collected by filtration and washed well with cold EtOH followed by Et_2O, furnishing **4a** (150 mg, 70%), mp 156–158 °C.

Anal. Calcd for $C_{12}H_{16}N_2O_3S$: C, 53.7; H, 6.01; N, 10.4; S, 11.9. Found: C, 53.6; H, 6.02; N, 10.1; S, 12.1.

The product (40 mg) was recrystallized as under A furnishing 90% **5**, mp 213–215 °C.

C. To a finely ground mixture of **3** (20 mg, 135 μmol) and Meoz ala (8, 34 mg, 140 μmol) at −20 °C was added with vigorous agitation TFA (1 ml) precooled to the same temperature. The colorless solution was allowed to warm to 0 °C. TFA was then evaporated, and the reaction was treated as described for **4a** under **3** (A), except that the temperature was maintained at 0 °C. After 30 min at 0 °C the precipitate was collected and air dried (18 mg, 49%), mp 151–155 °C. The product had the same ^1H NMR spectrum as **4a** and a mixture melting point with **4a** was undepressed. Recrystallization as described under **5** (A) gave 10 mg, mp 209–214 °C. This had the same ^1H NMR spectrum as **5** and showed no depression in a mixture melting point with **5**.

Hydrolyses of 5. A. To **5** (5.8 mg, 21.5 μmol) was added 0.2 ml of 1 N NaOH and the mixture was allowed to stand at room temperature. After 3 h the turbid solution gave a strong nitroprusside

reaction. After 3 days this reaction was negative and 92% asp was present on amino acid analysis. The crystalline deposit was collected by centrifugation, 1.24 mg, mp 98–100 °C. A mixture melting point was undepressed with a reference sample of 4-methoxybenzyl disulfide, mp 99–100 °C, synthesized from anisaldehyde and $(NH_4)_2S$.[11] Ir spectra likewise were identical.

B. A solution of **5** (0.1 g, 0.37 mmol) in 15 ml of 1.5 N HCl was heated under reflux for 1.5 h and yielded 95% asp. The mixture was cooled and extracted with EtOAc. The extract was dried ($MgSO_4$) and evaporated to furnish a yellow oil that was dissolved in 1 ml of EtOH and treated dropwise with a solution of I_2 in EtOH until a nitroprusside test became negative. Cooling led to crystallization of 4-methoxybenzyl disulfide (35 mg, 56%), mp 98–100 °C, that was identical with the reference material in the criteria given under A and also had the same ^1H NMR spectrum: ($CDCl_3$) δ 3.72 (4 H, m, SCH_2), 3.82 (6 H, s, OCH_3), 6.8–7.4 (8 H, aromatic).

***S*-*p*-Methoxybenzyl-L-cysteine (10). A.** To a solution of L-cysteine (500 mg, 4.1 mmol) in 5 ml of TFA cooled to −15 to −20 °C was added in portions over 30 min *p*-methoxybenzyl carbazate (810 mg, 4.1 mmol). The mixture was allowed to stand at 0 °C for 10 min and then was concentrated to dryness. The residue was taken up in H_2O and adjusted to pH 5. The precipitated **10** was collected and dried (920 mg, 92%). The dried precipitate was dissolved in H_2O at 50 °C with addition of a few drops of 3 N HCl and was reprecipitated by adjustment to pH 5. The product was filtered, washed with H_2O, then with EtOH, and dried (810 mg, 81%), mp 205–207 °C (placed in bath at 180 °C) (lit.[18] mp 198–199 °C). A mixture melting point with a reference sample of **10**, mp 206–208 °C, was undepressed. ^1H NMR spectra in TFA were likewise identical. The reaction in the presence of 2.6 equiv of anisole gave 6% **10**.

On amino acid analysis in system 2, **10** eluted at 114 ml as a single peak. Its ninhydrin color constant was 16.4.

B. To a finely ground mixture of 8 (104 mg, 0.41 mmol) and **9** (50 mg, 0.41 mmol) at −20 °C was added TFA (1 ml) precooled to −15 °C. After 7 min the resulting clear solution was allowed to warm to 0 °C where it was kept for 5 min. It was then concentrated and treated as described under **10** (A) to give a crude product (80 mg, 80%), mp 199–200 °C; after reprecipitation (75 mg, 75%), mp 204–206 °C. This was identical with **10** in ^1H NMR spectrum and amino acid analysis.

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Registry No.—**1a**, 31883-91-7; **1b**, 45159-34-0; **1c**, 3309-41-9; **2a**, 58208-20-1; **2a** DCHA salt, 58208-21-2; **2b**, 58208-22-3; **2b** DCHA salt, 58208-23-4; **2c**, 58208-24-5; **2c** DCHA salt, 58208-25-6; **3**, 58208-26-7; **8**, 16944-75-5; **9**, 52-90-4; TFA, 76-05-1; *p*-methoxybenzyl carbazate, 18912-37-3.

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Synthesis of *N*-Chloroacetyl Derivatives of Amino Acids and Their Use for the Conjugation of Polypeptides to Thiol-Carrying Compounds[1]

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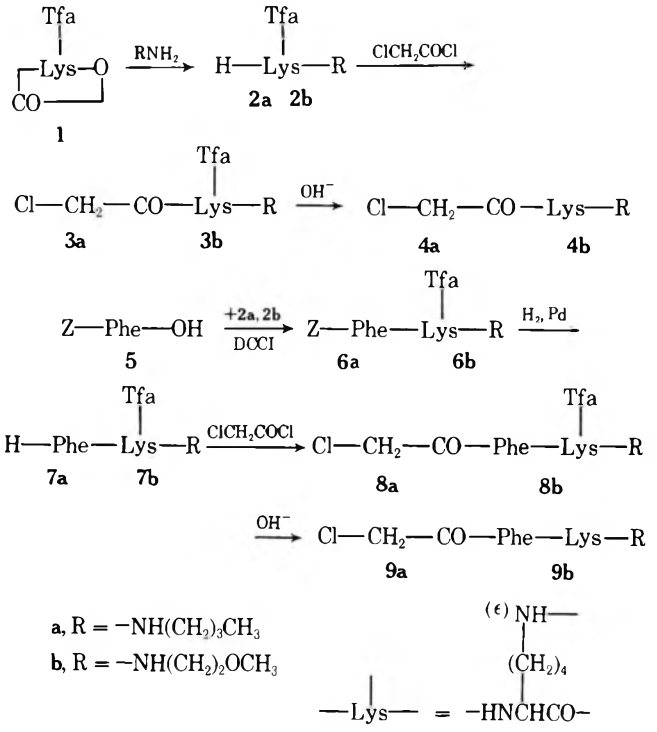
The synthesis of the α-*N*-chloroacetyl derivatives of lysine *n*-butylamide (**4a**), lysine 2-methoxyethylamide (**4b**), phenylalanyllysine *n*-butylamide (**9a**), and phenylalanyllysine 2-methoxyethylamide (**9b**) is described. The free ε-NH_2 group of these compounds can initiate the growth of a polypeptide by polymerization of amino acid *N*-carboxyanhydrides, and this polypeptide can be coupled to thiol-carrying compounds via its *N*-chloroacetyl group, as illustrated by the use of **4a** to attach a polyalanine chain to the SH group of cysteine (**11**).

The compounds described in the present article were designed as coupling agents permitting the attachment of bulky substituent groups, such as artificial polypeptides, to the thiol groups of proteins.

The principle of their use is as follows. In a first step, the free ε-amino group of **4a, 4b, 9a,** or **9b** serves both as the initiator and the starting point for the growth of an artificial polypeptide obtained by polymerization of the *N*-carboxyanhydrides of the desired amino acids. This reaction is carried out either in organic media or in an aqueous buffer solution (Experimental Section). During a second step, the chlorine from the chloroacetyl group which now forms the head of the resulting polypeptide is allowed to react specifically with the free thiol group from the molecule to which conjugation is aimed. In principle a thiol group from a protein molecule (e.g., an antibody) would be used, but this will not be considered in the present article. Reported herein are the synthesis of **4a, 4b, 9a** and **9b,** as well as their re-

Scheme I



activity toward *N*-carboxyanhydrides of amino acids and toward simple model compounds carrying thiol groups (Experimental Section).

The syntheses depicted in Scheme I do not involve any novel reactions, but some of the steps may require justification.

The use of the α-*N*-carboxyanhydride of ε-trifluoroacetyllysine has proven a convenient way to obtain **2a** and **2b** in nearly quantitative yields. The use of trifluoroacetyl and benzyloxycarbonyl groups has allowed selective nonsimultaneous cleavages while preserving the chloroacetyl group previously introduced.

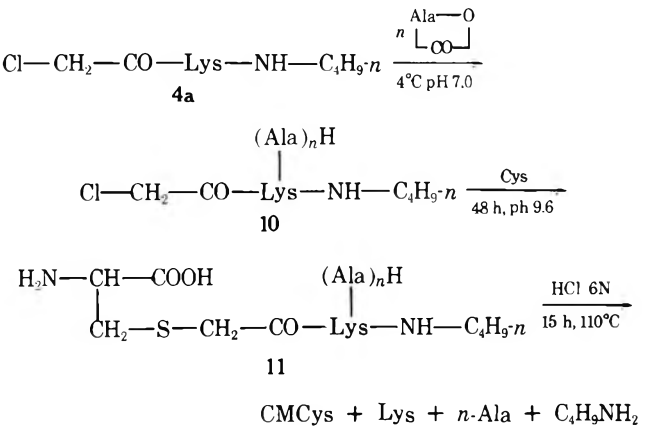
The removal of the protecting trifluoroacetyl group from the ε-amino group of **3a** or **3b** must be carried out within strict constraints of time and pH (Experimental Section) to avoid hydrolytic cleavage of the chlorine. The cleavage of the relevant amide bond proceeds faster with **3b** than with **3a**, probably owing to the influence of the methoxy group of the former. A similar difference was found between **8a** and **8b** during the removal of their protecting ε-*N*-trifluoroacetyl group.

The yields obtained by the formation of peptides **6a** and **6b** can appear rather low if we consider the values given in the Experimental Section. However, it must be pointed out that these are yields of very pure products. The constraints born upon difficult separations reduce those real yields to half.

All four compounds (**4a, 4b, 9a, 9b**) efficiently initiated the growth of peptide chains by polymerization of amino acid *N*-carboxyanhydrides. A typical reaction using the ε-NH_2 group of **4a** as the starting point for a polyalanine chain (**10**) is described in Scheme II and the Experimental Section.

Neither the true composition nor the yield of the reaction product can be determined from the 1:35 molar ratio for lysine vs. alanine that was found upon acid hydrolysis. This is because the initiator NH_2 from **4a** is not necessarily incorporated into the nascent polymer, so that some of the peptide chains must have been devoid of lysine. These uncertainties are, however, partially dissipated by the subsequent experiment in which the chloroacetyl group of **10**

Scheme II



(freed of residual **4a**) was used to conjugate this polymer to the thiol group of cysteine (Scheme II, below, and Experimental Section). This revealed that at least 40% of the polyalanine chains possessed a chloroacetyl group capable of reacting with the SH group from cysteine.

For the purpose set out in the introduction it was necessary that the active group intended as a reagent for thiol groups be unreactive toward other substituent groups found in proteins, particularly the NH_2 group. The *N*-chloroacetyl group appears to suit this need. Feinstein[2] and Hanson[3] have already reported upon the alkylation of the SH group of cysteine by the *N*-chloroacetyl derivatives of tyrosine and phenylalanine, but they did not specifically examine the nonreactivity of the NH_2 group of cysteine with these compounds. Here we show that the latter reaction does not occur under the conditions used since no self-conjugation of **4a** was observed, as testified by the absence of its expected reaction product, ε-*N*-carboxymethyllysine, from the acid hydrolysate. The same selectivity for thiol groups was observed with a different compound carrying both an SH and an NH_2 group, viz., γ-Glu-Cys-Gly (reduced glutathione).

We have also verified that none of the compounds **4a, 4b, 9a,** or **9b** reacted in detectable measure with *n*-butylamine, arginine, histidine, lysine, methionine, tryptophan, or tyrosine, at pH 8.2 or 9.6 (24 h, 25 °C). This was shown in two ways. Firstly, when reaction mixtures containing **4a, 4b, 9a,** or **9b** and one of these potential reaction partners were analyzed by high-voltage electrophoreses, the ninhydrin-positive spot of the latter compound persisted unchanged in intensity. Secondly, the subsequent addition of cysteine to such mixtures (24 h, 25 °C) caused the typical ninhydrin-positive spot of the *S*-alkyl derivative of cysteine to appear at the expected position and with an intensity similar to that seen in the absence of the potential competitor (Experimental Section). Amino acid analyses of the acid hydrolysates of the latter reaction mixtures confirmed that cysteine had been S-alkylated with unaltered yields (50–80%) despite prior exposure of the halogen compound to the potential competitor. This selectivity of the chloroacetyl group for thiols contrasts with the known reactivity, under similar conditions, of bromoacetyl or iodoacetyl groups toward amines and phenols.[4]

A further advantage of the chloroacetyl group compared to the iodoacetyl group is its relative stability, notably to light. Salts of these compounds can be stored for many months at 4 °C. In aqueous solution they are relatively stable up to pH 9.6. For example, a 10 mM aqueous solution of **4b** was found to have retained 20% of its cysteine-fixing capacity after 5 months storage at 25 °C, pH 9.6.

Compound **4b** is well soluble in water, compared to **4a,**

9a, or **9b**. The synthesis of **9a** and **9b** was undertaken with the aim of obtaining compounds having the same conjugating properties as **4a** and **4b** but with the added advantage of being themselves easily cleaved by the enzyme α-chymotrypsin which splits the peptide bond between phenylalanine and lysine (Experimental Section). Compounds **9a** and **9b** can therefore be used for the reversible attachment of substituent polypeptide chains to proteins resistant to this enzyme, as will be shown in a later publication.

Experimental Section

Amino acid analyses were carried out using a Beckman Unichrom apparatus. Infrared spectra were recorded on a Perkin-Elmer Model 457 grating infrared spectrophotometer. Elementary compositions were determined by A. Bernhardt Mikroanalytisches Laboratorium, Elbach, West Germany. Specific rotations were determined on a Perkin-Elmer Model 141 polarimeter with mercury lamp, spectral line 579.066 nm at 25 °C, concentration range 0.5–1%, in a 1:1 (v/v) mixture of water and methanol.

High-voltage electrophoresis (HVE) was performed on Whatman 3 MM paper at pH 1.9 and at 60 V/cm for 1 h. The migration rate of ε-DNP-Lys was used as the reference. The ratio of the migration rates x/N-ε-DNP-Lys was represented by high-voltage electrophoresis ratio of x.

Chromatographic Solvents (v/v). Solvent system (s.s.) 1, a 40:40:20 mixture of methanol, 2-propanol, and cyclohexane; s.s. 2, a 10:5:85 mixture of 2-propanol, ethyl acetate, and cyclohexane; s.s. 3, a 5:5:90 mixture of methanol, 2-propanol, and cyclohexane; s.s. 4, a 1:1 mixture of 2-propanol and cyclohexane; s.s. 5, a 30:30:40 mixture of methanol, 2-propanol, and cyclohexane; s.s. 6, a 35:35:30 mixture of methanol, 2-propanol, and cyclohexane; s.s. 7, a 20:10:70 mixture of 2-propanol, ethyl acetate, and cyclohexane.

ε-Trifluoroacetyl-L-lysine *N*-Carboxyanhydride (1). Dry $COCl_2$ was slowly bubbled through a suspension of 5 g (19 mmol) of ε-trifluoroacetyl-L-lysine[5] in 120 ml of dry dioxane for 4 h at 25 °C. After overnight stirring, dioxane, HCl, and $COCl_2$ were distilled off at 20 °C and 20 mmHg. The dry residue was taken up with dioxane, which was distilled off as before. During this step, **1** crystallized as a fine powder. Vacuum was maintained until all traces of HCl had been removed: mp 49–51 °C; ir (KBr) 3340, 1860, 1810, 1695, 1205, 1170 cm^{-1}.

Anal. Calcd for $C_9H_{11}N_2O_4F_3$: C, 40.30; H, 4.10. Found: C, 40.65; H, 4.25.

ε-Trifluoroacetyl-L-lysine *n*-Butylamide (2a). A solution of 5.36 g (20 mmol) of **1** in 120 ml of dioxane was rapidly mixed with a solution of 1.46 g (20 mmol) of *n*-butylamine in 50 ml of dioxane. After 15 min the solvent was evaporated at 0.1 mmHg. Silica gel thin layer chromatography using s.s. 1 revealed the absence of ε-trifluoroacetyllysine, less than 1% residual *n*-butylamine, and the presence of a ninhydrin-staining derivative of ε-trifluoroacetyllysine, indicating quantitative conversion of **1** into **2a**. Product **2a** was a white solid: mp 70–72 °C; ir (KBr) 3326, 1703, 1650, 1212, 1188, 1155 cm^{-1}.

Anal. Calcd for $C_{12}H_{22}N_3O_2F_3$: C, 48.48; H, 7.41. Found: C, 48.75; H, 7.65.

ε-Trifluoroacetyl-L-lysine 2-Methoxyethylamide (2b). The procedure was the same as for the conversion of **1** to **2a** except that a solution of 1.48 g (20 mmol) of 2-methoxyethylamine was used. The yield of **2b** from **1** was also quantitative. Product **2b** was a viscous oil: ir (KBr) 3310, 1710, 1655, 1211, 1189, 1155 cm^{-1}.

Anal. Calcd for $C_{11}H_{20}N_3O_3F_3$: C, 44.15; H, 6.69. Found: C, 44.35; H, 6.88.

α-*N*-Chloroacetyl-ε-trifluoroacetyl-L-lysine *n*-Butylamide (3a). To a solution of 3 g (10 mmol) of **2a** in 40 ml of dioxane were added slowly, simultaneously, under vigorous stirring, and with exclusion of atmospheric moisture, 1.13 g (10 mmol) of chloroacetyl chloride and 1 g (10 mmol) of triethylamine. After 30 min of stirring at 25 °C the precipitate of triethylamine hydrochloride was removed by filtration, the filtrate was taken to dryness at 20 mmHg, and the residue was purified by chromatography on a silica gel column (90 cm, diameter 30 mm) using as the eluent s.s. 2. This yielded 1.9 g (5 mmol) of **3a** (yield 50%) as a white solid: ninhydrin negative; mp 150–152 °C; ir (KBr) 3287, 1694, 1635, 1208, 1175 cm^{-1}.

Anal. Calcd for $C_{14}H_{23}N_3O_3ClF_3$: C, 44.97; H, 6.15; N, 11.24; Cl, 9.5. Found: C, 44.78; H, 6.01; N, 11.25; Cl, 9.8.

Mol wt. Calcd: 373. Found (Rast): 384.

α-*N*-Chloroacetyl-ε-trifluoroacetyl-L-lysine 2-Methoxyethylamide (3b). The procedure was the same as for the conversion of **2a** to **3a**, until the purification step, except that **2a** was replaced by 3 g (10 mmol) of **2b**. Product **3b** was purified by chromatography on a silica gel column (90 cm, diameter 30 mm) which was first eluted with 500 ml of s.s. 3. This eluate was discarded and product **3b** was then eluted with 2000 ml of s.s. 4. Evaporation of the solvent furnished 1.8 g (4.8 mmol) of **3b** as a white product (yield 48%): ninhydrin negative; mp 133–135 °C; ir (KBr) 3282, 1690, 1630, 1208, 1175 cm^{-1}.

Anal. Calcd for $C_{13}H_{21}N_3O_4ClF_3$: C, 41.54; H, 5.59; N, 11.18; Cl, 9.45. Found: C, 41.73; H, 5.70; N, 11.06; Cl, 9.72.

Mol wt. Calcd: 375. Found (Rast): 367.

α-*N*-Chloroacetyl-L-lysine *n*-Butylamide (4a). To 370 mg (1 mmol) of **3a** dissolved in 60 ml of methanol was added 60 ml of an aqueous solution (pH 9.6) of 0.63 g (6 mmol) of Na_2CO_3 and 1 g (12 mmol) of $NaHCO_3$. Alkaline hydrolysis of the trifluoroacetyl group was essentially complete after 3 days at 25 °C. The solution was then adjusted to pH 8.5 and evaporated to dryness (20 mmHg). The residue was dissolved in 2 ml of water and extracted with two 20-ml portions of chloroform. The organic solution was dried on Na_2SO_4, filtrated, and evaporated to give 240 mg (0.86 mmol) of **4a** as a white solid (yield 86%) soluble in water (2 mg/ml): HVE ratio of **4a** 1.67; mp 90–95 °C dec; ir (KBr) 3266, 2950, 2920, 1640 cm^{-1}; [M] +0.8°.

Anal. Calcd for $C_{12}H_{24}N_3O_2Cl$: C, 51.89; H, 8.64; N, 15.13; Cl, 12.79. Found: C, 51.73; H, 8.59; N, 15.07; Cl, 12.50.

α-*N*-Chloroacetyl-L-lysine 2-Methoxyethylamide (4b). The same procedure starting from 370 mg (1 mmol) of **3b** yielded 230 mg (0.82 mmol) of **4b** after 30 h of alkaline hydrolysis (yield 82%). Product **4b** was a white, water-soluble (10 mg/ml) solid: HVE ratio of **4b** 1.68; mp 50–60 °C dec; ir (KBr) 3270, 2920, 1640 cm^{-1}; [M] +1.3°.

Anal. Calcd for $C_{11}H_{22}N_3O_3Cl$: C, 47.22; H, 7.87; N, 15.02; Cl, 12.70. Found: C, 47.35; H, 7.82; N, 15.11; Cl, 12.89.

***N*-Benzyloxycarbonyl-L-phenylalanine-ε-trifluoroacetyl-L-lysine *n*-Butylamide (6a).** To a solution of 1.48 g (5 mmol) of **2a** and 1.5 g (5 mmol) of *N*-benzyloxycarbonyl-L-phenylalanine (**5**)[6] in 40 ml of chloroform was added 1.03 g (5 mmol) of dicyclohexylcarbodiimide, at 15 °C, under stirring. After 1 h at 25 °C the precipitate of dicyclohexylurea was removed by filtration and the filtrate was evaporated to dryness (20 mmHg), without an attempt being made to remove residual dicyclohexylurea and by-products.

Filtrate analysis carried out on silica gel thin layer developed in s.s. 1, revealed with ninhydrin, indicates the absence of **2a**. Longer reaction times (24 and 48 h) were not found useful: ir (KBr) 3310, 1700, 1640, 1260, 1210, 1180, 695 cm^{-1}.

Anal. Calcd for $C_{29}H_{37}N_4O_5F_3$: C, 60.21; H, 6.40. Found: C, 60.68; H, 6.62.

***N*-Benzyloxycarbonyl-L-phenylalanyl-ε-trifluoroacetyl-L-lysine 2-Methoxyethylamide (6b).** The same procedure was followed as for the conjugation of **2a** and **5** but starting from 1.49 g (5 mmol) of **2b**: ir (KBr) 3318, 1700, 1640, 1260, 1210, 1185, 695 cm^{-1}.

Anal. Calcd for $C_{28}H_{35}N_4O_6F_3$: C, 57.93; H, 6.03. Found: C, 58.26; H, 6.18.

L-Phenylalanyl-ε-trifluoroacetyl-L-lysine *n*-Butylamide (7a). Catalytic reduction with Pd black[7] was used to remove the benzyloxycarbonyl group from 2.5 mmol of crude **6a** (in methanol), and the catalyst was filtered off.

The filtrates were evaporated to dryness (20 mmHg) and **7a** was purified by chromatography on a silica gel column (80 cm, diameter 20 mm, flow rate 7 ml/min) with s.s. 4 as the eluent. The initial 400-ml fraction containing 300 mg of a mixture of substituted urea and **7a** was discarded. The next 500-ml fraction was evaporated (20 mmHg) and furnished 250 mg (0.56 mmol) of **7a** as a white solid (yield 22%). The product was homogeneous upon thin layer silica gel chromatography developed with s.s. 4. Different attempts to purify compounds **7** and **8** by crystallization appeared less practical and safe than purification by column chromatography.

Acid hydrolysis of **7a** produced lysine and phenylalanine in the expected equimolecular amounts: mp 122–124 °C; ir (KBr) 3330, 1710, 1630, 1210, 1185, 1160, 695 cm^{-1}.

Anal. Calcd for $C_{21}H_{31}N_4O_3F_3$: C, 56.75; H, 6.98; N, 12.61. Found: C, 56.52; H, 6.92; N, 12.68.

L-Phenylalanyl-ε-trifluoroacetyl-L-lysine 2-Methoxyethylamide (7b). The same procedure was used as for the conversion of **6a** to **7a** except for the final purification, which was carried out on 2 g of crude **6b**. The silica gel column was eluted with s.s. 5. The initial 750-ml fraction containing 450 mg of a mixture of substituted urea and **7b** was discarded. After evaporation the next 350-ml

fraction furnished 300 mg (0.67 mmol) of **7b** (yield 19%). This was a white solid which gave a single spot on a thin layer silica gel plate developed with s.s. 6. Acid hydrolysis of **7b** produced lysine and phenylalanine in equimolecular proportions: mp 88–90 °C; ir (KBr) 3330, 1710, 1630, 1210, 1186, 1163, 698 cm^{-1}.

Anal. Calcd for $C_{20}H_{29}N_4O_4F_3$: C 53.81; H, 6.50; N, 12.55. Found: C, 53.95; H, 6.59; N, 12.48.

α-*N*-Chloroacetyl-L-phenylalanyl-ε-trifluoroacetyl-L-lysine n-Butylamide (8a). The chloroacetylation of 440 mg (1 mmol) of **7a** was carried out as described for the preparation of **3a** from **2a.** The product was purified by chromatography on a silica gel column (90 cm, diameter 20 mm, flow rate 7 ml/min) with s.s. 7 as the eluent (monitoring at 254 nm). The initial 250-ml fraction of eluate was discarded. The next 500-ml fraction was evaporated (20 mmHg) and furnished 170 mg (0.33 mmol) of **8a** as a white solid (yield 33%): mp 188–190 °C; ir (KBr) 3290, 1703, 1638, 1205, 1183, 1170, 692 cm^{-1}.

Anal. Calcd for $C_{23}H_{32}N_4O_4ClF_3$: C 53.02; H, 6.14; N, 10.75; Cl, 6.82. Found: C, 52.87; H, 6.14; N, 10.40; Cl, 7.02.

Mol wt. Calcd: 520.5. Found (Rast): 535.

α-*N*-Chloroacetyl-L-phenylalanyl-ε-trifluoroacetyl-L-lysine 2-Methoxyethylamide (8b). The procedure was the same as for **8a,** but starting from 440 mg (1 mmol) of **7b.** The initial 400 ml of eluate was discarded and the next 800 ml furnished 180 mg (0.34 mmol) of **8b** as a white solid (yield 34%): mp 155–157 °C dec; ir (KBr) 3285, 1695, 1630, 1210, 1185, 700 cm^{-1}.

Anal. Calcd for $C_{22}H_{30}N_4O_5ClF_3$: C, 50.52; H, 5.74; N, 10.71; Cl, 6.79. Found: C, 50.74; H, 5.90; N, 10.61; Cl, 6.69.

Mol wt. Calcd: 522.5. Found (Rast): 508.

α-*N*-Chloroacetyl-L-phenylalanyl-L-lysine *n*-Butylamide (9a). The trifluoroacetyl group was removed from **8a** as described for the conversion of **3a** to **4a,** furnishing **9a** as a white solid insoluble in water (yield 78%). The product was homogeneous upon thin layer silica gel chromatography developed with s.s. 1 HVE ratio of **9a** 1.35. Acid hydrolysis of **9a** produced lysine and phenylalanine in the expected equimolecular amounts: mp 90 °C dec; ir (KBr) 3300, 2960, 2930, 1645, 695 cm^{-1}; [M] +15.9°.

Anal. Calcd for $C_{21}H_{33}N_4O_3Cl$: C, 59.36; H, 7.77; N, 13.19; Cl, 8.36. Found: C, 59.15; H, 7.82; N, 13.13; Cl, 8.15.

α-*N*-Chloroacetyl-L-phenylalanyl-L-lysine 2-Methoxyethylamide (9b). As for the conversion of **3b** to **4b.** Product **9b** was a white solid insoluble in water (yield 75%). The product was homogeneous upon thin layer silica gel chromatography (conditions as for **9a**). HVE ratio of **9b** 1.33. Acid hydrolysis of **9b** produced lysine and phenylalanine in the expected equimolecular amounts: mp 135 °C dec; ir (KBr) 3300, 2930, 1645, 698 cm^{-1}; [M] −68.3°.

Anal. Calcd for $C_{20}H_{31}N_4O_4Cl$: C, 56.27; H, 7.26; N, 13.13; Cl, 8.32. Found: C, 56.13; H, 7.20; N, 13.21; Cl, 8.20.

Synthesis of a Polymer of L-Alanine (10) with 4a as an Initiator of Polymerization. To 139 mg (0.5 mmol) of **4a** dissolved in 5 ml of dioxane and 10 ml of 0.05 M phosphate buffer, pH 7.0, was added, at 4 °C 1.15 g (10 mmol) of L-alanine *N*-carboxyanhydride dissolved in 5 ml of dioxane. After 24 h of stirring at 4 °C the solvent was evaporated at 20 mmHg. The dry residue was dissolved in 1 ml of water, filtered, and freed of excess **4a** by chromatography on Sephadex G-15 using 0.05 M NH_4HCO_3 as the eluent. The first fractions yielded 150 mg of **10** which by acid hydrolysis was identified as a polypeptide with an average lysine:alanine ratio of 1:35. The average molecular weight can be estimated from this ratio at a maximum value of 2500. On the other hand, the test for halogen detection is positive (Lassaigne–Beilstein), yield (from the *N*-carboxy anhydride) 20%. Note: similar results were obtained with compound **4b.**

Compounds **9a** and **9b** have been used successfully as initiator for *N*-carboxyanhydride of alanine, in an organic medium (dioxane).

Synthesis of 11 by Conjugation of the Thiol Group of Cysteine to the α-*N*-Chloroacetyl Group of Polypeptide 10. To 20 mg (about 0.02 mmol) of **10,** dissolved in 0.5 ml of 0.05 M $NaHCO_3$–Na_2CO_3 buffer, pH 9.6 (free of O_2 by saturation with N_2), was added 2.42 mg (0.02 mmol) of L-cysteine dissolved in 0.5 ml of the same buffer. The reaction was stopped after 2 days stirring at 25 °C under N_2. Acid hydrolysis (6 N HCl, 110 °C, 15 h) of the reaction product yielded *S*-carboxymethylcysteine, lysine, and alanine in a molar ratio of 0.4:1:35, besides some cysteine. The 40% yield indicated by this ratio is an underestimate because *S*-carboxymethylcysteine, the reaction product of the cysteine SH group with the α-*N*-chloroacetyl group of **4a,** is partially degraded under the hydrolysis conditions used.

Electrophoresis of Conjugation Products of Cysteine and 4a, 4b, 9a, 9b. HVE ratio of **4a** + Cys, 1.78; HVE ratio of **4b** + Cys, 1.81; HVE ratio of **9a** + Cys, 1.49; HVE ratio of **9b** + Cys, 1.54.

Enzymatic Cleavage by α-Chymotrypsin. To 4.2 mg (0.01 mmol) of **9a** dissolved in 1 ml of CH_3OH was added 3 mg (0.01 mmol) of reduced glutathione dissolved in 1 ml of 0.1 M $NaHCO_3$–Na_2CO_3 buffer, pH 9.6 (free of O_2). The reaction was stopped after 1 day stirring at 25°C under N_2, HVE ratio of conjugation product 1.27. The reaction mixture was evaporated under vacuum (20 mmHg) at 25 °C and dissolved in 1 ml of water. To this solution was added 3 mg of α-chymotrypsin dissolved in 0.1 ml of HCl (0.02 N) and pH adjusted to 8.5. The reaction of enzymatic cleavage was stopped after 18 h at 25 °C. Analysis carried out by high-voltage electrophoresis showed complete disappearance of the starting compound and formation of two new products: one, Lys-NH-C_4H_9, with a HVE ratio of 3.44, the other with a ratio of 0.34. This last compound after elution, acid hydrolysis, and amino acid analysis appeared to contain equimolar amounts of Glu, Gly, Phe, and CMCys.

Exactly similar results were obtained with compound **9b.**

Registry No.—**1,** 42267-27-6; **2a,** 58191-15-4; **2b,** 58191-16-5; **3a,** 58191-17-6; **3b,** 58191-18-7; **4a,** 58191-19-8; **4b,** 58191-20-1; **5,** 1161-13-3; **6a,** 58191-21-2; **6b,** 58191-22-3; **7a,** 58191-23-4; **7b,** 58191-24-5; **8a,** 58191-25-6; **8b,** 58191-26-7; **9a,** 58191-27-8; **9b,** 58191-28-9; $COCl_2$, 75-44-5; ε-trifluoroacetyl-L-lysine 10009-20-8; *n*-butylamine, 109-73-9; 2-methoxyethylamine, 109-85-3; chloroacetyl chloride, 79-04-9; L-alanine *N*-carboxyanhydride, 2224-52-4; L-cysteine, 52-90-4; α-chymotrypsin, 9035-75-0.

References and Notes

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Synthesis of Some Dehydrophenylalanine Peptides[1]

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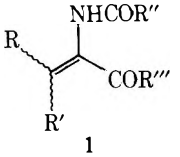
The bromo pseudoazlactones, **3**, were found to dehydrobrominate readily giving the unsaturated azlactones, **4**. These compounds, generated in situ, were converted into *N*-trifluoroacetyldehydro amino acid anilides (**5**) and peptides (**6**, **7** and **10**) and perhydro-1,4-thiazepin-5-ones (**11**). The trifluoroacetyl group was removed from the dehydrophenylalanine peptides in good yields. *N*-Trifluoroacetyldehydrovaline, isoleucine, leucine, alanine, and α-aminobutyric acid anilides and peptides were not deblocked by gaseous ammonia. The mechanism of the deblocking reaction is discussed.

A great deal of interest has been generated recently[3] in the synthesis of dehydro amino acids (DHA) and peptides (DHP) and their derivatives. DHA appear in numerous peptides of microbial origin[4] and are thought to be biological intermediates in the synthesis of important biologically active compounds such as penicillin.[5]

Several approaches to the synthesis of DHA have been developed. One method[6] depends on the elimination of the elements of water from β-hydroxyamino acids, while a second more general approach[7] uses pyrolytic elimination of an α,β-sulfoxido group to introduce the double bond. The first method is limited by the availability of β-hydroxyamino acids. The second requires the synthesis of the amino acid carbon chain by condensation reactions which often afford low yields especially when polyfunctional amino acids are involved. Our approach[8] to the synthesis of DHA has been that of direct introduction of the double bond into the intact amino acid chain by the oxidation of amino acid azlactones.[9] Our earlier work[8a] led to the synthesis of DHA derivatives in which an α-methylcinnamoyl group [**1**, R″ = $C_6H_5CH{=}C(CH_3)$–] remained on the nitrogen atom after introduction of the double bond. Hydrolytic removal of the



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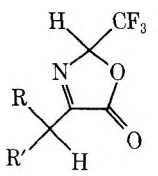
N-acyl group led, of course, to hydrolysis of the resulting enamine giving the α-keto acid. Clearly, if **1** could be prepared such that the *N*-acyl group were removable under *non*hydrolytic conditions, the free enamino acid could be obtained. This report describes in detail our more recent efforts[8b] to use the trifluoroacetyl group in the synthesis of **1** (R″ = CF_3) and our studies related to its nonhydrolytic removal.

Some years ago, Weygand reported[10] that amino acids could be converted into "pseudo" azlactones (**2**) by heating with trifluoroacetic anhydride and that these were readily brominated α to the azomethine function giving **3**. We found that when compounds of type **3** (Table I) were treated with *exactly*[11] 1 equiv of triethylamine, the unsaturated azlactones (**4**) were formed in excellent yield. The pseudo-



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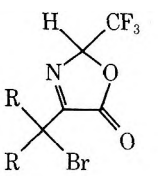
a, R = Ph; R′ = H
b, R = CH_3; R′ = CH_3
c, R = *i*-Pr; R′ = H



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d, R = C_2H_5; R′ = CH_3
e, R = R′ = H
f, R = CH_3; R′ = H

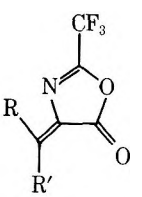

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Table I

Compd	R	R′	% yield	Bp, °C (mm)
3a	Ph	H	62	102–103[a] (CCl_4)[b]
3c	$(CH_3)_2CH$	H	86	91–94 (0.4)
3d	C_2H_5	CH_3	78	87–91 (12)

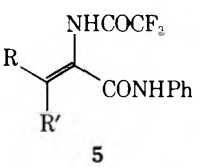
[a] Melting point. [b] Recrystallization solvent.

Table II

Compd	R	R′	% yield	Mp, °C
5a	Ph	H	83	191.5–193
5b	CH_3	CH_3	81	227–229
5c	$(CH_3)_2CH$	H	74	195–196
5d	C_2H_5	CH_3	64	220–222
5e	H	H	46	124–126

azlactones derived from alanine (**2e**) and butyrine (**2f**) showed a tendency to dibrominate,[10] but careful avoidance of excess bromine and fractional distillation of the bromo compounds allowed their isolation in acceptable yields. In this investigation, only the phenylalanine azlactone (**4a**) was isolated and its chemistry studied carefully. All of the other unsaturated azlactones were prepared and allowed to react in situ with aniline or an amino ester to form the isolated products.

The anilides (**5a–e**) could be prepared from the required bromo compounds (**3**) by treatment with 1 mol of triethylamine followed by 1 mol of aniline or, more conveniently, with 2 equiv of aniline alone. The anilides were crystalline compounds, easily characterized, and are described in Table II. When the azlactones (**4a–d**) were allowed to react with various amino esters, the dehydro dipeptide esters (**6a–m**) (Table III) were formed in 40–80% yields. One



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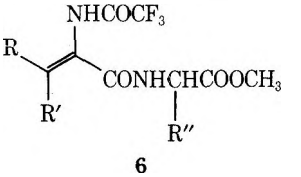

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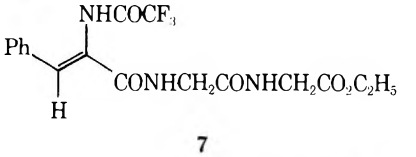

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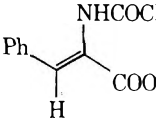

8a, R = H
b, R = CH_3

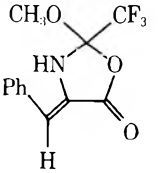

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Table III

Compd	R	R′	R″	% yield	Mp, °C (solvent)
6a	Ph	H	$PhCH_2$	76	143.5–144 ($CHCl_3$)
6b	Ph	H	$(CH_3)_2CHCH_2$	48	173.5–175 (CH_3O–H_2O)
6c	Ph	H	Ph	67	117–119 (Et_2O–ether)
6d	Ph	H	CH_2OH	81.5	169–171 (CH_3OH–H_2O)
6e	CH_3	CH_3	$PhCH_2$	70	143.5–145 (CH_3OH–H_2O)
6f	CH_3	CH_3	$(CH_3)_2CHCH_2$	62	158–162 (C_2H_5OH–H_2O)
6g	CH_3	CH_3	Ph	71	173.5–176 (CH_3OH–H_2O)
6h	$(CH_3)_2CH$	H	$PhCH_2$	57	87–90 (CH_3OH–H_2O)
6i	$(CH_3)_2CH$	H	$(CH_3)_2CHCH_2$	41	126–128 (CH_3OH–H_2O)
6j	$(CH_3)_2CH$	H	CH_2OH	47	97–99 (CH_3OH–H_2O)
6k	C_2H_5	CH_3	$PhCH_2$	50	131–136 (CH_3OH–H_2O)
6l	C_2H_5	CH_3	$(CH_3)_2CHCH_2$	58	139–146 (CH_3OH–H_2O)
6m[a]	Ph	H	H	76	118–120 (C_2H_5OH–H_2O)
6n[b]	Ph	H	H	73	165–168, 225–230 dec (CH_3OH–H_2O)
6p[c]	Ph	H	$PhCH_2$	26	182–188 (CH_3OH–H_2O)
10b	CH_3	CH_3	CH_2SH	45	181–184
10d	C_2H_5	CH_3	CH_2SH	38	183–187 (CH_3OH–H_2O)

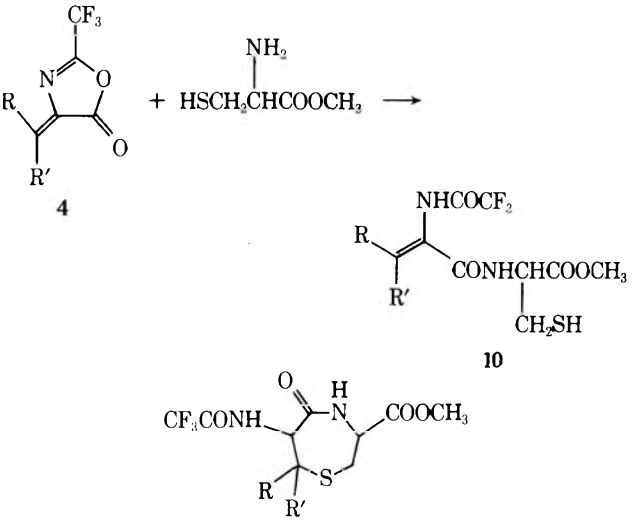
[a] Prepared as the ethyl ester. [b] Prepared as the amide. [c] Prepared as the acid.

Table IV

Compd	R	R′	% yield	Mp, °C (solvent)
11a	Ph	H	36	197–199 (MeOH–H_2O)
11c	$(CH_3)_2CH$	H	32	197–199.5 (CH_3OH–H_2O)
11e	H	H	41	236–240 (THF)
11f	CH_3	H	49	242–245 (CH_3OH)

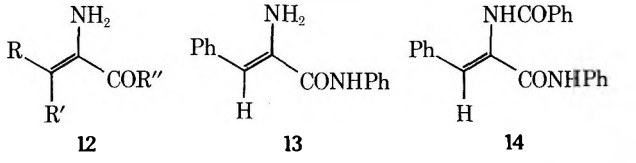
dehydro tripeptide (**7**) was also prepared from glycylglycine ethyl ester in 86% yield. The excellent yield of this compound showed clearly that the rate of the bimolecular reaction between **4a** and the dipeptide ester, generated in situ from the hydrochloride, was sufficiently great to compete favorably with the rate of unimolecular diketopiperazine formation from the free dipeptide ester. The rate of hydrolysis of **4a** in aqueous acetone forming the acid (**8a**) was also considerably greater that of other unsaturated azlactones which we have studied in earlier work.[8a] The presence of the trifluoromethyl group in the 2 position of the azlactone ring apparently enhanced the reactivity of the 5-carbonyl function toward nucleophiles. Surprisingly, when **4a** was allowed to react with excess methanol, a complex mixture was formed. A crystalline product, isolated in only 28% yield, was finally assigned the structure **9** based on the NH (3340 cm^{-1}) and carbonyl (1795 cm^{-1}) absorptions in the infrared spectrum and the methoxyl protons in the ^1H NMR spectrum at δ 3.43 ppm. The fact that the CF_3 peak appeared as a singlet in the ^{19}F NMR spectrum confirmed this structure. The methyl ester, prepared by the treatment of **8a** with diazomethane, was different from **9** and had the expected physical properties. The azlactone **4a** was also allowed to react with an aqueous solution of sodium phenylalaninate to form, after acidification, the dehydro dipeptide acid **5p** in only 26% yield Concurrent hydrolysis of the azlactone may have been responsible for the low yield.

Some very interesting results were obtained when several of the azlactones (**4a–f**), formed in situ, were allowed to react with cysteine methyl ester Azlactones **4a,c,e,f** gave perhydro-1,4-thiazepin-5-ones (**11**) (Table IV) while **4b** and **4d** gave the unsaturated peptides (**10b,d**) only. These results indicated that ring closure occurred only when R′ was hydrogen and that the presence of even a methyl group at the R′ position was sufficient to prevent it. This result indicates that cysteinyldehydrovaline peptides, postulated as intermediates in the biosynthesis of penicillin[5], would not ring close spontaneously to thiazepinones during penicillin biosynthesis.[12] The facile ring closure of **10e,f** are examples of the type of Michael addition proposed by Gross[13] in the biogenesis of lanthionine and cyclolanthionine and reported by Zervas[6] in a recent synthesis of these compounds. Perhydro-1,4-thiazepin-5-ones of the type **11**,

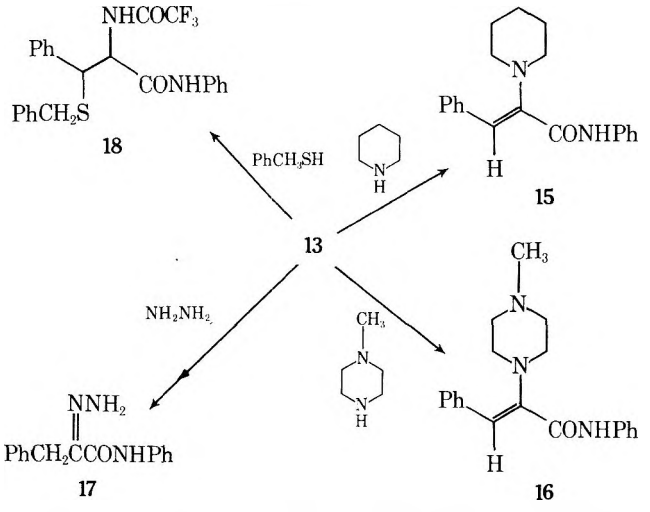


formed enzymatically, might be converted[14a,b] to penicillin by a transannular ring closure across the 4 and 7 positions, although this has not been accomplished chemically.[14c] Our method gives easy access to many different 7-substituted thiazepinones for further investigation of this possibility. The thiazepinones, isolated in 30–50% yields, obtained by our method were of unknown stereochemistry. Since the physical data indicated that they were most probably single entities, they probably represent the most stable isomer since they were formed under equilibrating conditions. Assuming a planar amide function and a trans manner of addition of the mercapto group to the double bond (*Z* configuration), models indicate that the all-cis compound will probably be formed preferentially since all three groups can then be in a pseudoequatorial conformation.

We were interested in the conversion of the *N*-trifluoroacetyl DHA and DHP into the free enamines (**12**) by non-

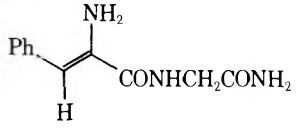


hydrolytic means so that further conversion to more complex dehydro peptides might be possible. In order to study the deblocking step, we elected to study the reactions of the anilide **5a** with various deblocking agents. It has been reported that sodium hydroxide and ammonium hydroxide,[15a] Amberlite IR-4B ion exchange resin,[15b] imidazole,[15c] various amines,[15d] and alcoholic sodium borohydride[15e] can be used to remove the trifluoroacetyl group. None of these reagents reacted with **5a** to any extent, as shown by thin layer chromatography (TLC) of the reaction mixtures. The blocking group was, however, removed by treatment of a solution of **5a** in THF with gaseous ammonia over a 15-h period and the crystalline enamine **13** was isolated in 74% yield. The structure of **13** was secured by elemental and spectral analyses and by its conversion to the benzamido anilide **14**, an authentic sample of which was prepared by treatment of the appropriate unsaturated azlactone with aniline. Acid-catalyzed hydrolysis of **13** to phenyl pyruvanilide was, surprisingly, very slow at room temperature. Some further surprising results were obtained when **13** was treated with piperidine and *N*-methylpiperidine. An exchange reaction occurred giving the α-piperidino- and α-piperazinocinnamanilides, **15** and **16**, respectively, in 80–90% yields. Hydrazine hydrate converted **13** into the hydrazone **17**, isolated in 33% yield. The anilide **13** also reacted with benzyl mercaptan giving the expected Michael addition product (**18**) in 85% yield. This reaction was, however,



very slow, requiring a large excess of mercaptan and the addition of triethylamine to the refluxing reaction mixture in order to drive it to completion.

Treatment of dehydro dipeptide amide (**6n**) and the dehydro tripeptide **7** with the NH_3–THF reagent gave the enamino dipeptide **19** and tripeptide ester **20** in good yields. These were stable crystalline compounds which

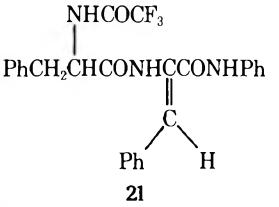


19

20

could be recrystallized from aqueous ethanol without significant loss of the enamine function by hydrolysis. It appears that DHP having N-terminal DHA, at least where the DHA is dehydrophenylalanine, are much less rapidly hydrolyzed under neutral conditions than might be expected.

Another aspect of the chemistry of the enamine system was the extreme lack of reactivity of **13** toward coupling with an "activated" acid. Attempts to couple **13** with acids using *N,N'*-dicyclohexylcarbodiimide, Woodward's reagent K, or by an isobutyl chlorocarbonate mixed anhydride procedure failed. No reaction at all occurred. As previously mentioned, **13** did react with benzoyl chloride to yield the amide **14**, so that treatment of **13** with *N*-trifluoroacetylphenylalanyl chloride[15b] gave the dehydro dipeptide derivative **21** in 41% yield, as expected. Similarly, the tetrapeptide derivative **22** was obtained in 57% yield from the ena-



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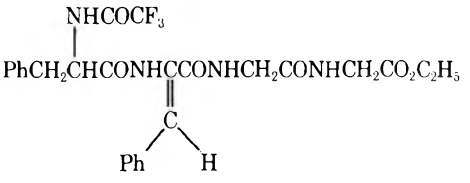
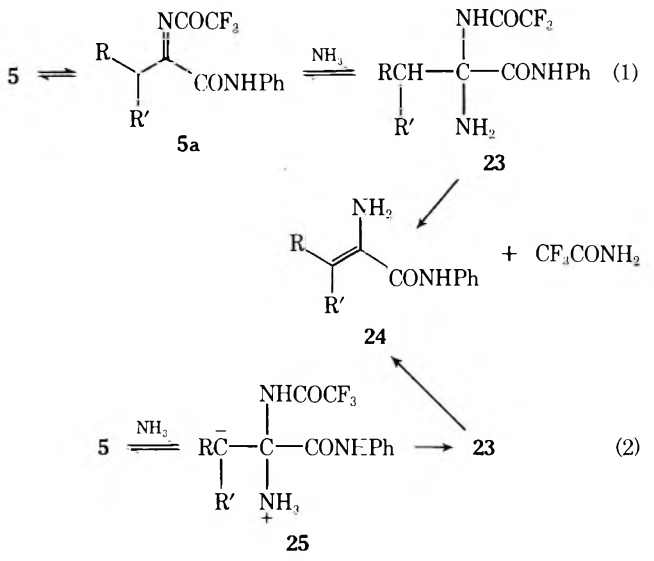


22

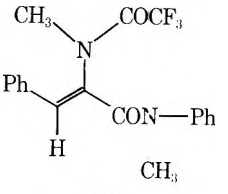
mino tripeptide **20**. No attempt was made to determine the optical purity of the single asymmetric centers in these compounds. It might be expected that the enamine nitrogen atom would be less nucleophilic than nitrogen in a similar saturated system owing to conjugation of the nonbonded electrons with the π electrons of the double bond. We might also predict that this effect would be enhanced in the dehydrophenylalanine system since the amino group is also conjugated through the double bond with the benzene ring. The amino groups of other less conjugated DHA might, consequently, be more reactive and more easily converted into dehydro peptides.

When the ammonia deblocking procedure and piperidine displacement reactions were applied to the other *N*-trifluoroacetyl DHA anilides, we found that only the phenylalanine derivative reacted cleanly.[16] We also found that the *saturated* anilide, *N*-trifluoroacetyl-DL-phenylalanine anilide, did not react with the NH_3–THF reagent. We interpreted these and our previous findings in terms of two possible deblocking mechanisms (Scheme I). Mechanism 1 requires that ammonia add to the tautomer **5a** giving an intermediate **23** which eliminates trifluoroacetamide to form the enamine **24**. This mechanism should be operable on any of the dehydro anilides (**5**) or peptides. It would seem also that the equilibrium **5** $\rightleftharpoons$ **5a** might have a smaller equilibrium constant in the case of phenylalanine owing to the favorable conjugation of the double bond in the enamine tautomer with the benzene ring. Mechanism 2 requires the formation of a carbanion (**25**) as the primary adduct, followed by proton transfer and elimination of trifluoroacetamide. This mechanism is consistent with the fact that the dehydrophenylalanine derivative is the only one found to react with ammonia, since the anion **25** should be stabilized more by the presence of a β-phenyl than by a β-alkyl group. This mechanism predicts that other anion stabilizing groups, such as carbonyl, should allow ammonolysis of *N*-trifluoroacetyl enamines. The fact that the *N,N'*-dimethyl derivative (**26**) of **13** does not react (TLC) with ammonia or piperidine, even under forcing conditions, might indicate that the imine tautomer (**5a**) is required for the reaction to

Scheme I



proceed. However, steric effects may play a role in this failure of **26** to react. Furthermore, the fact that benzyl mer-



captan added to the β-carbon atom of **5**, albeit slowly, rather than the α carbon is unexplained by either of these mechanisms. Perhaps the "softer" sulfur nucleophile is more likely to add to the "softer" β carbon,[17] while the "harder" nitrogen atom reacts more readily with the "harder" α carbon—its hardness being due to the electron-withdrawing effects of the adjacent trifluoroacetamido and carbonyl groups. We are in the process of studying further the reactions of *N*-acyl enamines.

Experimental Section

Instrumentation. All melting points were determined on a Nalge Model Y6 micro hot stage and are uncorrected. Infrared spectra (Nujol) were recorded on a Perkin-Elmer Model 257 or 631 recording spectrometer with polystyrene as the standard. The ^{1}H NMR spectra were recorded on a Varian HA-100 spectrometer using tetramethylsilane as internal or external standard, and ^{13}C NMR spectra were determined on a JEOL PFT-100 spectrometer with Me_4Si as internal standard; chemical shifts were obtained from the computer output. Optical rotations were obtained on a Perkin-Elmer Model 141 polarimeter. Elemental analyses were carried out by Atlantic Microlabs, Atlanta, Ga. Thin layer chromatography was carried out on Kodak ultraviolet-sensitive silica gel sheets, which were visualized by uv.

Materials. The α-amino acids and dipeptides were purchased from Sigma Chemical Co. and used as received.

General Procedure. 2-Trifluoromethyl 4-Substituted 3-Oxazolin-5-ones (2). A mixture of 0.1 mol of the α-amino acid and 32 ml (0.23 mol) of trifluoroacetic anhydride was refluxed (hot water bath) for 40 min. After removing the excess reagents, the residue was distilled at reduced pressure. All of the pseudoazlactones used in this work have been previously reported by Weygand[10] except **2a** and **2f**. **2a:** 50% yield; bp 115–118 °C (0.4 Torr); ir (neat) 1805 (C=O), 1645 (C=N), 1175 cm^{-1} (C–F); NMR ($CDCl_3$) δ 3.85 (d, 2 H, J = 2.5 Hz, $PhCH_2$), 5.86 (m, 1 H, CF_3CH), 7.25 ppm (s, 5 H, C_6H_5); ^{19}F NMR ($CFCl_3$) 79.5383 ppm (d, CF_3CH). **2f:** 66% yield; bp 56–60 °C (12 Torr); ir (neat) 1810 (C=O), 1655 (C=N), 1170 cm^{-1} (C–F); NMR ($CDCl_3$) 1.35 (t, 3 H, J = 7.5 Hz, CH_3CH_2), 2.76 (2 q, 2 H, J = 7.5 and 2.1 Hz, CH_3CH_2), 6.26 ppm (m, 1 H, CF_3CH).

General Procedure. 2-Trifluoromethyl-4-(1-bromoalkyl)-3-oxazolin-5-ones (3). To a cold (ice bath) solution of 50 mmol of **2** in 90 ml of 1,2-dichloroethane was added 5 ml of a solution of 8.0 g (50 mmol) of bromine in 35 ml of 1,2-dichloroethane. A small sample was withdrawn from the reaction mixture, heated until decolorization occurred, and returned to the reaction flask. This process was frequently repreated two to three times to obtain decolorization of the reaction mixture. The remaining bromine solution was then added. After decolorization was complete, the solution was stirred for an additional 1 h, the solvent was removed in vacuo, and the residue was distilled under reduced pressure. The physical data for **3a,c,d** are given in Table I. Compounds **3b,e,f** were previously reported by Weygand.[10]

2-Trifluoromethyl-4-benzylidene-2-oxazolin-5-one (4a). A. Using Triethylamine (TEA). To a solution of 4.0 g (12.4 mmol) of **3a** in 300 ml of anhydrous ether was added over a 5-min period 1.71 ml (12.4 mmol) of TEA in 75 ml of ether. After 15 min the white precipitate was filtered (1.96 g, 87%) and the filtrate was concentrated to dryness in vacuo, giving 2.6 g of a solid residue. Crystallization from 6:1 isopropyl alcohol–water gave 2.3 g (77%) of crystalline **4a:** mp 102–103 °C; ir (Nujol) 1835, 1818, 1785 (C=O), 1670 (C=N), 1655 shoulder (C=C), 1170 cm^{-1} (C–F); NMR ($CDCl_3$) δ 7.34–7.60 (m, 4 H, vinyl H, 2 H meta, 1 H para), 8.0–8.18 ppm (m, 2 H, 2 H ortho).

Anal. Calcd for $C_{11}H_6NO_2F_3$: C, 54.80; H, 2.49; N, 5.81. Found: C, 54.78; H, 2.50; N, 5.90.

(*Z*)-α-Trifluoroacetamidocinnamic Acid (8a). To a solution of 1.0 g (3.1 mmol) of **3a** in 150 ml of ether was slowly added 0.427 ml (3.1 mmol) of TEA in 55 ml of anhydrous ether. After 15 min TEA·HCl was filtered (0.549 g, 95%) and the filtrate was concentrated in vacuo. The resulting white residue was dissolved in a 20:7 acetone–water solution. After 20 h at room temperature, the solvent was removed in vacuo and the solid residue (0.6 g) was crystallized from chloroform containing a few drops of hexane to give 0.503 g (63%) of **8a:** mp 196–199 °C; ir (Nujol) 3255 (NH), 1715 (CF_3C=O), 1700 (COOH), 1640 (C=C), 1175 cm^{-1} (C–F); ^{1}H NMR [$(CD_3)_2CO$] δ 7.30–7.48 (m, 3 H, 2 H meta, 1 H para), 7.50–7.66 (m, 2 H, 2 H ortho), 7.70 (s, 1 H, vinyl H), 9.47 and 9.71 ppm (2 broad s, 2 H, COOH, CF_3CONH); ^{13}C NMR [$(CD_3)_2CO$] δ 116.8 (CF_3), 124.6, 129.5, 130.6, 130.9, 133.8, 137.8 (aromatic and olefinic carbons), 157.6 (CF_3C=O), 165.21 (COOH).

Anal. Calcd for $C_{11}H_8NO_3F_3$: C, 51.00; H, 3.08; N, 5.40. Found: C, 50.92; H, 3.09; N, 5.51.

(*Z*)-Methyl α-Trifluoroacetamidocinnamate (8b). To a clear solution of 0.457 g (1.84 mmol) of **8** (R = H) in 15 ml of anhydrous ether was added 35 ml of ethereal diazomethane. After 10 min the excess diazomethane was removed under nitrogen and evaporation of the solvents in vacuo gave a clear oil which was crystallized from 3:1 diethyl ether–petroleum ether forming 350 mg (71%) of **8b,** mp 76–80 °C. An analytical sample, mp 79–80 °C, was recrystallized from methanol–water: ir (Nujol) 3200 (NH), 1730 ($COOCH_3$), 1700 (CF_3CO), 1635 (C=C), 1160 cm^{-1} (C–F); NMR ($CDCl_3$) δ 3.78 (s, 3 H, $COOCH_3$), 7.35 (s, 5 H, C_6H_5), 7.54 (s, 1 H, PhC**H**=), 8.04 ppm (broad s, 1 H, $NHCOCF_3$).

Anal. Calcd for $C_{12}N_{10}NO_3F_3$: C, 52.75; H, 3.67; N, 5.14. Found: C, 52.76; H, 3.55; N, 5.12.

2-Methoxy-2-trifluoromethyl-4-benzylidene-1,3-oxazolidin-5-one (9). A solution of 1.0 g (3.1 mmol) of **3a,** 0.43 ml (3.1 mmol) of TEA, and 6 ml of methanol in 110 ml diethyl ether was stirred at room temperature for 4 h. The reaction mixture was filtered, the filtrate was evaporated in vacuo, and the residue was chromatographed on a silica gel column using methylene chloride. The yellow solid (0.42 g) obtained was crystallized from CCl_4–petroleum ether to give 0.25 g (28%) of **9**: mp 126–128 °C; ir (Nujol) 3340 (NH), 1795 (C=O), 1665 cm^{-1} (C=C); ^{1}H NMR ($CDCl_3$) δ 3.43 (s, 3 H, OCH_3), 5.56 (broad s, 1 H, NH), 6.46 (s, 1 H, vinyl H), 7.36 ppm (s, 5 H, C_6H_5); ^{19}F NMR ($CFCl_3$) 86.54 ppm (5, CH_3OCCF_3).

Anal. Calcd for $C_{12}H_{10}NO_3F_3$: C, 52.75; H, 3.66; N, 5.14. Found: C, 52.60; H, 3.73; N, 5.17.

General Procedure. *N*-Trifluoroacetyldehydroamino Acid Anilides (5). To a solution of 5 mmol of **3** in 50 ml of anhydrous ether was slowly added 0.92 ml (10.1 mmol) of aniline in 5 ml of ether. After standing at room temperature for 12 h, the aniline hydrobromide was filtered (0.87 g, 100%) and the filtrate was concentrated to 10 ml in vacuo. The insoluble anilide was filtered and further evaporation of the filtrate in vacuo gave a residue which, after trituration with ether, was dried in vacuo. The combined crops of **5** were crystallized from 4:1 methanol–water. The physical data for these anilides are given in Table II.

General Procedure. *N*-Trifluoroacetyldehydro Peptides (6) and Perhydro-1,4-thiazepin-5-ones (11). A solution of 3.0 mmol of the required amino ester hydrochloride in 100 ml of DMF and 0.835 ml (6 mmol) of triethylamine was stirred at room temperature for 45 min. To this solution was added, over a 5-min period, 3.0 mmol of **3**, dissolved in 20 ml of DMF. After stirring at room temperature for 24 h, the solvent was removed in vacuo and the semisolid residue was dissolved in 85 ml of ethyl acetate. The solution was washed with two 25-ml portions of water and once with 20 ml of 0.1 N HCl solution and dried (anhydrous $MgSO_4$) and the solvent was removed in vacuo. The residue was triturated with anhydrous ether and the insoluble product was collected and crystallized. If the residue was soluble in ether, it was directly crystallized from the appropriate solvents. The physical data for **6** and **11** are recorded in Tables III and IV, respectively.

***N*-Trifluoroacetyldehydrophenylalanylphenylalanine (6p).** To a solution of 0.512 g (3.1 mmol) of DL-phenylalanine and 0.65 g (6.2 mmol) of sodium carbonate in 25 ml of water was added 1.0 g (3.1 mmol) of **3a** dissolved in 30 ml of 1,2-dimethoxyethane. After 13 h at room temperature, the reaction mixture was filtered, the filtrate was concentrated in vacuo and diluted with ice water, and the pH was adjusted to 1 and concentrated HCl. This solution was extracted with two 30-ml portions of ether, and the combined extracts were dried (anhydrous $MgSO_4$) and concentrated in vacuo. The oily residue was crystallized from 3:1 chloroform–petroleum ether, giving 0.32 g (26%) of **6p**, mp 182–188.5 °C. An analytical sample was recrystallized from methanol–water: mp 188–190 °C; ir (Nujol) 3255 (NH), 2600–2750 (COOH), 1728 (CF_3C=O), 1700 (COOH), 1655 (C=C), 1628 (CONH), 1175 cm^{-1} (C–F).

Anal. Calcd for $C_{20}H_{17}F_3N_2O_4$: C, 59.00; H, 4.18; N, 6.88. Found: C, 59.02; H, 4.20; N, 6.87.

(*Z*)-Dehydrophenylalanine Anilide (13). Into one neck of a 50-ml three-necked round-bottomed flask, fitted with a drying tube and containing a solution of 1.70 g (5 mmol) of **5a** in 45 ml of THF, was bubbled ammonia for 15 h, the course of the reaction being followed by TLC ($CHCl_3$ elution). Evaporation of the solvent in vacuo gave a solid which was triturated with 20 ml of ether, and, after chilling, the insoluble solid was collected and dried giving 0.52 g of **13**, mp 118–124 °C. Concentration of the filtrate in vacuo followed by trituration of the residue with ether gave a second crop of **13**, 0.36 g, mp 121–126 °C, total yield 0.88 g (74%). An analytical sample was crystallized from 2:1 ethyl acetate–petroleum ether: mp 117–122 °C; ir (Nujol) 3390 (broad, NH), 1655 (C=C), 1625 cm^{-1} (CONHPh); ^1H NMR (Me_2SO-d_6) δ 5.06 (s, 2 H, NH_2, exchanged in D_2O), 6.12 (s, 1 H, vinyl H), 7.00–7.78 (m, 10 H, 2 C_6H_5), 10.01 ppm (s, 1 H, CONHPh); ^{13}C NMR (Me_2SO-d_6) δ 102.36 (PhCH=), 165.15 (C=O), 120.46, 123.57, 125.46, 127.84, 128.45, 136.86, 137.16, 138.93 (aromatic carbons and $C{=}CNH_2$).

Anal. Calcd for $C_{15}H_{14}N_2O$: C, 75.59; H, 5.88; N, 11.77. Found: C, 75.38; H, 5.93; N, 11.72.

(*Z*)-α-Benzamidocinnamic Acid Anilide (14). To a cold solution (ice bath) of 0.22 g (0.93 mmol) of **13** in 10 ml of ethyl acetate containing 0.2 ml (2.5 mmol) of pyridine was added 0.12 ml (1 mmol) of benzoyl chloride. After 1 h, the reaction mixture was allowed to come to room temperature for 4 h. The precipitated **14**, 0.151 g (49%), was filtered and dried in vacuo. Crystallization from methanol–water gave an analytical sample: mp 231–235 °C; ir (Nujol) 3280 (broad, NH), 1650 (C=C), 1600 cm^{-1} (CONHPh); NMR (Me_2SO-d_6) δ 6.95–8.14 (m, 16 H, 3 C_6H_5, vinyl H), 10.20 (broad, NH).

An authentic sample of **14** was prepared according to the procedure of Jansen et al.[18]

(*Z*)-2-(Piperidin-1-yl)cinnamic Acid Anilide (15). A solution of 1.06 g (3.17 mmol) of **13** and 0.32 ml (3.2 mmol) of piperidine in 25 ml of THF was stirred at room temperature for 18 h. After evaporation of the THF in vacuo, the solid residue was triturated with anhydrous ether and the insolubles were filtered, wt 0.76 g. A second crop of 0.13 g was obtained by the repetition of this procedure, total wt 0.89 g (92%) of **15**, mp 133–138 °C. An analytical sample, mp 138–140 °C, was crystallized from methanol: ir (Nujol) 3325 (NH), 1655–1660 (C=C), 1600 cm^{-1} (CONHPh); NMR (Me_2SO-d_6) δ 1.55 (broad s, 6 H, piperidine ring), 2.98 (broad s, 4 H, piperidine ring), 5.50 (s, 1 H, vinyl H), 6.90–7.69 (m, 10 H, 2 C_6H_5), 10.21 ppm (s, 1 H, NH).

Anal. Calcd for $C_{20}H_{22}N_2O$: C, 78.40; H, 7.24; N, 9.14. Found: C, 78.26; H, 7.27; N, 9.18.

(*Z*)-2-(4-Methylpiperidin-1-yl)cinnamic Acid Anilide (16). A solution of 1.19 g (3.57 mmol) of **13** and 0.41 ml (3.7 mmol) of *N*-methylpiperazine in 35 ml of THF was stirred at room temperature for 26 h. The solvent was evaporated in vacuo, giving a solid residue which was triturated with anhydrous ether and the insolubles were filtered, giving 0.96 g (84%) of **16** mp 168–176 °C. An anayltical sample was crystallized from ethyl acetate: mp 171.5–174.5 °C; ir (Nujol) 3220 (broad NH), 1650 (C=C), 1605 cm^{-1} (CONHPh); NMR (Me_2SO-d_6) δ 2.28 (s, 3 H, NCH_3), 2.48 (broad s, 4 H, piperidine ring), 3.08 (broad s, 4 H, piperidine ring), 5.62 (s, 1 H, vinyl H), 7.0–7.9 (m, 10 H, 2 C_6H_5), 10.2 ppm (s, 1 H, NH).

Anal. Calcd for $C_{20}H_{23}N_3O$: C, 74.74; H, 7.21; N, 13.07. Found: C, 74.55; H, 7.26; N, 13.11.

3-Phenylpyruvanilide Hydrazone (17). A solution of 1.16 g (3.37 mmol) of **13** and 0.18 ml of 95% hydrazine hydrate in 35 ml of THF was stirred at room temperature for 18 h. The solvent was removed in vacuo and the oily residue was dissolved in ether. After 24 h at 0 °C, the solution gave 0.146 g of **17** which was collected and dried in vacuo. Concentration of the filtrate, followed by trituration of the residue with 10 ml of ether, gave another 0.132 g of **17**: total wt 0.278 g (33%); mp 100–103 °C; ir (Nujol) 3220, 3305, 3340, 3400 (NH), 1650 (C=C), 1600 cm^{-1} (CONHPh); NMR (Me_2SO-d_6) δ 3.93 (s, 2 H, $PhCH_2$), 6.90–7.80 (m, 10 H, 2 C_6H_5), 7.49 (broad s, 2 H, NNH_2, exchanged with D_2O), 9.50 ppm (s, 1 H, NHPh).

Anal. Calcd for $C_{15}H_{15}N_3O$: C, 71.13; H, 5.97; N, 16.59. Found: C, 71.08; H, 5.72; N, 16.54.

***N*-Trifluoroacetyl-3-benzylthio-DL-phenylalanine Anilide (18).** A solution of 2.79 g (8.35 mmol) of **13** and 1.76 ml (15 mmol) of benzyl mercaptan in 100 ml of THF containing 5 drops of TEA was refluxed for 54 h. Since TLC showed the reaction to be incomplete, an additional 10 ml of benzyl mercaptan was added and the solution refluxed for a period of 10 days. The crude product was separated by column chromatography on silica gel, eluting first with *n*-hexane and then with 1:1 CH_2Cl_2–$CHCl_3$. The oily residue obtained was crystallized from 1:2 ether–petroleum ether, giving three crops of **18** totaling 3.24 g (85%), mp 118–126 °C. An analytical sample was recrystallized from the same solvent mixture: mp 126–128 °C; ir (Nujol) 3325, 3355 (NH), 1732 (CF_3CO), 1665 cm^{-1} (CONHPh); NMR ($CDCl_3$) δ 3.35 (d, 1 H, J = 14 Hz, $PhCHSCH_2Ph$), 3.68 (s, 2 H, $PhCH_2S$), 4.03 (d, 1 H, J = 14 Hz, $CF_3CONHCH$), 6.98–7.40 (m, 15 H, 3 C_6H_5), 8.09, 8.69 ppm (2 s, 2 H, $NHCOCF_3$, CONHPh).

Anal. Calcd for $C_{24}H_{21}N_2O_2SF_3$: C, 62.90; H, 4.59; N, 6.12. Found: C, 62.77; H, 4.64; N, 6.03.

(*Z*)-2-(*N*-Methyltrifluoroacetamido)cinnamic Acid *N*-Methylanilide (26). A mixture of 0.37 g (1.1 mmol) of **5a**, 1.0 g (7.25 mmol) of finely divided potassium carbonate, and 0.14 ml (2.23 mmol) of methyl iodide in 25 ml of DMF was stirred at room temperature for 7 h. The solvent was removed in vacuo, leaving a residue which was partitioned between ethyl acetate and water. The organic layer was washed with two 20-ml portions of water, dried (anhydrous $MgSO_4$), and concentrated in vacuo, giving an oily residue. Crystallization of the oil from ether–petroleum ether gave 0.31 g (77%) of the dimethyl compound (**26**): mp 129–131 °C; ir (Nujol) 1730 (CF_3 C=O), 1660 (C=C, CONHPh), 1170 cm^{-1} (C–F); NMR (Me_2SO-d_6) δ 2.74 [s, 3 H, $CON(CH_3)Ph$], 3.40 (s, 3 H, CH_3NCOCF_3), 6.40 (s, 1 H, vinyl H), 7.23–7.52 ppm (m, 10 H, 2 C_6H_5).

Anal. Calcd for $C_{19}H_{17}N_2O_2F_3$: C, 63.00; H, 4.70; N, 7.74. Found: C, 63.11; H, 4.75; N, 7.79.

Dehydrophenylalanylglycine Amide (19). Ammonia gas was bubbled for 2 days into a solution of 0.624 g (1.98 mmol) of **6n** in 40 ml of THF. Evaporation of the solvent in vacuo gave a solid residue which was triturated with ether and chilled, and the insoluble **19** (0.4 g) was collected, mp 121–135 °C. Crystallization from ethanol–water gave 0.32 g (73%) of **19**, mp 136–142 °C. An analytical sample was obtained from ethanol–water: mp 143–146 °C; ir (Nujol) 3180, 3325, 3385, 3500 (NH), 1660, 1645, 1610 (C=C, CONH); NMR (Me_2SO-d_6) δ 3.80 (d, 2 H, $NHCH_2CO$), 5.08 (s, 2 H, NH_2C=C, exchanged with D_2O), 6.00 (s, 1 H, vinyl H), 7.00–7.50 (m, 7 H, C_6H_5, $CONH_2$), 8.4 ppm (broad t, 1 H, $CONHCH_2$).

Anal. Calcd for $C_{11}H_{13}O_2N_3$: C, 60.26; H, 5.98; N, 19.17. Found: C, 60.22; H, 5.77; N, 19.20.

Dehydrophenylalanylglycylglycine Ethyl Ester (20). Ammonia gas was bubbled for 4 days into a solution of 0.921 g (2.3 mmol) of **7m** in 45 ml of THF. Evaporation of solvent in vacuo gave a white solid residue, which was triturated with 12 ml of anhydrous ether. After cooling to 5 °C, the insoluble **20** (0.45 g) was collected, mp 109–117 °C. The trituration process was repeated with 10 ml of ether, giving a total of 0.48 g (69%) of **20**. An analytical sample was crystallized from ethanol–water: mp 121–124 °C; ir (Nujol) 3245, 3330, 3420 (broad, NH), 1740 ($COOC_2H_5$), 1650, 1625 cm^{-1} (C=C, CONH); NMR (Me_2SO-d_6) δ 1.21 (t, 3 H, J = 7 Hz,

CH_3CH_2), 3.88 (d, 4 H, 2 $COCH_2NH$), 4.12 (q, 2 H, J = 7 Hz, CH_3CH_2), 5.06 (s, 2 H, $NH_2C{=}C$, exchanged with D_2O), 6.00 (s, 1 H, vinyl H), 7.05–7.52 (m, 5 H, C_6H_5), 8.27, 8.52 ppm (2 broad t, 2 H, $CONHCH_2$, both exchanged in D_2O).

Anal. Calcd for $C_{15}H_{19}N_3O_4$: C, 59.01; H, 6.27; N, 13.76. Found: C, 59.09; H, 6.29; N, 13.84.

***N*-Trifluoroacetylphenylalanyldehydrophenylalanine Anilide (21).** A solution of 0.38 g (1.6 mmol) of **13** and 0.39 g (1.4 mmol) of *N*-trifluoroacetylphenylalanyl chloride[15b] in 20 ml of THF was stirred at room temperature for 8 h. The solvent was evaporated in vacuo, the residue was dissolved in ethyl acetate, and the solution was washed with 10 ml of water and 15 ml of 5% $NaHCO_3$ solution. The organic layer was dried (anhydrous Na_2SO_4) and evaporated in vacuo leaving an oily residue. Crystallization from ethanol–water gave 0.294 g (44%) of **21**: mp 206–209 °C; ir (Nujol) 3200–3270 (broad, NH), 1700 (CF_3CO) 1660, 1635 (C=C, CONH), 1160 cm^{-1} (C–F); NMR (Me_2SO-d_6) δ 3.35 (m, 2 H, $PhCH_2$), 4.87 (m, 1 H, $PhCH_2CH$), 7.00–7.82 (m, 16 H, 3 C_6H_5, vinyl H), 9.83 (d, 1 H, $NHCOCF_3$), 10.00, 10.26 ppm (2 s, 2H, PhNHCO, CONHC=).

Anal Calcd for $C_{26}H_{22}N_3O_3F_3$: C, 64.75; H, 4.57; N, 8.73. Found: C, 64.82; H, 4.62; N, 8.78.

***N*-Trifluoroacetylphenylalanyldehydrophenylalanylglycylglycine Ethyl Ester (22).** A solution of 0.21 (0.69 mmol) of **20** and 0.21 g (0.75 mmol) of *N*-trifluoroacetylphenylalanyl chloride[15b] in 20 ml of THF was stirred at room temperature for 13 h. The solvent was evaporated in vacuo, giving a residue which was crystallized from an ethanol–water solution in two crops, total wt 0.215 g (57%), mp 183–200 °C. Three recrystallizations from ethanol–water gave an analytical sample: mp 200–206 °C; ir (Nujol) 3250 (NH), 1752 ($COOC_2H_5$), 1710 (CF_3CO), 1675, 1660, 1620 (C=C, CONH), 1175 cm^{-1} (C–F); NMR (Me_2SO-d_6) δ 1.21 (t, 3 H, J = 7.0 Hz, CH_3CH_2), 3.38 (m, 2 H, $PhCH_2$), 4.39 (m, 4 H, 2 CH_2NH), 4.11 (q, 2 H, J = 7 Hz, CH_3CH_2OCO), 4.86 (broad, 1 H, $PhCH_2CH$), 7.07–7.65 (m, 11 H, 2 C_6H_5, vinyl H), 8.20 (broad, 2 H, 2 $NHCH_2$), 9.70 (broad d, 1 H, $NHCOCF_3$), 10.08 ppm (s, 1 H, NHC=).

Anal. Calcd for $C_{26}H_{27}F_3N_4O_6$: C, 56.93; H, 4.92; N, 10.22. Found: C, 56.52; H, 4.90; N, 9.97.

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Registry No.—**2a,** 2261-95-2; **2b,** 2248-03-5; **3a,** 57103-30-7; **3c,** 58219-56-0; **3d,** 58219-57-1; **4a,** 58219-58-2; **5a,** 58219-59-3; **5b,** 58219-60-6; **5c,** 58219-61-7; **5d,** 58219-62-8; **5e,** 58219-63-9; **6a,** 58219-64-0; **6b,** 58228-74-3; **6c,** 58219-65-1; **6d,** 58219-66-2; **6e,** 58219-67-3; **6f,** 58219-68-4; **6g,** 58219-69-5; **6h,** 58219-70-8; **6i,** 58219-71-9; **6j,** 58219-72-0; **6k,** 58219-73-1; **6l,** 58219-74-2; **6m,** 58219-75-3; **6n,** 58219-76-4; **6p,** 58219-77-5; **7,** 58219-78-6; **8a,** 58219-79-7; **8b,** 58219-80-0; **9,** 58219-81-1; **10b,** 58219-82-2; **10d,** 58219-83-3; **11a,** 58219-84-4; **11c,** 58219-85-5; **11e,** 58219-86-6; **11f,** 58219-87-7; **13,** 58219-88-8; **14,** 58219-89-9; **15,** 58219-90-2; **16,** 58219-91-3; **17,** 57103-37-4; **18,** 57103-38-5; **19,** 58219-92-4; **20,** 58219-93-5; **21,** 58219-94-6; **22,** 58219-95-7; **26,** 58219-96-8; DL-phenylalanine, 150-30-1.

Supplementary Material Available. Ir and NMR data for **3a, 3c, 3d,** and **5a–e** and NMR data for **6a–p** and **10a–f** (5 pages). Ordering information is given on any current masthead page.

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An Improved Polystyrene Support for Solid Phase Peptide Synthesis

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By placing a long spacer chain between the point of attachment of the first amino acid and the polystyrene support, an improved resin was obtained for use in solid phase peptide synthesis. A three-fold improvement in the overall yield of a 19-residue peptide from apolipoprotein C-III was realized.

Chloromethylpolystyrene cross-linked with 1% or 2% divinylbenzene has been widely used as the solid support for the synthesis of peptides by the Merrifield procedure.[1] Inherent problems in the use of this support have been encountered by many workers as well as the author. Hancock et al.[2] in a synthesis of acyl carrier protein from *E. coli* attempted to overcome some of these difficulties by repeated swelling, shrinking, and reswelling of the resin during the synthetic procedure. When this procedure was used during the synthesis[3] of peptide fragments of apolipoprotein C-III (apoC-III) from the human very low density lipoproteins,[4] a slight improvement was observed, but the yields were still relatively low, being in the range of 5–10% based on the initial loading of amino acid on the resin. Thus, studies were initiated to develop an improved resin support to overcome these difficulties.

Several approaches have been reported in the past[5,6] using shorter spacer molecules between the point of attachment of the first residue and the polymer matrix. Since these resins offered little advantage over the unmodified resin, we chose to incorporate a long aliphatic spacer molecule as has been done in affinity chromatography[7] to displace both small and large molecules from solid supports. This report describes the synthetic approach (Scheme I) used to obtain a support having a long spacer chain between the resin matrix and the point of attachment of the first residue. Its use in the synthesis of one 19-residue fragment (Figure 1) from apoC-III is presented and compared to the results obtained previously.

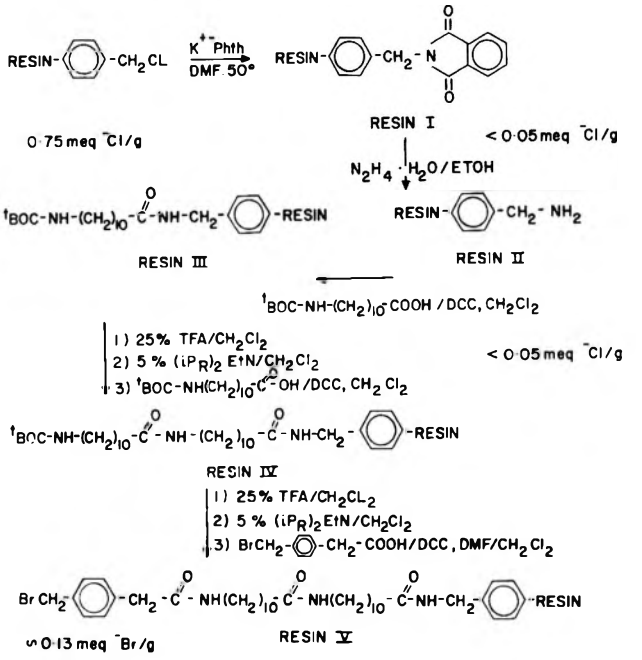
Phe-Ser-Glu-Phe-Trp-Asp-Leu-Asp-Pro-
Glu-Val-Arg-Pro-Thr-Ser-Ala-Val-Ala-Ala

Figure 1. Amino acid sequence of residues 61 to 79 of apolipoprotein C-III from the human serum very low density lipoproteins.

Results and Discussion

The displacement of chloride from commercial chloromethylated polystyrene (0.75 mequiv Cl^-/g) with potassium phthalimide in dimethylformamide at 50 °C proceeded to give resin I which contained <0.05 mequiv Cl^-/g of resin and whose ir spectrum displayed bands at 1710 and 1775 cm^{-1}, characteristic of the phthalimide ring. Treatment of resin I with hydrazine hydrate in refluxing ethanol overnight gave resin II whose ir spectrum after washing lacked the bands at 1710 and 1775 cm^{-1} and was highly fluorescent when treated with fluorescamine in methylene chloride according to the procedure of Felix and Jimenez.[8] The first residue of Boc-11-aminohendecanoic acid was coupled to resin II using dicyclohexylcarbodiimide (DCCI) in CH_2Cl_2. Although the resulting resin II was negative in the fluorescamine test after two couplings, it was treated with acetic anhydride in pyridine to acetylate any amino groups unavailable for coupling or to the fluorescamine reagent. Resin II was treated with 25% trifluoroacetic acid in CH_2Cl_2 and upon neutralization with 5% *i*-Pr_2EtN in CH_2Cl_2 displayed a very positive fluorescence after treatment with fluorescamine. A second residue of Boc-11-aminohendecanoic acid was introduced via DCCI coupling to give resin IV, which was also acetylated. Deprotection with 25% TFA–CH_2Cl_2 and neutralization with 5% *i*-Pr_2EtN–CH_2Cl_2 followed by DCCI coupling of (*p*-bromomethylphenyl)acetic acid in 50% DMF–CH_2Cl_2 gave resin V, which contained approximately 0.13 mequiv Br^-/g of resin. Resin V was acetylated after the introduction of the first Boc-amino acid to preclude formation of quaternary amine sites. Boc-amino acids were introduced quantitatively on resin V by the procedure of Gisin[9] using a two- to five-fold excess of their cesium salts. These amino acid resins contained <0.05 mequiv halide/g.

Scheme I



Using a Boc-alanine resin prepared by the above procedure, a 19-residue peptide (Figure 1) was synthesized using the same automatic synthesizer program as described for the earlier synthesis.[3] Throughout the synthesis increased incorporation of amino acid residues was observed as determined by amino acid analysis of the hydrolyzed peptide resins and peptide losses from the resin had diminished. A spin label attached to the NH_2 terminus of a peptide on this improved resin (Figure 2B) exhibited a narrower line EPR spectrum[10] than was observed with the unmodified commercial resin (Figure 2A). This result strongly suggested that at least the NH_2-terminal residue of the growing peptide (and perhaps even the complete peptide) on the modified resin was significantly more mobile and by inference provided greater steric accessibility of the reactive amino group for the incoming Boc-amino acid anhydride.

Cleavage of the peptide from the resin at 0 °C with anhydrous hydrogen fluoride and gel filtration on Bio-Gel P-10

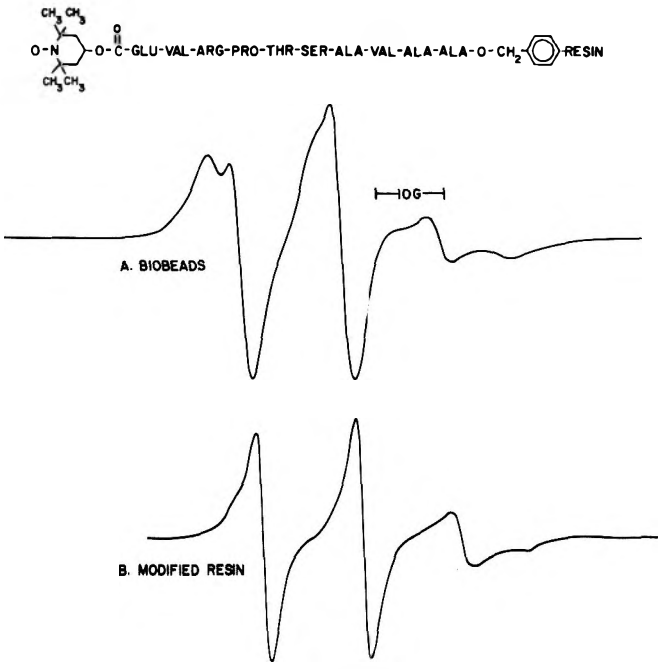


Figure 2. Electron paramagnetic resonance spectrum of 1-oxido-2,2,6,6-tetramethylpiperidinyloxycarbonyl peptide resins in methylene chloride: curve A, peptide-Bio-Beads; curve B, peptide-modified resin.

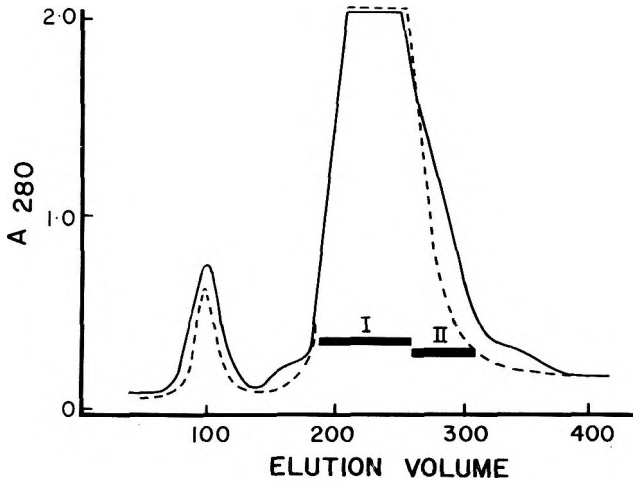


Figure 3. Elution profile of the HF cleaved products on Bio-Gel P-10 in 0.1 M ammonium bicarbonate: —, Bio-Beads product; - -, modified resin product.

in 0.1 M ammonium bicarbonate gave a symmetrical peak (Figure 3) which analyzed correctly for the 19-residue fragment (Table I). The total yield of peptide was 38.7% based on 0.13 mmol of alanine per gram of starting resin in contrast to 31.7% yield using the commercial resin loaded at 0.25 mmol/g. Further chromatography on AG 1X2 ion exchange resin permitted a 70% recovery of pure peptide for an overall yield of 27.1% with the modified resin, as contrasted to a 27.6% recovery (8.7% overall yield) of material from the synthesis on the unmodified resin (Figure 4 and Table II).

Based on these results and those obtained from the synthesis of similar peptides, this new resin appears to offer these two important advantages: (1) higher overall yields of hydrogen fluoride cleavable peptide and (2) peptides of greater homogeneity. It seems plausible that the increased yields result from reduced peptide–resin interactions of the growing peptide chains thereby freeing the amino terminus for coupling and reducing premature termination.

Table I. Amino Acid Analysis of Peptide Fractions from Bio-Gel P-10

Amino Acid	Improved Resin [a]		Biobeads [b]		Theoretical
	I	II	I	II	
Aspartic Acid	2.03	0.92	2.14	2.14	2
Threonine	0.96	0.64	0.96	0.85	1
Serine [c]	1.80	1.04	1.83	1.70	2
Glutamic Acid	1.99	1.08	2.11	1.94	2
Proline	1.90	1.29	2.11	2.19	2
Alanine	3.00	3.00	3.00	3.00	3
Valine	2.05	1.51	2.26	2.14	2
Leucine	0.99	0.42	1.01	1.02	1
Phenylalanine	2.06	0.64	2.05	1.61	2
Arginine	1.09	0.72	1.04	1.13	1
Tryptophan [d]	-	-	-	-	1

[a] Amino acid analysis of Fractions I and II from Fig. 3. Modified Resin Product (---).
[b] Amino acid analysis of Fractions I and II from Fig. 3. Bio Beads Product (—).
[c] Uncorrected for destruction
[d] Not quantitated, but present in amino acid hydrolysis profile.

Table II. Amino Acid Analysis of Peptide Isolated from AG 1X2

	Improved Resin	Bio Beads
Aspartic Acid	2.09	1.96
Threonine	0.99	0.94
Serine [a]	1.76	1.74
Glutamic Acid	2.01	2.04
Proline	2.06	2.03
Alanine	3.00	3.00
Valine	1.97	2.07
Leucine	1.00	1.03
Phenylalanine	2.00	2.05
Arginine	0.98	0.97

[a] Uncorrected for destruction

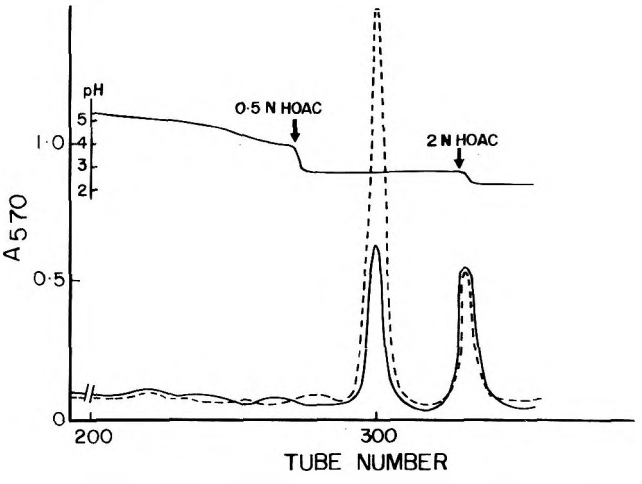


Figure 4. Elution profile on AG 1X2 of fraction I from Bio-Gel P-10: —, Bio-Beads product; - -, modified resin product. The column was eluted in a stepwise manner according to Hirs.[12] The peptide eluted with 0.5 N HOAc.

Experimental Section

Melting points were determined on a Fisher-Johns apparatus and are uncorrected. Microanalyses were performed by Micro-Tech Laboratories, Skokie, Ill. Infrared spectra were recorded on a Beckman Acculab IV. Boc-amino acids were purchased from Peninsula Labs, Beckman, and Bachem and checked by TLC in two solvent systems before use. Other chemicals were of reagent quality.

Phthalimidomethylpolystyrene (Resin I). Chloromethylpolystyrene cross-linked with 1% divinylbenzene (20 g Bio-Beads, 0.75

mequiv Cl^-/g) was suspended in 150 ml of dry distilled dimethylformamide (DMF) and 2.77 g of potassium phthalimide was added. The mixture was stirred at 50 °C for 18 h, after which the resin was washed three times each with DMF, methanol, water, and methanol. After drying in vacuo overnight, an active chloride determination[11] indicated <0.05 mequiv Cl^-/g. The ir spectrum in a KBr disk showed phthalimide bands at 1710 and 1775 cm^{-1}.

Aminomethylpolystyrene (Resin II). Resin I (20 g) was treated overnight with 1.5 ml of hydrazine hydrate in refluxing ethanol. The resin was filtered from the hot ethanol and washed three times with ethanol, 5% aqueous KOH, water, and ethanol. After drying overnight in a vacuum desiccator, the resin gave a strong fluorescamine test by the procedure of Felix and Jimenez[8] and the ir bands at 1710 and 1775 cm^{-1} were absent.

(*p*-Bromomethylphenyl)acetamido-11-hendecanamido-11-hendecanamidomethylpolystyrene (Resin V). Resin II (5 g) was transferred to the shaker vessel of a Schwarz/Mann peptide synthesizer and washed with 30 ml of the following reagents: CH_2Cl_2 (5×), *t*-BuOH (3×), CH_2Cl_2 (5×), 5% *i*-Pr_2EtN in CH_2Cl_2 (2×), CH_2Cl_2 (5×), *t*-BuOH (3×), and CH_2Cl_2 (5×). Each washing was for 1 min. The second treatment with *i*-Pr_2EtN was for 5 min. The Boc-11-aminohendecanoic acid (4 mmol in 10 ml of CH_2Cl_2) was added and shaken with the resin for 1 min, and 15 ml (2 mmol) of DCCI–CH_2Cl_2 solution was then added and the coupling was allowed to proceed for 1 h. The resin was then washed with 30 ml of the following reagents: 10% EtOH–CH_2Cl_2 (3×), CH_2Cl_2 (3×), *t*-BuOH (3×), CH_2Cl_2 (5×), 5% *i*-Pr_2EtN–CH_2Cl_2 (2×), and CH_2Cl_2 (5×). The coupling sequence was repeated as above and the resin washed in the same manner. A resin aliquot was removed at this point and treated with fluorescamine. Acetylation was carried out by washing the resin with 30 ml of 10% Ac_2O–py and then treating for 10 min with 30 ml of this reagent. The resin was then washed five times with CH_2Cl_2 to complete the program.

A second residue of Boc-11-aminohendecanoic acid was added after the following deblocking program: 25% TFA–CH_2Cl_2 (2×), CH_2Cl_2 (3×), *t*-BuOH (3×), CH_2Cl_2 (5×), 25% TFA–CH_2Cl_2 (2×). The second TFA treatment in each case was for 10 min. The washings, neutralizations, and couplings were performed as described above. A sample was likewise removed before acetylation for testing with fluorescamine. The (*p*-bromomethylphenyl)acetic acid was coupled according to the above program except the acid was dissolved in DMF and the coupling done in DMF–CH_2Cl_2. The acetylation step was omitted. The resin was analyzed for active bromide by the procedure described by Stewart and Young.[11] Resins were obtained that contained from 0.13 to 0.17 mequiv of bromide/g.

Boc Alanine-Resin V. According to the method of Gisin,[9] resin V (5 g) was treated in DMF at 50 °C with dry cesium Boc-alaninate prepared from 1.89 g of Boc-alanine and 1 equiv of CsOH in MeOH. The resin was washed three times with the following solvents: DMF, MeOH, H_2O, MeOH, and CH_2Cl_2. The degree of amino acid substitution was determined by amino acid analysis after HF cleavage and/or hydrolysis with 12 N HCl–propionic acid (1:1 v/v) at 135 °C for 2 h. The resin was found to contain 0.130 mmol of alanine/g. An active halide determination indicated <0.05 mequiv X^-/g. The resin was placed in the shaker vessel and washed with 30 ml of the following: CH_2Cl_2 (5×), *t*-BuOH (3×), CH_2Cl_2 (5×). The resin was acetylated by the procedure described in the preparation of resin V.

Synthesis of Phe-Ser-Glu-Phe-Trp-Asp-Leu-Asp-Pro-Glu-Val-Arg-Pro-Thr-Ser-Ala-Val-Ala-Ala. The amino acids were coupled using the same program employed in the preparation of resin V except that after the coupling of Boc-Trp, 0.5% ethanedithiol was added to the TFA deblocking reagent and 0.25% to the CH_2Cl_2 washes following the deblocking. Boc-Thr and Boc-Val were coupled using 8 mmol of protected amino acid and 4 mmol of DCCI–CH_2Cl_2 instead of the 4 mmol of amino acid and 2 mmol of DCCI used in the other couplings. The following side-chain protecting groups were employed: benzyl esters for Asp, and Glu, benzyl ethers for Thr and Ser, and G-tosyl for Arg.

HF Cleavage Procedure. The peptide resin (500 mg) was stirred in the reaction vessel of a Toho Kasei hydrogen fluoride apparatus for 30 min with 2 ml of anisole and 0.5 ml of ethanedithiol. Anhydrous hydrogen fluoride (10 ml) was condensed into the evacuated reaction vessel which had been precooled with liquid nitrogen. After warming to 0 °C, the resin was stirred for 30 min at 0 °C and the hydrogen fluoride evaporated at 0 °C with a vacuum pump protected with a train of CaO, liquid N_2, KOH traps. The resin was transferred to a sintered glass funnel with anhydrous ether and the peptide extracted with trifluoroacetic acid. The TFA was removed in vacuo at 15 °C. The peptide was solubilized in 7.5 ml of 1 M Tris and the pH adjusted to 8. This solution was applied to a 2.5 × 100 cm column of Bio-Gel P-10 equilibrated with 0.1 M ammonium bicarbonate, pH 8.0. The peptide containing fractions (Figure 3) were lyophilized and an aliquot of the solubilized peptide hydrolyzed for amino acid analysis (Table I). The yield was calculated on the basis of the original load of alanine. The peptide was further purified by chromatography[12] on AG 1X2 (Figure 4). The peptide was eluted with 0.5 N acetic acid. Recoveries were determined by amino acid analysis of an aliquot and by the absorbance at 280 nm (Table II). The peptide appeared as a single spot on cellulose F plates developed with 1-butanol–pyridine–glacial acetic acid–water (30:20:6:24) and visualized with ninhydrin.

Boc-11-aminohendecanoic Acid (Method A). The amino acid (20.13 g, Aldrich) was suspended in 250 ml of Me_2SO and 25 ml of Et_3N was added followed by 15 ml of Boc azide. The reaction mixture was stirred for several days until the amino acid had dissolved. In several preparations, it was necessary to add an additional 5 ml of Boc-N_3. After diluting with water and adjusting the pH to 10, the excess Boc-N_3 was extracted with diethyl ether. The aqueous phase was carefully acidified to pH 3.5 with cooling. The precipitate of Boc-11-aminohendecanoic acid was extracted with ethyl acetate. The ethyl acetate was dried over $MgSO_4$ and evaporated to give a residue which crystallized from hot hexane-benzene, yield 18.0 g (60%), mp 67–68 °C.

Anal. Calcd for $C_{16}H_{31}NO_4$: C, 63.75; H, 10.37; N, 4.65. Found: C, 63.41; H, 10.46; N, 4.59.

Method B. 11-Aminohendecanoic acid (20.13 g) was suspended in 200 ml of 1.5 N NaOH solution and warmed to 40 °C until the acid had dissolved. At 40 °C, Boc azide (15 ml) was added slowly during which time the temperature increased to 55 °C. After standing for 12 h at 50 °C, the reaction mixture was diluted with 1 l. of H_2O and the pH adjusted to 3.5 with cooling. The precipitated product was extracted with ethyl acetate. The organic layer was washed with H_2O, dried with $MgSO_4$, and evaporated. The solid residue (29.45 g) was crystallized from hexane–benzene, yield 23.4 g (78%), mp 67–68 °C.

***p*-Bromomethylphenylacetic Acid.** A solution of 27.5 g of tolylacetic acid and 11 ml of Br_2 in 400 ml of CCl_4 was brought to a reflux. The reaction mixture was illuminated with a 150-W tungsten lamp until HBr evolution had begun. After refluxing overnight, the reaction mixture was cooled and the precipitated product filtered off and washed with CCl_4. This solution was again heated at reflux temperature overnight, and the cooling and filtration repeated. In this manner, 22.3 g (63% yield) of pure product could be obtained after crystallization from benzene–hexane, mp 178–179 °C (lit.[13] mp 177–179 °C).

***p*-Nitrophenyl 1-Oxido-2,2,6,6-tetramethylpiperidinyl Carbonate.** A cold solution of 1-oxido-2,2,6,6-tetramethylpiperidinol (1.74 g) and 1.55 ml of triethylamine in 25 ml of dry ethyl acetate was treated with a solution of 2.02 g of *p*-nitrophenyl chloroformate in 25 ml of ethyl acetate. After standing at 5 °C overnight, the reaction mixture was poured over ice water and more ethyl acetate added. After washing well with H_2O, the ethyl acetate was dried with $MgSO_4$ and evaporated. The red product was crystallized from hexane–ether, yield 2.02 g (60%), mp 114–116 °C.

Anal. Calcd for $C_{16}H_{22}N_2O_6$: C, 56.96; H, 6.28; N, 8.31. Found: C, 56.85; H, 6.39, N, 8.22.

Labeling of Peptide Resins. Approximately 10 mg of deblocked and neutralized peptide resin was treated for 2 h with 200 μl of a 1% solution (w/v) of the above carbonate in CH_2Cl_2. The resin was washed with CH_2Cl_2, 10% HOAc–CH_2Cl_2, CH_2Cl_2, 5% *i*-Pr_2EtN–CH_2Cl_2, CH_2Cl_2, EtOH, and CH_2Cl_2 and suspended in CH_2Cl_2 before recording the electron paramagnetic resonance spectrum with a Varian E-12 spectrometer.

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Registry No.—Phe-Ser-Glu-Phe-Trp-Asp-Leu-Asp-Pro-Glu-Val-Arg-Pro-Thr-Ser-Ala-Val-Ala-Ala, 49777-12-0; *t*-Boc-11-aminohendecanoic acid, 10436-25-6; 11-aminohendecanoic acid, 2432-99-7; *t*-Boc azide, 1070-19-5; *p*-nitrophenyl 1-oxido-2,2,6,6-

tetramethylpiperidinyl carbonate, 58229-35-9; 1-oxido-2,2,6,6-tetramethylpiperidinol, 58229-36-0; p-nitrophenyl chloroformate, 7693-46-1.

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Synthesis of Specifically Deuterated *S*-Benzylcysteines and of Oxytocin and Related Diastereomers Deuterated in the Half-Cystine Positions[1,2]

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S-Benzylcysteine derivatives specifically deuterated at the α carbon only, the β carbon only, and at both the α and β carbons have been synthesized. These labeled compounds have been enzymatically resolved and the enantiomers and reacemates have been converted to the *N*-*tert*-butyloxycarbonyl derivatives. The deuterium labels were not exchanged under the conditions of the syntheses. Condensation of the sodium salt of diethyl α-acetamidomalonate with benzyl chloromethyl sulfide followed by hydrolysis with DCl afforded *S*-benzyl-DL-[α-$^2H_1$]cysteine. Acetylation followed by treatment with hog renal acylase separated the stereoisomers. A Mannich reaction with [$^2H_2$]methylene diacetate, diethyl α-acetamidomalonate, and dimethylamine followed by quaternization of the amino nitrogen with methyl iodide gave diethyl α-acetamido-α-dimethylamino[$^2H_2$]methylmalonate methiodide (**15**). Treatment of **15** with sodium benzylmercaptide gave diethyl α-acetamido-α-benzylthio[$^2H_2$]methylmalonate, which was hydrolyzed with HCl to yield *S*-benzyl-DL-[β,β-$^2H_2$]cysteine or with DCl to afford *S*-benzyl-DL-[α,β,β-$^2H_3$]cysteine. These compounds were resolved as before. The preparation of *S*-benzyl-DL-[α,β,β-$^2H_3$]cysteine required an efficient source of ethanol-*d*. This deuterated solvent was prepared in quantitative yield in 2 h from tetraethoxysilane, D_2O, and a catalytic amount of thionyl chloride. The protected deuterated amino acids were used in the preparation of several oxytocin analogues in which the specific deuteration appears in either the 1-hemicystine or the 6-hemicystine residues.

Specific deuterium labels in amino acids, peptides, and proteins are very useful for studying the chemical, biological, and especially the physical properties of these molecules. If the label is introduced at nonexchangeable positions, it provides a durable marker which does not significantly alter the properties of the molecule.[3-13]

The usefulness of such labels has been demonstrated for proteins in studies of structure and folding.[14-19] Unambiguous proton[8-11,20-22] and carbon-13[12,13,23] nuclear magnetic resonance assignments for many peptides have been made using specifically deuterated derivatives. The development of deuteron magnetic resonance spectroscopy has opened the way for a direct study of the microdynamical behavior of specific segments of the neurohypophyseal peptide hormones and their binding to the neurophysins, their biological carrier proteins.[24,25] These studies have begun to provide insights into the conformational aspects of these biologically active compounds, giving more direct evidence for structure–activity relationships than has been available from amino acid substitutions, which are more likely to perturb the structure of the molecule.[26-29]

In order to perform these experiments it is necessary to prepare the appropriate specifically deuterium labeled amino acid or amino acid derivative by a synthetic route which maintains the integrity of the deuterium label throughout the synthesis.

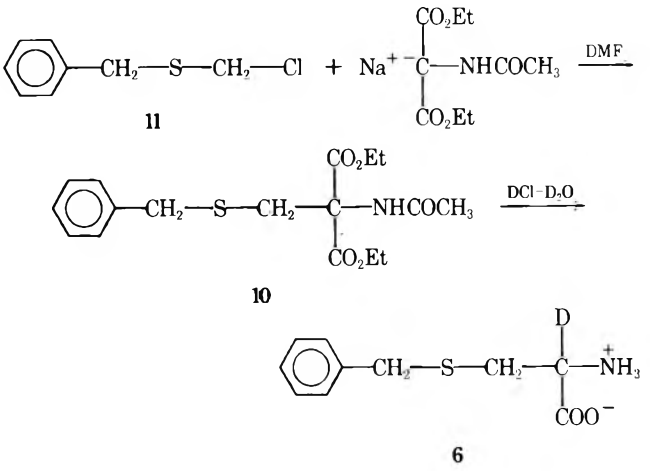
We report here the total synthesis of *S*-benzylcysteine deuterated specifically in the α position only, the β positions only, and in both the α and β positions. The specifically deuterated cysteine derivatives were also resolved into their enantiomeric pairs without loss of the label, and one was used for the synthesis of the specifically labeled oxytocin [6-hemi[β,β-$^2H_2$]cystine]oxytocin (**2**). The racemic compounds were used to incorporate specifically deuterated cysteine into the half-cystine positions of the oxytocin derivatives [6-hemi-DL-[α-$^2H_1$]cystine]oxytocin (**3**), [1-hemi-DL-[β,β-$^2H_2$]cystine]oxytocin (**4**), and [1-hemi-DL-[α,β,β-$^2H_3$]cystine]oxytocin (**5**) and the diastereomeric pairs were separated by partition chromatography on Sephadex G-25.[31,32,45]

H-Cys-Tyr-Ile-Gln-Asn-Cys-Pro-Leu-Gly-NH_2
1 2 3 4 5 6 7 8 9
1

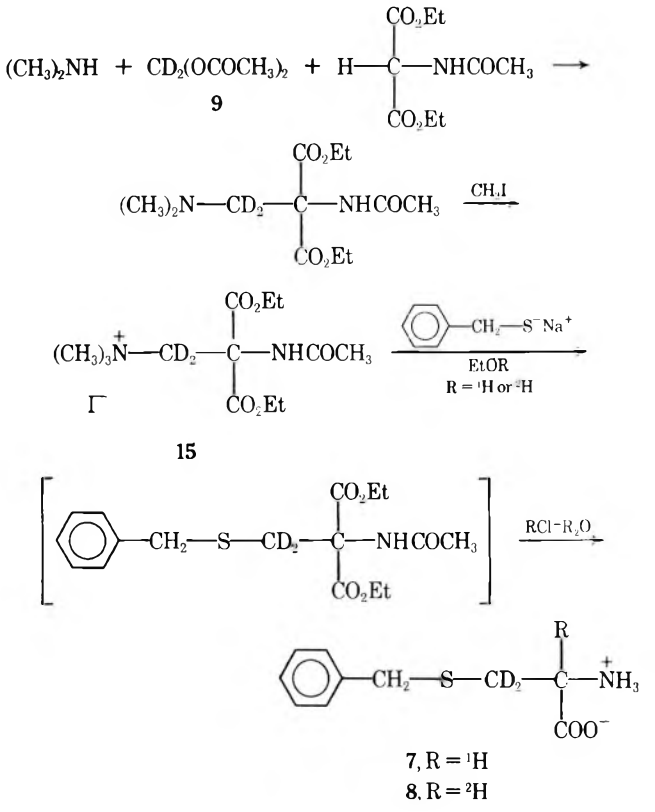
The synthesis of each of the partially deuterated *S*-benzylcysteine derivatives was accomplished using different approaches. The *S*-benzyl-DL-[α-$^2H_1$]cysteine (**6**) was made by displacement of chloride from benzyl chloromethyl sulfide by sodium diethyl acetamidomalonate followed by hydrolysis of the adduct with 11 N DCl in D_2O (Scheme I).

The *S*-benzyl-DL-[β,β-$^2H_2$]cysteine (**7**) and *S*-benzyl-DL-[α,β,β-$^2H_3$]cysteine (**8**) were made using a modification of the methods of Cornelius[30] and Atkinson, et al.[33] This approach involved making the Mannich adduct of diethyl acetamidomalonate, formaldehyde, or its equivalent, and

Scheme I



Scheme II



dimethylamine. The adduct was quaternized with methyl iodide, and the product was treated with sodium benzylmercaptide. Upon hydrolysis, the resulting product gave *S*-benzyl-DL-cysteine (Scheme II).

In place of formaldehyde we used [α,α-$^2H_2$]methylene diacetate (**9**). Scrupulously anhydrous conditions were required before **9** could be isolated in good yield. Since the Mannich adduct is deuterated, one expects to obtain **7** when HCl is used in the hydrolysis step, and **8** when DCl is used. This approach gave **7** as expected with >95% deuteration at the β positions. However, when the synthesis of **8** was attempted in this manner, we obtained the *S*-benzyl-DL-cysteine derivative which was >90% **7** (virtually undeuterated in the α position). The reaction of sodium benzylmercaptide with the quaternary salt was done for 6 days in refluxing ethanol. Isolation and characterization (NMR) of the reaction product revealed that it was not the expected adduct but was ethyl *N*-acetyl-*S*-benzyl-DL-[β,β-$^2H_2$]cysteinate (>90%). Apparently, during the course of the reaction, ethanolysis, decarboxylation, and subsequent proton abstraction from the solvent by the attendant carbanion lead to the unexpected product. When the displacement reaction was run in ethanol-*d* (**12**), however, the same ethanolysis and decarboxylation occurred, but this time a deuteron was abstracted from the solvent rather than a proton. After DCl hydrolysis **8** was obtained with >95% deuteration at both the α and β positions. These experiments required a rapid and inexpensive source of ethanol-*d*. The published[34] preparation of ethanol-*d* from tetraethoxysilane and D_2O gave a 90% yield after 24 h reaction and distillation of the product. We modified this approach by the addition of a catalytic amount (ca. 0.3%) of thionyl chloride which produced a slight concentration of D^+ in solution.[35] We have obtained ethanol-*d* in 99.9% yield after only 2 h reaction time which was pure as judged by NMR and gas chromatography. *S*-Benzyl-DL-[β,β-$^2H_2$]cysteine (**7**) was readily resolved into its enantiomers by N-acetylation followed by reaction with hog renal acylase.[36] A similar treatment of **6** and **8** separated the enantiomers without loss of label at either the α or β positions. The resulting *S*-benzyl-L-[β,β-$^2H_2$]cysteine (**7a**) as well as **6**, **7**, and **8** were readily converted to *N*-*tert*-butyloxycarbonyl (N-Boc) derivatives using the general method employing *tert*-butyl azidoformate.[37] No exchange of deuterium was noted in either of the above procedures.

The solid-phase synthesis[38] of the oxytocin derivatives was carried out on an automated Vega Model 95 synthesizer, a solid-state version of our automated instrument,[39] or on a semiautomated apparatus designed and built in our laboratory. The methodology used is shown in Table I. Each coupling was >99.4% complete as judged by the ninhydrin test.[40] It was of considerable interest that the active ester couplings of asparagine and glutamine catalyzed by the presence of 1 molar equiv of 1-hydroxybenzotriazole were complete after 3.5 and 5 h, respectively. Without the catalyst, these couplings normally require 8–14 h. Similar catalysis of nitrophenyl ester coupling in solution peptide synthesis has been reported.[41] At the conclusion of the synthesis, the N-terminal Boc group was removed and the protected nonapeptide amide was obtained by ammonolysis (in methanol) of the corresponding peptide-resin ester.

The nonapeptide was deprotected with sodium in liquid ammonia[42] and then oxidized under nitrogen[43] with 0.01 N $K_3Fe(CN)_6$.[44] The isomers were separated from each other and from by-products by partition chromatography on Sephadex G-25 using the solvent system 1-butanol–3.5% HOAc in 1.5% aqueous pyridine (1:1).[45] At R_f 0.32, the peak for the hemi-D-cysteine derivatives of oxytocin appeared, and at R_f 0.24, the peak for the oxytocin derivatives appeared, both R_f values in close agreement with our previous experience with diastereomeric mixtures.[45] The diastereomers were isolated and further purified by gel filtration on Sephadex G-25 using 0.2 N HOAc as eluting solvent. The purity of the products was checked by thin layer chromatography in three solvent systems, quantitative amino acid analysis, and optical rotation determination.

The milk ejecting activities[46] of the partially deuterated oxytocin derivatives were indistinguishable within experimental error from those of the native hormone. The partially deuterated hemi-D-cystine derivatives all had milk ejecting activities greatly reduced compared to those of oxytocin. These derivatives have been used for the assignment of α,β and carbonyl carbons in ^{13}C NMR spectra,[13,47] and except for these carbon atoms the ^{13}C NMR spectra were indistinguishable from those of authentic oxytocin.

Experimental Section

Thin layer chromatography (TLC) was done on silica gel G plates using the following solvent systems: (A) 1-butanol–acetic

Table I. Solid-Phase Peptide Synthesis Methodology

	Normal DCC Coupling			Nitrophenyl ester coupling (for Asn and Gln only)			
Step	Solvent or reagent	Time, min	No. of times	Step	Solvent or reagent	Time, min	No. of times
1	CH_2Cl_2	1	4	1	CH_2Cl_2	1	4
2	Ninhydrin test		1	2	Ninhydrin test		1
3	TFA–CH_2Cl_2–anisole (25:73:2)	2	1	3	TFA–CH_2Cl_2–anisole (25:73:2)	2	1
4	TFA–CH_2Cl_2–anisole (25:73:2)	20	1	4	TFA–CH_2Cl_2–anisole (25:73:2)	20	1
5	CH_2Cl_2	1	3	5	CH_2Cl_2	1	3
6	DIEA–CH_2Cl_2 (10:90)	2	2	6	DIEA–CH_2Cl_2 (10:90)	2	2
7	CH_2Cl_2	1	4	7	CH_2Cl_2	1	4
8	Amino acid[a] (1.5 equiv)–CH_2Cl_2		1	8	DMF	1	5
9	DCC (1.2 equiv)–CH_2Cl_2	20	1	9	Amino acid[a] (4 equiv)–DMF, 1-Hydroxybenzotriazole (4 equiv)	210–300	1
10	CH_2Cl_2	1	2				
11	100% EtOH	1	2	10	DMF	1	3
12	CH_2Cl_2	1	3	11	CH_2Cl_2	1	2
13	Amino acid (1.5 equiv)–CH_2Cl_2		1	12	100% EtOH	1	2
14	DCC (1.2 equiv)–CH_2Cl_2	20	1				
15	CH_2Cl_2	1	2				
16	100% EtOH	1	2				

[a] All amino acids are N^{α}-Boc protected.

acid–water (4:1:5, upper phase only); (B) 1-butanol–acetic acid–pyridine–water (15:3:10:12); (C) 1-pentanol–pyridine–water (35:35:30). Capillary melting points were determined on a Thomas-Hoover melting point apparatus and are uncorrected. Nuclear magnetic resonance (NMR) spectra were obtained using a Varian T-60 NMR spectrometer or a Bruker WH-90 NMR spectrometer. Amino acid analyses were obtained by the method of Spackman, Stein, and Moore[48] on a Beckman 120 C amino acid analyzer after hydrolysis in 6 N HCl for 22 h. Optical rotation values were measured at the mercury green line (547 nm) using a Zeiss Old 4 polarimeter. Elemental analyses were performed by Spang Microanalytical Laboratory or Heterocyclic Chemical Corp., and deuterium analyses were performed by Joseph Nemeth, Urbana, Ill.

Benzyl Chloromethyl Sulfide (11). The title compound was made in 59% yield following the reported procedure:[49] bp 102 °C (2 mm) [lit. 102 °C (2 mm)]; NMR (neat) δ 3.55 (s, 2 H), 4.10 (s, 2 H), 7.00 (s, 5 H).

Diethyl α-Acetamido-α-benzylthiomethylmalonate (10). A 1.73-g portion of sodium hydride (50% in oil, 0.036 mol) was placed in a dry, nitrogen-filled reaction flask, covered with dry dimethylformamide (DMF), and cooled to 0 °C. A solution of 7.83 g (0.036 mol) of diethyl α-acetamidomalonate in 40 ml of DMF was added to the cold hydride mixture over 20 min. Stirring was continued until hydrogen evolution ceased (ca. 1 h). Benzyl chloromethyl sulfide (6.15 g, 0.036 mol) was added, and the flask was placed in a 90–100 °C bath for 66 h. The mixture was cooled, filtered, and concentrated in vacuo to a brown oil. Trituration with 20 ml of water was followed by three 5-ml chloroform extractions. The combined organic layers were dried (K_2CO_3) and filtered, and the filtrate concentrated in vacuo to a brown solid which was treated eight times with 20-ml portions of boiling hexane. Each time the clear hexane layer was decanted from an oily lower layer. As the hexane cooled, white needles were deposited: yield 6.68 g (53% of theory); mp 87.3–88 °C; NMR ($CDCl_3$) δ 1.25 (t, 6 H), 2.05 (s, 3 H), 3.55 (s, 2 H), 3.75 (s, 2 H), 4.25 (q, 4 H), 6.95 (s, broad, 1 H), 7.30 (s, 5 H). Anal. Calcd for $C_{17}H_{23}NS$: C, 57.79; H, 6.53; N, 3.98. Found: C, 57.35; H, 6.54; N, 4.13.

S-Benzyl-DL-[α-$^2H_1$]cysteine (6). A 6.0-g portion of **10** was treated with ca. 11 M DCl in D_2O (made by adding 13 ml of $SOCl_2$ dropwise to 31.3 ml of cold D_2O) at reflux for 6 h. After cooling slightly, Norit was added and the mixture was briefly brought to boiling. The mixture was rapidly filtered and the filtrate was evaporated to dryness in vacuo. The residue was taken up in about 25 ml of water, and concentrated NH_4OH was added to pH 5.5. After filtration of the resulting crystals and drying over NaOH in vacuo, there was obtained 2.33 g (65% of theory) of **6**: mp 215.5–217 °C (lit. for protio compound,[49] 215–216 °C); NMR (CF_3COOH) δ 2.75 (s, 2 H), 3.40 (s, 2 H), 3.60–3.80 (α-CH, undetectable), 6.90 (s, 5 H).

***N*-Boc-*S*-benzyl-DL-[α-$^2H_1$]cysteine (13).** The title compound was made in 70% yield following the reported procedure,[37] mp 110.5–111.0 °C (lit.[45] 111–111.3 °C, lit.[37] 63–65 °C). Single, uniform spots were obtained on TLC using systems A, B, and C with R_f values identical with those of the protio analog: NMR ($CDCl_3$) δ 1.45 (s, 9 H), 2.90 (s, 2 H), 3.75 (s, 2 H), 4.40–4.60 (α-CH, undetectable), 5.35 (broad, 1 H), 7.30 (s, 5 H). Quantitative deuterium analysis indicated 96% deuteration (calcd 4.75 atom %, found 4.55 atom %).

***S*-Benzyl-L-[α-$^2H_1$]cysteine (6a).** The resolution of **6** was done using the reported procedure for the protio compound[36] with minor modifications. The starting material, *N*-acetyl-*S*-benzyl-DL-[α-$^2H_1$]cysteine, was obtained by adding 1.25 g of **6** to 3 ml of H_2O and treating the resulting slurry with 0.9 g of Na_2CO_3 and 1.15 ml of acetic anhydride. After 20 min, the homogenous mixture was acidified with concentrated HCl to pH 1. There was obtained 1.42 g (95%), mp 154.5–155.2 °C (lit.[36] for protio analog, mp 157 °C). The acetylated amino acid was slurried in 90 ml of water and the pH was adjusted to 7.5 with NH_4OH. The total volume was brought to 110 ml and acylase I (hog kidney, Calbiochem, 0.23 g) was added and the mixture was stirred at 38 °C for 2 days maintaining the pH. An additional 57 mg of enzyme was added and the mixture stirred 2 days more. The pH was lowered to 5 with acetic acid, a few milliliters of butanol were added and the mixture was concentrated to about 20 ml. The mixture was filtered and the filtrate was acidified with concentrated HCl to give 640 mg of *N*-acetyl-*S*-benzyl-D-[α-$^2H_1$]cysteine (90.5%), mp 140–141 °C. The residue on the filter was transferred to a flask where it was boiled with 1 N HCl and filtered. This process was repeated and the combined filtrates were neutralized with NH_4OH, giving 390 mg of *S*-benzyl-L-[α-$^2H_1$]cysteine (64%), mp 215–218 °C, $[\alpha]^{21}_{547}$ −17.4° (c 1, 5 N HCl) [lit.[36] $[\alpha]^{25}D$ −19.5° (*c* 1, 5 N HCl), commercial amino acid (Fox 4978) $[\alpha]^{24}_{547}$ −17.1°]. A quantitative deuterium analysis showed the compound to be 97% deuterated (calcd 7.69 atom %, found 7.52 atom %).

Dibromo[$^2H_2$]methane (14).[28] Dibromomethane (55 g) was successively exchanged with protions of 10% NaOD in D_2O by rapidly stirring at reflux for 24-h periods. After five exchanges using 22-, 13-, 12-, 11-, and 7-ml portions of base, the exchange was judged to be about 80% complete by NMR. Three additional exchanges employing 12 ml each of 10% NaOD in D_2O gave 20.2 g of **14** which was >95% deuterated.

[α,α-$^2H_2$]Methylene Diacetate (9).[33] A 20-g portion of **14** was mixed with 66 ml of anhydrous acetic acid (distilled from triacetyl-

borate), 6.7 ml of acetic anhydride (freshly distilled after standing over P_2O_5), and 32.2 g of anhydrous potassium acetate under dry nitrogen in a flask equipped with a mechanical stirrer. After all the reagents were added, the nitrogen inlet was replaced with a condenser, and the mixture was refluxed for 24 h. Stirring was continued while the mixture cooled to room temperature. Ether (200 ml) was added and the mixture was filtered. The filter cake was washed with four 50-ml portions of ether. The ether and acetic acid were distilled from the mixture at atmospheric pressure. At 54–55 °C (10 mm) [lit.[33] 61–63 °C (12 mm)] there was obtained 7.63 g (49% of theory) of **9** which was >95% deuterated.

Diethyl α-Acetamido-α-dimethylamino[$^2H_2$]methylmalonate Methiodide (15). An 11.2-g portion of **9** (0.083 mol) was cooled to −10 °C and 27.8 ml of a 40% aqueous solution of dimethylamine was added dropwise such that the temperature did not exceed 0 °C. Then 14.9 g (0.083 mol) of diethyl α-acetamidomalonate was added in one portion. The flask was sealed and the mixture was stirred at 40 °C for 1 h. The flask was cooled to −10 °C and 20% aqueous NaOH was added to pH 11. The cold mixture was extracted with two 50-ml portions of ether. The combined organic extracts were dried over Na_2SO_4, filtered, and freed of solvent giving a semisolid residue. The residue was taken up in 150 ml of dry ether and 25 ml of methyl iodide was added. The mixture was stirred at 40 °C for 24 h, and then allowed to stand at room temperature for 24 h. The white product was filtered and dried in vacuo to give 24.24 g (70% of theory) of **15**: mp 174–175 °C (lit.[30] 171–173 °C); NMR (D_2O) δ 1.20 (t, 6 H), 2.10 (s, 3 H), 3.15 (s, 9 H), 4.35 (q, 4 H), 4.35 (s, absent).

***S*-Benzyl-DL-[β,β-$^2H_2$]cysteine (7).** Under dry nitrogen, 0.32 g (0.014 mol) of sodium was added to 30 ml of absolute ethanol. When all the sodium had reacted, 1.74 g (0.014 mol) of benzyl mercaptan was added followed by 5.84 g (0.014 mol) of **15**. The mixture was refluxed for 6 days, cooled, and freed of solvent. The residue was disolved in 20 ml of chloroform and 10 ml of cold water was added. The mixture was shaken and separated, and the organic layer was dried over anhydrous K_2CO_3. The drying agent was filtered off and the solvent removed leaving a residue which solidified on standing. Without further purification, the residue was treated with concentrated HCl at reflux for 5.5 h. The mixture was cooled, treated with Norit, and again boiled. The mixture was filtered hot and the filtrate was evaporated to dryness in vacuo. The residue was dissolved in about 20 ml of H_2O and the pH was adjusted to 5.5 with NH_4OH. After filtering and drying, there was obtained 2.14 g (72% from **15**) of white crystals melting at 209–211 °C: NMR (CF_3COOH) δ 2.75 (β,β-CH_2, undetectable), 3.20 (s, 2 H), 3.40–3.60 (1 H), 6.80 (s, 5 H). Quantitative deuterium analysis indicated 97% deuteration (calcd 15.40 atom %, found 14.95 atom %).

***N*-Boc-*S*-benzyl-DL-[β,β-$^2H_2$]cysteine (16).** Employing the same method used to convert **6** to **13**, 3.00 g (0.014 mol) of **7** gave 3.80 g of **16** (87%). The white crystals melted at 110.5–111.0 °C; NMR ($CDCl_3$) δ 1.45 (s, 9 H), 2.90 (β,β-CH_2, undetectable), 3.75 (s, 2 H), 4.40–4.60 (1 H), 5.35 (broad, 1 H), 7.25 (s, 5 H). A single spot was obtained in TLC using systems A, B, and C with R_f values identical with those of the protio analogue.

***S*-Benzyl-L-[β,β-$^2H_2$]cysteine (7a).** A sample of **7** was acetylated and resolved with hog renal acylase as described above for compound **6**. The resolved L isomer (**7a**) had mp 215–218 °C $[\alpha]^{21}_{547}$ −20.7° (c 1, 5 N HCl).

***N*-Boc-*S*-benzyl-L-[β,β-$^2H_2$]cysteine (17).** Employing the same method used to convert **6** to **13**, 0.75 g (0.0025 mol) of **7** was converted to 1.01 g of **17** (92%) which remained an oil: NMR ($CDCl_3$) δ 1.50 (s, 9 H), 2.90 (β,β-CH_2, undetectable), 3.75 (s, 2 H), 4.40–4.60 (1 H), 5.40 (broad, 1 H), 7.30 (s, 5 H), 11.60 (s, 1 H); $[\alpha]^{22.5}_{547}$ −48.8° (c 1.0, CH_3COOH), for all-protio analogue (Biosynthetica 6145) $[\alpha]^{22.5}_{547}$ −52.2° (c 1.0, CH_3COOH). A single spot was obtained on TLC using systems A, B, and C, with R_f values identical with those of the protio analogue.

Ethanol-*d* (12). Under a nitrogen atmosphere, 104.2 g (0.50 mol) of tetraethoxysilane was mixed with 40 g (2.0 mol) of D_2O and a catalytic amount of thionyl chloride (ca. 0.5 ml). After stirring at room temperature for 2 h, the mixture was distilled at 2 mm. The last traces of product were obtained by increasing the vacuum and warming the distillation flask to about 30 °C. There was obtained 93.9 g (99.9% of theory) of **12**. No starting materials contaminated the product as ascertained by gas chromatography and NMR. The infrared spectrum was consistent with spectra of other deuterated alcohols.[50]

***S*-Benzyl-DL-[α,β,β-$^2H_3$]cysteine (8).** The reaction of 13.30 g (0.032 mol) of **15** with sodium benzylmercaptide in ethanol-*d* gave ethyl *N*-acetyl-*S*-benzyl-DL-[α,β,β-$^2H_3$]cysteinate, which was then treated with 11 N DCl in D_2O to give 5.55 g of **8** (81% from **15**). The white crystals melted at 211–212 °C; NMR (CF_3COOH) δ 2.75 (β,β-CH_2, undetectable), 3.40 (s, 2 H), 3.60–3.80 (α-CH, undetectable), 6.90 (s, 5 H).

***N*-Boc-*S*-benzyl-DL-[α,β,β-$^2H_3$]cysteine (18).** A 2.50-g portion (0.0117 mol) of **8** was converted to 3.45 g of **18** (94% of theory) using the same method as used to convert **6** to **13**. The white crystals melted at 111.5–111.8 °C; NMR ($CDCl_3$) δ 1.50 (s, 9 H), 2.90 (β,β-CH_2, undetectable), 3.75 (s, 2 H), 4.40–4.60 (α-CH, undetectable), 5.35 (broad, 1 H), 7.30 (s, 5 H). A single spot was obtained on TLC using systems A, B, and C, with R_f values identical with those of the protio analogue. Quantitative deuterium analysis indicated 95% deuteration (calcd 14.28 atom %, found 13.50 atom %).

Boc-Leucylglycinate-Resin (19). A 5.00-g portion of Boc-glycinate-resin (polystyrene crosslinked with 1% divinylbenzene, LS 601 Merrifield Resin, Lab Systems, Inc., San Mateo, Calif.) substituted with Boc-glycine at the level of 0.64 mmol/g by the method of Gisen[51] was deprotected and neutralized as described in steps 1–7 of Table I. Limited coupling was done with 0.585 g (2.35 mmol) of Boc-leucine-H_2O and an equivalent molar quantity of dicyclohexylcarbodiimide (DCC). The reaction was allowed to proceed for 30 min. After the appropriate washes (see Table I, steps 10–12), the unreacted amino groups were treated with 0.35 g (3.2 mmol) of *N*-acetylimidazole in CH_2Cl_2 for 3 h. At the conclusion, a ninhydrin test was negative. The average of four modified[52] aldimine[53] determinations gave a leucyl substitution level of 0.495 mmol/g.

Solid-Phase Synthesis of *S*-3,4-Dimethylbenzylcysteinyl-*O*-benzyltyrosylisoleucylglutaminylasparaginyl-*S*-benzyl-DL-[α-$^2H_1$]cysteinylprolylleucylglycinate-Resin (20). The solid-phase synthesis of **20** was performed as a Vega Model 95 synthesizer, an automated machine similar to that described by Hruby et al.[39] The preparation was done on a 1.5-mmol scale, which required 3.19 g of the resin **19**. The synthetic cycles are outlined in Table I. All reactions and washes were carried out with 30-ml portions. After the last coupling, the terminal Boc group was removed (Table I, steps 1–6). The peptide-resin was filtered and dried in vacuo and found to have increased in weight by 1.42 g (85% of theory). The peptide-resin **20** was ammonolyzed and the peptide was extracted into DMF and precipitated with water as described elsewhere.[45] There was obtained 1.44 g (74% of theory) of the protected nonapeptide amide H-Cys(DMB)-Tyr(Bzl)-Ile-Gln-Asn-DL-[α-$^2H_1$]Cys(Bzl)-Pro-Leu-Gly-NH_2 (**21**), mp 210–214 °C. Anal. Calcd for $C_{66}H_{90}N_{12}O_{12}S_2 \cdot 4H_2O$: C, 57.47; H, 6.82. Found: C, 57.30; H, 6.95.

[6-Hemi-DL-[α-$^2H_1$]cystine]oxytocin (3). The protecting groups were removed by treatment of 325 mg (0.25 mmol) of **21** with sodium in liquid ammonia (freshly distilled from sodium) and the sulfhydryl groups were oxidized under nitrogen with 50 ml of 0.01 N $K_3Fe(CN)_6$ solution.[44] The product [6-hemi-DL-[α-$^2H_1$]cystine]oxytocin (**3**) was purified by partition chromatography using the solvent system 1-butanol–3.5% aqueous acetic acid in 1.5% pyridine (1:1).[45] Analysis by the Folin–Lowry method[54] showed a small by-product peak at R_f 0.61, and a large, poorly resolved peak at R_f 0.38–0.20 of the incompletely separated diastereomeric oxytocin derivatives. The fractions corresponding to the diastereomeric mixture were pooled and the peptide mixture obtained after isolation was subjected to the same solvent system as above. As found previously[45] the diastereomers were nicely separated with peaks at R_f 0.32 and 0.24 corresponding to [6-hemi-D-[α-$^2H_1$]cystine]oxytocin (**3b**) and [6-hemi[α-$^2H_1$]cystine]oxytocin (**3a**), respectively. The oxytocin peak (R_f 0.24) was isolated to give 70 mg of uncontaminated product. The 6-hemi-D oxytocin derivative as isolated contained small amounts of oxytocin. Repurification by partition chromatography gave 51.4 mg of the pure 6-hemi-D diastereomer **3b**. Both **3a** and **3b** were separately purified by gel filtration chromatography on Sephadex G-25 (200–270 mesh) using 0.2 N acetic acid as eluent solvent. Final purified yields were 64 mg of **3a** and 50 mg of **3b**. Each of the isomers gave single spots on TLC in solvent systems A, B, and C, identical with those of authentic protio analogues. Diastereomer **3a** exhibited a carbon-13 spectrum identical with that of authentic oxytocin except for the absence of the peak corresponding to the 6-hemicystine α carbon. It had $[\alpha]^{22}_{547}$ −22.6° (c 0.5, 1 N HOAc). A sample of **3a** was hydrolyzed in 6 N HCl for 24 h at 110 °C. Amino acid analysis gave the following molar ratios: aspartic acid, 1.0; glutamic acid, 1.1; proline, 0.9; glycine, 1.0; half-cystine, 1.9; isoleucine, 1.0; leucine, 1.1; tyrosine, 0.9. Milk-ejecting activity determined using mouse-mammary tissue in vitro[46] was identical with that of authentic oxytocin within experimental error.

Diastereomer **3b** had $[\alpha]^{22}_{547}$ −108.1° (c 0.5, 1 N HOAc) [lit.[55] $[\alpha]^{20}D$ −81° (c 0.5, 1 N HOAc)]. Amino acid analysis gave the following molar ratios: aspartic acid, 1.0; glutamic acid, 1.0; proline, 1.0; glycine, 1.0; half-cystine, 2.0; isoleucine, 0.9; leucine, 1.0; tyrosine, 0.9. Milk-ejecting activity was ca. 34.7 units/mg. Anal. Calcd for $C_{43}H_{65}DN_{12}O_{12}S_2 \cdot CH_3CO_2H$: C, 50.75; H, 6.39; N, 15.79. Found: C, 50.78; H, 6.37; N, 16.19.

Solid-Phase Synthesis of [6-Hemi[β,β-$^2H_2$]cystine]oxytocin (2). Boc-leucylglycinate-resin with a substitution level of 0.27 mmol/g was prepared in an analogous manner to that described for the preparation of **19**. A 3.80-g portion of this resin was used to synthesize the title compound on a 1-mmol scale. A semiautomated apparatus designed and built in our laboratory was used which allowed the reaction vessel to be filled and emptied by application of vacuum at the top and bottom, respectively, of the vessel, and to be shaken mechanically. For each step, 35 ml of solvent was used except for the DIEA neutralization step in which case 40 ml was used. For this synthesis 0.8 equiv of DCC was used for each equivalent of Boc-amino acid.[56] The N-terminal Boc group was removed. The resin was dried and found to have increased in weight by 1.08 g (105%). The protected nonapeptide was cleaved from the resin by ammonolysis. After extraction into DMF, precipitation, filtering, and drying, there was obtained 725 mg of nonapeptide, mp 215–217 °C, and a second crop weighing 390 mg, mp 173–178 °C. A portion of the first crop (325 mg, 0.25 mmol) was deprotected with sodium in liquid ammonia and oxidized with 0.01 N aqueous $K_3Fe(CN)_6$. Purification by partition chromatography using the solvent system 1-butanol–3.5% aqueous acetic acid in 1.5% pyridine (1:1) gave a peak centered at R_f 0.23 corresponding to the title compound **2**. The fractions corresponding to the peak were pooled and lyophilized. Final purification by gel filtration chromatography afforded 63 mg of [6-hemi[β,β-$^2H_2$]cystine]oxytocin. It had $[\alpha]^{24.5}_{547}$ −23.7° (c 0.5, 1 N HOAc). Analysis on TLC in solvent systems A, B, and C gave single spots identical with those of an authentic protio analogue. A sample was hydrolyzed in 6 N HCl for 24 h at 110 °C. Amino acid analysis gave the following molar ratios: aspartic acid, 1.0; glutamic acid, 1.0; proline, 1.1; glycine, 1.0; half-cystine, 2.0; isoleucine, 0.9; leucine, 1.0; tyrosine, 0.9. Milk-ejecting activity was identical with that of authentic oxytocin within experimental error.

Solid-Phase Synthesis of Boc-*O*-benzyltyrosylisoleucylglutaminylasparaginyl-*S*-3,4-dimethylbenzylcysteinylprolylleucylglycinate-Resin (22). Boc-leucylglycinate-resin with a substitution level of 0.36 mmol/g was prepared in an analogous manner to that described for the preparation of **19**. A 7.50-g portion of this resin was used to synthesize the title compound on a 2.7-mmol scale using the semiautomated apparatus described above in the preparation of **2**. In each step 50 ml of solvent was used except for the DIEA neutralization step in which case 60 ml was used. Again, 0.8 equiv of DCC was used for each equivalent of Boc-amino acid.[56] After each coupling series, a ninhydrin test indicated >99.4% coupling for all but Boc-*O*-benzyltyrosine; in this case a third coupling using 0.5 equiv was performed, but the reaction was only about 94% complete as judged by the ninhydrin test. The unreacted amino groups were acetyl terminated with *N*-acetylimidazole in CH_2Cl_2. The peptide-resin was filtered and dried in vacuo and found to have increased in weight by 2.89 g.

[1-Hemi-DL-[β,β-$^2H_2$]cystine]oxytocin (4) and Separation of the Diastereomers. A 4.75-g portion of the Boc-octapeptide resin **22** was deprotected and neutralized in the usual way (Table I, steps 1–6) and then treated with 0.55 g (1.74 mmol) of **16** and 0.32 g (1.57 mmol) of DCC in CH_2Cl_2 for 30 min. Following the reaction, a ninhydrin test indicated that the reaction was ca. 94% complete. A second coupling with 0.27 g (0.85 mmol) of **16** and 0.16 g (0.80 mmol) of DCC gave >99.4% coupling as judged by the ninhydrin test. The Boc group was removed and the resin dried to give 4.87 g of the protected peptide-resin precursor of **4**. After cleavage from the resin by ammonolysis, extraction of the peptide into DMF, and precipitation with water, 1.43 g of the protected nonapeptide amide was obtained, mp 220–225 °C. A 325-mg portion was deprotected with sodium in liquid ammonia and oxidized in the manner described for compound **21**. After purification by partition chromatography, the uncontaminated L diastereomer was gel filtered on Sephadex G-25 using 0.2 N acetic acid as eluent, and lyophilized to give 40 mg of [1-hemi[β,β-$^2H_2$]cystine]oxytocin (**4a**). It had $[\alpha]^{22}_{547}$ −22.2° (c 0.5, 1 N HOAc). A sample of **4a** was hydrolyzed in 6 N HCl for 24 h at 110 °C. Amino acid analysis gave the following molar ratios: aspartic acid, 1.0; glutamic acid, 1.0; proline, 0.9; glycine, 1.0; half-cystine, 2.0; isoleucine, 1.0; leucine, 1.0; tyrosine, 1.0. Development on TLC in systems A, B, and C gave single, uniform spots identical with those of the protio analogue. Milk-ejecting activity was identical with that of authentic oxytocin within experimental error.

A sample of [1-hemi-D-[β,β-$^2H_2$]cystine]oxytocin had $[\alpha]^{22}_{547}$ −68.9° (c 0.5, 1 N HOAc) [lit.[32] $[\alpha]^{20}D$ −56° (c 0.5, 1 N HOAc)]. Amino acid analysis following hydrolysis for 24 h at 110 °C in 6 N HCl gave the following molar ratios: aspartic acid, 1.0; glutamic acid, 1.0; proline, 1.0; glycine, 1.0; half-cystine, 2.0; isoleucine, 1.0; leucine, 1.0; tyrosine, 0.9. Development on TLC in systems A, B, and C gave single, uniform spots identical with those of the protio analogue. Milk-ejecting activity was ca. 38.6 units/mg.

[1-Hemi-DL-[α,β,β-$^2H_3$]cystine]oxytocin (5) and Separation of the Diastereomers. The same process described for the preparation of **4** was repeated, substituting **18** for **16**. There was obtained 4.87 g of nonapeptide-resin which after ammonolysis, extraction, and precipitation gave 1.24 g of the protected nonapeptide amide, mp 227–228 °C. Anal. Calcd for $C_{66}H_{87}D_3N_{12}O_{12}S_2 \cdot 2H_2O$: C, 58.86; H, 7.26; N, 12.48. Found: C, 58.82; H, 6.86; N, 12.49. A 325-mg sample was deprotected and oxidized as described for compound **21**. After the usual chromatographic purifications, there was obtained 77.5 mg of [1-hemi-L-[α,β,β-$^2H_3$]cystine]oxytocin (**5a**) and 72.2 mg of [1-hemi-D-[α,β,β-$^2H_3$]cystine]oxytocin (**5b**). Compound **5a** had $[\alpha]^{22}_{547}$ −24.5° (c 0.5, 1 N HOAc). A sample of **5a** was hydrolyzed in 6 N HCl for 24 h at 110 °C. Amino acid analysis gave the following molar ratios: aspartic acid, 1.0; glutamic acid, 1.1; proline, 1.0; glycine, 1.1; half-cystine, 2.0; isoleucine, 1.0; leucine, 1.0; tyrosine, 0.88. On TLC, **5a** gave single, uniform spots in systems A, B, and C. Milk-ejection activity was identical with that of authentic oxytocin within experimental error.

Compound **5b** had $[\alpha]^{22}_{547}$ −68.4° (c 0.5, 1 N HOAc). Amino acid analysis gave the following molar ratios: aspartic acid, 1.0; glutamic acid, 1.0; proline, 1.1; glycine, 1.0; half-cystine, 1.9; isoleucine, 0.9; leucine, 1.0; tyrosine, 1.0. Milk-ejecting activity was ca. 32.6 units/mg.

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Registry No.—**2**, 57866-58-7; **3**, 57866-59-8; **3a**, 57866-60-1; **3b**, 57866-61-2; **4**, 57866-62-3; **4a**, 57866-63-4; **4b**, 57866-64-5; **5**, 51548-05-1; **5a**, 51493-96-0; **5b**, 51548-06-2; **6**, 57866-70-3; **6a**, 57866-71-4; **7**, 57866-72-5; **7a**, 57866-73-6; **8**, 51494-04-3; **9**, 22117-87-9; **10**, 57866-74-7; **11**, 3970-13-6; **13**, 57866-75-8; **14**, 22117-86-8; **15**, 57866-76-9; **16**, 57866-77-0; **17**, 57866-78-1; **18**, 51493-98-2; **19** resin free, 32991-17-6; **21**, 57866-68-9; **22** resin free, 57866-69-0; diethyl α-acetamidomalonate, 1068-90-2; *N*-acetyl-*S*-benzyl-DL-[α-$^2H_1$]cysteine, 57866-79-2; *N*-acetyl-*S*-benzyl-D-[α-$^2H_1$]cysteine, 57866-80-5.

References and Notes

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(2) All amino acics except glycine are of the L configuration, unless otherwise noted. Standard abbreviations for amino acids, protecting groups, and peptides as recommended by the IUPAC-IUB Commission on Biochemical Nomenclature [*J. Biol. Chem.*, **247**, 977 (1972)] are used. Other abbreviations include DCC, dicylohexylcarbodiimide; DIEA, diisopropylethylamine; TFA, trifluoroacetic acid; DMB, 3,4-dimethylbenzyl.
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Carbon-13 Nuclear Magnetic Resonance Spectra of the Streptovaricins and Related Compounds[1,2]

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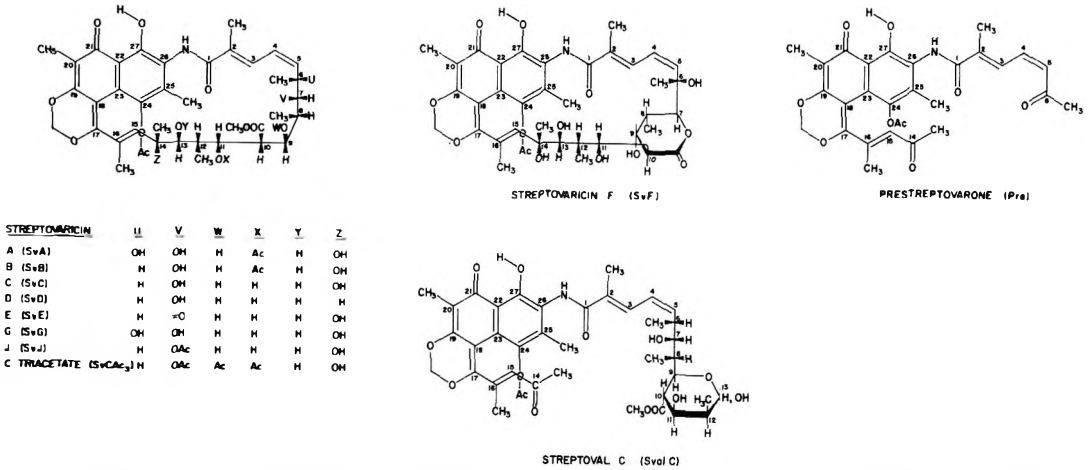
Absorptions of the 40 carbon atoms of streptovaricin C have been assigned in the carbon magnetic resonance spectrum of that ansamycin antibiotic. Carbon absorptions of other streptovaricins, including streptovaricin D, whose biosynthesis has recently been studied, have also been assigned. Methods employed in assigning the individual carbons include off-resonance decoupling, specific proton decoupling, and comparison of the streptovaricins' spectra with spectra of one another, of compounds derived from the streptovaricins, and of model compounds.

During the course of our extensive studies of the chemistry and biochemistry of the streptovaricins,[1,3] members of the ansamycin class of antibiotics,[3] it has become necessary to assign the chemical shifts of individual carbon atoms in their carbon magnetic resonance (^{13}C NMR) spectra, both for studying the biosynthesis of streptovaricins[2] and for the characterization of new, related compounds. In the present paper, we report these ^{13}C NMR assignments.

Discussion

Chemical shifts for the carbon atoms of streptovaricins A–E, G, and J (SvA–SvE, SvG, and SvJ, respectively)[4] and for compounds derived from the streptovaricins (all of whose structures are shown in Figure 1) were determined on proton decoupled spectra and are summarized in Table I. Assignments were made by comparison of the spectra with proton off-resonance decoupled spectra, by single-frequency proton decoupling experiments, from standard chemical shift data, and by comparison with chemical shifts of model compounds, as discussed below. The most abundant component of the complex, SvC, was employed as the reference compound for the assignments and the spectra of other compounds were compared with that of SvC. This was especially valuable since SvC occupies a central position in the streptovaricin family (Figure 1). Thus, SvD is 14-deoxy-SvC, SvB is SvC 11-acetate, SvJ is SvC 7-acetate, SvG is 6-hydroxy-SvC, and SvE is 7-oxo-7-deoxy-SvC. Streptovaricin A is SvG 11-acetate and SvF is *O*-demethyl-SvG-7-lactone. The spectrum of SvD is of special significance, since it is the component isolated in our biosynthetic studies employing ^{13}C-labeled precursors.[2]

Carbon atom absorptions were divided initially into the groups shown in Table I according to the number of attached hydrogen atoms (i.e., methyl, methylene, methine, quaternary carbons) by observations of the off-resonance decoupled spectra. Following this, some of the carbons—the methoxy carbon, the quaternary aliphatic C-14, the methylenedioxy carbon, and the quinonoid carbonyl carbon (C-21)[5]—were assigned unambiguously from their off-resonance multiplicities and characteristic chemical shifts[6]



STREPTOVARICIN	U	V	W	X	Y	Z
A (SvA)	OH	OH	H	Ac	H	OH
B (SvB)	H	OH	H	Ac	H	OH
C (SvC)	H	OH	H	H	H	OH
D (SvD)	H	OH	H	H	H	H
E (SvE)	H	=O	H	H	H	OH
G (SvG)	OH	OH	H	H	H	OH
J (SvJ)	H	OAc	H	H	H	OH
C TRIACETATE (SvCAc$_3$)	H	OAc	Ac	Ac	H	OH

Figure 1. Structures of streptovaricins and compounds derived from them. ASvC is atropisostreptovaricin C, in which C-15 and C-16 are *below* the aromatic acetate instead of above it as shown in the figure; SvCH$_2$ is 4,5-dihydrostreptovaricin C; Isopre is $\Delta^{4,5}$-*trans*-prestreptovarone.

as the signals at 51.9, 77.3, 89.7, and 188.5 ppm, respectively, for SvC. The remaining carbons were assigned through the more detailed analyses which follow.

CH_3 Carbons. There are nine methyl carbons attached to other carbon atoms in SvC; these were assigned as follows. The *acetate methyl* carbon of SvC was found at 21.2 ppm and those of the other compounds between 20.9 and 21.3 ppm (see Table I), in agreement with the reported range of acetate methyl carbons (19.6–21.1 ppm).[6]

The 6-methyl, 8-methyl, and 14-methyl carbons were assigned by comparison of the chemical shifts of individual streptovaricins, whose structures are known. Chemical shifts of the methyl carbons of SvC and SvD are nearly identical, except for that at 21.9 ppm[7] in the spectrum of SvC, which appears at 15.1 ppm in the spectrum of SvD. This absorption must be due to the *14-methyl*, since SvD differs from SvC only in its lack of a 14-hydroxyl (compare pentane with 2-pentanol in Figure 2). Next, comparison of

Table I. Carbon Magnetic Resonance Assignments for Streptovaricins and Related Compounds

Carbon Type	No.[d]	δ, ppm[a,b,c] SvA[e]	SvB[e]	SvC	SvD	SvE[e]	SvF	SvG[e]	SvJ	SvCAc$_3$	SvalC	Pre	Isopre	SvCH$_2$	ASvC
$-CH_3$	2-CH_3	13.3*	13.1	13.1	12.9	12.9	13.4*	13.3*	13.2	13.4	13.2	13.3	13.8*	13.3*	13.3*
	6-CH_3	25.0	22.4	22.1*	22.2	18.8	27.8	25.8	22.3*	19.3*	18.7	31.9	28.0	20.2	21.9†
	8-CH_3	19.0†	19.4	15.8	15.7	14.0	16.5	18.8	15.9	18.6*	13.9			14.9	15.6
	12-CH_3	10.8	10.6	10.4	9.1	10.4	12.3	10.4	10.3	10.7	10.6			10.4	11.1
	14-CH_3	23.4†	19.4	21.9*	15.1	22.0	25.1	22.1	21.3*	22.8*	32.3	32.2	32.2	22.2	21.6†
	16-CH_3	12.6	12.4	12.7	12.7	12.6	12.9*	12.5	12.5	12.4	16.9	16.8	16.8	12.8	12.9*
	20-CH_3	7.5	7.4	7.4	7.4	7.4	7.5	7.4	7.4	7.5	7.6	7.6	7.5	7.5	7.4
	25-CH_3	13.6*	13.4	13.9	14.2	13.8	14.1	13.5*	14.1	13.4	13.9	13.9	14.1*	13.5*	14.5
	Acetate	21.3	21.2	21.2	21.3	21.2	21.0	21.3	21.3	20.9	20.8	20.7	20.7	21.3	21.3
		21.3	21.2						21.3	21.0					
										21.3					
										21.3					
$-CH_2-$	C-4													25.5	
	C-5													29.9	
>CH–	C-6		38.1*	41.6	41.9	51.6*			41.6	37.9†	40.9			40.3	41.6
	C-8	36.9	37.9*	38.9†	38.8	45.6	40.7	39.0	38.4	36.9†	38.7*			37.2	39.0
	C-10	46.8	50.6	47.6	47.4	46.4	54.9	46.2	48.8	50.3	49.3			46.6	48.5
	C-12	34.9	36.8	38.7†	38.5*	37.7	30.4	36.8	37.5	35.9†	36.0*			38.9	38.5
	C-14				37.5*										
CH_3O-		52.2	52.2	51.9	51.9	51.8*		52.1	51.8	52.2	52.3			52.0	52.1
>CHO–	C-7	82.1	81.5	82.7	83.6		88.5	83.0	81.9	79.1	77.8			82.0	82.1
	C-9	77.1‡	76.3†	77.6	77.6	73.7	75.8†	77.4	75.1	76.2	71.5†			78.8	77.5
	C-11	75.0#	75.5‡	74.0‡	73.4†	73.7†	75.3†	73.4†	74.4†	73.2‡	69.2†			73.7†	72.1‡
	C-13	71.6#	74.2‡	70.6‡	70.4†	70.4†	71.7†	71.0†	70.7†	72.4‡				70.9†	71.3‡
>CO–	C-6	75.0					78.1	76.4							
	C-14	77.6‡	77.2†	77.3		77.4	77.3	77.4	77.4	77.0				77.4	76.3
$-OCH_2O-$		89.7	89.9	89.7	89.8	89.7	90.9	89.8	89.8	89.8	90.1	89.9	90.0	89.8	90.0
-OCHO–	C-13										97.0				
=CH–	C-3	132.1	132.6	135.0	134.7	134.0	132.1	134.4	134.8	131.8	130.4	135.3	136.8	144.7	134.9
	C-4	124.6	123.6	124.2	124.0	124.8	126.2	124.1	124.5	124.0	124.5	128.9*	134.9		125.6
	C-5	142.4	143.1	143.9	144.1	139.2	140.0	144.7	141.5	140.2	140.4	128.6*	131.9		143.1
	C-15	154.8	152.0	153.9	153.6	154.7	148.7	153.4	154.0	151.5	131.6	131.5	131.6	154.0	149.3
=C<	C-2	130.8	129.3	126.7	127.5‡	127.9	131.2	129.4	127.1	130.3#	130.7	140.2	139.6	127.5	126.1
	C-16	132.1	130.8	130.3	127.9‡	130.0	134.0	131.1	130.4	130.7#	144.2	143.9	144.0	130.9	127.4
	C-17	168.5**	168.9	168.8#	169.0	168.3‡	171.1‡	168.9‡	168.4	168.9	162.6	162.3	162.6	169.1‡	169.1#
	C-18	102.3	102.6	102.0	101.9	102.0	102.6	102.2	102.2	102.6	106.4	106.3	106.3	102.2	101.9
	C-19	159.3	159.6	159.4	159.6	159.5	161.2	159.4	159.7	159.6	159.5	159.2	159.4	159.7	159.6
	C-20	113.4	113.6	113.3	113.4	113.6	114.3	113.7	113.4	113.6	113.0	112.9	113.0	113.6	114.0
	C-22	107.3	107.3	107.2	106.9	107.1	107.5	107.4	107.3	107.3	109.2	109.0	109.1	107.4	107.7
	C-23	125.4	125.4	125.4	125.6	125.5	126.7	126.4	125.4	125.6	125.3	124.8	124.7	126.0	126.4
	C-24	138.3	136.7	136.6	136.9	138.3	137.3	136.5	136.8	136.8	137.4	137.2	137.3	136.7	136.6
	C-25	122.3	122.7	121.7	121.5	121.5	123.1	121.1	122.1	122.5	123.2	123.2	122.9	121.6	122.0
	C-26	135.9	135.9	135.0	134.5	136.6	137.3	136.0	135.1	135.8	135.2	134.9	135.5	135.8	135.1
	C-27	150.5	155.2	153.5	153.1	153.1	156.4	155.2	153.6	155.2	154.5	154.3	154.4	154.4	154.8
-C-	C-1	168.7**	168.9	169.0#	169.4	169.3‡	170.2‡	170.2‡	169.3‡	169.1**	168.5‡	167.7	167.1	170.5	169.3#
O	C-6											198.4	198.1		
	C-7					178.3									
	C-14										199.0	199.0	198.6		
	C-21	188.7	189.0	188.5	188.7	188.5	189.7	188.7	188.8	188.9	189.1	188.9	189.0	188.8	189.0
	-COOMe	173.4	173.9	173.4	173.0	173.1	173.1	173.5	173.7	172.2	174.9			173.6	174.0
	Acetate	169.8	169.8	169.0	169.0	168.8‡	172.7	169.2	169.0‡	169.4**	168.6‡	168.2	168.4	169.3‡	170.6
		171.7	171.8						170.9	170.3					
										170.4					
										171.0					

[a] CD_2Cl_2 solvent, except for SvF (CD_3OD solvent). [b] For abbreviations employed, see note 4. [c] Signals marked *, †, ‡, #, ** may be interchanged in the column where they appear. [d] The numbering system is that shown in Figure 1. [e] Proton off-resonance spectra were obtained for all compounds except these.

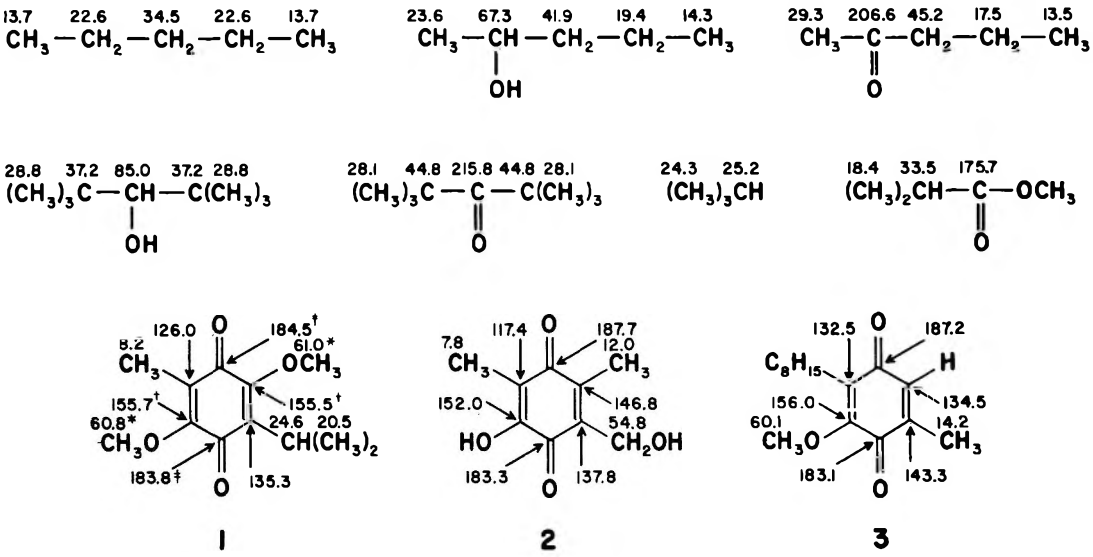


Figure 2. Chemical shifts of carbon atoms in model compounds. Values for pentane, 2-pentanol, 2-pentanone, di-*tert*-butylcarbinol, di-*tert*-butyl ketone, isobutane, and methyl isobutyrate are from ref 6b, values for 3,6-dimethoxythymoquinone (1) from ref 6a, values for shanorellin (2) from ref 10, values for 3-*O*-methylperezone (3) from ref 12.

the spectra of SvC and SvE (which differ only in the keto group at C-7 in SvE) shows that the two methyl carbons at 15.8 and 22.1[7] ppm in the SvC spectrum are shifted upfield to 14.0 and 18.8 ppm in the SvE spectrum; no other methyl carbons are shifted more than 0.3 ppm. These carbons must then be the 6- and 8-methyl carbons (compare di-*tert*-butylcarbinol with di-*tert*-butyl ketone in Figure 2). The signal at 15.8 ppm moves to 19.4 ppm in the spectrum of SvB with its 11-acetate and is thus assigned to the 8-methyl, while the signal at 22.1 ppm shifts only slightly and is assigned to the 6-methyl. Both the 6-methyl (22.1 ppm) and the 8-methyl (15.8 ppm) absorptions are shifted downfield (to 25.8 and 18.8 ppm, respectively) in the spectrum of SvG, reflecting β and δ effects of the 6-hydroxyl group in SvG.

Assignments of the remaining five methyl carbon absorptions can be made by comparing the ^{13}C NMR spectra of SvC and the oxidation products SvalC[4] (obtained from the periodate cleavage of SvC)[1b,8] and Pre[4] (obtained from the 2-mol periodate cleavage of SvA).[9] Comparison of the structures of SvC, SvalC, and Pre indicates that four methyl groups are structurally constant throughout—the acetate methyl, the 2-methyl, the 20-methyl, and the 25-methyl. Indeed, four methyl carbon absorptions do not change among the ^{13}C NMR spectra of SvC, SvalC, and Pre—those at 7.4, 13.1, 13.8, and 21.2 ppm. The last is the acetate methyl; thus the first three are one or another of the 2-, 20-, and 25-methyls. The methyl carbon on the quinone ring in 3,6-dimethoxythymoquinone (1, Figure 2) absorbs at 8.2 ppm[6b] and the corresponding methyl carbon in shanorellin (2) at 7.8 ppm;[10] this allows assignment of the 20-methyl carbon to the signal at 7.4 ppm. On standing, Pre isomerizes about the $\Delta^{4,5}$ double bond (cis → trans).[9] In the spectrum of the resulting isoprestreptovarone (Isopre)[4,11] the methyl signal at 13.3 ppm in the spectrum of Pre has shifted to 14.1 ppm but the methyl signal at 13.9 remains at 13.8 ppm. This allows assignment of the signal at 13.3 in Pre (13.1 in SvC) to the *2-methyl* and the signal at 13.9 in Pre (13.8 in SvC) to the *25-methyl*. It is of some interest that the cis → trans isomerization of the $\Delta^{4,5}$ double bond also shifts the 6-methyl carbon (acetyl methyl) from 31.9 ppm to 28.0 ppm, confirming the assignment of the 6-methyl in Pre.

The foregoing discussion has assigned all of the methyl carbon signals of SvC except those due to the 12- and 16-methyls, which must give the signals at 10.4 and 12.7 ppm. The ^{13}C NMR spectrum of SvalC contains a signal at 10.6 ppm but none near 12.7 ppm. This implies that the *16-methyl* appears at 12.7 and the *12-methyl* at 10.4 ppm in the SvC spectrum, since the carbons which are expected to shift most in SvalC vs. SvC are the 16-methyl and 14-methyl carbons. To locate the 16-methyl in the SvalC spectrum we note that the carbons which remain structurally the same in SvalC and Pre (in addition to the acetate, 2-, 20-, and 25-methyl carbons discussed in the preceding paragraph) are the 14-methyl and 16-methyl carbons, which are found at 16.9 and 32.3 ppm. Since the latter must be due to the acetyl methyl (14-methyl, see mesityl oxide in Figure 2), the 16-methyl has shifted in SvalC to 16.9 from 12.7 ppm in SvC. The assignment of the 12-methyl to the signal at 10.4 ppm is confirmed by its disappearance in the spectrum of Pre. It may be noted finally that the shift of the absorption at 21.9 ppm[7] in the SvC spectrum to 32.3 ppm in that of SvalC confirms the assignment of the 14-methyl carbon as the 21.9-ppm signal.

>CH– Carbons. There are four methine groups without oxygen substitution in SvC. The chemical shifts of these carbons can be assigned by comparison of the spectra of SvC, SvD, SvE, and SvG. First, a signal observed at 41.6 ppm in SvC is missing from the spectrum of SvG and must be assigned to the *C-6* carbon, which is substituted by hydrogen in SvC but by oxygen in SvG. This assignment is confirmed by the downfield shift of the 41.6-ppm signal to 51.6 ppm in SvE, where C-6 is deshielded by the carbonyl group at C-7 (compare di-*tert*-butylcarbinol and di-*tert*-butyl ketone in Figure 2). A second methine carbon signal of SvC, that at 38.9 ppm, is also shifted downfield in the spectrum of SvE, to 45.6 ppm. The signal at 38.9 ppm can then be assigned to *C-8*. Of the two remaining methine carbon signals (38.7 and 47.6 ppm) that at lower field (47.6) can be assigned to *C-10*, since that carbon is attached to a deshielding carbomethoxy group (compare isobutane and methyl isobutyrate in Figure 1). Consequently, the remaining methine carbon of SvC, *C-12*, is assigned the signal at 38.7 ppm. Streptovaricin D has one methine carbon more than SvC, *C-14;* this can be assigned to the signal at 37.5 ppm if one assumes that the signal at 38.5 ppm in the spectrum of SvD corresponds to the signal at 38.7 ppm (C-12) in the SvC spectrum. However, the absorption of the C-12 carbon is at somewhat lower field in SvC than in other

streptovaricins, being at 37.7 ppm in SvE, at 37.7 ppm in SvJ, and at 36.8 ppm in SvG. Thus, the C-14 carbon in SvD can only be assigned tentatively to the 37.5-ppm signal and the C-12 carbon to that at 38.5 ppm.

>CHO– Carbons. There are four methine carbons in SvC bearing hydroxyl substituents; these were assigned by comparison of spectra of streptovaricins SvC, SvE, SvJ, and $SvCAc_3$.

The signal of SvC at 82.7 ppm can be assigned to *C-7*, since it is missing in the spectrum of SvE, which has a 7-keto group. Moreover, the SvC signal at 77.6 has shifted in the spectrum of SvE to 73.7 ppm and can be assigned to *C-9*, reflecting the β effect[6] of the carbonyl group of SvE (compare 2-pentanol with 2-pentanone in Figure 2).

The effect of acetylation on the carbinol carbons' chemical shifts is rather unpredictable and appears to depend on conformational changes as much as electronegativity. Nevertheless, C-7 shifts upfield on acetylation of SvC to SvJ (from 82.7 to 81.9 ppm) and C-7 and C-9 both shift upfield on acetylation of SvC to $SvCAc_3$ (from 82.7 to 79.1 and from 77.6 to 76.2, respectively). The third signal of SvC which shifts upfield on acetylation of SvC to $SvCAc_3$ is that at 74.0 ppm which gives either the 73.2 or 72.4 ppm signal of $SvCAc_3$. Thus *C-11* is assigned tentatively the SvC signal at 74.0 and *C-13* the SvC signal at 70.6 ppm.

=CH Carbons. There are four olefinic methine carbons in the streptovaricins—C-3, C-4, C-5, and C-15. Single proton decoupling of SvD assigned the first two. Irradiation of the SvD proton at 7.66 ppm (H-3) collapsed completely the ^{13}C NMR doublet at 134.7 ppm and partially collapsed the doublet at 124.0 ppm (due to overlap of the irradiating frequency with the H-4 frequency at 6.48 ppm in the ^1H NMR spectrum) but had essentially no effect on the ^{13}C NMR doublets at 144.1 and 153.6 ppm. Therefore, *C-3* and *C-4* of SvD are assigned to the signals at 134.7 and 124.0 ppm (135.0 and 124.2 ppm for SvC), respectively. Assignment of *C-15* was made by observing that the SvC signal at 153.9 ppm has shifted dramatically upfield in its oxidation product SvalC, to 131.6 ppm. That C-15 appears at 131.6 ppm in the latter compound follows from its appearance at the same position (131.5) in the spectrum of Pre. The fourth olefinic methine carbon of SvC (*C-5*) can then be assigned the absorption at 143.9 ppm by difference. The assignments are confirmed by the ^{13}C NMR spectrum of 4,5-dihydrostreptovaricin C ($SvCH_2$),[4] which retains the olefinic carbon absorption of C-15 at 154.0 ppm, which has lost the olefinic carbon absorptions for C-4 and C-5 (124.0 and 143.9 ppm), and which shows a shift of C-3 to 144.7 ppm (from 134.7 ppm in SvC). Additional confirmation of the C-15 assignment is found in the considerable shift of the C-15 absorption in the spectrum of atropisostreptovaricin C (ASvC)[1b,4] to 149.3 ppm. Atropisostreptovaricin C differs from SvC only in the absolute configuration of the helicity (P in the natural compound, M in its atropisomer) caused by steric compression of the enol acetate and $\Delta^{15,16}$ alkene groups. Thus, the spectra of ASvC and SvC should differ most in the region of steric compression. In these spectra (Table I) the acetate carbonyl carbon differs by 1.6 ppm, C-15 by 3.4 ppm (as noted above), and C-16 by 2.9 ppm (as we shall see below).

=C< Carbons. There are 12 quaternary olefinic or aromatic carbons in the streptovaricins. These quaternary sp^2 carbons can be divided further into two groups—those whose chemical environment should remain constant in the conversion SvC → SvalC (seven carbons, C-22–C-27 plus C-2) and those which should shift in that conversion (five carbons, C-16–C-20).

Instead of five, there are only four quaternary carbon peaks whose chemical shifts differ considerably (by ≥4 ppm) between the spectra of SvC and SvalC. These carbons are at 102.0, 126.7, 130.3, and 168.8 ppm in the spectrum of SvC and respectively at 106.4, 130.7, 144.2, and 162.6 ppm in the spectrum of SvalC.

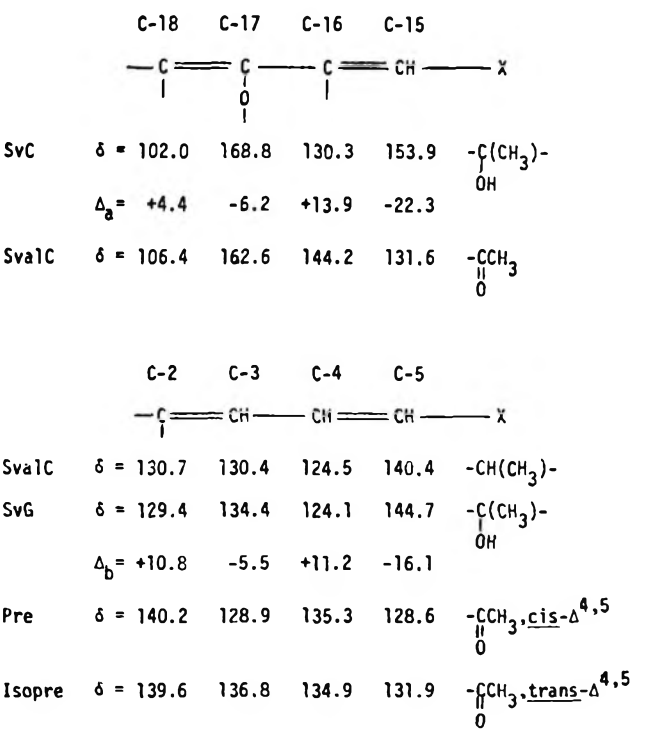


Figure 3. Changes in chemical shifts (ppm) of diene carbons on conversion of dienol to dienone systems; $\Delta_a = \delta_{SvC} - \delta_{SvalC}$, $\Delta_b = \delta_{Pre} - \delta_{SvG}$.

The carbons α and γ to the new carbonyl group at C-14 should shift upfield.[6] We already saw that the α carbon, the methine C-15, shifted upfield from 153.9 to 131.6 ppm. The *C-17* carbon is then assigned to the signal at 168.8 ppm since it shifts upfield to 162.6 on conversion of C-14 to a carbonyl group (γ effect). This assignment is in good agreement with the character of C-17, which is an enol ether and γ to the quinone carbonyl. The carbons β and δ to the new carbonyl group should shift downfield, the β carbon much more than the δ (compare allyl alcohol with acrolein in Figure 2). The carbon showing the greatest downfield shift in the SvC → SvalC conversion is that at 130.3 ppm in SvC, which moves to 144.2 ppm in SvalC; it is therefore assigned from the β effect as *C-16*. This agrees with the observation above that the signal at 130.3 ppm in SvC (C-16) is one of the two which shift most in the spectrum of ASvC due to steric compression of C-15 and C-16 by the aromatic acetate. The signal at 102.0 ppm, which shifts downfield to 106.4 ppm (δ effect), is assigned to *C-18*. The chemical shift (102.0 ppm) is appropriately upfield for the β carbon of an enol ether.[6] The fourth quaternary carbon which shifts ≥4 ppm in the SvC → SvalC conversion absorbs at 126.7 ppm in the SvC spectrum (130.7 ppm in the SvalC spectrum), a position inappropriate for a β carbon of an enol ether. The changes in C-15–C-18 are summarized in Figure 3.

As seen in Table I and Figure 3, a qualitatively similar, though quantitatively different, pattern is seen for the olefinic carbons near C-6 on conversion of C-6 from a carbinol carbon (SvG) to a carbonyl carbon (Pre and Isopre). Assignments of C-2 to C-5 in Pre were made by comparison of its chemical shifts to those of Isopre. From comparison of the spectra of SvalC (or SvG) and Pre it is clear that the signal at 130.7 ppm in the spectrum of SvalC (at 129.4 ppm in that of SvG) has moved downfield to 140.2 ppm in the spectrum of Pre. This must be the same quaternary carbon

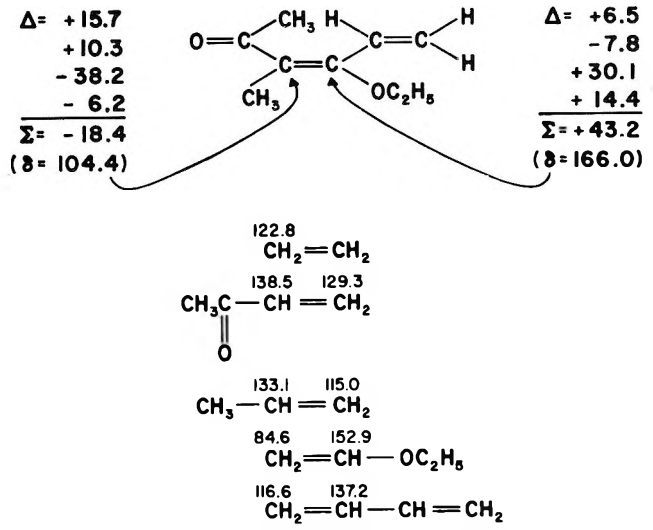


Figure 4. Calculated chemical shifts for the olefinic carbons of a model compound substituted like C-19 and C-20 of SvC. The substituent effects (Δ) at each olefinic carbon are listed in the order acetyl, methyl, ethoxyl, vinyl. The chemical shifts (δ) for the olefinic carbons are calculated as δ = 122.8 ($\delta_{C_2H_4}$) + Σ. Chemical shifts of model compounds are shown at the bottom.

(C-2) as that giving the signal at 126.7 ppm in the spectrum of SvC. Its shift in SvalC to 130.7 must then be due to greater chromophore coplanarity in SvalC, where the constraining *ansa* bridge has been cleaved.

The other two carbons of the C-15–C-20 group (C-19 and C-20) were located by application of the substituent effects calculated in Figure 4. Starting with ethene, the effects of carbonyl group, methyl, alkoxy, and vinyl substituents can be estimated from methyl vinyl ketone, propene, ethyl vinyl ether, and butadiene, as shown, with the α carbon (C-20) being that attached to the carbonyl group (C-21). From these calculations *C-19* (β carbon) would be estimated to appear near 166.0 ppm (122.8 + 43.2) and C-20 (α carbon) near 104.4 ppm (122.8 − 18.4). Of the signals heretofore unassigned, only that at 159.4 ppm can be considered for C-19, since that at 168.8 ppm has already been assigned to C-17 and those at 169.0 and 173.4 ppm are reserved for carbonyl carbons (see below). The signals at 107.2 and 113.3 ppm can then be considered for C-20. The signal at 113.3 ppm is slightly split in the off-resonance proton decoupled spectrum and this can be attributed to long-range coupling with a methyl group, which allows the 113.3-ppm signal to be assigned to C-20.

The six peaks which remain unassigned in the spectrum of SvC are those at 107.2, 121.7, 125.4, 135.0, 136.6, and 153.5 ppm. From simple chemical shift considerations the last three signals (but not the first three) should be due to carbons bearing oxygen or nitrogen (C-24, C-26, C-27). For example, C-1 of phenol is found at 155.6, C-1 of phenyl acetate at 151.7 and C-1 of acetanilide at 139.8 ppm.[6] On this simple basis *C-24* should give the signal at 136.6, *C-26* that at 135.0, and *C-27* that at 153.5. Of course, the chemical shift of an aromatic carbon is not determined solely by its own substituent, but by the other substituents on the ring as well. Rough chemical shifts can be calculated for the carbons of the model compound in Figure 5, based on the downfield (+) or upfield (−) shifts introduced by the six substituents shown[6] and benzene's absorption at 128.7 ppm. Although the predictions are quantitatively different, the predicted order of C-24, C-26, and C-27 is the same. In addition, the model (Figure 5) suggests the order of the final three carbons: it indicates that *C-22* should give the signal at 107.2 but cannot distinguish between C-23 and C-25 (121.7 and 125.4 ppm). Like the signal at 113.3 ppm (C-20) that at 121.7 ppm is slightly split in the proton off-resonance spectrum owing to long-range coupling to the hydrogens of an attached methyl group. Similar long-range coupling with C-20 and C-25 was observed in off-resonance decoupled spectra of SvJ, ASvC, $SvCAc_3$, and $SvCH_2$. Thus, the signal at 121.7 ppm is assigned to the methyl-bearing *C-25*, leaving the signal at 125.4 ppm for *C-23*. In connection with the latter assignment it is of some interest that the signals for both C-22 and C-23 shift downfield somewhat, by 2.0 and 1.5 ppm, respectively, in the conversion SvC → SvalC.

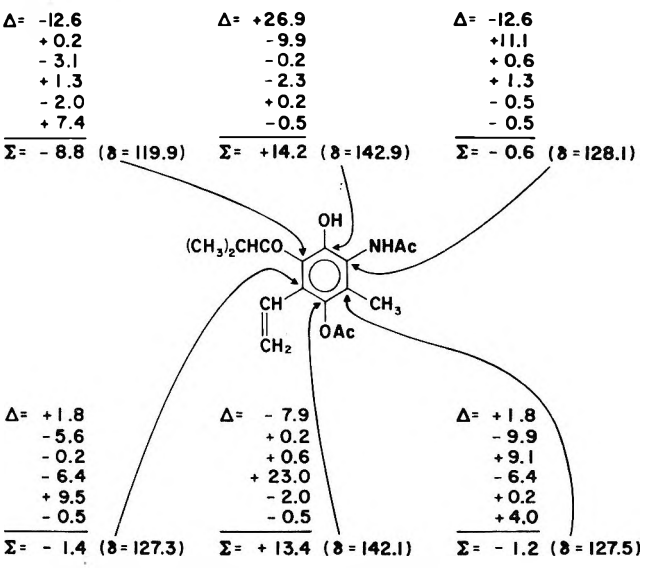


Figure 5. Calculated chemical shifts for a model aromatic compound substituted like SvC. The substituent effects (Δ) at each carbon are listed in the order hydroxyl, acetamido, methyl, acetoxyl, vinyl, isobutyryl. The chemical shifts (δ) for individual carbons are calculated as δ = 128.7 ($\delta_{C_6H_6}$) + Σ.

>C=O Carbons. The carbonyl signals were assigned by comparison of the chemical shifts observed to those of model compounds. Thus, the quinone methide carbonyl carbon, *C-21*, was assigned to the signal at 188.7 ppm, since the quinones **1–3** (Figure 2) absorb in this region.[6b,10,12] The *carbomethoxy carbonyl* carbon was found at 173.3 ppm (methyl isobutyrate, 175.7 ppm),[6b] the amide carbonyl carbon (*C-1*) at 169.0 ppm (acetanilide, 169.5 ppm),[6a] and the phenolic acetate carbonyl carbon at 169.0 ppm (isopropenyl acetate, 168.9 ppm)[6c] in SvC.

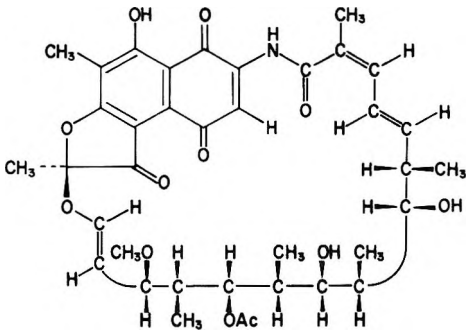
Chemical Shifts of Other Streptovaricins. The assignments of carbon absorptions of other streptovaricins were made by comparison of their signals with those of SvC (Table I). Some carbons shift almost none (≤1 ppm), in particular, $-OCH_2O-$, $-COOCH_3$, $-OCOCH_3$, C-1.[13] The chemical shifts for C-17–C-23 of other streptovaricins are all within 1.0 ppm of those for SvC, while those for C-2–C-5, C-15, C-16, and C-24–C-27 differ by more, but still less than 4 ppm, as shown in Table I. Similarly, the methyl carbons on C-2, C-16, C-20, and C-25 show essentially the same chemical shifts for all streptovaricins. Absorptions of other methyl carbons (those on C-6, C-8, C-12, C-14) of the ansa chain differ, however, for individual streptovaricins, mainly owing to the introduction of hydroxyl groups (SvD → SvC, SvB, SvJ → SvG, SvA); introduction of acetates (SvC → SvB → $SvCAc_3$ and SvG → SvA) has only a small effect. These methyl shifts depend mainly on the electronegativity of the attached carbons. Thus, the C-14 methyl moves upfield to 15.1 ppm in SvD (21.9 ppm in SvC) and the C-12 methyl to 9.1 ppm (10.4 ppm in SvC) owing to replacement of the C-14 hydroxyl of SvC by a hydrogen in

SvD. Similarly, the C-6 methyl is found at 22.1 ppm in SvC, but at 25.8 ppm in SvG and 25.0 ppm in SvA, and the C-8 methyl, which appears at 15.8 ppm in SvD, is also shifted downfield, to 19.0 and 18.8 ppm in SvA and SvG, respectively. All of the methyl groups are assigned, then, as shown in Table I.

Chemical shifts of the methyl-substituted methine carbons (C-6, C-8, C-10, and C-12) remain relatively constant (±1.4 ppm) for streptovaricins C, D, and J. Those carbons tend to shift together for streptovaricins with acetate groups at C-11 (SvA, SvB, $SvCAc_3$), C-6, and C-10 moving downfield by about 3 ppm, C-8 remaining constant, and C-12 moving upfield by 2–4 ppm. C-10 and C-12 of SvE remain constant but C-6 and C-8 move sharply downfield (7–10 ppm).

Methine carbons with oxygen substitution (C-7, C-9, C-11, C-13) have nearly the same chemical shift (±1.5 ppm) for all streptovaricins except SvE and SvJ, which differ by ca. 3 ppm for C-9. These assignments are again based on those of SvC as shown in Table I.

Comparison of ^{13}C NMR Spectra of the Streptovaricins and Rifamycin S.[14] The ^{13}C NMR spectrum of rifamycin S (**4**), one of the naturally occurring rifamycins,[14]



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has been assigned (and reassigned) in recent publications.[14] Since there is general structural similarity between the rifamycins and the streptovaricins, it is of interest to compare their chemical shifts. However, the rifamycins and the streptovaricins differ in a number of ways including the aromatic nuclei, an oxygen in the *ansa* chain of the rifamycins, the methylenedioxy bridge in the streptovaricins, and some stereochemical features, and it may not be meaningful to compare ^{13}C NMR spectra of these ansamycins in detail. Nevertheless, there are very similar chemical shifts for many carbons, including the dienamide carbons in spite of different stereochemistry ($\Delta^{2,3}$-trans, $\Delta^{4,5}$-cis double bonds in streptovaricins and $\Delta^{2,3}$-cis, $\Delta^{4,5}$-trans double bonds in rifamycin S); C-3, C-4, and C-5 are observed at 135.0, 124.2, and 143.9 ppm in SvC and at 133.8, 124.0, and 142.1 ppm in rifamycin S, respectively.

Experimental Section[15]

Carbon magnetic resonance spectra were recorded by the Fourier transform technique on a Varian XL-100 spectrometer coupled to a Digilab computer. Solvent was deuterated methylene chloride, except as noted, and this was also used as deuterium lock. Chemical shifts (δ) are reported as parts per million from tetramethylsilane as internal standard.

Streptovaricin A (SvA), purified by chromatography as described earlier,[16] was crystallized from dioxane–benzene–ether to yield deep orange needles, mp 200–203 °C (lit.[16] 200–201 °C).

Streptovaricin B (SvB), purified by chromatography as described earlier,[16] was crystallized twice from acetone–ether to remove small quantities of SvC, giving pure SvB, mp 186–189 °C (lit.[16] 187–189 °C).

Streptovaricins C, D, E, and G (SvC, SvD, SvE, SvG). The main fraction (fraction 2,[16] 108.01 g) obtained by *n*-hexane precipitation of a dioxane solution of streptovaricin complex (Upjohn 11560-3) was separated by development chromatography on 4000 g of silica gel (Brinkmann, deactivated with 10% H_2O) employing benzene–acetone (7:3) as solvent. After development was completed, the column was cut into appropriate fractions which were extracted to give 4.69 g of crude SvE, 4.41 g of crude SvD, 44.80 g of a mixture of SvC and SvG, and 10.60 g of a mixture of SvC, SvG, and SvA. A portion (12.01 g) of the mixture of SvC and SvG was further chromatographed on 1000 g of silica gel (Brinkmann) by elution of a column 60 × 770 mm with chloroform–methanol (98:2) to give 2.40 g of pure SvC, mp 187–190 °C (lit.[16] 189–191 °C), and 4.60 g of impure SvG which was rechromatographed over 600 g of silica gel (Brinkmann) in a column 50 × 900 mm employing benzene–acetone (4:1) as eluent. Appropriate fractions were combined, concentrated under reduced pressure, and precipitated by *n*-hexane addition to give 1.55 g of pure SvG, mp 194–196 °C (lit.[16] 190–192 °C).

A portion (4.00 g) of the SvD fraction obtained from the development chromatography column above was purified by successive chromatography over 400 g of silica gel (Brinkmann) in a column 50 × 490 mm employing benzene–acetone (9:1) as eluting solvent, over 120 g of silica gel (Brinkmann) in a column 28 × 400 mm employing chloroform–methanol (98.2) as solvent, and over 100 g of Bio-Sil A silicic acid (Bio-Rad Laboratories) in a column 28 × 350 mm employing hexane–acetone (2:1) as eluent to give 0.69 g of pure SvD, mp 183–186 °C (lit.[16] 172–175 °C).

A portion (1.68 g) of the SvE fraction obtained from the development chromatography column above was purified on 230 g of silica gel (Brinkmann) in a column 37 × 400 mm eluted with benzene–acetone (9:1). Crystallization of the SvE isolated, from 1-chlorobutane, gave 0.30 g of crystals, mp 199–202 °C (lit.[16] 198–202 °C).

Streptovaricin F (SvF). Crude streptovaricin F (12.40 g), obtained from streptovaricin line product (Upjohn 11560-3) by elution column chromatography on silica gel,[16] was further purified over 500 g of silica gel (Brinkmann) in a column 50 × 920 mm employing chloroform–methanol (93:7) as solvent. Appropriate fractions were combined and crystallized from ethyl acetate to give 400 mg of needles, which was recrystallized from the same solvent to yield 330 mg of pure SvF, mp 215–217 °C (lit.[16] 222–224 °C).

Streptovaricin J (SvJ). A sample of crude streptovaricin J[16] (3.17 g, Upjohn 10-666-JWS-36C) was purified on 200 g of silica gel (Brinkmann) in a column 40 × 500 mm employing chloroform–methanol (98:2) as eluent. Appropriate fractions were combined and evaporated to dryness under reduced pressure to give 1.80 g of pure SvJ, mp 176–180 °C (lit.[16] 177–180 °C).

Streptovaricin C triacetate ($SvCAc_3$) was prepared as described previously[16] and purified by chromatography over Bio-Sil A silicic acid employing chloroform–methanol (98:2) as eluent, followed by crystallization from methylene chloride–ether, mp 228–229 °C (lit.[16] 228.5–229.5 °C).

Streptoval C (SvalC). A mixture of 5.00 g of streptovaricin C (Upjohn 7623-WMH-59-1), 2 g of sodium metaperiodate, 300 ml of ethanol, and 40 ml of water was stirred at room temperature in a flask wrapped with aluminum foil. The reaction was followed by TLC on silica gel (Eastman Chromagram) employing chloroform–methanol (98:2) as solvent. An additional 24 g of sodium metaperiodate in 29 ml of water was added during 7 h. After reaction was complete, insoluble inorganic material was removed by filtration and the filtrate was concentrated at reduced pressure to remove ethanol. The residual aqueous suspension was extracted three times with 300-ml portions of ethyl acetate and the combined extract was dried over anhydrous sodium sulfate. The deep red residue was chromatographed on 450 g of silica gel (Brinkmann) in a column 45 × 600 mm employing chloroform–methanol (97:3) as solvent to give 0.71 g (14%) of recovered SvC and 3.76 g (75%) of SvalC, mp 140–143 °C.

Anal. Calcd for $C_{40}H_{49}NO_{14}$: C, 62.57; H, 6.43; N, 1.82; mol wt, 767. Found: C, 62.22; H, 6.59; N, 1.47; mol wt, 767 (mass spectrum).

Prestreptovarone (Pre). A mixture of 413 mg of streptovaricin A, 2.0 g of sodium metaperiodate, 50 ml of ethanol, and 30 ml of water was stirred at room temperature in a flask wrapped with aluminum foil. After 1.5 h, the mixture was filtered, most of the ethanol was removed from the filtrate in vacuo, and the resulting suspension was diluted with 50 ml of water and extracted three times with 50-ml portions of ethyl acetate. The extracts were combined and dried over anhydrous magnesium sulfate. The reddish-orange residue was chromatographed over 60 g of silica gel (Brinkmann) using chloroform–methanol (97:3) as eluent to give orange-red

prestreptovarone (Pre), which was crystallized from ethyl acetate to give 176 mg (84%) of Pre, mp 182.5–183.5 °C (lit.[11] 194–197 °C).

Anal. Calcd for $C_{29}H_{29}NO_9$: C, 65.03; H, 5.46; N, 2.62. Found: C, 64.01; H, 5.54; N, 2.28.

$\Delta^{4,5}$-*trans*-Prestreptovarone (Isopre). Prestreptovarone isomerized[3,9] on standing at room temperature in deuteriomethylene chloride solution for 26 days to give $\Delta^{4,5}$-*trans*-prestreptovarone (Isopre), whose proton NMR spectrum was identical with that of an authentic sample.[9] Isopre was used for ^{13}C NMR determination without isolation.

Atropisostreptovaricin C (ASvC). Streptovaricin C (2.35 g) was heated in 50 ml of refluxing acetonitrile for 5 h while the reaction was followed by TLC on Uniplate silica gel GF (Analtech, Inc.) using chloroform–methanol (97:3). The solution was concentrated in vacuo and the residue was chromatographed on 300 g of Bio-Sil A silicic acid in a column 40 × 600 mm employing chloroform–methanol (98:2) as eluent, with all fractions examined by TLC as above. Appropriate fractions were combined and evaporated to dryness under reduced pressure to provide 2.05 g (87%) of recovered SvC and 0.229 g (10%) of ASvC, mp 188–193 °C (lit.[1b] 188–193 °C).

4,5-Dihydrostreptovaricin C ($SvCH_2$) and 2,3,4,5-Tetrahydrostreptovaricin C. When streptovaricin C (5.0 g, Upjohn 7623-WMH-59-1) was hydrogenated over 1 g of 5% palladium–charcoal in 250 ml of ethanol, ca. 315 ml of hydrogen was absorbed during 5 h. The solution was filtered to remove catalyst, the filtrate was evaporated to dryness under reduced pressure, and the residue was chromatographed on 400 g of silica gel (Brinkmann) in a column 50 × 600 mm employing chloroform–methanol (98:2) as eluent to afford 0.50 g (10%) of 4,5-dihydrostreptovaricin C ($SvCH_2$), an amorphous powder, mp 163–165 °C, $[\alpha]^{25}D$ +637° (*c* 0.16, $CHCl_3$). In the ^1H NMR spectrum one of the olefinic protons (H-3) of SvC was shifted to 6.93 ppm (t, J = 6 Hz), while the olefinic proton absorptions of SvC[9] for H-4 and H-5 were absent.

Anal. Calcd for $C_{40}H_{53}NO_{14}$: C, 62.24; H, 6.92; N, 1.81; mol wt, 771. Found: C, 61.66; H, 7.26; N, 1.81; mol wt, 771 (mass spectrum).

Continued elution of the column gave 1.20 g (24%) of a mixture of $SvCH_2$ and 2,3,4,5-tetrahydrostreptovaricin C, an amorphous powder, mp 175–179 °C. The ^1H NMR spectrum contained no olefinic absorption for H-3, H-4, or H-5.

Anal. Calcd for $C_{40}H_{55}NO_{14}$: C, 62.08; H 7.16; N, 1.81; mol wt, 773. Found: C, 61.26; H, 7.16; N, 1.64; mol wt, 773 (mass spectrum).

Acknowledgment. This work was supported by Contract NIH-NCI-C-72-3208 from the Division of Cancer Treatment, National Cancer Institute, and by Research Grant AI 01278 from the National Institute of Allergy and Infectious Diseases. The ^{13}C NMR spectrometer was purchased with an instrumentation grant from the National Science Foundation.

Registry No.—SvA, 23344-16-3; SvB, 11031-82-6; SvC, 23344-17-4; SvD, 32164-26-4; SvE, 35413-63-9; SvF, 35512-37-9; SvG, 11031-85-9; SvJ, 52275-61-3; $SvCAc_3$, 54955-22-5; SvalC, 54955-14-5; Pre, 58074-37-6; Isopre, 58117-89-8; ASvC, 54984-97-3; $SvCH_2$, 58150-57-5; $SvCH_4$, 58074-38-7.

References and Notes

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(4) Abbreviations: SvA = streptovaricin A; SvB = streptovaricin B; SvC = streptovaricin C, SvD = streptovaricin D; SvE = streptovaricin E; SvG = streptovaricin G; SvJ = streptovaricin J; $SvCAc_3$ = streptovaricin C triacetate; SvalC = streptoval C; Pre = prestreptovarone; Isopre = $\Delta^{4,5}$-*trans*-prestreptovarone; $SvCH_2$ = 4,5-dihydrostreptovaricin C; ASvC = atropisostreptovaricin C.
(5) As well as the anomeric carbon of SvalC at 97.0 ppm.
(6) (a) L. F. Johnson and W. C. Jankowski, "Carbon-13 NMR Spectra", Wiley-Interscience, New York, N.Y., 1972; (b) J. B. Stothers, "Carbon-13 NMR Spectroscopy", Academic Press, New York, N.Y., 1972; (c) G. C. Levy and G. L. Nelson, "Carbon-13 Nuclear Magnetic Resonance for Organic Chemists", Wiley-Interscience, New York, N.Y., 1972.
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Proton Magnetic Resonance Study on Solubilization by Micellar Alkylammonium Propionates in Carbon Tetrachloride

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Solubilization of imidazole, methanol, 2-methyl-3-butyn-2-ol, *N*-methylimidazole, and pyrazole by micellar butylammonium propionate (BAP), hexylammonium propionate (HAP), octylammonium propionate (OAP), and dodecylammonium propionate (DAP) in carbon tetrachloride was studied using proton magnetic resonance spectroscopy. Association constants (K) for the substrate–micelle complexes were calculated from chemical shift data. The association constants depend on the substrate structure and the number of carbon atoms (X) in the alkylammonium ion. For example, in case of association with DAP, imidazole binds more strongly than *N*-methylimidazole (K = 65.3 ± 1.2, 28.8 ± 1.1 M^{-1}, respectively) and 2-methyl-3-butyn-2-ol binds more strongly than methanol (K = 51.8 ± 4.0, 39.0 ± 3.4 M^{-1}, respectively). For most of the solubilizates the association increases in going from BAP to OAP then decreases for DAP. For example, K for imidazole increases from 62.7 ± 1.8 to 105.8 ± 3.2 then decreases to 65.0 ± 1.2 M^{-1} and for *N*-methylimidazole the corresponding K values increase from 32.2 ± 0.4 to 46.3 ± 3.0 then decrease to 28.8 ± 1.2 M^{-1}, respectively.

Catalysis by micellar systems has received much attention during the past few years.[1–3] Micellar catalysis, both in water and in nonaqueous solvents, has been rationalized in terms of favorable substrate partitioning in the micellar pseudophase (or at its interface) where reactions take place. Data on the location and orientation of the substrates in the micelle and on the substrate–micelle association constants are, therefore, very important in understanding micellar catalysis. Solubilization by aqueous micelles is more studied than that by inverted micelles (surfactants in nonaqueous solvents).[3] Recently ^1H NMR was used to study the solubilization of a number of substrates by DAP and Aerosol-OT in several organic solvents.[4,5] Substrate–micelle association constants were found to be a function of the surfactant head group, the substrate structure, and the solvent polarity. Alkylammonium carboxylates' reversed micelles are efficient catalysts for several types of reactions.[6–10] The rate enhancement depends, among other factors, upon the alkyl chain length of the ammonium and/or the carboxylate ion of the surfactant.[8–10] In order to understand better the effects of increasing the chain length of the alkylammonium ion on the association micelle–substrate, hence on the catalysis, the solubilization of different substrates by a series of alkylammonium propionates in carbon tetrachloride was carried out using ^1H NMR as a probing tool.

Experimental Section

Spectroscopic grade carbon tetrachloride (Merck, Uvasol) was further dried by storing on activated Linde type 4A molecular sieve for several weeks. Imidazole (Baker) was recrystallized from benzene–acetone and dried in vacuo over P_2O_5. Methanol (Aldrich, spectroscopic grade), 2-methyl-3-butyn-2-ol (Eastman Kodak), and *N*-methylimidazole (Aldrich) were distilled from calcium hydride and the middle fraction stored on activated molecular sieve type 4A for several weeks. Pyrazole (Matheson Coleman and Bell) was recrystallized from ligroin and dried in vacuo over P_2O_5. Butyl-, hexyl-, octyl-, and dodecylamines (Aldrich) were distilled from calcium hydride. The surfactants were prepared according to the established procedure,[11] and were further purified by repeated distillation or recrystallization and their purity was established by their melting or boiling points and from the ir and ^1H NMR spectra.

Since solubilized water can affect the results, special care was taken to exclude moisture during sample preparations. All solid substances were weighed, then dried for 12 h in vacuo over P_2O_5 and reweighed before making up the stock solution with dry carbon tetrachloride. Owing to limited solubility of imidazole in the solvent it was dissolved in 20% v/v deuteriochloroform in carbon tetrachloride.

The 60-MHz ^1H NMR spectra were obtained on a Varian T-60 spectrometer and the probe temperature was 36 ± 0.5 °C. All spectra were determined on freshly prepared solutions after the sample acquired the ambient probe temperature. Each spectrum was recorded at least three times. Chemical shifts, with the exception of the downfield resonances, were obtained from spectra recorded at 250 Hz sweep width and are given on the δ scale in parts per million relative to Me_4Si (δ 0 ppm). The reference Me_4Si (10% v/v in carbon tetrachloride) was contained in a sealed capillary inserted in the NMR tube. Individual measurements are accurate to ±0.5 Hz. Chemical shifts of the solubilizate protons in absence of detergent were the mean of several measurements and any experiment in which this initial reading deviates more than 0.5 Hz was discarded. Least-squares analysis of the results was carried out using a Hewlett-Packard Model 9820A programmable calculator.

Results and Discussion

The ^1H NMR spectra of the surfactants in carbon tetrachloride show, in order of decreasing chemical shift, a low field sharp singlet for the ammonium protons, a triplet for the methylene protons adjacent to the ammonium ion, a quartet for the CH_2 group of the propionate ion, a broad singlet for the intermediate methylene protons of the alkylammonium ion, and two triplets for the terminal methyl groups of the propionate and alkylammonium ions. The critical micelle concentration (cmc) values in carbon tetrachloride are between 2.1 and 3.1 × 10^{-2} M.[11] The inverted micelles of these surfactants are rather small aggregates in which the polar head ions are grouped around a micellar core from which the solvent is largely excluded whereas the hydrophobic tails are in contact with the solvent.[12]

For comparison purposes, most of the investigated solubilizates were those used in previous studies.[4,5] Methanol is the simplest alcohol and can bind through its OH group whereas 2-methyl-3-butyn-2-ol has two sites for bonding, viz., the OH and the acetylenic protons. The isomeric diazoles, imidazole and pyrazole have different pK_a values and each has two sites for H bonding whereas in *N*-methylimidazole one bonding site is already blocked (vide infra).

We will first examine the effect of adding solubilizates in the concentration range 0–0.05 M to 0.5 M BAP solution. Only the $^+NH_3$ protons shift appreciably as a function of solubilizates as shown in Figure 1. Since the BAP concentration is well above its cmc value, the $^+NH_3$ chemical shift variation indicates that the solubilization site of BAP is its micellar core. A similar conclusion has been reached for DAP in other solvents.[4] Table I gives the changes in the chemical shift of the ammonium protons as a function of solubilizate concentrations for BAP and DAP. The magnitude and direction of the shift depends on several factors, such as the H-bonding ability of the substrate, its self-asso-

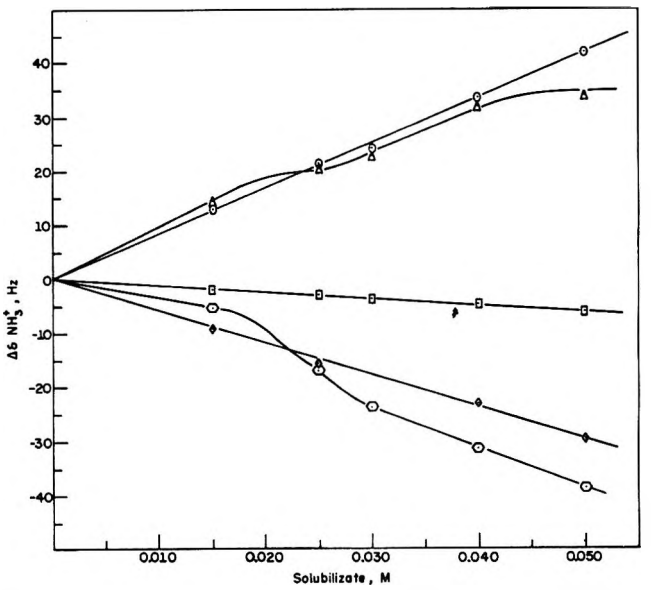


Figure 1. Effect of solubilizates on the chemical shifts of the ammonium protons of BAP: $\Delta\delta$-$_{NH_3}$ = chemical shift in presence of solubilizate − chemical shift in its absence; ⊙, imidazole; ⊙, methanol; △, 2-methyl-3-butyn-2-ol; ⊡, *N*-methylimidazole; ◇, pyrazole.

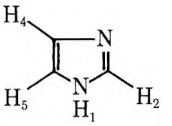
Table I. Effect of Solubilizates on the Chemical Shift of the $^+NH_3$ Group of BAP and DAP in Nonaqueous Solvents

		$\Delta\delta_{+NH_3}$, ppm[c]	
Solubilizate[a]	Solvent	DAP[b]	BAP
Imidazole	C_6H_6	−0.185	
	$CDCl_3$	−0.117	
	CH_2Cl_2	−0.170[d]	
	CCl_4		−0.640
Methanol	C_6H_6	0.112	
	$CDCl_3$	0.553	
	CH_2Cl_2	0.225[d]	
	CCl_4		0.700
2-Methyl-3-butyn-2-ol	CCl_4		0.567
N-Methylimidazole	CCl_4		−0.100
Pyrazole	C_6H_6	−0.158	
	$CDCl_3$	−0.198[d]	
	CH_2Cl_2	−0.190[d]	
	CCl_4		−0.492

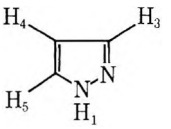
[a] Solubilizate concentration 0–0.05 M. [b] Calculated from ref 4. [c] $\Delta\delta_{+NH_3}$ = chemical shift in absence of solubilizate − chemical shift in the presence of 0.05 M. [d] Maximum solubilizate concentration 0.06 M.

ciation, as well as its local and long-range diamagnetic shielding effects. Additionally interactions between the solubilizates and the surfactant head groups will be at the expense of the ammonium carboxylate ions mutual attraction and will be reflected on the observed $^+NH_3$ chemical shift. Table I shows that for the same solubilizate the sign of the chemical shift difference is the same but the magnitude is greater for BAP than for DAP. Data for DAP in carbon tetrachloride are not available but Table I shows that its chemical shift differences are not very solvent dependent so that one expects results not far from those in benzene. The equilibrium constant for DAP micelle formation in carbon tetrachloride is some 55 times greater than that for BAP micelle.[11] This reflects stronger interactions between the $^+NH_3$ and CO_2^- groups in the former case which may manifest itself as smaller chemical shift differences. The small difference between the shifts due to methanol and 2-methyl-3-butyn-2-ol may indicate that binding in both cases is the same, i.e., via H bonding involving the OH group, and that the triple bond lies outside the micellar core. A noticable difference is observed for the solubilization of imidazole (pK_a = 6.953) and *N*-methylimidazole (pK_a = 6.95). The latter shifts the ammonium protons much less than the former. One can assume that for both solubilizates contributions to the chemical shifts from the electrostatic fields of the heteroatoms and the diamagnetic anisotropy of the nitrogen lone pair and of the aromatic π system are approximately equal. The difference can be due to the more favorable partitioning of imidazole in the polar micellar core and to the difference in the H-bonding abilities of the two substrates. Imidazole has a basic "pyridine type" nitrogen atom and a weakly acidic "pyrrole type" amino nitrogen and can act as proton acceptor and donor, i.e., it can interact with both BAP head groups whereas *N*-methylimidazole interacts only with the $^+NH_3$ group as proton acceptor.

We now turn our attention to the effect of addition of surfactants (0–0.5 M) on the chemical shifts of the solubilizate's discrete protons. Methanol shows a doublet and a quartet (J = 4.5 Hz) for the methyl and OH protons, respectively; 2-methyl-3-butyn-2-ol shows three singlets due to the two equivalent methyl groups, the OH, and the acetylenic protons. In imidazole



H(1) exchanges rapidly between the two nitrogen atoms so that H(4) and H(5) are magnetically equivalent and appear as an upfield doublet whereas H(2) appears as a lower field triplet ($J_{2\text{-}4,5}$ = 1 Hz). H(1) cannot be observed under the experimental conditions used.[13,14] *N*-Methylimidazole shows a singlet for the *N*-methyl group and three resonance lines, a lower field relatively broad one due to H(2), whereas H(4), H(5) show two triplets ($J_{2\text{-}5} = J_{4\text{-}5}$ = 1 Hz).[14] Pyrazole



shows lower field doublets for H(3), H(5) and an upfield triplet for H(4) ($J_{4\text{-}3,5}$ = 2.05 Hz).[13]

The addition of surfactants does not result in any changes in the degeneracy of the resonance lines or the coupling constants except for methanol, whose doublet collapses and quartet disappears, and for 2-methyl-3-butyn-2-ol, whose OH singlet disappears. This is the result of the fast OH proton exchange with the acidic $^+NH_3$ protons. The effects of increasing surfactants concentration on the chemical shifts of the substrate's discrete protons are shown in Figure 2. Chemical shift changes allow the calculation of binding constants K of the solubilizates (S) to the micelles (M) as given by equilibrium 1

$$M + S \overset{K}{\rightleftharpoons} MS \qquad (1)$$

where MS is the micelle–substrate complex, by using eq 2[15]

$$\frac{\Delta}{M} = -\Delta K + \Delta_c K \qquad (2)$$

where Δ is the difference between the observed chemical shift and that of the uncomplexed or "free" solubilizate, and Δ_c is the difference between the chemical shift of the micelle complexed and that of the uncomplexed solubili-

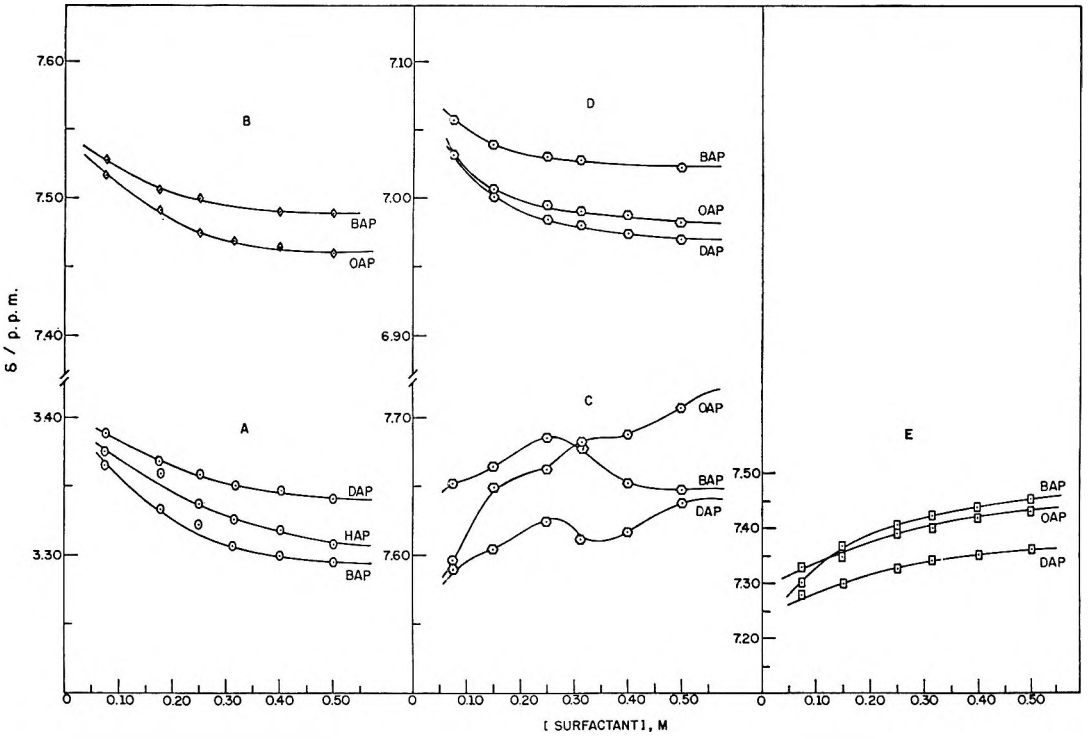


Figure 2. Chemical shift values of the solubilizate protons as a function of surfactants: A, methanol CH_3; B, pyrazole H(3,5); C, imidazole, H(2); D, imidazole H(4,5); E, *N*-methylimidazole H(2).

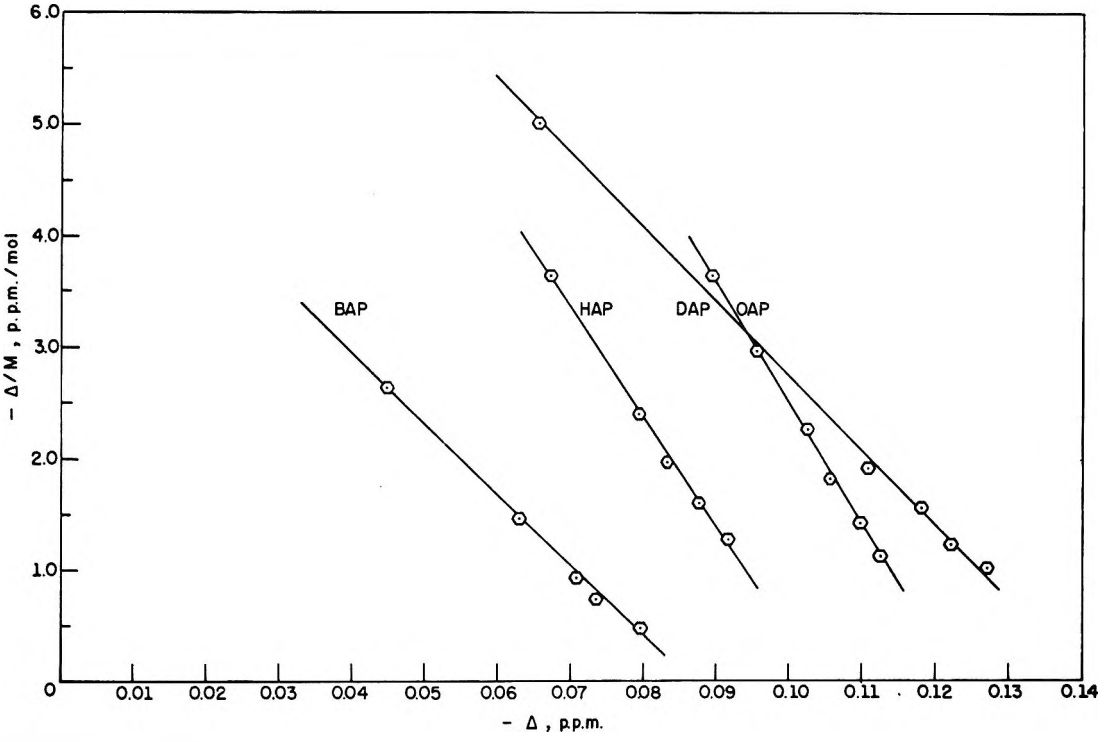


Figure 3. Binding constant plots for imidazole H(4,5).

zate. Chemical shifts of the "free" solubilizates were those measured in absence of the surfactants since chemical shifts for the protons followed were practically concentration independent over the concentration range 0.02–0.075 M.[4,5] M is the micellar concentration calculated from eq 3[4]

$$(\mathrm{M}) = \frac{C_D - \mathrm{cmc}}{N} \qquad (3)$$

where C_D is the total detergent concentration and N is the aggregation number taken from ref 11.[16] Plots of Δ/M against Δ yield good straight lines whose slope is equal to $-K$ and intercept equal to $K\Delta_c$. A typical binding constant plot is shown in Figure 3 and the results are given in Table II and Figure 4. We were not able to compute the association constant values for imidazole H(2) because its chemical shift did not change systematically as a function of surfactant concentration (Figure 2). Typically the correlation coefficient was 0.99; however, K values for which the coefficient was less than 0.95, e.g., some of the values of *N*-methylimidazole and the values for the CH_3 group of 2-methyl-3-butyn-2-ol, are not reported in the table.

Association constants determined by following different

Table II. Association of Solubilizates with Alkylammonium Propionates in Carbon Tetrachloride

Registry no.	Solubilizate	Proton used	K,[a] M^{-1} BAP	HAP	OAP	DAP	Δ_c,[b] ppm
288-32-4	Imidazole[c]	H(4,5)	62.7 ± 1.8	97.0 ± 2.9	105.8 ± 3.2	65.3 ± 1.2	8.7, 10.5 12.4, 14.2
67-56-1	Methanol	CH_3	26.1 ± 1.6	30.2 ± 1	37.7 ± 0.9	39.5 ± 3.4	9.2, 16.3 10.0, 14.7
115-19-5	2-Methyl-3-butyn-2-ol	-C≡CH	33.8 ± 4			51.8 ± 4	4.2, 6.9
616-47-7	*N*-Methylimidazole	H(2)	32.2 ± 0.4	46 ± 0.8	46.3 ± 3	28.8 ± 1.2	30.3, 37.1 28.4, 20.0
		H(4)	48.7 ± 3.6		44.9 ± 5	37.3 ± 5	7.5, 5.8 2.7
		CH_3	45.4 ± 2.9				7.7
288-13-1	Pyrazole	H(3,5)	76 ± 4	74.6 ± 0.7	49.7 ± 0.6	62.6 ± 5	10.4, 10.6 11.2, 13.4
		H(4)	49 ± 5	88.1 ± 2.4	101.4 ± 3.2	94.9 ± 4	8.1, 8.0 6.9, 8.4

[a] Temperature 36 ± 0.5 °C. [b] Δ_c for BAP, HAP, OAP, and DAP, respectively. Values for imidazole, methanol, 2-methyl-3-butyn-2-ol, and pyrazole should be multiplied by −0.01 and that for *N*-methylimidazole by 0.01. [c] Solvent $CDCl_3$–CCl_4 (20:80 v/v).

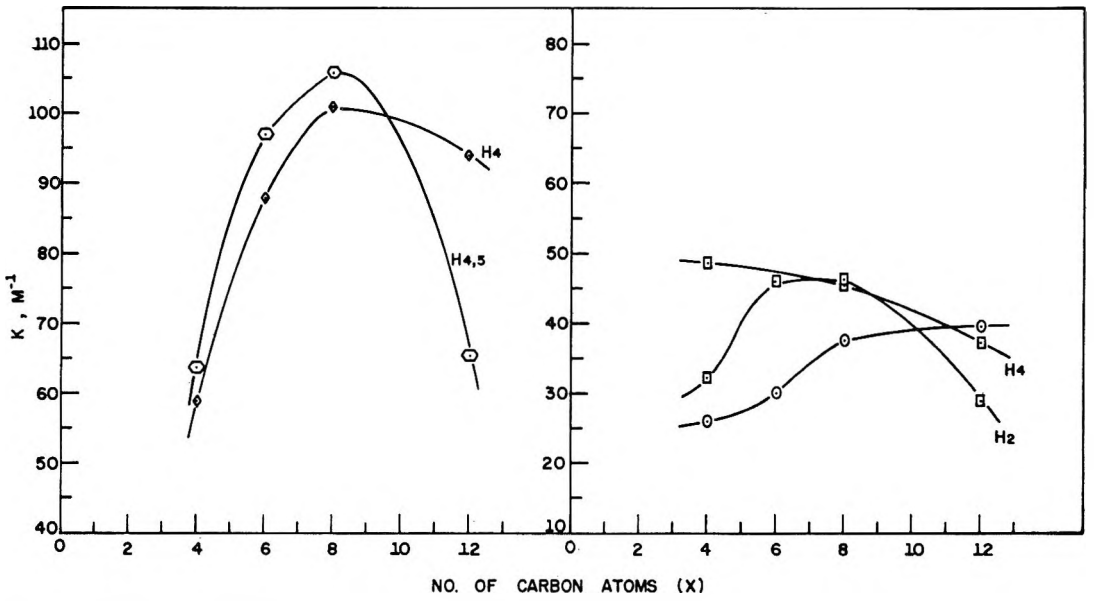


Figure 4. Effect of the number of carbon atoms (X) in the alkylammonium ion on some of the association constants: ⊙, imidazole; ⊙, methanol; ⊡, *N*-methylimidazole; ◈, pyrazole.

protons in the same solubilizate agree well as shown for pyrazole H(3,5), H(4) and for *N*-methylimidazole H(2), H(4) and the methyl group. Any discussion of K values has to take into account the autoassociation of the solubilizates, the possible effect of the surfactant on this self-association, the distribution coefficient of the substrate between the micellar and bulk phases, and the pK_a values of the alkylamines. The association of imidazole is due to intermolecular H bonding.[17] In carbon tetrachloride at 18 °C the dimerization constant is 234 ± 5 M^{-1} and the subsequent stepwise association constant is 760 ± 20 M^{-1}. Methanol exists as monomers, dimers with either cyclic or open structures, trimers, tetramers, and higher polymers.[18] At 21 °C the equilibrium constant for monomer ⇌ tetramer is 28.4 M^{-3},[19] at 40 °C the association constant for monomer ⇌ dimer is 17.9, for dimer ⇌ trimer is 30.1, and for trimer ⇌ tetramer is 44.4. [20] *N*-Methylimidazole does not self-associate in carbon tetrachloride[21] whereas 2-methyl-3-butyn-2-ol forms cyclic and open dimers with the latter dominating.[22] Pyrazole is intermolecularly H bonded to form cyclic dimers and trimers.[23,24] At 18 °C the equilibrium constant for dimerization is 47.5 M^{-1} and that for trimerization is 7540 M^{-2}.[24] It is recalled here that exchange between aggregated species is fast on the NMR time scale so that only average spectra and hence average K values are obtained.

Comparison of these data with the equilibrium data of Table II gives an idea about the extent of micelle–substrate association in relation to its self-association. For simplicity we assume that only monomers and open-ended polymers can H bond and that the bigger the aggregate the weaker its binding to the micelle. One has to take into consideration also the possible effect of the surfactant on the distribution of the substrate aggregates especially in the case of methanol and imidazole where several aggregates are formed. Association constants for methanol–surfactants are comparable with its autoassociation values. It seems that owing to its relatively smaller size methanol can penetrate and bind itself strongly to the micelle. On the other hand, the imidazole–surfactants association constants are well below the values for its autoassociation which may be the result of the weaker binding of the micelles with imidazole linear oligomers (vide supra). *N*-Methylimidazole does not self-associate and interacts with the surfactant via H bonding to the ammonium group. Its distribution between the micellar and bulk phases may show little variation from BAP to DAP and consequently its K values do

not change appreciably as a function of (X). Owing to similar pK_a values of imidazole and *N*-methylimidazole one can assume that the difference between their K values reflects the part due to H bonding between imidazole H(1) and the surfactant carboxylate group.

The effect of increasing the number of carbon atoms (X) in the alkylammonium ion on the observed K values is a modest one when compared with the corresponding case for aqueous micelles[25,26] where hydrophobic interactions are operative. The variation of K as a function of increasing (X) is not easy to rationalize because of the complexity of the variables involved (vide supra), but one can attempt to explain the trend of variation. Two factors can be considered, viz., the tightness of the micelle and the steric effects of the surfactant alkyl groups. The possibility of steric interactions between the solubilizates and the hydrophobic tails increases as (X) increases. This makes the penetration of the substrate into the micelle more difficult and its K falls off as (X) increases.[27] On the other hand, the equilibrium constant and the pK_a of the amines (both indicate micelle tightness)[9] change in a different way,[28,29] so that their contribution to K does not parallel that due to the steric effects. The delicate balance of these forces seems to favor association with OAP for most of the solubilizates (see Table II). Complete understanding of the factors affecting solubilization by these surfactants and by reversed micelles in general has to wait for the separation and quantitative estimation of the above-mentioned variables and for more data on the effects of solubilization on the micellar structure.[3]

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Registry No.—BAP, 17081-35-5; HAP, 39107-99-8; OAP, 39108-00-4; DAP, 17448-65-6.

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Base-Catalyzed β-Elimination Reactions. VI. Elimination from *tert*-Butyl 3-(Para-substituted phenoxy)- and 3-(Para-substituted benzoyloxy)thiolpropionates in 45% (Weight/Weight) Dioxane–Water[1]

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Triethylamine catalyzed and hydroxide ion catalyzed β-elimination reactions of the title compounds are second order overall. The Elcb mechanism with thiol ester carbanion formation rate determining is postulated on the basis of the insensitivity of the second-order rate constants to leaving group tendencies (small ρ's) and the linear relationship between log k_{OH} for thiol esters of this study and log k_{OH} for analogously substituted β-oxy-2-butanones for which the Elcb mechanism likely operates.

The probability that enzyme-catalyzed dehydration of β-hydroxythiol esters proceeds via a carbanion mechanism[2,3] prompted us to examine nonenzymic, base-catalyzed elimination reactions of *tert*-butyl β-oxythiol esters

Table I. *tert*-Butyl 3-(Para-substituted phenoxy)thiolpropionates

Registry no.	Compd		Bp,[b] °C	% yield[c]	Column[d] eluent
58228-77-6	1	4-CH_3	100 (3)	76.3	PE
58228-78-7	2	4-H	95–97 (70)	75.5	PE
58228-79-8	3	4-Cl	122–124 (3)	42.2	B
58228-80-1	4	4-CN	65–67 (mp)	91.0	B, H[e]
58228-81-2	5	4-NO_2	155–156 (10) (43–45, mp)	58.3	B, B–PE[e]
58228-82-3		4-OCH_3	123–124 (1)	54.0	H

[a] Satisfactory combustion analytical data for C, H (±0.4%) were provided for these compounds. Ed. [b] Pressure in microns. [c] Based on amount of analytically pure sample. [d] B = benzene; PE = petroleum ether (bp 30–60 °C); H = hexane; B–PE = benzene–petroleum ether mixture. [e] Recrystallization solvent.

as models for the enzyme-catalyzed reaction. It was soon apparent to us that elimination of methanol from *tert*-butyl β-methoxythiolpropionate is not competitive with thiol ester aminolysis and hydrolysis and we took the approach of studying elimination reactions of β-oxythiol esters with good leaving groups so as to make elimination competitive with ester cleavage. We justified this approach to the problem on the grounds that the proton transfer aspect of elimination (dehydration) of this biologically important class of compounds could be conveniently studied. As well we proposed that if a carbanion mechanism operates for crotonase and β-hydroxydecanoyl thiol ester dehydratase, the enzyme may mediate proton transfer (the α-H of the thiol ester?) to the departing OH group so as to facilitate β-C–O bond breaking; thus the models could be more representative of the enzymic reactions than might at first appear.

Elimination of acetate ion from β-acetoxythiol esters was previously shown to be catalyzed by tertiary amines and hydroxide ion.[4] This result was interpreted to mean that β-acetoxythiol esters undergo β-elimination by a concerted mechanism or by an Elcb mechanism with proton transfer from thiol esters to general bases rate determining. Here we report the results of base-catalyzed β-elimination reactions of *tert*-butyl β-phenoxythiolpropionates (**1–5**) and *tert*-butyl β-benzoyloxythiolpropionates (**6–10**) (eq 1).

$$ROCH_2CH_2COSC(CH_3)_3 \rightarrow CH_2{=}CHCOSC(CH_3)_3 + ROH \quad (1)$$

R = *p*-XC_6H_4 [X = CH_3 (**1**); H (**2**); Cl (**3**); CN (**4**); NO_2 (**5**)]; R = *p*-XC_6H_4CO [X = CH_3 (**6**); H (**7**); Cl (**8**); CN (**9**); NO_2 (**10**)]

These compounds were chosen for study with the expectation of distinguishing between the concerted mechanism and the Elcb mechanism with proton transfer rate determining: for the latter mechanism ρ should be small, consistent with nonparticipation of β-C–O bond cleavage in the rate-determining step and in analogy to the small ρ value obtained for analogous reactions of similarly constituted methyl ketones.[5,6] As well the rate law for reactions of **1–5** could prove diagnostic of the Elcb mechanism as is the case for the above-mentioned ketones.[6]

Experimental Section

Apparatus. The apparatus was previously described.

Reagents. Fisher certified ACS grade inorganic reagents were used. Tap distilled water was redistilled through a Corning AGla still before use. Organic reagents were purchased from Aldrich Chemical Co. and Fisher Chemical Co. Para-substituted phenoxypropionic acids were prepared by the reaction of the appropriately substituted phenol in aqueous sodium hydroxide with β-propiolactone by the procedure of Gresham et al.[7] β-(*p*-Cyanophenoxy)propionic acid was fractionally crystallized from acetonitrile, mp 144–147 °C.

***tert*-Butyl 3-(Para-substituted phenoxy)thiolpropionates.** Under anhydrous conditions 10 ml of thionyl chloride was added in one portion to a stirred solution of the appropriately para-substituted β-phenoxypropionic acid (0.02 mol) in 25–30 ml of sodium-dried benzene. The mixture was refluxed for 24 h and the system continuously purged with dried nitrogen (flow, ca. 10 ml/min) to remove the HCl and SO_2 gas formed in the reaction. The residue which remained after codistilling the excess thionyl chloride with dry benzene (3 × 20 ml) in vacuo on the rotary evaporator was dissolved in 30 ml each of dry 2-methyl-2-propanethiol distilled from calcium hydride and dry benzene. The latter mixture was then refluxed for 72 h with continuous purging with dry nitrogen. After removal of excess mercaptan and solvent, first by distillation at atmospheric pressure and then by momentary warming at reduced pressure, the light yellow oily residue was rapidly filtered through 30 g of silica gel (70–328 mesh) in a 20–22 mm i.d. glass column with a distilled, nonpolar eluent. The one spot (TLC) column fractions were collected and the oil which remained after removal of the solvent was either distilled or crystallized (Table I). The ir and NMR spectra supported the structure assignments.

3-Trifluoroacetoxypropionic Acid. Freshly distilled β-propiolactone was added via a constant rate addition funnel over a 4.5-h period at room temperature to a rapidly stirred solution of trifluoroacetic acid in 100 ml of dry dichloromethane maintained at 5–7 °C. The reaction was allowed to continue for an additional 3 h at the same temperature. The solvent and unreacted trifluoroacetic acid were removed in vacuo while maintaining the temperature below 50 °C. The product was distilled, bp 104–106 °C (7.5 mmHg), 48.0 g, 51.8% yield.

***tert*-Butyl 3-Trifluoroacetoxythiolpropionate.** Under anhydrous conditions, a solution of 3-trifluoroacetoxypropionic acid (37.2 g, 0.2 mol) and thionyl chloride (47.5 g, 35.0 ml, 0.4 mol) in sodium-dried benzene (65 ml) was refluxed for 24 h while continuously purging the system with dry nitrogen. Codistilling the unreacted thionyl chloride with dry benzene (3 × 50 ml) in vacuo left a residue which was immediately refluxed, in the same flask without further purification, for 72 h with 2-methyl-2-propanethiol (36.1 g, 0.4 mol) (distilled from calcium hydride) in 65 ml of dry benzene. The system was continuously purged with dry N_2 for the duration of the reflux period. The solvent and excess mercaptan were distilled from the reaction mixture at atmospheric pressure leaving a residue, which was distilled at 86–89 °C (4.5–5.0 mmHg), yielding 37.2–40.1 g of product (72–77.5%).

***tert*-Butyl 3-Hydroxythiolpropionate.** Water was added in 75-ml portions every 0.5 h (over a 2-h period) to a stirred solution of *tert*-butyl 3-trifluoroacetoxythiolpropionate (53.7 g, 0.21 mol) in 100 ml of methanol at room temperature. The aqueous solution was stirred for an additional 2 h and then extracted with ether (3 × 100 ml). The ethereal extracts were combined, dried, and filtered and the ether was removed in vacuo. The residual oil was distilled, bp 96–98 °C (4.8–5.0 mmHg), to give 28.7 g (85%).

Anal. Calcd for $C_7H_{14}O_2S$: C, 51.88; H, 8.69; S, 19.77. Found: C, 52.08; H, 8.87; S, 20.02.

***tert*-Butyl 3-(Para-substituted benzoyloxy)thiolpropionates.** To a stirred solution of the appropriate acyl chloride (0.025 mol) in 25 ml of dry dichloromethane maintained at 5–10 °C was added dropwise a solution of dry distilled pyridine (1.66 g, 0.021 mol) in 15 ml of dry dichloromethane. After the mixture was stirred for 15–20 min a solution of distilled *tert*-butyl 3-hydroxythiolpropionate (3.25 g, 0.020 mol) in 15 ml of dry dichloromethane was added dropwise to the stirred mixture which was maintained at 0–4 °C. Stirring was continued at 4 °C for 30 min and then at room temperature for a total of 8–12 h (Table II). The reaction mixture was diluted with 100 ml of ether and washed with 25 ml of 5% aqueous HCl solution, two 25-ml portions of saturated aqueous sodium bicarbonate, 50 ml of water, and finally 50 ml of saturated sodium chloride solution. The ethereal extract was dried and the ether was removed in vacuo. The residue was either distilled or crystallized from the indicated solvent system. (Table II) All final products gave the expected ir and NMR spectra.

Kinetics. Reactions were carried out in 45% w/w dioxane–water solutions, μ = 0.1 M (KCl), *t* = 30 °C, using pseudo-first-order conditions as previously described.[4] Reactions were monitored at the following λ (nm) (compound): 275 (**1–4, 6–9**); 410 (**5**); 310 (**10**). Absorbance vs. time data were treated as previously described[4] except for **5** where 4-nitrophenolate absorbance was monitored and pseudo-first-order rate constants were obtained from slopes of

Table II. *tert*-Butyl 3-(Para-substituted benzoyloxy)thiolpropionates

Registry no.	Compd[a]		Mp or bp,[b] °C	% yield[c]	Total reaction time, h
58228-83-4	**6**	4-CH_3	120–122[b]	48.6	2
58228-84-5	**7**	4-H	115–116[b]	96.5	8
58228-85-6	**8**	4-Cl	32–33	36.7, H[d]	8
58228-86-7	**9**	4-CN	56–58	37.8, C–H[d]	10
58228-87-8	**10**	4-NO_2	78–80	86.7, C[d]	8
58228-88-9		4-OCH_3[e]	142–144[b]	52.3	12

[a] Footnote *a*, Table I. [b] Boiling point at 1 μm pressure. [c] Based on amount of analytically pure sample. [d] Recrystallization solvent: C = cyclohexane; H = hexane; C–H = cyclohexane–hexane mixture. [e] This compound was not used in this study; it gave unreliable kinetics data.

Table III. Rate Constants for the Hydroxide Ion Catalyzed β-Elimination Reactions of 1–10[a]

Compd	k_{OH},[b] M^{-1} min^{-1}	No. of runs
p-CH_3O[c]	121 ± 3	9
1	120 ± 5	9
2	154 ± 21	9
3	204 ± 9	9
4	469 ± 29	9
5	598 ± 76	9
6	339 ± 9	4
7	375 ± 5	4
8	444 ± 15	4
9	791 ± 29	8
10	823 ± 34	6

[a] Solvent, 45% (w/w) dioxane–water, t = 30 °C, μ = 0.1 M (KCl). [b] pH range 12.19–13.37 (**1–5**) and 12.65–13.02 (**6–10**). [c] *tert*-Butyl 3-(*p*-methoxyphenoxy)thiolpropionate.

plots of log $OD_\infty/(OD_\infty - OD_t)$ vs. time. pK_a values were determined by the method of fractional neutralization using the pH meter. Hydroxide ion activity was determined from K_w/a_H where $-\log K_w = 15.59$.[8]

Products. Scans of the absorption spectra during reactions showed that the products are *tert*-butyl thiolacrylate and 4-substituted benzoates and 4-substituted phenoxides. The thiolacrylate product is unstable, as shown by a decrease in absorbance following the initial increase in absorbance. Formation of this product was confirmed by the near identity of the pseudo-first-order rate constants for absorbance loss following initial product formation for some of the compounds of this study. Thus k_{obsd} = 0.203 ± 0.016 min^{-1} for absorbance loss at 275 nm, 0.1 M KOH, for **1, 2, 3, 7, 8, 9, 10**; under identical conditions, *tert*-butyl thiolacrylate lost absorbance with k_{obsd} = 0.198 ± 0.003 min^{-1}. *tert*-Butyl 3-methoxythiolpropionate, synthesized for use in this study, was found not to undergo β-elimination reactions in dilute alkali; instead this compound undergoes hydrolysis as measured by absorbance loss at 235 nm. In 0.1 M KOH solution, pH 13.87, k_{OH} = 8 M^{-1} min^{-1}. Infinity absorbance values slowly decrease with time, presumably owing to oxidation of *tert*-butyl thiolate ion to the disulfide. Comparison of k_{OH} with k_{elim} for **1–10** (Table III) shows that elimination is much faster than hydrolysis.

Results

The reactions of **1–10** to give *tert*-butyl thiolacrylate and para-substituted phenols and para-substituted benzoic acids (eq 1) in 45% (w/w) dioxane–water solutions of catalytic tertiary amine buffers obey the kinetics law of eq 2.

$$v/[\mathbf{1\text{–}10}] = k_{obsd} = [k_2K_a/(K_a + H^+)][\text{amine}]_t + k_{OH}K_w/a_{OH} \quad (2)$$

At constant pH, plots of k_{obsd} vs. $[\text{amine}]_t$ are linear with slope $k_2K_a/(K_a + H^+)$ and intercept $k_{OH}K_w/a_{OH}$. Division of the slope by $K_a/(K_a + H^+)$, the mole fraction of the base form of the buffer, gave k_2 (Table IV). The values of k_{OH} were determined by dividing k_{obsd} values by K_w/a_{OH} for reactions of **1–10** run in 0.01–0.04 M KOH solution (Table III).

For reactions of **1–5** and **6–10** catalyzed by triethylamine, ρ (k_2) = 0.25 ± 0.11 and ρ (k_2) = 0.05 ± 0.07, respectively. For reactions of **1–5** and **6–10** catalyzed by hydroxide ions, ρ (k_{OH}) = 0.72 ± 0.03 and ρ (k_{OH}) = 0.43 ± 0.04, respectively. For comparison purposes, we determined ρ's for elimination reactions of 4-(para-substituted phenoxy)-2-butanones and 4-(para-substituted benzoyloxy)-2-butanones catalyzed by hydroxide ions in 45% (w/w) dioxane–water: they are ρ (k_{OH}) = 0.57 ± 0.03 and ρ (k_{OH}) = 0.37 ± 0.05, respectively. A plot of log k_{OH} for **1–8, 10** vs. log k_{OH} for identically substituted β-oxy-2-butanones (water solvent) gave slope 2.7 ± 0.16 (r = 0.988) for nine pairs of compounds for which data were available.[5,6] A similar plot of log k_{OH} for **1–5** vs. log k_{OH} for identically substituted β-phenoxy-2-butanones (45% w/w dioxane–water solvent) gave slope 1.2 ± 0.13 (r = 0.982).

Discussion

Results of elimination reactions of β-substituted phenoxy ketones[6] and β-substituted benzoyloxy ketones[7] suggest that these compounds undergo β-elimination via an Elcb mechanism. The major lines of support for this conclusion are (1) the Hammett ρ values are quite small and positive, (2) for certain phenoxy ketones there is kinetics evidence for formation of an intermediate enolate ion whose partitioning is dependent on the concentration of

Table IV. Rate Constants for the Amine Catalyzed β-Elimination Reactions of 1–10[a]

Compd	Base[b]	k_2, M^{-1} min^{-1}	Fr base	No. of runs	Concn range, M
2	TEDA	0.06 ± 0.004	0.8, 0.96	12	0.06–0.40
5	TEDA	0.14 ± 0.02	0.8, 0.96	18	0.06–0.50
1	TEA	0.22 ± 0.07	0.67, 0.8, 0.9	18	0.06–0.3
2	TEA	0.27 ± 0.05	0.67, 0.8, 0.9	18	0.06–0.3
3	TEA	0.43 ± 0.03	0.67, 0.8, 0.9	18	0.06–0.3
4	TEA	0.35 ± 0.08	0.67, 0.8, 0.9	18	0.06–0.3
5	TEA	0.45 ± 0.06	0.67, 0.8, 0.9	18	0.06–0.3
6	TEA	0.67 ± 0.06	0.67, 0.8, 0.9	18	0.06–0.3
7	TEA	0.66 ± 0.05	0.67, 0.8, 0.9	18	0.06–0.3
8	TEA	0.79 ± 0.05	0.67, 0.8, 0.9	18	0.06–0.3
9	TEA	0.87 ± 0.13	0.67, 0.8, 0.9	18	0.06–0.3
10	TEA	0.65 ± 0.11	0.67, 0.8, 0.9	18	0.06–0.3
5	DMAE	0.109 ± 0.007	0.5, 0.75, 0.8	18	0.05–0.5

[a] Solvent, 45% (w/w) dioxane–water, t = 30 °C, μ = 0.1 M (KCl). [b] TEDA = triethylenediamine; TEA = triethylamine; DMAE = *N,N*-dimethylaminoethanol.

general acid, and (3) the equation log $k_{OH} = -1.16\ pK_a + 6.25$, where k_{OH} is the second-order rate constant for hydroxide ion catalyzed elimination reactions of β-oxy ketones and hydroxide ion catalyzed hydrogen–deuterium exchange in 4-methoxy-2-butanone, and pK_a is that for the appropriately substituted phenoxyacetic acid, benzoyloxyacetic acid, and methoxyacetic acid, reasonably establishes a mechanisms relationship among the members of this family of ketones. In a comprehensive related study, Hupe et al.[10] presented detailed kinetics evidence for operation of the Elcb mechanism in the amine-catalyzed dehydration of 9-hydroxy-10-methyl-*cis*-decalone-2. We believe that the results and conclusions from these studies are pertinent to those from β-elimination reactions of **1–10** because of the demonstrated similarity of ketones and thiol esters with respect to reactions occurring at carbon α to the carbonyl functional group.[11–13]

At the outset of this study we anticipated finding kinetics evidence for a thiol ester anion; finding such evidence would establish the Elcb mechanism for β-oxythiol esters. Experience with β-oxy ketones suggested to us that detection of thiol ester anions among **1–10** in a given catalytic amine buffer system would be most probable for reactions of **1** and **2**: this is based on the result that partitioning of the anion depends on the leaving tendency of the β-oxy group as well as on the rate of protonation of the anion to give **1–10**, and in a given buffer the latter rate should be largely independent of the leaving group, except as it influences carbon acid acidity. Respecting this latter point there is a rough correlation between acidity of tertiary amine general acids and the tendency of enolates to undergo protonation to give β-phenoxy ketones such that low pK_a amines favor the proton transfer. Accordingly we examined reactions of **2** with triethylenediamine (mole fraction of acid form 0.2) and found that k_{obsd} is linearly dependent on the concentration of total amine: no evidence was found for curvature in the plot. In an effort to make partitioning of putative carbanion to **2** more favorable, we attempted a similar experiment (mole fraction of acid form 0.5): reactions were very slow and the first-order rate data were unreliable. We conclude that if thiol ester carbanions are formed on the reaction pathway to elimination products, they are not sufficiently stable to assure detection in a convincing way using catalytic tertiary amine buffers and our reaction conditions.

We next sought indirect evidence for the operation of the Elcb mechanism for **1–10**. For the aforementioned benzoyloxy ketones, their elimination reactions are characterized by small, positive ρ values which show that β-C–O bond breaking is likely not a feature of the transition state, i.e., proton transfer from the ketones is rate determining, giving rise to enolates which quickly undergo β-C–O bond breaking to give the products. Similarly, for phenoxy ketones ρ is small and positive for the initial proton transfer reaction which generates enolates. Similar insensitivity of **1–10** to electronic effects of para substituents in the departing group would provide indirect evidence for rate-determining formation of carbanions and the Elcb mechanism. At least, small ρ values could be interpreted in terms of a concerted reaction with an Elcb-like transition state. Perhaps the distinction is somewhat artificial since the difference involves the stability of the thiol ester carbanion, which in terms of its partitioning is already presumed to be unstable (vide supra); thus the Elcb mechanism merges to the E2 mechanism as one limit.[14,15] The reactions of **1–10** catalyzed by triethylamine provide dramatic evidence for the insensitivity of the elimination reactions to the leaving tendencies of para-substituted phenoxides and para-substituted benzoates. For **1–5**, $\rho = 0.25 \pm 0.11$; for **6–10**, $\rho = 0.05 \pm 0.07$. Although these ρ values could be identical, the apparent greater sensitivity of **1–5** to electronic effects could reflect the shorter distance between para substituents and the incipient carbanion for **1–5** vs. **6–10**. These data may be compared with those for elimination reactions of 4-(para-substituted phenoxy)-2-butanones catalyzed by *N,N*-dimethylaminoethanol in water solution ($\rho = 0.17$) and for similar reactions of 4-(para-substituted benzoyloxy)-2-butanones ($\rho = 0.14$). It seems clear that for triethylamine-catalyzed reactions of **1–10** there is an insensitivity to electronic effects of leaving groups which is similar to that shown by analogous ketones for which the Elcb mechanism appears to operate.

A similar, if less dramatic, result was obtained for hydroxide ion catalyzed reactions of **1–10**: for **1–5**, $\rho\ (k_{OH}) = 0.72 \pm 0.03$; for **6–10**, $\rho\ (k_{OH}) = 0.43 \pm 0.04$. For comparison purposes, $\rho\ (k_{OH}) = 0.57 \pm 0.03$ for reactions of phenoxy ketones and $\rho\ (k_{OH}) = 0.37 \pm 0.05$ for reactions of benzoyloxy ketones in 45% (w/w) dioxane–water solution. Comparison of the ρ values shows that **1–10** are approximately 1.3 times more sensitive to electronic effects of para substituents than the comparable ketones which likely reflects, in part, the different capability of thiol esters and ketones to stabilize carbanions; for **1–10** more of the developing anionic charge is supported by para substituents.

A plot of log k_{OH} for **1–8, 10** vs. log k_{OH} for identically substituted β-oxy-2-butanones gave slope 2.7 ± 0.16; a similar linear plot using k_{OH} for **1–5** and k_{OH} determined for reactions of identically substituted β-phenoxy-2-butanones in 45% (w/w) dioxane–water gave slope 1.2 ± 0.13. Gregory and Bruice[16] showed that for nucleophilic reactions of 2,2,2-trifluoroethyl thiolacetate and *p*-nitrophenyl acetate the linear log k_s − log $k_{p\text{-NPA}}$ plot, a consequence of transition state theory, requires a linear relationship between the free energy changes of one reaction series (thiol ester and nucleophiles) and the free energy changes of another (*p*-NPA and the same nucleophiles). For these reactions the further implication is that their transition states (and mechanisms) are similar. This argument, applied to reactions of **1–8, 10** (**1–5**) and analogous β-oxy ketones with hydroxide ions, permits the conclusion that E2 reactions of thiol esters and ketones pass through similar transition states and that their mechanisms are similar.

The insensitivity of **1–10** and analogous ketones to leaving group tendency and the proportionality between log k_{OH}'s provide evidence for similar mechanisms of β-elimination. The liklihood that β-oxy ketones undergo β-elimination via the Elcb mechanism suggests that **1–10** similarly undergo β-elimination via that mechanism with carbanion formation rate determining under the conditions of this study. Although direct kinetics evidence for carbanion formation was not found during the course of this study, evidence was found for carbanions during the amine-catalyzed isomerization of *tert*-butyl thiolbut-3-enoate to *tert*-butyl thiolcrotonate. The evidence took the form of a deuterium solvent kinetic isotope effect $k^H/k^D > 6$ for the apparent general-base-catalyzed isomerization, a result interpreted as general acid catalysis of proton transfer to the thiolester carbanion (allylic carbanion) formed in a prior equilibrium. As well the previously cited stereochemical evidence for a multistep mechanism for crotonase-catalyzed dehydration of L-(+)-β-hydroxybutyryl coenzyme A supports the intermediacy of carbanions (carbonium ions?) in transformations of thiol esters which involve β-methylene protons. We suggest that these collective results support the formation of carbanion intermediates for reactions of **1–10** with bases.

Registry No.—β-(*p*-Cyanophenoxy)propionic acid, 58228-89-0; β-(*p*-methylphenoxy)propionic acid, 25173-37-9; β-phenoxypro-

pionic acid, 7170-38-9; β-(*p*-chlorophenoxy)propionic acid, 3284-79-5; β-(*p*-nitrophenoxy)propionic acid, 10572-16-4; β-(*p*-methoxyphenoxy)propionic acid, 20811-60-3; 2-methyl-2-propanethiol, 75-66-1; 3-trifluoroacetoxypropionic acid, 58228-90-3; β-propiolactone, 57-57-8; trifluoroacetic acid, 76-05-1; *tert*-butyl 3-trifluoroacetoxythiolpropionate, 58228-91-4; *tert*-butyl 3-hydroxythiolpropionate, 58228-92-5; *p*-methylbenzoyl chloride, 87-60-2; benzoyl chloride, 98-88-4; *p*-chlorobenzoyl chloride, 122-01-0; *p*-cyanobenzoyl chloride, 6068-72-0; *p*-nitrobenzoyl chloride, 122-04-3; *p*-methoxybenzoyl chloride, 100-07-2.

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Esterification by Alkylation of Carboxylate Salts. Influence of Steric Factors and Other Parameters on Reaction Rates[1]

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Alkylation of carboxylate salts with alkyl halides in dipolar aprotic solvents is an efficient method of esterification. The reaction kinetics were studied to determine the effects of variation of such parameters as gegenions (alkali metals), solvents, alkyl halide, and carboxylate structures. The reactions of numerous unhindered and hindered carboxylates with alkyl halides show small variation in rate relative to the large divergent rates observed in conventional acid-catalyzed esterification of the corresponding carboxylic acids. However, over a restricted range, the rate data for a group of carboxylate structures provided a correlation with increasing steric bulk leading to a converse application of Newman's rule of six. Rate constants for salts of aromatic acids were correlated well by Hammett parameters.

The classical acid-catalyzed methods of esterification of carboxylic acids with alcohols are recognized as having limited applications.[3,4] They are generally ineffective for the esterification of sterically hindered acids and of compounds containing acid-sensitive functional groups. Esterification of most carboxylic acids with diazoalkanes[4] or with the newer reagents, 1-alkyl-3-*p*-tolyltriazenes,[5] are effective but restricted in practicality to analytical preparations of methyl, ethyl, and propyl esters. Other recently developed procedures of reacting carboxylic acids with triethyloxonium fluoroborate[6] or of carboxylate ion with dimethyl sulfate,[7] while applicable to sterically hindered acids, are similarly limited to the preparations of ethyl and methyl esters, respectively. Less direct methods that require severe thermal conditions or conversion to more reactive intermediates such as the acid chlorides, the 2-butyl chlorosulfite,[8] or the tetramethylammonium salt[4] lack quantitation, convenience, and generality.

Reaction of metal salts of carboxylic acids with organic halides is a simple, though neglected, method of preparing esters. Although several reports[9-11] have disclaimed the value of metal salt alkylations, recent studies[12-15] have uncovered the method's general potentialities. Earlier uses of silver or alkali metal carboxylate salts in the presence or absence of amine[16,17] or in aprotic solvent[18,19] were confined to preparations of esters derived from the reactive benzyl or allylic halides. However, quaternary ammonium salts and highly polar aprotic solvents, either alone or in combination, have been shown to facilitate the direct alkylation of carboxylate salts for preparations of glycidyl esters,[20,21] lactones,[22] triglycerides,[23,24] and straight-chain aliphatic esters.[9,10,12,13,25-28a]

We have recently introduced and developed carboxylate salt alkylations in hexamethylphosphoramide[28b] (HMPA)–ethanol cosolvent as a rapid, quantitative method of preparing esters.[13] More importantly, we found the method to be uniquely superior for esterifications of highly hindered aliphatic and aromatic acids, the classes of acids that had been bypassed by former investigators of carboxylate salt alkylations. A subsequent report[14] confirmed these findings and provided indications of more rapid alkylations in neat HMPA. A comparable rapid, mild, and quantitative esterification of severely hindered carboxylic acids has been unattainable under acid-catalyzed conditions.[29-31]

To date, there has been no systematic and quantitative investigation of rates of carboxylate salt alkylations; all former reaction conditions were determined empirically. The present kinetic study was therefore initiated to acquire essential data for the factors affecting rates including the correlation of structural variations in the carboxylate salts.

Results and Discussion

The second-order alkylation rates of carboxylate salts are influenced by the nature of the cation, solvent, and organic halide. Clarification of the effects of these parameters with model carboxylates was essential for establishing efficient conditions for rate measurements of the series of carboxylate structures.

Carboxylate anions in association with large (soft) counterions are more reactive than with small (hard) counterions because of higher charge separation with the former.[32] The extent of the cation effect in salt alkylations was examined under a prescribed set of experimental conditions for which the results are recorded in Table I. Although the

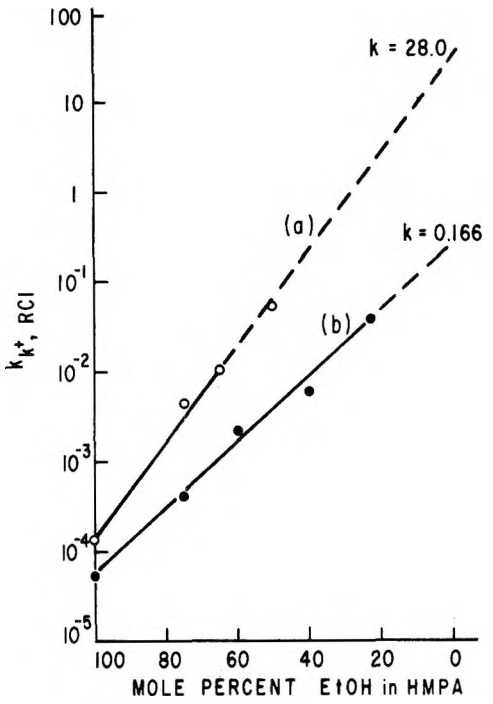


Figure 1. Determination of rate constants for the alkylation of potassium 2-methyl-2-propylpentanoate with (a) 1-iodopentane in mixtures of HMPA–EtOH; (b) 1-bromopentane in HMPA–EtOH. Rate constants k_{K^+}: (a) 28.0 l./mol s and (b) 1.66×10^{-1} l./mol s obtained for the pure aprotic solvents were determined by extrapolation to 0 mol % EtOH concentration.

anticipated order of increasing reactivity Li < Na < K < Cs was observed in the series, the relative acceleration of Cs/Li was only a doubling in rate. Consequently, potassium was chosen as a convenient standard cation for the kinetic measurements obtained in this work.

Alkylation rates with primary alkyl iodides and bromides were inconveniently slow in alcoholic solutions and too rapid in dipolar aprotic solvents for accurate measurements. Attempts to reduce the rates to an acceptable measurement range in the latter solvents by high dilution were unsuccessful owing to inaccuracies in measurement of the potentiometric end points used to follow the changes in carboxylate anion concentration. An effective compromise for moderation of the rates in dipolar aprotic solvents was attained by alcoholic dilution in which the dipolar aprotic solvents ranged in concentration from 0–50 mol % for 1-iodopentane and 0–80 mol % for 1-bromopentane reactions. In each series, the specific rate constant k was plotted against the mole ratio of solvent composition and the absolute value of k in the neat solvent was obtained by extrapolation.[33] The semilogarithm plot of rate constants vs. mol % ethanol–HMPA in Figure 1 illustrates the efficacy of the extrapolation technique.

The structure of the diluent alcohol also influenced the rate. The rate constants increased by more than fourfold from methanol (relative rate 1) to ethanol (3.8) to 2-propanol (4.3) in 25:75 mol % HMPA–alcohol. The rate sequence is apparently a function of the relative differences in hydrogen bonding of the alcohols to carboxylate anion, the more acidic alcohol providing the more effective proton donation.

Rapid and nearly complete alkylation of carboxylate salt with reactive organic halides has been previously demonstrated in nonpolar[16,17] and polar solvents.[18,19] With less reactive alkyl halides, the use of dipolar aprotic solvents for alkylation has been marginally successful.[12,24] Normant[12] obtained only moderate yields of esters in HMPA–tetrahydrofuran mixtures, although he anticipated higher conversions at higher concentrations. The method was subsequently applied by Mitchell[24] for preparations of triglycerides that were obtained in low to moderate yields by reaction of sodium carboxylate with mono- and diacyloxychloropropanes in neat HMPA, *N,N*-dimethylformamide (DMF), or dimethyl sulfoxide (Me_2SO). In the present solvent study, potassium 3,3-dimethyl-2-ethylbutanoate was selected as the model reactant and 1-chlorohexane as the unactivated alkyl halide. The results of alkylations at 60 °C in four dipolar aprotic solvents are listed in Table II. Under these conditions, no reaction took place in pure ethanol as expected, although other workers[9,24] had reported forcing the reaction between unactivated alkyl chlorides and carboxylate anions at elevated temperatures up to 165 °C. In our present studies, we have found HMPA to be the most effective solvent for halogen displacement. The rates of displacement were tenfold greater than in DMF and sevenfold greater than in either Me_2SO or *N*-methylpyrrolidone (NMP). The order of increasing effectiveness of the solvents on anion reactivity paralleled the order of their corresponding potassium solvation potential described by Parker and Owensby.[34] Thus, the greater cation separation induced by more effective solvation of the potassium counterion generated a relatively more reactive carboxylate anion.

The order of reactivity of halogen in organic halides in SN2 reactions is I > Br > Cl. The order is also observed for alkylation of potassium 2-methyl-2-propylpentanoate with primary halide (Table III) whereby iodide and bromide react 590 and 35 times, respectively, more rapidly than chloride. While the rate constant for the alkyl chloride alkylation could be determined in pure HMPA, the rate constants of the very rapid bromide and iodide alkylations ne-

Table I. Effect of Gegenion on Alkylation Rate of 2-Methyl-2-propylpentanoate with 1-Iodopentane at 60 °C[a]

Gegenion	$k \times 10^3$, l./mol s[a]	Rel rate
Cs^+	4.2	2
K^+	3.3	1.5
Na^+	2.3	1.1
Li^+	2.1	1

[a] Solvent: HMPA–EtOH (1:1 v/v).

Table II. Rates of Alkylation in Dipolar Aprotic Solvents. Reaction of 1-Chlorohexane and Potassium 3,3-Dimethyl-2-ethylbutanoate at 60 °C

Solvent	$k \times 10^2$, l./mol s	k_{HMPA}/k_s[a]
HMPA	8.2	1
NMP[b]	1.2	6.8
Me_2SO	1.2	6.8
DMF	0.83	9.8

[a] k_s indicates other solvents in series. [b] *N*-methylpyrrolidone.

Table III. Halogen Leaving Group Effect on the Alkylation Rate of Potassium 2-Methyl-2-propylpentanoate in HMPA at 60 °C

Primary alkyl halide	k, l./mol s[a]	Rel rate
1-Iodopentane	28.0	587
1-Bromopentane	0.166	35
1-Chlorohexane	0.00470[b]	1

[a] Rate constant obtained by the graphical extrapolation of the alcohol dilution rate data (Figure 1). [b] Measured directly in pure HMPA.

Table IV. Comparison of Alkylation of Potassium Carboxylates in Me_2SO with Acid-Catalyzed Esterification of Free Carboxylic Acids in Methanol

Registry no.	Carboxylic acid	pK$_a$	$k_{K^+,RCl} \times 10^3$, l./mol s[a]	$k_{K^+,RI}$, l./mol s[b]	$k_{H^+,MEOH}$, l./mol s[c]	"6" number	$k_{K^+,RI}$[d]/$k_{H^+,MeOH}$
327-62-8	$CH_3CH_2CO_2H$	5.93	4.61	2.70	0.440	0	6.13
19455-23-3	$(CH_3)_3CCO_2H$	6.45	4.90	2.8	0.019	0	147
19455-00-6	$CH_3(CH_2)_4CO_2H$	5.90	5.50	3.2	0.260	3	12.3
58220-00-1	$(CH_3CH_2CH_2)_2(CH_3)CCO_2H$	6.59	7.00	4.10[e]		6	
58220-01-2	$CH_3CH_2CH_2CH_2(CH_3CH_2CH_2)$-$CHCO_2H$	6.37	6.95	4.07	0.0048	6	900
58220-02-3	$(CH_3)_3CCH_2CO_2H$	6.26	8.40	4.93	0.012	9	400
58220-03-4	$(CH_3)_3CCH(CH_2CH_3)CO_2H$	6.50	11.7	6.86	$<4.0 \times 10^{-5}$	12	$>1.7 \times 10^5$
58220-04-5	$[(CH_3)_2CH]_2CHCO_2H$	6.48	10.2	5.98	$<4.0 \times 10^{-5}$	15	$>2.1 \times 10^5$
58220-05-6	$[(CH_3)_2CH]CH[(CH_3)_3C]CO_2H$	6.76	14.5	8.51	$<4.0 \times 10^{-5}$	15	$>2.1 \times 10^5$
58220-06-7	$[(CH_3)_2CH]_3CCO_2H$	7.36				18	
58220-08-9	9(10)-Carbomethoxystearic acid		4.6	2.70		3	
58267-05-3	Methyl 9(10)-Carboxystearate		9.9	5.81		6	
58220-07-8	(*E*)-$CH_3CH_2CH_2CH{=}CHCO_2H$		2.50	1.46		3	
58229-38-2	(*E*)-$CH_3CH_2CH{=}CHCH_2CO_2H$		2.71	1.59		2	
112-80-1	(*Z*)-$CH_3(CH_2)_7CH{=}CH(CH_2)_7C$-$O_2H$		7.60	4.46		3	

[a] Rate constants for reaction with 1-chlorohexane were determined at 60 °C over 3 half-lives. [b] $k_{K^+,RI}$ (rate constant with 1-iodopentane) was calculated by multiplication of $k_{K^+,RCl}$ by the appropriate conversion factor 587. [c] Data from Loening et al. (ref 30). All rates have been corrected to 60 °C. [d] $k_{K^+,RI}/k_{H^+,MeOH}$ is the relative rate of alkylation with 1-iodopentane compared with acid-catalyzed methanol esterification. [e] Note that multiplication of this rate by the appropriate conversion factor obtained for k_{HMPA}/k_{Me_2SO} (Table III) yields 27.8, the value obtained in the extrapolation of the plot in Figure 1.

cessitated determination by the alcohol dilution–extrapolation method described above.

Reaction of a long-chain primary alkyl halide, 1-iododecane, and potassium 2-methyl-2-propylpentanoate in HMPA (60 °C) gave no indication of a competitive elimination process as shown by the absence of decene. The corresponding reaction with a long-chain secondary alkyl halide, 2-bromooctane, under the same conditions produced appreciable quantities of octene (36%) and starting free acid. The same amount of olefin was also produced at 25 °C. Although an earlier report[14] has demonstrated the quantitative formation of ester in alkylations of carboxylate salts with secondary halides, it should be emphasized that these reactions were performed in solutions containing both base and alkyl halide in excess. In the latter work, competitive elimination has undoubtedly taken place, but since the carboxylic acid produced is rapidly deprotonated by excess base it is not lost and alkylation may be quantitative. Although the reaction may be deemed useful for the preparation of secondary alkyl esters, the rates with secondary halides were not determined because of the complications of the dehydrohalogenations.

Elucidation of rates with variation in cation, solvent, and halide permit the establishment of optimum alkylation conditions for preparative use as well as for kinetic measurements. The combination of alkyl iodides and cesium salts in HMPA offers the most rapid alkylations. The rate data, however, may permit more practical choices. For the kinetic measurements of a series of carboxylic acid structures, our choice of potassium counterion, primary alkyl chloride, and Me_2SO was considered propitious for accurate measurements in a convenient concentration range and time span. The rate constants reported for 1-iodopentane alkylations $k_{K^+,RI}$ are calculated values obtained by multiplying the appropriate chloride alkylation rate constant $k_{K^+,RCl}$ by the conversion factor derived from data in Figure 1. The results permit a parallel comparison of anion alkylation rates with acid-catalyzed esterification rates for a series of carboxylate structures. The pseudo-second-order rate constants for the acid-catalyzed process k_{H^+} are literature values corrected to 60 °C.[29] It is well known that the rate of acid-catalyzed esterification diminishes with increasing steric bulk of the carboxylic acid as indicated by the data assembled in Table IV, column 4. Comparison of the anion alkylation rate constants (column 3) shows these constants to be larger than the acid-catalyzed rate constants (column 4) and further shows a slight overall increase in the former k's with an increase in steric bulk. This suggested that steric effects increased the nucleophilicity of the carboxylate anion. The increased reactivity may be attributed to steric inhibition to solvation of the crowded anion.

In an effort to correlate the dependence of carboxylate structure with reactivity, we attempted a comparison of the nucleophilicity of the carboxylate anion as measured by the log $k_{K^+,RCl}$ with proton affinity as characterized by the pK of the corresponding free acids. pK measurements were performed in aqueous methanol (50:50 v/v), a solvent mixture chosen for convenient comparison of the pK data with data of other investigators[31] (see column 1, Table IV). The pK of 3,3-dimethylbutanoic acid was periodically measured throughout the study to monitor the accuracy of the new constants. A semilog plot of the anion alkylation rate constants of α-alkyl substituted potassium carboxylates vs. apparent pK of the corresponding free carboxylic acids in aqueous methanol at 40 °C showed wide scattering. In two comparative examples, propionate vs. 2,2,2-trimethylacetate and 2-propylhexanoate vs. 2-methyl-2-propylpentanoate, we find the same $k_{K^+,RCl}$ but different pK values. The grid evidently does not provide any discernible correlation between aliphatic carboxylate structure and nucleophilicity.

A well-known method of correlating structure with nucleophilicity is Newman's rule of six or six-number.[30] Newman's rule provides an empirical correlation of the steric effects of substituents for reactions at an unsaturated function such as the addition of alcohol to the carbonyl of a carboxylic acid. The rule has also been amplified to include the attacking atom in the six-rule scheme.[35] In accordance with the rule, the atoms effectively providing steric hindrance to addition to a carbonyl function are separated from the attacking atom in the transition state by a chain of four atoms. By designating either the carbonyl oxygen or the attacking atom as the "1" position, the interfering atoms will be located at the "6" position (Figure 2a). In the coiled aliphatic chain with normal bond lengths and bond

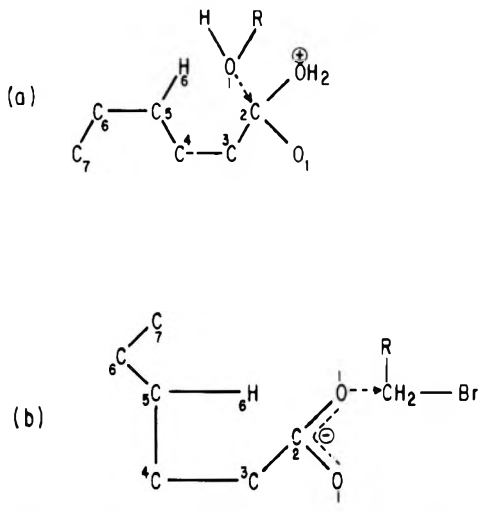


Figure 2. (a) Coiled conformation for transition state of acids in esterification. (b) Coiled conformation for transition state of anions in alkylation.

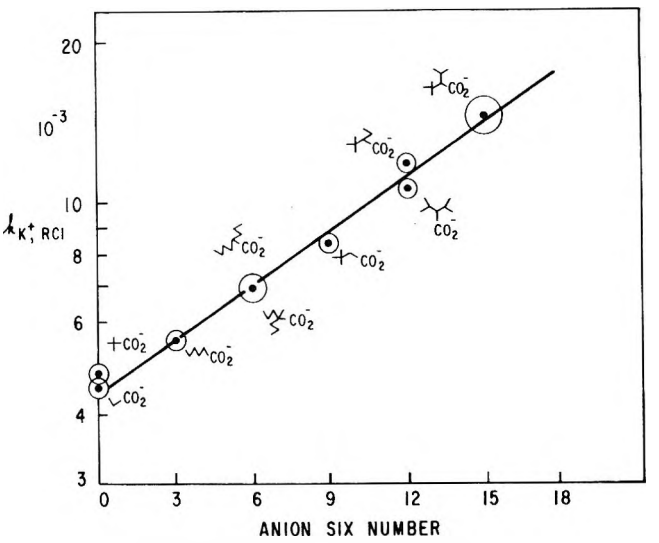


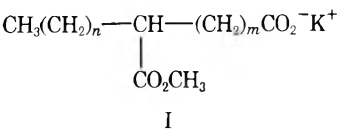
Figure 3. Plot of log k_{K^+}, l./mol s, for alkyl-substituted potassium carboxylates reacting with 1-chlorohexane in Me_2SO at 60 °C vs. six-number; correlation coefficient 0.992.

angles, the attacking atom is blocked more effectively by an atom at the 6 position than at the 5 or 7 positions.[30] In the case of a few (three or six) atoms in the 6 positions, rotation about the C_3–C_4 bond displaces the blocking atom from the path of the attacking nucleophile whereas the presence of nine or more atoms in the 6 positions increases the difficulty of twisting the chain into permissible conformations to avoid interactions with the 1 position. In Table IV, columns 4 and 5, it is evident that acid-catalyzed esterification rates are slow ($\sim 10^{-2}$) for a six-number of 9 and rapidly diminish to 10^{-5}–10^{-6} l./mol s for a six-number of 12 and higher.

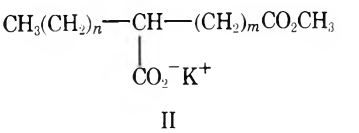
In contrast to the order of reactivity for acid-catalyzed esterifications, carboxylate alkylations show the converse effect of an overall increase in rate with increase in bulk (Table IV, columns 3, 4, and 5). Since the six-number is a qualitative expression of steric effects in acid-catalyzed esterification, it seemed reasonable to expect the six-number to also be applicable to a correlation of steric bulk in anion alkylation rate constants except that increasing bulk would be directly related to increasing reactivity. In the coiled conformation of the carboxylate chain in the transition state, the oxygen atoms are designated the 1 positions and the atoms located at the 6 positions exercise steric effects on the cation–anion association. Interference with the cation–anion interaction or exclusion of solvation of the anion increases the anion activity (Figure 2b). Unlike the alcohol oxygen in acid-catalyzed esterification, the reacting carbon atom of the alkylating reagent lies outside the direct sphere of influence of the 6 position atoms and is, therefore, excluded from the numbering scheme. The conformation of the carboxylate anion chain is a five-member ring arrangement compared to the six-atom ring system in acid-catalyzed alcoholysis.

In a plot of log $k_{K^+,RCl}$ vs. six-number (Figure 3) an excellent linear correlation was obtained for which the correlation coefficient is 0.992. Although the overall effect of steric bulk on rate seems subtle because of the relatively narrow rate constant range, the implications for the consequences of structural crowding are evident. Steric inhibition to solvation induced by increased crowding about the carboxylate center may raise the energy of the ground state relative to the transition state. The larger the observed rate constant, the greater would be the relative degree of "nakedness" [36,37] associated with the reacting anion. For structurally dissimilar carboxylates having a six-number of zero such as 2,2,2-trimethylacetate (a trialkyl acetate) and propionate (a monoalkyl acetate) or carboxylates with a six-number of 6 such as 2-methyl-2-propylpentanoate (a trialkyl acetate) and 2-propylhexanoate (a dialkyl acetate), the anion six-number correlation necessitates that each pair of anions have the same rate constant. It is evident in Figure 3 that these predictions are in agreement with our findings. On the basis of inductive effects, the more highly α-substituted salts would be expected to react faster than the less substituted members. Inductive effects of aliphatic substitutions at the α carbon, unlike steric crowding at the 6 position, do not appear to exert a measurable change in reactivity. The plot further suggests that both 6-position carbon and hydrogen atoms produce a comparable rate acceleration since all plotted compounds have been classified without regard to the size of the 6-position atom. In contrast, Newman's[30] findings showed a larger relative decrease in rate with increase in size of the blocking atom. Based on the excellent correlation given by the log $k_{K^+,RCl}$ vs. six-number, extrapolation of the plot in Figure 3 permits the prediction of rate constants for the alkylation of many hindered carboxylates.

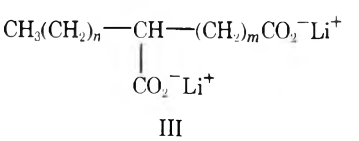
As an illustration of competitive alkylation for positionally isomeric dibasic acid salts, we studied the reaction of potassium 9(10)-carbomethoxystearate (I) and methyl 9(10)-potassium carboxystearate (II). The results in Table



I



II



III

$n = 7$, $m = 8$ or $n = 8$, $m = 7$

IV indicate that the internal carboxylate in isomer II is alkylated more than twice as rapidly as the terminal carboxylate of isomer I. The difference in reactivity is further em-

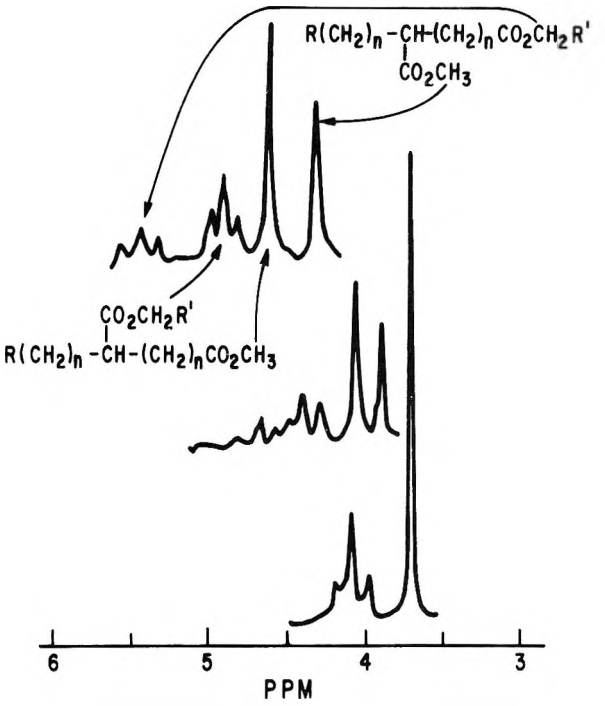


Figure 4. Proton NMR spectrum of a mixture of methyl 9(10)-carbopentoxystearate and pentyl 9(10)-carbomethoxystearate: sample in 350 μl of CCl_4; Me_4Si as internal standard. Lower spectrum, 40 mg of mixed esters. Middle spectrum, 40 mg of mixed esters plus 5 μl of 0.288 M CCl_4 solution of $Eu(fod)_3$. Upper spectrum, 40 mg of mixed esters plus 10 μl of 0.288 M CCl_4 solution of $Eu(fod)_3$.

phasized by the competitive alkylation of the dilithium salt of 9(10)-carboxystearic acid (III).[38] Reaction of III in HMPA with 1 equiv of *n*-pentyl iodide yielded a mixture of unalkylated (16%), monoalkylated (41%), and dialkylated (43%) products.[39] After acidification of the reaction mixture, the remaining free carboxylic acid sites were esterified with diazomethane. However, GLC resolution of the mixed esters was unsuccessful. Analysis of the mixture of the two isomeric mixed methyl pentyl esters which was first isolated by preparative GLC as a mixture in a single fraction was performed by proton NMR using $Eu(fod)_3$ pseudocontact shift reagent. The peak intensities illustrated in Figure 4 revealed that the methyl substitution at the terminal carboxyl group was double the methyl substitution at the central carboxyl group. The product distribution by NMR analysis corroborates the relative alkylation reactivities established by the kinetic data for I and II. Although in this example the alkylation technique does not lend itself to unusually high positional alkylation specificity, the alkylation is distinctly advantageous for the esterification of dioic acids. Specifically, utilizing either half-ester salts such as I or II, it is possible to synthesize positionally pure mixed diesters, thereby obviating the problem of random transesterification generally associated with acid-catalyzed procedures.[40]

The effect of unsaturation in proximate positions to the carboxylate function was examined for the members listed in Table IV. The rates of alkylation of isomeric unsaturated carboxylates, potassium (*E*)-3-hexenoate and potassium (*E*)-2-hexenoate, were each one-half the rate of potassium hexanoate. However, a double bond located at an isolated position with respect to the reactive site as in potassium (*Z*)-9-octadecenoate does not appear to diminish the reactivity to alkylation. Unexpectedly, the rate constant for potassium (*Z*)-9-octadecenoate was approximately 50% larger than the constant for the shorter chain saturated hexanoate. A larger relative reaction rate was also noted for the alkylation of the internal carboxylate of the long-chain methyl 9(10)-carboxystearate relative to similarly hindered (six-number, 6) short-chain carboxylate salts (see Table IV, entries 4, 5, and 11). It is conceivable that the longer chain salts exclude solvent from the reactive site, thereby increasing their reactivity relative to the short-chain homologues. Unfortunately, reliable rate constants for the potassium salt of long-chain saturated fatty acids such as stearic acid could not be obtained owing to their extreme insolubility in Me_2SO. Notwithstanding this hindrance to its kinetic measurement, potassium stearate may nevertheless be rapidly and quantitatively alkylated routinely by this method of esterification.

The alkylation of salts of substituted aromatic carboxylates were similarly studied to assess the effects of electron donation and withdrawal on the rapidity of reaction. The entries in Table V, column 1, demonstrate that alkylation rates were diminished by electron withdrawal and accelerated by electron donation. The same trend has been observed for acid-catalyzed esterification of substituted benzoic acid derivatives (Table V, column 3).[29] The kinetics of alkylation were directly dependent on the reactivity of the nucleophilic carboxylate anion. Hammett plots comparing the sensitivity of anion alkylation and acid-catalyzed esterification to substituents are shown in Figure 5. The least-squares probable error for the reaction constant ρ obtained for both acid-catalyzed esterification[29] and alkylation was 0.05. This value compares favorably with Hammett's probable error of 0.067 for a series of 39 reactions.[41] Comparison of slopes for carboxylate alkylation ($\rho = -0.79$) and acid-catalyzed esterification ($\rho = -0.58$) shows the former to be 30% more sensitive to substituent effects.

Like the aliphatic series, the aromatic carboxylate salts also show increased reactivity with increase in steric crowding (Table V). β-Isodurylic acid (2,4,6-trimethylbenzoic acid) cannot be esterified under normal acid-catalyzed conditions, even though the three methyl groups are activating. The compound's resistance to esterification by alcohol

Table V. Comparison of Aromatic Carboxylic Acid Esterifications. Alkylation of Potassium Carboxylates in Me_2SO vs. HCl-Catalyzed Methanolysis of Carboxylic Acids

Registry no.	Potassium carboxylate salt	$k_{K^+,RCl} \times 10^4$ [a]	$k_{K^+,RI}$ [b]	$k_{H^+,MeOH} \times 10^3$ [c]	$k_{K^+,RI}/k_{H^+,MeOH}$
15922-01-7	*p*-Nitrobenzoate	3.12	0.183	1.15	122
15163-59-4	*o*-Nitrobenzoate	2.42	0.142	0.172	825
51550-68-6	*p*-Bromobenzoate	7.72	0.453	1.57	288
582-25-2	Benzoate	10.3	0.604	2.93	206
16518-25-5	*p*-Methylbenzoate	14.0	0.821	2.25[d]	364
52509-81-6	*p*-Methoxybenzoate	20.0	1.17		
53756-55-1	2,4,6-Trimethylbenzoate	20.0	1.17	Too slow	

[a] RCl = $C_6H_{13}Cl$, $k_{K^+,RCl}$ in l./mol s. [b] RI = $C_5H_{11}I$, $k_{K^+,RI}$ in l./mol s calculated from 1-chlorohexane data by multiplication by 587. [c] Data taken from Hartman and Borders (ref 29) for $k_{H^+,MeOH}$ at 60 °C. [d] This point falls off the line; however, the least-squares probable error for ρ of 0.05 does not reflect this because more than ten points were used in the original study.

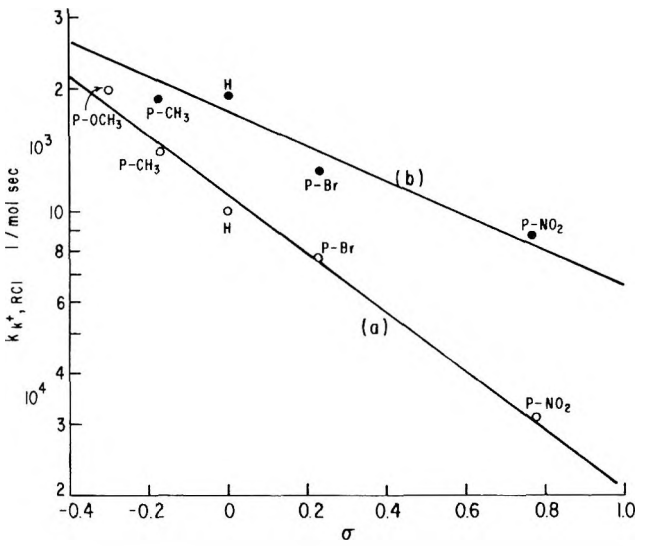
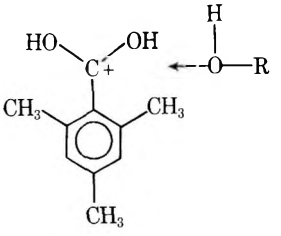


Figure 5. Hammett semilogarithm plot of rate constants of reaction vs. σ constants. (a) Rates of alkylation of aromatic carboxylates with 1-chlorohexane in Me_2SO (60 °C) $\rho = -0.73$. (b) Rates of acid-catalyzed esterification (0.02–0.1 M HCl) in methanol (60 °C) $\rho = -0.58$, data obtained from Hartman and Borders (ref 29).

is due primarily to the steric restrictions imposed about the protonated tetrahedral intermediate IV. Alkylation of the



IV

corresponding carboxylate salts circumvents the problem of steric hindrance at the tetrahedral carbonium ion site in IV by attack at either of the nonhindered oxygen anions in the sp^2-hybridized carboxylate structure. β-Isodurylate is one of the fastest reacting carboxylates in the aromatic series, the reactivity being attributed to desolvation of the anion in its ground state. For this type of highly hindered aromatic acid, anion alkylation with alkyl iodide is a highly efficient mode of preparing esters as indicated by the ratio of rate constants of anion alkylation to acid alcoholysis (Table V, column 5). The *o*-nitro substituted benzoate in which the nitro group hinders the carboxylic function shows the largest relative rate ratio among the members of the series. The field effect as well as the inductive effect of the nitro substituent is evidently attenuated at the oxygen atoms one carbon removed from the ring in the anion relative to the strong deactivating ortho effect felt at the ring bonded carbonyl site in the corresponding acid.

Experimental Section

Materials. All solvents were carefully purified by fractional distillation. Hexamethylphosphoramide was distilled from calcium hydride at reduced pressure and the center cut refractionated, bp 56 °C (0.3 mm). *N,N*-Dimethylformamide, bp 148–150 °C, was stirred over potassium hydroxide, decanted, and distilled from sodium bicarbonate. Me_2SO was distilled at 70 °C (10 mm). *N*-Methylpyrrolidone was initially dried by azeotropic distillation with benzene followed by fractional distillation at 80 °C (10 mm).

Detection of free base in each solvent was obtained by potentiometric titration with 0.01 M $HClO_4$ in 2-propanol–ethylene glycol (1:1 by volume). Solvents requiring 0.5 ml of titrant per 20 ml were repurified. A blank determination was made prior to each kinetic experiment.

Instrumentation. Potentiometric titrations were carried out with a standard glass electrode and a Fischer Model 320 expanded scale research pH meter.[42]

GLC analysis was performed on a Model 5750 Hewlett-Packard F & M programmable gas chromatograph equipped with an Infotronics Model CRS-11HSB digital readout system.

NMR analysis was performed on a JEOL C-60H spectrometer.

Kinetic Measurements. Carboxylate salt (approximate concentrations 0.0150 M) and alkyl halide (approximate concentration 0.0450 M) were accurately weighed and dissolved in the appropriate solvents and thermostated at 60 °C. To each of four 50-ml volumetric flasks in the thermostated bath were pipetted the carboxylate salt solution (10 ml) and the alkyl halide solution (10 ml), the resulting mixture containing alkyl halide to carboxylate salt in the approximate molar ratio of 3:1. At periodic intervals the contents of each flask were quenched in a 250-ml Erlenmeyer flask containing 15 ml of 2-propanol–ethylene glycol 50:50 v/v solution at −70 °C. Quantitative transfer of the reaction solution was completed with an additional washing of 15 ml of the solvent mixture and the contents titrated potentiometrically with a standard solution of approximately 0.010 M $HClO_4$ in 50:50 v/v 2-propanol–ethylene glycol using a glass electrode. The inflection point of each titration curve corresponding to the remaining unreacted salt was determined by evaluation of the second derivative of the potentiometric curve using two points above and two points below the sharp change in millivolt potential (apparent pH). Rate constants were calculated from the standard second-order expression

$$k = \frac{a \ln (A/A_0)(B_0/B)}{t(bA_0 - aB_0)}$$

where A_0 = initial concentration of carboxylate salt, A = concentration of carboxylate salt remaining at time t, B_0 = initial concentration of alkyl halide, B = concentration of alkyl halide remaining at time t, and a and b are integral coefficients in the balanced chemical equation.

All rate constants were examined for competency by least-squares analysis, correlation coefficients, and standard deviation calculations. In general all k's gave a correlation coefficient for second-order kinetic of 0.995 or better.

Preparation of Di- and Trialkyl Acetic Acids. Di- and trialkyl acetic acids were prepared according to the α-anion alkylation procedure previously described.[43] However, unlike ordinary monoalkyl acetic acids, 3-methylbutanoic acid dianion was insoluble and, therefore, required heating for 2 h at 50 °C in THF–HMPA prior to alkylation. Owing to the increased solubility imparted by the branching of the *tert*-butyl acetate dianion, no HMPA was required as cosolvent.

Using the α-anion procedure[43] for the metalation of 3-methylbutanoic acid we obtained 90% alkylation with 1-iodoethane to give 2-ethyl-3-methylbutanoic acid. 2-Isopropyl-3-methylbutanoic acid was prepared similarly through the α-alkylation of 3-methylbutanoic acid with 2-bromopropane in approximately 50% yield.

Preparation of Carboxylate Salts. All carboxylate salts were prepared by titration of the corresponding carboxylic acids in ethanol with standard solutions of CsOH, KOH, NaOH, and LiOH, using phenolphthalein as end point indicator. The solvent was removed by rotary film evaporation and the salts dried in vacuo (0.01 mm) at 50 °C for 24 h. When additional purification was required, the salts were crystallized from appropriate solvents and triturated with hydrocarbon. Potassium nonanoate was recrystallized from THF, potassium 2-methyl-2-propylpentanoate was recrystallized from isopropyl alcohol, and potassium 2-propylhexanoate was triturated with hexane, as were the remaining salts when additional purity was desired. The salts were kept dry by storage in a desiccator over P_2O_5.

p*K* Measurements of Carboxylic Acids. The ionization constants were measured according to the method of Newman and Fukunaga.[31] The determinations were made by potentiometric titration using a glass electrode and standard pH meter in 50 vol % methanol–water at 40 °C. The ionization constants were calculated by the standard pH equation at ¼, ½, and ¾ neutralization points. The system was standardized before and after each titration with 0.05 M phthalate buffer for pH 4.03, 0.05 M phosphate buffer for pH 6.84, and 0.01 M borax buffer for pH 9.07.

Reaction of Dilithio 9(10)-Carboxystearate with 1-Iodopentane. Dilithium 9(10)-carboxystearate (0.50 g, 1.52 mm) was dissolved in 15 ml of HMPA (containing 3 ml of ethyl alcohol to increase the salt's solubility). To this solution at 85 °C (0.347 g, 1.75 mm) of 1-iodopentane was added with mechanical stirring. The reaction was allowed to proceed for 15 min, quenched with water

(200 ml), acidified with 10% hydrochloric acid, and extracted three times with petroleum ether. The petroleum ether layer was washed four times with 30-ml portions of dilute HCl and water followed by sodium thiosulfate solution to remove any liberated iodine. The organic layer was dried and solvent removed by rotary evaporation to yield 0.66 g of crude product. The crude product was treated with an ethereal solution of diazomethane and the mixture of esters examined by GLC using a 5 ft × 0.125 in. 5% SE-30 column programmed from 180 to 260 °C at 4 °C/min. The chromatogram showed the presence of four products: (1) methyl 9(10)-carbomethoxystearate (16%), retention time 3 min; (2) a mixture of methyl 9(10)-carbopentoxystearate and (3) pentyl 9(10)-carbomethoxystearate (total 41%), retention times 6 and 6.2 min, respectively (peaks were not resolvable); and (4) pentyl 9(10)-carbopentoxystearate (43%), retention time 12 min. The above mixture was injected onto a 2-ft 10% silicone gum rubber GLC column at 180 °C and the unresolved mixture of peaks 2 and 3 were preparatively trapped. Analysis of the products of this mixture (2 + 3) was performed by NMR using $Eu(fod)_3$ shift reagent.

NMR Analysis of 9(10)-Carboxystearic Acid Esters Using $Eu(fod)_3$ in CCl_4. GLC-trapped samples containing a mixture of isomers, methyl 9(10)-carbopentoxystearate and pentyl 9(10)-carbomethoxystearate, were analyzed as follows. Approximately 40 mg of sample mixture was dissolved in 350 μl of CCl_4 containing 2% Me_4Si. The spectrum of this mixture displayed a sharp methoxy singlet at δ 3.7. Upon addition of 10 μl of $Eu(fod)_3$ solution (0.288 M) the methoxy singlet split into two distinct singlets at δ 4.3 and 4.6. The lower field singlet was attributed to methyl 9(10)-carbopentoxystearate and the upper field singlet to pentyl 9(10)-carbomethoxystearate after comparison with the spectra of known mixtures of these two pure components. The integrated ratio of the δ 4.3 to the δ 4.6 resonances was 2:1, respectively.

Preparation of Potassium 9(10)-Carbomethoxystearate by Selective Hydrolysis of Methyl 9(10)-Carbomethoxystearate.[44] Methyl 9(10)-carbomethoxystearate (5 g, 0.0154 mol) was dissolved in 25 ml of methanol containing H_2O (0.277 g, 0.0154 mol) and KOH (0.954 g, 0.0145 mol). The solution was stirred and refluxed for 2 h and solvent removed on a rotary film evaporator. The solid residue was extracted with ether to remove any unreacted dimethyl ester. A small sample of the remaining half methyl ester potassium salt was checked for isomeric purity by treating it with excess *n*-pentyl iodide in HMPA at 80 °C for 1 h. The resulting mixed ester was examined by GLC using a 5 ft × 0.125 in. 5% SE-30 column programmed from 180 to 260 °C at 4 °C/min. The chromatogram showed one peak which corresponded to the mixed esters methyl 9(10)-carbopentoxy- and pentyl 9(10)-carbomethoxystearate and a trace of pentyl 9(10)-carbopentoxystearate. NMR analysis using the $Eu(fod)_3$ technique described above confirmed that the reaction product was 96% pentyl 9(10)-carbomethoxystearate and 4% methyl 9(10)-carbopentoxystearate.

Acknowledgment. We wish to thank Drs. E. N. Frankel and E. J. Dufek of the Northern Regional Research Center, USDA, Peoria, Ill., for providing us with samples of 9(10)-carboxystearic acid.

Registry No.—1-Iodopentane, 628-17-1; 1-bromopentane, 110-53-2; 1-chlorohexane, 544-10-5.

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The Stereodependent Effect of Oxygen on the Chemical Shifts and Vicinal Coupling Constants of Tetrahydropyran

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The analysis of the ^{1}H NMR spectra of two selectively deuterated derivatives of tetrahydropyran at −115 °C has provided accurate values for proton chemical shifts and vicinal coupling constants about the C(2)–C(3) bond. A comparison with the corresponding parameters of cyclohexane allows a precise definition of the stereodependent effect of oxygen ($^3J_{2a3a}$, $^3J_{2e3e}$, $^3J_{2a3e}$ are reduced while $^3J_{2e3a}$ is increased) in this fundamental molecule. An explanation of the trends observed is given and the conformational and stereochemical implications of the results are discussed.

The field of conformational and stereochemical analysis of basic six-membered ring systems is often considered fundamental in organic chemistry. NMR spectroscopy ranks among the most useful tools of experimental investigation in this domain and, when appropriate reference parameters are available, its application to molecules with readily analyzable spectra has become rather straightforward.[1] Vicinal coupling constants recently published[2] for cyclohexane-d_8 have provided the reference basis for many applications through an empirically determined dependence on dihedral angles.

It is well known that heteroatoms affect the values of vicinal couplings according to their electronegativity, and many efforts have been aimed at providing information on the magnitude of this effect. In particular, approximate coupling values have been proposed for pyranoid derivatives from studies on carbohydrate derivatives,[3] but there is at present no knowledge of the quantitative effect of oxygen in $-CH_2CH_2O-$ fragments from cyclic systems and more specifically from the parent compound, tetrahydrofuran.

Because of the fundamental nature of tetrahydropyran both for theoretical reasons and for practical conformational and stereochemical applications to many classes of heterocyclic organic compounds, it appeared to us that accurate chemical shift and coupling information for this basic compound should be a necessary prerequisite to quantitative deductions which go beyond merely drawing parallels between carbocyclic and heterocyclic rings.

Because of the complexity of the ^{1}H NMR spectrum of tetrahydropyran and the need to obtain very accurate coupling constants we have prepared stereospecifically deuterated derivatives with simpler spectra and because ring inversion is rapid at normal room temperature[4] we have analyzed the spectra at low temperatures in order to obtain parameters characteristic of the noninverting chair conformation of this molecule.

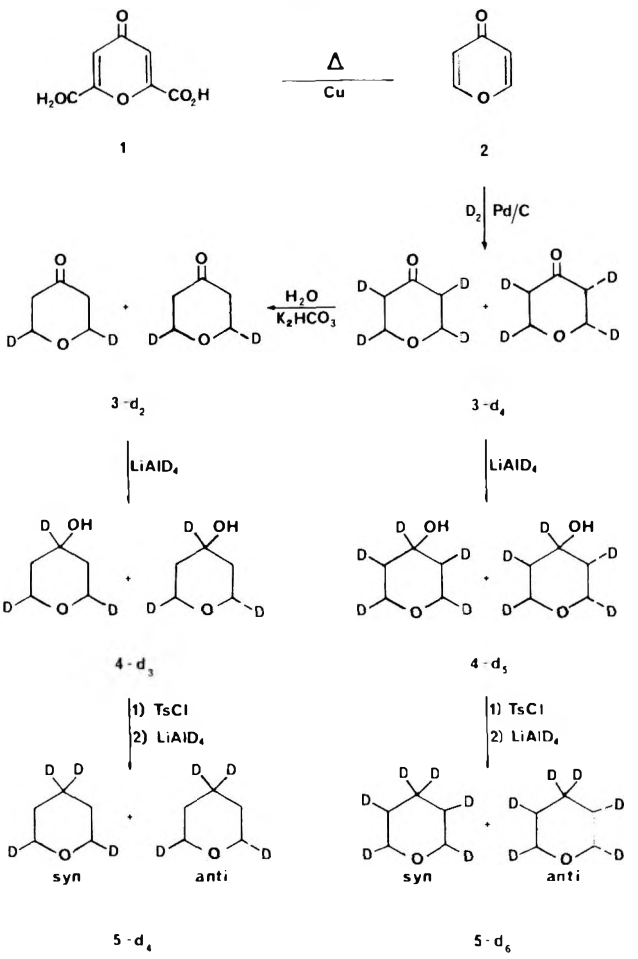
Results

As illustrated in Scheme I, γ-pyranone (**2**) obtained from chelidonic acid (**1**)[5] was deuterated with deuterium gas in the presence of palladium on carbon to give a mixture of syn and anti isomers[6] of tetrahydropyranone-*cis*-2,3,*cis*-5,6-d_4 (**3**-d_4) which were reduced with lithium aluminum deuteride to give the alcohols **4**-d_5 which were converted to tetrahydropyran-4,4,*cis*-2,3,*cis*-5,6-d_6 (**5**-d_6). Protonic exchange of the α deuterium in **3**-d_4 gave a mixture of syn and anti isomers tetrahydropyranone-2,6-d_2 (**3**-d_2) which were reduced to the alcohols **4**-d_3 followed by transformation to tetrahydropyran-2,4,4,6-d_4 (**5**-d_4).

Spectral Analysis. Deuterium decoupled, 100 MHz, ^{1}H NMR spectra of **5**-d_6 are shown in Figure 1. At 25 °C the spectrum contains two equally intense multiplets centered at 3.46 (α protons) and 1.45 ppm (β protons) while the spectrum at −115 °C reveals that a marked change, associated with the slowing down of ring inversion,[4] has taken place to give three multiplets of relative intensity 1:1:2 with increasing field.

Analysis of these spectra is not straightforward because both the syn and anti isomers of **5**-d_6 exist as a mixture of two equally populated conformations (**6**–**9**) differing only by the location of the deuterium atoms. If both sides of the molecules of **5**-d_6 were independent of each other, the time-averaged spectrum observed at 25 °C should consist of only four lines resulting from the superposition of AX patterns. Clearly this is not observed and the additional splitting may be due to a combination of several factors: (a) the presence of isotopic impurities[7] of the type

Scheme I



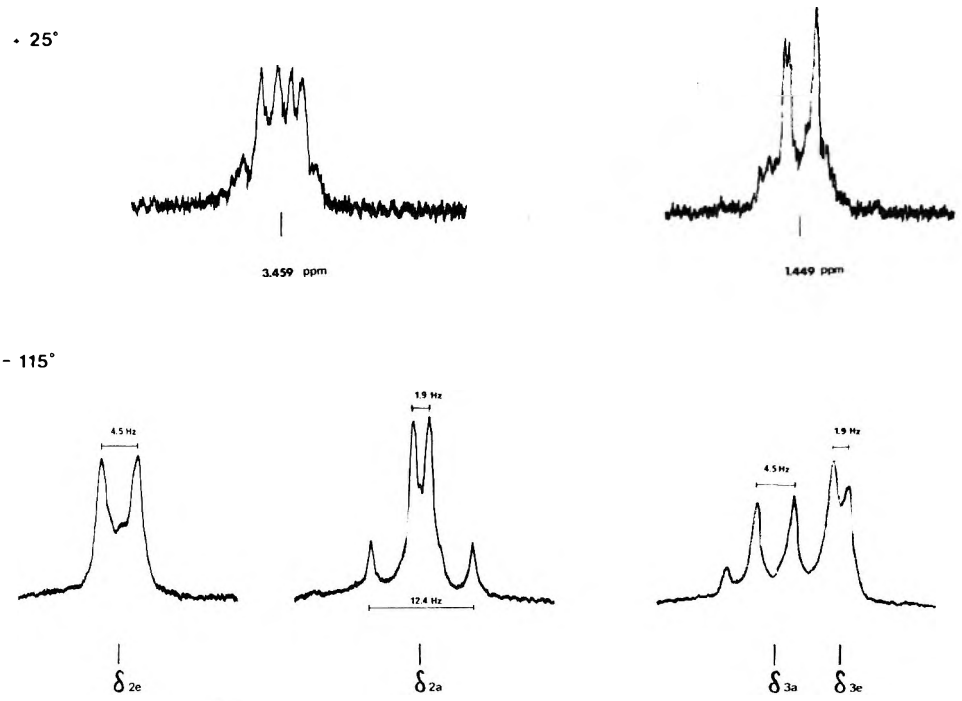
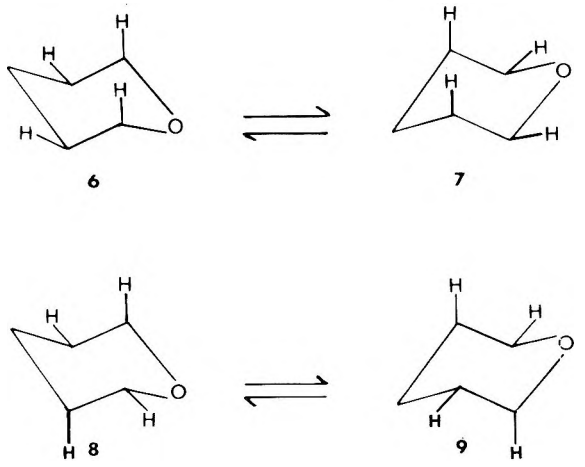


Figure 1. Deuterium decoupled 100 MHz ^{1}H NMR spectra of 5-d_6 in carbon disulfide at 25 and −115 °C.



–CHDCHD– trans and –CHDCH$_2$– suggested by the mass spectrum, (b) second-order effects arising from appreciable four-bond coupling between magnetically equivalent equatorial protons, and (c) a possible but small long-range isotope.[6] Fortunately, the more meaningful ^{1}H NMR parameters are revealed from the low-temperature spectrum and a detailed analysis of the averaged spectrum at 25 °C is not necessary.

The spectrum of 5-d_6 at −115 °C, on the other hand, appears to be much simpler since signals from isotopic impurities no longer coincide with those of the main product. In fact, the eight intense lines observed can readily be identified as two apparent AX patterns (one with a splitting of 4.5 Hz and the other of 1.9 Hz) expected for the two possible cis arrangements about the C(2)–C(3) bond (namely $H_{2e}H_{3a}$ and $H_{2a}H_{3e}$) when both sides of the molecules are treated as independent of one another, except for line broadening effects. First-order analysis and the knowledge that H_{2a} absorbs at higher field[8] than H_{2e} lead to the identification of the environment of protons on C(3) as written at the bottom of Figure 1 where it is shown that H_{3e} absorbs at higher field than H_{3a}.

The symmetry properties of conformations **6**–**9** suggest that second-order effects should be largest for the syn conformers **6** and **7** for which appreciable four-bond couplings are expected between the magnetically equivalent equatorial protons. On the other hand, the anti conformers **8** and **9** are expected to show little second-order effect because of the absence of magnetic equivalence and relatively small axial–equatorial four-bond coupling constants.[9,10] Computer simulations of AA′XX′ or ABXY patterns for the various forms have demonstrated convincingly that the anti isomer gives a first-order spectrum at −115 °C for which any small coupling between H_{2e} and H_{6a} would only broaden the spectral lines. Furthermore, the calculated spectra for **6** and **7** are slightly perturbed by second-order effects but since they represent only 50% of total intensity, the superposition of spectra for the syn and anti isomers gives a resultant spectrum for which the second-order effects only broaden the base of each peak so that separations measured from the experimental spectrum effectively are equal to the coupling constants expected for the two cis arrangements of protons about the C(2)–C(3) bond of tetrahydropyran. Isotopic impurities present in small amount would also affect the spectrum mostly at the base of the spectral lines of 5-d_6.

In addition to the intense doublet with the 1.9-Hz splitting, the signal identified by δ_{2a} in the spectrum at −115 °C (Figure 1) shows another, less intense, doublet possessing a 12.4-Hz splitting. Owing to the lack of exclusive cis selectivity[7] of the catalytic reduction in Scheme I, it is reasonable to assign this doublet to trans species (isotopic impurities) and consequently to conclude that $^3J_{2a3a}$ = 12.4 Hz. Careful examination of the high-field signal shows that the other half of the trans AX pattern is symmetrically disposed about δ_{3a}. One component of the doublet is readily visible at the left of the multiplet whereas the upfield component falls under a line from the cis species to give the most intense line of that multiplet. Since J_{2e3e} is small, the other trans AX pattern is not resolved.

It is therefore reasonable to conclude that first-order analysis of the low-temperature spectrum of 5-d_6 provides accurate vicinal coupling constants and that second-order effects broaden the lines. Accordingly the experimental error in the coupling constants is within 0.2 Hz.

Figure 2 shows the deuterium decoupled, 100 MHz, ^{1}H NMR spectrum of 5-d_4. The parameters obtained from the

Table I. ^{1}H NMR Parameters for Deuterated Derivatives of Tetrahydropyran and Cyclohexane

Parameter	Tetrahydropyran[a]	Cyclohexane[b]	Coupling differences
J_{2a3e}	1.9 Hz	3.65 Hz	−1.7 Hz[c]
J_{2e3e}	1.5	2.96	−1.5
J_{2a3a}	12.4	13.12	−0.7
J_{2e3a}	4.5	3.65	+0.8
$\Delta\nu_{2e2a}$	+0.527 ppm[d,e]	+0.479 ppm[e]	
$\Delta\nu_{3e3a}$	−0.074	+0.479[f]	
R	2.17	2.16	

[a] From the analysis of 5-d_4 and 5-d_6 in this work. [b] Values taken from ref 2 for cyclohexane-d_8. [c] The sign is negative when the coupling constant is smaller in tetrahydropyran than in cyclohexane. [d] Chemical shift differences were measured directly from the spectrum of 5-d_6. [e] The sign is positive when the axial proton chemical shift is smaller than the equatorial proton chemical shift. [f] Obviously C(2) and C(3) are identical for cyclohexane.

spectral analysis of 5-d_6 have enabled the computer simulation shown. The calculated spectrum consists of the sum of two equally intense ABX patterns whereby long-range coupling constants were considered to broaden the lines.[6-8] The X regions of each ABX system (B in Figure 2) are well separated from each other and their analysis provided an accurate value for J_{2e3e} = 1.5 Hz in addition to confirming the magnitude of 12.4 Hz for J_{2a3a}.

The fact that the chemical shift difference between H_{3a} and H_{3e} is quite small has made the analysis of the AB part of the spectrum (A in Figure 2) more difficult because several lines are closely spaced and one of the subspectra has an effective chemical shift difference smaller than J_{AB}.[11] The solid and broken lines of the stick diagram under the calculated spectrum identify the two ABX patterns.

Table I contains a summary of the pertinent ^{1}H NMR parameters characteristic of tetrahydropyran together with those for cyclohexane.[2]

Discussion

It is well known that among the various factors[12] affecting vicinal coupling constants, dihedral angles and the orientation of electronegative substituents[13] are most significant. Tetrahydropyran possesses some of the desired geometrical properties enabling a valuable test of existing concepts. Consequently, at the outset, it is important to define the geometrical properties of its chair conformation as precisely as possible.

Although the chair conformation of cyclohexane is well characterized,[14a] the extent of possible chair deformation for tetrahydropyran is not known with much certainty.[14b,c] In the last years the need for similar information concerning various six-membered cyclic compounds has led to the formulation of the R-value method[15,16] whereby a ratio R is defined for a $-CH_2CH_2-$ fragment such that

$$R = \frac{J_{trans}}{J_{cis}} \qquad J_{trans} = \tfrac{1}{2}(J_{aa} + J_{ee}) \qquad J_{cis} = \tfrac{1}{2}(J_{ae} + J_{ea})$$

Deviations from R = 2.16 (cyclohexane) are interpreted in terms of puckering (increase of R) or flattening (decrease of R) of the ring.

For tetrahydropyran R = 1.91 (J_{trans} = 7.4 and J_{cis} = 3.87 Hz)[15a] has been calculated from averaged couplings at ambient temperature. Using the individual vicinal coupling constants reported in Table I, the value R = 2.17 (J_{trans} = 6.95 and J_{cis} = 3.20 Hz) is calculated. The difference between these results lies outside the experimental error of our work and since isotope effects are unlikely for vicinal coupling constants,[17] we are tempted to suggest that part of the difference might lie in the limited accuracy of the averaged couplings obtained from the analysis of the averaged AA′XX′ spectrum[15a] of tetrahydropyran-*4,4*-d_2.

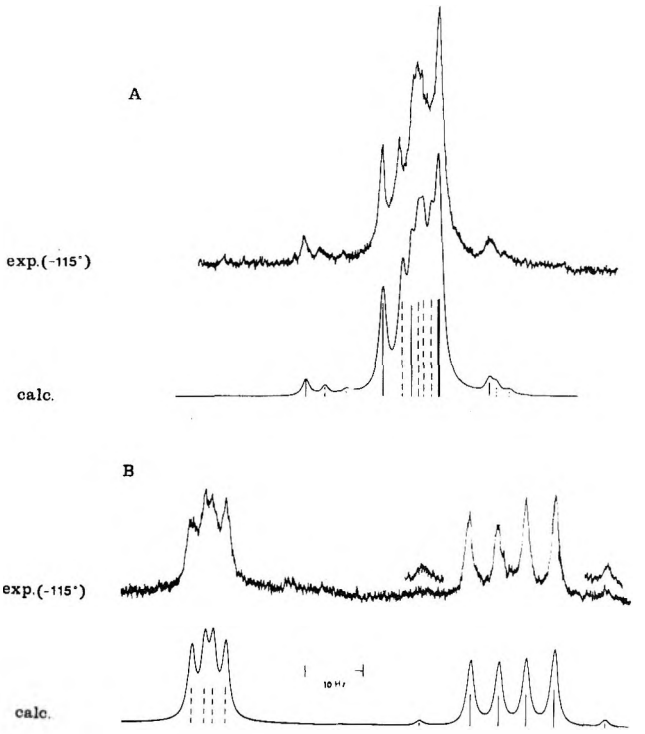
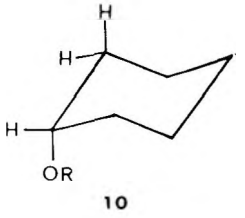


Figure 2. Deuterium decoupled 100 MHz ^{1}H NMR spectrum of 5-d_4 in carbon disulfide at −115 °C. (A) Experimental and calculated portion of the β protons. (B) Experimental and calculated portion of the α protons. The stick diagram identifies the lines of each of two ABX pattern comprising the spectrum.

It is of considerable interest to observe that our R value (2.17) for tetrahydropyran is very similar to the value R = 2.20 for 1,4-dioxane[15] and that both numbers are very close to the value R = 2.16 characterizing cyclohexane.

Table I further reveals that all the vicinal coupling constants change in a somewhat synchronous manner when oxygen replaces a methylene group (three couplings decrease while one increases). The net changes in J_{trans} and J_{cis} cancel each other and maintain R constant.

We now turn our attention temporarily to the concepts proposed to rationalize the stereodependence of the electronegativity effects of oxygen on vicinal couplings. Two different approaches using six-membered rings as substrates have been used. In one investigation Booth[18] determined the effect of axial and equatorial substituents on vicinal coupling which was found to be stereodependent whereby the decrease is maximum when the O–C–C–H relationship is trans coplanar as illustrated in structure **10**.



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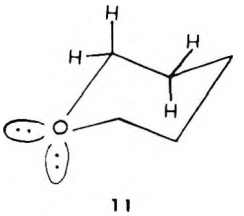
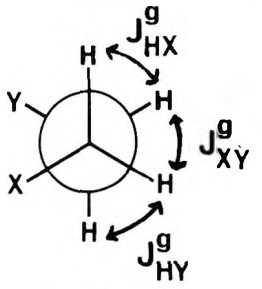


11

Later, work by Anteunis[19] and Crabb and co-workers[10] revealed that the stereodependent effect of oxygen is even more subtle when the heteroatom is part of the ring as in heterocycles of structure **11**. It has been suggested[19] that, in addition to the above effect, eclipsing of a lone pair on oxygen with an adjacent C–H significantly raises vicinal couplings involving this proton. However, since eclipsing is expected to be small in six-membered cyclic compounds

existing in a chair conformation, the predominant effect of oxygen should be through the β proton trans to it, namely H_{3e}.

Systematic investigations of experimental results[20] and theoretical calculations[21] have revealed that gauche couplings are not affected equally by the presence of heteroatom-containing substituents in 1,2-disubstituted ethane derivatives. It has been suggested[20b] that, for the gauche conformer (12), $J_{HX}{}^{g}$ increases with increasing electronegativity of Y when X is kept constant and equal to C whereas both $J_{HY}{}^{g}$ and $J_{XY}{}^{g}$ decrease.



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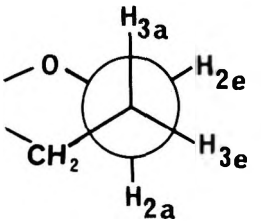

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The coupling data given in Table I are readily interpretable in terms of the above generalizations. Specifically, it is observed that the magnitudes of J_{2a3e} and J_{2e3e}, both involving H_{3e} trans to oxygen, are reduced appreciably, J_{2a3a} is decreased slightly whereas J_{2e3a} is slightly larger in tetrahydropyran. Structure 13 shows that J_{2e3a} is analogous to $J_{HX}{}^{g}$ in 12 and consequently the observed increase of 0.8 Hz is normal[20] and in accord with recent theoretical predictions.[21]

Although a small flattening of the tetrahydropyran chair relative to that of cyclohexane and the associated reduction of the $H_{2e}H_{3a}$ dihedral angle by about 3° would also account for the observed increase in J_{2e3a}, it is felt that the close R values (Table I), the rather similar bond lengths[22] for C–O (1.41 Å) and C–C (1.54 Å) as well as essentially equal internal bond angles (about 112°), the similar torsional strain as reflected by the barriers to rotation about C–C and C–O segments (e.g., about 3.4 and 2.7 kcal/mol, respectively), together with the plausibility of the above discussion suggest that the observed couplings changes are a consequence mainly of the stereodependence of the electronegativity effect of the oxygen atom.

It is relevant to compare the slight decrease in J_{2a3a} (from 13.1 to 12.4 Hz) reported in Table I to that observed when a second oxygen is present as in 1,4-dioxane. The effect of the second oxygen (reduction from 12.4 to 11.7 Hz)[23] is very similar to that of the first and since the R values suggest nearly identical dihedral angles for all three molecules it can be concluded that ring oxygen atoms cause only a small additive decrease in the axial–axial coupling constant (i.e., linear relationship in $E_X + E_Y$[20b]).

The chemical shifts of the various protons also show an interesting stereodependence relative to oxygen. Table I shows that $\Delta\nu_{2e2a}$ is of comparable magnitude[24] for both cyclohexane and tetrahydropyran in accord with an earlier demonstration[8] that the axial proton next to the oxygen atom absorbs at higher fields than the equatorial proton as is the case for cyclohexane. Analysis of the spectrum of 5-d_6 (Figure 1) shows clearly that the reverse is true for the β-methylene protons whereby H_{3a} absorbs at lower field than H_{3e}. This chemical shift reversal has been noted previously in other compounds[25,26] and its origin has been attributed to an appreciable upfield shift of H_{3e} as a result of electronic polarization favored by the trans coplanar relationship of H_{3e} with the oxygen atom.

It is significant that accurate vicinal coupling constants and chemical shifts determined for benzocycloheptene and 5-oxabenzocycloheptene[6] show trends similar to those reported in Table I. Although small differences do exist between the results for the two series (probably because the seven-membered chair is more puckered than the six-membered chair), the stereodependent effect of oxygen is analogous.

Hence the stereodependence of coupling constants and chemical shifts observed for tetrahydropyran should also persist to a large extent in other pyranoid derivatives, especially carbohydrates for which modified Karplus equations,[3,27,28] ignoring this effect, continue to be used in conformational and stereochemical studies. Our results further demonstrate that factors affecting vicinal coupling constants in heterocyclic compounds are complex and suggest that many attempts to extract quantitative geometrical information must be judged with skepticism.

Thus the individual coupling constants determined for tetrahydropyran constitute a complementary set of fundamental parameters on which rapid qualitative and stereochemical deductions in many heterocyclic compounds can be based. Furthermore, the insight gained through the above discussion provides the necessary quantitative framework on which the limitations of such conclusions can be formulated confidently.

Experimental Section

The VPC analyses and separations were carried out on a Varian Aerograph A90-P3 instrument using a 0.25 in. × 15 ft SE-30 column (A) and a 0.375 in. × 20 ft SE-30 column (B) and helium as carrier gas. Mass spectral analyses were performed on an Hitachi Perkin-Elmer Model RMU-6D instrument operating at 70 and 6 eV.

Routine analytical ^{1}H NMR spectra were recorded on a JEOL C-60H spectrometer operating at 60 MHz in the external lock mode. The low-temperature ^{1}H NMR spectra were obtained at 100 MHz using a JEOL JNM-4H-100 spectrometer. Solutions containing a small quantity of Me_4Si were degassed and sealed. Deuterium decoupling, when required, was effected by means of the JEOL Hetero Spin Decoupler Model JNM-SD-HC.

Temperatures were monitored by means of a JEOL temperature control unit Model JES-VT-3 and determined accurately with a calibrated thermocouple placed inside a solvent-containing dummy NMR tube.

The computer spectral simulations were obtained with a LAOCN-3 program,[29] a CDC CYBER 74 computer, and a CALCOMP plotter at our University Computer Centre.

γ-Tetrahydropyranone-*2,3,5,6-d*$_4$ (3-*d*$_4$). To a solution of 1.5 g of γ-pyranone (2) prepared from commercial chelidonic acid[5] (1) (Aldrich) in 30 ml of D_2O was added 200 mg of Pd/C (5%) catalyst in a flask which was then attached to a compact deuteration apparatus.[6] The reduction with deuterium gas was allowed to proceed for 8 h, after which deuterium gas uptake had ceased. The solution was then filtered on diatomaceous earth, saturated with NaCl, and extracted three times with 30 ml of dichloromethane. The organic solution was then dried over $MgSO_4$ and stripped of its solvent. About 1.2 g (80%) of product was isolated on column B; it showed a VPC retention time identical with that of nondeuterated γ-tetrahydropyranone.

The product was further characterized by its 100-MHz, deuterium decoupled, ^{1}H NMR spectrum in $CDCl_3$: doublet (3.6 Hz, 2 H) at 2.49 ppm and doublet (3.6 Hz, 2 H) at 3.97 ppm. The isotopic composition obtained from a mass spectrum at 6 eV is d_6 = 3%, d_5 = 11%, d_4 = 75%, d_3 = 9%, d_2 = 2%.

γ-Tetrahydropyranone-*2,6-d*$_2$ (3-*d*$_2$). To 100 ml of an aqueous solution of K_2CO_3 (pH 11.0) were added 900 mg of 3-d_4. After being stirred for 48 h, the solution was saturated with NaCl and extracted six times with 25 ml of chloroform. The organic solution was then dried over $MgSO_4$ and the solvent was evaporated. VPC analysis showed a retention time identical with that of 3-d_4. The 100-MHz ^{1}H NMR spectrum in $CDCl_3$ showed a doublet (6.0 Hz, 4 H) at 2.49 ppm and a broadened triplet (6.0 Hz, 2 H) at 3.95 ppm. A mass spectrum showed the following isotopic composition: d_4 = 5%, d_3 = 8%, d_2 = 82%, d_1 = 5%.

γ-Tetrahydropyranol-2,3,4,5,6-d_5 (4-d_5). A solution of 3.90 g of 3-d_4 in 30 ml of anhydrous ether was slowly added to a suspension of 1.65 g of $LiAlD_4$ in 65 ml of ether. After 6 h, the excess deuteride was destroyed with 10% H_2SO_4; the organic phase was then separated and the aqueous phase was extracted with chloroform. The combined organic phases were washed with a $NaHCO_3$ solution and water and then dried over $MgSO_4$. The solvent was then stripped. About 2.68 g (70%) of alcohol was obtained.

The identity of the product was determined to be 4-d_5 through characterization by its tosylate derivative (see below).

γ-Tetrahydropyranol-2,4,6-d_3 (4-d_3). Compound 4-d_3 was obtained from 3-d_2 by a procedure identical with that described above. The identity of the product was confirmed through the identification of its tosylate derivative (see below).

Tetrahydropyran-2,3,4,4,5,6-d_6 (5-d_6). A solution of 1.73 g of alcohol 4-d_5 in 15 ml of anhydrous pyridine was added to a solution of 4.0 g of *p*-toluenesulfonyl chloride (freshly recrystallized from petroleum ether) in 20 ml of pyridine and left standing for 48 h at 0 °C. Water (40 ml) and 55 ml of ether were then added and the organic phase was isolated. The aqueous solution was then extracted five times with 30 ml of ether. The combined ethereal solution was then washed successively with 3 N HCl, a saturated solution of $NaHCO_3$, and water, after which it was dried over $MgSO_4$ and stripped of its ether. The product was recrystallized from absolute ethanol and 3.17 g (90%) of pure tosylate was obtained, mp 55–56 °C (lit.[5] 56 °C).

The pure tosylate was then dissolved in 15 ml of anhydrous tetrahydrofuran and added slowly to a suspension of 700 mg of $LiAlD_4$ in 25 ml of tetrahydrofuran. After 90 h of reflux, 15 ml of water and 10% H_2SO_4 were added to destroy the deuteride left. The solution was then extracted five times with 30 ml of pentane and the organic phase was washed with a solution of $NaHCO_3$ and water. After drying over $MgSO_4$, the solution was concentrated by controlled distillation to about 7 ml. The product (5-d_6) was then obtained pure by preparative VPC using column B at 55 °C. It possessed a retention time equal to that of nondeuterated tetrahydropyran.

The product was then characterized by its ^1H NMR spectrum in carbon disulfide (Figure 1) and its isotopic composition was determined from its mass spectrum at 6 eV: d_8 = 2%, d_7 = 14%, d_6 = 64%, d_5 = 16%, d_4 = 3%.

Tetrahydropyran-2,4,4,6-d_4 (5-d_4). Compound 5-d_4 was prepared from 4-d_3 by a procedure identical with that described above. Purification by VPC provided pure 5-d_4 which showed a retention time identical with that of 5-d_6 and a ^1H NMR spectrum in carbon disulfide in accord with its proposed structure (Figure 2).

Acknowledgment. We wish to acknowledge the technical assistance of Mr. Robert Mayer with the recording of the ^1H NMR spectra at low temperatures and we are grateful to the National Council of Canada for financial assistance.

Registry No.—**2**, 108-97-4; *syn*-3-d_2, 58241-27-3; *anti*-3-d_2, 58241-28-4; *syn*-3-d_4, 58267-59-7; *anti*-3-d_4, 58267-60-0; *syn*-4-d_3, 58241-29-5; *anti*-4-d_3, 58241-30-8; *syn*-4-d_5, 58241-31-9; *anti*-4-d_5, 58267-61-1; *syn*-5-d_4, 58241-32-0; *anti*-5-d_4, 58241-33-1; *syn*-5-d_6, 58267-62-2; *anti*-5-d_6, 58267-63-3; tetrahydropyran, 142-68-7.

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Expoxidation of Olefins with Molecular Oxygen in the Presence of Cobalt Complexes

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The epoxidation of *tert*-butylethylene, norbornylene, and 1,1-dineopentylethylene using molecular oxygen has been studied in the presence of cobalt(III) acetylacetonate. Epoxidations under these conditions show an induction period and other characteristics of a radical chain process, being inhibited by hydroquinone and promoted by azobisisobutyronitrile. A mechanistic scheme is presented in which the reaction between cobalt(III) acetylacetonate and oxygen initiates radical chain processes. β-Peroxyalkyl radicals are the key intermediates in the oxidation. Epoxide formation under these conditions bears a resemblance to the autoxidation of olefins studied by Mayo and co-workers. The olefins in this study were specifically chosen to preclude the formation of hydroperoxides. The results, thus, emphasize the caution which must be exercised in attributing the formation of epoxides solely to hydroperoxide intermediates in metal-catalyzed oxidations.

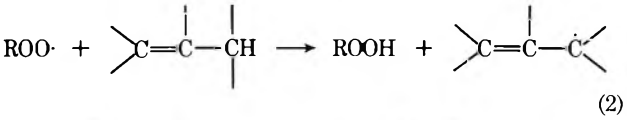
The oxidation of olefins catalyzed by transition metal complexes has become a subject of renewed interest, provoked by the desire to find evidence for the direct activation of molecular oxygen by metal complexes.[1-3] In most

cases, however, the oxidation of the olefin can be traced to the presence of adventitious quantities of peroxidic impurities. For example, in 1967 Collman et al.[4] suggested the direct activation of molecular oxygen in order to explain the autoxidation of cyclohexene and cyclopentene by rhodium, iridium, and platinum complexes. A subsequent reexamination of the rhodium system[5] showed that hydroperoxides were involved. Indeed, a number of metal complexes including those of iron, cobalt, and rhodium catalytically decompose hydroperoxides via the redox processes represented in eq 1.[1,6]

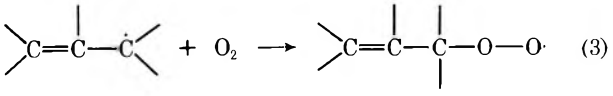
$$RO_2H + M^n \longrightarrow RO\cdot + M^{n+1}(OH) \quad (1a)$$

$$RO_2H + M^{n+1} \longrightarrow RO_2\cdot + M^n + H^+ \quad (1b)$$

The resulting peroxy and oxy radicals usually initiate autoxidation by abstracting hydrogens from the olefin. The propagation steps, given in eq 2 and 3, lead primarily to products of allylic oxidation.

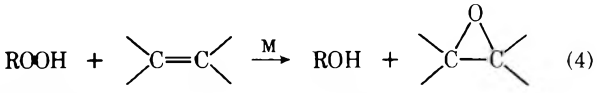


(2)



(3)

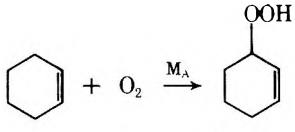
In 1973, Kaneda and co-workers[7] also reexamined the oxidation of cyclohexene with a rhodium catalyst.[7] They showed that the products of allylic oxidation resulted from reactions 1–3, but the formation of epoxide could not be accounted for by reactions proceeding via similar intermediates. Moreover, they ruled out a heterolytic process given in eq 4,[1,8] which is commonly observed for soluble metal complexes of vanadium, molybdenum, and tungsten.[8]



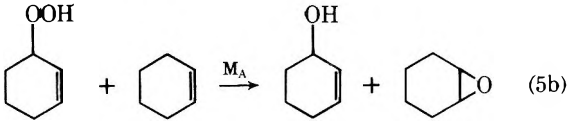
(4)

While the mechanism of the epoxide formation in Kaneda's studies has not been determined, it is clear that hydroperoxides are not directly involved. Although this system has been studied for the past 8 years, no satisfactory mechanism for epoxide formation has yet been demonstrated. In another example showing similar behavior, the autoxidation of cyclohexene in the presence of cobalt complexes gives oxidation products mainly from the reactions represented by eq 1–3.[6]

Recently, mixed catalyst systems have been used to give improved yields of epoxides in the autoxidation of cyclohexene.[9,10] One metal complex (M_A) is thought to catalyze the formation of hydroperoxide in eq 5a, while the second metal complex (M_B) is involved in the catalytic formation of epoxides according to eq 5b.



(5a)



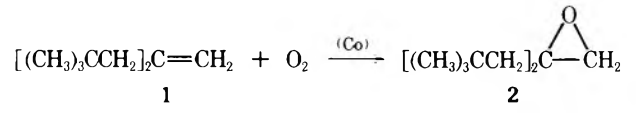
(5b)

The sequence of reactions given in eq 5a and 5b requires the ratio of epoxide to allylic alcohol to be less than or equal to unity. However, for a variety of mixed catalysts including cobalt complexes, ratios of epoxide/alcohol which are greater than unity have been observed. Thus, all of the epoxide cannot be explained as simply arising from the catalytic decomposition presented in eq 5b.

In the systems described above, olefin oxidations occur by at least two routes, one of which involves hydroperoxidic intermediates and the other which does not. With the most commonly used olefins such as cyclohexene, the facile reactions involving hydroperoxidic intermediates effectively mask the alternative routes for oxidation and make the study of the latter extremely difficult. With this complication in mind, we examined the reaction of cobalt acetylacetonate with olefins which do not easily undergo allylic oxidation in order to eliminate the ambiguities caused by hydroperoxides. Our results show that cobalt complexes can react with oxygen by homolytic pathways to convert olefins into epoxides. These processes do not involve hydroperoxides as such. Epoxide formation under our conditions bears a resemblance to the radical chain autoxidation of olefins previously delineated by Mayo and co-workers in the absence of metal complexes. The purpose of presenting our results here is to stress the participation of alternative routes for epoxide formation which do not involve hydroperoxidic intermediates when autoxidation of olefins are carried out in the presence of cobalt complexes. We have not attempted to elaborate on the earlier mechanistic studies of olefin autoxidation.

Results

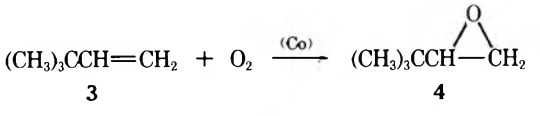
The reaction of cobalt(III) acetylacetonate (1.0 mmol) with an excess of 1,1-dineopentylethylene[11] (25 mmol) in benzene (25 ml) under 10 atm of oxygen at 77 °C gave 0.95 mmol of 1,1-dineopentylethylene oxide after 17 h.



1 2

No reaction was observed in the absence of either oxygen or the metal complex. Under similar conditions cobalt(II) acetate tetrahydrate and cobalt(II) acetylacetonate gave **2** in yields of 0.95 and 0.10 equiv, respectively. No products of allylic oxidation or other volatile materials were found. Furthermore, no hydroperoxides were detected by iodometric titration.[12] Oxymolybdenum(VI) acetylacetonate, sodium acetate, or acetylacetone failed to give any olefin oxidation under the same conditions.

Reactions of *tert*-butylethylene (125 mmol) with cobalt(III) acetylacetonate (1 mmol) at 80 °C did not afford *tert*-butylethylene oxide. However, raising the temperature to 95 °C produced 1.70 mmol of the epoxide in 36 h. Under the latter conditions, iron(III) acetylacetonate afforded only 0.06 mmol of epoxide **4**.



3 4

In addition to *tert*-butylethylene oxide, substantial amounts of acetone (0.77 mmol) and *tert*-butyl alcohol (0.81 mmol) were also formed during the oxidation employing cobalt(III) acetylacetonate. Iodometric titration detected no hydroperoxides when oxidations were carried out in the absence of the metal complex (even with added sodium acetylacetonate).

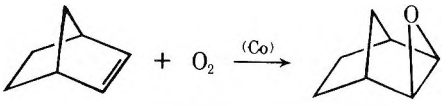
The conversion of olefin to oxidation products was very low for both dineopentyl- and *tert*-butylethylenes. On the contrary, norbornylene was easily oxidized in the presence of cobalt(III). Reaction of a benzene solution of norbornylene (56 mmol) with oxygen in the presence of cobalt(III)

Table I. Effect of Temperature on the Oxidation of Olefins[a]

Olefin	Temp, °C	Epoxide, mmol	CO_2, mmol
1[b]	60	0	*f*
1[b]	80	0.9[d]	*f*
1[b]	85	1.1[d]	*f*
1[b]	90	5.0[d]	*f*
1[c]	80	0.7[e]	1.4
1[c]	95	2.8[e]	4.2
1[c]	107	3.4[e]	5.2
1[c]	130	2.7[e]	5.2

[a] Using 1.0 mmol of $Co(acac)_3$ in 25 ml of benzene; initial oxygen pressure 150 psi at 22 °C. [b] 1 = 1,1-dineopentylethylene, 25 mmol. [c] 2:1 mixture of 1,1-dineopentylethylene and 1-*tert*-butyl-2-neopentylpropene, 25 mmol. [d] Yield of 2 after 18 h. [e] Mixture of 2 and 1-*tert*-butyl-2-neopentylpropylene oxide after 18 h. [f] Not determined.

acetylacetonate (1 mmol) at 70 °C for 18 h resulted in greater than 95% conversion to oxidation products. *exo*-Norbornylene oxide (24 mmol, 43%) was the only volatile product obtained. The nonvolatile residue appears to be an



oxygenated polymer containing less than 0.2% hydroperoxides by iodometric titration. A blank reaction carried out in the absence of the cobalt complex gave very low conversions (less than 1% epoxide) and less than 0.1% hydroperoxide by titration.

Effect of Temperature and Oxygen Pressure. To determine the range of reaction conditions over which epoxide formation occurred we varied the temperature and oxygen pressure. The effects of these changes upon epoxide formation from 1,1-dineopentylethylene in the presence of cobalt(III) acetylacetonate are shown in Tables I and II. The temperature studies were performed using both pure 1,1-dineopentylethylene and a mixture of triisobutylene isomers. The triisobutylene isomers were prepared by dehydration of *tert*-butyl alcohol in sulfuric acid[13] followed by treatment with alkaline permanganate solution.[11] The mixture of olefins consisted of 1,1-dineopentylethylene (64%) and 1-*tert*-butyl-2-neopentylpropene (36%) as determined by NMR spectroscopy. Oxidations using this olefinic mixture showed no significant amounts of the products of allylic oxidation or hydroperoxides. The composition of the mixture of epoxides was the same as that of the olefinic mixture used (see Experimental Section for details).

No oxidation of olefins was detected at or below 60 °C. The yields of epoxides reached a maximum at 107 °C. The lower yield of products observed at 130 °C were attributed to the subsequent decomposition of the epoxides at the high temperature, since control experiments showed that epoxides, which are stable at 90 °C, were decomposed to an extent of 33% after 19 h at 140 °C.

The effect of oxygen pressure was studied at 82 °C with cobalt(III) acetylacetonate using the mixture of triisobutylenes. No oxidation was observed when the oxygen atmosphere was replaced by argon (150 psi), or when low oxygen pressures (15 psi) were used.

The formation of carbon dioxide can also be used as a measure of the extent of reaction. Separately, the oxidation of a benzene solution of cobalt(III) acetylacetonate (1.0 mmol) in the absence of olefins at 130 °C produced 3.0 mmol of carbon dioxide. None of the cobalt(III) acetylacetonate could be recovered. In the absence of oxygen, no carbon dioxide was observed and most of the cobalt(III) acetylacetonate could be recovered after heating for 18 h at 130 °C. At 107 °C in the presence of the triisobutylene mixture all of the cobalt(III) complex was consumed, but at temperatures below 60 °C the cobalt(III) acetylacetonate was recovered unchanged after 18 h. Similarly at 82 °C under 1 atm of oxygen in the presence of dineopentylethylene no decomposition of the cobalt(III) acetylacetonate was detected. Under higher oxygen pressures (150 psi), increasing the temperatures resulted in increased cobalt(III) acetylacetonate decomposition. Monitoring the epoxide formation at 90 °C by GLC showed induction periods of greater than 6 h. When cobalt(III) acetylacetonate is consumed as described above, it changes from a green species soluble in benzene to an insoluble brown cobalt residue (presumably cobalt oxide since it no longer contains any organic components). This residue is an ineffective catalyst for the oxidation of olefins.

Table II. Effect of Oxygen Pressure on the Oxidation of Olefins[a]

Olefin[b]	O_2 pressure, psi	Epoxide,[c] mmol	CO_2,[d] mmol
1	0	0	0
1	15	0	0
1	100	0.50	0.8
1	150	0.65	1.4
1	200	0.60	1.3

[a] Using 1.0 mmol of $Co(acac)_3$ in 25 ml of benzene. [b] 2:1 mixture; see Table I, footnote *c*. [c] Yield of 2 after 18 h at 82 °C. [d] Yield after 18 h at 82 °C.

Effect of Additives. The effects of adding radical inhibitors and initiators are shown in Table III. The addition of free-radical traps such as hydroquinone severely retards the oxidation of olefins. Furthermore, radical initiators such as azobisisobutyronitrile (AIBN) increased the yields of epoxides without significantly changing the distribution of volatile products.

Oxidations Using Cobalt Carboxylates. Cobalt complexes in which acetylacetonato ligands have been replaced by various carboxylato ligands are also effective in promoting the oxidation of olefins as shown in Table IV. The change from the soluble cobalt(III) acetylacetonate to the much less soluble cobalt(II) species resulted in lower yields of epoxide. Some of the cobalt(II) is apparently converted to cobalt(III) under the reaction conditions as shown by the development of a green color during the reaction. The undissolved cobalt(II) compound can be recovered after the reaction. The addition of extra sodium acetylacetonate to the reaction had no effect upon the formation of epoxides. The more soluble cobalt(II) octoate gave epoxide yields comparable to those obtained with cobalt(III) acetylacetonate despite the presence of free carboxylic acid. Use of carboxylates such as pivalate and neodecanoate, however, gave significant increases in the yields of epoxides.

Discussion

Many of the previous studies[4,6,7,14] of olefin oxidation have employed cyclic alkenes such as cyclohexene which easily undergo allylic oxidation via reactions 1–3. Any less facile oxidation process can be masked by the more dominant autoxidation reaction. To avoid this problem we specifically chose olefins in which abstraction of an allylic hydrogen is disfavored relative to addition to the olefinic double bonds.[15,16] Thus, the autoxidation of norbornylene could be carried out to rather high conversions and reasonable yields of epoxide in the presence of cobalt complexes.

Table III. Effect of Additives on the Oxidation[a] of Olefins

Temp, °C	Olefin[b]	$Co(acac)_3$, mmol	Additive,[c] mmol	Epoxide, mmol	Acetone, mmol	*t*-BuOH, mmol
90	1	1.0		5.02[d]		
90	1	1.0	0.01 HQ	0.20[d]		
90	1	1.0	0.18 HQ	0.11[d]		
90	1	1.0	1.00 HQ	<0.05[d]		
95	3	1.0		1.70[e]	0.77	0.81
95	3	0	0.14 AIBN	1.30[e]	1.09	0.93
95	3	0	0.22 AIBN	2.12[e]	1.26	1.64
95	3	1.0	0.14 AIBN	4.10[e]	2.80	2.60

[a] Using 1.0 mmol of $Co(acac)_3$ in 25 ml of benzene for 18 h; initial O_2 pressure 150 psi. [b] 1 = 1,1-dineopentylethylene, 25 mmol; 3 = *tert*-butylethylene, 125 mmol. [c] HQ = hydroquinone; AIBN = azobisisobutyronitrile. [d] Epoxide 2. [e] Epoxide 4.

Table IV. Effect of Ligand Structure on Oxidation[a] of Olefins

Olefin[b]	Temp, °C	Metal complex,[c] mmol	Additive,[d] mmol	Epoxide, mmol	CO_2, mmol
3	95	1.0 $Co(acac)_3$		1.70[e]	*h*
3	95	1.0 $Co(acac)_2$		0.75[e]	2.20
3	95	1.0 $Co(acac)_2$	1.0 Na(acac)	0.72[e]	2.60
3	95	1.0 Co(II)oct	1.5 Hoct	1.36[e]	3.60
1	77	1.0 $Co(OAc)_2 \cdot 4H_2O$		0.95[f]	*h*
1*	80	1.0 $Co(acac)_3$		0.65[g]	1.40
1*	80	1.0 $Co(OAc)_3$		0.18[g]	0.10
1*	80	1.0 $Co(OAc)_3$	10.0 Na piv	2.14[g]	5.00
1*	80	1.2 Co(II) nd	0.8 Hnd	3.80[g]	3.60

[a] Reactions run in 25 ml of benzene for 18 h; initial O_2 pressure 150 psi at 22 °C. [b] 3 = *tert*-butylethylene, 125 mmol; 1 = dineopentylethylene; 1* = 2:1 mixture of 1,1-dineopentylethylene and 1-*tert*-butyl-2-neopentylpropene, 25 mmol. [c] acac = acetylacetonate; OAc = acetate; oct = 2-ethylhexanoate; nd = 2,2-dimethyloctanoate. [d] Na piv = sodium pivalate. [e] Epoxide 4. [f] Epoxide 2. [g] Mixture of 2 and 1-*tert*-butyl-3-neopentylpropylene oxide. [h] Not determined.

Since small amounts of hydroperoxides were detected in the latter, we focused our attention in these studies on the less easily autoxidized *tert*-butylethylene and dineopentylethylene which showed no evidence of hydroperoxide formation.

The results we have obtained from the oxidation of these olefins cannot be explained by either the allylic oxidation sequence in reactions 1–3 or by metal-catalyzed reaction between hydroperoxides and olefins described in reaction 4. The latter reaction can be dismissed for several reasons. First, it requires that at least equal amounts of alcohol and epoxide are formed. Second, no alcohol was formed in our reactions nor was any hydroperoxide detected. The substitution of molybdenum(VI) for cobalt(III) compounds resulted in no epoxide, although molybdenum complexes are known to catalyze the reaction between hydroperoxides and olefins.[5] Allylic oxidation can be ruled out by the absence of products of allylic oxidation and by the absence of hydroperoxides.

Our results are consistent with a direct reaction between oxygen and the metal complex. Thus, cobalt(III) acetylacetonate in benzene is stable in an inert atmosphere but it is decomposed in an oxygen atmosphere (150 psi) at 130 °C to produce ultimately carbon dioxide and a cobalt oxide. In the presence of olefins, oxidation occurs by a radical chain process, which shows long induction periods. Furthermore, radical inhibitors such as hydroquinone significantly retard the formation of epoxides and radical initiators such as AIBN increase the yields of epoxides. The close similarities between the product distributions obtained from the oxidation of *tert*-butylethylene using cobalt(III) acetylacetonate and the distribution obtained using AIBN suggests that similar propagation steps are involved in both systems.

The oxidation of olefins which accompanies the reaction of oxygen with the cobalt complex can be explained by the sequence of reactions in Scheme I. According to this formulation, the cobalt complex serves as an initiator by producing free radicals during the reaction represented in eq 6. Peroxy radicals are readily formed by the subsequent reaction with oxygen. In the absence of any readily abstractable allylic hydrogens, addition to the ethylenic bond is favored to form the key intermediate 7. Epoxides are known to result from the fragmentation in eq 9 of β-peroxyalkyl radicals such as 7.[15]

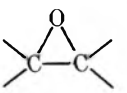
Scheme I

Initiation: $Co(acac)_3 + O_2 \longrightarrow Co(oxide) + CO_2 + R\cdot$ (6)

Propagation: $R\cdot + O_2 \longrightarrow RO_2\cdot$ (7)

$RO_2\cdot + >C{=}C< \longrightarrow RO{-}O{-}C{-}C\cdot$ (8)

7

$7 \longrightarrow$  $+ RO\cdot$, etc. (9)

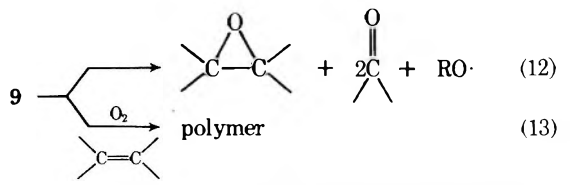
The postulation of the β-peroxyalkyl radical 7 as an intermediate also allows the explanation of the other observations. Thus the competitive oxygenation of 7 in eq 10 produces the peroxy radical 8 which can add to another olefin in eq 11 forming the diperoxide radical 9. In turn, 9 may

$RO_2C{-}\dot{C}< + O_2 \longrightarrow RO_2C{-}C{-}O{-}O\cdot$ (10)

8

$8 + >C{=}C< \longrightarrow RO_2C{-}C{-}O{-}O{-}C{-}\dot{C}<$ (11)

9



break down to epoxide and carbonyl compounds and generate an alkoxy radical (eq 12) or it may continue to react with more oxygen and olefin, ultimately producing oxygenated polymers.

The propagation sequence represented in Scheme I and in eq 10–13 is based on the studies of the autoxidation of olefins by Mayo and co-workers.[16] No doubt cobalt(II) and cobalt(III) species extant in the system are also capable of interacting with the alkyl, alkylperoxy, and alkoxy radical intermediates.[1,17] The extent to which these processes occur will certainly affect the distribution of the products of oxidation. Thus, the precise composition of the mixture of products will differ in the cobalt-induced autoxidation from that in the AIBN-initiated systems. All of these complex factors must be considered in any detailed study of the autoxidation of olefins.

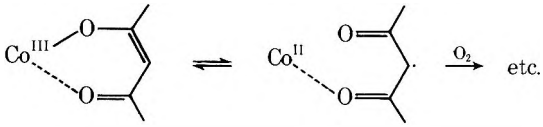
The mechanism by which cobalt complexes initiate the chain process involved in oxidation is not completely clear at this juncture. The formation of alkyl radicals during thermolysis of cobalt(III) carboxylates has been shown to lead to the radical chain decarboxylation of acids in the presence of oxygen, e.g.[18]

$$Co^{III}(O_2CR)_3 \longrightarrow Co^{II}(O_2CR)_2 + R\cdot + CO_2 \quad (14)$$

$$R\cdot + O_2 \longrightarrow RO_2\cdot \longrightarrow RO\cdot \quad (15)$$

$$RO\cdot + Co^{II}(O_2CR)_2 + RCO_2H \longrightarrow ROH + Co^{III}(O_2CR)_3, \text{ etc.} \quad (16)$$

The ease of decarboxylation of acids follows the stability of the resulting radicals, i.e., tertiary > secondary > primary. Our results for cobalt carboxylates shown in Table IV can be interpreted on a similar basis. Thus, olefin oxidations in the presence of cobalt pivalate and neodecanoate, which form more stable tertiary alkyl radicals upon decomposition, gave higher yields of epoxides than oxidations promoted by cobalt acetate (which forms methyl radicals). Unlike the cobalt carboxylate complexes, a solution of cobalt(III) acetylacetonate in benzene is stable in an inert atmosphere. However, it is capable of initiating autoxidation of olefins at 80 °C in an oxygen atmosphere at pressures greater than 150 psi. Two explanations are possible. On one hand, cobalt(III) acetylacetonate may undergo a reductive fission analogous to that in reaction 14, except for its reversibility due to the bidentate nature of the acetylacetonato ligand. Reaction with oxygen could render the homolysis irreversible and lead to the initiation of radical chain processes. Alternatively, there may be a direct reaction between the cobalt center and molecular oxygen.[19] Indeed a wide variety of cobalt complexes, especially those of cobalt(II), are known to react with oxygen.[20] However, the chemistry associated with metal–peroxy radical species is largely undeveloped, especially with regard to the addition to olefins. Whereas the direct activation of molecular oxygen by cobalt cannot be ruled out for these systems, results on hand can be adequately explained by an initiation process in which radicals are formed during the reaction of soluble cobalt compounds with oxygen.



Experimental Section

Materials. Benzene, reagent grade, was distilled from a solution of sodium benzophenone ketyl and benzophenone dianion. It was passed over an alumina column prior to use. Triisobutylene was prepared following the method of McCubbin.[13] *tert*-Butylethylene was obtained from Sinclair Petrochemicals, Inc. Norbornylene was obtained from Aldrich Chemical Co., Inc. Pure 1,1-dineopentylethylene was obtained from triisobutylene following the method of Bartlett, Fraser, and Woodward.[11] All of the olefins were distilled from sodium, stored over sodium metal under nitrogen, and passed over an activated alumina column prior to use.

Authentic samples of epoxides were prepared from peracid oxidation of the appropriate olefins. An authentic sample of 1,1-dineopentylethylene oxide was prepared by treating dineopentylethylene with a 15% excess of *m*-chloroperbenzoic acid in methylene chloride at 0 °C for 2 h followed by 14 h at reflux (~40 °C). The solution was cooled to 0 °C and filtered to remove most of the *m*-chlorobenzoic acid. The filtrate was washed with 20% sodium bisulfite solution, 10% sodium bicarbonate solution, and finally with a saturated sodium chloride solution. The organic layer was dried over magnesium sulfate and filtered and the solvent removed in vacuo. The crude product was distilled in vacuo to give dineopentylethylene oxide, 72%: bp 49 °C (1 mm); NMR ($CDCl_3$) δ 2.62 (s, 2 H, oxirane ring hydrogens), 1.85 and 1.45 (coupled AB, J = 16 Hz, 4 H, methylene hydrogens), 1.00 (s, 18 H, methyl groups); low-resolution mass spectrum showed no molecular ion but gave *m/e* 169 ($M^+ - 15$), 113, 95, 85, 81, 72, 57, 43, 41, 29; ir (neat) 2960, 1470, 1250, 960, 820 cm^{-1}.

tert-Butylethylene oxide was prepared in 48% yield using the peracid procedure described above: bp 95°; NMR ($CDCl_3$) δ 2.65 (m, 3 H, oxirane ring protons), 2.65 (s, 9 H, *tert*-butyl group); mass spectrum again shows no parent ion at 100 but shows *m/e* 85 ($M^+ - 15$), 70, 55 as major fragments; ir spectrum shows no functional groups.

Norbornylene oxide[22] was prepared as above using the peracid oxidation of norbornylene. The crude product was sublimed at 85 °C: mp 118°; NMR (CCl_4) δ 2.90 (s, 2 H, $H_{1,2}$), 2.40 (s, 2 H, $H_{3,6}$), 1.0–1.6 (m, 5 H, H_4, H_5, H_{7syn}), 0.6 (m, 1 H, H_{7anti}); ir (CCl_4) epoxide bands at 1230 and 850 cm^{-1}.

A mixture of triisobutylene oxides was prepared according to the above procedure from triisobutylene.[13] The composition of the triisobutylene mixture used was determined by NMR integration based upon the following NMR assignments: 1,1-dineopentylethylene (CCl_4), 4.80 (s, 2 H, olefinic protons), 1.95 (s, 4 H, methylenes), 0.90 (s, 18 H, methyls of the neopentyl); 1-*tert*-butyl-2-neopentylpropene (CCl_4), 5.1 (s, 1 H, olefinic proton), 1.80 (m, 5 H, methylenes), 1.10 (s, 9 H, methyls of the *tert*-butyl group), 0.90 (s, 9 H, methyls of the neopentyl group). NMR integration showed a 2:1 mixture of the olefins, respectively. The composition of the epoxide mixture obtained after peracid oxidation of the olefin mixture was estimated by NMR integration to be 2:1 based upon the relative epoxide ring protons at δ 2.62 vs. 2.50. NMR of 2-*tert*-butyl-1-neopentylethylene oxide ($CDCl_3$): δ 2.50 (s, 1 H, ring proton), 1.45 (m, 5 H, allylic protons), 0.9–1.00 (m, 18 H, methyls of the neopentyl and *tert*-butyl groups, obscured by resonances from dineopentylethylene).

Metal acetylacetonates and carboxylates were obtained from the Shepherd Chemical Co. Sodium acetylacetonate and pivalate were obtained by neutralization of the protic species with sodium hydroxide. Cobalt(III) acetate was prepared by the ozonation of cobaltous acetate[21] obtained from Matheson Coleman and Bell. All other chemicals used were reagent grade.

Olefin Oxidation Reactions. Oxidations were carried out in a 300-cm Magnedrive Packless Autoclave using glass liners. In a typical run, the liner was charged with the cobalt complex (1.0 mmol), the olefin (either 25 or 125 mmol), and 25 ml of benzene. The autoclave was sealed and pressurized to 150 psi of oxygen at 22 °C. The gas was vented and repressurized twice to remove any air. The sealed autoclave was then heated to the desired temperature over a 1-h period with stirring rate of 1725 rpm. In some runs samples were periodically withdrawn through a sampling valve in order to monitor the reaction. At the end of the reaction, the contents of the autoclave were rapidly cooled to room temperature by passing cold water through the jacket.

Analysis of Products. The head gas was analyzed by venting a known portion of the noncondensible gases into an evacuated stoppered flask. Ethane was added as an internal standard and the mixture was analyzed for CO_2 on a 2-ft Porapak Q column carefully calibrated under the reaction conditions.

After venting the noncondensible gases the recovered solution was analyzed by gas–liquid chromatography. For reactions using *tert*-butylethylene, the volatile products (acetone, *tert*-butyl alcohol, and *tert*-butylethylene oxide) were analyzed on a 6-ft 15% FFAP column on Chromosorb P at 80 °C using methylcyclohexane as the internal standard. The products of the oxidation of norbornylene were analyzed on a 6-ft 15% TCEP column on Chromosorb W at 110 °C using *tert*-butylbenzene as the internal standard. The products of dineopentylethylene oxidation were analyzed using a 6-ft 15% TCEP column on Chromosorb W at 125 °C using *n*-tetradecane as the internal standard. GLC on a 6-ft SE-30 column at 200 °C showed that components boiling higher than the epoxides were not present.

A portion of the solution was titrated iodometrically for active oxygen following the procedure of Wibaut.[12]

The nonvolatile polymeric products were not analyzed in detail. Only the oxidation of norbornylene gave significant amounts of polymeric oxygenated products. The cobalt residues were separated from the solution by filtration, washed with organic solvents, and dried in vacuo. The volatile epoxides were separated by preparative GLC and identified by comparison of spectral properties with authentic samples prepared by peracid oxidation of the appropriate olefins.

Acknowledgment. We wish to thank the National Science Foundation for partial financial support of this work.

Registry No.—**1**, 141-70-8; **2**, 4737-48-8; **3**, 558-37-2; **4**, 2245-30-9; *m*-chloroperbenzoic acid, 937-14-4; norbornylene oxide, 3146-39-2; norbornylene, 498-66-8; triisobutylene, 7756-94-7; 1-*tert*-butyl-2-neopentylpropene, 123-48-8; 2-*tert*-butyl-1-neopentylethylene oxide, 58191-06-3; 1-*tert*-butyl-2-neopentylpropylene oxide, 58191-07-4; $Co(acac)_3$, 21679-46-9; $Co(acac)_2$, 14020-48-7; Co(II)oct, 136-52-7; $Co(OAc)_2$, 71-48-7; $Co(OAc)_3$, 917-69-1; Co(II) nd, 32276-75-8.

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Copper-Catalyzed Oxidation of *o*-Phenylenediamines to *cis,cis*-Muconononitriles

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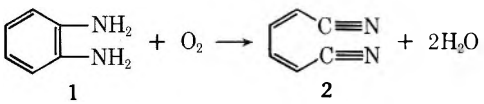
Oxidation of o-phenylenediamine (1) with molecular oxygen in the presence of CuCl in pyridine to give *cis,cis*-muconononitrile [(*Z,Z*)-2,4-hexadienedinitrile] was achieved in a high yield by selecting suitable reaction conditions. The molar ratio of 1 to CuCl in the reaction medium should be maintained below 0.5 in order to prevent intermolecular coupling of 1. o-Phenylenediamines substituted by electron-donating groups on the benzene ring gave the corresponding *cis,cis*-muconononitriles such as 3-methylmuconononitrile, 3,4-dimethylmuconononitrile, 3-methoxymuconononitrile, and 3-chloromuconononitrile, while no muconononitrile was obtained when electron-withdrawing groups were present. From 1,2-naphthalenediamine *o*-cyano-*cis*-cinnamonitrile was obtained. The structures of the products and the reaction mechanism are discussed.

Oxidation of organic compounds, especially phenols and aromatic amines, with molecular oxygen activated by metal salts is a well-established reaction. Oxidative coupling of aniline with oxygen catalyzed by CuCl gives azobenzene.[2] Also *o*-phenylenediamine (1) is oxidized in the presence of ferric chloride[3] to afford 2,3-diaminophenazine or 2-amino-3-oxophenazine in low yields. We have found that the oxidation of 1 can take a course completely different from the above ones by selecting proper reaction conditions; namely the ring cleavage reaction to give *cis,cis*-muconononitrile [(*Z,Z*)-2,4-hexadienedinitrile, 2] in a high yield proceeded smoothly at room temperature and under atmospheric pressure in the presence of CuCl in pyridine. Although 1



1 2

was oxidized to 2 by using a stoichiometric amount of nickel peroxide[4] or lead tetraacetate,[5] the yields were low and the metal salts cannot be reused. In contrast, the oxidation with CuCl gives an excellent yield of 2 and CuCl can be reused. This ring cleavage reaction resembles an enzymatic reaction of an oxygenase in regard to mild reaction conditions and participation of redox metals such as copper or iron.[6] The ring cleavage of pyrocatechol to *cis,cis*-muconic acid with pyrocatecase is a typical example.[7] A preliminary

Table I. Oxidation of 1 to 2 with CuCl in Various Amines[a]

Amine	Yield, %
Pyridine	96
α-Pycoline	57
2,2'-Bipyridyl[b]	29
1,4-Diazabicyclo[2.2.2]octane[b]	38
Triethylamine	5
Quinoline, *N,N*-dimethylbenzylamine,[b] *N,N*-dimethylaniline, tri-*n*-butylamine, morpholine, or 2-hydroxyethylamine	0
Pyridine containing 2% H_2O	96
Pyridine containing 10% H_2O	94
Pyridine containing 20% H_2O	35

[a] 0.01 mol of 1 in 20 ml of amine or acetonitrile was added dropwise in 30 min to 50 ml of amine or acetonitrile solution[b] containing 0.02 mol of CuCl with continuous bubbling of air. [b] 10 g of amine was dissolved in 45 ml of acetonitrile.

Table II. Effect of Diluent in the Oxidation of 1 to 2 with CuCl in Pyridine[a]

Diluent	Yield, %
Acetonitrile	96
Benzene	45
Tetrahydrofuran	20

[a] In 70 ml of diluent 0.06 mol of pyridine and 0.03 mol of CuCl were dissolved and 0.01 mol of 1 in 15 ml of the same solvent as diluent was slowly added with continuous bubbling of air.

account has been reported[8] and details of the reaction are presented in this paper.

Results and Discussion

Cuprous chloride is slightly soluble in pyridine under an inert atmosphere at room temperature, but a mixture of CuCl and pyridine absorbs oxygen with stirring under oxygen atmosphere to give a deep green solution. Exactly 1 mol of oxygen is absorbed per four atoms of copper. From this solution an oxygen complex was precipitated by addition of ethyl ether and its elemental analysis supported a composition of $(CuCl)_4(C_5H_5N)_4O_2$. When a pyridine solution of 1 (0.5 molar equiv to CuCl) was added slowly to a pyridine solution of CuCl pretreated with oxygen, further absorption of oxygen was observed showing that the oxidation took place. The amount of oxygen absorbed during the oxidation was equimolar to 1 added, and after the usual work-up 2 was obtained nearly quantitatively. During the oxidation reaction the solution was purple, but it changed to deep green after the reaction suggesting the regeneration of the oxygen complex. The complex was isolated from the solution.

In addition to CuCl, CuBr showed the same activity, but other uni- and bivalent copper salts such as CuI, $[CuIP(C_4H_9)_3]_4$, Cu_2O, CuOAc, CuOH, $CuCl_2$, and $CuSO_4$ were inactive. Furthermore, FeO, $CoCl_2$, $NiCl_2$, $SnCl_2$, and $VOCl_3$ were useless.

For the catalytic activity, the coordination of pyridine seems to be essential. In place of pyridine, other amines such as α-picoline, 2,2'-bipyridyl, and 1,4-diazabicyclo[2.2.2]octane were used, but found to be less effective (Table I). Pyridine plays roles of both ligand and solvent. Other solvents such as acetonitrile, benzene, and tetrahydrofuran can be used when mixed with pyridine (Table II). By using acetonitrile as the solvent, the influence of a ratio of pyridine to copper in the reaction medium was studied. Acetonitrile solutions of CuCl and pyridine were prepared with pyridine/copper ratios of 0.5, 1, and 3. Each solution absorbed about 1 mol of oxygen for four atoms of copper.

Table III. Oxidation of 1 to 2 in the Presence of a Small Amount of Pyridine in Acetonitrile with CuCl[a]

Pyridine/CuCl (mol/mol)	O_2 absorption, mol/mol CuCl: Before addition of 1	O_2 absorption, mol/mol CuCl: After addition of 1	Yield, %
0.5	0.25	0.63	13.0
1	0.25	0.85	74.8
3	0.25	0.99	83.5

[a] 0.01 mol of 1 in 15 ml of acetonitrile was added dropwise in 15 min with stirring under O_2 atmosphere to 55 ml of acetonitrile solution containing CuCl (0.02 mol) and pyridine (0.01, 0.02, or 0.06 mol) which was allowed to absorb O_2 in advance.

Table IV. Oxidation of 1 to 2 with CuCl at Different Initial 1/CuCl Ratio in the Reaction Medium[a]

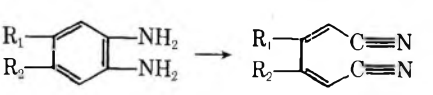
1/CuCl (mol/mol)	Yield, %	1/CuCl (mol/mol)	Yield, %
1/3	95	2/3	49
1/2	92	1/1	11

[a] Oxygen was introduced into 70 ml of pyridine containing 0.01 mol of 1 and 0.01, 0.015, 0.02, or 0.03 mol of CuCl.

Then 1 (0.5 molar equiv to CuCl) in acetonitrile was added slowly. The results of the oxidation in Table III show that the ratio of pyridine to copper higher than one seems to be essential for giving 2 in a high yield. Accumulation of certain amounts of water in the reaction medium showed no critical effect, but an unfavorable effect was observed in the presence of a larger amount of water (Table I). In these cases, even when the yield of 2 was low, almost no 1 was detected in the reaction mixture.

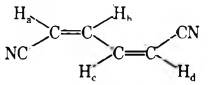
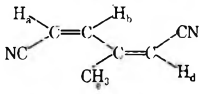
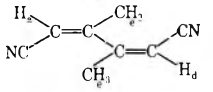
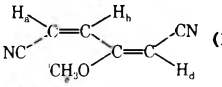
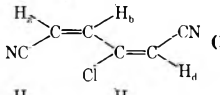
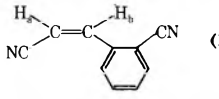
The ratio of 1 to copper in the reaction medium is the most important factor. Under argon atmosphere pyridine solutions of CuCl containing different amounts of 1 were prepared and then oxygen was introduced. The yields of 2 shown in Table IV were obtained. This result shows that it is necessary to keep the actual amount of 1 in the reaction medium below 0.5 molar equiv to CuCl in order to achieve a high yield of 2. This consideration clearly explains the fact that the oxidation of 1 in the presence of a so-called catalytic amount of CuCl in pyridine gave intractable polymer by the intermolecular reaction of 1. When the solution of 1 is added slowly to the pyridine solution of CuCl, 1 is oxidized rapidly to 2 as soon as it is added and the actual concentration of 1 in the reaction medium is always kept low and the active copper catalyst is regenerated. By this high dilution technique more than equimolar amounts of 1 can be oxidized to 2 nearly quantitatively. Also the oxidation reaction can be carried out successfully in a preparative scale.[9]

Following derivatives of 1 bearing an electron-donating group on the aromatic ring were oxidized similarly to give the corresponding muconononitrile derivatives. In the pres-



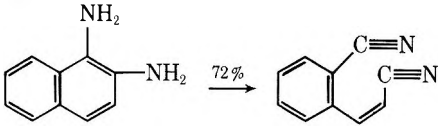
		yield
3, R_1 = Me; R_2 = H	9, R_1 = Me; R_2 = H	(62%)
4, R_1 = R_2 = Me	10, R_1 = R_2 = Me	(95%)
5, R_1 = MeO; R_2 = H	11, R_1 = MeO; R_2 = H	(75%)
6, R_1 = Cl; R_2 = H	12, R_1 = Cl; R_2 = H	(43%)
7, R_1 = Ac; R_2 = H		
8, R_1 = NO_2; R_2 = H		

Table V. Nuclear Magnetic Resonance Spectra Data of Muconononitriles and o-Cyanocinnamonitrile Obtained by the Oxidation with CuCl[a]

Compd	Chemical shifts, δ, ppm					Spin–spin coupling constants, Hz					
	H_a	H_d	H_c	H_b	H_e	J_{ab}	J_{ac}	J_{ad}	J_{bc}	J_{bd}	J_{cd}	J_{de}
 (2)		5.74 (8)		7.21 (8)		10.8	−1.1	1.4	11.5	−1.1	10.8	
 (9)	5.67 (4)	5.53 (m)		7.27 (2)	2.37 (2)	12.0		1.2		<0.5		2.0
 (10)		5.47 (4)			2.11 (2)			<0.1				1.7
 (11)	5.74 (4)	4.89		7.11 (2)	3.87	12.1		1.3		<0.5		
 (12)	5.90 (4)	5.96 (4)		7.25 (2)		12.2		1.4		0.7		
 (14)	5.84			7.62		12.1						

[a] Measured in $CDCl_3$ on a Varian A-60 except 2 which was measured on a Varian HA-100 (100 MHz) with Me_4Si as internal standard and the number in the parentheses shows multiplicity of the peak.

ence of an electron-withdrawing group on the aromatic ring the oxidation took place to give a polymeric product rather than the corresponding muconononitrile. Smooth ring cleavage was observed with 1,2-naphthalenediamine (**13**) giving o-cyano-*cis*-cinnamonitrile (**14**).



13 14

This unique oxidation method with CuCl in pyridine was extended to the oxidation of dihydrazones of α-diketones to acetylenes[10] and that of catechol to *cis,cis*-muconate.[11]

Geometrical Configuration of the Products. The muconononitriles obtained by the oxidation of *o*-phenylenediamines were found to have the cis,cis configuration of the 1,3-butadiene system as described below. It is reported that spin–spin coupling constants of vinyl protons in nuclear magnetic resonance spectra are 6–15 Hz for J_{cis} and 15–22 Hz for J_{trans}.[12] Long-range coupling constants of protons in 1,3-butadiene systems were reported to be 1.3–1.9 Hz in cis,cis isomers and 0.5–0.8 Hz in cis,trans isomers.[13] The nuclear magnetic resonance spectrum of muconononitrile obtained showed an A_2B_2 pattern and its chemical shifts and spin–spin coupling constants were calculated by the least-squares method of five Newton iterations to a root mean square error of 0.070 with the aid of a computer.[14] The calculated coupling constants are in good agreement with values reported by Elvidge and Ralph[15] for cis,cis isomer except J_{ad}. The latter is 1.4 Hz in the present analysis, while 1.7 Hz was given by them, and Hall and Patterson[16] reported 0.6 Hz. The observed data of **9**, **11**, and **12** are in good agreement with those reported for cis,cis isomers,[16] where each J_{ad} is between 1.2 and 1.4 Hz suggesting cis,cis configuration. No nuclear magnetic resonance spectrum of **10** was reported and the geometrical configuration of **10** can not be determined from data shown in Table V. It is considered to be cis,cis isomer by analogy with other products. The negligibly small value of J_{ad} of **10** suggests that **10** exists in a nonplanar conformation.[13] The data of *o*-cyanocinnamonitrile are also in agreement with those reported for the cis configuration.[16]

Table VI. Ultraviolet[a] and Infrared Absorption Spectra Data of Muconononitriles and *o*-Cyanocinnamonitrile Obtained by the Oxidation with CuCl

Compd	Ultraviolet spectra λ_{max}, nm	ϵ_{max}	Infrared spectra in KBr, selected bands, cm^{-1}
2	260	27800	2219 (s), 1764 (w), 1701 (w),
	270	20600	1555 (m), 1349 (m), 1201 (s),
	s 252	22200	940 (m), 756 (vs)
9	264.5	22370	2200 (s), 1754 (w), 1570 (m),
	274	18000	1435 (m), 1409 (w), 1380 (m),
	s 254	18900	1330 (w), 1184 (w), 1053 (m),
			1032 (m), 788 (s), 777 (s)
10	204	13000	2200 (s), 1622 (s), 1443 (s),
	s 222	7420	1382 (s), 1060 (m), 1037 (s),
			1024 (m), 842 (s), 825 (s)
11	235	11900	2200 (s), 1767 (w), 1630 (m),
	256	7000	1568 (vs), 1464 (s), 1438 (m),
	287	9400	1404 (s), 1325 (m), 1266 (s),
	s 248	8400	1209 (s), 1030 (s), 934 (m),
			797 (s), 778 (s)
12	267	19400	1190 (s), 1745 (w), 1669 (w),
	s 274	18300	1552 (s), 1404 (w), 1305 (w),
	s 259	16800	1110 (s), 1009 (m), 954 (w),
			912 (m), 838 (s), 778 (s), 709 (s)
14	271	14300	2210 (m), 1585 (m), 1473 (m),
	230	15500	1447 (m), 1240 (m), 968 (w),
	223	15700	940 (m), 780 (vs), 715 (m)
	s 237	11600	
	s 315	680	

[a] Measured in ethanol.

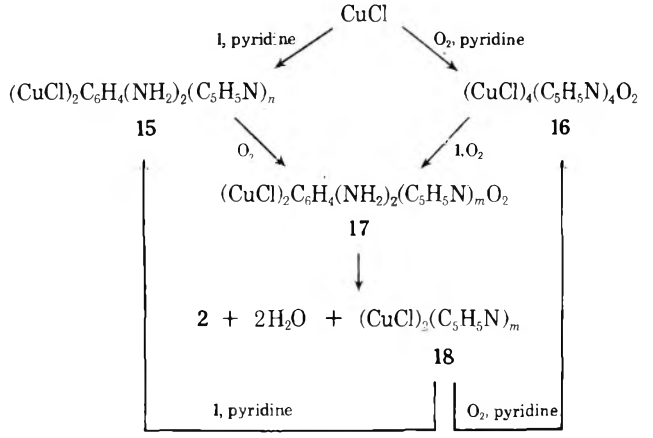
The infrared absorption spectra of the dinitriles are shown in Table VI. Precise data of cis,cis, cis,trans, and trans,trans isomers have been reported and the observed spectra of **2** are in good agreement with those of the cis,cis isomer.[15] The presence of a set of cis hydrogens in **9**, **11**, **12**, and **14** is suggested from their absorption spectra in the range of 778–788 cm^{-1}.

The ultraviolet spectra of the dinitriles are shown in Table VI. The main absorption band of **2** was observed at

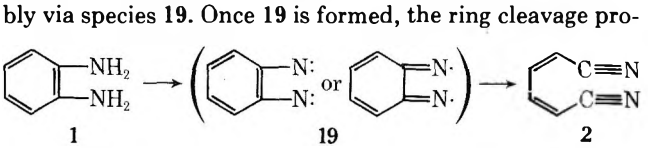
260 nm and its shifts induced by monosubstitution of β carbon with methyl, chloro, and methoxy groups are +4.5, +7, and +27 nm, respectively. The effect of substitution is similar to those reported by Woodward on 1,3-butadienes.[17] The main absorption band of **10** was observed at 204 nm, a lower wavelength absorption like that of acrylonitrile (200 nm), indicating that two double bonds are not in conjugation with each other but in conjugation with the respective triple bond of the cyano group. It is quite interesting that conjugation of the double bonds is forbidden by introduction of another methyl group at β′ position of **9** in which steric hindrance by both the methyl and cyano groups should be considered.

Reaction Mechanism. For this stereospecific and catalytic reaction, the following reaction mechanism (Scheme I) can be proposed.

Scheme I



Cuprous chloride and **1** in pyridine form in the absence of oxygen a yellow complex **15** which is converted into an oxygen complex **17** by introducing oxygen. The complex **17** is also formed by the addition of **1** to O_2–pyridine–CuCl complex **16** in pyridine. In the coordination sphere of the complex **17** electron transfer from the nitrogen to the oxidized form of copper takes place leading to species **2**, possibly via species **19**. Once **19** is formed, the ring cleavage proceeds smoothly to give **2**. Thus the cis,cis configuration of protons on the aromatic ring is retained during the reaction and only the cis,cis isomer of muconononitrile is formed selectively. When **1** of more than 0.5 molar equiv to CuCl is present in the reaction system, some pyridine molecules coordinated to copper in the complex **17** are replaced with another molecule of **1** and polymer of **1** is formed by an intermolecular coulpling reaction by radical species which are derived from **1**. Thus, it is important to control the ratio of **1** to copper in the reaction mixture to give **2** in a high yield. The complexes **15** or **16** can be regenerated via complex **18** and recycled as a catalyst.



1 **19** **2**

Experimental Section

Melting points are uncorrected. Infrared spectra were recorded on a Shimazu Model IR-27 infrared spectrophotometer, ultraviolet spectra on a Varian-Cary 14M spectrometer, and nuclear magnetic resonance spectra on a Varian HA-100 (100 MHz) and a Varian A-60 (60 MHz) using tetramethylsilane as internal standard in $CDCl_3$. All metal salts and diamines were obtained commercially.

General Procedure of Oxidation. A. Procedure I. Cuprous chloride and pyridine were added in a glass flask immersed in a water bath under argon atmosphere with vigorous stirring and then the atmosphere was replaced with oxygen. After the absorption of oxygen ceased, the diamine in pyridine was added slowly with further absorption of oxygen. The amount of oxygen absorbed was measured with a gas buret. Pyridine was distilled off under reduced pressure after the reaction, and the residue was extracted with ether to give a crude product which was recrystallized from ether or other solvents. More conveniently the reaction was carried out by bubbling air in the reaction mixture.

B. Procedure II. Under argon atmosphere, CuCl, pyridine, and diamine were mixed in a flask stirred magnetically and then the atmosphere was replaced with oxygen. After the absorption of oxygen ceased, the reaction mixture was treated by the same method as in procedure I (see Table IV).

***cis,cis*-Muconononitrile (2).** *o*-Phenylenediamine (**1**, 1.08 g) in 20 ml of pyridine was treated by procedure I with CuCl (1.98 g) in 50 ml of pyridine to give **2** (0.98 g), mp 128–129 °C.

Anal. Calcd for $C_6H_4N_2$: C, 69.22; H, 3.87; N, 26.91. Found: C, 69.16; H, 3.85; N, 26.96.

3-Methyl-*cis,cis*-muconononitrile (9). 4-Methyl-*o*-phenylenediamine (**3**, 1.22 g) in 20 ml of pyridine was treated by procedure I with CuCl (1.98 g) in 50 ml of pyridine to give **9** (0.73 g), mp 53–54 °C.

Anal. Calcd for $C_7H_4N_2$: C, 71.16; H, 5.12; N, 23.72. Found: C, 71.35; H, 4.98; N, 23.92.

3,4-Dimethyl-*cis,cis*-muconononitrile (10). 4,5-Dimethyl-*o*-phenylenediamine (**4**, 1.36 g) in 20 ml of pyridine was treated by procedure I with CuCl (1.98 g) in 50 ml of pyridine to give **10** (1.25 g), mp 95 °C.

Anal. Calcd for $C_8H_8N_2$: C, 72.70; H, 6.10; N, 21.20. Found: C, 72.48; H, 6.20; N, 21.02.

3-Methoxy-*cis,cis*-muconononitrile (11). 4-Methoxy-*o*-phenylenediamine (**5**, 1.38 g) in 20 ml of pyridine was treated by procedure I with CuCl (1.98 g) in 50 ml of pyridine to give **11** (1.01 g), mp 115–117 °C.

Anal. Calcd for $C_7H_6N_2O$: C, 60.85; H, 7.30; N, 20.28. Found: C, 60.56; H, 7.33; N, 20.50.

3-Chloro-*cis,cis*-muconononitrile (12). 4-Chloro-*o*-phenylenediamine (**6**, 1.43 g) in 20 ml of pyridine was treated by procedure I with CuCl (3.37 g) in 50 ml of pyridine to give **12** (0.6 g) (recrystallized from *n*-hexane), mp 85–86 °C.

Anal. Calcd for $C_6H_7ClN_2$: C, 52.00; H, 2.19; Cl, 25.60; N, 20.21. Found: C, 52.02; H, 2.23; Cl, 25.90; N, 20.30.

***o*-Cyano-*cis*-cinnamonitrile (14).** 1,2-Naphthalenediamine (**13**, 9.0 g) in 100 ml of pyridine was treated by procedure I with CuCl (15 g) in 400 ml of pyridine to give **14** (6.6 g) (recrystallized from *n*-hexane–CCl_4), mp 68–69 °C.

Anal. Calcd for $C_{10}H_6N_2$: C, 77.90; H, 3.92; N, 18.17. Found: C, 77.90; H, 3.93; N, 17.95.

O_2–pyridine–CuCl Complex (16). An oxygen complex of CuCl was isolated by adding a large amount of ether to a pyridine solution of CuCl pretreated with oxygen (Complex **16a**). Another complex was isolated from the reaction mixture of the oxidation of **1** by procedure I as a residue of extraction with ether (complex **16b**). Both complexes showed the same infrared spectra.

Anal. Calcd for $C_{20}H_{20}Cl_4Cu_4N_4O_2[(CuCl)_4(C_5H_5N)_4O_2]$: C, 32.27; H, 2.71; Cl, 19.05; N, 7.53. Found for complex **16a**: C, 30.38; H, 3.22; Cl, 19.53; N, 7.03. Found for complex **16b**: C, 31.45; H, 2.57; Cl, 20.8; N, 6.64.

Acknowledgment. We are indebted to Dr. K. Nukada and Mr. Y. Yoshizawa for the theoretical calculation of the nuclear magnetic resonance spectra of **2**.

Registry No.—**1**, 95-54-5; **2**, 49840-57-5; **3**, 496-72-0; **4**, 3171-45-7; **5**, 102-51-2; **6**, 95-83-0; **9**, 1789-45-3; **10**, 1557-61-5; **11**, 1789-46-4; **12**, 17566-11-9; **13**, 938-25-0; **14**, 4508-50-3; CuCl, 7758-89-6.

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Silane Reductions in Acidic Media. VII. Aluminum Chloride Catalyzed Hydrogen–Halogen Exchange between Organosilanes and Alkyl Halides. An Efficient Hydrocarbon Synthesis[1a]

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Alkyl halides are conveniently reduced to hydrocarbons by organosilanes in good yields when a catalytic amount of aluminum chloride is used. Hydrogen–halogen exchange between organosilanes and tertiary, secondary, primary, or methyl halides is rapid, and no significant difference in reactivity between alkyl bromides and chlorides is observed. Reduction by triethylsilane is competitive with the rearrangement of bromocycloheptane to 1-bromo-1-methylcyclohexane and with Friedel–Crafts alkylation reactions. Deuterium transfer from triethyldeuteriosilane to the alkyl cation formed from 1-bromohexane or cyclohexylmethyl bromide and aluminum chloride gives 2-deuteriohexane or 1-deuterio-1-methylcyclohexane, demonstrating that rearrangement to a more stable carbenium ion precedes reduction in these cases. The scope and limitations in the use of organosilanes for aluminum chloride catalyzed alkyl halide reductions is discussed.

Alkanes have long been known to transfer hydrogen intermolecularly to carbenium ions formed from alkyl halides and catalytic amounts of aluminum chloride.[2] By comparison, Lewis acid catalyzed reductions of alkyl halides by organosilanes have received limited attention; and the synthetic potential of this process for hydrocarbon formation has not been examined. Whitmore, Pietrusza, and Sommer have shown that an aluminum chloride catalyzed hydrogen–halogen exchange of triethylsilane with primary alkyl chlorides can be used to trap carbenium ions but point out that the experimental method is beset by a relatively long "induction period" followed by an often violent exothermic reaction.[3] In a subsequent investigation Sommer, Citron, and Lyons described a palladium-catalyzed reaction between triorganosilicon hydrides and halocarbons that is reported to be superior to the Lewis acid catalyzed exchange reaction for silyl halide formation;[4] this method, however, is not satisfactory as a synthetic procedure for hydrocarbon formation owing to the often complex nature of the reduction products.[5]

We have found that alkyl halides are readily reduced to hydrocarbons by organosilanes in good yields when catalytic amounts of aluminum chloride are used, that there is no observable "induction period" when tertiary alkyl halides are involved, and that organosilanes are clearly superior to hydrocarbons in hydrogen transfer reactions with carbenium ions. In this paper we report the scope and limitations in the use of organosilanes for aluminum chloride catalyzed alkyl halide reductions.

Results and Discussion

Addition of anhydrous aluminum chloride (usually ≤5 mol %) to a solution of an alkyl halide and organosilane, cooled in an ice–water bath, produced a rapid exothermic reaction. A solvent, usually pentane, was required only when the alkyl halide and silane were not mutually soluble. Product analysis of the reaction mixture after heating at 40 °C for usually less than 1 h showed only alkane and silyl halide (eq 1).

$$RX + R'_3SiH \xrightarrow{AlCl_3} RH + R'_3SiX \quad (1)$$

Results from organosilane reductions of representative alkyl halides are given in Table I. No major difference in product yields was observed when the alkyl halide was alternatively added to the cooled mixture of silane and aluminum chloride. The reaction temperature could, however, be more effectively controlled by the slow addition of the alkyl halides to the $AlCl_3$–silane mixture (method II) than by the addition of aluminum chloride to the alkyl halide–silane solution (method I).

Tertiary alkyl halides reacted smoothly with organosilanes in the presence of a catalytic amount of aluminum chloride and gave no evidence of an initial induction period. A short time period in which no apparent reaction occurred was usually observed with both secondary (≤1 min) and primary (2 min) alkyl halides when the aluminum chloride was added to the alkyl halide–organosilane solution or when the alkyl halide was added to the silane–aluminum chloride mixture. In no case, however, was a long induction period followed by a violent exothermic reaction, similar to that previously observed,[3] noted for the reactions reported in Table I. No significant difference in reactivity was observed in silane reductions of comparable alkyl chlorides and bromides.

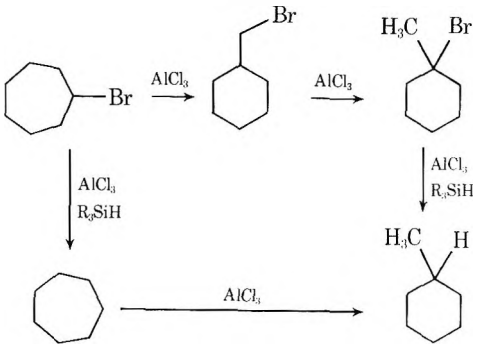
The aluminum chloride catalyzed reaction of organosilanes with alkyl halides provides an alternative and potentially useful synthetic route to hydrocarbons. Compared to the organotin hydrides,[6] organosilicon hydrides are stable to air and to acids and bases. Reductions of alkyl chlorides and bromides by organosilanes occur under the same reaction conditions; toward organotin hydrides alkyl chlorides are much less reactive than are the corresponding alkyl bromides and require reaction temperatures in excess of 100 °C for reasonable reaction times.[6] In addition, the organosilane reduction method favors tertiary alkyl halides over primary or secondary substrates; reactions with primary or secondary alkyl halides are usually preferred in procedures employing nucleophilic reducing agents.[7,8] Hy-

Table I. Aluminum Chloride Catalyzed Organosilane Reductions of Alkyl Halides

Registry no.	Alkyl halide	Organosilane	Method[a]	Hydrocarbon	% yield
768-90-1	1-Bromoadamantane[b]	Et_3SiH[h]	I	Adamantane	79[c]
7314-85-4	2-Bromoadamantane[b]	Et_3SiH	II	Adamantane	84[c]
13187-99-0	2-Bromododecane	n-$BuSiH_3$[i]	I	Dodecane	82[d,e]
	2-Bromododecane	n-Bu_3SiH	I	Dodecane	87[d]
90-99-3	Benzhydryl chloride	Et_3SiH	II	Diphenylmethane	100[f]
2114-39-8	2-Bromo-1-phenylpropane	Et_3SiH	I	n-Propylbenzene	43[f]
2404-35-5	Bromocycloheptane	Et_3SiH	II	Cycloheptane	39[d]
				Methylcyclohexane	26[d]
	Bromocycloheptane	n-$BuSiH_3$	II	Cycloheptane	<1[d]
				Methylcyclohexane	65[d]
2550-36-9	Cyclohexylmethyl bromide	Et_3SiH	II	Methylcyclohexane	52[d]
108-85-0	Bromocyclohexane	Et_3SiH	I	Cyclohexane	90[f]
542-18-7	Chlorocyclohexane	Et_3SiH	II	Cyclohexane	71[d]
137-43-9	Bromocyclopentane	Et_3SiH	II	Cyclopentane	71[d]
2534-77-2	*exo*-2-Bromonorbornane	Et_3SiH	II	Norbornane	96[d]
111-25-1	1-Bromohexane	Et_3SiH	I	Hexane	64[d,g]
629-06-1	1-Chloroheptane	Et_3SiH	II	Heptane	73[d]

[a] Method I, anhydrous aluminum chloride added to cooled solution of alkyl halide and organosilane; method II, alkyl halide added to cooled mixture of aluminum chloride and organosilane. [b] Pentane was used to dissolve the alkyl halide, 3 ml/10 mmol of halide. [c] Isolated recrystallized product yield. [d] Yield of product after quenching based on GLC analysis using an internal standard. [e] Dodecane isolated by distillation in 59% yield. [f] Yield based on ^1H NMR analysis. [g] Hexane isolated by distillation in 46% yield. [h] Registry no., 617-86-7. [i] Registry no., 1600-29-9.

Scheme I



drocarbon syntheses by organosilane reductions are limited to alkyl halides that do not undergo extensive structural rearrangement with aluminum chloride, to phenyl-substituted alkyl halides for which the Friedel–Crafts alkylation process does not predominate, and to functionalized alkyl halides possessing neither a nitro nor a cyano substituent.

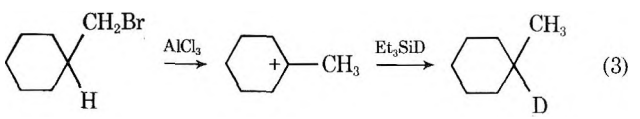
Reduction of bromocycloheptane by triethylsilane using 5 mol % aluminum chloride gave after 30 min reaction time a mixture of 26% methylcyclohexane and 39% cycloheptane (Table I); after 3 h 31% methylcyclohexane and 31% cycloheptane were observed. Without the organosilane present, cycloheptyl bromide isomerized under the same reaction conditions to a mixture composed of 1-bromo-1-methylcyclohexane, cyclohexylmethyl bromide, and bromocycloheptane in a 3.5:2:1 ratio after 2 h. Similarly, cycloheptane slowly isomerized to methylcyclohexane in the presence of aluminum chloride: after 1 h the ratio of methylcyclohexane to cycloheptane was 1:2, while after 2 h this hydrocarbon ratio was 1:1. As expected, rearrangement of cycloheptyl bromide occurred at a faster rate than did rearrangement of cycloheptane. These results show that the rate of reduction by triethylsilane is competitive with the rate of the aluminum chloride catalyzed isomerization of cycloheptyl bromide (Scheme I). In contrast, only methylcyclohexane was produced from the reaction of n-butylsilane with bromocycloheptane, indicating that hydrogen transfer from trialkylsilanes is appreciably faster than from monoalkylsilanes. A similar rearrangement process in silane reductions of cyclohexyl halides leading to methylcyclopentane was not observed.

2-Bromo-1-phenylpropane gave in addition to n-propylbenzene (43% yield) Friedel–Crafts alkylation products. However, only diphenylmethane was obtained from the reaction of triethylsilane with benzhydryl chloride. Thus, the stability of the carbenium ion produced by the interaction of an alkyl halide and aluminum chloride is a major determinant of the extent of reactions competing with organosilane reductions.

Attempts to reduce p-nitrobenzyl bromide to p-nitrotoluene with triethylsilane were unsuccessful. In pentane, methylene chloride, or nitromethane, using as much as 50 mol % of aluminum chloride and reaction times as long as 95 h, only unreacted starting material was recovered. Similarly, neither 3-bromopropanonitrile nor 5-bromopentanonitrile were reduced by organosilanes to the corresponding nitriles, even when a 10 mol % excess of aluminum chloride was used. However, both methyl iodide and ethyl bromide reacted vigorously with triethylsilane in the presence of aluminum chloride,[10] which suggests that relatively basic functional groups of functionalized alkyl halides modify the catalytic activity of the aluminum chloride. Such a catalyst modification might decrease the degree of ionization of the carbon–halogen bond from that required in reactions with organosilanes.[11]

In order to determine the extent of intramolecular hydrogen transfer in organosilane reductions of primary alkyl halides, 1-bromohexane and cyclohexylmethyl bromide were separately reacted with triethyldeuteriosilane according to the procedure outlined in Table I. 1-Bromohexane gave 2-deuteriohexane which was isolated and identified by ^1H NMR and mass spectroscopy. Cyclohexylmethyl bromide yielded 1-deuterio-1-methylcyclohexane which was isolated and likewise identified by spectrometric methods. In neither case was evidence obtained for deuterium transfer to the primary position. Thus rearrangement to the more stable secondary or tertiary carbenium ion (eq 2, 3) precedes reduction in these cases, although, as is evident from the observed reductions of methyl iodide and ethyl

$$CH_3(CH_2)_4CH_2Br \xrightarrow{AlCl_3} CH_3(CH_2)_3\overset{+}{C}HCH_3 \xrightarrow{Et_3SiD} CH_3(CH_2)_3CHDCH_3 \quad (2)$$



(3)

bromide by triethylsilane, formation of a secondary or tertiary alkyl cation is not a necessary prerequisite for hydrogen–halogen exchange. These reactions also suggest that specific labeling at a fixed position of a hydrocarbon is possible through deuterium transfer from an organosilicon deuteride to the most stable carbenium ion formed from an alkyl halide and aluminum chloride.

The aluminum chloride catalyzed organosilane reductions of primary and secondary alkyl halides represent the only procedure by which hydride transfer from silicon occurs to a primary or secondary carbon position. In previous studies, which have employed trifluoroacetic acid and alkenes,[12] alcohols,[13] or alcohol derivatives,[9,14] hydrocarbon formation has been limited to substrates that could form carbenium ions at least as stable as a tertiary alkyl cation.[15] No such limitation is found when aluminum chloride is employed as the catalyst. Indeed, since numerous procedures using aluminum chloride are known to efficiently catalyze Friedel–Crafts reactions of benzene with a wide variety of organic substrates, similar procedures may expand the scope of aluminum chloride catalyzed organosilane reductions. Since aluminum chloride can be easily removed from the reaction mixture, its use simplifies the procedures required for product isolation.

Halogenation of organosilanes by *tert*-butyl halides is effectively promoted by aluminum chloride. Only a catalytic quantity of aluminum chloride is required, hydrogen–halogen transfer is spontaneous and occurs smoothly, and the hydrocarbon product is a gas. No solvent is required and no hydrogen chloride is evolved in this halogenation process. We have previously shown that di-*tert*-butylchlorosilanes are conveniently produced through this process.[16] In this study, tri-*n*-hexylchlorosilane was produced in the same manner. With other alkyl halide substrates (Table I), triethylsilane and tri-*n*-butylsilane formed their respective chloride or bromide derivative which was identified as the only organosilicon reaction product. Two of the three available hydrogens of *n*-butylsilane were readily transferred in reactions with alkyl halides. Polymethyl hydrogen siloxane (PMHS) did not undergo hydrogen–halogen exchange with alkyl halides.

Intermolecular hydrogen transfer from tertiary carbon centers of hydrocarbons to the *tert*-butyl cation, generated from *tert*-butyl chloride and a catalytic amount of aluminum chloride, has proven to be a rapid and efficient procedure for hydrogen-halogen exchange.[17,18] However, secondary reactions, including elimination–carbenium ion addition reactions, can be predominant, particularly if reaction times are not carefully controlled.[17] Hydrogen transfer from secondary carbon positions to the *tert*-butyl cation has also been observed, but the extent of this process is usually low.[19] We have found that when adamantane is employed as the hydrogen donor with a fivefold molar excess of cyclohexyl bromide and a catalytic amount of aluminum chloride in carbon tetrachloride, 49% 1-bromoadamantane, 9% 1-chloroadamantane, and 58% cyclohexane (based on adamantane) were formed after 16 h at 40 °C.[20] Likewise, hydrogen–halogen transfer between adamantane and cyclohexyl chloride under the same reaction conditions was far from complete (18% 1-chloroadamantane formed) even after 21 h at 40 °C. Thus, although hydrogen–halogen exchange between tertiary carbon centers is rapid and usually occurs in high yield, this method is not generally suitable for hydrocarbon synthesis.

Experimental Section

General. Instrumentation has been previously described.[21] Use was made of 5 ft columns of 10% SE-30 and 15% SF-96, each on Chromosorb P. A Varian Model 485 digital integrator was used to determine peak areas in GLC analyses; reported yields were determined with the use of experimentally determined thermal conductivity ratios. With the exception of *n*-butylsilane,[22] organosilanes were obtained commercially. Alkyl halides and alkanes employed as standards were commercial samples that were used without prior purification. Finely powdered aluminum chloride was stored in a desiccator over phosphorus pentoxide. All glassware was oven dried and assembled in a dry atmosphere.

Triethyldeuteriosilane. To a stirred mixture of lithium aluminum deuteride (96% D, 1.0 g, 23 mmol) in 60 ml of anhydrous ether contained in a three-necked flask, equipped with a water condenser, addition funnel, and drying tube, was added triethylchlorosilane (12.3 g, 82 mmol) dropwise over a 30-min period. After the addition was complete the mixture was refluxed for 2 h. Ether and 5 g of ice were slowly added to the reaction mixture followed by 50 ml of a cold 25% aqueous sulfuric acid solution. The ether layer was separated, and the aqueous solution was washed with two 20-ml portions of ether. The combined ether solution was washed with 20-ml portions of 25% aqueous sulfuric acid, 10% aqueous sodium hydroxide, and water, and then dried with anhydrous magnesium sulfate. Fractional distillation through a 10-cm Vigreux column gave 5.52 g (47 mmol, 57% yield) of triethyldeuteriosilane: bp 105–106.5 °C; ir (film) 1550 cm^{-1} (Si–D), no Si–H adsorption observed at 2100 cm^{-1}; ^1H NMR (CCl_4) δ 1.0 (m, 6 H) and 0.62 (m, 9 H).

Organosilane Reductions of Alkyl Halides. In a typical experiment the silane (12 mmol) and anhydrous aluminum chloride (0.05 g, 0.4 mmol) were weighed into a dry three-necked flask equipped with a reflux condenser, drying tube, and addition funnel. The alkyl halide was added dropwise to the stirred mixture cooled in an ice–water bath. In an alternate procedure the aluminum chloride was added to a stirred organosilane–alkyl halide solution cooled in an ice–water bath. A solvent, pentane, was employed to dissolve the bromoadamantanes. After the addition of the alkyl halide or aluminum chloride, the reaction mixture was heated at 40 °C until GLC analysis indicated complete reduction. Reaction times were generally less than 1 h. For reactions requiring longer times, an additional 0.05-g portion of aluminum chloride was added to hasten reduction. Solid sodium carbonate (0.2 g) was used to destroy the aluminum chloride catalyst and had little effect on the halosilane product. Adamantane was isolated by removal of the pentane solvent and recrystallized from acetone. Dodecane and hexane were fractionally distilled from excess silane and silyl halide. Hydrocarbon and silyl halide products were identified by ^1H NMR and/or GLC methods. Cycloheptane, methylcyclohexane, and triethylsilane were separable on 15% SF-96 columns.

Reductions with Triethyldeuteriosilane. Reactions were run as previously described through the addition of the alkyl halide to the silane–aluminum chloride mixture. Hexane-d_1 was fractionally distilled, bp 66–67 °C. Spectral analysis by comparison with undeuterated hexane showed the most probable position of deuterium incorporation to be position 2: ^1H NMR (CCl_4) δ 1.55–1.05 (m, 7 H) and 1.05–0.80 (m, 6 H); mass spectrum *m/e* (rel intensity) 87 (8, parent ion), 72 (4), 71 (2.5), 58 (78), 57 (73), 43 (100), 42 (94), 41 (88).

Methylcyclohexane-d_1 was collected by GLC methods. Spectral analysis by comparison with undeuterated methylcyclohexane showed the most probable position of deuterium incorporation to be position 1 of the cyclohexane ring: ^1H NMR (CCl_4) δ 1.80–1.30 (m, 6 H), 1.30–1.00 (m, 4 H), and 0.93 (distorted s, 3 H); mass spectrum *m/e* (rel intensity) 99 (8, parent ion), 85 (27), 84 (47), 71 (20), 70 (20), 57 (63), 56 (100), 16 (1.5), 15 (12).

Reactions of Alkyl Halides with Adamantane. The cyclohexyl halide (25 mmol) was added dropwise to an ice–water bath cooled mixture of adamantane (10 mmol) and anhydrous aluminum chloride (0.057 g, 0.3 mmol) in 5 ml of carbon tetrachloride. After the addition was complete, the stirred reaction mixture was heated at 40 °C. The progress of the reaction was monitored by GLC analysis. In pentane 2-bromoadamantane is completely isomerized by aluminum chloride to 1-bromoadamantane within 1 h; adamantane is formed in low yield under these reaction conditions.

Acknowledgment. We gratefully acknowledge the support of the Research Corporation for this work.

Registry No.—$AlCl_3$, 7446-70-0; triethyldeuteriosilane, 1631-33-0; lithium aluminum deuteride, 14128-54-2; triethylchlorosilane, 994-30-9; hexane-2-d_1, 32740-26-4; methylcyclohexane-1-d_1, 34097-86-4; adamantane, 281-23-2.

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Synthesis of a Cytotoxic Vernolepin Prototype. Ozonization of Silyloxyalkenes[1]

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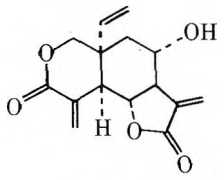
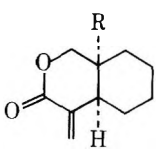
Regiospecific silyloxyalkene formation, followed by ozonization, has been used in two syntheses of α-methylene-δ-lactone **2**, a prototype of vernolepin, a sesquiterpene lactone possessing antitumor and cytotoxic properties. Compound **2** has been found to have moderate in vitro toxicity toward cells derived from human carcinoma of the nasopharynx (KB) in cell culture. Silyloxyalkenes react rapidly with ozone in methanol at −78 °C to give carboxylic acids. The silyloxyalkene double bond is sufficiently reactive that it may be selectively ozonized in the presence of certain normal double bonds. Since silyloxyalkenes may often be generated regiospecifically, the reaction constitutes an effective method for the regiospecific cleavage of ketones. Silyloxyalkenes derived from esters (alkyl silyl ketene acetals) give mixtures of the cleavage product (one-carbon degradation of the ester) and the corresponding α-silyloxy ester. This "abnormal" mode of oxidation is also observed for the hindered silyloxyalkene derived from camphor.

Vernolepin (**1**) is a sesquiterpene bislactone of the elemane class,[2] which has been found to show in vitro cytotoxicity toward cells derived from human carcinoma of the nasopharynx (KB) in cell culture, and in vivo antitumor activity against the Walker intramuscular carcinosarcoma 256.[3,4]



1

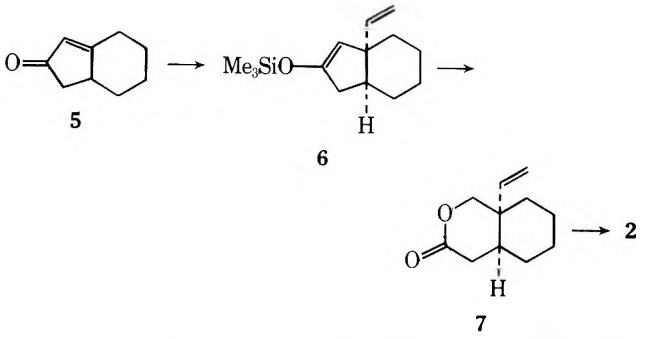


2, R = $CH{=}CH_2$
3, R = CH_3
4, R = CH_2CH_3

As a part of a general project aimed at the total synthesis of sesquiterpene antitumor lactones, we have developed two efficient synthetic routes to **2**, a prototype of vernolepin which contains only one of the two α-methylene lactone functions. One of the routes has also been utilized to synthesize vernolepin analogues **3** and **4**.

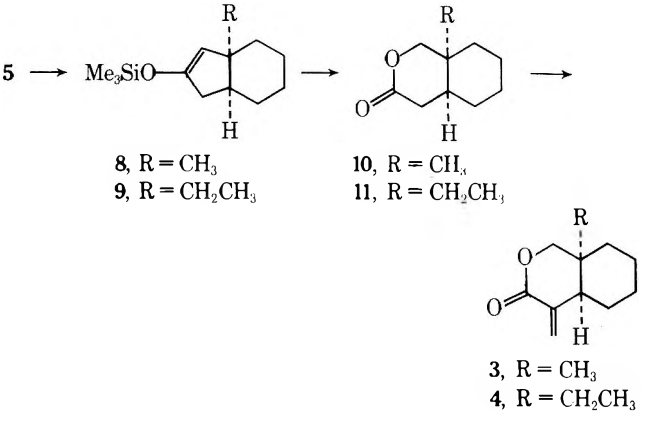
A key step in both synthetic routes involves ozonization of a silyloxyalkene. We have carried out a brief study of the scope of this new reaction. In this paper we report the results of these studies. Since we embarked upon this project, several other syntheses of lactone **2** have been reported.[5-8]

Lithium divinylcuprate is added to enone **5**[9] at −75 °C in dimethyl sulfide–THF, and the resulting reaction mixture is worked up by the addition of trimethylsilyl chloride, HMPT, and triethylamine.[10] Silyloxydiene **6** is obtained in 75% yield. Selective ozonization of the silyloxyalkene linkage in **6** proceeds at −75 °C without incident. After reduction of the intermediate methoxy hydroperoxide with sodium borohydride, the reaction mixture is acidified and worked up to obtain lactone **7** in 93% yield. Grieco's two-stage procedure was used to introduce the α-methylene group (**7** → **2**).[5,11] One advantage of this process for constructing the vernolepin A ring is that analogues may be prepared in which the angular vinyl group is replaced by other groups. Since Kupchan has shown that dihydrovernolepin retains the cytotoxic and antitumor properties of



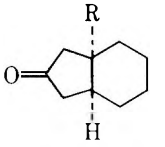
5 6 7 2

the parent,[4] such analogues may show physiological activity (vide infra). For example, we have prepared analogues **3** and **4** by similar procedures.



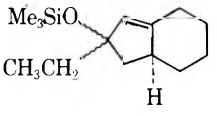
8, R = CH_3
9, R = CH_2CH_3
10, R = CH_3
11, R = CH_2CH_3
3, R = CH_3
4, R = CH_2CH_3

The procedure we have developed for the angular vinylation (**5** → **6**) is convenient and furnishes the 1,4 adduct in high yield, uncontaminated by the 1,2 adduct. We initially utilized Corey's procedure (vinyllithium and cuprous iodide in diisopropyl sulfide–THF).[12] However, the use of the volatile dimethyl sulfide as the solubilizing ligand for cuprous iodide in formation of the cuprate results in a much more convenient work-up procedure. House and coworkers have also discovered the efficacy of dimethyl sulfide in this context, and have introduced the use of the crystalline Me_2S–CuBr and Me_2S–CuI complexes as precursors for generation of cuprates.[13] A recent synthesis of the vinyl hydrindanone **12**, in which the vinyl group is introduced by a cuprate addition utilizing tributylphosphine as ligand, provided the material in poor yield.[14,15] A major disadvantage of the method is the current unavailability of good quality vinyllithium.[17]



12, R = CH=CH_2
13, R = CH_3

Compound **8** was prepared by the addition of lithium dimethylcuprate to enone **5** in ether at 0 °C; again, only the 1,4 adduct was produced. The ethyl derivative **9** was prepared by the copper-catalyzed addition of ethylmagnesium bromide in THF.[18] In this case, the desired 1,4 adduct was accompanied by about 30% of the 1,2 adduct **14**.

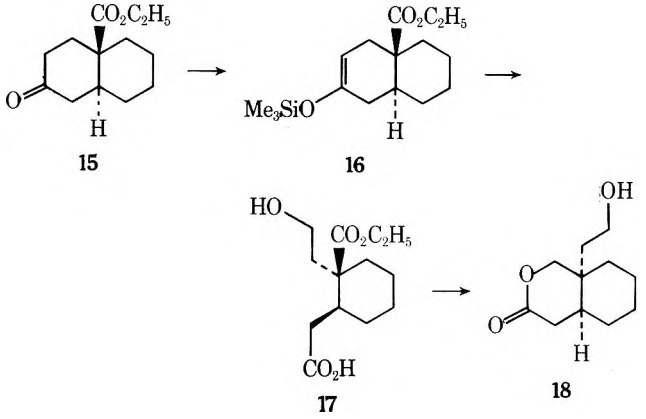


14

Compounds **6**, **8**, and **9** were produced in only one stereoisomeric form. On the basis of analogy,[12] the cis ring junction may be assumed. This assumption was confirmed in the case of compound **8** when it was hydrolyzed to the known[19] *cis*-8-methylhydrindanone (**13**).

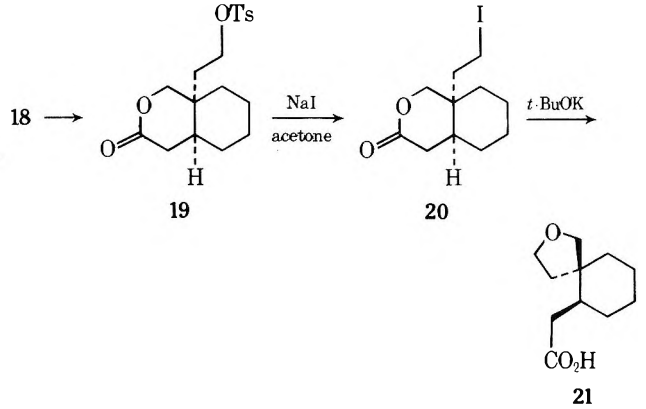
Ozonization of silyloxydiene **6** is highly selective, as shown by the excellent yield of lactone **7** (93%). When the amount of ozone used is carefully monitored, we find no evidence of attack at the angular vinyl group. Since silyloxyalkenes may be regiospecifically generated in several ways,[10,20] this reaction constitutes a useful method for the regiospecific cleavage of a ketone.

We have employed the silyloxyalkene ozonization in an alternate synthesis of lactone **2**. Keto ester **15** reacts with trimethylsilyl chloride and triethylamine in DMF[20] to give silyloxyalkene **16** in 92% yield.[21] Ozonolysis of **16** at −70 °C in 1:1 methanol–methylene chloride, followed by sodium borohydride reduction, gives hydroxy acid **17**. Reduction of **17** with sodium in ethanol–ammonia, followed by acidic work-up, affords lactone **18** in 73% overall yield.



15 **16** **17** **18**

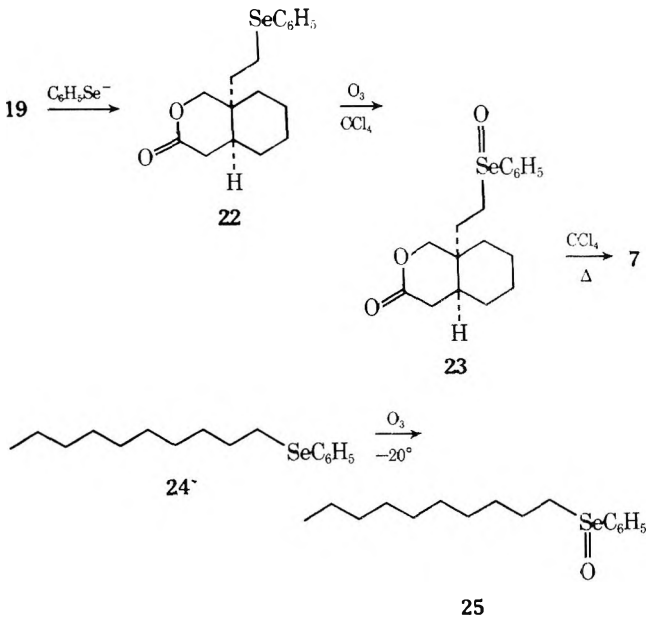
Conventional methods for conversion of the hydroxyethyl side chain to a vinyl group, such as elimination of iodide **20** with DBN or pyridine, gave no recognizable products. Attempted elimination with potassium *tert*-butoxide leads to acid **21**, presumably via a ketene intermediate.



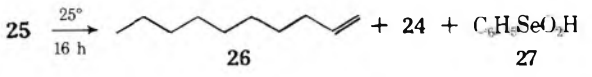
19 **20** **21**

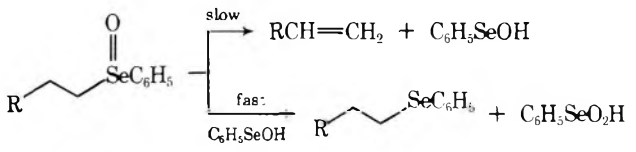
This problem was solved by conversion of tosylate **19** into phenyl selenide **22**, which is oxidized to selenoxide **23** by ozone in CCl_4 at −20 °C. When a cold solution of crude selenoxide **23** is added to refluxing CCl_4,[22] elimination is rapid, and vinyl lactone **7** is obtained in 60% overall yield from tosylate **19**.

The mode in which selenoxide **23** is thermolyzed is important. If thermolysis is carried out by heating a CCl_4 solution of **23** from room temperature to reflux, a mixture of **7** and selenide **22** results. This phenomenon was explored briefly with phenyl 1-decylselenoxide (**25**), which was pre-



pared by the ozone oxidation of selenide **24** in CCl_4 or CH_2Cl_2 at −20 °C. When these oxidation mixtures are evaporated, selenoxide **25** is produced in quantitative yield. In contrast to secondary alkyl selenoxides, primary alkyl selenoxides such as **25** are relatively stable at room temperature. However, after sitting overnight at room temperature, a CCl_4 solution of **25** is converted into an equimolar mixture of 1-decene and selenide **24**; an equivalent amount of crystalline phenylselenic acid (**27**) separates from solution. Apparently, with primary alkyl selenoxides, thermolysis to alkene is slow, and the phenylseleninic acid produced rapidly reduces unreacted selenoxide back to selenide.

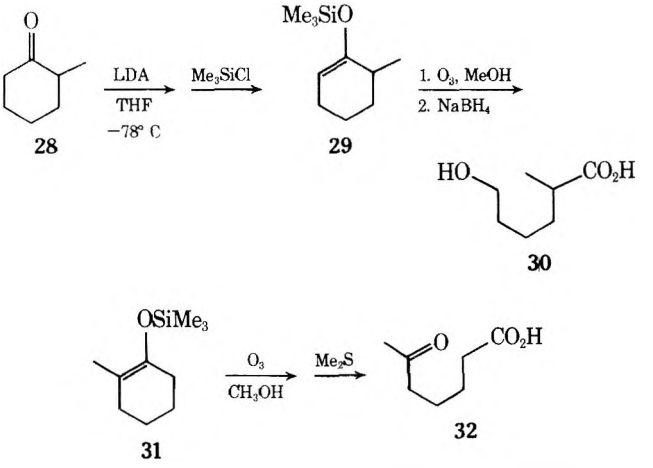




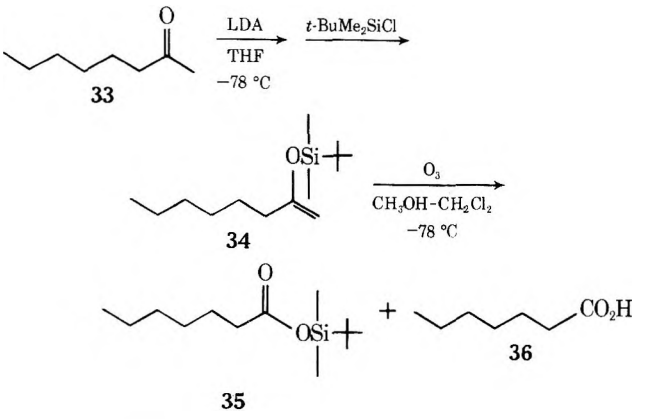
While we were investigating this phenomenon, we became aware of Reich's method for circumventing the problem,[22] which serves admirably. The disproportionation has also been observed by Sharpless[23] and by Grieco,[8,24] who introduced the idea of using nitrophenyl selenoxides, which decompose at much lower temperatures than do phenyl selenoxides.

Lactone **2** shows moderate in vitro toxicity in the KB cell culture screen (ED_{50} = 4.4–15 μg ml^{-1}).[25,26] For comparison, vernolepin (**1**) has ED_{50} = 1.8 μg ml^{-1} in this screen.[4] In vivo results on lactone **2** have not yet been obtained. Lactone **3** is ineffective toward the L-1210 lymphoid leukemia (in vivo) at dose levels of 10 and 20 mg/kg. The compound is toxic (zero of six survivors) at doses of 400, 200, 100, and 40 mg/kg.

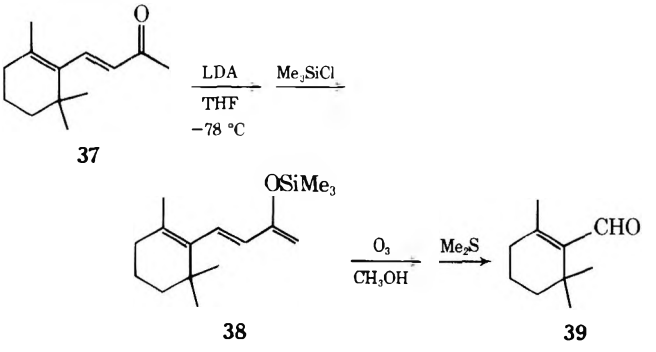
The silyloxyalkene ozonization reaction seemed sufficiently interesting to warrant a brief survey of its scope. Silyloxyalkene **29**, obtained by silylation of the kinetic enolate of 2-methylcyclohexanone (**28**),[10] was converted into hydroxy acid **30** in 94% yield. To further demonstrate the generality of the method, silyloxyalkene **31**[10] was cleaved. In this case, the initial oxidation product was reduced with dimethyl sulfide to produce keto acid **32** in 90% yield. To



provide a further example of the regiospecific cleavage of an unsymmetrical ketone *away from the more highly alkylated side*, we oxidized 2-octanone (**33**) to heptanoic acid (**36**). In this case, we formed the silyloxyalkene from the kinetic enolate[27] with *tert*-butyldimethylsilyl chloride.[29] Upon work-up, *tert*-butyldimethylsilyl ester **35** and heptanoic acid are obtained in a 4:1 ratio in a total yield of 90%. Since the *tert*-butyldimethylsilyloxy grouping is more stable to nucleophilic cleavage than the trimethylsilyloxy grouping,[29] it is necessary to hydrolyze the reaction product with mild acid to obtain acid **36**. Undoubtedly, use of trimethylsilyl chloride would provide heptanoic acid directly.

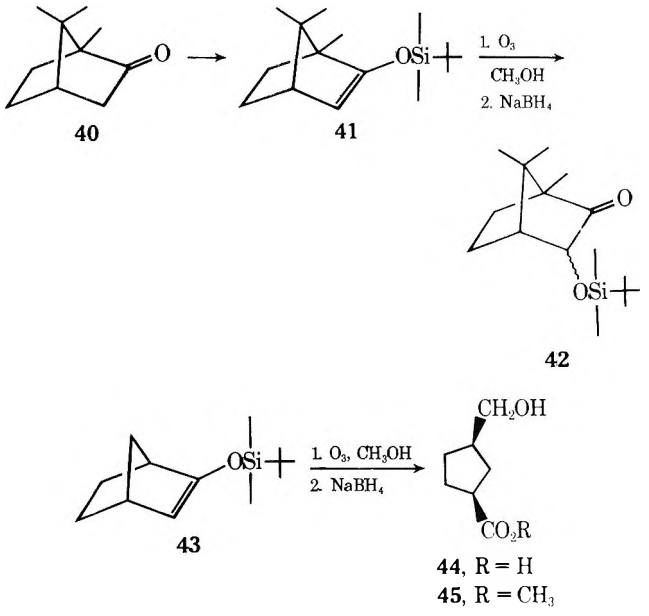


The trimethylsilyloxytriene **38** obtained in 82% yield from β-ionone (**37**) reacted anomalously. Even though only 1 equiv was used, oxidation occurred cleanly at the center double bond (which would appear to be the *least nucleophilic* of the three), giving β-cyclocitral (**39**) in good yield. From a preparative point of view, conversion of β-ionone to the silyl ether **38** is not necessary, since we found that selective ozonolysis of β-ionone itself gives **39** in good yield.



The silyloxyalkene **40** produced from camphor also gave an anomalous (and different) oxidation product; α-trial-

kylsilyloxy camphor **42** was produced in quantitative yield.[30] However, the analogous silyl ether prepared from norbornanone (**43**) reacted normally, giving hydroxy acid **44** as the only product.

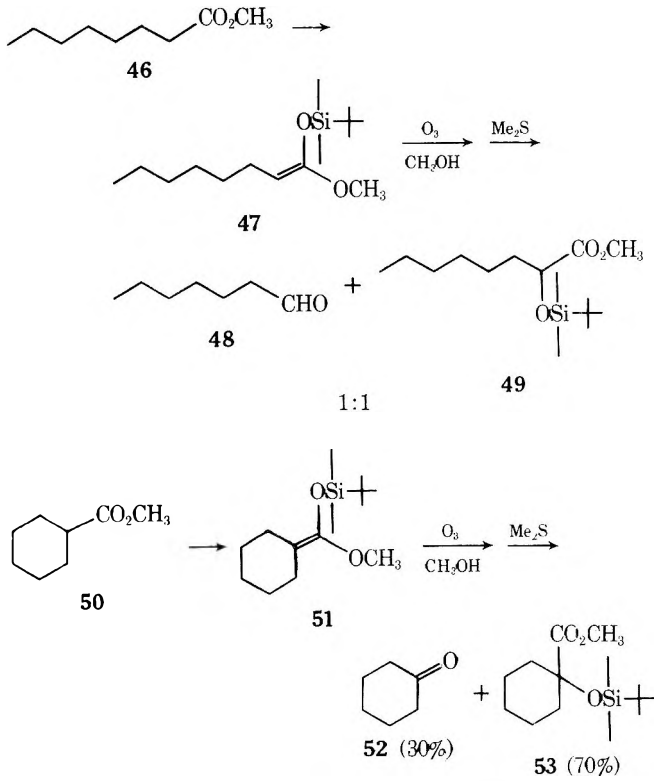


40 **41** **42**

43

44, R = H
45, R = CH_3

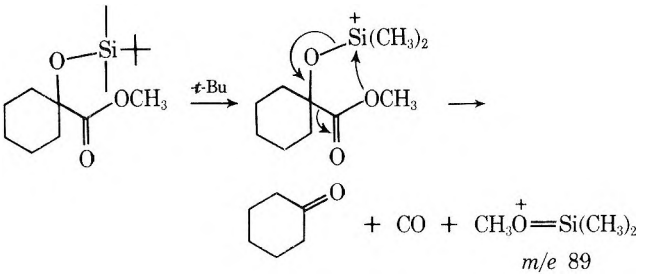
Silyloxyalkenes derived from ester enolates[31] (trialkylsilyloxy alkyl ketene acetals) give mixture of the normal ozonization product (representing one-carbon degradation of the ester) and the α-trialkylsilyloxy ester. Thus, methyl octanoate is converted, via ketene acetal **47**, into an equimolar mixture of heptanal (**48**) and methyl α-(*tert*-butyldimethylsilyloxy)octanoate (**49**). Similar results are obtained with methyl cyclohexanecarboxylate.



46 **47** **48** **49** (1:1)

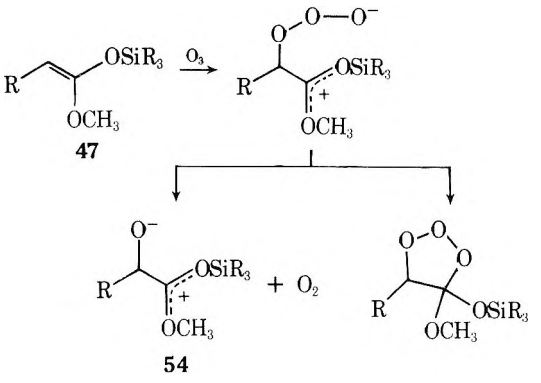
50 **51** **52** (30%) **53** (70%)

Both of the abnormal ozonization products **49** and **53** display a base peak in the mass spectrum at *m/e* 89 which corresponds to the fragment $[(CH_3)_2Si{=}OCH_3]^+$. This fragment probably arises from rearrangement of the initially formed ion as shown below.



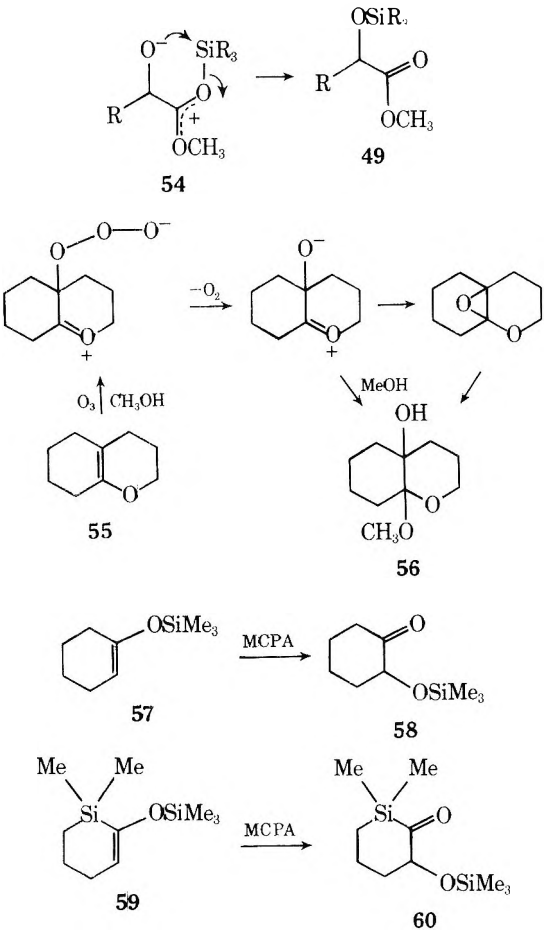
m/e 89

A reasonable mechanistic hypothesis which explains the anomalous oxidation of silyloxyalkenes **42**, **47**, and **51** involves formation of an intermediate zwitterion rather than a molozonide in the ozonization reaction. This might be expected to occur with an alkene which can give exceptional stabilization to the positive charge, such as **32** or **36**. Intramolecular silatropy in **54** would then yield the observed α-trialkylsilyloxy ester. Borowitz has found that ozonization



47 **54**

of certain enol ethers also gives products which might be produced via a similar zwitterion (**55** → **56**).[32] Subsequent



54 **49** **55** **56** **57** **58** **59** **60**

to our initial discovery of this unusual oxidation of silyloxyalkenes, similar reactions of silyloxyalkenes with peracids were observed by others (**57** → **58**,[33] **59** → **60**[34]).

Experimental Section

All melting and boiling points are uncorrected. Nuclear magnetic resonance (NMR) spectra were determined on a Varian T-60 spectrometer (in δ units with tetramethylsilane as internal reference). Infrared (ir) spectra were recorded on a Perkin-Elmer 137 infrared spectrophotometer. Mass spectra (MS) were obtained on a MS-12 mass spectrometer. Mass spectra are given as *m/e* with the relative intensity in parentheses. Preparative and analytical gas–liquid chromatography (GLC) was carried out on an Aerograph Model A90-P3 gas chromatograph, using the following stainless steel (10 ft × 0.25 in.) columns: column A, 5% SE-30; column B, 15% NPGS; column C, 15% SF-96. Microanalyses were performed by the University of California Microanalytical Laboratory, Berkeley, Calif.

3aβ-Ethenyl-2-trimethylsilyloxy-3a,4,5,6,7,7aβ-hexahydroindene (6). Vinyllithium (12.5 ml of a 2.4 M solution in THF, 30 mmol) was added to a suspension of purified copper(I) iodide[35] (3.30 g, 17.4 mmol) in ether (10 ml) and dimethyl sulfide (5 ml) at −75 °C. The black mixture was stirred for an additional 45 min at −75 °C, followed by the dropwise addition of enone **5** (1.36 g, 10 mmol) in ether (10 ml). The solution was stirred for 45 min at −75 °C and 15 min at −40 °C. The −40 °C solution was treated with HMPT (2 ml), triethylamine (3 ml), and trimethylchlorosilane (3 ml), then allowed to warm to room temperature over 1 h. After dilution with pentane (120 ml), the mixture was poured into cold 5% hydrochloric acid and the pentane layer was washed with 5% hydrochloric acid, water, and brine. The pentane was dried and evaporated and the residue distilled to give 1.75 g (74.2%) of silyl ether **6**: bp 70–75 °C (0.3 mm); ir (film) 6.12, 8.00, 11.56, 11.76 μ; NMR (CCl_4) δ 0.18 (s, 9 H), 1.2–1.6 (m, 9 H), 2.10 (m, 2 H), 4.40 (t, 1 H), 4.73–5.13 (BC portion of ABC, J_{AB} = 18, J_{AC} = 10, J_{BC} = 2 Hz, 2 H), 5.87 (A portion of ABC, 1 H); MS *m/e* 236 (40), 221 (14), 194 (23), 193 (100), 181 (18), 147 (18), 75 (21), 73 (66).

Anal. Calcd for $C_{14}H_{24}OSi$: C, 71.14; H, 10.02. Found: C, 70.96; H, 10.09.

8aβ-Ethenyl-4aβ-octahydro-3*H*-2-benzopyran-3-one (7). Ozone (2.42 mmol) from a Welsbach generator was passed into a −78 °C solution of silyl ether **6** (572 mg, 2.42 mmol) in methanol (10 ml) and methylene chloride (2 ml). The −78 °C solution was treated with sodium borohydride (320 mg, 8.46 mmol) over a 90-min period. After warming to room temperature, the mixture was evaporated and partitioned between 10% hydrochloric acid and ether. The ether was dried and evaporated to 402 mg (93%) of lactone **7** as a thick oil which slowly crystallized. An analytical sample was obtained by preparative GLC (column A, 200 °C): mp 44–46 °C (lit.[5,8] mp 44–45 °C; ir (film) 5.78, 6.10, 8.40, 9.43, 10.80 μ; NMR (CCl_4) δ 2.17, 2.62 (AB portion of ABX, J_{AB} = 18, J_{AX} = 7, J_{BX} = 5 Hz, 2 H), 4.13 (AB, Δν = 14.7 Hz, *J* = 11 Hz), 5.00–5.98 (eight-line ABC pattern, 3 H); MS *m/e* 180 (1), 150 (20), 108 (100), 93 (47), 79 (59), 78 (12), 77 (14).

Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.33; H, 8.89. Found: C, 73.13; H, 8.87.

8aβ-Ethenyl-4-methylene-4aβ-octahydro-3*H*-2-benzopyran-3-one (2). This material was prepared in 40% yield from **7** according to the previously described procedure of Grieco,[11] and had spectral data in complete accord with that reported:[5,8] ir (film) 5.83, 6.10, 6.19, 8.00, 8.77, 9.61 μ; NMR (CCl_4) δ 2.53 (broad t, 1 H), 4.12 (AB, Δν = 24.6 Hz, *J* = 11 Hz, 2 H), 5.00–5.98 (eight-line ABC pattern, 3 H), 5.50 (t, *J* = 1 Hz, 1 H), 6.36 (t, *J* = 1 Hz, 1 H).

3aβ-Ethenyl-7aβ-hexahydroinden-2(1*H*)-one (12). Hydrolysis of silyl ether **6** with 5% hydrochloric acid gave the vinylated hydrindenone **12**, a colorless oil: ir (film) 3.14, 5.71, 6.10, 6.90, 7.14, 10.98 μ; NMR (CCl_4) δ 1.55 (broad s, 9 H), 2.15 (s, 4 H), 5.03 (dd, B portion of ABC, J_{AB} = 18, J_{BC} = 2 Hz, 1 H), 5.08 (dd, C portion of ABC, J_{BC} = 2, J_{AC} = 10 Hz, 1 H), 5.93 (six-line complex A portion of ABC, 1 H).

Anal. Calcd for $C_{11}H_{16}O$: C, 80.44; H, 9.82. Found: C, 80.35; H, 9.77.

3aβ-Methyl-2-trimethylsilyloxy-3a,4,5,6,7,7aβ-hexahydroindene (8). A solution of lithium dimethylcuprate was prepared from 3.02 g (16 mmol) of copper(I) iodide in ether (30 ml) and 18.2 ml of 1.6 M ethereal methyllithium at 0 °C. The colorless solution was cooled to −20 °C, and enone **5** (1.36 g, 10 mmol) in ether (25 ml) was added. The resulting bright yellow mixture was stirred for an additional 45 min at −20 °C, followed by the addition of HMPT (2.0 ml), triethylamine (3.5 ml), and trimethylchlorosilane (3.0 ml). After 3 h at room temperature the mixture was diluted with pentane and poured into cold 5% hydrochloric acid. The mixture was filtered through Celite and the pentane layer was washed with brine, dried, and evaporated to 2.24 g (96%) of silyl ether **8**, of suitable purity for the next conversion: ir (film) 6.10, 8.00 μ; NMR (CCl_4) δ 0.18 (s, 9 H), 0.94 (s, 3 H), 2.10 (m, 2 H), 4.40 (t, *J* = 1 Hz, 1 H).

8aβ-Methyl-4aβ-octahydro-3*H*-2-benzopyran-3-one (10). Ozonolysis of silyl ether **8** (2.0 g, 8.8 mmol) according to the procedure described for the preparation of **7** gave 1.05 g (70%) of lactone **10** after distillation: bp 105 °C (0.5 mm); ir (film) 5.78, 8.33, 9.43 μ; NMR (CCl_4) δ 1.07 (s, 3 H), 2.19 (dd, A portion of ABX, J_{AB} = 18, J_{AX} = 5 Hz, 1 H), 2.63 (dd, B portion of ABX, J_{BX} = 7 Hz, 1 H), 4.00 (AB, Δν = 27.5 Hz, *J* = 12 Hz, 2 H); MS *m/e* 150 (4), 96 (40), 81 (67), 79 (24), 68 (29), 67 (61), 41 (100).

Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 71.06; H, 9.50.

8aβ-Methyl-4-methylene-4aβ-octahydro-3*H*-2-benzopyran-3-one (3). Methylenation according to Grieco's procedure[11] gave **3** in 45% yield after distillation: bp 115 °C (0.3 mm); ir (film) 5.80, 7.19, 7.81, 8.70 μ; NMR (CCl_4) δ 1.05 (s, 3 H), 2.13 (m, 1 H), 4.03 (AB, Δν = 39.5 Hz, *J* = 11 Hz, 2 H), 5.43 (t, *J* = 1 Hz, 1 H), 6.33 (t, *J* = 1 Hz, 1 H); MS *m/e* 180 (4), 136 (24), 108 (41), 107 (100), 93 (80), 91 (40), 81 (65), 79 (91), 77 (41).

Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.33; H, 8.89. Found: c, 73.03; H, 8.74.

3aβ-Methyl-7aβ-hexahydroinden-2(1*H*)-one (13). Hydrolysis of silyl ether **8** by stirring in 10% hydrochloric acid, followed by ether extraction, gave the crystalline ketone **13**: mp 38–39 °C (lit.[19b] mp 37–39 °C); ir (CCl_4) 5.73, 6.93, 7.13, 7.28, 7.98 μ; NMR (CCl_4) δ 1.13 (s, 3 H), 1.47 (broad s, 8 H), 2.00–2.40 (m, 5 H).

Anal. Calcd for $C_{10}H_{16}O$: C, 78.90; H, 10.59. Found: C, 78.78; H, 10.70.

8aβ-Ethyl-4-methylene-4aβ-octahydro-3*H*-2-benzopyran-3-one (4). A solution of ethylmagnesium bromide (100 mmol) in ether (100 ml) was cooled to 0 °C and copper(I) iodide (1.90 g, 10 mmol) was added. Enone **5** (6.80 g, 50 mmol) in ether (25 ml) was added dropwise to the black solution over a 25-min period. After an additional 30 min at 0 °C, the mixture was treated with HMPT (10 ml), triethylamine (10.1 g, 100 mmol), and trimethylchlorosilane (10.8 g, 100 mmol). The solution was stirred for 1 h, then diluted with pentane and washed with 5% hydrochloric acid and brine. The pentane was dried and evaporated to a colorless oil which was a 70:30 mixture of **9** and **14** by NMR analysis: ir (film) 6.10 μ; NMR (CCl_4) δ 4.40 (s, silyl ether vinyl, 1 H), 5.18 (s, 1,2 adduct vinyl, 1 H).

This material was ozonized in methanol–methylene chloride (1:1, 100 ml) at −70 °C and then treated with sodium borohydride (3.4 g). After solvent evaporation, the residue was taken into water and washed with methylene chloride. Acidification of the aqueous layer and methylene chloride extraction gave a colorless oil which was distilled to give 3.85 g (42.5% overall) of lactone **11**: bp 125 °C (1 mm); ir (film) 5.80 μ; NMR ($CDCl_3$) δ 0.87 (t, *J* = 7 Hz, 3 H), 2.46 (eight-line portion of ABX, 2 H), 4.10 (AB, Δν = 26.1 Hz, *J* = 12 Hz, 2 H).

Methylenation[11] of this material gave **4** in 38% yield after distillation (oven 100 °C, 5 μ): ir (film) 5.80, 7.18, 7.80, 8.70 μ; NMR ($CDCl_3$) δ 0.83 (t, *J* = 7 Hz, 3 H), 2.35 (m, 1 H), 4.25 (AB, Δν = 36.1 Hz, *J* = 12 Hz, 2 H), 5.56 (s, 1 H), 6.45 (s, 1 H); MS *m/e* 194 (3), 165 (14), 135 (50), 121 (62), 107 (66), 93 (60), 81 (68), 79 (83), 67 (69), 41 (100).

Anal. Calcd for $C_{12}H_{18}O_2$: C, 74.19; H, 9.34. Found: C, 74.16; H, 9.40.

4aβ-Ethoxycarbonyl-2-trimethylsilyloxy-1,4,4a,5,6,7,8,8aα-octahydronaphthalene (16). A solution of keto ester **15**[36] (55.0 g, 246 mmol) in DMF (100 ml) and triethylamine (82.6 ml) was treated with trimethylchlorosilane (38.1 ml), and the resulting slurry was refluxed for 20 h. The cooled mixture was diluted with pentane (300 ml) and washed with cold 5% sodium bicarbonate and water. The pentane was dried and evaporated and the residue was distilled to give 66.3 g (90.8%) of silyl ether **16**: bp 120 °C (2.0 mm); ir (film) 5.76, 6.01, 8.00, 8.40, 10.98 μ; NMR (CCl_4) δ 0.18 (s, 9 H), 1.26 (t, *J* = 7 Hz, 3 H), 4.10 (quartet, 2 H), 4.66 (m, 1 H); MS M^+ *m/e* 296 (9), 223 (56, M − CO_2Et), 222 (68), 75 (49).

8aβ-(2-Hydroxyethyl)-4aβ-octahydro-3*H*-2-benzopyran-3-one (18). A solution of silyl ether **16** (3.41 g, 11.5 mmol) in methanol (10 ml) and methylene chloride (10 ml) at −70 °C was treated with excess ozone. After purging with nitrogen, the cold solution was treated with sodium borohydride (0.5 g, 13 mmol) and allowed

to warm to room temperature. Extractive work-up gave 2.95 g (99.3%) of crude hydroxy acid **17**, ir (film) 2.8–4.3, 5.80 μ.

This material was dissolved in THF (10 ml) and added to a solution of ethanol (5 ml) and liquid ammonia (100 ml).[37] Small pieces of sodium were added until a blue color persisted, and the mixture was then quenched by addition of methanol. The ammonia was allowed to evaporate and the residue was taken into water and washed with ether. Acidification and extraction with methylene chloride gave 1.68 g (73.6% overall) of **18** as a colorless oil: ir (film) 2.90, 5.75, 6.90, 7.91, 9.51 μ; NMR ($CDCl_3$) δ 1.72 (t, J = 6 Hz, CH_2CH_2OH, 2 H), 2.26 (dd, A portion of ABX, J_{AB} = 18, J_{AX} = 4 Hz, 1 H), 2.80 (dd, B portion of ABX, J_{BX} = 7 Hz), 3.43 (s, hydroxyl H, 1 H), 3.73 (t, J = 6 Hz, 2 H), 4.23 (AB, $\Delta\nu$ = 20.7 Hz, J = 11 Hz, 2 H); MS *m/e* 198 (8), 180 (2), 144 (17), 108 (100), 95 (39), 74 (36), 58 (35).

Anal. Calcd for $C_{11}H_{18}O_3$: 198.1256. Found: 198.1293.

8aβ-(2-*p*-Toluenesulfonyloxyethyl)-4aβ-octahydro-3*H*-2-benzopyran-3-one (19). A mixture of alcohol **18** (460 mg, 2.32 mmol) and *p*-toluenesulfonyl chloride (572 mg, 3.00 mmol) in pyridine (5 ml) was maintained at 0 °C for 16 h. The solution was poured into water and extracted with ether to give 651 mg (80%) of tosylate **19** as a thick oil: ir (film) 5.75; 6.25; 7.41; 8.40, 9.51; 10.5 μ; NMR ($CDCl_3$) δ 1.82 (t, J = 6 Hz, 2 H), 2.23–2.76 (AB portion of ABX, J_{AB} = 18, J_{AX} = 4, J_{BX} = 7 Hz, 2 H), 2.46 (s, 3 H), 4.13 (t, J = 6 Hz, 2 H), 4.16 (AB, $\Delta\nu$ = 28.2 Hz, J = 11 Hz, 2 H).

2c-(2-Oxa-(5rC[1])-spiro[4.5]decanyl)acetic Acid[38] (21). The tosylate **19** (443 mg, 1.26 mmol) was refluxed overnight in acetone (20 ml) with sodium iodide (1.50 g) to give 389 mg (100%) of iodide **20** as a thick, colorless oil: NMR (CCl_4) δ 3.16 (t, J = 7 Hz, 2 H), 4.10 (AB, $\Delta\nu$ = 20.8 Hz, J = 12 Hz, 2 H).

A solution of iodide **20** (74 mg, 0.24 mmol) in *tert*-butyl alcohol (1 ml) was treated with 0.6 ml of 0.44 M potassium *tert*-butoxide in *tert*-butyl alcohol. A white solid separated immediately from the reaction mixture. After 1 h at room temperature, the solution was poured into 5% hydrochloric acid and extracted with ether to give 45.0 mg of acid **21**: ir (film) 2.80–4.00, 5.80, 8.56, 9.51 μ; NMR (CCl_4) δ 2.00–2.42 (m, 2 H), 3.46 (AB, $\Delta\nu$ = 16.7 Hz, J = 9 Hz, $CH_2OCH_2CH_2$, 2 H), 3.73 (t, J = 6 Hz, OCH_2CH_2, 2 H).

Esterification of **21** with diazomethane gave a methyl ester: ir (film) 5.73, 8.00, 8.50, 9.52 μ; NMR (CCl_4) δ 2.00–2.40 (m, 2 H), 3.53 (AB, $\Delta\nu$ = 13.4 Hz, J = 9 Hz, 2 H), 3.67 (s, 3 H), 3.76 (t, J = 6 Hz, 2 H); MS *m/e* 181 (19, loss of OCH_3), 152 (38), 109 (43), 108 (70), 107 (30), 93 (70), 79 (81), 74 (44), 67 (69), 55 (61), 41 (100).

8aβ-Ethenyl-4aβ-octahydro-3*H*-2-benzopyran-3-one (7). Diphenyl diselenide (1.08 g, 3.47 mmol) in ethanol (25 ml) was treated with sodium borohydride (0.26 g, 6.94 mmol) in small portions until the solution was colorless. The solution was cooled in an ice bath, and tosylate **19** in THF (8 ml) was added. The mixture was stirred at room temperature for 4 h and then poured into 5% sodium carbonate and extracted with ether to give 2.08 g (98%) of crude selenide **22**: ir (film) 5.75, 6.31, 6.80, 8.55 μ; NMR ($CDCl_3$) δ 3.78 (t, J = 6 Hz, CH_2SePh, 2 H).

The crude selenide **22** (10.28 mmol) was ozonized at −20 °C in carbon tetrachloride (30 ml) with excess ozone until the solution was light blue. The cold solution, from which a white solid had precipitated, was then added over a 10-min period to 100 ml of refluxing carbon tetrachloride, using a small volume of methylene chloride to transfer the solid. Evaporation of solvents left a yellow oil which was chromatographed on 100 g of silica gel. Elution with pentane gave fractions containing diphenyl diselenide. Further elution with ether gave 1.12 g (60.5% from **19**) of crystalline lactone **7**, identical with that previously prepared in our laboratory.

Ozonization of Silyl Ether 29. A solution of silyloxyalkene **29**[10] (5.48 g, 29.8 mmol) in methylene chloride (5 ml) and methanol (20 ml) was treated with excess ozone at −70 °C. After nitrogen purge, the −70 °C solution was treated with sodium borohydride (1.13 g, 29.8 mmol). After stirring at −70 °C for 1 h, a second portion of sodium borohydride was added and the solution was allowed to warm to room temperature. The solvent was evaporated and the residue was partitioned between 5% hydrochloric acid and chloroform. The aqueous layer was extracted with chloroform, and the combined organic layers were dried and evaporated to 4.10 g (94.3%) of hydroxy acid **30**.

Esterification of this product (methanol–sulfuric acid) gave 3.50 g (73.5%) of methyl 6-hydroxy-2-methylhexanoate after distillation: bp 80 °C (1.0 mm); ir (film) 2.94, 5.75, 8.40, 8.62 μ; NMR (CCl_4) δ 1.13 (d, 3 H), 2.33 (m, 1 H), 2.98 (s, hydroxyl H, 1 H), 3.50 (t, 2 H), 3.64 (s, 3 H).

Anal. Calcd for $C_8H_{16}O_3$: C, 59.98; H, 10.07. Found: C, 60.01; H, 10.03.

Ozonization of Silyl Ether 31. Silyloxyalkene **31**[10] (1.0 g, 5.42 mmol) in methanol (10 ml) and methylene chloride (8 ml) was ozonized at −70 °C and then treated with dimethyl sulfide (1.0 ml) and allowed to warm to room temperature. Evaporation gave a mixture of dimethyl sulfoxide and keto acid **32** (>90% yield).

Esterification of this mixture with diazomethane and extractive work-up gave 602 mg (71.5%) of methyl 6-oxoheptanoate: ir (film) 5.75, 5.83, 7.40, 8.62 μ; NMR (CCl_4) δ 2.03 (s, 3 H), 2.10–2.50 (m, 4 H), 3.60 (s, 3 H).

Anal. Calcd for $C_8H_{14}O_3$: C, 60.74; H, 8.92. Found: C, 60.68; H, 9.14.

2-*tert*-Butyldimethylsilyloxy-1-octene (34). A solution of 2-octanone **33** (2.56 g, 20 mmol) in THF (7 ml) was added dropwise to a −70 °C solution of lithium diisopropylamide (24 mmol) in THF (20 ml). After stirring for 45 min at −70 °C, the solution was treated with HMPT (3 ml) and *tert*-butyldimethylsilyl chloride (3.30 g, 22 mmol) in pentane (5 ml). After warming to room temperature the mixture was diluted with pentane, washed with water, dried, and evaporated. Distillation gave **34** (2.60 g, 54%) as a colorless liquid which was pure by NMR and GLC (column B, 150 °C) analysis: bp 50 °C (0.3 mm); ir (film) 6.01, 6.12, 8.00, 9.09, 9.70, 11.97 μ; NMR (CCl_4) δ 0.17 (s, 6 H), 0.97 (s, 9 H), 2.00 (broad t, 2 H), 3.90 (sharp s, 2 H).

Anal. Calcd for $C_{14}H_{30}OSi$: C, 69.42; H, 12.44. Found: C, 69.36; H, 12.54.

Ozonization of Silyloxyalkene 34. A solution of **34** (2.37 g, 9.8 mmol) in 10 ml of methylene chloride and 20 ml of methanol was treated with excess ozone at −78°. Dimethyl sulfide (2 ml) was added and the solution was allowed to warm to room temperature. The solvent was evaporated and the residue was taken into ether and esterified with diazomethane to give 1.96 g of colorless oil. This was shown by NMR and GLC analysis (column B) to be an 80:20 mixture of silyloxy ester **35** and methyl heptanoate. Ester **35** was obtained by preparative GLC: ir (film) 5.80, 8.00, 8.47, 9.09, 11.23, 11.76 μ; NMR (CCl_4) δ 0.20 (s, 6 H), 0.90 (s, 9 H), 2.15 (t, J = 6 Hz, 2 H); MS *m/e* 229 (2), 187 (83), 131 (22), 87 (16), 75 (100), 73 (70), 60 (85). The methyl heptanoate was identical with an authentic sample by NMR and GLC comparison.

The following silyl enol ethers were prepared under conditions analogous to those described for the preparation of **34**.

Trimethylsilyl Ether from β-Ionone (38) (82.0% yield): ir (film) 6.12, 6.31, 7.66, 8.00, 9.80, 10.31 , 12.00 μ; NMR (CCl_4) δ 0.23 (s, 9 H), 1.07 (s, 6 H), 1.73 (s, 3 H), 2.00 (t, 2 H), 4.23 (s, 2 H), 5.77 (d, J = 11 Hz, 1 H), 6.33 (d, J = 11 Hz, 1 H).

***tert*-Butylmethylsilyl Ether from Camphor (41)** (90% yield): ir (film) 6.18, 6.85, 7.58, 8.20, 8.81, 9.98, 10.90 μ; NMR (CCl_4) δ 0.18 (s, 6 H), 0.73 (s, 3 H), 0.90 (s, 6 H), 0.98 (s, 9 H), 4.50 (d, J = 3 Hz, 1 H).

***tert*-Butyldimethylsilyl Ether from Norbornanone (43)** (95% yield): ir (film) 6.20, 6.85, 7.53, 8.15, 10.81 μ; NMR (CCl_4) δ 0.17 (s, 6 H), 0.98 (s, 9 H), 4.63 (d, J = 3 Hz, 1 H).

1-*tert*-Butyldimethylsilyloxy-1-methoxy-1-octene (47) (~95% yield): ir (film) 5.95, 6.83, 8.00, 8.60, 11.90 μ; NMR (CCl_4) δ 0.16 (s, 6 H), 0.98 (s, 9 H), 1.80 (broad t, 2 H), 3.46 (s, 3 H), 3.56 (m, 1 H).

Ketene Acetal 51 (>95% yield): ir (film) 5.90, 8.01, 8.60, 9.42, 10.58 μ; NMR (CCl_4) δ 0.12 (s, 6 H), 0.98 (s, 9 H), 3.43 (s, 3 H).

Ozonization of Silyl Ether 38. Silyl ether **38** (1.0 g, 3.8 mmol) was ozonized according to the procedure described for the ozonolysis of **34** (3.8 mmol of ozone). Evaporation of solvent and extractive work-up gave 503 mg (87%) of β-cyclocitral **39** which was pure by NMR and GLC analysis (column B): ir (film) 3.57, 5.97, 6.19, 7.30, 7.40 μ; NMR (CCl_4) δ 1.18 (s, 6 H), 2.08 (s, 3 H), 10.10 (s, 1 H).

Anal. Calcd for $C_{10}H_{16}O$: C, 78.90; H, 10.59. Found: C, 78.67; H, 10.77.

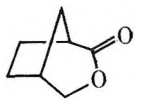
Ozonization of Silyl Ether 41. Silyl ether **41** was ozonized and worked up according to the procedure described for the ozonolysis of **6**. A colorless oil (2.44 g) was obtained which displayed two overlapping peaks on GLC at retention times 9.1 and 10.2 min (column B, 160 °C). The pure mixture of epimers **42** was obtained by preparative GLC: ir (film) 5.71, 8.00, 8.47, 10.52 μ; NMR (CCl_4) δ 0.13 (s, 6 H), 0.97 (s, 9 H), 0.90–1.0 (three overlapping singlets, 9 H), 1.3–1.9 (m, 5 H), 3.57–3.93 (m, $-CHOSiR_3$, two epimers, 1 H); MS *m/e* 267 (2), 225 (79), 171 (35), 169 (49), 115 (26), 75 (51), 73 (100).

Anal. Calcd for $C_{16}H_{30}O_2Si$: C, 68.08; H, 10.64. Found: C, 68.22; H, 10.57.

Ozonization of Silyl Ether 43. Ozonolysis of **43** (11.2 g, 50 mmol), followed by sodium borohydride reduction, gave 7.1 g of crude hydroxy acid **44**, which was esterified with diazomethane.

Distillation gave 3.95 g (50%) of hydroxy ester **45**: bp 100 °C (1.0 mm); ir (film) 2.90, 5.78, 8.35, 8.60 μ; NMR (CCl_4) δ 3.66 (d, J = 6 Hz, 2 H), 3.76 (s, 3 H).

Compound **45** lactonized on GLC (column C, 190 °C) to give **61**. An analytical sample of lactone **61** was obtained by preparative



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GLC (column C): ir (film) 5.74, 8.10, 9.30, 9.70 μ; NMR ($CDCl_3$) δ 4.16 (eight-line ABX, J_{AB} = 11, J_{AX} = 3, J_{BX} = 0.5 Hz, CH_2OCO, 2 H).

Anal. Calcd for $C_7H_{10}O_2$: 126.0701. Found: 126.0691.

Ozonization of 47. Ozonolysis of **47** (4.60 g, 15 mmol) with dimethyl sulfide reduction gave 3.21 g of colorless oil after extractive work-up to remove dimethyl sulfoxide. NMR and GLC analysis (column B, 170 °C) showed a 1:1 mixture of heptanal (by comparison with an authentic sample) and ester **49**. Compound **49** was obtained by preparative GLC: ir (film) 5.73, 8.01, 8.77, 11.00 μ; NMR (CCl_4) δ 0.12 (s, 6 H), 0.95 (s, 9 H), 3.67 (s, 3 H), 4.08 [broad t, $-CH(OSiR_3)CO_2Me$]; MS *m/e* 273 (3), 231 (83), 203 (23), 97 (32), 89 (100), 75 (34), 73 (73).

Ozonization of 51. Ozonolysis of compound **51** (1.28 g, 5 mmol) with dimethyl sulfide reduction gave a mixture of dimethyl sulfoxide, cyclohexanone **52**, and ester **53** after solvent evaporation. The ratio of **52** to **53** was 30:70 by NMR analysis. Compound **53** was obtained by preparative GLC (column B, 190 °C): ir (film) 5.73, 8.00, 8.70, 9.21 μ; NMR (CCl_4) δ 0.12 (s, 6 H), 0.95 (s, 9 H), 1.40–1.80 (m, 10 H), 3.70 (s, 3 H); MS *m/e* 257 (3), 215 (86), 213 (40), 187 (78), 89 (100), 75 (53), 73 (81).

Anal. Calcd for $C_{14}H_{28}O_3Si$: C, 61.76; H, 10.29. Found: C, 61.76; H, 10.18.

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Registry No.—**2**, 42391-68-4; **3**, 53883-18-4; **4**, 58240-78-1; **5**, 39163-29-6; **6**, 53883-15-1; **7**, 42391-78-6; **8**, 53883-16-2; **9**, 58240-79-2; **10**, 53883-17-3; **11**, 58240-80-5; **12**, 58240-81-6; **13**, 13351-29-6; **14**, 58240-82-7; **15**, 1209-32-3; **16**, 58240-83-8; **17**, 58240-84-9; **18**, 58240-85-0; **19**, 58240-86-1; **20**, 58240-87-2; **21**, 58240-88-3; **22**, 58240-89-4; **29**, 19980-33-7; **31**, 19980-35-9; **33**, 111-13-7; **34**, 54251-60-4; **35**, 54251-63-7; **38**, 35156-36-6; **39**, 432-25-7; **41**, 54251-61-5; *exo*-**42**, 58240-90-7; *endo*-**42**, 58240-91-8; **43**, 58240-92-9; **45**, 58240-93-0; **47**, 54326-35-1; **49**, 54251-65-9; **51**, 54251-62-6; **53**, 54326-36-2; **61**, 766-71-2; trimethylchlorosilane, 75-77-4; *p*-toluenesulfonyl chloride, 98-59-9; 2*c*-(2-oxa-(5*rC*^{1})-spiro[4.5]decanyl)acetic acid methyl ester, 58240-94-1; diphenyl diselenide, 1666-13-3; methyl 6-hydroxy-2-methylhexanoate, 58240-95-2; methyl 6-oxoheptanoate, 2046-21-1; *tert*-butyldimethylsilyl chloride, 18162-48-6.

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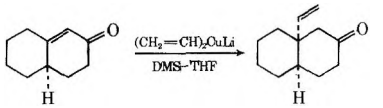
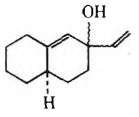
(14) A further demonstration of the utility of this procedure is provided by the conversion of octalone i to the *cis*-9-vinyl-2-decalone ii, uncontaminated by 1,2 adduct, in 90% yield.[16]



i ii

Copper-catalyzed addition of vinylmagnesium bromide to octalone i gives decalone ii and the 1,2 adduct iii in a ratio of 4:1.



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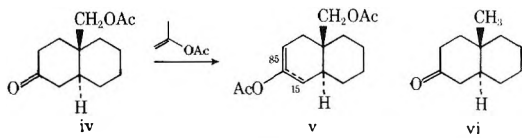
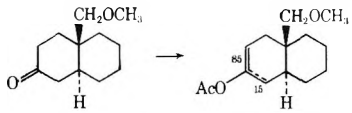
(21) Compound **15** gives only the $\Delta^{2,3}$ isomer upon enol acetylation or enol trimethylsilylation. We found that iv, on the other hand, gave ca. 15% of the $\Delta^{3,4}$ isomer. Compound vi also gives ca. 15% of the $\Delta^{3,4}$ enol acetate (D. Hart, private communication).



iv v vi

Grieco has obtained a similar mixture with compound vii.[8]



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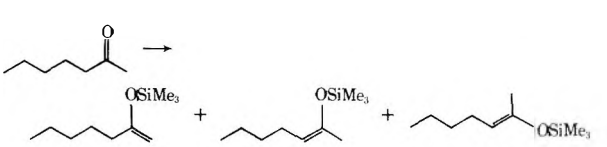
(25) Tests were done by the Drug Research and Development Section of the National Cancer Institute, Bethesda, Md.
(26) Note that compound **2** is racemic. If the reasonable assumption is made that only one enantiomer is cytotoxic, then its ED_{50} would be 2.2–7.5 $\mu g\ ml^{-1}$. We are currently preparing resolved samples of lactone **2** in order to test this assumption.
(27) The *tert*-butyldimethylsilyloxyalkene **34** is the sole product of this reaction. Neither of the isomeric 2-alkenes can be detected by GLC or ^1H NMR. This result is in contrast to the results of House and co-workers,[28] who formed the kinetic enolate from 2-heptanone with lithium diisopropylamide in 1,2-dimethoxyethane. Upon quenching with trimethylsilyl chloride, silyloxyalkenes ix, x, and xi were produced in a ratio of 84:7:9.



ix x xi

(28) H. O. House, L. J. Czuba, M. Gall, and H. D. Olmstead, *J. Org. Chem.*, **34**, 2324 (1969).
(29) E. J. Corey and A. Venkateswarlu, *J. Am. Chem. Soc.*, **94**, 6190 (1972).
(30) The same anomalous oxidation has been observed in the ozonization of a hindered steroidal *tert*-butyldimethylsilyloxyalkene by Dr. M. Tanabe and co-workers at the Stanford Research Institute, Menlo Park, Calif. We thank Dr. Tanabe for communicating his results to us prior to publication.
(31) M. W. Rathke and D. F. Sullivan, *Snyth. Commun.*, **3**, 67 (1973).
(32) I. J. Borowitz and R. D. Rapp, *J. Org. Chem.*, **34**, 1370 (1969).
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(34) G. M. Rubottom, M. A. Vazquez, and D. R. Pelegrina, *Teahedron Lett.*, 4319 (1974).

(35) Commercial copper(I) iodide (Ventron) was recrystallized from aqueous potassium odide and then extracted with THF in a Soxhlet extractor for several hours. Copper iodide which was not purified in this way gave erratic results in this reaction. For preparation of lithium dimethylcuprate, commercial copper iodide was used with no purification.

(36) L. S. Minckler, A. S. Hussey, and R. H. Baker, *J. Am. Chem. Soc.*, **78**, 1009 (1956).
(37) L. A. Paquette and N. A. Nelson, *J. Org. Chem.*, **27**, 2272 (1962).
(38) For an explanation of this nomenclature, see J. A. Marshall and P. C. Johnson, *J. Org. Chem.*, **35**, 192 (1970).

Carbon–Phosphorus Heterocycles. A One-Step Synthesis of Phosphindolines and Phosphinolines. Cyclization of Diphenylalkenylphosphine Oxides with Polyphosphoric Acid[1]

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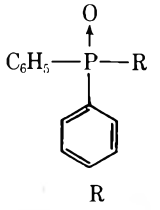
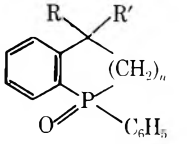
A convenient method of wide scope for the synthesis of phosphindoline and phosphinoline derivatives has been developed from the readily available starting materials. Cyclization of diphenylalkenylphosphine oxides occurred in the presence of 115% polyphosphoric acid (PPA) at 180 °C for 4 h to give C–P heterocyclic systems in modest to good yield (40–70%). Work-up of the reaction mixtures simply involved addition to ice–water. The resulting homogeneous solution was extracted with chloroform and dried; the solvent was evaporated under reduced pressure to yield the respective phosphindoline or phosphinoline. ^{1}H NMR, ^{31}P NMR, elemental, infrared, and mass spectral analyses supported the structure of these phosphorus analogues of the corresponding indole and tetrahydroquinoline heterocycles. This method of synthesis of phosphindoline and phosphinoline offers not only the merit of being simple and inexpensive but also a one-step and rapid process from appropriately substituted alkenyl (aryl) phosphine oxides.

In our studies directed toward the development of simple, new synthetic methods for the production of carbon–phosphorus heterocyclic compounds, we have investigated the possibility of cyclization of diphenylalkenylphosphine oxides in the presence of 115% polyphosphoric acid (PPA) as cyclizing agent. At present, reported pathways leading to the synthesis of phosphindoline or phosphinoline systems involve cyclization by intramolecular quaternization[3,4] and cyclization by cycloaddition of trivalent phosphorus compounds with a diene or diyne derivative.[5–7] Both methods usually employ very uncommon starting materials and long overall reaction times. The rare intermediates needed for the synthesis also limit their versatility. The ready availability of diphenylalkenylphosphine oxides **1a–g** encouraged us to investigate the possibility of their cyclization in the presence of PPA as the cyclizing agent. Certain oxides of **1** possess the correct functionality and geometry for cyclizations to give the corresponding phosphindoline and/or phosphinoline **2**. 3-Methyl-1-phenylphosphindoline 1-oxide (**2a**), which has been prepared from *o*-bromobenzoic acid through a long series of reactions (12 steps),[8] can be synthesized by the cyclization of diphenylallylphosphine oxide (**1a**) with PPA in one step.

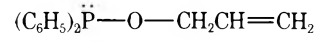


	R
1a	$CH_2CH{=}CH_2$
b	$CH_2CH{=}CHCH_3$
c	$CH_2CH_2CH{=}CH_2$
d	$CH_2C(CH_3){=}CH_2$
e	$CH_2CH{=}C(CH_3)_2$
f	$CH(CH_3)CH{=}CH_2$
g	$CH(C_6H_5)CH{=}CH_2$



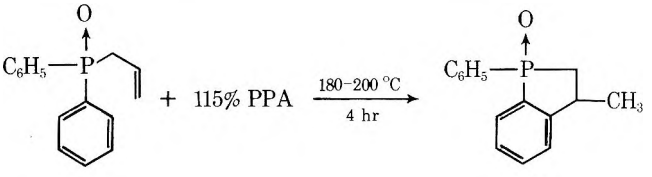
	R	R′	*n*
2a	H	CH_3	1
b	H	CH_3	2
c	CH_3	CH_3	1
d	CH_3	CH_3	2

Diphenylallylphosphine oxide can be obtained from chlorodiphenylphosphine and allyl alcohol in the presence of pyridine without the isolation of allyl diphenylphosphinite (**3**). The latter can be converted into oxide **1a** by heating



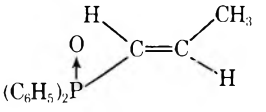
3

in situ at 140 °C.[9,10] In the presence of 115% PPA[11] at 180–200 °C for 4 h, the phosphine oxide **1a** underwent ring closure to 3-methyl-1-phenylphosphindoline 1-oxide (**2a**) in moderate yield (37%) along with a polymer. After 4 h,



1a **2a**

the reaction mixture was slowly poured into ice–water with stirring to give a homogeneous solution. Normal work-up gave a viscous yellow oil, which on distillation yielded pure **2a**. Oxide **2a** could be crystallized only with difficulty. In our attempts to optimize the reaction conditions, decreasing the reaction temperature to 120–150 °C gave the starting material *trans*-propenyldiphenylphosphine oxide[12] (**4**) and a polymeric product.



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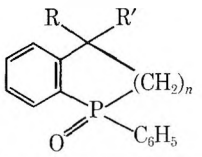
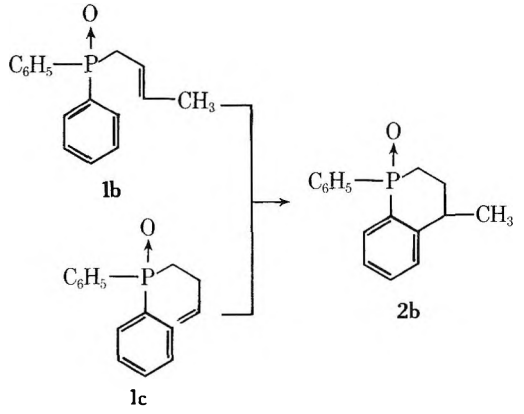
Interestingly, the phosphine oxides **1b** and **1c** also underwent ring closure to produce 1,2,3,4-tetrahydro-4-methyl-1-phenylphosphinoline 1-oxide (**2b**). Tentatively, one could assume that protonation had occurred at the β carbon in **1b** and at the δ carbon in **1c** to create a secondary cation. The second step could reasonably involve an elec-

Table I



Compd	R	R′	n	Mp, °C	Yield, %	Molecular formula	Anal, %	C	H	P
2a[a]	H	CH_3	1		37	$C_{15}H_{15}OP$				
2b	H	CH_3	2	105–115	70	$C_{16}H_{17}OP$	Calcd			12.1
							Found			12.08
2c	CH_3	CH_3	1	114–115	50	$C_{16}H_{17}OP$	Calcd	74.98	6.68	12.08
							Found	74.86	6.65	12.03
2d	CH_3	CH_3	2	99–101	40	$C_{17}H_{19}OP$	Calcd	75.53	7.08	11.45
							Found	75.39	6.90	11.45

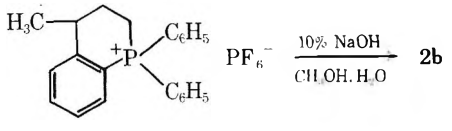
[a] This compound was previously reported in ref 8.



1b 2b 1c

trophilic attack on the benzene ring, followed by a proton loss to regenerate the aromatic ring. This postulated reaction mechanism has been recently supported by other work[13,14] which concerned the extensive study of the mechanism of alkenyl-substituted phosphonium salts by PPA. It was found that the reaction proceeded through a mechanism reminiscent of a cation alkylation process to give phosphinolinium systems and/or an isophosphinolinium salt, respectively.

Surprisingly, oxide **2b** could also be prepared in high yield from a base-cleavage reaction of 1,2,3,4-tetrahydro-4-methyl-1,1-diphenylphosphinolinium hexafluorophosphate (**5**).[14] This served as proof of structure for **2b**. Under



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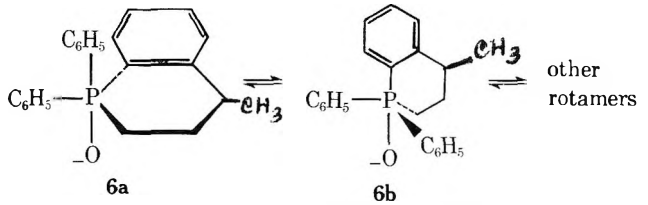
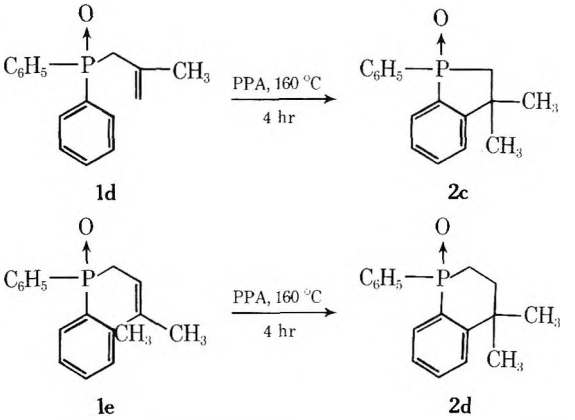
the conditions of cleavage employed, the phenyl group was lost, presumably expelled from the apical position of the postulated intermediate **6a** with no C–P ring opening ob-



6a 6b

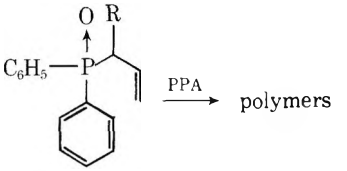
served. Marsi has suggested that an intermediate phosphorane generated from attack of a nucleophile on a system possessing a phosphorinane unit could have the CPC ring bonds diequatorially positioned.[15] The high yield of the ring-containing **2b** could result from a precursor rotamer like **6a** present in high concentration in an equilibrating system.

Similar cyclizations were performed with 2-methylallyldiphenylphosphine oxide (**1d**) and 3-methylbut-2-enyldiphenylphosphine oxide (**1e**) to give 3,3-dimethyl-1-phenylphosphindoline 1-oxide (**2c**) and 1,2,3,4-tetrahydro-4,4-dimethyl-1-phenylphosphinoline 1-oxide (**2d**), respectively.



1d 2c 1e 2d

Again, cation stability may be one controlling factor in determining the ring size. Changing the position of the branch on the alkenyl group proved determinal. From 50 to 200 °C in the presence of 115% PPA, 1-methylallyldiphenylphosphine oxide (**1f**) and 1-phenylallyldiphenylphosphine oxide (**1g**) gave only polymeric compounds. Possibly,



1f, R = CH_3
g, R = C_6H_5

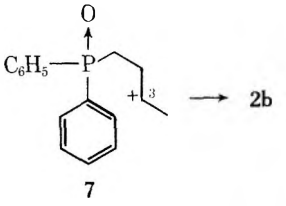
a steric factor involving an intermediate cation associated with $OPPA^{n-}$ may greatly decrease the rate of ring closure[13] but this must await a mechanistic study.

Structural identification of members of the phosphindoline and phosphinoline ring systems rests on elemental, infrared, mass spectral, and NMR analyses given in Tables I and II. The ^1H NMR spectrum of **2b** showed the methyl protons as two doublets (δ 1.32, 1.42 ppm, total 3 H). The observation of two doublets for the methyl proton signals almost assuredly arises from methyl groups in geometric isomers that form from attack of the ring from either face of the cation at C-3 in intermediate **7**. Thus, cis, trans iso-

Table II. NMR Spectral Data for the Starting Phosphine Oxides 1 and Reaction Products

Compd	Ir absorption spectra in KBr,[a] selected bands, cm^{-1}	^1H NMR spectral assignments, chemical shifts, δ [b]	^{31}P NMR, δ [c]
2b	1428 (s), 1176 (vs), 1114 (s), 904 (s), 809 (s), 727 (s), 704 (m)	1.32 [d (J_{HCCH} = OHz), trans CH_3] 1.42 [d (J_{HCCH} = OHz), cis CH_3] cis 45% and trans 55%, 3 H 1.62–2.84 [m, CH_2CH_2, 4 H] 2.88–3.40 [m, CH, 1 H] 7.05–7.84 [m, ArH, 9 H]	−23.54
2c	1428 (s), 1183 (vs), 1104 (s), 813 (vs), 769 (s), 740 (s), 680 (s)	1.44 [s, CH_3, 3 H] 1.56 [s, CH_3, 3 H] 2.04–2.60 [m, P-CH_2, 2 H] 7.20–7.80 [m, ArH, 9 H]	−46.68
2d	1428 (s), 1176 (vs), 1111 (s), 909 (s), 877 (s), 800 (vs), 769 (s)	1.38 [s, CH_3, 3 H] 1.42 [s, CH_3, 3 H] 1.80–2.60 [m, PCH_2CH_2, 4 H] 7.10–8.00 [m, ArH, 9 H]	−24.64
1b	1432 (s), 1183 (vs), 1122 (s), 1104 (s), 972 (vs), 738 (s), 719 (s), 693 (s)	1.40–1.72 [m, CH_3, 3 H] 3.06 [dd (J_{HCCH} = 6, J_{PCH} = 14 Hz, PCH_2, 2 H] 5.3–5.7 [m, CHCH, 2 H] 7.26–7.94 [m, $(C_6H_5)_2P$, 10 H]	−28.65
1c	1428 (s), 1164 (vs), 1113 (s), 1098 (s) 990 (s), 910 (m), 784 (s), 735 (s)	2.12–2.60 [m, PCH_2CH_2, 4 H] 4.86–5.19 [m, CH=CH_2, 2 H] 5.62–6.06 [m, CH=CH_2, 1 H] 7.30–7.69 [m, $(C_6H_5)_2P$, 10 H]	−30.35
1d	1626 (w), 1428 (s), 1183 (vs), 1136 (s), 900 (vs), 704 (s)	1.60–1.94 [m, CH_3, 3 H] 3.11 [d (J_{PCH} = 14 Hz), 2 H]; 4.60–4.94 [m, C=CH_2, 2 H] 7.26–7.98 [m, $(C_6H_5)_2P$, 10 H]	−27.59
1e	1666 (w), 1428 (s), 1219 (m), 1176 (vs), 1123 (s), 1031 (s), 740 (vs), 694 (vs)	1.45 [d (J_{HCCCH} = 3 Hz, trans CH_3, 3 H] 1.64 [d (J_{HCCCH} = 5 Hz, cis CH_3, 3 H] 3.09 [dd (J_{HCCH} = 7 Hz, J_{PCCH} = 14 Hz), PCH_2 4 H] 5.06–5.40 [m, CH=C, 1 H] 7.20–8.00 [m, $(C_6H_5)_2P$, 10 H]	−30.69
1f	1639 (w), 1428 (s), 1176 (vs), 1129 (s), 749 (s), 722 (vs), 699 (vs)	1.32 [dd (J_{HCCH} = 7, J_{PCCH} = 14 Hz, CH_3, 3 H] 2.90–3.50 [m, PCH, 1 H] 4.92–5.25 [m, CH=CH_2, 2 H] 5.62–6.12 [m, CH=CH_2, 1 H] 7.26–8.00 [m, $(C_6H_5)_2P$, 10 H]	−33.09

[a] The spectra were obtained on samples (4 mg) with KBr (400 mg) pellets. All compounds displayed strong absorption in the regions 1429–1432 and 1104–1129 cm^{-1} which has often been assigned to the C_6H_5–P bond. Many examples are reported to support the assignment ranges. See L. C. Thomas, "Interpretation of the Infrared Spectra of Organophosphorus Compounds", Heyden, London, 1974, Chapter 15. [b] Spectra obtained on $DCCl_3$ solution of each compound with Me_4Si as internal standard; peak positions quoted in the case of doublets are measured from the approximate center. [c] ^{31}P resonance is relative to 85% H_3PO_4. ^1H NMR spectra of 1a was previously reported in ref 10, 18.



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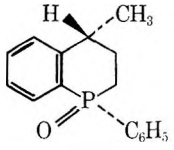
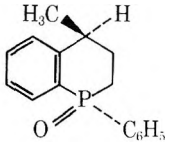
mers involving the methyl group with respect to the phosphoryl function could exist which would yield ^1H signals for two magnetically different methyl functions. In trans-



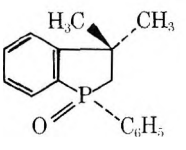
cis-**2b**



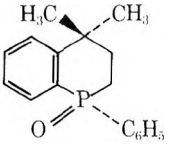
trans-**2d**

2b, the methyl protons might be expected to experience a deshielding effect due to the proximity of the oxygen atom of the phosphoryl group and hence could have a greater downfield chemical shift.[15] The relative intensities of the two signals indicate that about 45% of the cis form and 55% of the trans form were present in the $DCCl_3$ solution. There was also observed a J_{H_3CCH} of 7.0 Hz. The two methylene groups appear as a broad complex multiplet at δ 1.62–2.84 with apparently some long-range P–H coupling. Such NMR results are in accord with numerous studies available concerning the conformation of six-membered ring heterocyclic compounds containing phosphorus[16] or sulfur.[17]

The ^1H NMR spectrum of **2c** and **2d** showed the methyl protons as two singlets in each case. Conceivably, the deshielding effect of the oxygen of the phosphoryl group could cause the cis methyl group in **2c** to resonate at the lower field (δ 1.56 vs. 1.44) in **2d**, the signals are at δ 1.42 vs. 1.38.



2c

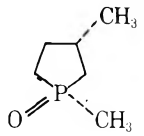


2d

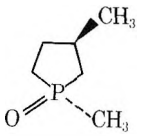
The negative ^{31}P chemical shift values for the open-chain phosphine oxides listed in Table II compare very well with those of many acyclic phosphine oxides.[18] For the 3-methylphosphindoline **2a**, two ^{31}P chemical shifts occur at −48.5 and −49.7 ppm. Substitution of the β proton by a methyl group as in **2c** also led to a deshielding effect (−46.7 ppm) at the phosphorus nucleus. Possibly, this extra deshielding could be attributed to steric crowding on the β carbon, which could result in modified bond angles about

the phosphorus. The phosphinolines **2b** and **2d** show the same effect but the difference is very small.

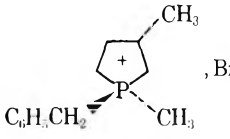
Some very recent work bears on this problem.[19,21] The identification of cis, trans isomers of 1,3-dimethylphospholane 1-oxide (**8**) included ^{31}P NMR values of −62.6 and −63.3 ppm (in C_6H_6).[19] Interestingly, the related salts **9** were reported to have identical values of −51.8 ppm.[19a] A mixture of phosphines **10a** and **10b** (precursors of **8a** and **8b**) has been reported[21] to display two signals (no proton decoupling) at +33.4 and 34.4 ppm but the assignment[19] of structure for each signal has not yet been accomplished. Recently, two isomers of **11** were separated[8] but ^{31}P NMR data were not included. ^1H NMR analysis revealed signals for CCH_3 protons centered at δ 1.45 and 1.53 but again individual structure assignments could not be made.



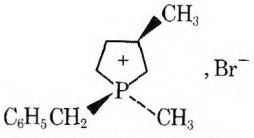
8a, mp 72–73.5 °C
(−62.6 ppm)



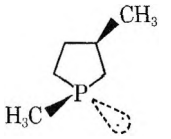
8b, mp 22 °C
(−63.3 ppm)



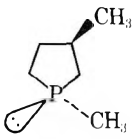
9a, mp 180–180.5 °C
(−51.8 ppm)



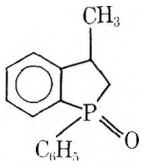
9b, mp 168.5–169.5 °C
(−51.8 ppm)



10a (bp 138.5°)



10b (bp 141°)



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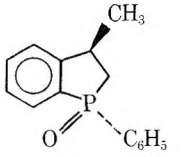
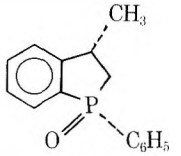
On the basis of proven structures **8a** and **8b**,[19b] we might conclude that *cis*-**2a** has the ^1H NMR signal for CH_3 pro-

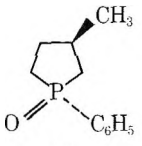


cis-**2a**

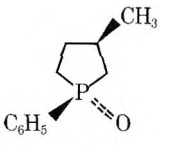


trans-**2a**

tons that occur at δ 1.54 and *trans*-**2a** has the value at δ 1.45.[8] This would be in agreement with ^1H NMR and x-ray data on **12a** and **12b** in which a cis (**12a**) and trans (**12b**) re-



12a



12b

lationship are present between the P=O and C–CH_3 groups.[19b,20] In $DCCl_3$ and C_6H_6, the ^1H NMR signal for the methyl group at C-3 was more deshielding when the P=O group was in a cis arrangement.[21] Interestingly, the ^{31}P NMR signal for *cis*-**2a** is at −48.5 ppm and that of *trans*-**2a** at −49.8 ppm. Unfortunately, similar data for **12a** and **12b** are not available at the moment. Our data appear to show that assignment of structure based on a correlation of ^{31}P NMR shift with shielding of C–CH_3 groups at a C-3 position in phospholane oxides (or as in **2a**) must be treated with care. Unless there is a severe steric parameter in *cis*-**2a** and *trans*-**2a**, we tentatively suggest that in the assignments of ^1H NMR signals, the P=O deshields the CH_3 group more than the C_6H_5 group.

Experimental Section

General Data. Melting points were obtained with a Thomas-Hoover melting point apparatus and are uncorrected. Infrared spectra were recorded on a Beckman IR-5A unit as KBr pellets. ^1H NMR and ^{31}P NMR spectra were recorded with an XL-100(15) Varian spectrometer and obtained in $DCCl_3$ with tetramethylsilane as an internal standard unless otherwise indicated. Mass spectral analyses were performed on a CEC Model 21 HR unit and are available upon request. Elemental analyses were carried out by Galbraith Laboratories, Knoxville, Tenn. Anhydrous solvents such as ether and benzene were dried over sodium and filtered prior to use.

Diphenylalkenylphosphine Oxides 1a–g. The key starting diphenylalkenylphosphine oxides for all heterocyclic compounds synthesized in this study were obtained by three different approaches.

A. Thermal Isomerization of Diphenylalkenylphosphinites at 140 °C.[9,10] By modification of a known method, it was possible to prepare diphenylallylphosphine oxide (**1a**) and diphenyl-2-methallylphosphine oxide (**1d**). The latter was obtained as follows. A solution of 7.2 g (0.1 mol) of 2-methyl-2-propen-1-ol (methallyl alcohol) in 100 ml of anhydrous ether containing 7.9 g (0.1 mol) of pyridine was cooled to 0 °C. Addition of 22.05 g (0.1 mol) of diphenylphosphinous chloride in 50 ml of anhydrous ether caused immediate reaction and the precipitation of pyridine hydrochloride. After the addition was completed (1 h), the reaction mixture was stirred for 2 h at room temperature. The mixture was filtered and the solvent was evaporated from the filtrate to yield 25 g (97%) of an oil. The oil was heated at 140 °C for 2 h, with stirring, to give a slightly yellow oil which crystallized on cooling to a colorless solid. This solid was chromatographed on alumina (Merck neutral) using benzene as eluent to give colorless crystals. Recrystallization (benzene–hexane) gave **1d**, mp 143–145 °C.

Anal. Calcd for $C_{16}H_{17}PO$: P, 12.08. Found: P, 12.17.

Diphenylallylphosphine oxide (**1a**) was prepared by the same procedure and gave the same physical data as reported in the literature.[9,10]

B. From Methyl Diphenylphosphinite with Alkyl Halide. The reaction vessel consisted of a 500-ml round-bottom flask equipped with a stirrer, N_2 inlet tube, dropping funnel, and a condenser. A solution of crotyl bromide (13.5 g, 0.1 mol) and methyl diphenylphosphinite (21.6 g, 0.1 mol, freshly prepared) in 200 ml of benzene was boiled for 24 h under conditions to allow the escape of methyl bromide. Evaporation of the solvent under reduced pressure gave a solid residue which was chromatographed on alumina (Merck neutral) using benzene as eluent. Colorless crystals of **1b** were obtained, mp 114–116 °C (lit.[20] mp 84–86 °C). Because the melting point difference was great, the sample was analyzed.

Anal. Calcd for $C_{16}H_{17}PO$: P, 12.08. Found P, 12.22.

C. Alkaline Hydrolysis of Alkenyltriphenylphosphonium Salts. 3-Butenyltriphenylphosphonium bromide[20] was converted to **1c** by a known method.[20] Oxide **1c** (91%, mp 102–103 °C) was identified with that described in the literature.

Ring Closures to Produce Phosphindoline and Phosphinoline. A typical experiment was performed as follows.

3-Methyl-1-phenylphosphindoline 1-Oxide (2a). In a 300-ml beaker was placed 200 ml of 115% PPA, which was then heated to 180 °C. To this was slowly added 4.0 g (16.5 mmol) of diphenylallylphosphine oxide (**1a**) over a 1-h period followed by 4 h of stirring. Upon completion of the addition, the solution became dark brown. Following the reaction period, the solution was cooled to 120 °C and slowly poured into ice–water (1000 ml) which produced a homogeneous solution upon stirring for 6 h with the separation of a sticky black resin. The solution was filtered, and the filtrate was extracted with $HCCl_3$ (five times with 100-ml portions). The combined organic layers, after washing with water, saturated sodium carbonate solution, and water, were dried ($CaCl_2$) and concentrated in vacuo. The resulting slightly yellow oil (1.5 g, 37%) was

distilled under vacuum (Kugelrohr), bp 160–170 °C (0.002 mm). Separation of the diastereomers of **2a** was effected by careful chromatography on a silica gel column using benzene with an increasing amount of chloroform. The oxide **2a** was identical in all respects with that reported in the literature.[8] A series of experiments were performed in which the ratio of PPA to **1a** was reduced from 50 ml:1 g to 40 ml:1 g to 30 ml:1 g to give **2a** but this procedure only resulted in decreasing yield of **2a**. Lowering the temperature of cyclization gave *trans*-1-(1-propenyl)diphenylphosphine oxide (4) which was identical in all respects with that prepared earlier,[12] along with the starting **1a** and a polymeric product.

1,2,3,4-Tetrahydro-4-methyl-1-phenylphosphinoline 1-Oxide (2b). Method A. The phosphine oxide (**1b** or **1c**, 2 g, 7.81 mmol) was slowly added to 100 ml of 115% PPA at 180 °C and, when the addition was complete, a stirring period of 4 h followed. When cooled to 110 °C, the solution was poured into 500 ml of ice–water and stirring produced a homogeneous solution. Extraction ($HCCl_3$, five times with 60-ml portions) gave a clear organic solution which was dried ($CaCl_2$). The chloroform was evaporated under vacuum to give a viscous oil which, upon scratching, solidified. This solid **2b** was twice sublimed at 100 °C (0.005 mm) to give a pure crystalline compound (Table I).

Method B. Base Hydrolysis of 1,2,3,4-Tetrahydro-4-methyl-1,1-diphenylphosphinolinium Hexafluorophosphate. The phosphonium compound **6** (1 g, 2.2 mmol) was boiled for 12 h in 100 ml of methanol–water (4:1) containing 10 g of NaOH. The mixture was cooled and 150 ml of water was added. The water layer was extracted ($HCCl_3$) and, after drying ($CaCl_2$), the solvent was evaporated to give solid **2b** (0.5 g, 90%) which was sublimed. It was identical in all respects with that prepared by method A.

3,3-Dimethyl-1-phenylphosphindoline 1-Oxide (2c). In a procedure directly analogous to the preceding one, the reaction of phosphine oxide **1d** (2 g, 7.81 mmol) and 100 ml of PPA at 180 °C gave **2c** in a yield of 1.0 g (50%). Sublimation was carried out at 100 °C (0.005 mm) (Table I).

1,2,3,4-Tetrahydro-4-4-dimethyl-1-phenylphosphindoline 1-Oxide (2d). Reaction of the phosphine oxide **1e** (2 g, 7.4 mmol) and 100 ml of PPA at 160 °C gave **2d** in good yield, 0.8 g (40%) (Table I).

Registry No.—**1a**, 4141-48-4; **1b**, 16540-56-0; **1c**, 16958-43-3; **1d**, 4455-75-8; **1e**, 13303-61-2; **1f**, 13303-58-7; **1g**, 13303-57-6; *cis*-**2a**, 58191-09-6; *trans*-**2a**, 58191-10-9; *cis*-**2b**, 58191-11-0; *trans*-**2b**, 58191-12-1; **2c**, 58191-13-2; **2d**, 58191-14-3; **5**, 54230-12-5; 2-methyl-2-propen-1-ol, 513-42-8; diphenylphosphinous chloride, 1079-66-9; crotyl bromide, 4784-77-4; methyl diphenylphosphinite, 4020-99-9; 3-butenylphosphonium bromide, 16958-42-2.

References and Notes

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(21) K. L. Marsi, F. R. Burns, and R. T. Clark, *J. Org. Chem.*, **37**, 238 (1972). A private communication from Dr. Marsi has indicated that **12a** has the following properties: bp 120 °C (0.01 mm); ^1H NMR ($DCCl_3$) δ 1.23 ($C-CH_3$) and (in C_6H_6) δ 0.853 ($C-CH_3$). Isomer **12b** has mp 60–61 °C; ^1H NMR ($DCCl_3$) δ 0.776 ($C-CH_3$) and (in C_6H_6) δ 1.19 ($C-CH_3$).

Direct Synthesis of Fluorinated Peroxides. IV. Addition of Pentafluorosulfur Peroxyhypochlorite to Alkenes

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Pentafluorosulfur peroxyhypochlorite, SF_5OOCl, undergoes addition reactions with alkenes forming pentafluorosulfurperoxy derivatives in good yield. The additions are predominantly unidirectional and proceed by an electrophilic mechanism. Reactions with C_2H_4, C_2F_4, C_2F_3Cl, CF_2CCl_2, CF_2CH_2, and *cis*-CFHCFH occur readily below 0 °C, whereas C_3F_6, 2-C_4F_6, and c-C_5F_8 were unreactive under all conditions. With *cis*-CFHCFH the addition was stereospecific. The new peroxides are stable at 22 °C and have been characterized by their physical properties and ir and NMR spectra. Comparison of SF_5OOCl reactions with those of the related compound CF_3OOCl are discussed.

The systematic synthesis of fluorocarbon peroxides and the resultant change in their classification from isolated laboratory curiosities to a well-established class of compounds was made possible by the reagents CF_3OOH,[2] CF_3OOCl,[3] CF_3OOF,[4] and CF_3OOOCF_3.[5] It has been shown that the only available route at present to a variety of peroxides is their direct synthesis via reactions in which the CF_3OO group is added to suitable substrates. In order to expand this interesting area of chemistry, the development of other reagents of the type R_FOOX has been a

Table I. Reactions of SF_5OOCl with Alkenes

Registry no.	Alkene[a]	SF_5OOCl[a]	Conditions	SF_5O– products[b]	Registry no.
74-85-1	C_2H_4, 4.2	2.0	0.5 h, −78 °C	$SF_5OOCH_2CH_2Cl$, 58%; $SF_5OCH_2CH_2Cl$, 25%	58249-50-6
75-38-7	CH_2CF_2, 4.6	2.0	5 h, −78 °C	$SF_5OOCF_2CH_2Cl$, 47%; $SF_5OCF_2CH_2Cl$, 6%	58249-51-7
1630-77-9	*cis*-CHFCHF, 3.7	2.0	12 h, −78 to −20 °C	*erythro*-$SF_5OOCFHCFHCl$, 70%; $SF_5O(CFHCFH)Cl$, 9%	58267-74-6
116-14-3	C_2F_4, 5.5	2.0	12 h, −78 °C	$SF_5OOCF_2CF_2Cl$, ~30%; $SF_5OCF_2CF_2Cl$, <5%; $SF_5OCF_2CF_2CF_2CF_2Cl$, ~10%	58249-52-8
79-38-9	C_2F_3Cl, 3.0	1.8	18 h, −95 °C	$SF_5OOCF_2CFCl_2$– $SF_5OOCFClCF_2Cl$, ~8%; $SF_5OCF_2CFCl_2$– $SF_5OCFClCF_2Cl$, 23%	58249-53-9 58249-54-0
79-35-6	CF_2CCl_2, 4.3	2.5	18 h, −111 to −78 °C and 12 h, −78 °C	$SF_5OOCF_2CCl_3$, ~4%; $SF_5OOCCl_2CF_2Cl$, ~8%; $SF_5OCF_2CCl_3$;[c] $SF_5OCCl_2CF_2CCl$[c]	58249-55-1 58249-56-2
116-15-4	C_3F_6, 4.7	2.0	8 days, −78 °C 2 days, 0 °C	No SF_5O– addition products	
692-50-2	2-C_4F_6, 2.4	1.0	10 days, −78 °C 2 days, 0 °C	No SF_5O– addition products	
559-40-0	c-C_5F_8, 3.0	2.0	6 days, −78 °C 2 days, 0 °C	No SF_5O– addition products	

[a] Amounts in millimoles. Registry no., 58249-49-3. [b] Yields are for purified products after GLC and are based on the amount of SF_5OOCl added. [c] Yields not determined, but considerably greater than the yields of peroxide based on ^{19}F NMR and GLC.

major goal in our laboratories. The recent synthesis by us of SF_5OOH,[6,7] SF_5OOCl,[7] and SF_5OOF[7] now allows for the systematic preparation of pentafluorosulfur peroxides.

This paper is concerned with the reactions of SF_5OOCl with olefins, and comparison with the similar reactions of CF_3OOCl.[3] The latter was shown to add to alkenes by an electrophilic mechanism. The additions were unidirectional in the case of unsymmetrical alkenes, and the direction of addition was easily predictable based on qualitative electrostatics. In one instance, the addition was shown to be stereospecific and most probably cis. The additions of SF_5OOCl parallel those of CF_3OOCl in most instances, but there are surprising differences.

Experimental Section

General. All compounds were handled in Pyrex or stainless steel vacuum systems equipped with glass–Teflon or stainless steel valves. Pressures were measured with a Wallace and Tiernan differential pressure gauge or a precision Heise-Bourdon tube gauge. Infrared spectra were obtained on a Perkin-Elmer Model 180 or Model 337 spectrometer using a 10-cm path length glass cell fitted with silver chloride windows. NMR spectra were recorded on a Varian XL-100-15 spectrometer using ~80 mol % CCl_3F solutions of the samples. Vapor pressures were determined by a static method employing the isotensiscope principle.[8] Equations describing vapor pressure as a function of temperature were obtained by a least-squares fit of the data. Volatile mixtures were separated by trap-to-trap distillation and by GLC using 41% Halocarbon 11-21 polymer oil on acid-washed Chromosorb P. Chromatography was carried out at temperatures between 22 and 40 °C using a 1 ft × 0.375 in. ss column and gas injection.

Reagents. The olefins C_2F_3Cl, CF_2CCl_2, CF_2CH_2, *cis*-CHFCHF, C_3F_6, c-C_5F_8, and the acetylene 2-C_4F_6 were obtained from PCR Inc., C_2H_4 from Matheson Co., and C_2F_4 from the pyrolysis of Teflon.[9] The chloroperoxide, SF_5OOCl, was prepared by the literature method.[7]

Reaction of SF_5OOCl with Olefins. All the reactions were carried out in 100-ml glass vessels fitted with glass–Teflon valves. The peroxide was prepared separately for each reaction and condensed into the bottom of the reaction vessel held at −196 °C. The olefin was condensed into the top portion of the bulb which was then placed in a low-temperature bath. The reaction was followed by the disappearance of the yellow color due to SF_5OOCl. In most cases the reactions were continued until a faint yellow color persisted, this color being due to a small amount of chlorine present. The products were collected in a −112 °C trap for the C_2F_4 and C_2H_4 reactions and a −78 °C trap for the others. These fractions were further separated by GLC. A variety of products were formed in the reactions including SOF_4, fluorinated, and fluorochlorinated olefins as well as SF_5O– and peroxide addition products. No effort was made to identify all the products. The ether and peroxy addition products, which usually formed the major part of the mixture, are reported in Table I.

Although no explosions occurred during this work, fluorinated peroxides can detonate when subjected to thermal or mechanical shock. Precautions should be taken when handling these compounds. Pentafluorosulfur peroxyhypochlorite is especially reactive.

The main identification of the ether products was by ^{19}F NMR and molecular weight. The ethers $SF_5OCH_2CH_2Cl$, $SF_5O(CF_2CFCl)Cl$, and $SF_5OCF_2CF_2Cl$[10,11] have been previously reported and nearly all others are currently being investigated by Fox and co-workers.[12]

In the reactions of SF_5OOCl with C_3F_6, c-C_5F_8, and $CF_3C{\equiv}CCF_3$ no evidence was found for the formation of peroxides, the olefins remaining mostly unreacted even at 0 °C. In these cases decomposition products of SF_5OOCl were observed together with unreacted olefin and a small amount of less volatile material, shown by ^{19}F NMR to contain no SF_5 groups.

$SF_5OOCH_2CH_2Cl$: bp 119.3 °C; mp (glassed at low temperature); mol wt 221.3 (calcd, 222.6); ir 2962 (w), 1442 (vw), 1371 (vw), 1308 (vw), 1254 (w), 1059 (vw), 974 (m sh), 915 (vs), 869 (vs), 785 (m), 767 (m), 730 (m), 685 (w), 605 (s), 585 cm^{-1} (m); NMR $F^A_4SF^B_4OOCH^C_2$–CH^D_2Cl, ϕ^*_A −63.6, ϕ^*_B −45.6, δ_C 4.71, δ_D 3.90, J_{AB} = 155.0, $J_{AC} \simeq 0$, J_{BC} = 0.9, J_{CD} = 6.0 Hz; ΔH_{vapor} = 8.40 kcal/mol, ΔS_{vapor} = 21.4 eu; log P (mm) = 7.6968 − 1945.8/T + 21779/T^2.

$SF_5OOCF_2CF_2Cl$: bp 61.4 °C; mp (glassed at low temperature); mol wt 290.7 (calcd, 294.4); ir 2502 (vw), 2400 (vw), 2350 (vw), 2290 (vw), 1668 (vw), 1615 (vw), 1509 (vw), 1484 (vw), 1356 (vw), 1312 (vw), 1263 (w), 1236 (m), 1208 (s), 1184 (s), 1117 (s), 980 (s), 931 (vs), 878 (vs), 842 (w), 824 (w), 800 (m), 734 (w), 680 (vw), 630 (w), 608 (s), 561 (w), 503 cm^{-1} (vw); NMR $F^A_4SF^B_4$–$OOCF^C_2$–CF^D_2Cl, major AB[4] peak at ϕ^* −57.12, ϕ^*_C 93.87, ϕ^*_D 70.56, $J_{AC} < 1.0$, $J_{BC} \simeq$ 4.0, J_{CD} = 2.7 Hz; ΔH_{vapor} = 8.17 kcal/mol; ΔS_{vapor} = 24.4 eu; log P (mm) = 8.2171 + 1785.6/T.

$SF_5OOCF_2CH_2Cl$: bp 83.5 °C; mp (glassed at low temperature); mol wt 257.7 (calcd, 258.6); ir 2968 (w), 1431 (w), 1318 (m), 1271 (s), 1236 (s), 1134 (s), 1088 (s), 926 (vs), 874 (vs), 857 (m), 803 (w), 742 (w), 700 (vw), 678 (w), 639 (w), 606 (s), 594 (m), 552 cm^{-1} (vw); NMR $F^A_4SF^B_4OOCF^C_2$–CH^D_2Cl, major AB[4] peak at ϕ^* −56.43, ϕ^*_C 83.66, δ_D 3.85, J_{AC} = 0.8, J_{BC} = 4.0, J_{CD} = 8.2 Hz; ΔH_{vapor} = 7.98 kcal/mol; ΔS_{vapor} = 22.4 eu; log P (mm) = 7.7692 − 1743.3/T.

$SF_5OOCFHCFHCl$: bp 94.8 °C; mp (glassed at low temperatures); mol wt 257.4 (calcd, 258.5); ir 2968 (w), 1431 (w), 1318 (m), 1271 (s), 1236 (s), 1134 (s), 1088 (s), 926 (vs), 874 (vs), 857 (m), 803 (w), 742 (w), 700 (vw), 678 (w), 639 (w), 606 (s), 594 (m), 552 cm^{-1} (vw); NMR $F^A_4SF^B_4OOCF^CH^D$–CF^EH^FCl, major AB[4] peak at ϕ^*

−57.50, ϕ_C^* 135.40, ϕ_E^* 152.98, δ_D 6.0, δ_F 6.2, J_{AC} = 4.0, J_{BC} = 4.0, J_{CD} = 59.0, J_{CE} = 14.1, J_{CF} = 3.5, J_{DE} = 4.0, J_{DF} = 5.1, J_{EF} = 49.2 Hz; ΔH_{vapor} = 8.93 kcal/mol; ΔS_{vapor} = 24.3 eu; log P (mm) = 8.1976 − 1952.6/T.

$SF_5OOCF_2CCl_3$: ir 1362 (m), 1243 (s), 1190 (s), 1175 (m), 1141 (s), 1082 (m), 928 (vs), 891 (s), 872 (vs), 853 (s), 834 (s), 789 (s), 729 (m), 652 (m), 605 (s), 558 cm^{-1} (m); NMR $F^A SF_4^B OOCF_2^C$–CCl_3, major AB^4 peak at ϕ^* −57.47, ϕ_C^* 89.85.[13]

$SF_5OOCCl_2CF_2Cl$: ir 1236 (m), 1193 (s), 1180 (s), 1146 (m), 1071 (s), 1047 (s), 980 (s), 931 (vs), 872 (vs), 826 (s), 798 (s), 743 (m), 687 (m), 652 (m), 633 (w), 609 (s), 594 (s), 568 cm^{-1} (m); NMR $F^A SF_4^B OOCCl_2$–$CF_2^C Cl$, major AB^4 peak at ϕ^* −58.74, ϕ_B^* 62.83.

$SF_5OOCF_2CFCl_2$–$SF_5OOCFClCF_2Cl$ (10/6 by NMR): mol wt 312.4 (calcd, 310.9); ir 1272 (m), 1240 (m), 1203 (s), 1175 (s), 1101 (s), 1044 (m), 985 (m), 931 (vs), 880 (vs), 810 (m), 770 (w), 745 (w), 731 (w), 722 (w), 655 (w), 608 (s), 592 (m), 560 cm^{-1} (w); NMR $F^A SF_4^B OOCF_2^C$–$CF^D Cl_2$ major AB^4 peak at ϕ^* −55.30, ϕ_C^* 91.85, ϕ_D^* 73.00, $J_{AC} < 1.0$, $J_{BC} \simeq 4.0$, J_{CD} = 7.38 Hz; $F^A SF_4^B OOCF^C ClCF_2^D Cl$ major AB^4 peak at ϕ^* −57.23, ϕ_C^* 78.90, ϕ_D 66.42, $J_{AC} < 1.0$, $J_{BC} \simeq 4.0$, J_{CD} = 6.75 Hz.

Results

The addition of SF_5OOCl to several olefins proceeds readily at low temperatures to give varying yields of SF_5OO peroxides, as well as significant amounts of SF_5O– ethers. The major SF_5O_n– products are given in Table I. The pentafluorosulfur ethers are presumably formed from the addition of SF_5OCl to the olefin, the SF_5OCl being the major decomposition product of the rather unstable SF_5OOCl. As observed previously with CF_3OOCl, C_2F_4 gave significant amounts of telemers or oligmers. These may also be formed in other reactions, but are probably too low in volatility to be observed by our methods. With CF_2H_2 and *cis*-CFHCFH, only one of two possible peroxide isomers is observed. Attempted reactions with C_3F_6, $CF_3C{\equiv}CCF_3$, and c-C_5F_8 were unsuccessful under conditions where reaction with the other olefins occurred readily. Temperatures higher than 0 °C could not be used in order to favor reaction, owing to the rapid decomposition of SF_5OOCl at 22 °C.

The new peroxides are clear, volatile liquids and are thermally stable in glass at 22 °C. They are probably stable at considerably higher temperatures, with those having the highest chlorine or hydrogen content expected to be the least stable. Each of the new compounds is most readily identified by its ^{19}F NMR spectrum. All show characteristic AB_4 patterns for the pentafluorosulfur group with a ϕ^* value of approximately −55 for the B fluorines and J_{AB} of ~150 Hz. Detailed analyses of the AB_4 spectra were not carried out in most cases because the exact J_{AB}, ϕ_A^*, and ϕ_B^* values are unnecessary in order to establish the identity of the compounds. In those compounds containing carbon–fluorine and carbon–hydrogen bonds, the ^{19}F and ^1H spectra were as expected. For methylene fluorines adjacent to an SF_5OO group, $J_{F\text{-}FB}$ was observed to be ~4.0 Hz and $J_{FF^A} < 1.0$ Hz. For methylene protons, $J_{HF^B} < 1.0$ and $J_{HF^A} \simeq 0$ Hz.

The distinction between SF_5OO– and SF_5O– products is obvious from the magnitude of J_{FF^A}, J_{FF^B}, J_{HF^A}, and J_{HF^B} coupling constants between the pentafluorosulfur fluorines and methylene protons and fluorines. For the ethers, these have values of approximately 2.0, 12.0, 1.0, and 4.0 Hz, respectively.[14] These coupling constants are thus approximately three times larger than for the peroxides, which is quite analogous to that situation in trifluoromethyl ethers and peroxides for the same coupling between CF_3.

The establishment of only a single isomer in the case of $SF_5OOCFHCFHCl$ was made by ^1H and ^{19}F NMR employing both homo- and heteronuclear decoupling. The magnitude of the vicinal J_{HH} coupling suggests that the compound is the erythro isomer and thus the addition of SF_5OOCl to *cis*-CFHCFH is cis.[3] The formation of two structural isomers in the reactions with C_2F_3Cl and CF_2CCl_2 was obvious from the ^{19}F NMR of fluorine on carbon and in the case of CF_2CCl_2 the two isomers were easily separable by GLC.

Infrared spectra of the peroxides support the proposed structures, but are not especially characteristic in each case. All show three strong bands for the SF_5OO– group in the region 915–931 and 869–880 cm^{-1} assignable to SF_5– stretching and 605–608 cm^{-1} (PQR) due to SF_5 deformation.[15]

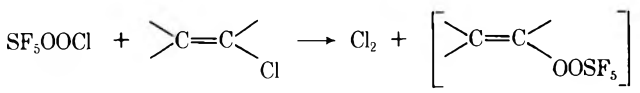
Discussion

The addition of SF_5OOCl to olefins significantly increases the number of pentafluorosulfurperoxyalkyl derivatives. Prior to this work, only one compound of this type was known, CF_3OOSF_5.[16] The latter was synthesized by a coupling reaction between $CF_3O\cdot$ and $SF_5O\cdot$ radicals. This type of reaction is responsible for only isolated examples of fluorinated peroxides and its generality has not been demonstrated. In contrast, this work clearly establishes the utility of reagents such as SF_5OOCl in the direct synthesis of a variety of new peroxides. The different olefins employed in this work suggest a wide applicability for the reaction.

The mechanism for the reaction appears to be that for electrophilic addition of the positive chlorine of SF_5OOCl followed by the addition of the SF_5OO group. This might occur in two steps or in a concerted manner. As we have previously argued for the related reactions of CF_3OOCl with olefins, a radical mechanism is unlikely owing to the lack of reactivity shown by C_3F_6 and c-C_5F_8. The latter are especially resistant to electrophilic additions but readily undergo free-radical additions. Furthermore, the stereospecific addition observed with *cis*-CFHCFH rules out a free-radical mechanism. The reactions of CF_3OOCl and SF_5OOCl are exactly analogous in the case of C_2H_4, C_2F_4, CF_2CH_2, *cis*-CFHCFH, C_3F_6, and c-C_5F_8. However, with C_2F_3Cl and CF_2CCl_2, high yields of single isomeric peroxide were observed with CF_3OOCl, whereas SF_5OOCl gives low yields of both possible structural isomers with these olefins. Initially, this was attributed to the poor control of experimental conditions, but repeated attempts under a variety of conditions always gave the same results: low yields and two isomers. There are many possible explanations for this, but we feel that the following has at least some evidence in its favor.

The two peroxyhypochlorites, CF_3OOCl and SF_5OOCl, are the only known examples of compounds of this type and as such, very little is known regarding the nature of the oxygen–chlorine bond in these materials. However, in reactions which are based on the positive halogen character of the chlorine atoms, two factors would seem to be important. First, the electron density at chlorine may be different in the two materials owing to differences in the electronegativity of CF_3 and SF_5, and second, the oxygen–chlorine bond energy could vary significantly between the two materials. By comparison of CF_3OSO_2F[17] and SF_5OSO_2F,[18] it is possible to gain some idea of the relative electronegativity of SF_5O and CF_3O by comparing the average of the asymmetric and symmetric SO_2 stretching frequencies.[19] On this basis, CF_3O is clearly more electronegative. A measure of the relative chlorine–oxygen bond strengths in the two compounds may be inferred from the difference in thermal stability between the two compounds.[20] Because CF_3OOCl has a half-life at 22 °C of a few hours and SF_5OOCl only a few minutes, the oxygen–chlorine bond in CF_3OOCl may be stronger.

The above considerations could account for the difference in reaction of the two peroxyhypochlorites with C_2F_3Cl and CF_2CCl_2. If SF_5OOCl is less electrophilic, the selectivity and ease of addition with these olefins may decrease. If the oxygen–chlorine bond is weaker in SF_5OOCl, a side reaction of the type



may be thermodynamically and/or kinetically more favorable. Some evidence for latter was obtained by the reaction of SF_5OOCl with $CH_3C(O)Cl$. The formation of Cl_2 and $CH_3C(O)OOSF_5$[21] occurred in high yield. There is at least some similarity between the carbon–chlorine bond in –C(O)Cl and >C=C–C and we believe the above side reaction takes place to give unstable peroxides as indicated, with a concomitant decrease in yield of the addition product.

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Pinacolyl Chloride Revisited. A Practical Synthesis

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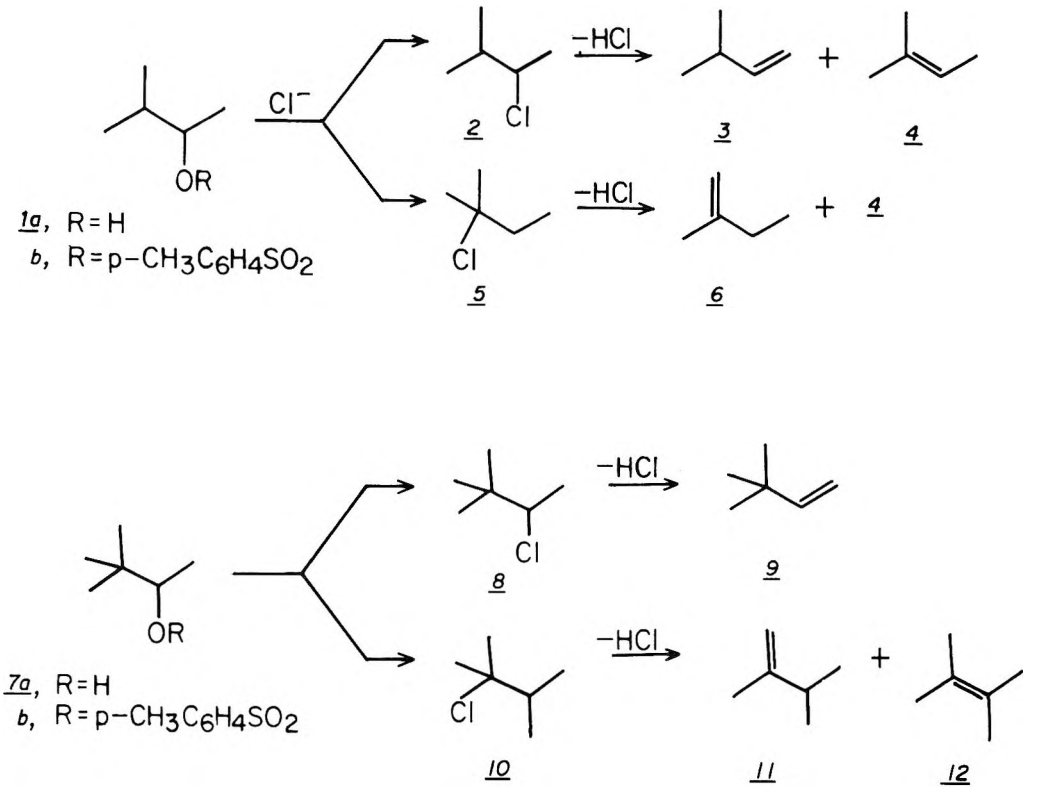
The synthesis of 3-methyl-2-chlorobutane in 90% yield and 3,3-dimethyl-2-chlorobutane (pinacolyl chloride) in 49% yield in which Wagner–Meerwein rearrangement products are completely absent is described. The method involves the displacement of the corresponding *p*-toluenesulfonyl esters with lithium chloride in dimethyl sulfoxide and hexamethylphosphoramide under moderate vacuum and temperature with concomitant evaporation of the chlorides produced. The application of several methods of halogenation to pinacolyl alcohol is discussed.

In connection with gas-phase kinetic studies pinacolyl chloride (**8**) was required in high purity. The tendency of this compound to rearrange under the conditions required for its synthesis is well known[1–4] and contaminants are usually difficult to separate. In fact, compound **8** and 2,3-dimethyl-2-chlorobutane (**10**), the Wagner–Meerwein rearrangement product of **8**, differ in boiling point by only 1 °C.[4] The inherent steric hindrance of the secondary neopentylic carbon implies the use of rather harsh reaction conditions for bimolecular displacements to take place. Consequently significant quantities of olefins are generally produced.

These difficulties thwarted all efforts directed toward the synthesis of pinacolyl chloride until Whitmore[5] was able to obtain it by means of the chlorination of 2,2-dimethylbutane, albeit in poor yield.

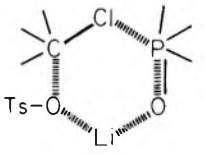
Although 3,3-dimethyl-2-chlorobutane has been the subject of a limited number of studies,[3,6,28] the literature is exceedingly scant of reports about its synthesis. Addition of hydrogen chloride to 3,3-dimethylbut-1-ene[2,3] makes the task of isolation of **8** nearly impossible for practical purposes, for considerable amounts of **10** are produced. Similar results would arise from the chlorination of the corresponding hydrocarbon.[5] The halogenation of pinacolyl alcohol (**7a**) or some derivative thereof, though not devoid of obstacles, represented a more viable approach. In the present report an efficient synthesis of pinacolyl chloride free of compound **10** is described.

Treatment of carbinol **7a** with thionyl chloride in pyridine,[7,8] acetyl chloride, or phosphorus halides[9] furnished small quantities of **8** in admixture with several carbenium ion derived products. The use of phosphorus reagents of the triphenyl phosphite type appeared more promising. The reaction of triphenyl phosphite–benzyl chloride adduct[10] with 3-methylbutan-2-ol (**1a**), a model compound less prone to rearrange than **7a**, in dimethylformamide at room temperature gave a mixture of 2-chloro-3-methylbutane (**2**) and 2-chloro-2-methylbutane (**5**) in a 2:3 ratio. Analogously, pinacolyl alcohol yielded both chlorides **8** and **10**. This result is in consonance with the observed rearrangement during the halogenation of neopentyl alcohol.[11,12] Wiley et al.,[13] inter alia,[12] introduced the use of a



triphenyl phosphite–chlorine complex for the halogenation of alcohols and were able to obtain a 92% yield of neopentyl chloride from the carbinol without detectable rearrangement. Unfortunately, in our hands this procedure met with failure when applied to 8 under strictly anhydrous conditions. The adduct of triphenylphosphine and carbon tetrachloride has allowed for the conversion of several rearrangement-prone carbinols to chlorides under very mild conditions.[14] Snyder showed recently that treatment of an allylic alcohol with this particular reagent provided the desired allylic chloride along with 11% of rearranged halide.[15] This encouraging result, however, found no success when applied to 8 under a variety of reaction conditions.[16,17] Addition of 1 equiv of pyridine or *N,N*-dimethylaniline in an attempt to control the pH of the reaction medium inhibited halogenation.

The direct displacement of *p*-toluenesulfonic acid esters by halide ions is well documented.[18,19] This transformation is strongly dependent on the steric environment around the reaction center as illustrated by the poor yield of 2-methyl-1-bromocyclopentane obtained from the reaction of the corresponding tosylate with sodium bromide in DMF.[19] Nevertheless, moderately hindered halides like *sec*-amyl bromide have been synthesized by this method and more importantly without appreciable rearrangement.[9] Accordingly, the reaction of the model compound **1b** with chloride ion was examined. The tosylate (20 mmol) was stirred with lithium chloride (28 mmol) in dimethyl sulfoxide or DMF at room temperature under anhydrous conditions for 72 h. Moderate vacuum was applied and volatile material trapped at −78 °C furnishing a 93% yield of a colorless liquid. VPC analysis showed it to contain 96% 2-chloro-3-methylbutane (**2**), less than 1% 2-chloro-2-methylbutane (**5**), and 3% of minor impurities. Distillation of this material yielded pure compound **2**.[20] The tosylate of pinacolyl alcohol (**7b**)[21] remained unaffected under these conditions after 100 h of contact. In DMF at temperatures above 60 °C elimination became predominant.[22] In Me_2SO, in turn, substitution became significant only at 115 °C but the pinacolyl chloride produced was accompanied by copious amounts of olefinic material. The addition of hexamethylphosphoramide[23] allowed the reaction to proceed smoothly at 50 °C only furnishing compound **8** in satisfactory yield containing no detectable amounts of compound **10** and a reduced percentage of olefins. The intermediacy of the six-membered transition state **13** in which HMPA appears associated with the inorganic salt has been proposed.[24] This



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participation would account for the lower activation energy of the substitution reaction when HMPA is added, although other still unknown factors may be involved.

Further studies on the gas-phase behavior of pinacolyl chloride are being conducted in our laboratory.

Experimental Section[25]

Preparation of 3,3-Dimethyl-2-chlorobutane (8). A dry 500-ml round-bottomed flask, flushed with nitrogen, and equipped with a magnetic stirrer and a 5-in. Vigreux column connected to a dry ice–acetone trap, was charged with 40 g (0.15 mol) of 3,3-dimethyl-2-butyl *p*-toluenesulfonate (**7b**),[21] 34 g (0.8 mol) of anhydrous lithium chloride, 200 ml of dry Me_2SO, and 70 ml of HMPA. The mixture was stirred at ca. 54 °C (oil bath) under 10-mm vacuum for 90 h while volatile materials were allowed to distill into the trap. Colorless liquid (14.9 g) was recovered, washed with 5% aqueous potassium bicarbonate and water, and dried briefly over magnesium sulfate. VPC analysis indicated the presence of 54% 3,3-dimethyl-2-chlorobutane (**8**, 50% yield), 19% 3,3-dimethylbut-1-ene (**9**), 14% 2,3-dimethylbut-1-ene (**11**), and 13% 2,3-dimethylbut-2-ene (**12**). The absence of compound **10** in the crude mixture was attested by the lack of a δ 1.59 ppm signal in the NMR spectrum corresponding to the *gem*-dimethyl grouping.[3,26]

Purification of 8. Purification of the chloride **8** was achieved by passing the crude material through a column of neutral alumina activity III in pentane followed by vacuum gradient distillation at a temperature not above 38 °C.[27] Pentane and the olefins were distilled at room temperature (100–50 Torr) and condensed in a cold

trap. Pure pinacolyl chloride (8, 9.2 g, 49% yield) distilled next at 30–35 °C (oil bath) (20 Torr): ir (neat)[28] 2975 (s), 2860 (m), 1455 (m), 1375 (m), 1360 (s), 1270 (m), 1190 (m), 1070 (s), 860 (m), 725 (m), and 664 cm^{-1} (s); NMR ($CDCl_3$, 4 M) δ 1.08 (s, 9, 3 CH_3), 1.51 (d, 3, CH_3CH, J = 7.0 Hz), 3.83 (q, 1, methyne, J = 7.0 Hz); mass spectrum m/e (rel intensity) 107, 105 ($M^+ - 15$) (2, 6), 69 (22), 57 (100).

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Registry No.—**7b**, 25966-61-4; **8**, 5750-00-5; lithium chloride, 7447-41-8.

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Charge-Transfer Polymers Containing 7,7,8,8-Tetracyanoquinodimethan and Tetrathiafulvalene

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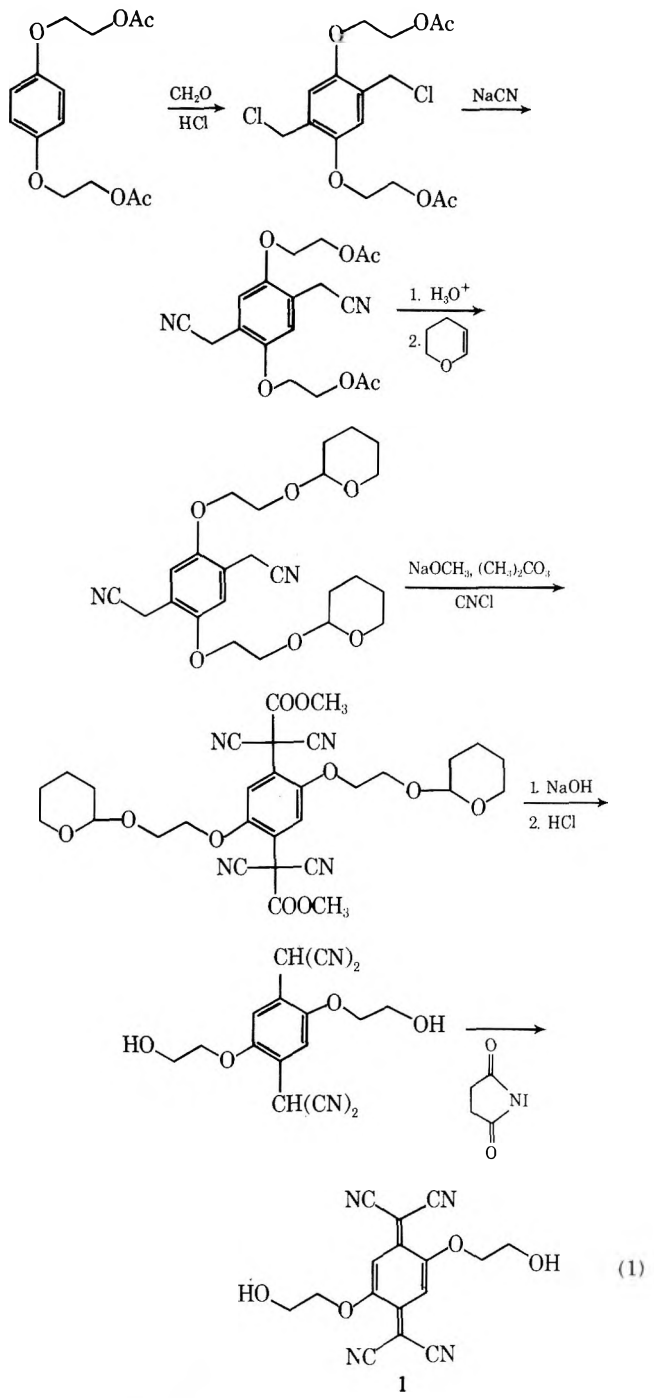
Semiconducting charge-transfer polyurethanes were prepared by condensation of 2,5-bis(2-hydroxyethoxy)-7,7,8,8-tetracyanoquinodimethan with 1,1′-diisocyanatoferrocene or 4,4′-diisocyanatotetrathiafulvalene. Powder compactions of the black polymers have electrical conductivities of 3×10^{-3} and 1.66×10^{-7} ohm^{-1} cm^{-1}, respectively. Condensation of 4,4′-bis(hydroxymethyl)tetrathiafulvalene with 4,4′-diisocyanatotetrathiafulvalene gave a polyurethane which was converted to its iodide. The iodide has an electrical conductivity of 2×10^{-6} ohm^{-1} cm^{-1}. The syntheses of monomers are described.

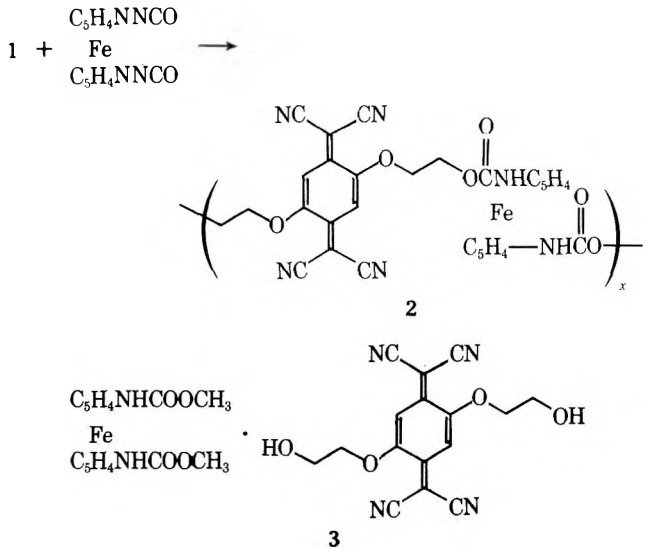
Although many semiconducting organic polymers have been synthesized, the goal of an organic polymer having metallic conductivity has remained elusive. The recent demonstration of metallic conductivity in the charge-transfer complex of 7,7,8,8-tetracyanoquinodimethan (TCNQ) and tetrathiafulvalene (TTF)[1,2] suggested that polymers containing these materials might display metallic conductivity if properly oriented. The literature contains many examples of electrically conductive polymers in which $TCNQ\cdot^-$ is present as a counterion in a polymeric quaternary ammonium ion.[3] To prepare a polymer containing covalently bound TCNQ, it was necessary to synthesize a TCNQ derivative containing suitable reactive functional groups on the ring. The sequence of reactions used to synthesize 2,5-bis(2-hydroxyethoxy)-7,7,8,8-tetracyanoquinodimethan (1) is shown in eq 1.

2,5-Bis(2-hydroxyethoxy)-7,7,8,8-tetracyanoquinodimethan (1) is a stable red compound with mp 228–232 °C. A charge-transfer polymer was prepared by reaction of **1** with 1,1′-diisocyanatoferrocene[4] to give a black polyurethane, **2**, containing electron-acceptor TCNQ units alternating with electron-donating ferrocene units. Inasmuch as the polymer is insoluble in organic solvents, electrical conductivity measurements were performed on a compacted powder. The value obtained was 3×10^{-3} ohm^{-1} cm^{-1}, which is similar to that reported for a TCNQ complex of poly(3-vinylbisfulvalenediiron).[5]

A nonpolymeric model charge-transfer complex of 2,5-bis(2-hydroxyethoxy)-7,7,8,8-tetracyanoquinodimethan and 1,1′-bis(methoxycarbonylamino)ferrocene[4] (**3**), was prepared to compare its properties with those of the charge-transfer polymer **2**. The donor and acceptor compo-

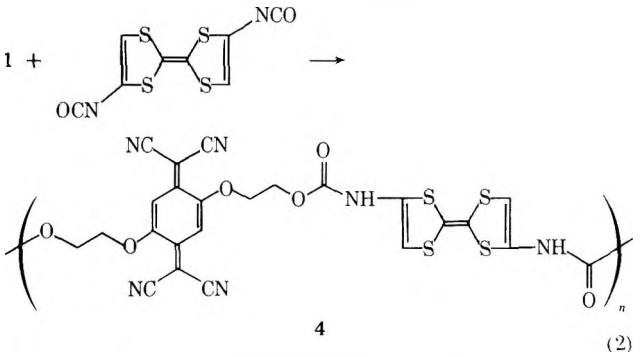


(1)



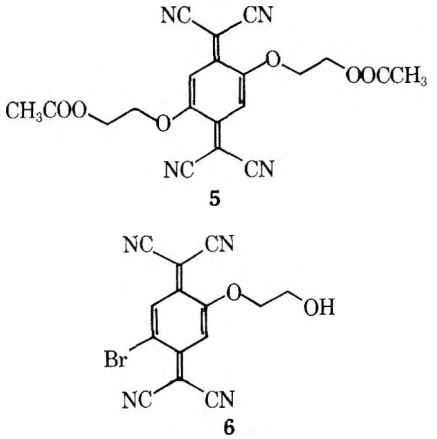
nents in each case should have similar redox potentials. The black charge-transfer complex **3** has an electrical conductivity of 2.4×10^{-1} ohm^{-1} cm^{-1}. The ultraviolet spectrum of **3** in acetonitrile solution shows mostly free 2,5-bis(2-hydroxyethoxy)-7,7,8,8-tetracyanoquinodimethan with only 1.5–2% of the corresponding anion radical. As is generally the case, the nonpolymeric charge-transfer complex showed substantially higher electrical conductivity than the polymeric charge-transfer complex.

A second charge-transfer polymer was prepared by reaction (eq 2) of the diol **1** with 4,4′-diisocyanatotetrathiafulvalene which was obtained from 4,4′-tetrathiafulvalenedicarboxylic acid[6] by the Curtius reaction. The resulting black polyurethane, **4**, was found to be amorphous by x-ray analysis. The polymer **4** has an electrical conductivity of 1.66×10^{-7} ohm^{-1} cm^{-1} and is, thus, substantially less conductive than the ferrocene-containing polymer, **2**. If the diisocyanatotetrathiafulvalene is a mixture of cis and trans (4,4′ and 4,5′) isomers, this would introduce disorder into the polymer perhaps accounting for the absence of crystallinity.



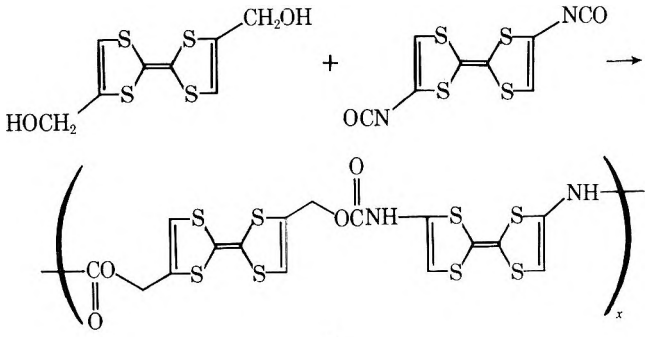
(2)

Polarographic reduction of **1** in acetonitrile solution showed two one-electron reduction waves with half-wave potentials of +0.16 and −0.40 V (vs. SCE). The difference of 0.56 V between the two waves is anomalously large. It is, in fact, the largest difference observed for any substituted TCNQ. The structurally similar 2,5-bis(2-acetoxyethoxy)-7,7,8,8-tetracyanoquinodimethan (**5**) showed half-wave potentials of +0.03 and −0.42 V. The difference in half-wave potentials of 0.45 V is more characteristic of other substituted TCNQ's. A possible explanation is that intramolecular hydrogen bonding occurs to stabilize the anion radical of **1**. However, the anomalous spread between half-wave potentials is not observed with 2-bromo-5-(2-hydroxyethoxy)-7,7,8,8-tetracyanoquinodimethan (**6**), which has half-wave potentials of +0.24 and −0.21 V.



To synthesize a polymer containing TTF units, 4,4′-bis(hydroxymethyl)tetrathiafulvalene was synthesized by

the reduction of 4,4′-tetrathiafulvalenedicarbonyl chloride using lithium tri-*tert*-butoxyaluminum hydride. The resulting diol was then combined with 4,4′-diisocyanatotetrathiafulvalene to give the polyurethane **7**.



7

The TTF polyurethane, **7**, is a brown polymer for which a solvent could not be found. Even in the absence of an added π acid, this polymer has a remarkably high electrical conductivity, 2×10^{-8} ohm^{-1} cm.$^{-1}$ When the polymer was suspended in an acetonitrile solution of iodine, a black polymeric complex was obtained containing about one iodine atom per TTF unit. The poly-TTF iodide has a conductivity of 2×10^{-6} ohm^{-1} cm^{-1}, two orders of magnitude greater than the uncomplexed polymer.

Ueno, Masuyama, and Okawara[7] have recently reported the synthesis of polymeric tetrathiafulvalenes by coupling of 4,4′-polymethylenebis(1,3-dithiole-2-ylium perchlorates). The polymers prepared by the Japanese workers, although insoluble, were converted to charge transfer complexes with TCNQ and DDQ.

The failure of the polymers in this study to show the very high electrical conductivities characteristic of several nonpolymeric charge-transfer complexes is probably a result of geometric constraints. The polymer is probably unable to achieve the high degree of orientation required to enable the donor units and acceptor units in the polymer backbone to form the face-to-face stacks[8-10] which play an important role in the conductivity of, for example, TTF–TCNQ.

Experimental Section

2,5-Bis(2-acetoxyethoxy)-*p*-xylylene Dichloride. In a 3-l. flask equipped with a mechanical stirrer, thermometer, reflux condenser, and gas inlet tube was placed 372 g (1.315 mol) of 1,4-bis(acetoxyethoxy)benzene (prepared from the reaction of acetyl chloride with 2,2′-*p*-phenylenedioxydiethanol at reflux), 99 g of paraformaldehyde, 220 ml of acetic acid, and 440 ml of concentrated hydrochloric acid. The mixture was stirred while bubbling in a stream of gaseous hydrogen chloride while maintaining the temperature at 50–55 °C. After 2 h, the mixture was cooled and filtered. The filter cake was washed with water and recrystallized from methylene chloride to give 120 g of 2,5-bis(2-acetoxyethoxy)-*p*-xylylene dichloride, mp 130.5–133 °C.

Anal. Calcd for $C_{16}H_{20}Cl_2O_6$: C, 50.67; H, 5.32. Found: C, 50.58; H, 5.70.

2,5-Bis(2-acetoxyethoxy)-*p*-xylylene Dicyanide. In a three-neck, 2-l. flask equipped with a mechanical stirrer, thermometer, and reflux condenser under a nitrogen atmosphere were placed 336 ml of anhydrous dimethyl sulfoxide and 58.5 g of sodium cyanide. Then 190.7 g of 2,5-bis(2-acetoxyethoxy)-*p*-xylylene dichloride was added portionwise at a rate such that the temperature rose to 50 °C and remained near 50 °C during the addition. When the addition was complete, stirring was continued at 50 °C for 1 h, and the mixture was then heated to 85 °C, cooled, diluted with a large volume of water, and filtered. The filter cake was washed with water and with ether. Recrystallization from dioxane gave 105 g of 2,5-bis(2-acetoxyethoxy)-*p*-xylylene dicyanide, mp 168–169.5 °C.

Anal. Calcd for $C_{18}H_{20}N_2O_6$: C, 59.99; H, 5.59; N, 7.77. Found: C, 59.97, 59.98; H, 5.89, 5.79; N, 7.41, 7.52.

2,5-Bis(2-hydroxyethoxy)-*p*-xylylene Dicyanide. A mixture of 20.8 g of 2,5-bis(acetoxyethoxy)-*p*-xylylene dicyanide, 200 ml of acetonitrile, and 200 ml of dioxane was warmed with stirring until solution was complete. Then 80 ml of 10% hydrochloric acid was added, and the solution was stirred at room temperature for 3 days at which time a precipitate was observed. In subsequent preparations an improved yield was obtained by allowing the hydrolysis to proceed for 6 or 7 days. The mixture was filtered, and the filter cake was washed with water, dioxane, and ether and dried to give 12.8 g of 2,5-bis(2-hydroxyethoxy)-*p*-xylylene dicyanide, mp 179–180.5 °C.

Anal. Calcd for $C_{14}H_{16}N_2O_4$: C, 60.86; H, 5.84; N, 10.14. Found: C, 60.84; H, 5.83; N, 9.91.

The infrared spectrum of the product shows no absorption attributable to carbonyl.

2,5-Bis[2-(tetrahydro-2-pyranyloxy)ethoxy]-*p*-xylylene Dicyanide. A mixture of 45 g of 2,5-bis(2-hydroxyethoxy)-*p*-xylylene dicyanide, 250 ml of tetrahydrofuran, 150 ml of dihydropyran (Aldrich Chemical Co.), and 330 mg of *p*-toluenesulfonic acid monohydrate was stirred at reflux for 1.5 h after a homogeneous solution was obtained. The solution was evaporated in vacuo, and the residue was stirred with cold water and dried in vacuo to give 78.5 g of solid. The crude product was dissolved in benzene and passed through a 3-in. column of basic alumina. The eluate was boiled while adding heptane. On cooling and adding additional heptane, there was obtained 49 g of 2,5-bis[2-(tetrahydro-2-pyranyloxy)-ethoxy]-*p*-xylylene dicyanide as an isomeric mixture. An analytical sample (mp 90–93 °C) was obtained by recrystallization from cyclohexane.

Anal. Calcd for $C_{24}H_{32}N_2O_6$: C, 64.85; H, 7.26; N, 6.30. Found: C, 65.19, 65.27; H, 7.30, 7.13; N, 5.91, 5.97.

2,5-Bis(2-hydroxyethoxy)-7,7,8,8-tetracyanoquinodimethan. A stirred mixture of 87.4 g of the 2,5-bis[2-(tetrahydro-2-pyranyloxy)ethoxy]-*p*-xylylene dicyanide, 25.6 g of sodium methoxide, and 400 ml of dimethyl carbonate was distilled over a period of 2.5 h until the temperature of the distillate reached 85 °C. An additional 200 ml of dimethyl carbonate was added, the mixture was cooled in an ice bath to 5–10 °C, and 31.5 ml of cyanogen chloride was slowly distilled into the reaction flask while stirring. After stirring for 2 h at 5 °C, the mixture was slowly warmed to 50 °C and then evaporated in vacuo. The gummy, dark residue was treated with 500 ml of warm 10% aqueous sodium hydroxide and Darco, and filtered. The filtrate was cooled and acidified with dilute hydrochloric acid. The dark gum which precipitated was extracted with methylene chloride, treated with Darco, dried, and evaporated to 11 g of red oil. The red oil was dissolved in acetonitrile and treated with a solution of 10.3 g of *N*-iodosuccinimide in acetonitrile. The solution was evaporated in vacuo, and the dark, gummy residue was washed well with water and hexane. The residue was treated with methanol, diluted with water, and filtered. The filter cake, which was free of iodine, was boiled with 350 ml of methanol and filtered hot to give 3.1 g of orange solid. Two recrystallizations from acetonitrile gave 2.3 g of dark purple-red needles of 2,5-bis(2-hydroxyethoxy)-7,7,8,8-tetracyanoquinodimethan, mp 228–232 °C. From a second extraction of the dark, gummy residue with 500 ml boiling 10% aqueous sodium hydroxide was obtained an additional 1.2 g of 2,5-bis(2-hydroxyethoxy)-7,7,8,8-tetracyanoquinodimethan, mp 225–230 °C.

Anal. Calcd for $C_{16}H_{12}N_4O_4$: C, 59.3; H, 3.73; N, 17.3. Found: C, 59.5; H, 3.73; N, 17.6.

Uv (acetonitrile) ϵ_{342} 44 700, ϵ_{412} 43 100.

Polymerization of 1,1′-Diisocyanatoferrocene with 2,5-Bis(2-hydroxyethoxy)-7,7,8,8-tetracyanoquinodimethan. To a stirred solution of 324.3 mg (1 mmol) of 1 and 268.0 mg (1 mmol) of 1,1′-diisocyanatoferrocene[4] (freshly recrystallized from hexane) in 8 ml of dimethylformamide under an argon atmosphere was added 0.015 ml of dibutyltin dilaurate. The solution, which was initially red in color, turned green and polymer precipitated. After stirring for 20 h, 4 ml of methanol was added, and the mixture was filtered. The filter cake was washed with dimethylformamide and then with methanol to give 185 mg of black, insoluble polymer.

Anal. Calcd for $(C_{28}H_{20}N_6O_6Fe)n$: C, 56.8; H, 3.40; N, 14.2. Found: C, 55.3, 55.5; H, 3.50, 3.51; N, 13.6, 13.6.

The resistivity of a compaction of the black polymer is 3×10^3 ohm cm. The x-ray powder pattern of the black polymer shows both crystalline and amorphous components.

Dilution of the filtrate with methanol gave additional precipitate. Filtration gave 362 mg of green-brown polymer.

Anal. Found: C, 54.2, 54.1; H, 3.65, 3.66; N, 13.1, 13.0.

The electrical resistivity of the green-brown polymer is 10^7 ohm

cm. The infrared spectra of the black and green-brown polymers differed greatly.

Nonpolymeric Model for Copolymer of 1 and 1,1′-Diisocyanatoferrocene. To a warm solution of 162.1 mg of 1 in 15 ml of acetonitrile was added 166.1 mg of 1,1′-bis(methoxycarbonylamino)ferrocene.[4] Upon concentrating the warm, deep-red solution under a stream of nitrogen, a mixture of black crystals and crystals of 1 separated. The crystals were redissolved, and the solution was treated with 100 mg of additional 1,1′-bis(methoxycarbonylamino)ferrocene. The warm solution was concentrated under a stream of nitrogen to a volume of about 10 ml. The solution was allowed to cool to room temperature, and black crystals separated. Filtration followed by rinsing with acetonitrile gave 268 mg of black 1:1 complex.

Anal. Calcd for $C_{30}H_{28}N_6O_8Fe$: C, 54.89; H, 4.30; N, 12.80. Found: C, 54.76; H, 4.38; N, 12.89.

The resistivity of a compaction of the product is 24 ohm cm. The ultraviolet spectrum of the complex in acetonitrile shows absorption characteristic of 1 and only 1.5–2% of the anion radical of **1**, indicating a high degree of dissociation of the complex in solution.

4,4′-Tetrathiafulvalene Dicarbonyl Chloride. A mixture of 1.2 g of 4,4′-tetrathiafulvalenedicarboxylic acid,[6] 20 ml of methylene chloride, 1 drop of pyridine, and 1.7 ml of oxalyl chloride was stirred overnight at room temperature and 3 days at reflux. The mixture was cooled to room temperature and filtered to give 1.04 g of 4,4′-tetrathiofulvalene dicarbonyl chloride as a purple solid, mp 240–245 °C, ir 1700 cm^{-1} (COCl).

Anal. Calcd for $C_8H_2O_2S_4Cl_2$: C, 29.18; H, 0.61. Found: C, 29.29; H, 0.76.

4,4′-Diisocyanatotetrathiafulvalene. A mixture of 5.5 g of 4,4′-tetrathiafulvalene dicarbonyl chloride, 100 ml of anhydrous acetonitrile, and 2.2 g of activated sodium azide was stirred at room temperature for 15 min, at reflux for 2 h, and at room temperature overnight. Then 400 ml of toluene was added, and the acetonitrile was removed by distillation. The mixture was then stirred at 104 °C for 1.5 h and filtered hot. The filtrate was evaporated in vacuo nearly to dryness, treated with hexane, cooled, and filtered. The red filter cake was recrystallized from benzene–heptane to give 2.82 g of 4,4′-diisocyanatotetrathiafulvalene as red crystals, mp 156 °C dec; ir 2250 cm^{-1} (NCO).

Anal. Calcd for $C_8H_2N_2S_4O_2$: C, 33.57; H, 0.70; N, 9.79. Found: C, 33.87; H, 1.16; N, 9.96.

Polymerization of Diisocyanatotetrathiafulvalene with 2,5-Bis(2-hydroxyethoxy)-7,7,8,8-tetracyanoquinodimethan. To a stirred solution of 324.3 mg (1 mmol) of 2,5-bis(2-hydroxyethoxy)-7,7,8,8-tetracyanoquinodimethan and 298.4 mg of 4,4′-diisocyanatotetrathiafulvalene in 8 ml of dimethylformamide under an argon atmosphere was added 0.015 ml of dibutyltin dilaurate. The solution gradually became viscous and gelled over a period of a few hours. After 24 h, a few drops of methanol were added. After 15 min, excess benzene and methanol were added. The black polymer (591 mg) was collected by filtration and dried at 65 °C (0.1 mm).

Anal. Calcd for $(C_{24}H_{14}N_6O_6S_4)x$: C, 47.2; H, 2.30; N, 11.62; S, 21.00. Found: C, 46.70, 46.20, 45.66; H, 3.17, 3.25, 3.24; N, 11.62, 11.20, 10.75; S, 20.98.

No solvent was found for the polymer.

The electrical resistivity of the compacted polymer is 6×10^{10} ohm cm. The powder pattern of the polymer shows it to be amorphous. Differential scanning calorimetry shows a glass transition at −32 °C, a small, broad endotherm at 88 °C, and a major exotherm at 270 °C.

2,5-Bis(2-acetoxyethoxy)-7,7,8,8-tetracyanoquinodimethan. A mixture of 500 mg of 2,5-bis(2-hydroxyethoxy)-7,7,8,8-tetracyanoquinodimethan, 40 ml of acetic anhydride, and 60 ml of acetonitrile was stirred at reflux for 1.5 h and evaporated in vacuo. The residue was recrystallized from cyclohexane–benzene and then from 1-chlorobutane to give 326 mg of maroon plates, mp 144–175 °C dec.

Anal. Calcd for $C_{20}H_{16}H_4O_6$: C, 58.88; H, 3.95; N, 13.72. Found: C, 58.87; H, 4.14; N, 13.88.

Uv (acetonitrile) 430 nm (ϵ 48 100), 410 (45 600).

2-(2-Acetoxyethoxy)-α,α′,5-tribromo-p-xylene. A mixture of 20.8 g of 2-(2-acetoxyethoxy)-*p*-xylene, prepared by acetylation of 2-(2-hydroxyethoxy)-*p*-xylene (prepared in turn by the reaction of 2,5-dimethylphenol with ethylene carbonate at 180 °C in the presence of powdered potassium hydroxide), 300 ml of 1,2-dichloroethane, 59 g of *N*-bromosuccinimide, and 0.6 g of benzoyl peroxide was stirred at reflux under a nitrogen atmosphere for 18 h. The mixture was cooled, filtered, washed with 10% aqueous sodium bisulfite, washed three times with water, dried, and evaporated. The residue was suspended in ether and filtered to give 17.8 g of 2-(2-acetoxyethoxy)-α,α′,5-tribromo-*p*-xylene, mp 112.5–115.5 °C. Recrystallization from cyclohexane raised the melting point to 114–117 °C.

Anal. Calcd for $C_{12}H_{13}Br_3O_3$: C, 32.39; H, 2.95; Br, 53.97. Found: C, 32.63; H, 3.00; Br, 53.21.

NMR ($CDCl_3$) δ 7.5 (s, aromatic, 1 H), 6.95 (s, aromatic, 1 H), 4.54 (s, CH_2Br), 4.45 (s, CH_2Br), 4.04–4.5 (m, OCH_2CH_2O, total intensity of 4.54–4.05, 8.5 H), 2.1 ppm (s, CH_3CO, 3 H).

2-(2-Acetoxyethoxy)-5-bromo-1-bromomethyl-4-dibromomethylbenzene. A mixture of 191 g of 2-(2-acetoxyethoxy)-*p*-xylene, 550 g of *N*-bromosuccinimide, 2.8 l. of 1,2-dichloroethane, and 5.5 g of benzoyl peroxide was stirred at reflux overnight, filtered, washed with dilute sodium bisulfite solution and water (three times), dried, and evaporated in vacuo. The residue, which slowly crystallized, was twice suspended in 200 ml of ether and filtered to give 183.4 g of solid, mp 94–109 °C. The product was crystallized from cyclohexane and then from butyl chloride to give 85.7 g of 2-(2-acetoxyethoxy)-α,α′,5-tribromo-*p*-xylene, mp 113–114 °C. The second crop (21.3 g), mp 90–94.5 °C, was recrystallized twice from butyl chloride–ether to give crystals of 2-(2-acetoxyethoxy)-5-bromo-1-bromomethyl-4-dibromomethylbenzene, mp 95.5–96.5 °C.

Anal. Calcd for $C_{12}H_{12}Br_4O_3$: C, 27.6; H, 2.31; Br, 61.0. Found: C, 27.9; H, 2.32; Br, 61.28.

NMR ($CDCl_3$) δ 8.0 (s, aromatic, 1 H), 7.0 (s, $CHBr_2$, 1 H), 6.95 (s, aromatic, 1 H), 4.52 (s, CH_2Br, 2 H), 4.15–4.56 (m, $-CH_2CH_2-$, 4 H), 2.1 ppm (s, CH_2CO, 3 H).

2-(2-Acetoxyethoxy)-5-bromo-p-xylylene Dicyanide. To an ice-cooled, stirred slurry of 3 g of sodium cyanide and 25 ml of anhydrous dimethylformamide was added 1.5 ml of trifluoroacetic acid at a rate such that the temperature did not exceed 10 °C. Then 4.45 g (0.01 mol) of 2-(2-acetoxyethoxy)-α,α′,5-tribromo-*p*-xylene was added portionwise at a rate such that the temperature ramained below 10 °C. After stirring overnight at ambient temperature (in subsequent experiments, 80 min at 10 °C was found to be sufficient reaction time), the mixture was poured into ice and water and filtered to give 3.03 g of solid. Recrystallization from butyl chloride–heptane gave 1.89 g of 2-(2-acetoxyethoxy)-5-bromo-*p*-xylene dicyanide, mp 121–124.5 °C. Recrystallization from dioxane–heptane raised the melting point to 125–126 °C.

Anal. Calcd for $C_{14}H_{13}N_2BrO_3$: C, 49.9; H, 3.88; N, 8.31; Br, 23.7. Found: C, 49.8; H, 4.01; N, 8.07; Br, 23.7.

NMR ($CDCl_3$) δ 7.54 (s, aromatic, 1 H), 7.01 (s, aromatic, 1 H), 4.12–4.59 (m, $-CH_2CH_2-$, 4 H), 3.82 (s, CH_2CN, 2 H), 3.66 (s, CH_2CN, 2 H), 2.10 ppm (s, CH_3CO, 3 H).

2-(2-Hydroxyethoxy)-5-bromo-p-xylylene Dicyanide. A solution of 3.37 g of 2-(2-acetoxyethoxy)-5-bromo-*p*-xylylene dicyanide in 20 ml of acetonitrile, 20 ml of dioxane, and 8 ml of 10% aqueous hydrochloric acid was stirred at 35 °C for 18 h and then poured into ice and water. Filtration gave 2.54 g of 2-(2-hydroxyethoxy)-5-bromo-*p*-xylylene dicyanide, mp 137.5–140.5 °C. Recrystallization from methanol raised the melting point to 142–144 °C.

Anal. Calcd for $C_{12}H_{11}N_2BrO_2$: C, 48.95; H, 3.76; N, 9.50; Br, 27.1. Found: C, 48.46, 48.33, 48.57; H, 3.72, 3.62, 4.12; N, 8.82, 8.89, 9.80; Br, 26.9.

2-(2-Hydroxyethoxy)-5-bromo-p-phenylenedimalononitrile. A stirred mixture of 19.9 g of 2-(2-hydroxyethoxy)-5-bromo-*p*-xylylene dicyanide (0.0674 mol), 7.38 g of sodium methoxide (0.137 mol), and 160 ml of methyl carbonate was slowly distilled until the head temperature reached 90 °C and all of the methanol had been removed azeotropically. A gum had formed but solidified on cooling. The solid was broken up manually and stirred at 5 °C while 20 ml (at 0 °C) of cyanogen chloride was slowly added through a gas inlet tube. The mixture was stirred overnight at ambient temperature after addition of methyl carbonate to facilitate mixing. The mixture was filtered, and the filtrate evaporated to 31.2 g of a pale yellow oil. After washing several times with heptane, the oil was boiled with 170 ml of 10% sodium hydroxide solution, and the resulting red solution was poured gradually into 240 ml of cold 10% hydrochloric acid. The gummy precipitate, on standing overnight in the acidic medium, solidified. The mixture was blended in a Waring blender and filtered to give 13.1 g of solid, mp 126–143 °C. Recrystallization from methylene chloride–heptane containing a little dioxane followed by crystallization from aqueous acetic acid gave 3.7 g of 2-(2-hydroxyethoxy)-5-bromo-*p*-phenylenedimalononitrile, mp 150.5–153 °C.

Anal. Calcd for $C_{14}H_9N_4BrO_2$: C, 48.71; H, 2.63; N, 16.23. Found: C, 49.04; H, 2.87; N, 15.99.

NMR (CD_3CN) δ 7.82 (s, aromatic, 1 H), 7.43 (s, aromatic, 1 H), 5.69 [s, $CH(CN)_2$, 1 H], 5.63 [s, $CH(CN)_2$, 1 H], 3.75–4.37 (m, $-CH_2CH_2$, 5 H), 3.1 ppm (s, broad, OH, 1 H).

2-(2-Hydroxyethoxy)-5-bromo-7,7,8,8-tetracyanoquinodimethan. A mixture of 500 mg of 2-(2-hydroxyethoxy)-5-bromo-*p*-phenylenedimalononitrile and 50 ml of bromine water was stirred for 30 min and filtered. The filter cake was recrystallized from benzene to give 236 mg of red crystals of 2-(2-hydroxyethoxy)-5-bromo-7,7,8,8-tetracyanoquinodimethan, mp 213–217 °C dec.

Anal. Calcd for $C_{14}H_7N_4BrO_2$: C, 49.00; H, 2.06; N, 16.33. Found: C, 48.86; H, 2.25; N, 16.23.

Uv (CH_3CN) 485 nm (ε 4461), 413 (41 521), 390 (sh, 39 805), 280 (3157).

4,4′-Bis(hydroxymethyl)tetrathiafulvalene. To a stirred slurry of 6.5 g (0.0256 mol) of lithium tri-*tert*-butoxyaluminum hydride and 30 ml of tetrahydrofuran under nitrogen cooled to −78 °C was added 1.81 g (0.00555 mol) of tetrathiafulvalenedicarbonyl chloride. The mixture was stirred for 1 h at −78 °C and then allowed to slowly warm to room temperature during which time the purple solid became amber. After 3 h, the solvent was removed in a stream of nitrogen and water was added to the residue under nitrogen. The mixture was filtered under nitrogen, and the filter cake was stirred under argon with 10% sodium hydroxide solution for 1 h and refiltered. The filter cake was extracted with methanol, and the extract was diluted with aqueous sodium hydroxide and concentrated somewhat in vacuo causing separation of rust-colored crystals which were collected by filtration and washed with water to give 368 mg of 4,4′-bis(hydroxymethyl)tetrathiafulvalene which begins to decompose at 160 °C.

Anal. Calcd for $C_8H_8S_4O_2$: C, 36.34; H, 3.05. Found: C, 36.67; H, 3.29.

NMR (Me_2SO-d_6) 6.41 (s, 2 ring H), 5.39 (t, J = 5.5 Hz, OH, 2 H), 4.15 (d, J = 5.5 Hz, $-CH_2O$, 4 H), 3.27 ppm (s, H_2O, 1 H). Addition of D_2O causes disappearance of the 5.39 and 3.27 ppm peaks and a new exchange singlet appears at 3.78 ppm while the 4.15 ppm CH_2 peak collapses to a singlet.

Tetrathiafulvalene Polyurethane (7). To a stirred, refluxing mixture of 108.9 mg of 4,4′-bis(hydroxymethyl)tetrathiafulvalene, 118 mg of 4,4′-diisocyanatotetrathiafulvalene, and 15 ml of acetonitrile under argon was added 0.1 μl of dibutyltin dilaurate catalyst. After 2 h, the mixture was filtered under argon, and the filter cake was twice mixed with acetonitrile and centrifuged to give 167 mg of brown polymer. The infrared spectrum shows carbonyl absorption at 1730 cm^{-1} and NH absorption at 3400 cm^{-1}.

Anal. Calcd for $(C_{16}H_{10}N_2S_8O_4)_x$: C, 34.89; H, 1.83; N, 5.09. Found: C, 33.52, 33.47; H, 2.17, 2.16; N, 5.35, 5.30.

Reaction of Tetrathiafulvalene Polyurethane with Iodine. A mixture of 30 mg of 7, 10 ml of acetonitrile, and 14 mg of iodine was stirred under argon for 3 h and filtered in a nitrogen atmosphere to give 35.5 mg of black polymer.

Anal. Calcd for $C_{16}H_{10}O_4S_8N_2I_2$: C, 23.88; H, 1.25; N, 3.48. Found: C, 23.94, 23.97; H, 1.56, 1.54; N, 4.16, 4.29.

Electrical resistivity of compaction 2 × 10^6 ohm cm.

Registry No.—**1**, 58268-29-4; **2**, 58312-83-7; **3**, 58312,84-8; **4**, 58268-60-3; **5**, 58268-30-7; **6**, 58268-31-8; **7**, 58268-59-0; 2,5-bis(2-acetoxyethoxy)-*p*-xylylene dichloride, 58268-32-9; 1,4-bis(acetoxyethoxy)benzene, 47096-64-0; 2,5-bis(2-acetoxyethoxy)-*p*-xylylene dicyanide, 58268-33-0; 2,5-bis(2-hydroxyethoxy)-*p*-xylene dicyanide, 58268-34-1; 2,5-bis[2-(tetrahydro-2-pyranyloxy)ethoxy]-*p*-xylylene dicyanide isomer 1, 58268-35-2; 2,5-bis[2-(tetrahydro-2-pyranyloxy)ethoxy]-*p*-xylene dicyanide isomer 2, 58268-36-3; *N*-iodosuccimide, 516-12-1; 1,1′-diisocyanatoferrocene, 12288-75-4; 1,1′-bis(methoxycarbonylamino)ferrocene, 12277-09-7; 4,4′-tetrathiafulvalenedicarbonyl chloride, 58268-37-4; 4,4′-tetrathiafulvalenedicarboxylic acid, 51751-19-0; methylene chloride, 75-19-2; 4,4′-diisocyanatotetrathiafulvalene, 58268-38-5; 2-(2-acetoxyethoxy-α,α′,5-tribromo-*p*-xylene, 58268-39-6; 2-(2-acetoxyethoxy)-*p*-xylene, 58268-40-9; 2-(2-acetoxyethoxy)-5-bromo-1-bromomethyl-4-dibromomethylbenzene, 58268-41-0; *N*-bromosuccinimide, 128-08-5; 2-(2-acetoxyethoxy)-5-bromo-*p*-xylene dicyanide, 58268-42-1; 2-(2-hydroxyethoxy)-5-bromo-*p*-xylylene dicyanide, 58268-43-2; 2-(2-hydroxyethoxy)-5-bromo-*p*-phenylenedimalononitrile, 58268-44-3; 4,4′-bis(hydroxymethyl)tetrathiafulvalene, 58268-45-4; 4,4′-diisocyanatotetrathiafulvalene polymer, 58268-58-9; 2,5-bis(hydroxyethoxy)-7,7,8,8-tetracyanoquinodimethan 1,1′-diisocyanatoferrocene polymer, 58298-32-1; 2,5-bis(hydroxyethoxy)-7,7,8,8-tetracyanoquinodimethan 4,4′-diisocyanatotetrathiafulvalene polymer, 58268-57-8.

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Synthesis of Halogen Substituted Bicyclo[2.1.1]hexan-2-ones

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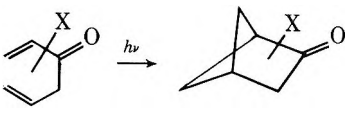
Photochemical irradiation of chlorine substituted 1,5-hexadien-3-ones has led to the synthesis of 1-chloro-, *exo*-5-chloro-, and *endo*-5-chlorobicyclo[2.1.1]hexan-2-one. The nature and utility of the photocycloaddition is discussed. Bromination of bicyclo[2.1.1]hexan-2-one has been carried out using lithium dialkylamide to form the enolate.

Strained bicyclic and polycyclic compounds continue to play an important role in the understanding of many aspects of organic chemistry,[1] including theoretical studies,[2] solvolytic reactivity,[3] thermal rearrangements,[4] and reactivity of strained σ bonds.[5] For this reason, synthetic efforts in this area have been extensive. For some time now, we and others have been interested in the chemistry of bicyclo[2.1.1]hexanes, an area far less studied than that of the homologous bicyclo[2.2.1]heptanes, owing to the ready availability of the latter. In this paper we report extension of our previously noted synthesis of bicyclo[2.1.1]hexan-2-one[6] to the preparation of functionally activated bicyclo[2.1.1]hexan-2-ones, needed for various studies, some of which are reported in the accompanying paper.[7]

Most synthetic routes to the bicyclo[2.1.1]hexane nucleus have involved either ring contractions from bicyclo[2.2.1]heptanes[1a,8] or bicyclo[3.1.1]heptanes[8g,h,9] or photochemical cycloaddition of acyclic precursors.[6,10] Other

routes of less general utility include acyloin condensation of a cyclobutane precursor,[11] photochemical cyclization of aryl ketones,[12] and miscellaneous specialized reactions.[13] As we were particularly interested in studying interactions between two different functional groups on the rigid bicyclo[2.1.1]hexane nucleus, and in the use of such derivatives for the preparation of even more highly strained compounds,[7] we investigated the preparation of halogen substituted bicyclo[2.1.1]hexan-2-ones.

There are a total of five such isomers, the 1-halo, 3-halo, 4-halo, and exo and endo 5-halo derivatives. Our major effort was to extend the facile photocycloaddition of 1,5-hexadien-3-one (**1a**)[6] to halogen substituted dienones, **1b**. It

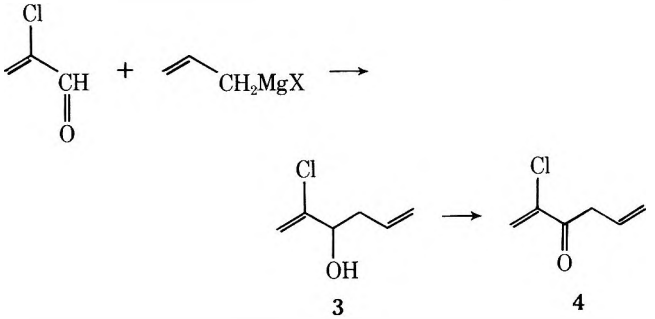


1a, X = H **2a**, X = H
b, X = Cl **b**, X = Cl
c, X = CH_3 **c**, X = CH_3

was felt that such a study might also shed light on the nature of this unusual cycloaddition which has become the main synthetic route to bicyclo[2.1.1]hexanes, but which has not been extended to the preparation of other ring systems. In this regard, our results are in complete agreement with the study of Gibson and Erman,[10a] who investigated the cycloaddition of the methyl dienones **1c**.

Results and Discussion

Synthesis of Precursors. The route previously used[6] for the synthesis of **1a** was applicable to only one of the halodienones, the 2-chloro isomer **4**, prepared from **3**[14] by oxidation with Jones reagent. The yield in the oxidation



3 **4**

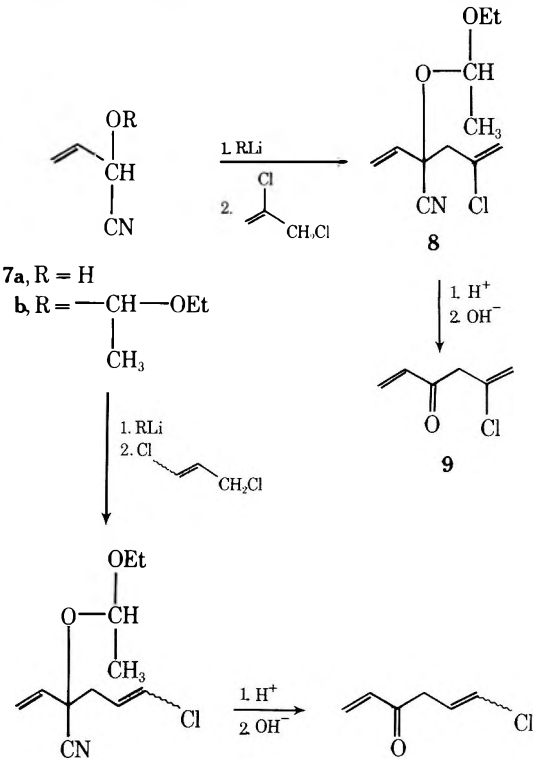
was low and could not be improved by excess reagent or extended reaction time, or by use of other conditions, including the Collins reagent, activate manganese dioxide, or dimethyl sulfoxide, which led to either overoxidation or no reaction. Lack of reactivity with demonstrably active manganese dioxide has precedent.[15] A cis–trans mixture of the 1-chloro isomer of **4** could be obtained from β-chloroacrolein by a similar route, but again the oxidation proceeded in low yield and the dienone underwent extensive polymerization upon photolysis. The desired products, in this case *exo*- and *endo*-5-chlorobicyclo[2.1.1]hexan-2-one, could be prepared as shown below, so that this sequence was not pursued.

Preparation of 4-chloro-1,5-hexadien-3-one (**6a**) was not attempted since its photolysis was expected to result in α

5a, X = OH (threo and erythro) **6a**, X = Cl
b, X = OAc (threo and erythro) **b**, X = OAc

cleavage. The corresponding acetate **6b** was prepared from **5a**[16] and indeed it proved to be less valuable as a precursor for 3-substituted bicyclo[2.1.1]hexan-2-ones than the parent ketone **2a** (vide supra).

The Grignard route to the 5- or 6-chloro isomers of **3** was unsuccessful as we were unable to prepare a Grignard reagent from either 1,3- or 2,3-dichloropropene. Such preparations have also not been reported in the literature. Therefore, the three remaining dienone precursors, **9**, **11a**, and **11b**, were prepared by the Stork procedure[17] from

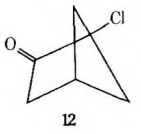
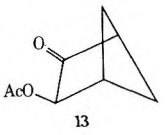
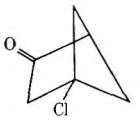
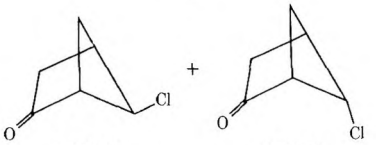


10a, cis **11a**, cis
b, trans **b**, trans

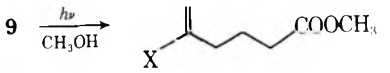
acrolein cyanohydrin (**7a**).[18] Treatment of **7a** with ethyl vinyl ether afforded the mixed acetal **7b** which was converted into its monoanion and alkylated with 2,3-dichloropropene to give **8**, or with 1,3-dichloropropene to give **10a** and/or **10b** depending on the stereochemistry of the starting dihalide. Hydrolysis in dilute acid generated the free cyanohydrins which were converted with base to the respective dienones, **9**, **11a**, and **11b**, all of which were irradiated without purification. Attempts at purification of the dienones led to extensive decomposition.

Irradiation of Dienones. Results of the irradiation studies are shown in Table I. The exact conditions are given in the Experimental Section and proved important in avoiding side reactions, particularly polymerization. Hydrocarbon solvents were used generally. Methanol as a solvent resulted in some reduction of the dienones and overirradiation of the bicyclic products.[19] Reproducible quantum yields could not be obtained, possibly because of minor impurities in the difficult to purify dienones. Low, but acceptable, isolated yields of **12** and **13** were obtained and **15** and **16** were formed in satisfactory amounts. Since 3-substituted isomers related to **13** can be prepared from **2a** as described below, only the 4-chloro isomer **14** cannot be easily prepared by the photocycloaddition route, which therefore seems preferable to the alternative ring contraction of di- or trisubstituted bicyclo[2.2.1]heptanes. In all cases except **9**, side products were either very volatile or polymeric so that product isolation was not difficult, provided that photoreduction to the dienol had been avoided.

Table I. Irradiation of Dienones

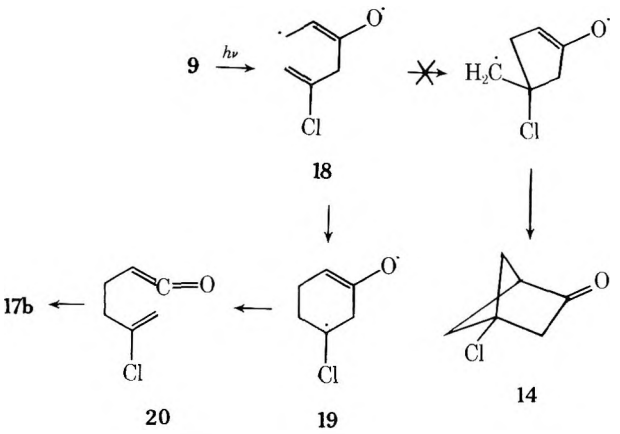
Dienone	Product	Isolated yield, %
4	 12	13
6b	 13	8
9	 14	~1
11a or 11b	 15 (40%) + 16 (60%)	52

These photochemical results are in remarkable agreement with those of Gibson and Erman on the photolysis of the methyl dienones, **1c**.[10a] They also noted a low yield with the 2-methyl isomer and no cycloaddition with the 5-methyl isomer. In the latter case they detected methyl ester **17a** when the photolysis was carried out in methanol. We



17a, X = CH_3
b, X = Cl

likewise obtained **17b** from **9** using methanol as solvent. These results are in agreement with the "biradical" mechanism for the photolysis illustrated for **9**. Excitation to **18** allows closure in either of two ways. The normal closure, predicted[20] by the "rule of five", to **14** is less favorable in this case owing to the added stabilization of **19** afforded by the halogen or methyl substituent. Fragmentation of **19** gives ketene **20** which presumably polymerizes in hydrocarbons, but affords some **17b** in methanol. It is interesting to note that Agosta[10b] observed cycloaddition upon irradiation of 5-methyl-1,5-hexadien-3-one using a uranium glass filter. In our hands the use of such a filter did not result in an increased yield of **14**. It should be noted that the structural assignment to **14** is based on its infrared spectrum (see Experimental Section).

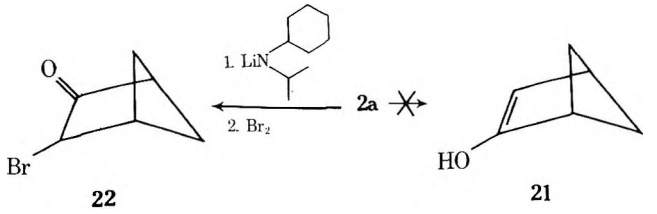


A halogen (or methyl) substituent at C-6 of the dienone should favor the normal closure, as observed. In addition, one would expect to observe the same ratio of **15:16** regardless of the stereochemistry of the starting dienone **11** since that is lost upon formation of the five-membered ring. This, again, was observed with the methyl substituent.[10a]

The remarkable similarity in product distribution from **1b** and **1c** suggests that the cyclizations occur by a similar mechanism. In the absence of more controlled experiments it is difficult to choose between a singlet and triplet pathway. Addition of standard triplet sensitizers (acetone, xanthone, acetophenone) did not affect the product distribution or approximate rate of product formation with dienones **1a**, **9**, or **11a**, though Gibson and Erman found excess acetophenone to be necessary for cycloaddition of 2,6-heptadien-4-one.[10a] Likewise piperylene did not quench the reaction, though such failure in an *intra*molecular reaction is not necessarily indicative. Perhaps the strongest suggestion for a singlet pathway is the close similarity between the methyl- and chlorodienone behavior. Were a triplet pathway involved, its facilitation due to the heavy atom effect might be expected to alter the product distribution.

Bromination of Bicyclo[2.1.1]hexan-2-one. A great deal of effort was expended in developing methods for introduction of substituents α to the carbonyl group of the parent ketone **2a**.[7] In particular, halogenation was studied as an alternative route to the 3-substituted bicyclo[2.1.1]hexan-2-ones, not easily prepared directly.

Ketone **2a** proved remarkably unreactive under a series of standard bromination conditions which readily converted camphor and norcamphor into their respective derivatives. In particular, bromination with Br_2–HBr either neat[21] or in acetic acid at 100 °C resulted in no reaction! Clearly formation of enol **21** is difficult, in agreement with theory.[2] Normal base conditions (*tert*-alkoxide, sodium amide, sodium hydride) followed by addition of bromine also failed to give the desired **22**. Sodium hydride, in fact, reduced **2a** to the corresponding alcohol. We were finally able to generate the enolate anion of **2a** using lithium cyclohexylisopropylamide as the base. Quenching of the anion in bromine afforded **22** in reasonable yield. Thus all of the halo-substituted bicyclo[2.1.1]hexan-2-ones except the 4 isomers are now readily available.



Experimental Section[22]

General Photolysis Conditions. The dienones were irradiated in dilute (ca. 1%) solution in pentane or in pentane–ether mixtures, using a Hanovia 450-W lamp (679 A-36) and a water-cooled quartz immersion well (no. 19434). Solutions were purged with nitrogen before photolysis and were maintained under a nitrogen atmosphere and magnetically stirred during photolysis. Irradiations were usually conducted in a hood owing to the lachrymatory nature of the dienones. Irradiations were followed by GLC using a 10-ft 5% DEGS column, monitoring disappearance of starting material and formation of product, the latter always with a longer retention time. Most solutions were irradiated for 10–20 h. Where polymer formed on the well, it was periodically removed by scraping.

1-Chlorobicyclo[2.1.1]hexan-2-one (12). A solution of 10.0 g

(0.076 mol) of 2-chloro-1,5-hexadien-3-ol[14] (**3**) in 500 ml of purified acetone was cooled to 10 °C and treated dropwise over a 30-min period with 20.6 ml (0.053 mol) of Jones reagent[23] under vigorous stirring. The solution was stirred for an additional 1 h at 10–15 °C, and 1.0 g of sodium bisulfite was added and then an excess of solid sodium bicarbonate. The solution was carefully decanted and the green residue washed with three 200-ml portions of pentane. The organic layers were combined, washed with 5% sodium bicarbonate and saturated salt solution, and dried over sodium sulfate. GLC (10 ft, 10% DEGS) showed a new peak, presumably due to **4**, with an area nine times that of unreacted **3**. The crude product has λ_{max} 230 nm (ethanol) and carbonyl absorption at 1692 cm^{-1} in the infrared. Attempts to isolate **4** led to decomposition.

This solution was added to the photolysis flask and sufficient pentane added to bring the volume to 1.9 l. Irradiation for 11.5 h was followed by GLC. Solvent was removed in vacuo to give a brown residue which was molecularly distilled to give 1.61 g of a light yellow liquid, bp 36–43 °C (0.5 mm). GLC analysis indicated that this mixture contained 15% of **3** and 85% of **12**. Pure **12** was collected by preparative GLC. Anal. Calcd for C_6H_7ClO: C, 55.09; H, 5.39; Cl, 27.25. Found: C, 54.96; H, 5.59; Cl, 27.34.

The ir spectrum shows carbonyl absorption as a doublet at 1792 and 1783 cm^{-1}. The NMR spectrum shows a complex broad pattern from 2.00 to 2.60 (6 H) and a multiplet at 2.90 ppm (1 H).

3-Acetoxybicyclo[2.1.1]hexan-2-one (13). A stirred solution of **5a**,[16] 57.0 g (0.5 mol), in 100 ml of pyridine was treated dropwise at 0 °C with 30.6 g (0.3 mol) of acetic anhydride. After storage at room temperature for 24 h the solution was poured onto ice–HCl and the product isolated with ether. The washed and dried ether was concentrated in vacuo to give a crude product which was fractionally distilled through a 24-in. Teflon spinning band column to give 40.1 g of **5b** as a mixture of threo and erythro isomers, bp 89–91 °C (9 mm), contaminated with a small amount of diacetates. This material was oxidized with Jones reagent as described above and the crude product irradiated immediately in pentane, followed by GLC. After 13.5 h the solution was worked up and distilled through the spinning band column to give, after removal of some **5b** and diacetate, the product **13** as a light yellow liquid, bp 110–113° (10 mm), yield 3.5 g (8% from **5a**). Anal. Calcd for $C_8H_{10}O_3$: C, 62.33; H, 6.54. Found: C, 62.18; H, 6.71.

The ir spectrum (in CCl_4) shows carbonyl absorption at 1780 and 1749 cm^{-1}. The NMR shows a complex pattern from 1.45 to 2.50 (4 H), a singlet at 2.17 (3 H), a multiplet at 2.93 (2 H), and a broad singlet at 5.55 ppm (1 H).

1-(1′-Cyano-2′-propenoxy)-1-ethoxyethane (7b). Freshly distilled acrolein cyanohydrin[18] (110.0 g, 1.28 mole), *prepared and handled in a good hood*, was placed into a 500-ml three-necked flask equipped with magnetic stirrer, dry ice condenser, and an addition funnel. The cyanohydrin was stirred and acidified with 3 drops of 5% HCl. Freshly distilled ethyl vinyl ether (100 g, 1.40 mol) was then added dropwise over the next 3 h. The solution was allowed to stand at room temperature overnight, then distilled through a 6-in. Vigreux column to give **7b**, 134.6 g (69%), bp 52–56 °C (0.2–0.3 mm) [lit.[17] bp 42–45 °C (0.1 mm)]. The product is a mixture of diastereoisomers as expected.

1-(3′-Cyano-5′-chloro-1′,5′-hexadienoxy)-1-ethoxyethane (8). Lithium diisopropylamide was prepared in 400 ml of THF from 78.4 ml (0.58 mol) of diisopropylamine and 0.6 mol of *n*-butyllithium. This solution was cooled in a dry ice–acetone bath and 75.0 g (0.48 mol) of **7b** in 70 ml of hexamethylphosphoric triamide was added dropwise over 1 h. The orange solution was stirred for an additional 5 min, still at −78 °C, and then was treated dropwise with 63.9 g (0.576 mol) of 2,3-dichloro-1-propene over a 1-h period. An additional 300 ml of THF was added, stirring was continued for 2 h, and the solution then allowed to warm to room temperature.

Water (15 ml) was added and the solution concentrated (15 mm) to a black slurry which was extracted with ether. Difficulty in visualizing the separation was a problem. The ether layer was finally separated, washed, and dried. The solution was concentrated in vacuo to a dark brown residue which was dissolved in 60 ml of hexane–benzene (1:1) and passed through a chromatographic column containing 500 g of silica gel using hexane–benzene. Four 250-ml fractions were collected, combined, and distilled through a 6-in. Vigreux column to give 35.5 g (38%) of **8**, bp 75–85 °C (0.4 mm). The NMR spectrum shows a complex pattern from 1.0 to 1.5 (6 H), a multiplet at 2.8 (2 H), a multiplet at 3.4 (2 H), a quartet at 4.85 (1 H), and a complex pattern from 5.3 to 5.9 ppm (5 H). The product is the expected mixture of diastereoisomers and was used as such.

4-Chlorobicyclo[2.1.1]hexan-2-one (14). To a 250-ml flask was added 35.5 g of **8** and 85 ml of methanol. The solution was stirred and 31 ml of 5% H_2SO_4 added rapidly, followed by sufficient methanol to afford a homogeneous solution. After 30 min the solution was concentrated in vacuo, extracted with ether, washed, and dried. Removal of the ether followed by distillation afforded 18.0 g (82%) of 5-chloro-1,5-hexadien-3-one cyanohydrin, bp 75–82 °C (0.4 mm).

In a 1-l. separatory flask was placed 7.2 g of this cyanohydrin, 350 ml of ether, and 40 ml of 0.5 N sodium hydroxide. The ether was separated and treated with a second 40-ml portion of base, shaken for 10 min, separated, washed with water, and dried. This ether solution was diluted with pentane for the photolysis studies. Evaporation of a small portion of the ether gave crude **9**, infrared carbonyl at 1680 cm^{-1} and NMR absorption at 3.50 singlet (2 H), 5.33 doublet (2 H), and complex two-proton patterns at 5.81 and 6.35 ppm. Attempts to distill this material led to extensive decomposition.

The ether–pentane solution (2.1 l.) was irradiated in the usual manner. Extensive polymer buildup was noted. Disappearance of starting material was followed by GLC and was complete in 12 h. The solution was washed, dried, and evaporated to a yellow gummy residue. Molecular distillation afforded 0.38 g of a yellow oil, GLC examination of which showed two major peaks, the second of which was collected and assigned structure **14** on the basis of its intense infrared carbonyl band at 1770 cm^{-1} and consistent mass spectrum for C_6H_7ClO. The other product was not identified.

Photolysis of 9 in Methanol. A second batch of 7.2 g of 5-chloro-1,5-hexadien-3-one cyanohydrin was converted into **9** as described above. The ether solution was diluted to 2.1 l. with methanol and irradiated as before for 21 h. Solvent was removed and the residue molecularly distilled to give 0.45 g of volatile material which showed four peaks in the GLC. The major peak was collected and assigned the structure methyl 5-chloro-5-hexenoate (**17b**), based on its spectral data.

The ir spectrum shows significant bands at 3010, 1740, 1630, 1250, and 1170 cm^{-1}. The mass spectrum shows molecular ions at *m/e* 162 and 164 ($C_7H_{11}O_2Cl$). The NMR spectrum shows absorption at 1.89 (multiplet, 2 H), 2.22 (triplet, 2 H), 2.40 (triplet, 2 H), 3.55 (singlet, 3 H), and two sharp peaks at 5.14 ppm (2 H).

Two of the minor products had retention times identical with those of the products from the pentane irradiation.

1-(3′-Cyano-*trans*-6′-chloro-1′,5′-hexadienoxy)-1-ethoxyethane (10b). Compound **10b** was prepared in 39% yield exactly as described above for **8**, except that the halide used was *trans*-1,3-dichloro-1-propene.

The product, bp 78–79 °C (0.4 mm), a diastereomeric mixture, has an NMR spectrum with a multiplet at 1.2 (6 H), two doublets centered at 2.5 (2 H), a multiplet at 3.45 (2 H), a quartet at 4.8 (1 H), and a multiplet centered at 5.8 ppm (5 H).

The cis isomer **10a** was prepared in a similar manner from *cis*-1,3-dichloro-1-propene, bp 75–79 °C (0.4 mm). The NMR spectrum has a multiplet at 1.2 (6 H), a doublet at 2.75 (2 H), a complex pattern at 3.45 (2 H), a quartet at 4.8 (1 H), and a complex pattern centered at 5.8 ppm (5 H).

***trans*-6-Chloro-1,5-hexadien-3-one (11b).** Pure **10b** was converted into **11b** by treatment first with acid and then base as described above for **8**. Again, the chlorodienone proved too unstable to isolate. The crude material, **11b**, exhibits carbonyl absorption at 1670 cm^{-1} and NMR absorption at 3.33 (doublet, 2 H) and 6.05 ppm (multiplet, 5 H).

The cis isomer, **11a**, was prepared from **10a** in the same manner and has carbonyl absorption at 1670 cm^{-1} and NMR bands at 3.50 (doublet, 2 H) and complex absorption centered at 6.1 ppm (5 H).

In a similar manner a cis–trans mixture of **11a** and **11b** could be obtained from **7** using the commercially available cis–trans mixture of 1,3-dichloropropene.

***exo*- and *endo*-5-Chlorobicyclo[2.1.1]hexan-2-one (15 and 16).** A mixture of crude *trans*- and *cis*-6-chloro-1,5-hexadien-3-one [obtained from 20.6 g (0.13 mol) of its cyanohydrin] was irradiated for 7 h in 2.2 l. of 4:1 ether–pentane. Removal of solvent followed by distillation through a 2-in. Vigreux column afforded 8.97 g (52%) of a mixture of *exo*-5-chlorobicyclo[2.1.1]hexan-2-one (**15**) and its endo isomer **16**, bp 48–56 °C (1.9 mm), in a ratio (by GLC) of 2:3. The mixture was fractionally distilled through a 24-in. spinning band column to afford 2.97 g of pure exo isomer[24] [bp 44 °C (1 mm)], three fractions of mixed isomers, and a fraction of 98% pure endo isomer, **16** [bp 48 °C (1 mm)]. Anal. Calcd for C_6H_7ClO: C, 54.96; H, 5.59. Found for **15**: C, 54.97; H, 5.35. For **16**: C, 55.50; H, 5.63.

Exo isomer **15** has its infrared carbonyl absorption at 1771 cm^{-1}.

The NMR spectrum[24] shows a triplet at 1.77 (J = 8.0 Hz, 1 H), a doublet of doublets at 2.26 (J = 5, 16 Hz, 1 H), a doublet at 2.41 (J = 16 Hz, 1 H), a multiplet at 2.74 (2 H), a multiplet at 3.24 (1 H), and a doublet at 4.07 ppm (J = 8.0 Hz, 1 H).

Endo isomer **16** exhibits carbonyl absorption at 1777 cm^{-1}. Its NMR spectrum[25] shows a doublet at 1.79 (J = 8 Hz, 1 H), a multiplet at 1.95 (1 H), a doublet of doublets at 2.08 (J = 16, 3 Hz, 1 H), a doublet of doublets at 2.49 (J = 16, 5 Hz, 1 H), a triplet at 3.05 (2 H), and a quartet at 4.4 ppm (1 H).

Photolysis of either **11a** or **11b** under similar conditions gave the same 2:3 ratio of **15:16**. This analysis is complicated by competitive isomerization of **11b** to **11a**, and by overirradiation decomposition of the products **15** and **16**.

3-Bromobicyclo[2.1.1]hexan-2-one (22). A 1-l. three-necked flask was equipped with a mechanical stirrer, an addition funnel, a septum inlet, and a Nujol bubbler. The flask was flame dried and placed under an argon atmosphere. A solution of 14.1 g (0.1 mol) of cyclohexylisopropylamine in 300 ml of dry tetrahydrofuran was introduced into the flask which was cooled in an ice–water bath. The solution was stirred continuously and then a solution of *n*-butyllithium (0.1 mol) in hexane was added dropwise over a period of 20 min by means of a hypodermic syringe. After the addition had been completed, the solution was stirred for 10 min at 0 °C and then it was cooled to −78 °C in a dry ice–acetone bath. A solution of 4.80 g (0.05 mol) of bicyclo[2.1.1]hexan-2-one in 200 ml of dry THF was added through an addition funnel over a period of 1 h.

A 2-l. three-necked dry flask with a mechanical stirrer was charged with 54.0 g (0.3 mol) of bromine and 200 ml of dry THF under an argon atmosphere and was cooled in a dry ice–acetone bath. The enolate anion solution was added dropwise into the bromine solution over a period of 1 h. After the addition had been completed, the resulting solution was stirred for 1 h at −78 °C and then was quenched with 10 ml of concentrated hydrochloric acid. Most of the solvent was removed on a rotary evaporator and then the residue was extracted with four 200-ml portions of ether. The ether solutions were combined and washed with saturated sodium bisulfite solution and sodium chloride solution, and then dried over anhydrous sodium sulfate. After the ether had been removed on a rotary evaporator, the crude product was distilled through a 5-in. Vigreux column under reduced pressure. The product was a light yellow liquid, bp 60–66 °C (0.9 mm), yield 4.0 g (46%). Anal. Calcd for C_6H_7BrO: C, 41.17; H, 4.03; Br, 45.65. Found: C, 41.33; H, 4.09; Br, 45.70.

The NMR spectrum (in CCl_4) has signals at 1.65–1.76 (doublet of doublets, J = 7.0 and 7.5 Hz, 1 H), 2.03–2.14 (doublet of doublets, J = 7.0 and 7.5 Hz, 1 H), 2.26–2.34 (multiplet, 1 H), 2.39–2.45 (multiplet, 1 H), 2.80–3.05 (multiplet, 2 H), and 4.26 (multiplet, 1 H). The infrared spectrum (in CCl_4) shows an intense carbonyl absorption band at 1773 cm^{-1}.

3-Chlorobicyclo[2.1.1]hexan-2-one was also prepared in a similar manner, though the yield was not optimized. The NMR spectrum (in CCl_4) of the chloro ketone shows signals at 1.60 (doublet of doublets, J = 7.0 and 7.5 Hz, 1 H), 2.08 (doublet of doublets, J = 7.0 and 7.5 Hz, 1 H), 2.21 (multiplet, 1 H), 2.35 (multiplet, 1 H), 2.91 (multiplet, 2 H), and 4.12 ppm (multiplet, 1 H), and the infrared spectrum (in CCl_4) exhibits its carbonyl band at 1780 cm^{-1}. Anal. Calcd for C_6H_7ClO: C, 55.17; H, 5.40. Found: C, 54.90; H, 5.63.

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Registry No.—**3**, 58208-02-9; **4**, 58208-03-0; *threo*-**5a**, 58208-04-1; *erythro*-**5a**, 19700-96-0; *threo*-**5b**, 18654-98-3; *erythro*-**5b**, 15895-82-6; **7a**, 5809-59-6; **7b** isomer 1, 58208-05-2; **7b** isomer 2, 58208-06-3; **8** isomer 1, 58208-07-4; **8**, isomer 2, 58208-08-5; **9**, 58208-09-6; **10a** isomer 1, 58208-10-9; **10a** isomer 2, 58208-11-0; **10b** isomer 1, 58208-12-1; **10b** isomer 2, 58219-00-4; **11a**, 54096-46-7; **11b**, 54096-47-8; **12**, 58191-39-2; **13**, 58191-42-7; **14**, 58208-13-2; **15**, 54096-48-9; **16**, 54096-49-0; **17b**, 58208-14-3; **22**, 58191-34-7; ethyl vinyl ether, 109-92-2; 2,3-dichloro-1-propene, 78-88-6; 5-chloro-1,5-hexadien-3-one cyanohydrin, 58208-15-4; *trans*-1,3-dichloro-1-propene, 10061-02-6; *cis*-1,3-dichloro-1-propene, 10061-01-5; bicyclo[2.1.1]hexan-2-one, 5164-64-7; 3-chlorobicyclo-[2.1.1]hexan-2-one, 58208-16-5.

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(24) The stereochemical assignment to **15** and **16** was based on the expected (ref 1a) long-range coupling between C_5 H and the endo C_6 H observed with **15** but not **16**. This was confirmed chemically (ref 7).

Chemical Transformations of Substituted Bicyclo[2.1.1]hexan-2-ones. Ring Contraction Studies and Synthesis of Tricyclo[2.2.0.0^{2,6}]hexan-3-one

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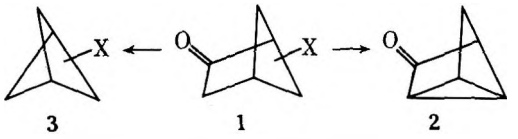
The synthesis of 3-formylbicyclo[2.1.1]hexan-2-one and 3-diazobicyclo[2.1.1]hexan-2-one has been accomplished. The latter, under ring contraction conditions, gives low yields of methylbicyclo[1.1.1]pentane carboxylate but primarily solvent insertion products. 2,3-Epoxybicyclo[2.1.1]hexane gives only bicyclo[2.1.1]hexan-2-one with base. Tricyclo[2.2.0.0^{2,6}]hexan-3-one has been prepared by dehydrochlorination of exo-5-chlorobicyclo[2.1.1]hexan-2-one.

One of the major reasons for our interest in the synthesis of functionally substituted bicyclo[2.1.1]hexan-2-ones, **1**,[1] was to investigate their further chemical transformation into either tricyclo[2.2.0.0^{2,6}]hexan-3-one (**2**) or into functionalized bicyclo[1.1.1]pentanes (**3**). The parent hydrocarbon of **2** is known,[2] and is now readily prepared,[3] but only two simple functionalized derivatives have been prepared,[4] and their chemistry has been virtually ignored. Substituted bicyclo[1.1.1]pentanes, **3**, have been prepared via free-radical substitution on the parent hydrocarbon,[5] itself available only in very low yield via either Wurtz cyclization[6] or decarbonylation of bicyclo[2.1.1]hexan-2-one.[7] In particular, since free-radical substitution on bicyclo[1.1.1]pentane gives predominantly 1-substituted products, we sought a ring contraction route to the 2-substituted derivatives.[8] In this paper we report the successful preparation of **2**,[9] the results of ring contraction studies on difunctional bicyclo[2.1.1]hexanes, and formation and chemistry of the enolate anion of bicyclo[2.1.1]hexan-2-one.

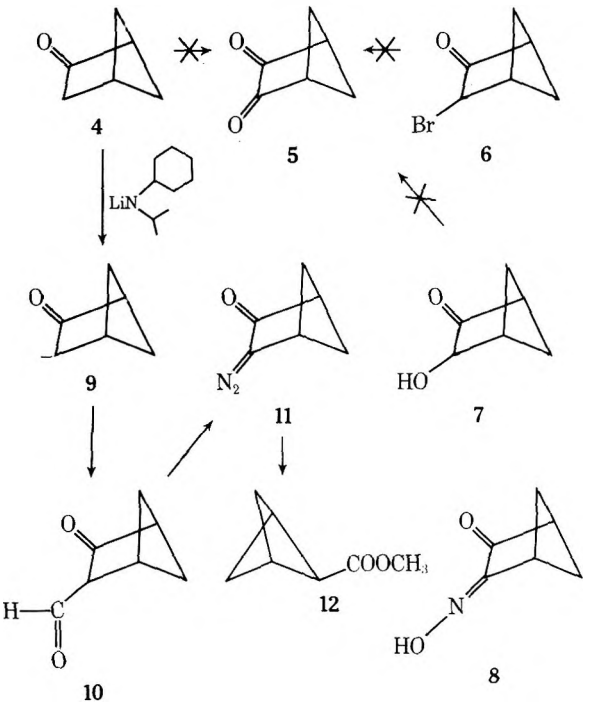


3 1 2

Synthesis of 3-Diazobicyclo[2.1.1]hexan-2-one (11). Our initial efforts were directed toward the preparation of diazo ketone **11**, an obvious precursor to both **2** and **3**. In particular, since the well-studied ring contraction of α-diazobicyclo[2.2.1]hexanones has resulted in numerous 5-substituted bicyclo[2.1.1]hexanes,[10] **11** was expected to give **12** on photolysis. The obvious route to **11** (Scheme I) was via α-diketone **5** and its mono-*p*-toluenesulfonylhydrazone. Unfortunately, selenium dioxide oxidation of **4**[11] under a variety of conditions[12] which produced bicyclo[2.2.1]heptane-2,3-dione from bicyclo[2.2.1]hexan-2-one all failed to give **5**. These conditions included heating at reflux in acetic acid, chlorobenzene, or *p*-xylene. This presumably reflects difficulty in preparing the highly strained[13] enol of **4**, since an even more highly strained, though heavily substituted, α-diketone has been reported.[14] Oxidation[15] of α-bromo ketone **6** or of **7**[16] all afforded recovered starting material. A variety of routes[17] to the α-oximino ketone **8**, a second possible precursor of **11**, were also unsuccessful. Likewise we were unable to prepare the enol ether, enol acetate, or any enamine of **4** under a wide range of conditions which were successful with the homologous bicyclo[2.2.1]heptan-2-one.

Although normally α substitution of ketones is more favorable via the enol (or enol acetate or enamine), our total lack of success forced us to attempt formation and trapping of enolate **9**. A variety of bases (potassium *tert*-butoxide in *tert*-butyl alcohol, sodium amide in ammonia, and sodium

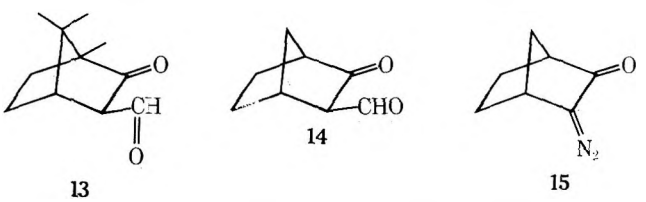
Scheme I



4 5 6 9 11 7 10 12 8

hydride in benzene) proved of little use, but lithium cyclohexylisopropylamide in THF was successful as demonstrated by trapping of **9** with D_2O, bromine,[1] and, for the purposes of ring contraction studies, with ethyl formate to give **10**.

The structure of **10** was easily assigned from its physical properties. One interesting feature was that NMR showed the α-formyl ketone to be essentially nonenolized in chloroform.[18] Even in Me_2SO-d_6,[19] the product is predominantly the 1,3-dicarbonyl tautomer. Comparison with 3-formylcamphor (**13**) and 3-formylnorcamphor (**14**) is given in Table I. The increase in strain resulting from introduction of two sp^2-hybridized centers into the bicyclo[2.1.1]hexane nucleus is obvious. Treatment of **10** with *p*-toluenesulfonyl



13 14 15

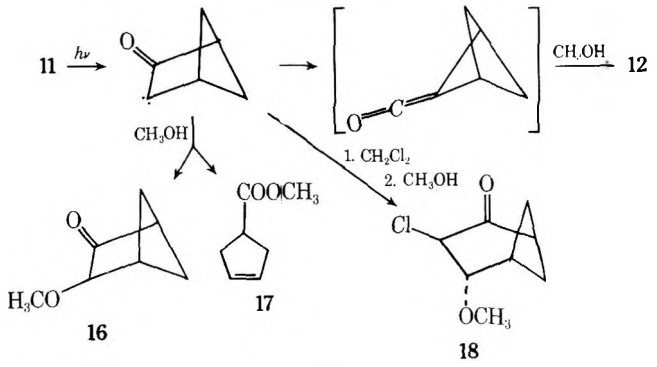
azide and triethylamine[20] gave a 61% yield of crude **11**, the physical properties of which compared well with those of **15**.[10a] Attempted distillation of **11** resulted in extensive decomposition.[21]

Table I. Percent Enol (by NMR)

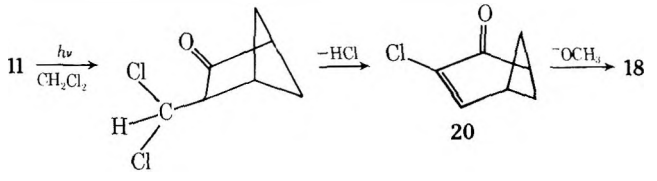
Compd	Solvent	
	$CHCl_3$	Me_2SO-d_6
10	0	12
13	55	100
14	33	91

Ring Contraction of 11. Photolysis of **11** was carried out under a wide variety of conditions,[10] summarized in Scheme II. In all cases a very low (<2%) yield of the desired ring contraction ester **12**[5,22] could be obtained, but the major products, **16** from irradiation in basic methanol, the corresponding alcohol from aqueous dioxane, and **18** from irradiation in dichloromethane[23] at −78 °C, all appear to arise from insertion of the α-diazo ketone into solvent taking preference over ring contraction to the highly strained ketene. Low yields of ring contraction products have been noted in other cases.[24] Apparently this route to 2-substituted *bicyclo[1.1.1]pentanes is even less satisfactory* than the original.[5]

Scheme II

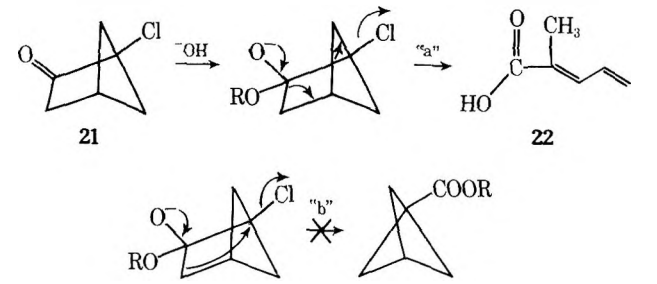


Compound **18** was the major product under conditions used by Eaton and Temme for a similar ring contraction synthesis of a highly strained [2.2.2]propellane.[23] The origin of **18** appears to be ring expansion of the carbene insertion product **19** to give **20** which, upon methoxide workup,[23] gives **18**. Indeed a compound with the molecular ion



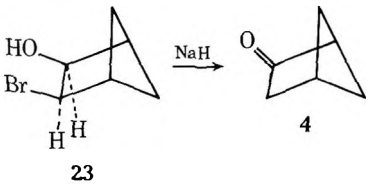
(GC–mass spectrum) expected for **20** could be detected in the crude photolysis product, but was not further characterized.

Other Ring Contraction Attempts. The availability of a number of bicyclo[2.1.1]hexane derivatives led us to attempt a series of ring contractions,[25,26] although the high strain of the desired products and less than favorable geometry for the quasi-Favorskii type pathways worked to prevent the desired reaction. Thus chloro ketone **21**[1] on

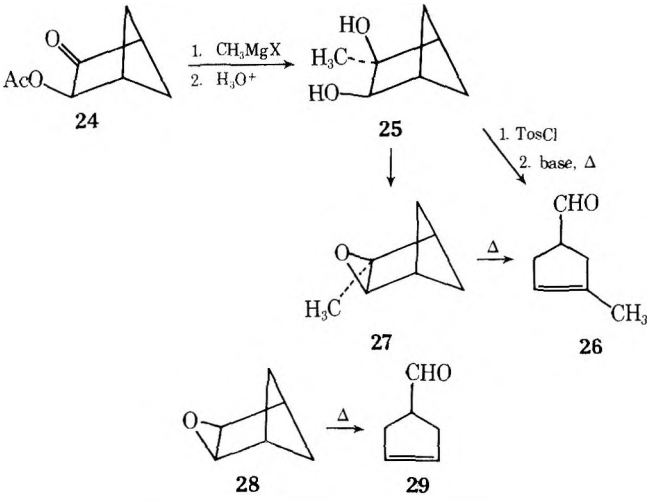


treatment with base gave the anion of **22** via path a followed by rearrangement, rather than ring contraction (path b).

Sodium borohydride reduction of **6** gave selectively the cis bromo alcohol **23**, which on treatment with sodium hydride gave only hydride shift product **4**. Acetoxy ketone **24**[1]

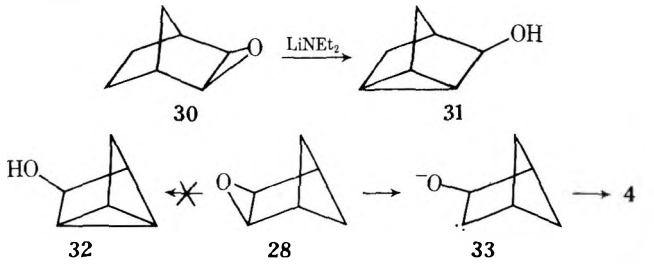


gave a single diol upon treatment with methyl Grignard reagent. The cis structure **25** is tentatively suggested in analogy with the results obtained in hydride reduction of **6** and on the basis of a strong intramolecular hydrogen bonded OH region in the infrared spectrum of **25**. Treatment of **25**



with tosyl chloride gave a monotosylate which with base gave two products, one of which was **26**, the other not yet identified but not a ring contraction product. Aldehyde **26** is presumably formed by thermolysis of **27**. Thermolysis of **28**, obtained by epoxidation of bicyclo[2.1.1]hex-2-ene[27] gives **29**. This thermal behavior has ample precedent.[28,29]

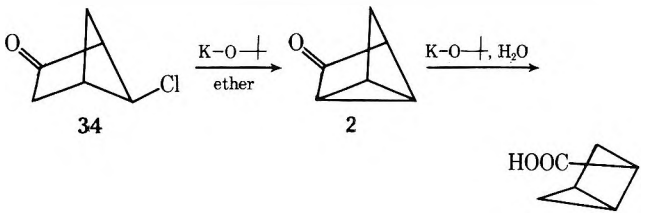
Tricyclo[2.2.0.0^{2,6}]hexan-3-one. Our initial attempt to prepare a derivative of the tricyclo[2.2.0.0^{2,6}]hexane ring system involved treatment of **28** with lithium diethylamide, a reaction known[29] to convert **30** into **31**. None of the de-



sired **32** was obtained; the only isolated product was bicyclo[2.1.1]hexan-2-one (**4**). The presumed intermediate, **33**, must therefore insert into the α C–H bond in preference to the β. The geometry for such β insertion in the bicyclo[2.1.1]hexane system is apparently far less favorable than that in the [2.2.1]heptanes, since the carbene derived from **4** gives only bicyclo[2.1.1]hex-2-ene and not tricyclo[2.2.0.0^{2,6}]hexane.[27b]

A successful synthesis of **2**[9] was obtained by base treatment of *exo*-5-chlorobicyclo[2.1.1]hexan-2-one (**34**)[1] under carefully controlled conditions (see Experimental Section). Such intramolecular displacements have become a valuable

route[4a,30] to strained bicyclic systems. The structure of **2** was supported by its particularly revealing NMR spec-



trum,[9] its mass spectrum, and infrared carbonyl absorption at 1775 and 1759 cm^{-1}. The latter compares well with that of the homologous nortricyclanone (1768 and 1755 cm^{-1}).[31] Haller–Bauer cleavage of **2** gave *endo*-bicyclo[2.1.0]pentane-2-carboxylic acid (**35**), the spectral properties of which were identical with those of authentic material.[32] The microwave spectrum of **2** has now been recorded[33] along with its high dipole moment (3.67 ± 0.02 D). A complete microwave study on the parent hydrocarbon has also been reported recently.[34] The chemistry of compound **2**, a dehydro derivative of already strained bicyclo[2.1.1]hexan-2-one,[11] bicyclo[2.2.0]hexan-2-one,[35] and bicyclo[2.1.1]hexan-5-one,[10a] is under present investigation.

Experimental Section[36]

3-Formylbicyclo[2.1.1]hexan-2-one (10). A 2-l. three-necked flask equipped with two addition funnels and a mechanical stirrer was connected by a glass tube to a 3-l. three-necked flask equipped with a mechanical stirrer. The system was thoroughly dried and kept under an argon atmosphere. THF (ca. 1 l.) and 72.5 ml (0.4 mol) of cyclohexylisopropylamine[37] were added to the first flask and cooled to 0 °C. With stirring and continued cooling, a solution of *n*-butyllithium in hexane was added dropwise over a 40-min period. After stirring at 0 °C for 1 h, the solution was further cooled via a dry ice–acetone bath after which bicyclo[2.1.1]hexan-2-one (**4**, 14.5 g, 0.15 mol) in 600 ml of THF was added dropwise over a 2-h period. Stirring at −78 °C was continued for 1 h. The resulting enolate solution was then transferred slowly using argon pressure, into the second flask which contained 54 ml (0.692 mol) of ethyl formate in 500 ml of dry THF at −78 °C. The addition took approximately 90 min, after which stirring was continued for 1 h at −78 °C followed by addition of 220 ml of 10% HCl. After warming to room temperature the organic layer was separated, the aqueous layer extracted five times with ether, and the combined organic layers worked up in the usual manner. The crude product was distilled through a 5-in. Vigreux column. After recovery of 1.5 g of **4** there was obtained 5.02 g (27%) of **10**, bp 57–60 °C (0.5 mm). There was a large pot residue of products which appeared to be aldol derived from attack of **9** on **4**.

Compound **10** has characteristic infrared absorption at 2825, 2730, 1769, and 1722 cm^{-1}. The mass spectrum shows the molecular ion at *m/e* 124 and the base peak at *m/e* 95. The NMR spectrum in $CDCl_3$ shows 1.64 (d of d, *J* = 7.5, 7.0 Hz, 1 H), 1.85 (d of d, *J* = 7.5, 7.0 Hz, 1 H), 2.31 (m, 2 H), 2.89 (m, 1 H), 3.10 (m, 1 H), 3.27 (d, *J* = 4 Hz, 1 H), and 9.75 ppm (s, 1 H). Anal. Calcd for $C_7H_8O_2$: C, 67.73; H, 6.50. Found: C, 67.59; H, 6.60.

3-Diazobicyclo[2.1.1]hexan-2-one (11). In a 500-ml round-bottom flask were mixed 9.90 g (0.08 mol) of **10**, 250 ml of methylene chloride, and 15.7 g (0.08 mol) of *p*-toluenesulfonyl azide. The flask was cooled to 0 °C and 55.8 g of triethylamine was added with stirring over a 30-min period. The mixture was stored overnight at 4 °C. A cold solution of 5.0 g of potassium hydroxide in 60 ml of water was added and the mixture stirred for 15 min at 0 °C. The methylene chloride layer was separated, the aqueous layer extracted twice with cold methylene chloride, and the combined methylene chloride layers washed with cold 1.4% KOH and cold water and dried in the refrigerator over sodium sulfate. The solvent was removed at 15 °C (5 mm) to give 11.61 g of crude diazo ketone. This material proved to be quite unstable and was best stored in solution at 0 °C.

The infrared spectrum shows significant bands at 2115, 2079, and 1727 cm^{-1}. The NMR spectrum has signals at 2.3 (m, 2 H), 2.47–2.80 (m, 3 H), and 3.27–3.5 ppm (m, 1 H).

Photolysis of 11. A. In Methanol. A solution of crude **11** (ca. one-fifth of the above solution) was concentrated in vacuo at 15 °C and dissolved in 1 l. of methanol containing 6.0 g of sodium bicarbonate.[38] The solution was irradiated at 0 °C with stirring through a Corex filter using a 450-W Hanovia lamp. The irradiation was followed by the disappearance of the diazo ketone bands in the infrared and required 6 h. Most of the solvent was removed through a 24-in. Vigreux column under reduced pressure and the yellow-brown residue worked up with pentane in the usual manner and evaporated to give 1.12 g of brown product. GLC analysis (10 ft, 10% NPGS) showed three peaks, A (10%), B (30%), and C (60%). Pure compounds were collected by preparative GLC.

Compound A was methylbicyclo[2.1.1]pentane 2-carboxylate (**12**). The infrared and NMR spectra were identical with those of the authentic compound.[5,22]

Compound B was methylcyclopent-3-ene carboxylate (**17**). The NMR spectrum has signals at 1.68 (d, *J* = 8.0 Hz, 4 H), 3.16 (d, *J* = 8.0 Hz, 1 H), 3.73 (s, 3 H), and 5.70 ppm (s, 2 H). The infrared spectrum exhibits absorption bands at 3060 (w), 3030 (w), 3000, 2965, 2860, and 1728 cm^{-1}. The mass spectrum shows the molecular ion at *m/e* 126.

Compound C was 3-methoxybicyclo[2.1.1]hexan-2-one (**16**), as established by its spectral data. The NMR spectrum has signals at 1.38–1.46 (t, *J* = 7.5 Hz, 1 H), 1.86–1.95 (t, *J* = 7.5 Hz, 1 H), 2.16–2.28 (m, 2 H), 2.76–2.86 (m, 1 H), 2.87–2.95 (m, 1 H), 3.56 (s, 3 H), and 3.74 ppm (s, further splitting, 1 H). The infrared spectrum indicates absorption bands at 2995, 2965, 2880, 2830, and 1766 cm^{-1}. The mass spectrum has its molecular ion at *m/e* 126.

B. In Dioxane–Water. Approximately one-tenth of the solution of **11** was concentrated and dissolved in 216 ml of purified dioxane and 108 ml of water containing 3.75 g of sodium bicarbonate. Irradiation was carried out followed as above. Most of the solvent was removed at 40 °C (5 mm) and the remaining aqueous layer extracted three times with ether to remove neutral products. Work-up of this material afforded 0.39 g of a yellow liquid shown by GLC (10 ft, 10% NPGS) to contain at least three products, the major one of which was identical in retention time and mass spectrum with 3-hydroxybicyclo[2.1.1]hexan-2-one.[1]

The basic layer from above was acidified with 6 N HCl and worked up with methylene chloride. Evaporation of the solvent afforded 0.11 g of crude material which was treated with excess ethereal diazomethane. GLC analysis, as above, showed A and B in an approximate 1:1 ratio. The components were identified by their retention times and mass spectra.

C. In Methylene Chloride. A solution of 9.0 g of crude **11** was dissolved in 1 l. of methylene chloride and irradiated at −78 °C for 5 h. The methylene chloride solution at this time showed a peak at 2381 cm^{-1} in the infrared. The cold solution was then treated at −78° with sodium methoxide prepared from 1.84 g of sodium and 200 ml of methanol. The resulting solution was stirred for 24 h and worked up with ether to give 7.14 g of crude residue. Short-path distillation afforded two fractions and a large tarry residue. The first, 0.19 g, bp 80–90 °C (35 mm), consisted mainly of **12** contaminated with a second component (GLC). The second fraction, 1.53 g (11%), bp 75–78 °C (3.0 mm), was assigned the structure *trans*-3-chloro-4-methoxybicyclo[3.1.1]heptan-2-one (**18**) on the basis of its spectral data.

The infrared spectrum shows carbonyl absorption at 1727 cm^{-1}. The mass spectrum has its molecular ion at *m/e* 174, 176 ($C_8H_{11}O_2Cl$). The NMR spectrum shows 2.27–2.46 (m, 4 H), 2.84–3.14 (m, 2 H), 3.61 (s, 3 H), 5.16 ppm (s, 2 H). Anal. Calcd for $C_8H_{11}O_2Cl$: C, 55.02; H, 6.35. Found: C, 54.84; H, 6.33.

(*E*)-2-Methyl-2,4-pentadienecarboxylic Acid (22). A mixture of 77.5 mg (0.6 mmol) of **21**[1] and 39 ml of 2 M KOH was placed in a glass pyrolysis tube, sealed under nitrogen, and heated at 155 °C for 18 h. The cooled solution was extracted with methylene chloride and worked up to give 34.6 mg (48%) of a light yellow solid. Pure **22** was collected by preparative GLC (10 ft, 10% FFAP) as a white solid, mp 63–65 °C, infrared and uv spectrum as reported[39] (mp 64–65 °C). The NMR spectrum was also consistent: 1.96 (s, 3 H), 5.3–5.7 (m, 2 H), 6.33–7.40 (m, 2 H), 10.66 ppm (s, 1 H).

***cis*-3-Bromobicyclo[2.1.1]hexan-2-ol (23).** A solution of 1.05 g (6 mmol) of **6** in 20 ml of absolute ethanol was treated for 1 h with 0.074 g (1.8 mmol) of sodium borohydride, quenched with 0.3 ml of acetone, and worked up with ether to give 0.83 g of a light yellow liquid. Short-path distillation gave 0.75 g (72%) of **23**, bp 41–42 °C (0.4 mm). GLC analysis (8 ft, 5% FFAP, 15 ft SE-30, or 10 ft 5% DEGS) indicated the presence of only one compound. The NMR spectrum shows 1.05 (t, some further splitting, 1 H), 1.80 (m, 3 H), 2.47 (d, 1 H), 2.55 (m, 1 H), 2.7 (m, 1 H), 4.12 (t, *J* = 6 Hz, 1 H), and 4.55 ppm (d, *J* = 6 Hz, 1 H). The 6-Hz coupling between C_2H and C_3H is consistent with the assigned cis stereochemistry.[40]

Anal. Calcd for C_6H_9BrO: C, 40.91; H, 5.12 Found: C, 40.51; H, 5.20.

2-Methylbicyclo[2.1.1]hexane-2,3-diol (25). An ice-cold solution of 2.5 g (16 mmol) of **24**[1] in 20 ml of dry ether was treated with 80 mmol of methylmagnesium bromide, and the solution was then heated at reflux for 4 hr, cooled, acidified, and worked up in the usual manner. Removal of solvent gave 1.91 g (92%) of **25** as an oily liquid, molecularly distilled to give 1.15 g of **25** [bp 59 °C (0.05 mm)]. The infrared spectrum was as expected. The NMR shows 0.7–1.9 (m, 4 H), 1.37 (s, 3 H), 2.3 (m, 2 H), 3.50 (s, 1 H), 4.2 ppm (broad, 2 H).

3-Methyl-3-cyclopentenecarboxaldehyde (26). A solution of 1.91 g (0.015 mol) of **25** in 15 ml of dry pyridine was treated with 2.99 g (0.016 mol) of *p*-toluenesulfonyl chloride at 0 °C for 35 h, then acidified and worked up to give 2.83 g of oily tosylate. Without purification this material was dissolved in 50 ml of *tert*-butyl alcohol, 1.12 g (0.01 mol) of potassium *tert*-butoxide was added, and the solution was heated at reflux for 5 h. Work-up afforded 0.80 g of a yellow liquid. GLC (10 ft, 10% Carbowax 20M) showed two components, A and B, in approximately equal amounts. Both were collected by preparative GLC.

Component A was assigned structure **26** on the basis of its spectral data. Important infrared bands are at 3020, 2855, 2700, and 1725 cm^{-1}. The NMR spectrum has 1.79 (s, 3 H), 2.20–2.30 (m, 5 H), 5.30 (m, 1 H), and 9.61 ppm (s, 1 H). The mass spectrum has the molecular ion at *m/e* 110 and base peak at *m/e* 95.

Component B has not yet been identified but was clearly not the desired 1-acetylbicyclo[1.1.1]pentane.

2,3-Epoxybicyclo[2.1.1]hexane (28). Bicyclo[2.1.1]hex-2-ene[27b] (2.20 g, 0.0275 mol), 5.83 g of sodium carbonate, and 35 ml of methylene chloride were cooled to 0 °C with stirring and treated with 5.88 g (0.029 mol) of *m*-chloroperbenzoic acid over an 80-min period. The solution was stirred for an additional 2 h, filtered, and worked up to give 3.0 g of crude **28** which proved to be unstable above 40 °C. Pure material was obtained by preparative GLC from a 5 ft 3% SE-30 column at 40 °C.The NMR spectrum has broad absorption from 1.20–2.40 (4 H), 2.48 (s, 2 H), and 3.66 ppm (s, 2 H). Anal. Calcd for C_6H_8O: C, 74.97; H, 8.38. Found: C, 74.75; H, 8.42.

3-Cyclopentene-1-carboxyaldehyde (29). The epoxide **28** was isomerized to **29** under a variety of conditions: neat at 80 °C for 18 h; in solution in THF at reflux overnight; or in benzene at 60 °C for 6 h in the presence of anhydrous zinc bromide.

The aldehyde **29** has ir, NMR, and mass spectral data identical with those of authentic **29**.[41] The spectra of **29** and **26** were similar, and were used in the assignment of structure to **26**.

Bicyclo[2.1.1]hexan-2-one (4). A. From 23. A mixture of 1.77 g (0.01 mol) of **23** and 0.425 g (0.01 mol) of sodium hydride in 7 ml of dry diglyme was heated at 80 °C for 2 days under nitrogen which was swept into a dry ice–acetone trap. The trap contained no aldehyde (infrared). The reaction mixture was poured onto ice and worked up in the usual manner to give 1.41 g of a residue which showed (GLC, 10 ft, 10% DEGS) the presence of starting material **23**, and **4** in a ratio of 2:1. Component **4** was collected and identified by its characteristic spectra.

B. From 28. Seventeen milliliters of a 22% solution (2.67 M) of commercial *n*-butyllithium in hexane was added to an ice-cold solution of 3.8 g (0.045 mol) of diethylamine in 15 ml of dry benzene and then stirred for 20 min. A solution of 1.44 g (0.015 mol) of **28** in 12 ml of benzene was added dropwise over a 30-min period and the solution stirred for an additional 65 h at room temperature. After work-up in the normal manner, most of the solvent was removed in vacuo at room temperature. GLC analysis of the residue showed only one product, **4**, in 46% yield. Ketone **4** was collected and characterized by its infrared and NMR spectra.

Under essentially these same conditions **31** was obtained from **30** in 43% yield.

Tricyclo[2.2.0.0^{2,6}]hexan-3-one (2). To a 250-ml flask was added 1.37 g (12.2 mmol) of freshly prepared potassium *tert*-butoxide and 60 ml of dry ether. The suspension was stirred and cooled in an ice–salt bath while adding 0.774 g (5.95 mmol) of **34**[1] in 30 ml of ether dropwise over a 90-min period. The mixture was maintained at −5 °C and became yellow-brown. After 6 h the suspension was filtered, and the ether was washed immediately with five 5-ml portions of saturated salt solution and dried over magnesium sulfate. The drying agent was removed and the ether distilled at 10 °C and aspirator pressure to give 0.46 g of crude product. GC and NMR analysis showed this to contain a small amount of *tert*-butyl alcohol. Pure **2** was collected by preparative GLC using a 5 ft glass column of 6.2% SE-30 with a column temperature of 58 °C. The compound is thermally unstable and base labile. The infrared spectrum has significant bands at 3060, 3030, 2950, 2870, 1775, and 1759 cm^{-1}. The ultraviolet spectrum has λ_{max} (cyclohexane) at 254 nm (ϵ 30). The NMR spectrum at 220 MHz has been reported in detail.[9] The mass spectrum shows the molecular ion as the parent peak at *m/e* 94. Anal. Calcd for C_6H_6O: C, 76.57; H, 6.43. Found: C, 76.66; H, 6.64.

***endo*-Bicyclo[2.1.0]pentane-2-carboxylic Acid (35).** To a 25-ml flask under an argon atmosphere was added 0.97 g (8.7 mmol) of freshly sublimed potassium *tert*-butoxide, 2.6 ml of dimethyl sulfoxide, and 45 μl of water. A solution of **2** (0.104 g, 1.1 mmol) in 0.5 ml of dimethyl sulfoxide was added dropwise from a syringe to the stirred suspension. Stirring at room temperature was continued for 4 h after which the mixture was poured onto ice, acidified, extracted four times with ether, and worked up to give 0.065 g (52%) of **35** which has an NMR spectrum identical with that of authentic **35**.[32,42]

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Registry No.—**2**, 54096-50-3; **4**, 5164-64-7; **6**, 58191-34-7; **10**, 58191-35-8; **11**, 58191-36-9; **12**, 22287-39-4; **16**, 58191-37-0; **17**, 58101-60-3; **18**, 58191-38-1; **21**, 58191-39-2; **22**, 58191-40-5; **23**, 58191-41-6; **24**, 58191-42-7; **25**, 58191-43-8; **26**, 58191-44-9; **28**, 58191-45-0; **29**, 20145-35-1; **34**, 54096-48-9; **35**, 58191-46-1; *p*-toluenesulfonyl azide, 941-55-9; bicyclo[2.1.1]hex-2-ene, 822-41-3; *m*-chloroperbenzoic acid, 937-14-4.

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(37) Diisopropylamine could also be used but a side product, diisopropylformamide, was difficult to separate from **10** by distillation.
(38) Sodium bicarbonate was added to somewhat suppress formation of **17** which apparently arises from **11** via a carbonium ion pathway. Ether **16** was the major product with and without this addition so we favor its formation via the ketocarbene.
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Molecular Design by Cycloaddition Reactions. XXIV.[1] Stereospecific Cycloaddition Reactions of Dibenzo[4,5-*c*]furotropone

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Marked differences in reactivities between [4,5-*c*]furotropone and dibenzo[4,5-*c*]furotropone in their cycloaddition reactions are observed. Reactions of dibenzo[4,5-*c*]furotropone, readily prepared from 3,6-epoxy-3,6-dihydrotribenzocycloheptatrienone with 3,6-diphenyltetrazine, with some electron-deficient and -rich dienophiles gave [4 + 2] adducts in good yields. The structures of these adducts were determined by spectral means and supported by mechanistic considerations.

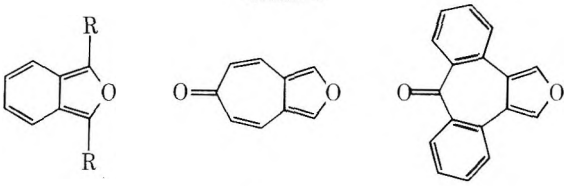
We have already investigated the photochemical and thermal cycloaddition reactions of benzoheterocycles such as isobenzofuran derivatives with some cyclic diene and triene compounds.[2]

Synthesis of a highly reactive isobenzofuran (**1a**) has also been reported; however, it rapidly polymerizes.[3] 1,3-Diphenylisobenzofuran (**1b**) is commercially available and has been used extensively as a trapping agent for reactive dienes but is very sensitive to oxygen.[4] By contrast, [4,5-*c*]furotropone (**2**) has proved to be inert to the Diels–Alder reactions even with a highly reactive dienophile as tetracyanoethylene.[5]

Therefore, it was of interest to prepare derivatives of these ring systems and to examine their reactivities.

The present paper describes a ready method for the preparation of dibenzo[4,5-*c*]furotropone (**3**) (dibenzo[*a*,*e*]furo[3,4-*c*]-8*H*-cycloheptatrienone),[6] and its reactivity in cycloaddition reactions with some dienophiles.

Chart I



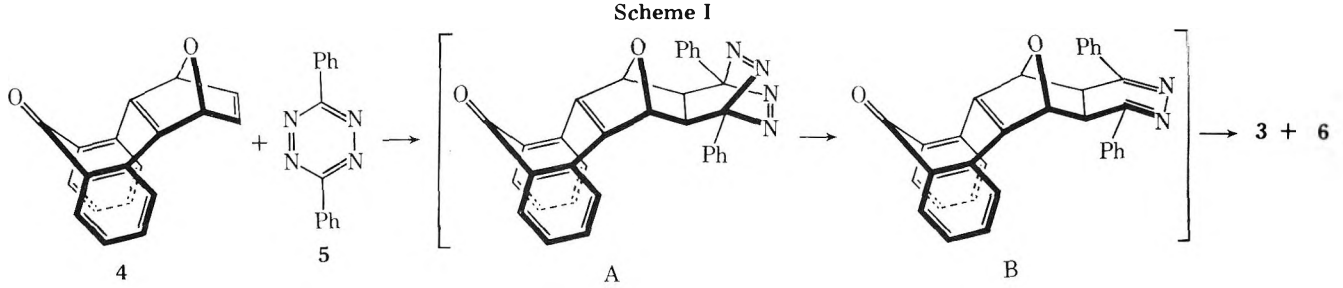
1a, R = H
b, R = Ph

2 **3**

Results and Discussion

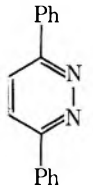
Preparation of Dibenzo[4,5-*c*]furotropone. Reaction of 3,6-epoxy-3,6-dihydrotribenzocycloheptatrienone (**4**)[6] with 3,6-diphenyltetrazine (**5**) under reflux in benzene afforded dibenzo[4,5-c]furotropone (**3**) in a high yield together with 3,6-diphenylpyridazine (**6**) as evidenced by the immediate disappearance of the purple color of the solution. Presumably the formation of **3** might proceed via initially

Scheme I



4 **5** **A** **B** → 3 + 6

produced [4 + 2] adduct (A) followed by loss of nitrogen to give an unstable intermediate (B) which decomposed rapidly to **3** and **6** as shown in Scheme I. These intermediates

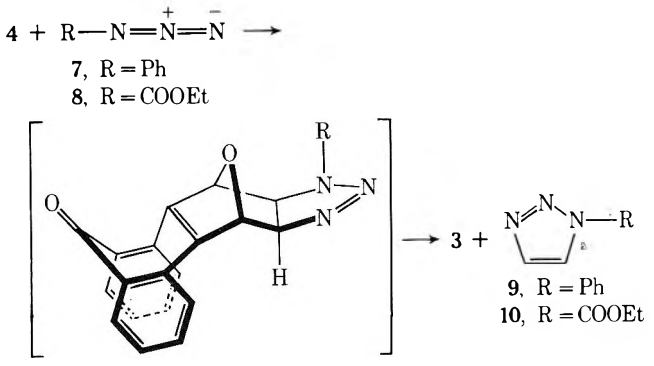


6

could not be isolated directly from the reaction mixture owing to their extreme thermal lability even under mild conditions.

Similarly, the reactions of **4** with phenyl azide (**7**) or ethoxycarbonyl azide (**8**) under the same conditions gave also compound **3** in a moderate yield (Scheme II).

Scheme II



7, R = Ph
8, R = COOEt

9, R = Ph
10, R = COOEt

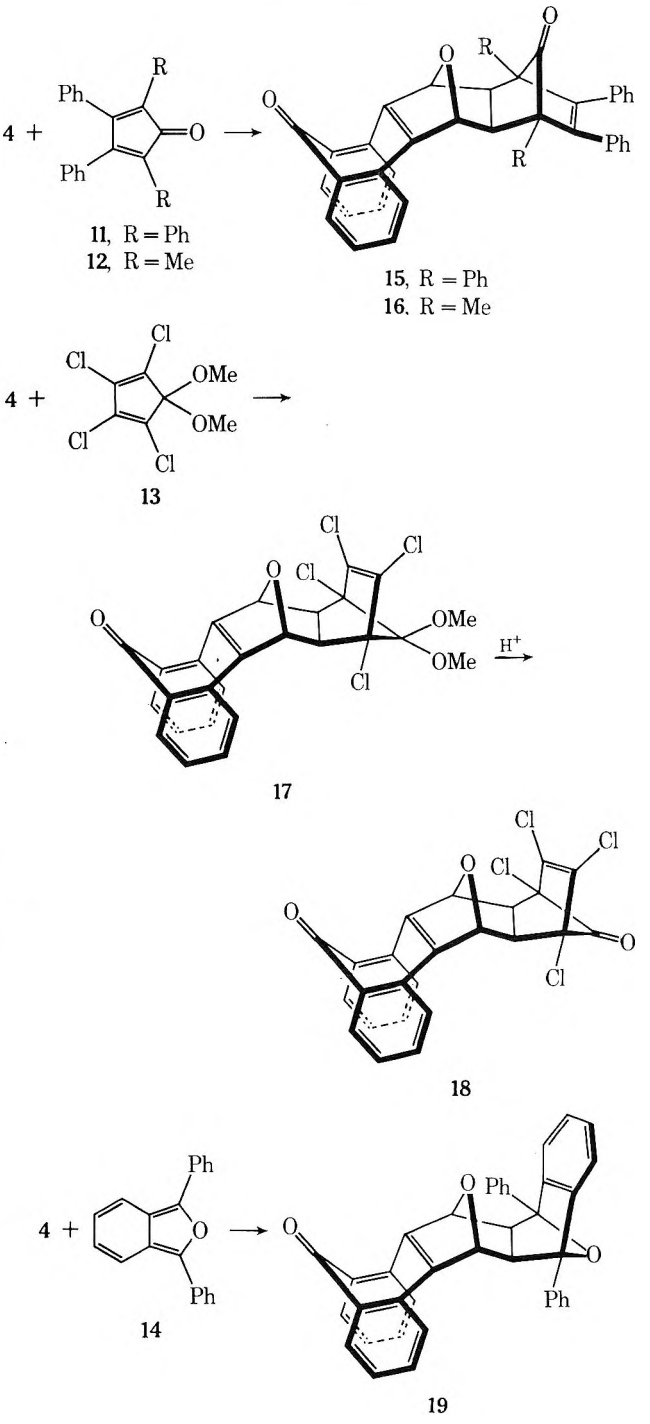
By contrast, the cycloaddition reactions of **4** with tetracyclone (**11**),[6] 2,5-dimethyl-3,4-diphenylcyclopentadienone (**12**), 1,1-dimethoxy-2,3,4,5-tetrachloropentadienone (**13**), and 1,3-diphenylisobenzofuran (**14**) under reflux in benzene gave [2 + 4] adducts, **15**, **16**, **17**, and **19**, respectively (Scheme III). The NMR data for these adducts are summarized in Table I;[7] the adducts **15** and **16** were confirmed by their NMR spectra to take the exo,exo configuration by the absence of vicinal couplings.[8] On the other hand, the adduct **17** was assigned to be the exo,endo configuration by the absence of vicinal coupling and by hydrolysis of **17** with 80% sulfuric acid to give compound **18**, which showed an endo methine proton signal at δ 1.60 due to influence of the bridged carbonyl group. Similarly, the exo,endo configuration of compound **19** was determined by the NMR inspection, which will be discussed separately (see Chart III).

Further heating of these adducts, **15**, **16**, and **18**, in chlorobenzene at 120 °C gave compound **3** in a moderate yield, but heating of the adduct **19** gave only the starting material even under more drastic conditions for much longer times.

From these results, it is concluded that the reaction of **4** with **5** proceeded at lower temperature than that of **4** with the cyclopentadienone derivatives and it is a convenient preparation of the dibenzo[4,5-c]furotropone (**3**) in a high yield.

Cycloaddition Reaction of Dibenzo[4,5-*c*]furotropone. The cycloaddition of dibenzo[4,5-c]furotropone (**3**) with *N*-phenylmaleimide (**20**), *p*-benzoquinone (**21**), dimethyl acetylenedicarboxylate (**22**), and tetracyanoethylene (**23**) as electron-deficient dienophiles afforded [4 + 2] cycloadducts, **24** (75%), **25** (50%), **26** (88%), and **27** (90%), respectively (Scheme IV).

Scheme III



11, R = Ph
12, R = Me

15, R = Ph
16, R = Me

13

17

18

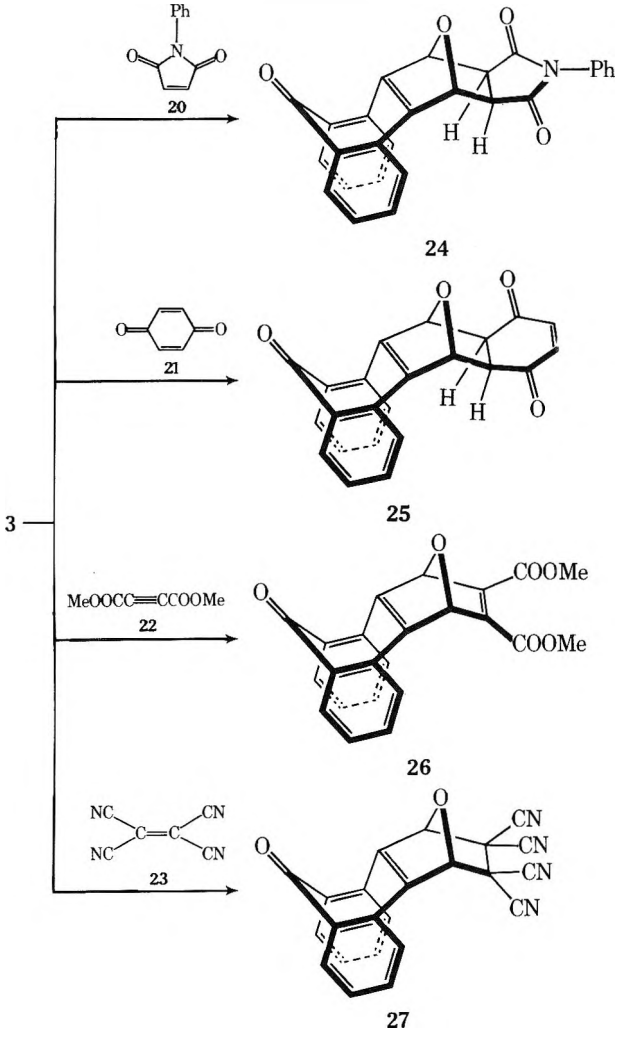
14

19

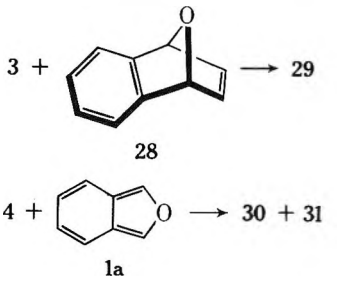
The absence of appreciable coupling between two methine proton signals in compounds **24** and **25** indicates the exo configuration.

The reaction of **3** with oxabenzonorbornadiene (1,4-epoxy-1,4-dihydronaphthalene, **28**) as an electron-rich and strained olefin gave a 1:1 adduct **29** in 85% yield (Scheme V). This adduct was thermally stable even under more drastic conditions for much longer times, suggesting no interconversions to the isomers. The NMR spectrum of compound **29** showed bridgehead protons at δ 2.78 (2 H, d, J = 4.1 Hz), 4.95 (2 H, s) and 5.77 (2 H, d, J = 4.1 Hz), and aromatic protons at δ 7.60–8.15 (12 H, m). However, the exact configuration for **29** could not be determined based on the NMR inspection, for which the two possible stereoisomeric structures (endo,exo and exo,endo configurations) are assumable. Therefore, the reaction of **4** with isobenzofuran, generated from thermal decomposition of the Diels–Alder

Scheme IV



Scheme V



adduct of **28** and **11**,[9] was attempted, and a mixture of isomeric 1:1 adducts **30** and **31** was obtained in the ratio of 1:1.1 in total yield of 54%. Interestingly, significant shifts of the chemical shifts and coupling constants for the oxygen bridgehead protons and the center bridgehead protons are observed in the NMR spectra of these adducts as summarized in Table II.[7]

Among the possible stereoisomers (C–F) as shown in Chart II, only the exo,exo isomer (C) was assigned for the adduct **31** because of the absence of appreciable coupling between H_a and H_b and between H_b and H_c;[10] the center bridgehead proton H_b lying over the aromatic rings showed at δ 2.19 due to the benzene ring current effect. The structures of the exo,endo (D) and endo,exo isomers (E) were examined by the stereomodel.[10] In the exo,endo isomer (D), the H_a proton lying over the oxabenzonorbornene moiety will be shielded by the benzene ring current effect and should appear as a singlet with no vicinal couplings. Therefore, the structure **30** was assigned to be the exo,endo cycloadduct. In the endo,exo isomer (E), the H_a proton will be deshielded by the anisotropic effect of the bridge oxygen atom in comparison with H_c and should be coupled with the vicinal hydrogen H_b, while the H_c proton lying over the dibenzo groups will be shielded by the benzene ring current effect and should appear as a singlet with no vicinal couplings.

Thus, the structure **29** was assigned to have the endo,exo configuration. By contrast, the adduct **19** was assigned to have the exo,endo configuration by the absence of vicinal coupling, which showed the center bridgehead proton H_b at δ 3.0 similar to that of compound **30** (δ 3.03).

On these evidences, it is concluded that the cycloaddition reactions of the dibenzo[4,5-c]furotropone with dienophiles under thermal conditions would proceed by a directive influence on the incoming dienophiles by steric interactions as depicted in Chart III; only two structures G and K might be formed by most favorable approaches of the dienophiles.

The above results show that the dibenzo[4,5-c]furotropone (**3**) is a valuable trapping agent for a number of ethyl-

Chart II

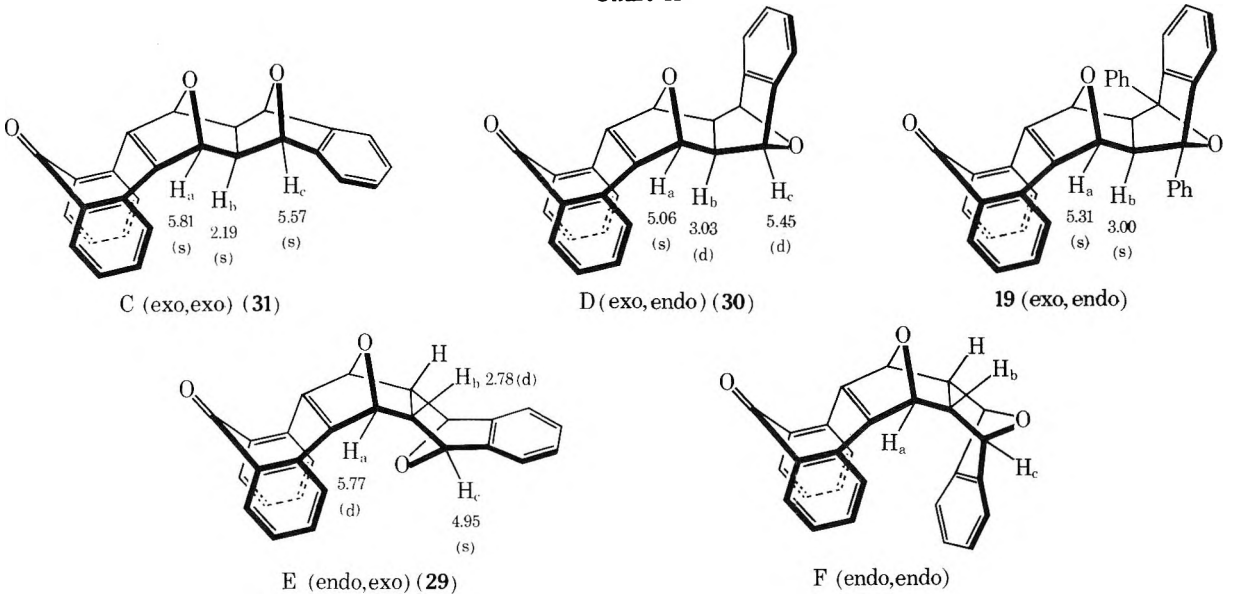
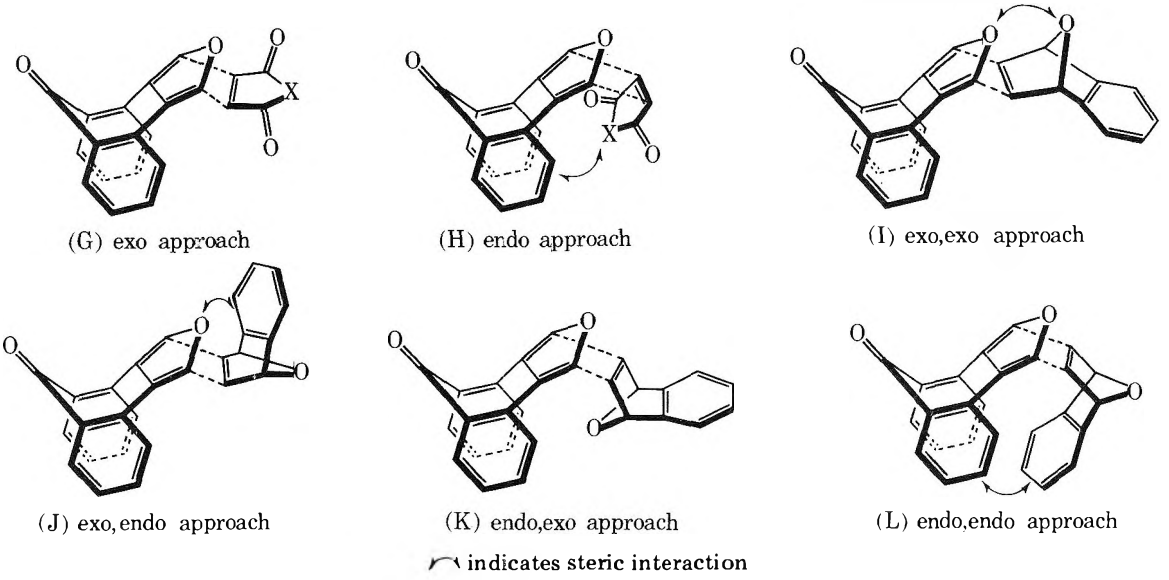


Chart III. Possible Approaches in Cycloaddition Reactions of Diene with Dienophile



enic dienophiles and more reactive than the [4,5-c]furotropone (2) in the cycloaddition reactions.

Experimental Section

The melting points were measured with a Yanagimoto micromelting point apparatus. Microanalyses were performed with a Perkin-Elmer 240 elemental analyzer. The NMR spectra were taken with a JEOL C-60-XL recording spectrometer with tetramethylsilane as an internal standard and the chemical shifts are expressed in δ values. The ir spectra were taken with a Jasco Model IRA-1 grating infrared spectrophotometer.

Reaction of 3,6-Epoxy-3,6-dihydrotribenzocycloheptatrienone (4) with 3,6-Diphenyl-1,2,4,5-tetrazine (5). A solution of compound **4** (2.18 g) and 3,6-diphenyl-1,2,4,5-tetrazine (**5**, 1.87 g) in benzene (80 ml) was refluxed for 3 h. Then 3,6-diphenylpyridazine (**6**, 1.79 g, 94%) was precipitated in the cooled solution. The filtrate was evaporated to dryness and recrystallization from methanol gave dibenzo[4,5-c]furotropone (**3**, 1.52 g, 82%) as colorless needles, mp 105–106 °C (lit.[6] 100–102 °C).

Reaction of 4 with Phenyl Azide (7). A solution of **4** (545 mg) and phenyl azide (**7**, 238 mg) in benzene (20 ml) was stirred at room temperature for 4 h. Evaporation to dryness and chromatography on silica gel using benzene–chloroform (1:1) gave **3** (340 mg, 77%) and phenyltriazole (**9**, 180 mg, 69%).

Reaction of 4 with Ethoxycarbonyl Azide (8). A solution of **4** (545 mg) and ethoxycarbonyl azide (8, 230 mg) in benzene (20 ml) was refluxed for 5 h. Similar work-up gave **3** (270 mg, 47%) and *N*-ethoxycarbonyltriazole (**10**, 100 mg, 40%).

Reaction of 4 with Tetracyclone (11). A solution of **4** (545 mg) and tetracyclone (745 mg) in benzene (30 ml) was refluxed for 1 day. Recrystallization from benzene gave a 1:1 adduct (**15**, 940 mg, 83%) as colorless needles: mp 210–212 °C; ir (KBr) 1780, 1640 cm^{-1}.

Anal. Calcd for $C_{48}H_{32}O_3$: C, 89.43: H, 5.01. Found: C, 89.30; H, 5.14.

Reaction of 4 with 2,5-Dimethyl-3,4-diphenylcyclopentadienone (12). A solution of **4** (545 mg) and a dimer of **12** (520 mg) in benzene (30 ml) was refluxed for 1 day. Recrystallization from benzene gave a 1:1 adduct (**16**, 430 mg, 68%) as colorless needles: mp 239–240 °C; ir (KBr) 1640, 1780 cm^{-1}.

Anal. Calcd for $C_{38}H_{28}O_3$: C, 85.70; H, 5.30. Found: C, 85.45; H, 5.35.

Reaction of 4 with 1,1-Dimethoxy-2,3,4,5-tetrachlorocyclopentadienone (13). A solution of **4** (272 mg) and the ketal **13** (300 mg) in benzene (30 ml) was refluxed for 15 h. Evaporation to dryness and chromatography on silica gel using benzene–chloroform (1:1) gave a 1:1 adduct (**17**, 390 mg, 90%) as colorless needles: mp 285–289 °C (benzene–chloroform); ir (KBr) 1640 cm^{-1}.

Anal. Calcd for $C_{26}H_{18}O_4Cl_4$: C, 60.82; H, 3.51. Found: C, 60.66; H, 3.49.

Hydrolysis of Compound 17. The adduct **17** (390 mg) was added to 80% H_2SO_4 (5 ml), and stirred at room temperature for 5 h. The solution was neutralized with aqueous $NaHCO_3$ (20 ml), and extracted with benzene (40 ml). Evaporation to dryness and recrystallization gave **18** (130 mg, 35%) as colorless needles: mp 235–237 °C ($CHCl_3$); ir (KBr) 1780, 1640 cm^{-1}.

Anal. Calcd for $C_{24}H_{12}O_3Cl_4$: C, 58.80; H, 2.47. Found: C, 58.82; H, 2.50.

Reaction of 4 with 1,3-Diphenylisobenzofuran (14). A solution of **4** (408 mg) and 1,3-diphenylisobenzofuran (**14**, 405 mg) in benzene (30 ml) was refluxed for 4 h. Evaporation to dryness and recrystallization gave a 1:1 adduct (**19**, 740 mg, 91%) as colorless needles: mp >300 °C (benzene–$CHCl_3$); ir (KBr) 1640 cm^{-1}.

Anal. Calcd for $C_{39}H_{26}O_3$: C, 86.32; H, 4.83. Found: C, 86.12; H, 5.06.

Pyrolysis of 15. A solution of the adduct **15** (300 mg) in chlorobenzene (10 ml) was heated in a sealed tube at 120 °C for 4 days. Chromatography on silica gel using benzene gave compound **3** (78 mg, 70%) and 1,2,3,4-tetraphenylbenzene (154 mg, 90%).

Pyrolysis of 16. A solution of the adduct **16** (300 mg) in chlorobenzene (10 ml) was heated in a sealed tube at 120 °C for 4 days. Similar work-up gave compound **3** (70 mg, 50%) and 1,4-dimethyl-2,3-diphenylbenzene (56 mg, 39%).

Pyrolysis of 18. A solution of the adduct **18** (100 mg) in chlorobenzene (5 ml) was heated in a sealed tube at 120 °C for 18 h. Evaporation to dryness and chromatography on silica gel using benzene gave compound **3** (25 mg, 58.6%) and 1,2,3,4-tetrachlorobenzene (40 mg, 95%).

Reaction of Dibenzo[4,5-c]furotropone (3) with *N*-Phenylmaleimide (20). A solution of **3** (246 mg) and *N*-phenylmaleimide (**20**, 207 mg) in chlorobenzene (10 ml) was heated at 120 °C for 7 h in a sealed tube. After evaporation to dryness chromatography on silica gel using benzene–chloroform gave a 1:1 adduct (**24**, 310 mg, 74%) as colorless needles: mp 278–279 °C ($CHCl_3$); ir (KBr) 1790, 1720, 1640 cm^{-1}.

Anal. Calcd for $C_{27}H_{17}O_4N$: C, 77.32; H, 4.09; N, 3.34. Found: C, 77.05; H, 4.00; N, 3.51.

Reaction of 3 with *p*-Benzoquinone (21). A solution of **3** (246 mg) and *p*-benzoquinone (**21**, 115 mg) in chlorobenzene (20 ml) was heated at 120 °C for 19 h. Similar work-up gave a 1:1 adduct (**25**, 120 mg, 50.3%) as yellow needles: mp 151–154 °C ($CHCl_3$); ir (KBr) 1665, 1640 cm^{-1}.

Anal. Calcd for $C_{23}H_{14}O_4$: C, 77.96; H, 3.98. Found: C, 78.10; H, 3.88.

Reaction of 3 with Dimethyl Acetylenedicarboxylate (22). A solution of **3** (246 mg) and dimethyl acetylenedicarboxylate (**22**, 170 mg) in chlorobenzene (10 ml) was heated at 120 °C for 7 h. Similar work-up gave a 1:1 adduct (**26**, 230 mg, 88%) as yellow needles: mp 199–201 °C ($CHCl_3$); ir (KBr) 1730, 1710, 1640 cm^{-1}.

Anal. Calcd for $C_{23}H_{16}O_6$: C, 71.13; H, 4.15. Found: C, 71.45; H, 4.26.

Reaction of 3 with Tetracyanoethylene (23). A solution of **3** (123 mg) and tetracyanoethylene (**23**, 64 mg) in benzene (20 ml) was stirred at room temperature for 1 day. Evaporation to dryness and recrystallization from benzene gave a 1:1 adduct (**27**) in a quantitative yield: mp 110–114 °C (benzene); ir (KBr) 1640 cm^{-1}. This compound was thermally unstable.

Anal. Calcd for $C_{23}H_{10}O_2N_4$: C, 73.77; H, 2.67; N, 14.42. Found: C, 73.70; H, 2.70; N, 14.51.

Reaction of 3 with Oxabenzonorbornadiene (28). A solution of **3** (246 mg) and oxabenzonorbornadiene (**28**, 144 mg) in chlorobenzene (4 ml) was heated in a sealed tube at 100 °C for 11 h. Evaporation to dryness and chromatography on silica gel using benzene–chloroform (1:1) gave a 1:1 adduct (**29**, 330 mg, 85%), mp 250–252 °C (benzene–$CHCl_3$).

Anal. Calcd for $C_{27}H_{18}O_3$: C, 83.06; H, 4.65. Found: C, 83.24; H, 4.51.

Reaction of 3 with Isobenzofuran (1a). A solution of the 1:1 adduct[9] of **28** and tetracyclone (275 mg) and **4** (136 mg) in *p*-xylene (10 ml) was heated in a sealed tube at 170 °C for 1 day. Work-up as described above gave compound **30** (50 mg) and **31** (55 mg) (total yield of 54%), and 1,2,3,4-tetraphenylbenzene (190 mg, 99.4%).

30: mp 294–295 °C ($CHCl_3$).

Anal. Calcd for $C_{27}H_{18}O_3$: C, 83.06; H, 4.65. Found: C, 82.96; H, 4.94.

31: mp > 300 °C ($CHCl_3$).

Anal. Calcd for $C_{27}H_{18}O_3$: C, 83.06; H, 4.65. Found: C, 82.99; H, 4.70.

Registry No.—**1a**, 270-75-7; **3**, 20457-17-4; **4**, 16567-36-5; **5**, 6830-78-0; **6**, 891-22-5; **7**, 622-37-7; **8**, 817-87-8; **11**, 479-33-4; **12**, 26307-17-5; **13**, 2207-27-4; **14**, 5471-63-6; **15**, 58241-44-4; **16**, 58241-45-5; **17**, 58241-53-5; **18**, 58241-46-6; **19**, 58241-52-4; **20**, 941-69-5; **21**, 106-51-4; **22**, 762-42-5; **23**, 670-54-2; **24**, 58241-47-7; **25**, 58241-48-8; **26**, 58241-49-9; **27**, 58241-50-2; **28**, 573-57-9; **29**, 58241-51-3; **30**, 58267-64-4; **31**, 58267-65-5.

Supplementary Material Available. Tables I and II, NMR data (2 pages). Ordering information is given on any current masthead page.

References and Notes

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(7) Tables I and II (NMR spectra) appear in the microfilm edition; see paragraph at end of paper regarding supplementary material.
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Gas Phase, Uncatalyzed Thermolysis of 3-Homoadamantyl Acetate

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3-Homoadamantyl acetate has been shown to undergo unimolecular gas phase thermolysis with $E_a = 48.1 \pm 0.4$ kcal/mol. The variation in product distribution with temperature, and upon 4 deuteration, has been taken as evidence for parallel pathways of thermal decomposition. A mechanistic scheme has been proposed involving competition of well-precedented six-membered and seven-membered transition states giving rise to two products (**3** and **4**) and one unique product (**2**), respectively. Moreover, substrates, such as **8** and **9**, which are structurally incapable of realizing a low energy seven-membered or a six-membered cyclic pathway which does not result in bridgehead olefin formation, seem to be completely stable under conditions which lead to extensive decomposition of **1**. However, the formation of an exocyclic cyclopropane at a bridgehead or an equivalent (relatively) stable diradical leading to **2a** or **2b**, stemming from the thermolysis of **1**, appears to take place readily via a seven-membered transition state.

Recently Kovacic and Adams[1] have disclosed that the gas phase thermolysis of 3-homoadamantyl acetate (**1**) in a Vycor (quartz)-packed reactor tube at 500–600 °C produces two olefinic products in a combined yield of ca. 30–40%, accompanied by a host of other products, each in very small amounts. Their report was particularly intriguing because the predominant products, 4-methyleneprotoadamantane (**2**) and 3-vinylnoradamantane (**3**), obtained in a ratio of ca. 2.5:1, obviously resulted from skeletal rearrangements.

We have for some time been interested in the course of the normal, six-centered, retroene thermolysis reaction by which the usual, unrearranged olefins are formed, as well as that of the less common thermolysis from which only rearranged products originate through the operation of a seven-centered or homoretroene pathway.[2] The data of Kovacic and Adams,[1] who did not provide any mechanistic interpretation, indicated that the relative quantities of **2** and **3** in the complex product mixture varied somewhat. This suggested the possibility that the multiplicity of products may arise from either a competition of reaction mechanisms or rate-determining formation of a common intermediate with more than one rapid, product-forming pathway available to it. In the search for evidence to elucidate the reaction routes producing **2** and **3**, under highly reproducible, noncatalytic, thermolysis conditions, a kinetic investigation of the thermolysis of **1** and related substrates was undertaken.

Results and Discussion

In contrast to the preparative scale, quartz-packed, hot tube previously employed[1] the kinetic studies of interest were carried out with a micro, gas phase, flow system utilizing a gold-coil reactor which has been established[3] to minimize or eliminate the wall-catalyzed reactions commonly found to take place in glass or quartz reactors. This system has been shown to exhibit even less catalytic activity in ester thermolysis than the well-seasoned reactor of Maccoll[4] which is most widely employed[5] as a means of *diminishing* the recognized catalytic activity of glass and quartz-based reactors.

The thermal decomposition of **1** studied in the gold-coil microreactor over the temperature range 445–500 °C followed a simple, unimolecular rate law. The rate data gathered from these measurements are compiled in Table I. In sharp contrast to the results obtained[1] with the use of the (apparently) catalytic Vycor reactor in the temperature range of 500–600 °C, only three, clean products are ob-

Table I. Gas Phase Thermolysis of 3-Homoadamantyl Acetate in the Gold Coil Microreactor

Temp, °C[a]	Rate, s^{-1} [a]	
497	1.09; 1.10	E_a = 48.1 ± 0.4 kcal/mol
488	0.75; 0.74	log A = 13.67 ± 0.16
476	0.46; 0.47	$\Delta S^{\ddagger}$ = 0.2 ± 0.6 eu
466	0.28; 0.28	
455	0.18; 0.17	$k = \frac{-\log C/C_0}{t}$ where C = concn of 3-homoadamantyl acetate; C_0 = initial concn
445	0.11; 0.11	

[a] Temperatures and rates rounded off after least-squares analysis.

served here at some 50–150 °C lower temperatures. Within the limits of GLC (6 ft, 5% UCW-98 on Chromosorb W AW, 70–225 °C, 20 °C/min, *o*-dichlorobenzene internal standard) detection, small side products (<1%) are completely absent in the effluent of the gold-coil microreactor. The first and second product peaks were indeed identical with those previously reported, respectively, the (vinyl) **3** and (methylene) **2** products. The third product peak, predicated on the basis of a seven-centered transition state, was identified as 4-homoadamantene (**4**). The proportions of products **3** and **4** relative to **2** increase somewhat in proceeding from the lowest to the highest temperatures of study. Since these products were shown to be stable under the reaction conditions, the results are consistent with **1** decomposing via two parallel paths having activation parameters of comparable magnitudes. While the activation parameters are not abnormally large (i.e., close to E_a = 48 kcal), they are more characteristic of the decomposition of a secondary rather than of a typical tertiary acetate; *tert*-butyl acetate is given variously as E_a = 40.5–42.1 kcal.[6]

The occurrence of two parallel pathways of decomposition of **1** is supported by evidence obtained in thermolysis of 4,4-dideuterio-3-homoadamantyl acetate (**1-*d***). Under identical reactor conditions the proportions of **3** and **4** maintained the same ratio with respect to each other as they had in the product composition arising from the protio substrate **1**. Moreover, a comparison of the rate constants for unimolecular decomposition of the protio (**1**) and deuterio (**1-*d***) substrates at 477 °C (k_H = 0.47 and k_D = 0.34 s^{-1}) affords a clear indication of a primary kinetic deuterium isotope effect;[7] that is to say, the thermolysis process can be identified as one in which hydrogen transfer is occurring in a transition state similar in structure to that of the cyclic, symmetrical activation step for six-centered retroene, thermolysis mechanisms.[8]

This conclusion can be reached when the data are analyzed in the following way.

Parallel Reaction Pathways[9a]

$$1 \xrightarrow{k_1} 2$$

$$1 \xrightarrow{k_2} 3 + 4$$

Since $k_H^{477\,°C}$ = 0.47 and $k_D^{477\,°C}$ = 0.34, and at 477 °C for a symmetrical transition state k_H/k_D = 2.1,[7] and since only the *sum* of components **3** + **4** is diminished by 4 deuteration, then at this temperature

$$k_1 + k_2 = 0.47 \qquad \text{for } \mathbf{1}$$

$$k_1 + \frac{k_2}{2.1} = 0.34 \qquad \text{for } \mathbf{1}\text{-}d$$

Thus, k_1 = 0.22 and k_2 = 0.25 s^{-1} for decomposition of **1** at 477 °C; from these values it is computed that the product composition should consist of 47% of **2** and 52% of **3** + **4**, in close agreement with experimental observation. The GLC shows the peak of **3** well resolved and equal to 30% of the total product. The peaks of **2** and **4** are partly overlapped and for most purposes cannot be completely separated. Nonetheless, the computation above confirms that **4** is formed to the extent of 22% in the decomposition of **1**.

For the deuterio analogue **1-*d*** the decomposition rate constants are calculated to be respectively k_1^D = 0.22 and k_2^D = 0.12. The calculated proportions of the products on this basis are respectively **2-*d*** 63%, **3-*d*** 21%, and **4-*d*** 16%. This is in close agreement with the most accurate (GLC) determination of the well-resolved, deuterated product **3-*d*** = 22%. These results can be readily construed to support symmetrical, concerted transition states[8] for both (k_1 and k_2) pathways of hydrogen transfer in the gas phase thermolysis of 3-homoadamantyl acetate.

An attractive way of representing these concerted pathways of decomposition, each involving skeletal rearrangements, is given in Chart I. Path A involves concerted hydrogen (deuterium) abstraction in a six-centered transition state accompanied by two nearly equally probable rearrangements: (1) delocalization of the C_5–C_6 bond via route a_i, (2) migration of the C_5 hydrogen to C_3 in synchronism with the departure of the C_3–oxygen bond via route a_{ii}. Path B depicts a seven-centered transition state reminiscent of one identified for the thermal rearrangement of neophyl esters.[2a,b] It involves here, however, the transient formation of a strained cyclopropane structure which may be presumed to rearrange spontaneously[9b] (as shown by route b_i) to the observed olefin **2**.

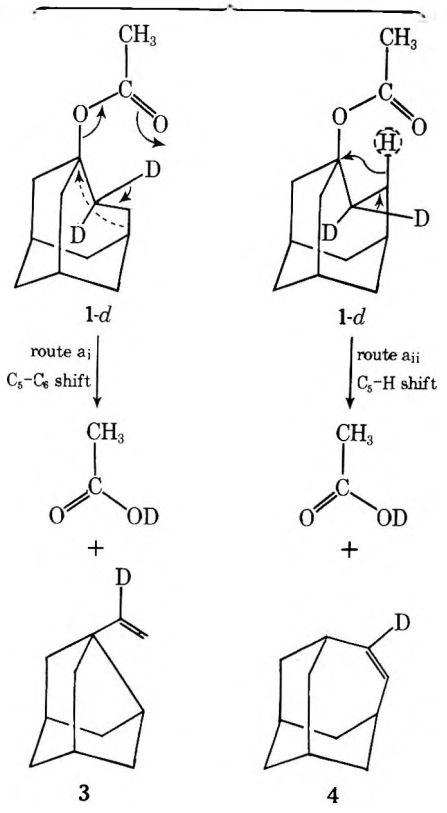
A mechanistic alternative involving formation of the bridgehead olefin intermediates, 2- and 3-homoadamantenes (**6** and **7**, respectively), can be visualized with the aid of the reaction scheme[9c] depicted in Chart II. An initial rate-determining, concerted, six-centered elimination is drawn to produce the highly strained products **6** and **7**, with **7** designated as the precursor of approximately 60% of the observed product composition. While this may appear to be also a very eligible and even an attractive interpretation of the results obtained here with the gold-coil microreactor, serious reservations come to mind upon detailed consideration of the data.

First it must be emphasized that thermolysis of **1** in the gold-coil microreactor occurs with an activation energy similar to what is normal for formation of unstrained olefins via (uncatalyzed) cyclic, concerted, transition states of thermolysis, which, by definition, reflect the product energies. The well-grounded hypothesis of Wiseman[10] guides us to the conclusion that a cyclic concerted transition state leading to the bridgehead olefins **6** and **7** should reflect, respectively, the very high strain energies of *trans*-cycloheptene and *trans*-cyclohexene. The results of Allinger[11] using molecular mechanics procedures have verified by these methods the approximately 20 kcal of excess strain energy in *trans*-cycloheptene compared to the stable cis isomer, and for *trans*- vs. *cis*-cyclohexene 42 kcal. It can therefore

Chart I

Path A

six-membered transition states



Path B

seven-membered transition states

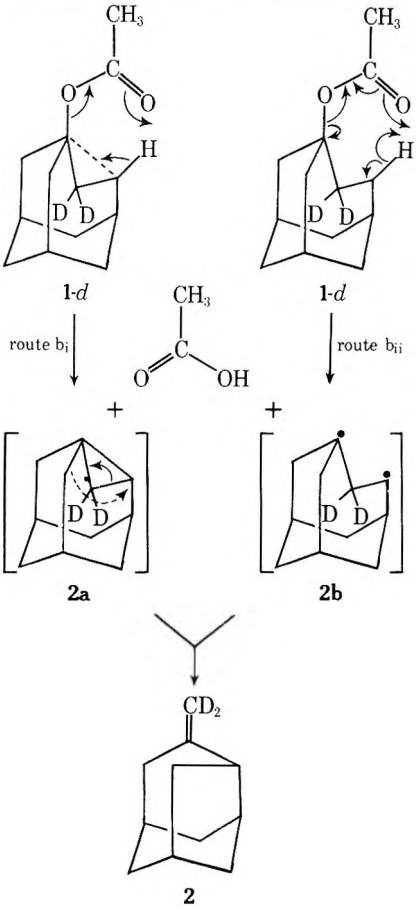
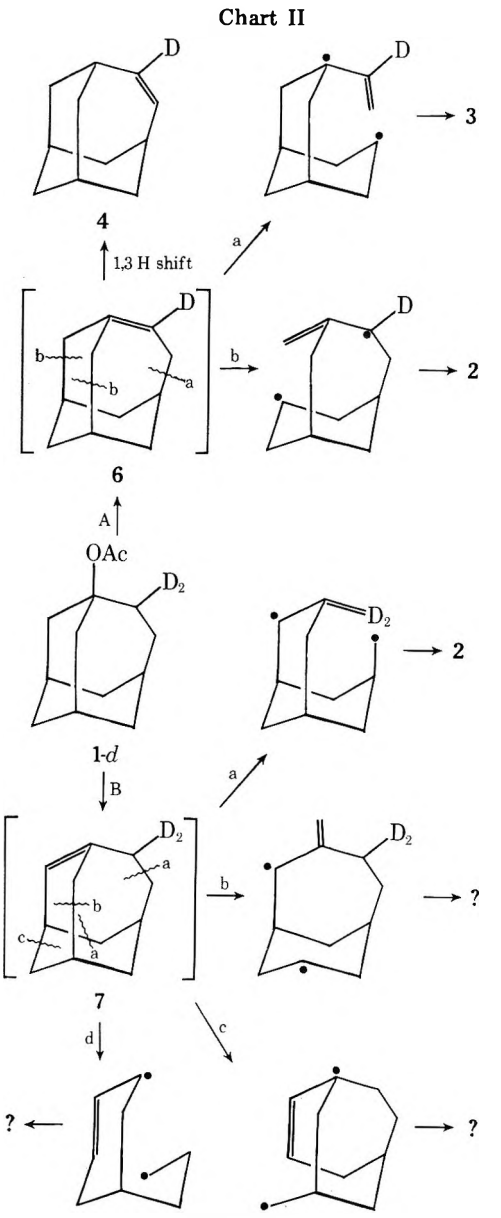


Chart II



be deduced that a concerted reaction process leading to the bridgehead olefins **6** and **7**, as pictured in Chart II, should involve activation energies which could be as much as 20–40 kcal higher than corresponding reaction mechanisms producing unstrained olefins. Since the observed thermolysis of **1** in the gold-coil microreactor takes place with activation parameters which are normal for the formation of (say) propylene from isopropyl acetate, the mechanism of Chart II does not seem appropriate.

Secondly, the nature and magnitude of the kinetic deuterium isotope effect is consistent with the six-membered, concerted transition states of rearrangement proposed for the routes (a_i) and (a_{ii}) shown to produce **3** and **4** in Chart I. The approximately 6–7 kcal increase in E_a compared to *tert*-butyl acetate thermolysis seems to be a reasonable increment of energy necessary to effect the rearrangement step. It is of no greater magnitude than the E_a distinguishing the thermolysis of ordinary secondary and tertiary acetates.

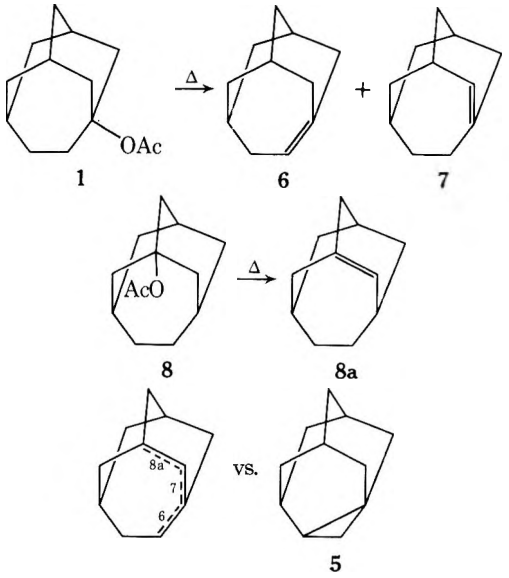
The third reaction pathway (route b_i) by which product **2** originates seems at first glance to be of surprisingly low E_a, since it is shown to involve formation of a strained bridgehead cyclopropane at an energy level which is characteristic of the formation of unstrained olefins. It is conceivable that the greater stability of benzocyclopropene (an

isolable intermediate compared to benzyne[12]) provides some justification for the assumption of far greater stability for a transient bridgehead cyclopropane with the strain energy of the *trans*-bicyclo[5.1.0]heptane intermediate **5** than for the *trans*-cycloheptene of which the bridgehead structure of **6** is constructed.[10]

On the other hand, it may not be necessary to assume formation of a transient cyclopropane in route b_i if this pathway is not fully concerted. Under such circumstances in an alternative path (route b_{ii}) a diradical intermediate **2b** might be realized, in which the radical centers are stabilized at neighboring tertiary and secondary carbon centers geometrically accommodated for rearrangement into the observed product **2**.

Considerations on the Feasibility of Bridgehead Olefin and Bridgehead Cyclopropane Intermediates in Ester Thermolysis. In the effort to shed some light on the possible formation of a transient, bridgehead olefin during thermolysis of substrates like **1**, experiments were devised based on the following reasoning. If bridgehead olefin formation is not energetically unfeasible, at energy levels consistent with observations on **1**, then it *must be* assumed that 2- and 3-homoadamantenes, though possessing respectively the very different energies[10] characteristic of *trans*-cyclohexene and cycloheptene, *nonetheless are equally stable. This assumption is imperative to be consistent with the fact that increasing E_a by ca. 1.1 kcal through introduction of deuterium* (*in* **1-d**) *is observed to change the product mixture considerably.* This assumption therefore anticipates that 1-homoadamantyl acetate (**8**) must undergo rate-determining thermolysis to the homoadamantene **8a** (Chart III) under comparable conditions and with approximately the same ease attending the decomposition of **1**. According to the mechanistic scheme of Chart II the formation of the bridgehead olefin **7** must be involved to account for some 60% of the observed product composition. Since **7**, like the putative product **8a**, is a bridgehead *trans*-cyclohexene strained olefin,[10] the activation requirements for formation of **7** and **8a** (i.e., the E_a for thermolysis of **1** and **8**) should be expected to be very similar.

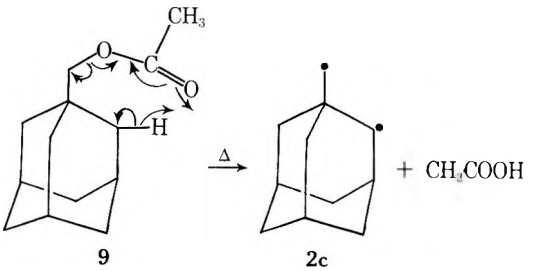
Chart III. View of Bridgehead Possibilities in Various Homoadamantenes



On the other hand, the decomposition of **8** is structurally excluded from taking place via cyclic, concerted pathways similar to those outlined in Chart I, i.e., pathways presumably of lower activation requirement than those involving bridgehead olefin intermediates. Consequently, **8** can be expected to be stable under conditions which cause **1** to undergo extensive thermolysis, since bridgehead olefin formation cannot be avoided in the course of an uncatalyzed decomposition of **8**. In this connection it is found that, for a residence time during which 50% decomposition of **1** has taken place at 485 °C, **8** *is completely unreacted.* Moreover, for the same residence time in the gold-coil reactor, a temperature of 600 °C is necessary to effect the disappearance of 50% of **8**, fully 100 °C above the maximum temperature required for practically complete decomposition of **1**. That is to say, an activation energy some 12 kcal greater than for **1** is necessary to produce thermolysis of **8**, a reaction which (if it can only occur via a cyclic concerted mechanism) must result in the transient formation of a bridgehead olefin. As a result of these data it may be said that the mechanistic course depicted in Chart II is improbable.

Finally, some consideration was given to the course of thermolysis of adamantylcarbinyl acetate[13] (**9**). Under solvolytic conditions[14,15] this substrate can be involved in a mobile equilibrium with the homoadamantyl substrate **1**. However, when subjected to thermolysis at temperatures up to 600 °C it would appear that **9** does not have available to it the facile pathways for cyclic concerted thermal decomposition established by the results obtained with **1**. At these temperatures, for short dwell times in the flow reactor at which **1** is completely decomposed, **9** shows unusual resistance. In excess of 600 °C where decomposition does begin to occur, only the formation of a large number of unidentified products believed to arise from various homolytic bond cleavages is observed to take place.

This observation may be of considerable significance in assessing the feasibility of the routes b_i and b_{ii} leading respectively to product **2**. Thus, if **9** could undergo a low-energy, retroene transition state of thermolysis similar to that considered in route b_i (Chart I) it should produce the same cyclopropane intermediate. The observed failure to achieve this result could be due to either of two causes: (a) the substrate **9** undergoes the route b_i decomposition, corresponding to the transition state of a primary acetate thermolysis whose E_a is usually at least 7 kcal higher[6] than for corresponding tertiary acetates; or (b) both **1** and **9** possess the geometric requirements for forming a diradical intermediate via a nonconcerted pathway, but the diradical **2b** leading from **1**, having a tertiary radical center, is considerably more stabilized than **2c** leading from **9** and having a corresponding unstable primary radical center (which is at least 6 kcal less stable[16]).



Experimental Section

1-Adamantylcarbinyl acetate was prepared according to the procedure of Norlander et al.,[14] bp 110–112 °C (2.5 mm) [lit.[14] bp 110–113 °C (2.5 mm)].

1-Adamantyl-1′,1′-dideuteriocarbinyl tosylate was prepared according to the method of Stetter et al.[17] except that 1-adamantyl-1′,1′-dideuteriocarbinol (from the lithium aluminum deuteride reduction of 1-adamantylcarboxylic acid) was used, mp 78.0–78.5 °C (lit.[14] mp 76 °C).

4,4 Dideuterio-3-homoadamantyl acetate was prepared according to the method of Schleyer et al.[14,15]

1-Homoadamantyl acetate was prepared from a sample of 1-homoadamantanol kindly provided by S. Godleski and P. v. R. Schleyer.

Registry No.—**1**, 14504-81-5.

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(9) (a) The use of a single rate constant k_2 as the parameter characterizing the total rate of formation of **3** and **4** via six-centered reaction pathways is merely a convenience. This constant may actually be factored into two separate constants for the formation of **3** and **4**, respectively, whose rates varies little over the temperature range of study. (b) It is common to assume that the preference for the indicated mode (in Chart I) of cyclopropane ring opening, among a host of alternatives, is an expression of the stereoelectronic factors controlling the course of concerted rearrangements. (c) B. L. Adams, Ph.D. Dissertation, University of Wisconsin—Milwaukee, 1974. We are obliged for the opportunity to examine Dr. Adams' thesis during the course of preparing this manuscript for publication. The principal evidence supporting the preference expressed for the bridgehead olefin mechanism (Chart II) is the reported finding of 20% of **2**-d_1 arising from the Vycor tube thermolysis[1] of **1**-*d*. This, however, is unconvincing because (a) there is no clear indication given as to the location of the single deuterium in the purported **2**-d_1 structure, and (b) even the NMR spectrum[1] reported for the product **3** indicates that it is incompletely monodeuterated. The suspicion that surface-catalyzed (wall) reactions are significant in Vycor tube reactors[1] (packed or unpacked) may be inferred from the following results disclosed by the studies of Dr. Adams: (1) the presence of both **2**-d_2 and **2**-d_1 as well as **3**-d_0 in the Vycor tube reaction product, (2) the fact that **4** comprises only 2% of the product mixture from the Vycor tube compared with ten times (ca. 22% of **4**) as much from the gold-coil microreactor, and (3) the low (30–40%) total yield of the two major products realized from the Vycor tube, compared with the quantitative conversion to only three products from the noncatalytic microreactor.
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Syntheses of the Pentacyclo[6.3.0.0^{2,6}.0^{3,10}.0^{5,9}]undecyl (Trishomocubyl) and Tetracyclo[6.3.0.0^{4,11}.0^{5,9}]undeca-2,6-dienyl (Homohypostrophenyl) Systems[1]

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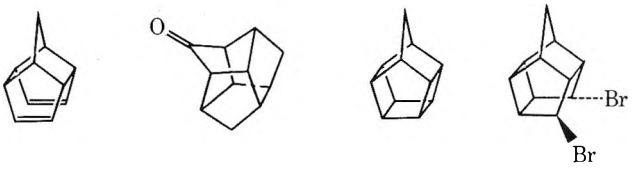
Acid-catalyzed rearrangement of the diol **6** obtained from the product of photocyclization of the *p*-benzoquinone–cyclopentadiene Diels–Alder adduct produces the C_3-symmetrical trishomocubane system. Diiodotrishomocubane (**1c**) produced either directly from **6** or by a sequence via bistosylate **1f** provides a good source of the diene homohypostrophene (**2**) by reductive dehalogenation. The hydrocarbon trishomocubane (**1a**) can be obtained in high yield from the diiodide **1c** by reduction with metallic zinc under acidic conditions.

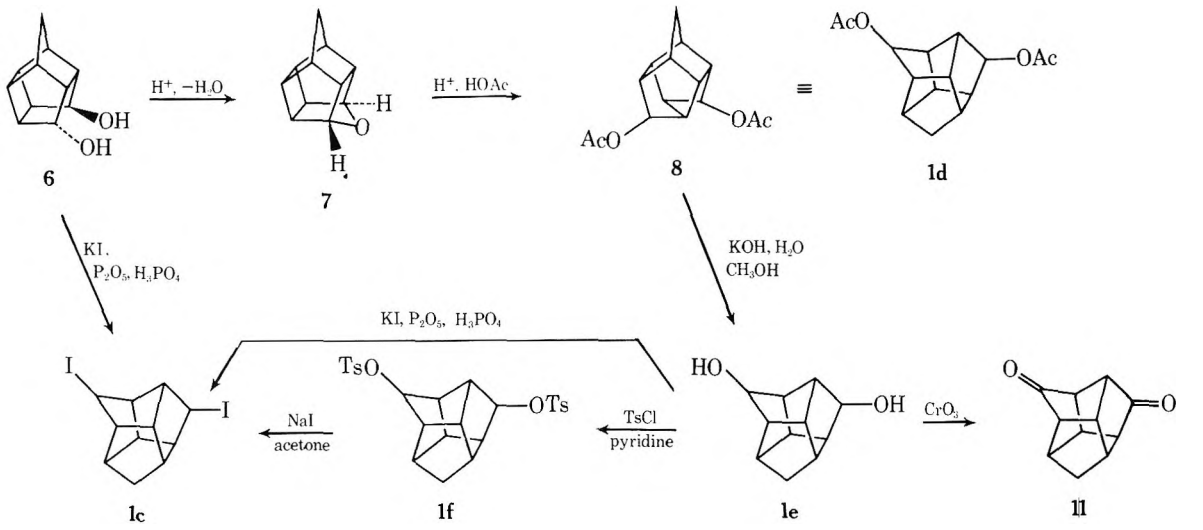
Several reports in the recent literature have dealt with the syntheses of the closely related trishomocubyl (**1**) and homohypostrophenyl (**2**) systems. The unsubstituted hydrocarbon **1a** has been produced by reductive dehalogenation of dibromotrishomocubane **1b** as one of a mixture of products,[2a] by zinc–acetic acid reduction of the diiodide **1c**,[2b,c] and by Wolff–Kishner reduction of trishomocubanone (**3**).[3a] The monofunctional trishomocubanone (**3**) was obtained in a four-step sequence starting with the dione produced by ultraviolet irradiation of the *p*-benzoquinone–cyclopentadiene Diels–Alder adduct,[3a] as well as by decomposition of an organometallic intermediate derived from the photocyclization product of dicyclopentadiene.[3b] The diene **2**, which had been required for the synthesis of the first-reported[2a] trishomocubane structure, had been observed as a by-product in the attempted synthesis of homopentaprismane (**4**) from the dibromide **5**.[4] Homohypostrophene (**2**) was also obtained as a minor component of the

1a, X = H
b, X = Br
c, X = I
d, X = OAc
e, X = OH
f, X = OTs



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

Scheme I



product mixture derived from treatment of the endo,endo ditosylate, prepared from the diol **6**, with NaI in hexamethylphosphoramide.[2c] As is often the case in initial syntheses of such polycyclic compounds, these approaches have usually been laborious or limited by high cost of reagents and low conversion to desired products.

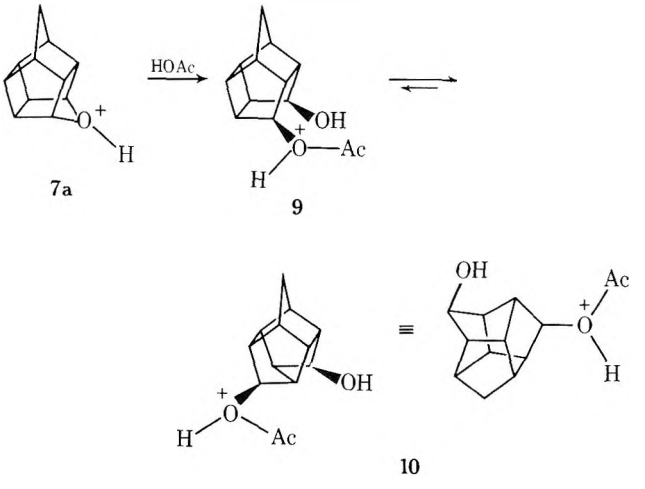
We report here syntheses of both title compounds by routes which are characterized by both convenience and reasonable yields, as well as by the fact that all starting materials are readily available. The precursor to the diene **2**, diiodotrishomocubane (**1c**), was obtained in two ways, the first by a directed synthesis via trishomocubanediol (**1e**) and the corresponding bistosylate **1f**, and the second which involves a single-step conversion of the diol **6** to **1c**.

The endo,endo diol **6** was readily synthesized from the corresponding dione by reduction with $LiAlH_4$ in tetrahydrofuran (THF), under conditions similar to published procedures.[5,6] Treatment of **6** with 48% aqueous HBr at elevated temperature resulted in good yields of cyclic ether **7**. This compound appeared to be identical in every respect but melting point[7] with an ether described by previous investigators as having been obtained simply by heating a sample of **6**.[4,6] Longer reaction times, at elevated temperature, gave products which apparently were the result of acid-catalyzed disruption of the ether linkage in **7**. The product appeared to be a mixture of compounds which presented serious separation problems, although one of these could be isolated as a crystalline solid of mp 128–130°, whose spectral properties were consistent with a structure which included both a bromine atom and a hydroxyl group. One interesting fact did emerge from this experiment, however. The NMR spectra of all cage intermediates prior to this step in the reaction sequence (e.g., the diol **6**, its dione precursor, and the ether **7**) exhibited a strongly characteristic AB-quartet pattern for the bridging methylene protons, indicating that the two protons are nonequivalent. After prolonged acid treatment of **6** (and hence **7**) the methylene protons in the NMR spectrum of products appeared as a narrow singlet absorption, suggesting equivalence. Obviously, skeletal reorganization had occurred, and it must have come about in such a way that the rearrangement product was symmetrical about an axis passing through the methylene in question.

Because aqueous HBr did not yield an easily workable set of products of rearrangement, other acidic media were investigated. Glacial acetic acid containing a catalytic amount of 98% sulfuric acid was found to be an efficient and mild medium by which to effect skeletal rearrangement (Scheme I). The diacetate produced in this way was identified as the trishomocubyl diacetate 8 (= **1d**) from its ir and NMR spectra, the latter of which exhibited the characteristic methylene singlet mentioned previously, as well as from the structures of the products of subsequent reactions. By examination of representation 8 of the diacetate in Scheme I, in which the diacetate is viewed as a derivative of bicyclo[2.2.1]heptane, the equivalence of the methylene protons is made more obvious, in the same way that structure **7** shows their nonequivalence.

The rearrangement presumably proceeds smoothly because the loss of a four-membered ring and its replacement with a five-membered ring serves as a driving force for the reaction. The protonated ether **7a** (Scheme II) is now vul-

Scheme II



nerable to nucleophilic attack by acetic acid, providing an intermediate **9** which includes a leaving group (HOAc) possessing the appropriate anti stereochemistry for opening of the four-membered ring, to produce a molecule which has the trishomocubane framework (**10**).[8] Such a mechanism predicts cis stereochemistry for the two substituents in structure **10**. We have not determined the stereochemistry of our disubstituted trishomocubanes; however, the high melting points of the diol **1e** and its tosylate **1f**, as well as the uniformity in shape of the tosylate crystals, suggests high stereochemical purity.

Hydrolysis of the diacetate in a mixture of KOH, methanol, and water resulted in formation of the corresponding

diol **1e**, a crystalline solid of low solubility. The diol was assigned its structure on the basis of infrared data and on the basis of elemental analysis. Further support of the diol's structure was derived from its CrO_3–acetone conversion to trishomocubanedione **11**. The dione, mp 213–214°, exhibited the expected simple NMR spectrum consisting of only three absorptions in the ratio 1:2:2, and provided a correct elemental analysis.

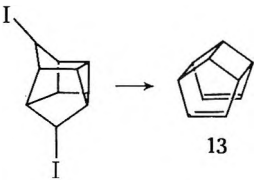
Treatment of the unpurified diol **1e** with *p*-toluenesulfonyl chloride in pyridine resulted in formation of the nicely crystalline bistosylate **1f**, whose NMR spectrum again was consistent with the assigned structure. The bistosylate, when solvolyzed in acetone in the presence of a large excess of NaI, gave the trishomocubyl diiodide **1c**. The structure of the diiodide, and hence of all preceding rearrangement molecules (**1d**, **1e**, **1f**, and **11**), followed from several pieces of data. Refluxing the diiodide with $LiAlH_4$ in THF produced only a single hydrocarbon product (albeit in low conversion) which we believe is trishomocubane (**1a**). Other reductive methods, among them sodium in liquid ammonia, sodium in THF–*tert*-butyl alcohol, and sodium–potassium alloy in tetrahydrofuran, produced varying amounts of two major components. One of these products was a saturated hydrocarbon identical with that obtained from the $LiAlH_4$–THF reduction, believed to be trishomocubane, and the other was the title compound tetracyclo[6.3.0.$0^{4,11}$.$0^{5,9}$]undeca-2,6-diene (**2**) (homohypostrophene). Trishomocubane **1a** could be prepared most conveniently, on a large scale and in excellent yields, simply by stirring diiodotrishomocubane (**1c**) with zinc dust in glacial acetic acid at elevated temperature.[2b] Another line of evidence supporting the structure of the diiodide is obtained from comparison of its NMR spectrum with that of the corresponding dibromide (**1b**) obtained from homohypostrophene (**2**) according to the procedure outlined by Underwood.[2a] The essential features of the two spectra are similar, the only significant differences being limited to those arising from the varying degree of deshielding experienced by the proton on the carbon bearing the halogen atom.

The 60-MHz ^1H NMR spectra of samples of trishomocubane (**1a**) obtained in the various reductions described above consisted of only two absorptions, broad singlets at δ 1.34 (6 H) and 1.97 (8 H), consistent with that expected based on consideration of the fact that the methinyl protons should appear at lower field than the methylene protons.[10] ^{13}C NMR spectra were identical with previously published results;[2b,3a] the proton-decoupled spectrum exhibited three singlets at δ 47.83 (6 C), 41.59 (2 C), and 33.27 (3 C). Undecoupled spectra showed the two lower field absorptions as doublets and the methylene carbon as a triplet, consistent with the symmetrical trishomocubane structure **1a**.

The diiodide **1c** could be most conveniently synthesized either by suitable manipulation of the rearranged diol **1e**, or in a single step from the endo,endo diol **6**. Treatment of **1e** with a mixture of H_3PO_4, P_2O_5, and KI[11] yielded **1c** in 85% yield as an epimeric mixture of diiodides. Since we were aware that **6** rearranged to the trishomocubyl skeleton under acidic conditions, it seemed reasonable that this diol would rearrange directly to **1c** in the H_3PO_4–P_2O_5–KI reaction medium; it was known that a diol mixture containing **6** in the presence of HI provided the diiodide **1c**.[2b]

At 105° in a mixture of H_3PO_4, P_2O_5, and KI, the diol **6** did in fact rearrange to a trishomocubane. After about 4 hr of reaction time rearrangement had taken place entirely, as evidenced by the disappearance of the methylene AB quartet in the NMR spectrum of **6** (and **7**) and replacement of this quartet by the methylene singlet discussed earlier. At this point, however, the NMR spectrum was quite complex, and showed evidence of the presence of some diiodide **1c** as well as hydroxyl absorptions, due presumably to the intermediacy of iodotrishomocubanol. After 12 hr of reaction time, the hydroxyl absorptions had disappeared and only diiodotrishomocubane (**1c**) was present. This approach has an obviously enormous time-saving advantage over the sequential approach described above.

The goal of these synthetic efforts, of course, was the conversion of the diiodide **1c** to homohypostrophene (**2**). We were encouraged by Underwood's report that treatment of dibromotrishomocubane (**1b**) under reductive conditions led to the formation of both the saturated hydrocarbon **1a** as well as the diene **2**,[2a] and especially by a report of a convenient synthesis of hypostrophene (**13**) by Paquette, in which reductive dehalogenation of diiodobishomocubane (**12**) resulted in diene formation.[12] It appeared that by a



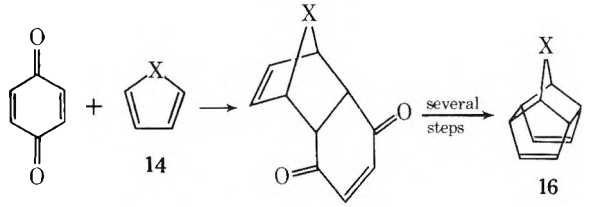
12 13

suitable choice of reducing conditions we could similarly obtain **2** in quantity.

A variety of reduction methods was attempted, among them sodium in liquid ammonia, sodium–potassium alloy in tetrahydrofuran, *n*-butyllithium in anhydrous ether, and *tert*-butyllithium in anhydrous ether. As pointed out earlier, all procedures were complicated by the formation of the saturated hydrocarbon trishomocubane (**1a**), as well as, in most cases, small amounts of apparently higher molecular weight products, whose identities have not been established. NMR spectra of these materials are very similar in appearance to that of **1a**, suggesting that perhaps they incorporate the trishomocubyl skeleton.

Most successful for the production of homohypostrophene proved to be reduction of the diiodide **1c** with alkyllithium reagents. Apparently in this case **1c** suffered lithium–iodide exchange to provide an unstable anion from which lithium iodide could be eliminated with concomitant ring opening to the desired diene **2**. In the cases where *n*-butyllithium was employed, the reaction was further complicated by production of a hydrocarbon which appears to incorporate a *n*-butyl group. This complication could be averted by use of the less nucleophilic, more basic *tert*-butyllithium. Use of this reagent provided high yields of a hydrocarbon mixture which consisted of two compounds, about 25% of which was trishomocubane (**1a**) and 75% of which was homohypostrophene (**2**). The diene could be isolated as a pure compound by chromatography on a 20% $AgNO_3$–silica gel column. Final purification was accomplished by sublimation, and the product thus obtained was identical in its physical properties with those of the previously reported diene.[2a]

The synthetic approach to the diene **2** reported here should find general applicability to the synthesis of a variety of compounds bearing structural similarity to trishomocubane and homohypostrophene. Variation of structure would be made in the initial step of the sequence, the Diels–Alder reaction of *p*-benzoquinone with the appropriate diene **14**, to produce the adduct **15** which is subsequently transformed in several steps to the diene of generalized structure **16**. An appreciable number of adducts of structure **15** are now known. The generality of this approach to dienes of the structure **16**, and the chemistry of these compounds, are currently being investigated.



Experimental Section

Pentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecane-8,11-diol (6). A solution of 100 g of the dione obtained by irradiation of the *p*-benzoquinone–cyclopentadiene Diels–Alder adduct in 400 ml of anhydrous tetrahydrofuran was added under N_2 to a mechanically stirred mixture of 30 g of $LiAlH_4$ in 200 ml of anhydrous tetrahydrofuran. After addition had been completed, the reaction mixture was refluxed for 10 hr. The mixture was cooled in an ice bath and cautiously decomposed by addition of 45 ml of H_2O followed by addition of sufficient 33% H_2SO_4 until inorganic salts had dissolved. The organic layer was separated, the aqueous portion extracted with chloroform, and the combined organic extracts washed with H_2O and dried over $MgSO_4$. Removal of chloroform yielded 92 g (90%) of the diol, which was used without further purification.

Pentacyclo[6.3.0.0^{2,6}.0^{3,10}.0^{5,9}]undec-4,7-yl Diacetate (1d). The diol 6[5,6] (1.1 g, 6.2 mmol) in 10 ml of glacial acetic acid containing 0.1 g of 98% H_2SO_4 was heated at 120° with stirring for 40 hr in a sealed reaction vessel. The reaction mixture was allowed to cool, then treated with 0.5 g of anhydrous NaOAc and subsequently with activated charcoal, and filtered, and most of the solvent was removed at diminished pressure with warming. Water was added to the residue, and the diacetate (**1d**) was extracted with Et_2O, the remaining acetic acid removed by extraction with aqueous $NaHCO_3$, the extracts dried over $MgSO_4$, and solvent removed at reduced pressure. The residue was chromatographed on a short silica gel column (13 × 2 cm) initially eluted with hexane. Elution with 20% Et_2O–hexane yielded 1.1 g (70%) of the diacetate **1d** as a colorless oil: NMR ($CDCl_3$) δ 1.42 (s, 2 H), 2.02 (6 H), 2.22 (br s, 6 H), 2.57 (br s, 2 H), 4.89 (2 H); ir (neat) 2988, 2884, 1737, 1367, 1248, 1050 and 737 cm^{-1}. For the usual applications, the diacetate was used without purification. The reaction may be scaled up without difficulty.

Pentacyclo[6.3.0.0^{2,6}.0^{3,10}.0^{5,9}]undecane-4,7-diol (1e). The diacetate **1d** (50 g) and 86 g of KOH were dissolved in 250 ml of 50% aqueous methanol and stirred for 30 hr at 60–65°. After cooling, the methanol was removed on a rotary evaporator, whereupon a light brown solid precipitated. This solid was filtered and washed with water and then with hexane to 32.5 g of the diol. Recrystallization from acetone afforded **1e** as colorless platelets: mp 203–205°; solubility difficulties precluded a suitable NMR spectrum; ir (KBr) 3280, 2960, 2895, 2875, 1350, 1274, 1190, 1100, 1077, 1066, and 778 cm^{-1}.

Anal. Calcd for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92. Found: C, 74.40; H, 7.62.

Pentacyclo[6.3.0.0^{2,6}.0^{3,10}.0^{5,9}]undecane-4,7-dione (11). To a stirred solution of 1.0 g (5.6 mmol) of **1e** in 50% v/v aqueous acetone at 0° was added 1.51 g of CrO_3 in 2.8 ml of H_2O and 1.35 ml of 98% H_2SO_4. After the addition was complete, the reaction mixture was stirred for 3.5 hr at room temperature. Water was added to dissolve the chromium salts and the mixture was extracted with Et_2O. Drying ($MgSO_4$), treatment with activated charcoal, and removal of solvent at reduced pressure gave 0.80 g of an oil which crystallized. Elution with 75% Et_2O–hexane on silica gel gave **11** as a white solid which was recrystallized from 66% Et_2O–heptane: mp 213–214°; NMR ($CDCl_3$) δ 1.79 (s, 2 H), 2.19 (br s, 4 H), 2.85 (br s, 4 H); ir (CCl_4) 3010, 2974, 1782, 1767, and 1152 cm^{-1}.

Anal. Calcd for $C_{11}H_{10}O_2$: C, 75.84; H, 5.79. Found: C, 76.13; H, 5.79.

Pentacyclo[6.3.0.0^{2,6}.0^{3,10}.0^{5,9}]undec-4,7-yl Bistosylate (1f). A cold solution of 2.3 g (12.9 mmol) of the diol **1e** in 16 ml of dry pyridine was added to 7.39 g (38.9 mmol) of *p*-toluenesulfonyl chloride dissolved in 12 ml of cold, dry pyridine. After standing at 5° overnight, the reaction mixture was poured into 20 ml of ice water and extracted with $CHCl_3$. The organic phase was then washed once with 15 ml of H_2O and with 4 × 15 ml of cold 4 *N* HCl. Treatment with $MgSO_4$ and activated charcoal and removal of solvent at reduced pressure gave an orange-yellow oil which crystallized by trituration with a small amount of Et_2O. Removal of the ether afforded 5.05 g (80%) of the bistosylate **1f** as white crystals which were recrystallized from aqueous acetone: mp 151.5–153°; NMR ($CDCl_3$) δ 1.33 (s, 2 H), 2.17 (8 H), 2.46 (s, 6 H), 4.70 (br s, 2 H), 7.60 (AB quartet, 8 H).

Anal. Calcd for $C_{25}H_{26}O_6S_2$: C, 61.71; H, 5.38. Found: C, 61.69; H, 5.33.

4,7-Diiodopentacyclo[6.3.0.0^{2,6}.0^{3,10}.0^{5,9}]undecane (1c). A. From 1f. Into a 200-ml pressure bottle were placed 14.3 g of bistosylate **1f**, 19.1 g of anhydrous NaI, and 100 ml of dry acetone. The flask was sealed and heated at 110–120° for 70 hr with magnetic stirring. The reaction mixture was cooled and poured into water, and the mixture carefully extracted with $CHCl_3$. The organic phase was washed with water, dried over $MgSO_4$, and treated with activated charcoal. Removal of solvent at reduced pressure yielded a white solid (10.2 g, 87%). Purification could be effected by recrystallization from Et_2O or acetone. Presumably owing to the presence of stereoisomers, the diiodide was not well behaved with respect to a melting point: NMR ($CDCl_3$) δ 1.51 (s, 2 H), 2–3.4 (complex, 8 H), 3.96 (s, 2 H); ir (CS_2) 2988, 2880, 1304, 1279, 1275, 1250, 1188, 788, 778, 769, and 681 cm^{-1}.

B. From Diol 6. The procedure employed here closely followed one which appears in the literature.[11] To 7.8 g of 85% H_3PO_4 in a 100-ml round-bottom flask was added 5.9 g of P_2O_5. After the initial exothermic reaction had subsided, 11.2 g of KI and 2.0 g of endo,endo diol **6** were added. The flask was fitted with a reflux condenser and drying tube and stirred for 12 hr at 105–110°. The cooled, dark, viscous mass was transferred to a 125-ml separatory funnel using Et_2O and water. After extracting with Et_2O, the organic phase was shaken with 2 × 10 ml of 10% aqueous $Na_2S_2O_3$ and twice with water (10 ml). The ethereal solution was dried and treated with activated charcoal. Removal of solvent in vacuo gave 4.06 g (91%) of the crude diiodide as an oil which partially crystallized. Material sufficiently pure for further reactions was obtained by trituration of the semisolid with acetone and cooling the mixture overnight. The NMR spectrum of this stereoisomeric mixture was identical with that of the diiodide described in part A.

C. From Diol 1e. Results similar to those described in part B were realized when the trishomocubyl diol **1e** was substituted, the yield of the crude diiodide being 85%.

Pentacyclo[6.3.0.0^{2,6}.0^{3,10}.0^{5,9}]undecane (1a). A. From 1c Using $LiAlH_4$. To a stirred suspension of 0.6 g of $LiAlH_4$ in 25 ml of freshly distilled tetrahydrofuran was added a solution of 1.1 g of diiodide **1c** in 30 ml of THF. The mixture was refluxed for 20 hr. Work-up involved decomposition of excess $LiAlH_4$ with 15% aqueous NaOH, filtration of residual solids, and washing with 30–60° petroleum ether. The filtrate was extracted with water in order to remove THF. The organic phase was dried and solvent was removed with a rotary evaporator at slightly reduced pressure. Sublimation of the residue (90°, 20 mm) yielded a white solid, the spectral properties of which were identical with those of trishomocubane **1a** prepared by the following method.

B. From 1c with Zn–HOAc. A mixture of the diiodide **1c** (2.0 g, 5.0 mmol), 4 g of zinc dust, and 40 ml of glacial acetic acid was stirred for 14 hr at 70°. The mixture was cooled and filtered, and the filtered solids washed carefully with petroleum ether. The combined filtrates were poured into water, layers separated, and the aqueous portion extracted twice with petroleum ether. The extracts were washed with water and saturated $NaHCO_3$ solution and dried ($MgSO_4$), and the solvent removed by distillation through a short Vigreux column. The residue was sublimed to provide 650 mg (90%) of trishomocubane (**1a**): mp 150.5–152° (lit. 147–149°);[2a] ^{1}H NMR ($CDCl_3$) δ 1.34 (s, 6 H), 1.97 (br s, 8 H); ^{13}C NMR ($CDCl_3$, undecoupled) δ 47.83 (d, 6 C), 41.59 (d, 2 C), 33.27 (t, 3 C) (proton decoupling resulted in collapse of all multiple absorptions to singlets); ir (CCl_4) 2970, 2883, 1465, 1301, 1280, and 967 cm^{-1}.

Tetracyclo[6.3.0.0^{4,11}.0^{5,9}]undeca-2,6-diene (Homohypostrophene, 2). A. Reduction in Na–Liquid NH_3. Sodium (5.0 g) was dissolved in 100 ml of NH_3 at −33° in a 250-ml round-bottom flask. A solution of 2.0 g of diiodide **1c** in 15 ml of freshly distilled (CaH_2) THF was added slowly, and the resulting mixture was stirred for 1 hr. The mixture was decomposed by careful addition of 15 g of NH_4Cl, petroleum ether was added, and the ammonia was allowed to evaporate. The mixture was then poured into water, layers separated, the aqueous portion extracted with petroleum ether, and the combined extracts dried over $MgSO_4$. Solvent was removed by distillation through a Vigreux column, and the residue sublimed (90°, 20 mm) to provide 380 mg of a mixture of **2** and trishomocubane (**1a**). The mixture was separated by chromatogra-

phy on 20% $AgNO_3$–silica gel. Elution with hexane removed **1a**, while 50% Et_2O–hexane provided 285 mg (39% from **1c**) of homohypostrophene: mp 143–145° (lit. 143.5–144.5°);[2a] ^1H NMR ($CDCl_3$) δ 1.65 (br s, 2 H), 2.35 (br s, 4 H), 3.18 (unresolved multiplet, 2 H), 5.93 (s, 4 H); ir (CCl_4) 3066, 2956, 2872, 1332, and 848 cm^{-1}.

B. Reduction with NaK Alloy in THF. A solution of 10.4 g of **1c** in 30 ml of freshly distilled (from NaK alloy) THF was added under N_2 to a mixture of 21 g of NaK (50% by weight) and 200 ml of THF. Vigorous stirring was continued for 1.5 hr after addition had been completed. The reaction mixture was carefully filtered under a blanket of N_2, the residues washed thoroughly with petroleum ether, and the combined filtrates poured into water. Layers were separated and the aqueous layer extracted with petroleum ether. The combined extracts were washed with water and dried ($MgSO_4$), and solvent was removed by distillation through a Vigreux column. Sublimation of the residue as described previously yielded 2.24 g of a mixture of the hydrocarbons **1a** and **2**, from which 1.34 g of **2** could be isolated by chromatography on a 20% $AgNO_3$–silica gel column (36% from **1c**).

C. Reaction with *tert*-Butyllithium in Et_2O. To a mixture of 5.0 g of **1c** in 60 ml of anhydrous diethyl ether under N_2, 15 ml of *tert*-butyllithium (1.6 *M* in pentane) was added slowly. The reaction was exothermic. After addition had been completed, the reaction mixture was stirred for 10 min at room temperature. Water was added to decompose unreacted *tert*-butyllithium and to dissolve inorganic salts, the organic material separated, the aqueous portion extracted with Et_2O, and the combined extracts dried over $MgSO_4$. Solvent was removed by distillation through a Vigreux column, and the residue sublimed as before to provide 1.5 g of a hydrocarbon mixture consisting of 75% **2** and 25% **1a**, which could be separated (as described above) by chromatography on 20% $AgNO_3$–silica gel.

Acknowledgment. The authors are indebted to E. I. du Pont de Nemours and Co., Wilmington, Del., for ^{13}C NMR spectra.

Registry No.—**1a**, 30114-56-8; **1c**, 56061-35-9; **1d**, 57237-84-0; **1e**, 57237-85-1; **1f**, 57237-86-2; **2**, 30114-57-9; **6**, 56143-86-3; **6** diketone analogue, 2958-72-7; **11**, 57237-87-3; *tert*-butyllithium, 594-19-4.

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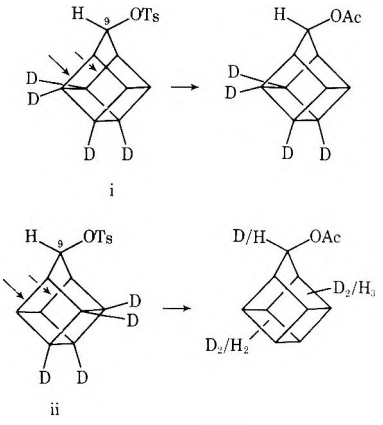
(7) We observed mp 228–230°, whereas two independent sources (ref 4 and 6) reported 190–191°. We have repeated their experiment by heating the diol **6** in vacuo and subsequently sublimed the decomposition product, and found its melting point (228–230°) to be identical with that of our acid-produced compound. NMR and ir spectral data for the compound from all sources are identical.
(8) In rearrangements of this sort, it appears that a leaving group anti to the migrating bond is a prerequisite to rearrangement. As one of a numerous set of examples of such a requirement, appropriately labeled homocubyl tosylate i undergoes solvolysis in acetic acid to produce acetate in which no deuterium appears at C-9, whereas the tosylate ii scrambles the deuterium label. Such a result requires that only the bonds indicated by arrows in the figure below are available for migration (ref 9).



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(10) In polycyclic hydrocarbons of this sort, the NMR spectra invariably exhibit absorptions for protons on relatively strained, more highly substituted carbons at lower fields than those attached to less strained carbons. See, for example, the NMR spectral data for the unsubstituted hydrocarbon whose carbon framework is identical with that of the diol **6** [R. J. Stedman, L. S. Miller, L. D. Davis, and J. R. E. Hoover, *J. Org. Chem.*, **35**, 4169 (1970)], for homocubane [W. J. Dauben and D. H. Whalen, *Tetrahedron Lett.*, 3743 (1966)], and for pentacyclo[4.3.0.$0^{2,4}$.$0^{3,8}$.$0^{5,7}$]nonane [H. Prinzbach and D. Hunkler, *Chem. Ber.*, **106**, 1804 (1973)].
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Synthesis of Tetracyclo[6.3.0.0^{4,11}.0^{5,9}]undeca-2,6-diene ("Homohypostrophene"), 10-Oxatetracyclo[6.3.0.0^{4,11}.0^{5,9}]undeca-2,6-diene ("10-Oxahomohypostrophene"), and Hexacyclo[5.4.0.0^{2,6}.0^{4,11}.0^{5,9}.0^{8,10}]undecane. Structure of *syn*-4,*syn*-7-Diiodopentacyclo[6.3.0.0^{2,6}.0^{3,10}.0^{5,9}]undecane. Synthesis and Rh(I)-Promoted Rearrangement of Hexacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}.0^{8,11}]undecane ("Homopentaprismane")[1]

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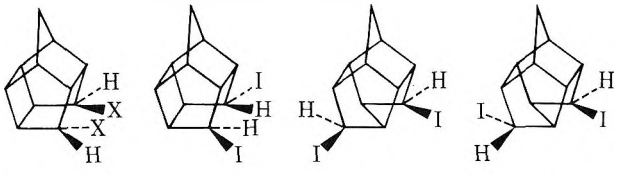
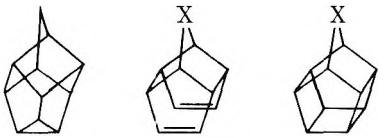
The reaction of ditosylate **1b** with sodium iodide in hexamethylphosphoramide affords five products: *exo*-8,*exo*-11-diiodopentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecane (**2**), *syn*-4,*anti*-7-diiodopentacyclo[6.3.0.0^{2,6}.0^{3,10}.0^{5,9}]undecane (**3**), *syn*-4,*syn*-7-diiodopentacyclo[6.3.0.0^{2,6}.0^{3,10}.0^{5,9}]undecane (**4**), hexacyclo[5.4.0.0^{2,6}.0^{4,11}.0^{5,9}.0^{8,10}]undecane (**5**), and homohypostrophene (**6a**). Confirmation of the structure and stereochemistry of diiodide **4** was obtained via single-crystal x-ray structural analysis. Control experiments revealed that products **3**–**6a** are formed from **2**; mechanisms for these conversions are suggested. A two-step synthesis of 10-oxahomohypostrophene (**6b**) from 11-oxa-3,4,5,*exo*-6-tetrachloropentacyclo[6.2.1.0^{2,7}.0^{4,10}.0^{5,9}]undecane-*endo*-3-carboxylic acid (**11**) is presented. Whereas **6a** could readily be photocyclized to homopentaprismane (**7a**), conditions whereby the corresponding photocyclization of **6b** to 4-oxahomopentaprismane (**7b**) might be effected could not be found. Homopentaprismane rearranged slowly to homohypostrophene upon treatment with either $(Ph_3P)_2Rh(CO)Cl$ ($CDCl_3$ solvent, 67 °C, 0.514 M in **7a**, 0.171 M in catalyst, $t_{1/2}$ = 9.8 h) or $[Rh(norbornadiene)Cl]_2$ (benzene-d_6, 40 °C, 0.456 M in **7a**, 0.0135 M in catalyst, $t_{1/2}$ = ca. 7.5 days). Compound **7a** did not undergo rearrangement when treated with Ag(I).

In a recent communication,[2] we reported some preliminary observations relating to the reaction of the ditosylate (**1b**) derived from *endo*-8,*endo*-11-dihydroxypentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecane (**1a**) with sodium iodide in hexamethylphosphoramide (HMPA) solvent. This reaction was found to afford thre isomeric diiodides (**2**–**4**), a saturated $C_{11}H_{12}$ hydrocarbon (**5**), and homohypostrophene (**6a**). We now report full experimental details surrounding the synthesis, isolation, and characterization of **2**–**6a**. In addition, the synthesis of 10-oxatetracyclo[6.3.0.0^{4,11}.0^{5,9}]undeca-2,6-diene ("10-oxahomohypostrophene", **6b**) is described. We also note the results of our attempts to photocyclize **6a** and **6b** to homopentaprismane (**7a**) and 4-oxahomopentaprismane (**7b**), respectively. Finally, the results of studies on the Rh(I)- and Ag(I)-promoted rearrangements of **7a** are discussed.



1a, X = OH; **b**, X = OTs — **2** — **3** — **4**



5 — **6a**, X = CH_2; **b**, X = O — **7a**, X = CH_2; **b**, X = O

Results

A. Reaction of 1b with Sodium Iodide–HMPA. This reaction, when carried out as described in the Experimental Section, afforded two product fractions: a nonvolatile fraction consisting of the isomeric diiodides **2**–**4** and a volatile fraction consisting of the two $C_{11}H_{12}$ hydrocarbons (**5** and **6a**). Separation of the mixture of diiodides was effected via elution chromatography; the $C_{11}H_{12}$ hydrocarbons could be separated using preparative VPC techniques.

Proof of structure of each of the isomeric diiodides was accomplished via a combination of chemical[3–5] and NMR spectral[6] methods. These results are summarized in Table I. The carbon skeleton of **2** was assigned via its dehalogenation with tri-*n*-butyltin hydride. This procedure afforded the corresponding hydrocarbon, pentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecane (**8**), which could be identified by comparison with an authentic sample.[3] The ^{13}C NMR spectral and chemical evidence are both consistent with **2** having the carbon–iodine bonds either endo,endo or exo,exo. We favor the latter on the basis of mechanistic considerations (i.e., **2** is most likely formed via SN2 displacement of the endo tosylate groups in **1b** by iodide).

8 — **9**

Dehalogenation of diiodides **3** and **4** with either zinc–acetic acid[4,5] or tri-*n*-butyltin hydride afforded trishomocubane (**9**). This fact, together with the ^{13}C NMR spectral evidence (Table I), requires that the carbon–iodine bonds in **3** have the syn,anti configuration. However, in the case of **4**, this same type of evidence is consistent with the carbon–iodine bonds being either syn,syn or anti,anti. The question of the configurations of these carbon–iodine bonds in **4** has been resolved via single-crystal x-ray structural analysis. The x-ray structure determination on **4** has shown these carbon–iodine bonds to be syn,syn (Figure 1).

Compound **4** contains a crystallographic twofold axis. Figure 2 shows the skeletal numbering, unique bond lengths, and unique bond angles. Symmetry-related pairs are I–I′, C(5)–C(3), C(6)–C(10), C(7)–C(11), C(8)–C(1), and C(9)–C(2). Carbon atom C(4) lies on the twofold axis.

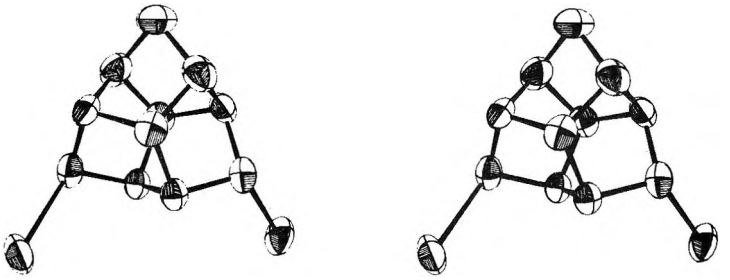


Figure 1. Stereoview of 4 generated by the ORTEP program.

One can recognize the presence of three norbornane systems in the carbon skeleton of 4: C(4)C(3)-C(10)C(9)C(5)C(6)C(2), C(7)C(8)C(9)C(5)C(6)C(2)C(1), and C(11)C(1)C(2)C(3)C(10)C(9)C(8). In 4 (as in norbornane itself), one can differentiate between only three different types of carbon–carbon bond distances: types C(6)–C(7), C(5)–C(6), and C(5)–C(9). The distances in the first two types range between 1.51 and 1.53 Å, while the last, which is the only type possessing ethano-bridge character, ranges from 1.56 to 1.57 Å. These distances are in agreement with those observed in norbornane[7] and in a derivative of a cage dimer of norbornane.[8] On the other hand, the strain in the cage structure of 4 becomes apparent upon inspection of the bond angles, which are all smaller than 109.5°, and especially upon inspection of the conformations of the five-membered rings. The pseudorotation phase angles[9] are −1, −3, and 8° for the independent rings C(5)C(6)C(7)C(8)C(9), C(6)C(5)C(4)C(3)C(2), and C(6)-C(7)C(8)C(1)C(2), respectively, indicating an approximate half-chair ($C2$) conformation. However, in norbornane, the five-membered rings are in the ideal envelope (Cs) conformation. There is one unusual feature in the molecular packing of the structure, i.e., there are short intermolecular I . . . I distances across the center of symmetry (¼, ¼, ½) of 3.80 Å, which are considerably shorter than the accepted van der Waals distance (3.95 Å[10]) but not as short as are the corresponding distances which occur in crystalline iodine (3.54 Å[11]).

Hydrocarbon 5 was identified via analysis of its proton

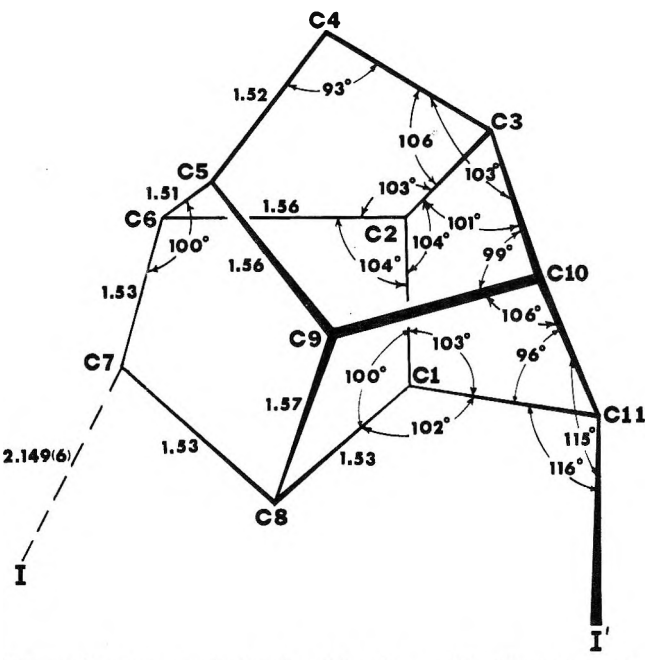
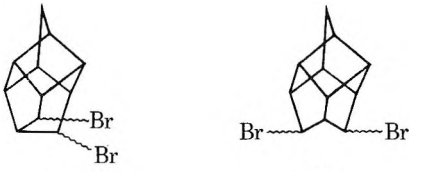


Figure 2. Atom numbering, bond lengths, and bond angles for 4. Standard deviations for bond lengths is 0.01 Å and for bond angles is 0.5°.

noise decoupled and off-resonance decoupled ^{13}C NMR spectra (Table I, which indicate that 5 possesses Cs point symmetry) and by the fact that 5 reacts with a solution of bromine in chloroform to afford a ca. 1:2.5 mixture of isomeric dibromides ($C_{11}H_{12}Br_2$, 10a and 10b, which indicates that 5 contains one cyclopropane ring). The structure indi-



10a 10b

Table I. Structure Proof of Compounds 2–6a

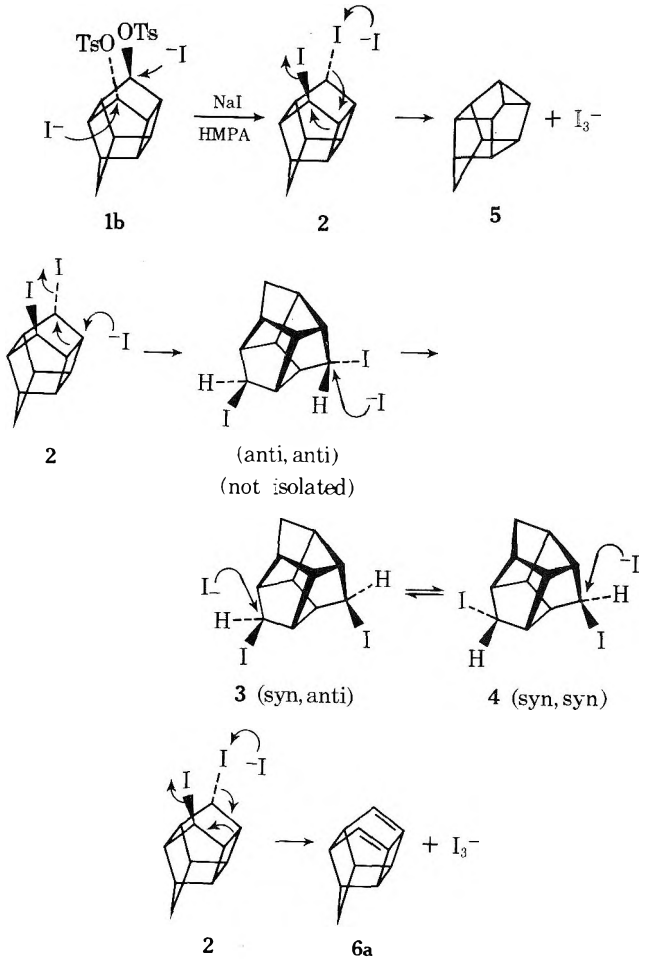
Compd	^{13}C NMR spectrum[a] Proton noise decoupled[b]	^{13}C NMR spectrum[a] Off-resonance decoupled[b]	Chemical method[c]	Ref
2	73.9 (2 C), 78.3 (2 C), 79.3 (2 C), 86.4 (2 C), 97.1 (2 C), 97.2 (1 C)	Five doublets and one triplet (97.2)	2 $\xrightarrow{(n\text{-Bu})_3\text{SnH}}$ 8	3
3	69.2 (1 C), 70.7 (1 C), 71.8 (1 C), 75.1 (1 C), 79.1 (1 C), 79.9 (1 C), 87.2 (1 C), 88.0 (1 C), 95.9 (1 C), 98.1 (1 C), 98.6 (1 C)	Ten doublets and one triplet (95.9)	3 $\xrightarrow{\text{Zn, HOAc}}$ 9 3 $\xrightarrow{(n\text{-Bu})_3\text{SnH}}$ 9	4, 5 4, 5
4	68.9 (2 C), 72.2 (2 C), 81.9 (2 C), 87.7 (2 C), 94.3 (1 C), 99.2 (2 C)	Five doublets and one triplet (94.3)	4 $\xrightarrow{\text{Zn, HOAc}}$ 9 4 $\xrightarrow{(n\text{-Bu})_3\text{SnH}}$ 9	4, 5 4, 5
5	66.4 (1 C), 71.2 (2 C), 75.8 (2 C), 79.8 (1 C), 87.6 (1 C), 88.5 (2 C), 88.7 (1 C), 92.4 (1 C)	Seven doublets and one triplet (88.7)	5 $\xrightarrow[\text{CHCl}_3]{\text{Br}_2}$ 10a + 10b	
6a	96.8 (1 C), 79.5 (2 C), 63.6 (4 C), −8.6 (4 C)	Three doublets and one triplet (96.8)	6a $\xrightarrow[\text{xanthone}]{h\nu}$ 7a	12

[a] Spectra of 2, 3, and 4 were measured at 25.2 MHz ($CDCl_3$ solvent, Me_4Si and benzene internal standards; spectra of 5 and 6a were measured at 22.63 MHz (CCl_4 solvent, CS_2 internal standard, benzene-d_6 lock). We thank Professor Michael Barfield, University of Arizona, for obtaining the ^{13}C NMR spectra of 5 and 6a. [b] Shifts are in parts per million relative to internal benzene. Positive numbers indicate upfield shifts, negative numbers indicate downfield shifts relative to benzene. [c] See text.

cated for **5** appears to be the only reasonable structure corresponding to a saturated $C_{11}H_{12}$ hydrocarbon which contains only one cyclopropane ring and which possesses *Cs* point symmetry. Homohypostrophene (**6a**) was similarly identified via analysis of its ^{13}C NMR spectra[12] and by the fact that it could be converted photochemically to homopentaprismane (**7a**, see Experimental Section).

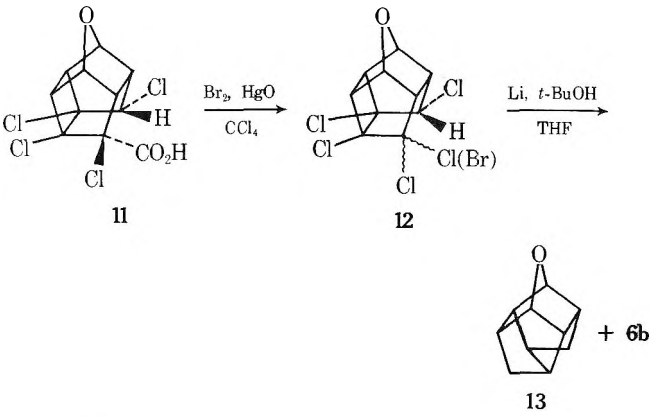
B. Mechanism of Formation of Products 2–6a. In order to gain information in this regard, diiodides **2–4** were each subjected in turn to the same experimental conditions under which ditosylate **1b** is converted to products **2–6a** (i.e., sodium iodide–HMPA, 125–130 °C, 45 h). Compound **2** when thus treated afforded all five products (**2–6a**). It was also demonstrated that **2** was stable to the VPC conditions under which the product analysis was performed. Either pure **3** or pure **4** when subjected to these reaction conditions afforded a *mixture* of **3** and **4** unaccompanied by **2, 5,** or **6a**. The foregoing results suggest that hydrocarbons **5** and **6a** may be formed only from **2**. The trishomocubyl diiodides **3** and **4** simply equilibrate under the reaction conditions without proceeding to afford the hydrocarbon products (**5** and **6a**). A mechanistic scheme which is consistent with the foregoing observations is shown in Scheme I.

Scheme I



C. Synthesis of 6b. Our synthesis of 10-oxahomohypostrophene (**6b**) is shown in Scheme II. Compound **11**, made available from another study,[13] was converted to **12** utilizing the Cristol–Firth modification[14] of the Hunsdiecker reaction. Dehalogenation of **12** with lithium–*tert*-butyl alcohol in tetrahydrofuran affords a mixture of **13** and **6b** which could be separated using preparative VPC techniques. Both compounds **13** and **6b** were identified via

Scheme II



their ^1H NMR,[12] ir, and mass spectra, and by elemental microanalyses.

It was noted earlier that **6a** could be cyclized photochemically to afford **7a**. However, despite repeated attempts, we were unable to find a suitable set of conditions whereby **6b** might be cyclized photochemically to 4-oxahomopentaprismane (**7b**, see Experimental Section). The reasons for our failure to effect the photochemical conversion of **6b** to **7b** are not clear at present.

D. Transition Metal Catalyzed Rearrangements of 7a. The role of transition metals in catalyzing symmetry-forbidden processes is a subject of much current interest.[15–18] Accordingly, we have examined the reactions of **7a** with Rh(I) and with Ag(I). The reaction of **7a** with $(Ph_3P)_2Rh(CO)Cl$ in chloroform at 70–75 °C cleanly afforded diene **6a** within 20 h, as confirmed by NMR analysis of the product. A kinetic study of this rearrangement was performed at 67 °C. The disappearance of **7a** and the concomitant formation of **6a** could be followed using ^1H NMR spectroscopy (see Experimental Section). The reaction was found to be cleanly second order, first order in each of the reactants (**7a** and the Rh(I) catalyst). Least-squares treatment of a plot of log $[\mathbf{7a}]_0/[\mathbf{7a}]_t$ vs. time afforded a straight line having slope = 0.070 from which a rate constant $k_2 = 5.7 \times 10^{-5}$ M^{-1} s^{-1} could be calculated. The calculated rate constant corresponds to a half-life of ca. 9.8 h for this process (0.171 M in catalyst).

We have also examined the $[Rh(norbornadiene)Cl]_2$-catalyzed isomerization of **7a** to **6a.** The reaction at 40 °C in benzene-d_6 solvent was extremely slow: for a solution 0.456 M in **7a** and 0.0135 M in catalyst, the half-life was found to be ca. 7.5 days. The plot of log $[\mathbf{7a}]_0/[\mathbf{7a}]_t$ vs. time displayed considerable curvature. The rate data which we observed for this reaction can be compared directly with the corresponding rate data obtained for the $[Rh(norbornadiene)Cl]_2$-catalyzed isomerization of cubane (for which k = 14 M^{-1} s^{-1} in $CDCl_3$ solvent at 40 °C)![18] Additionally, it has been reported that the $[Rh(norbornadiene)Cl]_2$-catalyzed isomerization of 9,10-dicarbomethoxy-1,8-bishomocubane at 40 °C in dry benzene is complete in 40 h.[19]

Unexpectedly, compound **7a** was found to be inert toward $AgBF_4$ in chloroform solution (58–62 °C, 4 days) and toward $AgClO_4$ in benzene solution at 78 °C. Unreacted **7a** could be recovered essentially quantitatively after 10 days' exposure to silver perchlorate at this temperature. One might anticipate the product of Ag(I)-catalyzed rearrangement of **7a** to be **5** by analogy to the course of Ag(I)-catalyzed rearrangements of other strained cage systems.[16]

The driving force behind many transition metal catalyzed rearrangements of systems containing strained σ bonds is thought to be relief of steric strain.[16] In a recent review, Paquette[16] stated: "the lower limit of inherent ring

strain required for rearrangement is yet to be established". Perhaps a better way to state this would be in terms of the minimum energy difference between reactants and products, ΔE, needed to promote these rearrangements. We can estimate the energy change for the transformation of **7a** to **5** in an approximate way by summing the strain energies of their composite fused rings.[20] Using published values of ring strain energies,[21] we arrive at ΔE = ca. 24 kcal/mol for the transformation of **7a** to **5**. Typical values for the relief of steric strain in transition metal catalyzed rearrangements of systems containing strained σ bonds usually fall in the range 35–50 kcal/mol.[16] We conclude that our failure to observe Ag(I)-catalyzed rearrangement of **7a** to **5** reflects the minimal driving force for this process.

Experimental Section

Melting points were obtained on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Ir spectra were recorded on a Beckman IR-8 infrared spectrophotometer and were calibrated against the 1601-cm^{-1} band of polystyrene. ^1H NMR spectra were recorded on a Varian T-60 NMR spectrometer (Me_4Si internal standard). ^{13}C NMR spectra were obtained using either a Brucker WH-90 FT NMR spectrometer operating at 22.63 MHz (University of Arizona) or a Varian XL-100-15 FT NMR spectrometer operating at 25.2 MHz (University of Oklahoma). Mass spectra were obtained at 70 eV (unless otherwise indicated) utilizing a Hitachi Perkin Elmer Model RMU-7E mass spectrometer. Values of *m/e* of each significant peak in the mass spectra are reported, followed parenthetically by the intensity of that peak (where the intensity of the base peak = 100). VPC studies were performed on a Varian Aerograph Model A90-P3 vapor phase chromatograph outfitted with a 0.25 in. × 5 ft column packed with 3% SE-30 on 45/60 mesh Chromosorb P. Column conditions (temperatures and He flow rates) are indicated in each case. Elemental microanalyses were performed by Chemalytics, Inc., Tempe, Ariz. Unless otherwise noted, all reagents and solvents were reagent grade and were used without additional purification.

Reaction of 1b with Sodium Iodide in Hexamethylphosphoramide (HMPA). To a 500-ml three-neck round-bottom flask fitted with a nitrogen inlet and a side arm leading to a receiving flask was placed a mixture of **1b** (12.1 g, 0.025 mol) and sodium iodide (60 g, 0.4 mol) in freshly distilled HMPA (150 ml). The resulting mixture was heated under nitrogen with stirring at 125–130 °C for 45 h. During this period, the temperature of the receiving flask was maintained at −78 °C via external cooling (dry ice–acetone bath). At the conclusion of the reaction, the volatile products which had collected in the receiver were taken up in pentane, washed with water, and then dried (Na_2SO_4) and filtered. The filtrate was concentrated via distillation through a 12-in. Vigreux column. The oily residue was sublimed (80–90 °C, 1 atm), affording a colorless, waxy solid (415 mg, 11.6%). VPC analysis (column temperature 80 °C, He flow rate 120 ml/min) indicated the presence of two components (ca. 1:2.3) which could be separated via preparative VPC (column temperature 130 °C, He flow rate 120 ml/min). The major (less volatile) component was identified[2] as hexacyclo[5.4.0.0^{2,6}.0^{4,11}.0^{5,9}.0^{8,10}]undecane (**5**): mp 132–134 °C (sealed tube); ir (CCl_4) 3040 (s), 2960 (s), 2850 (m), 1438 (w), 1301 (m), 1290 (m), 1198 (w), 1015 (w), 950 (w), and 930 cm^{-1} (w); ^1H NMR ($CDCl_3$) δ 1.43 (d, J = ca. 1 Hz, 2 H, 3-methylene protons), 1.83–2.48 (complex multiplet, 4 H), 2.48–3.17 (complex multiplet, 6 H); mass spectrum *m/e* 144 (molecular ion, 81), 129 (45), 128 (30), 116 (18), 115 (19), 79 (100), 78 (98), 77 (32), 66 (97), 51 (18), and 38 (30); ^{13}C NMR (see Table I).

Anal. Calcd for $C_{11}H_{12}$: C, 91.61; H, 8.39. Found: C, 91.78; H, 8.32.

The minor (more volatile) component of the mixture was identified as tetracyclo[6.3.0.0^{4,11}.0^{5,9}]undeca-2,6-diene ("homohypostrophene", **6a**): mp 141.5–142.5 °C (sealed tube) (lit.[22] mp 143.5–144.5 °C); ir (CCl_4) 3055 (m), 2950 (s), 2806 (m), 1325 (m), 1018 (m), and 835 cm^{-1} (m); ^1H NMR ($CDCl_3$) δ 1.63 (br s, 2 H, 10-methylene protons), 2.33 (br s, 4 H, 1,4,5,8-methine protons), 3.17 (m, 2 H, 9,11-methine protons), and 5.93 (s, 4 H, vinyl protons); mass spectrum *m/e* 144 (molecular ion, 12), 129 (8), 115 (9), 79 (100), 78 (32), 77 (31), and 66 (15). The ^{13}C NMR spectrum of **6a** (Table I) was identical with that of authentic material.[12]

The dark mixture left in the reaction flask (nonvolatile products) was poured into water, and the products were extracted into hexane (4 × 100 ml). The combined extracts were washed with saturated aqueous sodium bicarbonate solution (2 × 100 ml) and water (3 × 100 ml), and then dried (Na_2SO_4), filtered, and concentrated. A colorless, oily material was thereby obtained which, upon recrystallization from hexane, afforded a mixture of isomeric diiodides (4.3 g, 43.4%). The ^1H NMR spectrum of this mixture displayed two broad singlets at δ 3.97 and 4.47 (intensity ratio 15:11) and complex multiplets at δ 1.2–3.6. Separation of this mixture was effected via column chromatography on Merck TLC grade silica gel (200 g, 1.5 in. o.d. column, hexane eluent). Repeated recrystallization of the first few fractions from hexane afforded pure *exo*-8,*exo*-11-diiodopentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecane (**2**) as colorless prisms: mp 132–133 °C; ir (CCl_4) 2990 (s), 2870 (m), 1292 (m), 1273 (m), 1165 (m), 1128 (s), 865 (m), and 692 cm^{-1} (s); ^1H NMR ($CDCl_3$) AB pattern, δ_A 1.37, δ_B 1.78 (J_{AB} = 12 Hz, 2 H, 4-methylene protons), δ 2.57 (br s, 2 H, methine protons), 2.70–3.10 (m, 4 H, methine protons), 3.43 (m, 2 H, methine protons), and 4.47 (s, $W_{1/2}$ = ca. 2 Hz, 8,11 protons); mass spectrum *m/e* 398 (molecular ion, 0.2), 271 (37), 205 (15), 193 (18), 144 (41), 143 (18), 129 (12), 128 (12), 115 (10), 79 (100), 78 (29), 77 (23), and 66 (15); ^{13}C NMR (see Table I).

Anal. Calcd for $C_{11}H_{12}I_2$: C, 33.19; H, 3.04. Found: C, 33.17; H, 2.96.

Repeated recrystallization of the last few chromatography fractions (hexane) afforded pure *syn*-4,*anti*-7-diiodopentacyclo[6.3.0.0^{2,6}.0^{3,10}.0^{5,9}]undecane (**3**) as colorless needles: mp 122–123 °C; ir (CCl_4) 2985 (s), 2870 (m), 1298 (m), 1268 (s), 1172 (s), 1163 (s), and 670 cm^{-1} (s); ^1H NMR ($CDCl_3$) δ 1.50 (d, J = ca. 1 Hz, 2 H, 11-methine protons), 1.93–2.80 (complex m, 6 H, methine protons), 2.80–3.30 (complex m, 2 H, methine protons), and 3.97 (br s, $W_{1/2}$ = ca. 5 Hz, 2 H, 4,7 protons); mass spectrum *m/e* 398 (molecular ion, 0.6), 271 (5), 205 (4), 193 (4), 144 (13), 143 (18), 129 (10), 128 (13), 115 (12), 79 (100), 77 (28), and 66 (23); ^{13}C NMR (see Table I).

Anal. Calcd for $C_{11}H_{12}I_2$: C, 33.19; H, 3.04. Found: C, 33.04; H, 2.99.

It was subsequently found that the middle chromatography fractions contained a mixture of **3** and a third diiodide. This mixture could be separated via additional, carefully executed column chromatography. In this way, *syn*-4,*syn*-7-diiodopentacyclo[6.3.0.0^{2,6}.0^{3,10}.0^{5,9}]undecane (**4**) was isolated. Recrystallization from hexane afforded pure **4** as colorless needles: mp 151–152 °C; ir (CCl_4) 2985 (s), 2870 (m), 1290 (s), 1280 (s), 1275 (s), 1238 (m), 1195 (m), 1175 (s), 1155 (s), and 670 cm^{-1} (s); ^1H NMR ($CDCl_3$) δ 1.53 (s, $W_{1/2}$ = ca. 3 Hz, 2 H, 11-methylene protons), 2.20 (br s, 4 H, methine protons), 2.73 (br s, 2 H, methine protons), 3.03 (br s, 2 H, methine protons), and 3.97 (s, $W_{1/2}$ = ca. 3 Hz, 2 H, 4,7 protons); mass spectrum *m/e* 398 (molecular ion, 6), 271 (65), 205 (19), 193 (19), 144 (44), 143 (37), 79 (100), 78 (33), 77 (17), and 66 (15); ^{13}C NMR (see Table I).

Anal. Calcd for $C_{11}H_{12}I_2$: C, 33.19; H, 3.04. Found: C, 32.93; H, 3.07.

Dehalogenation of 2. A. Using Lithium–*tert*-Butyl Alcohol in Tetrahydrofuran. To a solution of **2** (635 mg, 1.6 mmol) in dry tetrahydrofuran (10 ml) were added *tert*-butyl alcohol (1 ml, 10.6 mmol) and lithium wire (140 mg, 20 mg-atoms). The reaction mixture was refluxed for 1 h and then poured into ice water. The product was extracted into pentane, and the pentane solution was washed with water and then dried (Na_2SO_4). The solution was then filtered, and the solvent was carefully removed via fractional distillation. The oily residue was sublimed (95 °C, 1 atm), affording a colorless, waxy solid (157 mg, 68.2%). VPC peak enhancement (column temperature 85 °C, He flow rate 120 ml/min) and analysis of the ^1H NMR spectrum of this product indicated it to be pure **6a**. No other product was found in this reaction.

B. Using Lithium Aluminum Hydride. A solution of **2** (520 mg, 1.3 mmol) in freshly distilled tetrahydrofuran (8 ml) was added dropwise over a 10-min period to a refluxing suspension of lithium aluminum hydride (0.38 g, 10 mmol) in tetrahydrofuran (5 ml) under nitrogen. Refluxing was continued for 1 h after the addition of **2** had been completed. The reaction mixture was then cooled to 0 °C (ice bath), and water was carefully added to destroy excess lithium aluminum hydride. The product (ca. 100 mg) was isolated and found to consist solely of diene **6a**.

C. Using Tri-*n*-butyltin Hydride. A solution of **2** (200 mg, 0.5 mmol) in anhydrous diethyl ether (10 ml) was heated to reflux under nitrogen. To the refluxing solution was added dropwise an excess of freshly distilled tri-*n*-butyltin hydride (0.5 ml, prepared via the reaction of tri-*n*-butyltin chloride with lithium aluminum hydride in diethyl ether[23]). After refluxing for 3 h, the reaction

Table II. Atomic Fractional Coordinates and Thermal Parameters of Unique Iodine and Carbon Atoms in 4[a]

	x	y	z	b_{11}	b_{22}	b_{33}	b_{23}	b_{13}	b_{12}
I	2018 (0)	5766 (1)	3562 (1)	34 (0)	224 (1)	161 (1)	−51 (1)	51 (1)	−59 (1)
C(5)	373 (5)	1153 (8)	1750 (8)	48 (3)	179 (11)	143 (9)	−87 (17)	59 (9)	14 (10)
C(8)	69 (4)	4294 (6)	1779 (5)	33 (2)	148 (9)	69 (5)	13 (11)	43 (6)	7 (7)
C(7)	1090 (4)	3861 (8)	2229 (6)	32 (2)	197 (11)	95 (6)	−39 (14)	50 (7)	−3 (8)
C(6)	1043 (4)	2158 (7)	2998 (6)	32 (2)	144 (9)	118 (7)	1 (13)	45 (6)	37 (7)
C(2)	407 (4)	2530 (7)	3862 (5)	40 (3)	173 (11)	86 (6)	43 (13)	40 (7)	14 (9)
C(4)	0 (0)	−205 (13)	2500 (0)	69 (6)	126 (14)	199 (17)	0 (0)	76 (16)	0 (0)

[a] The temperature factor is expressed as $\exp[-(h^2b_{11} + k^2b_{22} + l^2b_{33} + hkb_{12} + hlb_{13} + klb_{23})]$. All parameters are multiplied by 10^4. Standard deviations for last digits appear in parentheses.

mixture was cooled, washed with 5% aqueous sodium hydroxide solution (5 ml) and water (5 ml), and then dried (Na_2SO_4). The solution was then filtered through silica gel (ca. 3 g), and the filtrate was concentrated via careful fractional distillation. The residue was sublimed to afford a solid material (ca. 40 mg) which was found by VPC to consist of two compounds. Separation was effected via preparative VPC (column temperature 150 °C, He flow rate 130 ml/min); the products were identified as **6a** and pentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecane (**8**) (ratio **6a**:**8** 9:7). Compound **8** was identified via comparison of its ir and ^{1}H NMR spectra with those of an authentic sample[3] and via VPC techniques (i.e., enhancement of a peak corresponding to authentic **8**[3]).

Dehalogenation of a Mixture of 3 and 4. A. Using Zinc–Acetic Acid. To a stirred solution of diiodides **3** and **4** (1.02 g, 26 mmol) in glacial acetic acid (5 ml) was added zinc dust (1 g). The resulting mixture was heated at 100 °C (oil bath) for 2 h and then poured into ice water (50 ml). The product was extracted into pentane (3 × 30 ml), and the combined extracts were washed with 5% aqueous sodium bicarbonate solution (3 × 30 ml) and water (2 × 30 ml), and then dried (Na_2SO_4). The solution was then filtered, and solvent was removed via careful fractional distillation. The oily residue was sublimed (100–110 °C, 1 atm), affording pentacyclo[6.3.0.0^{2,6}.0^{3,10}.0^{5,9}]undecane ("trishomocubane", **9**) (0.300 g, 83.4%): mp 146–148 °C (sealed tube) (lit. 150–152,[4] 149–151,[5] 147–149 °C[22]); ir (CCl_4) 2960 (s), 2875 (s), 1455 (m), 1291 (s), and 1270 cm^{-1} (m); ^{1}H NMR ($CDCl_3$) δ 1.36 (br s, 6 H, methylene protons) and 1.97 (br s, 8 H, methine protons); mass spectrum *m/e* 146 (molecular ion) and 80 (100). The foregoing spectral data are in close agreement with the corresponding literature values for **9**.

B. Using Tri-*n*-butyltin Hydride. A mixture of diiodides **3** and **4** (590 mg, 1.5 mmol) in anhydrous diethyl ether (10 ml) was heated to reflux under nitrogen. An excess of freshly distilled tri-*n*-butyltin hydride (1.6 g) was added dropwise to this refluxing solution. The mixture was refluxed for 2.5 h after addition of the tri-*n*-butyltin hydride had been completed. The reaction mixture was then cooled, washed with 5% aqueous sodium hydroxide solution (5 ml) and water (5 ml), and then dried (Na_2SO_4). The dried solution was filtered through silica gel (ca. 4 g), and solvent was removed via careful fractional distillation. The residue was sublimed, affording a colorless solid (182 mg, 83.1%) which was identical in all respects with compound **9** prepared in part A above.

Single-Crystal X-Ray Structural Analysis of 4. The data crystal was obtained from an ethanol solution of **4**. It had ten faces with approximately an ellipsoidal shape having 0.3 and 0.6 mm as minimum and maximum dimensions. The mosaic spread was 1° measured at the peak base using an ω scan. The crystal data follow: $C_{11}H_{12}I_2$; mol wt 398.04; monoclinic; a = 15.650 (4), b = 7.698 (1), c = 9.951 (3) Å; β = 111.30 (2)°; V = 1123.6 Å^3; Z = 4; ρ_{calcd} = 2.368, ρ_{obsd} = 2.360 g cm^{-3} (aqueous thallous formate); $F(000)$ = 736; extinctions hkl ($h + k = 2n + 1$), $h0l$ ($h = 2n + 1, l = 2n + 1$), $0k0$ ($k = 2n + 1$), space group $C2/c$ as confirmed by structure determination; zirconium filtered Mo Kα radiation, λ(Mo Kα_1) = 0.70926 Å for 2θ data and $\bar{\lambda}$ (Mo Kα) = 0.71069 Å for intensity data.

The cell parameters were determined by a least-squares fit to the $+2\theta$ and -2θ values of 42 reflections distributed throughout all of reciprocal space. The 1348 data comprising all unique reflections with $\theta \leq 28°$ were measured using a θ–2θ scan technique. The scan widths were calculated as $\theta° = (1.2 + 0.12 \tan \theta)°$. The aperture was located 173 mm from the crystal; it had a horizontal width (mm) (= 4 + 0.4 tan θ) and vertical width of 6 mm. Maximum scan time was 90 s, with $\frac{2}{3}$ of the time spent on the peak scan and $\frac{1}{6}$ of the time spent on each the left and right background. For 173 reflections the net intensity was indistinguishable from the background, i.e., less than 2σ(T); these reflections were assigned intensities equal to 1.41 σ(T). The weighting scheme used has been described.[24]

Table III. Hydrogen Atom Parameters for 4[a]

	x	y	z	β, Å^2
H (5), H (3)	93 (8)	62 (10)	111 (10)	5.7 (28)
H (8), H (1)	0 (6)	536 (10)	117 (9)	3.6 (18)
H (7), H (11)	128 (6)	364 (13)	144 (9)	4.7 (20)
H (6), H (10)	173 (5)	169 (10)	347 (7)	2.4 (14)
H (2), H (9)	85 (7)	276 (12)	505 (10)	6.0 (24)
H (4), H (4)	− 56 (9)	−83 (9)	159 (11)	4.9 (23)

[a] The positional coordinates are multiplied by 10^3. Pairs of atoms are symmetry related by a twofold axis.

The structure was determined using the heavy-atom method. The least-squares refinement, using the block-diagonal method,[25] converged to a value for R (= $\Sigma||kF_o| - |F_c||\Sigma|kF_o|$) of 0.050 for all 1348 data. Anisotropic temperature factors were given to the iodine and carbon atoms. Anomalous dispersion corrections were made for the iodine. All six independent hydrogen atoms were located and included in the refinement with isotropic temperature factors. In the last cycle of refinement all parameter shifts were less than 0.5 σ. A final difference Fourier map showed peaks around the iodine location of 1.4 e Å^{-3}.

The scattering factors used were from the International Tables for X-Ray Crystallography.[26] The least-squares calculations minimized the quantity $\Sigma w_F(kF_o - F_c)^2$. The mean values for $w_F\Delta F^2$ calculated for ranges of F_o were quite constant, validating the weighting scheme used. The final parameters are shown in Tables II and III. The observed and calculated structure factors are available (see paragraph at end of paper regarding supplementary material).

Brominolysis of 5. Bromine was added dropwise to a solution of **5** (57 mg, 0.4 mmol) in chloroform (3 ml) at 0 °C until the color of bromine persisted. The solution was allowed to stand at room temperature for 24 h, at which time the solution was washed sequentially with aqueous sodium thiosulfate solution and with water. The organic layer was dried (Na_2SO_4), filtered, and then concentrated, affording a mixture of isomeric $C_{11}H_{12}Br_2$ dibromides as an oil (ca. 100 mg). This oil displayed the following spectral characteristics: ir (film) 2970 (s), 2870 (m), 1380 (s), 1200 (s), 780 (s), and 710 cm^{-1} (s); ^{1}H NMR ($CDCl_3$) δ 1.5 (br s) and 1.6 (center of an AB pattern, J_{AB} = ca. 1.5 Hz, total 2 H, methylene protons), 2.0–3.2 (complex m, 8 H, methine protons), and 4.2 (br s) and 4.35 (br s) (total 2 H, ratio ca. 2.5:1, CHBr); mass spectrum (10 eV) *m/e* 306 304 302 (molecular ion corresponding to $C_{11}H_{12}Br_2$, having the intensity profile characteristic of the Br_2 multiplet[27]), 224 (60), 223 (64), 145 (24), 144 (28), 143 (38), 79 (100), and 67 (38). Trituration of this oil with hexane afforded a solid which recrystallized from hexane to afford a colorless material, mp 89–105 °C. No further attempts were made to characterize this mixture.

Control Studies. A. Reaction of 2 with Sodium Iodide–HMPA. A mixture of **2** (718 mg, 2.36 mmol) and sodium iodide (4.1 g, 27.3 mmol) in freshly distilled HMPA (9 ml) was heated at 125–130 °C under nitrogen for 41 h. After this period, water (20 ml) and pentane (20 ml) were added and the layers were separated. The aqueous layer was extracted with pentane (3 × 20 ml), and the combined pentane extracts were washed with water (2 × 20 ml). The pentane solution was then dried (Na_2SO_4), filtered, and concentrated by careful distillation through a 6-in. Vigreux column. The residue (ca. 620 mg) was analyzed as follows: its ^{1}H NMR spectrum displayed signals at δ 4.47 (due to diiodide **2**) and 3.97 (due to diiodides **3** and **4**) having approximately equal areas; VPC

analysis (column temperature 75 °C, He flow rate 120 ml/min) additionally indicated the presence of **6a** and **5** in the ratio ca. 9.5:1. In a separate experiment, **2** was shown to be stable to the VPC conditions employed in the analysis of the above reaction mixture.

B. Reaction of 3 with Sodium Iodide–HMPA. A mixture of **3** (571 mg, 1.88 mmol) and sodium iodide (3.3 g, 22 mmol) in freshly distilled HMPA (8 ml) was heated at 125–130 °C under nitrogen for 47 h. Work-up as described above afforded a crude product (ca. 540 mg) which was analyzed as follows: TLC displayed only one spot with R_f value equal to that of **3**; VPC analysis indicated the absence of any trace of hydrocarbons **5** or **6a**; the ^{1}H NMR spectrum displayed absorption signals corresponding to a mixture of diiodides **3** and **4**, no trace of **2** being detected by this method.

C. Reaction of 4 with Sodium Iodide–HMPA. A mixture of **4** (467 mg, 1.54 mmol) and sodium iodide (3 g, 0.02 mol) in freshly distilled HMPA (8 ml) was heated at 125–130 °C under nitrogen for 41 h. Work-up as described in part A above afforded a crude product (ca. 400 mg) which was analyzed as follows: TLC displayed only one spot whose R_f value was equal to that of **4**; VPC analysis (column temperature 75 °C, He flow rate 120 ml/min) indicated the absence of any trace of hydrocarbons **5** or **6a**; the ^{1}H NMR spectrum of the product exhibited absorption signals corresponding to **3** and **4**, no trace of **2** being detected by this method.

Tetracyclo[6.3.0.0^{4,11}.0^{5,9}]undeca-2,6-diene (6a). To a stirred, refluxing suspension of sodium (0.75 g, 33 mg-atoms) in dry tetrahydrofuran (8 ml) was added dropwise a solution containing diiodides **2, 3,** and **4** (2.0 g, 6.6 mmol) in tetrahydrofuran (10 ml); the entire reaction was conducted under a nitrogen atmosphere. After the addition was complete (ca. 20 min), the milky reaction mixture was refluxed for an additional 1.5 h. The reaction mixture was then filtered to remove insoluble material, and the filtrate was poured into ice water and extracted with pentane. The pentane solution was washed with water, dried (Na_2SO_4), and filtered, and the filtrate was concentrated via careful distillation through a 6-in. Vigreux column. The oily residue was sublimed (125 °C, 1 atm), affording diene **6a** (0.54 g, 74.7%) which was identical in all respects with the corresponding diene obtained from the reaction of **1b** with sodium iodide–HMPA.

Hexacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}.0^{8,11}]undecane (7a). A solution of **6a** (1.45 g, 10.0 mmol) in pentane (350 ml) containing 9-xanthenone (4 g) as sensitizer was photolyzed under nitrogen with a Hanovia 200-W medium-pressure mercury lamp at 10–15 °C for 18 h. After this period, the reaction mixture was rapidly filtered through a short column of silica gel (20 g) to remove insoluble material. The solvent was removed via careful distillation through a 24-in. Vigreux column. The oily residue was sublimed (110 °C, 1 atm), affording a colorless solid (0.95 g). VPC analysis (column temperature 135 °C, He flow rate 120 ml/min) indicated the presence of an unidentified material (6.8%), unchanged **6a** (44.3%), and **7a** (48.9%); the retention times of these three products were ca. 10, 23, and 34 min, respectively. Pure **7a** was isolated via preparative VPC (column temperature 135 °C, flow rate 120 ml/min). An analytical sample of **7a** which was obtained via sublimation (90 °C, 1 atm) of the material thus obtained displayed mp 160–162 °C (sealed tube); ir (CCl_4) 2985 (s), 2870 (m), 1285 (m), 1245 (m), and 890 cm^{-1} (w); ^{1}H NMR ($CDCl_3$) δ 1.73 (t, J = ca. 1.5 Hz, 2 H, methylene protons), 2.67 (br s, 2 H, 3,5-bridgehead protons), and δ 3.03 (s, $W_{1/2}$ = ca. 3 Hz, 8 H, methine protons); mass spectrum *m/e* 144 (molecular ion, 3), 115 (11), 79 (100), 78 (41), 77 (46), 66 (23), 65 (12), 63 (10), 51 (17), and 39 (15). The foregoing ir and ^{1}H NMR spectra were essentially identical with the corresponding spectra obtained for authentic **7a**.[12]

Anal. Calcd for $C_{11}H_{12}$: C, 91.61; H, 8.39. Found: C, 91.66; 91.38; H, 8.37, 8.40.

Transition Metal Catalyzed Rearrangement of 7a. A. Using $(Ph_3P)_2Rh(CO)Cl$. A solution of **7a** (12 mg) in chloroform-*d* (ca. 0.5 ml) was placed in a standard 5-mm NMR sample tube. To this solution were added a few crystals of $(Ph_3P)_2Rh(CO)Cl$, and the mixture was degassed and sealed under vacuum. After 20 h at 70–75 °C, the ^{1}H NMR spectrum of this mixture was recorded; the resulting spectrum was found to be identical with that of diene **6a**. VPC analysis of the product revealed that **6a** was the only material formed in this reaction.

B. Using Silver Tetrafluoroborate. A mixture of **7a** (183 mg) and silver tetrafluoroborate (230 mg) in chloroform (7 ml) was sealed in a 20-ml test tube, and the mixture was heated at 58–62 °C for 4 days. After this period, the tube was opened and the chloroform solution was washed with brine. The organic layer was then dried (Na_2SO_4), filtered, and concentrated via careful distillation. A single volatile material could be separated from the oily residue via preparative VPC (Bentone 34, 5% SE-52 on 60/80 mesh Chromosorb W, 20 ft × 0.375 in. column, column temperature 130 °C, He flow rate 180 ml/min; under these conditions, the product isolated displayed a retention time of 44 min). The material thus collected (113 mg) exhibited a melting point (160–162 °C) and a ^{1}H NMR spectrum which were identical with those of the starting material (**7a**). No other volatile product could be isolated from this reaction.

C. Using Silver Perchlorate. A standard 5-mm NMR sample tube was washed first with dilute, aqueous ammonium hydroxide solution and then with distilled water. The tube was then dried (150 °C) and allowed to cool. A solution of **7a** (36 mg) in benzene-d_6 (0.5 ml) was placed in this tube; silver perchlorate (50 mg) was then added, and the NMR tube was flushed with nitrogen and then sealed. The tube and its contents were heated at 78 °C for 10 days. No change in the ^{1}H NMR spectrum of the reaction mixture was found to occur during (or at the conclusion of) this 10-day heating period. A similar lack of rearrangement of **7a** was observed when this mixture was further heated at 83–110 °C for 24 h.

Kinetic Measurements on the Rh(I)-Catalyzed Rearrangement of 7a. A. Using $(Ph_3P)_2Rh(CO)Cl$. A chloroform-*d* solution (0.5 ml) containing **7a** (37 mg, 0.514 M) and the Rh(I) complex (58.7 mg, 0.171 M) was placed in a standard 5-mm NMR sample tube, degassed (repetitive freeze–thaw method), and sealed under vacuum. The NMR tube was then thermostatted at 67 °C, and ^{1}H NMR spectra were obtained on the reaction mixture at measured intervals. Kinetic measurements were taken over a 24-h period (>2 half-lives). Integration of the signals corresponding to the olefinic protons of the diene (δ 6.0, 4 H, **6a**) and to the methylene protons [δ 1.65–1.75, 2 H (**6a** + **7a**)] permitted calculation of the homopentaprismane concentration at time t as

$$[\mathbf{7a}]_t = [\mathbf{7a}]_0 \times 1 - \left[\frac{\text{(integral of olefinic protons)/4}}{\text{(integral of methylene protons)/2}}\right]$$

B. Using Rhodium Norbornadiene Chloride Dimer. A benzene-d_6 solution (0.5 ml) of **7a** (32.8 mg, 0.456 M) and [Rh(norbornadiene)Cl]$_2$ (3.1 mg, 0.0135 M) was placed in a standard 5-mm NMR sample tube, and the NMR tube was sealed using the procedure described in part A above. Kinetic measurements were performed at 40 °C as described above for a period of 7.5 days (ca. 1 half-life).

Reaction of 11 with Bromine–Red Mercuric Oxide in Carbon Tetrachloride. A mixture of acid **11**[13] (4.4 g, 13.3 mmol) and red mercuric oxide (2.2 g, 10 mmol) in dry carbon tetrachloride (70 ml) was heated to reflux with stirring. A solution of bromine (3.0 g, 16.7 mmol) in carbon tetrachloride (25 ml) was added dropwise over a 1-h period to the refluxing mixture. Vigorous generation of carbon dioxide began in about 15 min, but the bromine color persisted throughout the entire addition period. After the addition of bromine had been completed, the reaction mixture was refluxed for an additional 100 min. The mixture was then cooled and filtered by suction through a Celite mat to remove mercury salts, and the residue was washed with carbon tetrachloride (25 ml). The clear filtrate was washed with 5% aqueous sodium hydroxide solution (30 ml), and the coagulated yellow material which formed during this process was removed via suction filtration. The organic layer was washed with water (2 × 30 ml) and then dried (Na_2SO_4), filtered, and concentrated to afford a colorless oil. Trituration of this oil with hexane afforded a solid which, upon recrystallization from hexane, afforded **12** as a colorless solid (3.95 g), mp 112–116 °C. Sublimation of this material (95 °C, 0.1 mm) followed by several recrystallizations of the sublimate from hexane raised its melting point to 117–120 °C: ir (KBr) 1200–1340 (complex absorption pattern, s) and 600–1090 cm^{-1} (complex absorption pattern, s); ^{1}H NMR ($CDCl_3$) δ 2.83–3.58 (complex m, 4 H, methine protons) and 5.3–5.73 (complex m, 3 H, containing a clearly defined doublet centered at δ 5.32, 1,6,8 protons); mass spectrum *m/e* (molecular ion not observable), 287 (23), 285 (49), 283 (37), 219 (35), 183 (36), 181 (37), 149 (58), 117 (30), 115 (100), 103 (30), and 69 (40). This product was judged to be a mixture of halogenated 11-oxapentacyclo[6.2.1.0^{2,7}.0^{4,10}.0^{5,9}]undecanes (see structure **12**, Scheme II). Accordingly, this material was not further characterized; it was instead dehalogenated to afford a mixture of **6b** and **13** (vide infra).

Dehalogenation of 12 with Lithium–*tert*-Butyl Alcohol in Tetrahydrofuran. To a stirred solution of **12** (7.2 g) and *tert*-butyl alcohol (20 ml, 0.22 mol) in anhydrous tetrahydrofuran (125 ml) under nitrogen was added finely cut lithium wire (3.0 g, 0.40 g-atom). A vigorous exothermic reaction ensued after a few minutes which could be moderated by external cooling (ice bath) to maintain a gentle reflux. When the reaction subsided, the mixture

was heated under reflux for an additional 3 h and then cooled. The mixture was then poured into crushed ice (300 ml), and the aqueous solution was extracted with pentane (3 × 100 ml). The pentane extracts were washed with water (3 × 100 ml), dried (Na_2SO_4), and then filtered. The solvent was removed from the filtrate by distillation through a 6-in. Vigreux column, and the oily residue was sublimed (80 °C, 20 mm) to afford a colorless, waxy material (2.23 g). VPC analysis (column temperature 95 °C, He flow rate 82 ml/min) indicated the presence of two major components (46 and 38%, respectively) and three minor components in this material. No further attempt was made to isolate and characterize the three minor components. However, the two major components could each be readily isolated from the product mixture via preparative VPC (column temperature 150 °C, He flow rate 144 ml/min). The predominant (more volatile, 46%) product was identified as 10-oxatetracyclo[6.3.0.$0^{4,11}$.$0^{5,9}$]undeca-2,6-diene (**6b**): mp 168–169 °C (sealed tube); ir (KBr) 3050 (m), 2960 (s), 1575 (w), 1330 (s), 1250 (m), 1055 (s), 1010 (s), 995 (s), and 895 cm^{-1} (m); ^1H NMR ($CDCl_3$) δ 2.46 (br s, 4 H, 1,4,5,8-methine protons), 5.41 (quintet, J = ca. 3 Hz, 2 H, 9,11 protons), and 5.88 (s, $W_{1/2}$ = ca. 2 Hz, 4 H, vinyl protons); mass spectrum m/e 146 (molecular ion, 7), 118 (17), 117 (100), 115 (26), 91 (14), and 81 (32). The ^1H NMR spectrum of **6b** was identical with that of authentic material.[12]

Anal. Calcd for $C_{10}H_{10}O$: C, 82.16; H, 6.89. Found: C, 82.26; H, 6.97.

The second (less volatile, 38%) of the two major products was identified as 4-oxapentacyclo[5.4.0.$0^{2,6}$.$0^{3,10}$.$0^{5,9}$]undecane (**13**): mp 235–236 °C (sealed tube); ir (KBr) 2970 (s), 2860 (m), 1330 (s), 1035 (s), 975 (s), and 895 cm^{-1} (s); ^1H NMR ($CDCl_3$) AB pattern, δ_A 1.13, δ_B 1.50 (J_{AB} = ca. 12 Hz, 4 H, 8,11-methylene protons; additional coupling is present in the pattern centered at δ 1.13), δ 2.35 (m, 2 H, methine protons), 2.60 (br s, 4 H, methine protons), and 4.73 (symmetrical m, 2 H, 3,5 protons); mass spectrum m/e 148 (molecular ion, 31), 92 (43), 91 (54), 82 (32), 80 (40), 79 (100), 77 (35), 70 (32), 69 (34), 66 (43), 41 (52), and 39 (57).

Anal. Calcd for $C_{10}H_{12}O$: C, 81.04; H, 8.16. Found: C, 81.07; H, 8.07.

Attempted Photocyclization of 6b to 7b. The light source was provided by the following lamps: (A) low-pressure "mercury pencil" lamp (quartz filter), Ultraviolet Products, Inc.; (B) Hanovia 200-W medium-pressure mercury lamp; (C) Hanovia 400-W high-pressure mercury lamp. Conditions for all VPC analysis were as follows: column temperature 80 °C, He flow rate 120 ml/min.

Photocyclization of **6b** to **7b** was attempted, without success, under the following conditions [solvent (sensitizer, if any), light source, temperature, irradiation time]: (a) acetone, lamp A, −78 to 25 °C, 15–20 h; (b) pentane (acetophenone sensitizer), lamp A, 0–25 °C, 10 h; (c) pentane (xanthone sensitizer), lamp A, 0–25 °C, 10 h; (d) pentane, lamp C, 10–15 °C, 20 h; (e) pentane (xanthone sensitizer), lamp C, 10–15 °C, 20 h; (f) pentane (xanthone sensitizer), lamp B, 10–15 °C, 63 h.

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Registry No.—**1b,** 58229-23-5; **2,** 58229-24-6; **3,** 56061-35-9; **4,** 58383-17-8; **5,** 58229-25-7; **6a,** 30114-57-9; **6b,** 58229-26-8; **7a,** 25107-14-6; **9,** 30114-56-8; **10a,** 58229-27-9; **10b,** 58229-28-0; **13,** 58229-29-1.

Supplementary Material Available. A listing of the structure factor amplitudes for compound 4 (6 pages). Ordering information is given on any current masthead page.

References and Notes

(1) (a) Presented in part at the First Chemical Congress of the North American Continent, Mexico City, Mexico, Nov 30–Dec 6, 1975, Paper No. ORGA-67. (b) Taken in part from the dissertation presented by T.-C. Chou, July 1975, to the Graduate College of the University of Oklahoma in partial fulfillment of the requirements for the Doctor of Philosophy Degree.
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Synthesis of Homopentaprismane and Homohypostrophene and Some Comments on the Mechanism of Metal Ion Catalyzed Rearrangements of Polycyclic Compounds[1]

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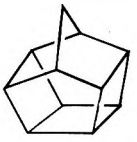
The synthesis of homohypostrophene (tetracyclo[6.3.0.0^{4,11}.0^{5,9}]undeca-2,6-diene) and homopentaprismane (hexacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}.0^{8,11}]undecane) is described. Proofs of structure based on ^{13}C nuclear magnetic resonance spectroscopy are given. The metal ion catalyzed reactions of homopentaprismane are considered. Certain aspects of the mechanism of the silver ion catalyzed rearrangements of polycyclic compounds are considered in some detail.

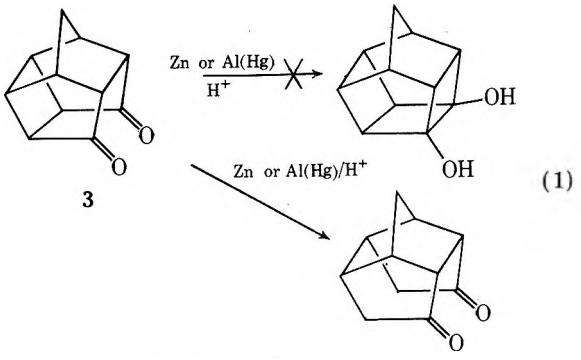
We have completed the synthesis and unambiguous proof of structure of homopentaprismane (**1**)[2a] and of its progenitor homohypostrophene (**2**).[2b] The skeleton of ho-



1

2

mopentaprismane has one more carbon–carbon bond (and one more ring) than that of the closely related and well-known pentacyclic diketone **3**.[3] However, direct closure of **3** or a relative to a homopentaprismane derivative, although tried in many laboratories, has not been achieved. Other reactions intervene. For example, attempted pinacol closure (eq 1) leads instead to quantitative reductive cleavage of the cyclobutane ring.[3,4] A previously reported synthesis of homopentaprismane,[2a] supposedly by a direct cyclization approach, is now known to be in error.[5]

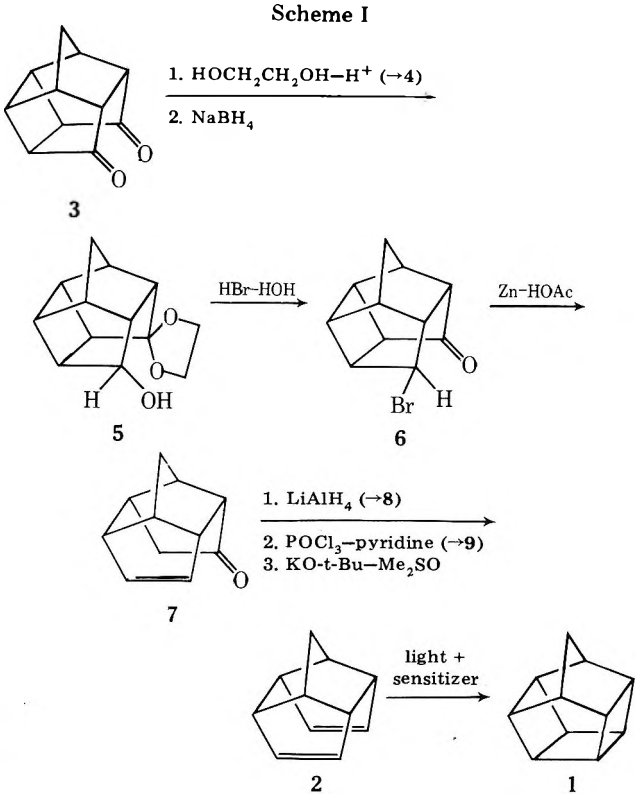


3 (1)

Synthesis. In our successful approach (Scheme I) we make use of the ready reductive cleavage of the cyclobutane ring in a derivative of **3** to establish a good, preparatively useful route to the tetracyclic diene homohypostrophene.[6] The diene is then closed to homopentaprismane by $2\pi + 2\pi$ intramolecular photocycloaddition.

Reaction of **3** with ethylene glycol and toluenesulfonic acid in boiling benzene gives the monoketal **4** in excellent yield. Bisketalization is not a problem. Reduction of **4** with sodium borohydride in ethanol and work-up in dilute hydrochloric acid produces the hydroxy ketal **5**, homogeneous by TLC and GLC after molecular distillation.[7,8] Treatment of **5** with 48% aqueous hydrobromic acid at 80 °C gives the bromo ketone **6** in 90% yield. Reductive cleavage of this bromo ketone with zinc metal powder in boiling acetic acid, the key step in the sequence, gives better than 90% yield of the enone **7**. We find no evidence for any substantial interaction between the chromophoric units in **7**: λ_{max} (cyclohexane) 299 nm (ϵ 17).

Scheme I

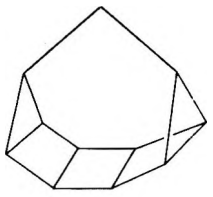


Lithium aluminum hydride reduction of the enone yields the corresponding enol **8**, which can be converted satisfactorily (70–80%) directly to the ene chloride **9** by reaction with phosphorus oxychloride in pyridine on the steam bath. Dehydrochlorination of crude enechloride to homohypostrophene occurs slowly, but effectively, upon reaction under nitrogen with potassium *tert*-butoxide in dimethyl sulfoxide on the steam bath. The pure diene (35% in two steps from the enol) can be isolated by extraction into pentane and separation from sulfurous contaminants by chromatography on alumina followed by careful bulb-to-bulb transfers under high vacuum. The gas-phase ultraviolet spectrum of homohypostrophene, λ_{max} 202 nm, indicates some interaction between the two pairs of sp^2 centers; the photoelectron spectrum will be of interest. Homohypostrophene rearranges slowly at room temperature, probably in Cope fashion, but we have not pursued this aspect of its chemistry. The diene is also somewhat sensitive to oxygen.

Ultraviolet irradiation of homohypostrophene in the presence of suitable sensitizers (xanthone or acetone) gives homopentaprismane. This reaction is not completely clean, but fortunately homopentaprismane is the only volatile

product formed in significant quantity. Isolated yields (preparative GLC) of 50% have been obtained.

Proofs of Structure. From the synthesis and the proton NMR data a strong case can be made in the usual manner for assigning the structures homopentaprismane and homohypostrophene to our synthetic products. Much more interesting is the point that *unequivocal, de novo proofs of structure are available from consideration of their* ^{13}C *NMR spectra:* compound **1** (22.63 MHz, $CDCl_3$), δ 40.7 (1 CH_2, t, J = 131 Hz), 42.6 (4 CH, d, J = 149 Hz), 49.0 (4 CH, d, J = 146 Hz), and 51.2 ppm (2 CH, d, J = 140 Hz); compound **2**, δ 31.8 (1 CH_2, t, J = 130 Hz), 49.0 (4 CH, d, J = 143 Hz), 64.9 (2 CH, d, J = 147 Hz), and 137.1 ppm (4 CH, d, J = 164 Hz). Of the possible $C_{11}H_{12}$ structures, only homopentaprismane and its isomer **10** and homohypostrophene and its isomers **11**–**13** have the correct hydrogen distribution and sufficient symmetry to give rise to the observed ^{13}C spectral patterns. If structure **10**, **11**, or **12** pertained, ^{13}C–H coupling constants in excess of 160 Hz would arise from the cyclopropyl CH units (cf.[9] cuneane). All observed coupling constants for the saturated CH units in **1** and **2** are well below this figure. If structure **13** (or **12**) were applicable, the vinyl ^{13}C–H coupling constant would be 170 Hz or greater (cf.[10] cyclobutene). The observed coupling is significantly below this value. It is certain, therefore, that the assigned structures are correct.



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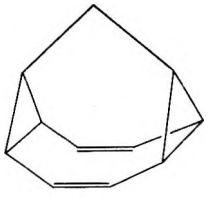

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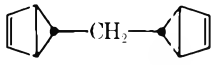
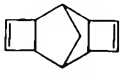


(syn,syn or anti,anti)

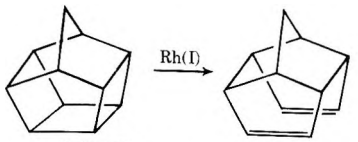
12



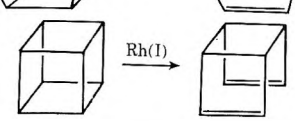
(bis-endo or bis-exo)

13

Metal Ion Catalyzed Rearrangements. Homopentaprismane is cleaved cleanly to homohypostrophene by rhodium(I) complexes, e.g., [Rh(norbornadiene)Cl]$_2$, acting catalytically (eq 2).[11] The reaction is analogous to that observed for cubane (eq 3), but the rate of reaction of cubane is orders of magnitude greater.[12] It seems clear, intuitively, that the release of strain on opening the cubane system would be greater than on cleaving homopentaprismane. The origin of the difference in rate of reaction may well be here and/or in the different p character of the carbon bonds. $J_{^{13}C-H}$ in cubane is 160 Hz,[13] whereas in homopentaprismane it is only 149 Hz at the relevant carbon atoms; it follows[14] that the p character of the carbon–carbon bonds is greater in cubane than in homopentaprismane. This should increase the ease of oxidative addition to the metal ion and the susceptibility to subsequent rearrangement.

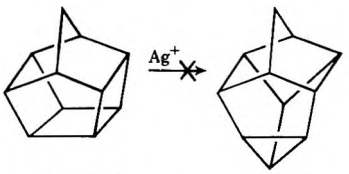


(2)

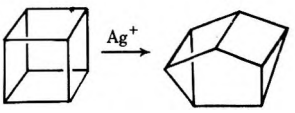


(3)

Silver salts do not rearrange homopentaprismane (eq 4),[15] even under conditions very much more drastic than



(4)



(5)

those required to rearrange cubane (eq 5),[9] or its less reactive relatives.[16] We believe that this observation bears importantly on the mechanism of silver ion catalyzed rearrangements of polycyclic systems.

The Chicago school originally proposed,[17] and still favors, a nonconcerted, carbonium ion rearrangement to account for the known silver ion catalyzed rearrangements of relevant systems. The proposed course of these reactions is outlined in simplified form in Chart I for various cubane systems and *syn*-tricyclo[4.2.0.0^{2,5}]octane (I–V).[9,16] For comparison, the hypothetical course of the conversion (unobserved) of homopentaprismane (VIa) to the less strained undecane VId is included. The first and the last steps in the rearrangements are common to each case. At the beginning (a → b), silver is introduced, and the central bond of a bicyclo[2.2.0]hexane subunit is broken. At the end (c → d), silver is extruded, and a cyclopropane ring is closed. In the first four cases, all of which proceed easily, the second step (b → c), in which a bond migrates, is accompanied by the formation of a cyclopropane ring at the expense of two cyclobutane rings—downhill by about 21 kcal/mol. (Note: for simplicity only the strain energies of the small rings are taken into account in these rough calculations.) In the fifth case, the conversion of *syn*-tricyclooctane to tetrahydrosemibullvalene, which also occurs readily, the bond migration in the second step is accompanied by the loss of one cyclobutane ring—downhill by about 24 kcal/mol. Only in the last case, the one that does not occur, is there no net loss of a strained ring in the bond migration step. Without this driving force, the reaction does not go.

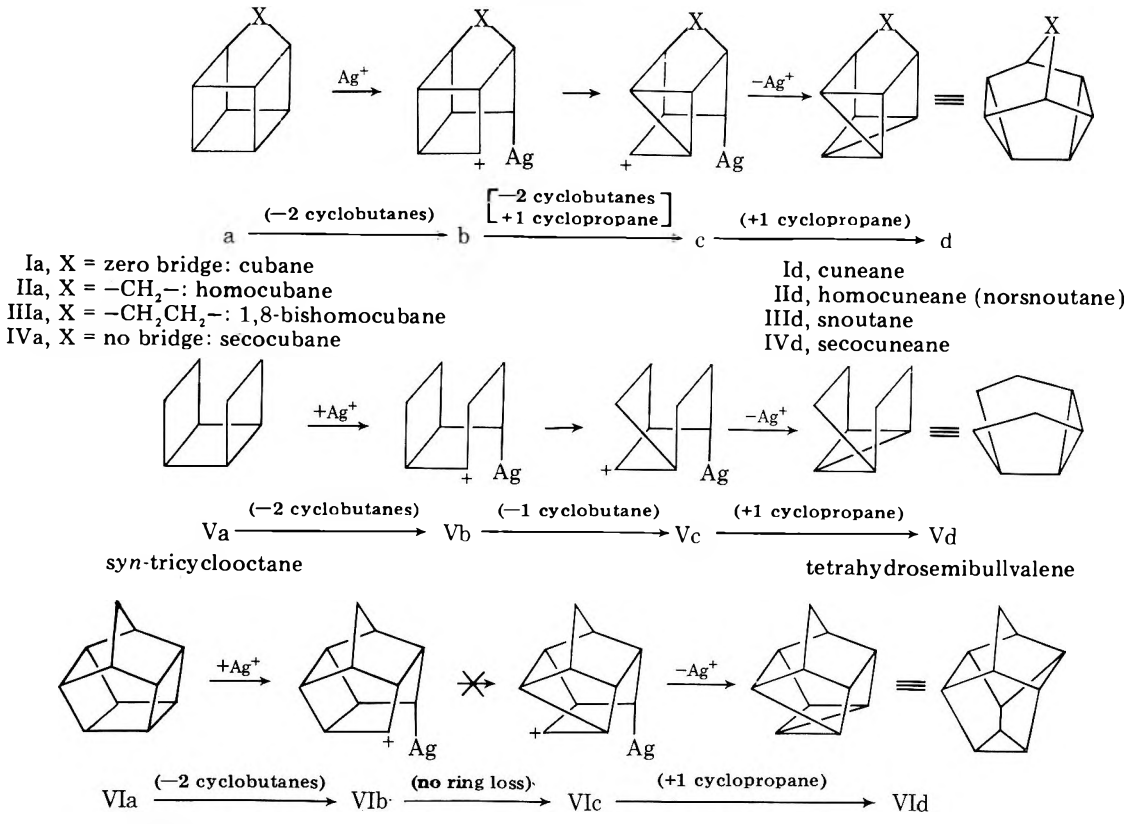
We conclude from this simple exercise in bookkeeping that it is altogether likely that the rate-determining step in these silver ion catalyzed rearrangements is the bond migration (b → c). It follows that the first step, the cleavage by the metal, must be reversible. In the case of 4-methylhomocubane the silver-catalyzed rearrangement is known to be preceded by the reversible formation of a "complex" between the homocubane and the metal ion.[16e] We speculate reservedly that this complex may be the ion that subsequently rearranges. We shall examine related cases in the future in detail.

Why should the bond migration step be rate determining? We suggest that there is a significant stabilizing interaction between silver and the carbonium ion in the intermediates Ib–VIb, namely[18]

In the rearranged intermediates Ic–VIc this stabilization would be less efficient, for the geometric arrangement

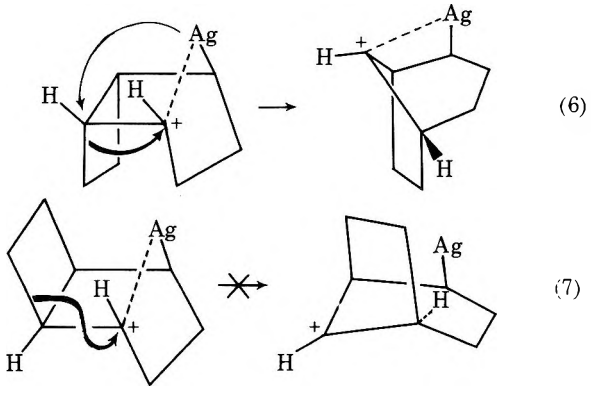
is distinctly less favorable. The decrease of stabilization energy would, of course, appear (in part) as an increase in the activation barrier to rearrangement. (Note also that rear-

Chart I



rangement from one silver stabilized ion to the other requires inversion of configuration at the origin and terminus of the migrating bond.) Without a significant difference in the degree of silver interaction with the carbonium ion, VIb and VIc appear approximately isoenergetic (in less stilted drawings), and the origin of an important barrier between them becomes obscure. Similarly, the interaction between silver and the carbonium ion in VIb can account for the lack of rearrangement of this ion into the (D_3)-trishomocubyl series—a rearrangement known to occur easily from this system in the absence of a silver substituent.[19]

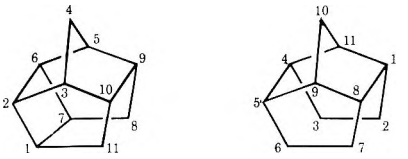
Although *syn*-tricyclooctane (Va) is rearranged readily by silver ion, the anti isomer is not. Contrary to some opinions,[16f] this observation is not only not troublesome, but helps confirm our mechanistic interpretation. The bond shift in the rate-determining step of these rearrangements occurs to the back side of the silver bridged ion—inversion at the site is required to account for cubane → cuneane type transformations. This geometric requirement is easily accommodated in the syn series (eq 6), but is not practica-



ble in the anti compound, as inspection of a model will show (eq 7).

Experimental Section

The position numbering systems used in the formal naming are illustrated.



Proton magnetic resonance spectra were taken at 270 MHz on solutions in deuteriochloroform and are referenced to internal Me_4Si. Most spectra were recorded for convenience on compressed scale (3 Hz/mm); therefore, quoted shifts are ±0.02 ppm and coupling constants are ±1 Hz, sufficient accuracy for the present purposes. Only interpretations relevant to the stereochemical assignments are given. Further interpretations are either obvious or moot. Infrared spectra were taken on solutions in chloroform unless otherwise noted; positions of interesting absorptions are quoted ±5 cm^{-1}. The high-resolution mass spectrum of each new compound was recorded on an MS-9 spectrometer operating at 50 eV ionization voltage. Each compound exhibited a proper parent peak at *m/e* within 30 ppm of the expected value.

Pentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecane-8-11-dione Monoethylene Ketal (4). A mixture of diketone 3[3] (10.0 g, 57.5 mmol), ethylene glycol (3.57 g, 57.6 mmol), *p*-toluenesulfonic acid (125 mg), and 50 ml of benzene was refluxed with good stirring for 5 h. The reaction mixture was then cooled and poured slowly into 50 ml of ice-cold 10% aqueous sodium carbonate. Work-up with methylene chloride and crystallization from ether–hexane afforded 11.07 g (87%) of the desired monoketal: mp 73.0–73.5 °C; ir ν 1750 cm^{-1}; ^1H NMR δ 3.91 (4 H, m), 3.0–2.5 (8 H, multiplet sets), 1.88, 1.58 ppm (1 H each, doublet pair, $J \sim 10$ Hz).

***exo*-11-Bromopentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecan-8-one (6).** The monoketal 4 (2.20 g) was dissolved in 25 ml of warm absolute ethanol. The solution was cooled in an ice bath. A freshly prepared, cold solution of sodium borohydride (0.76 g) in 17 ml of water was added with stirring over 6 min. The reaction mixture was left for 2 h in the ice bath and then removed to room temperature for 2 more h. The mixture was put back into the ice bath and 10 ml of 3% hydrochloric acid was added drop by drop. After a standard work-up with methylene chloride, 2.21 g of crude hydroxy ketal 5 was obtained. Molecular distillation at 139 °C (0.25

Torr) gave a clear, homogeneous oil:[7] ^{1}H NMR δ 4.62 [1 H, t, $J \sim 5$ Hz, HC(1)-**H(exo)**C(11)-HC(10)], 3.71, 3.79 (2 H each, m), 3.4 (1 H, bs, OH), 2.9–2.4 (8 H, multiplets), 1.56, 1.91 ppm (1 H each, doublet pair, $J \sim 10$ Hz).

The crude hydroxy ketal was usually taken on without distillation directly to the bromo ketone **6** by stirring it in a large excess of 48% hydrobromic acid at 80° for 3 h. The acid solution was then cooled to room temperature and quenched in iced water. The crystalline precipitate was collected, washed with water, and recrystallized from a small volume of methanol, giving, in various runs, about 90% yield overall of pure **6**: mp 84.5–85.3 °C; ir ν 1760 cm^{-1}; ^{1}H NMR δ 4.28 [1 H, bs, **H(endo)**C(11)Br], 3.29 (1 H, m), 3.15 (2 H, m), 2.98 (1 H, m), 2.79 (2 H, m), 2.61 (1 H, m), 2.40 (1 H, m), 1.67, 1.92 ppm (1 H each, doublet pair, $J \sim 11$ Hz).

Tetracyclo[6.3.0.0^{4,11}.0^{5,9}]undec-2-en-6-one (7). The bromo ketone **6** (17 g) was dissolved in 200 ml of glacial acetic acid. The solution was stirred mechanically (good stirring is essential); zinc powder (27 g) was added. The mixture was refluxed with stirring for 8 h, cooled, and filtered. The filter cake was washed carefully with ether. The filtrate and ether washings together were mixed with water. Standard work-up of the ether layer including washes with aqueous sodium bicarbonate to remove acetic acid gave 10.5 g (92%) of crystalline ene ketone **7** as shiny plates. A pure sample was obtained by crystallization from pentane: mp 192–193 °C; ir (CCl_4) ν 2970, 1745 cm^{-1}; ^{1}H NMR δ 6.05, 5.94 (1 H each, both d of d, $J \sim 6$ and 3 Hz), 3.06 (1 H, m), 2.82 (2 H, m), 2.63 (1 H, m), 2.44 (2 H, m), 2.18 [1 H, d of d, $J \sim 19$ and 6 Hz, HC(8)-**H(exo)**HC(7)]; 2.01 [1 H, d, $J \sim 19$ Hz, **H(endo)**HC(7)], 1.83, 1.72 ppm (1 H, each, doublet pair, $J \sim 11$ Hz).

***endo*-Tetracyclo[6.3.0.0^{4,11}.0^{5,9}]undec-2-en-6-ol (8).** A solution of 5.6 g of the ene ketone **7** in 40 ml of anhydrous ether was added under nitrogen to a stirred mixture of 1.5 g of lithium aluminum hydride and 40 ml of ether cooled in an ice bath. The mixture was stirred for 3 h cold and then left overnight at room temperature. The excess reducing agent was destroyed with aqueous sodium hydroxide according to the standard procedure.[20] The precipitate was removed by filtration and washed with ether. The filtrate was washed with water, dried, and concentrated, leaving 5.5 g (97%) of white, crystalline enol **8** sufficiently pure to be taken on in the next step. A pure sample of **8** was prepared by recrystallization from pentane and sublimation: mp 215–216 °C (sealed tube); ir ν 3600, 2975, 1410 cm^{-1}; ^{1}H NMR δ 6.39 (1 H, bs, $W_{1/2} \sim 10$ Hz), 5.94 (1 H, $W_{1/2} \sim 10$ Hz), 4.47 [1 H, 5 lines overlapping d of t (?), spacing ~4 Hz, H_2C(7)-**H(exo)**C(6)-HC(5)], 7.9 (1 H, bs, OH), 2.7–2.1 (7 H, multiplets), 1.60 (2 H, bs), 1.53 ppm [1 H, d of d, $J \sim$ 15 and 5 Hz, **H(endo)**HC(7)-H(exo)C(6)].

Tetracyclo[6.3.0.0^{4,11}.0^{5,9}]undeca-2,6-diene. Homohypostrophene (2). Phosphorus oxychloride (23 g) was added slowly with swirling to a solution of 4.86 g of the enol **8** in 40 ml of pyridine. The mixture was heated on the steam bath for 5 h. The dark brown solution was then cooled and poured into 200 ml of iced water. This mixture was extracted with pentane, and the extract was washed with 10% hydrochloric acid, 10% sodium bicarbonate solution, water, and saturated brine, in that order, and then dried carefully. The solvent was removed at atmospheric pressure through a 10-cm Vigreux column. The residue was the crude ene chloride **9**: ^{1}H NMR δ 6.09 (2 H, m, $W_{1/2} \sim 5$ Hz), 4.24 [1 H, clean d of d, $J \sim 7$ and 3 Hz, HC(5)-**H(endo)**C(6)-HC(7)], 2.99 (1 H, bs), 2.91 (1 H, bs), 2.54 (1 H, m), 2.43 (3 H, m), 2.89 [1 H, clean d of d, $J \sim$ 15 and 7 Hz, HC(6)-**H(endo)**HC(7)], 2.03 [1 H, d + additional smaller couplings, $J \sim 15$ Hz, probably HC(6)-**H(exo)**HC(7)-HC(8)], 1.68, 1.60 ppm (1 H each, doublet pair, $J \sim 12$ Hz).

The ene chloride was used without further purification. It was taken up in 20 ml of dry dimethyl sulfoxide, and this was added with shaking to a solution of 5 g of alcohol-free potassium *tert*-butoxide in 80 ml of dimethyl sulfoxide. The mixture was heated under nitrogen on the steam bath for 8–10 h, then cooled and quenched in water. The product was extracted into purified pentane. The brown-yellow extract was decolorized and freed from sulfurous impurities by passing it through a 1 × 10 cm column of alumina. The clear, colorless eluate was concentrated on the steam bath beneath a 20-cm Vigreux column. Residual pentane was removed by transfer at 20 mm pressure from the sample at room temperature to a trap at −70 °C. The diene was purified by repeated sublimation at high vacuum, keeping the middle cut; the final product (1.6 g, 35% in two steps from enol **8**) had mp 139–140 °C (sealed tube); ir (acetone-d_6) ν 3060, 1590, 843, 730 cm^{-1}; ^{1}H NMR δ 5.86 (4 H, $W_{1/2} \sim 3$ Hz), 3.13 (2 H, $W_{1/2} \sim 3$ Hz), (2.31 (4 H, $W_{1/2} \sim 5$ Hz), 1.64 ppm (2 H, $W_{1/2} \sim 3$ Hz).

Hexacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}.0^{8,11}]undecane. Homopentaprismane (1). A solution of 500 mg of homohypostrophene in 2 ml of benzene containing 10 mg of xanthone was prepared in a standard 1-cm quartz cuvette. The solution was exposed to the focused beam from a 500-W Osram mercury arc filtered through 5 cm of water and a single Pyrex plate 3 mm thick. The photoreaction was followed by GLC on OV-225. Irradiation was continued until the diene concentration had been reduced by 95%. Homopentaprismane was isolated from the reaction mixture by preparative GLC on a 3 ft × 0.25 in. column of 15% OV-225 on 60/80 Gas-Chrom Q at 120 °C. The material was purified by repeated sublimation under high vacuum. The yield of pure material was 40–50% in various runs on this scale: mp 160–161 °C (sealed tube); ^{1}H NMR δ 3.02 (8 H, $W_{1/2} \sim 3$ Hz), 2.70 (2 H, $W_{1/2} \sim 8$ Hz), 1.76 ppm (2 H, $W_{1/2} < 3$ Hz).

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Registry No.—**1**, 25107-14-6; **2**, 30114-57-9; **3**, 2958-72-7; **4**, 58228-93-6; **5**, 58228-94-7; **6**, 58228-95-8; **7**, 58228-96-9; **8**, 58228-97-0; **9**, 58228-98-1; ethylene glycol, 107-21-1.

References and Notes

(1) The synthetic work in this paper was first reported by one of us in an invited lecture at the 155th National Meeting of the American Chemical Society, San Francisco, Calif., April 1968.
(2) For the origin of the trivial names see (a) G. R. Underwood and B. Ramamoorthy, *Chem. Commun.*, 12 (1970); (b) J. S. McKennis, L. Brener, J. S. Ward, and R. Pettit, *J. Am. Chem. Soc.*, **93**, 4957 (1971).
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(6) Cf. G. R. Underwood and B. Ramamoorthy, *Tetrahedron Lett.*, 4125 (1970).
(7) Acid-catalyzed reorganization of the hydroxyl and ethylene ketal groups to $HOCH_2CH_2O$–C–O–C–H has been observed on occasion.
(8) Assignments of stereochemistry to this compound and the others reported here are based on simple mechanistic considerations strengthened by our analysis of the NMR spectra of these compounds (see Experimental Section).
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(11) In a typical run, a $CDCl_3$ solution 0.2 M in **1** and 0.06 M in catalyst was heated at 65 °C. The reaction was monitored by NMR and was complete in less than 3 h.
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(15) No reaction of **1** could be detected in a benzene-d_6 solution 0.2 M in **1** and 2.4 M in silver perchlorate heated at 65 °C for 3 h. The projected product is known and is detectable and stable under conditions similar to those of this experiment (A. Marchand and T.-C. Chou, private communication).
(16) (a) W. G. Dauben, C. H. Schallhorn, and D. L. Whalen, *J. Am. Chem. Soc.*, **93**, 1466 (1971); (b) L. A. Paquette and J. C. Stowell, *ibid.*, **92**, 2584 (1970); **93**, 2459 (1971); (c) L. A. Paquette and R. S. Beckley, *ibid.*, **97**, 1084 (1975); (d) L. A. Paquette, R. S. Beckley, and W. B. Farnham, *ibid.*, **97**, 1089 (1975); (e) L. A. Paquette, J. S. Ward, R. A. Boggs, and W. B. Farnham, *ibid.*, **97**, 1101 (1975); (f) J. Wristers, L. Brenner, and R. Pettit, *ibid.*, **92**, 7499 (1970).
(17) J. E. Byrd, L. Cassar, P. E. Eaton, and J. Halpern, *Chem. Commun.*, 40 (1971).
(18) The extreme of this interaction

corresponds to oxidative addition to silver(I) with formation of silver(III). As has been pointed out,[16d,f] this seems unfavorable energetically. We do not now propose * as an intermediate. The interaction we are concerned with here is much less extreme.
(19) S. A. Godleski, P. v. R. Schleyer, E. Osawa, and G. J. Kent, *J. Chem. Soc., Chem Commun.*, 976 (1974).
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Synthesis of υ-Triazolo[4,5-c]pyridine Nucleosides and 4-(β-D-Ribofuranosyl)amino-1,2,3-thiadiazolo[5,4-b]pyridine via a Rearrangement[1]

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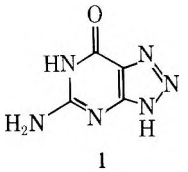
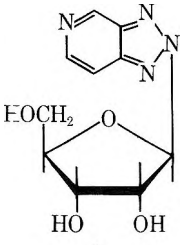
Nucleoside products isolated from the ribosylation of 4-chloro-υ-triazolo[4,5-c]pyridine have been identified as 4-chloro-1-(β-D-ribofuranosyl)-υ-triazolo[4,5-c]pyridine (major), 4-chloro-2-(β-D-ribofuranosyl)-υ-triazolo[4,5-c]pyridine (minor), and 4-chloro-3-(β-D-ribofuranosyl)-υ-triazolo[4,5-c]pyridine (minor). The isomer ratio was found to be dependent on the ribosylation conditions employed. Reaction of 4-chloro-1-(β-D-ribofuranosyl)-υ-triazolo[4,5-c]pyridine with the appropriate nucleophile has provided 4-amino-1-(β-D-ribofuranosyl)-υ-triazolo[4,5-c]pyridine (3-deaza-8-azaadenosine) and 4-methylthio-1-(β-D-ribofuranosyl)-υ-triazolo[4,5-c]pyridine. However, thiation of 4-chloro-1-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)-υ-triazolo[4,5-c]pyridine, followed by deprotection, gave 4-(β-D-ribofuranosyl)amino-1,2,3-thiadiazolo[5,4-b]pyridine via a υ-triazole–1,2,3-thiadiazole rearrangement. A comparison of the uv spectral data for 1-(β-D-ribofuranosyl)-υ-triazolo[4,5-c]pyridine (**25**) with that of 1-methyl-υ-triazolo[4,5-c]pyridine (**23**) has indicated that the site of ribosylation for **25** cannot be established by the empirical model methyl rule. Other procedures were used to establish the site of ribosylation for **25**.

The isolation[2] and characterization of the antibiotic pathocidin as 8-azaguanine (**1**) created considerable interest in the biochemical and chemotherapeutic properties of a variety of 8-azapurine derivatives. Certain 8-azapurine (υ-triazolo[4,5-d]pyrimidine) derivatives have been reported[3] to act as purine antimetabolites. Some recent reports[4–7] of interesting biological and chemotherapeutic activity for 8-azapurine nucleosides, specifically 8-azainosine, prompted us to initiate research designed to furnish the 3-deaza analogues of these nucleosides. A perusal of the literature during the initiation of this study revealed that only one 3-deaza-8-azapurine (υ-triazolo[4,5-c]pyridine) nucleoside had been reported[8] [**2**, 2-(β-D-ribofuranosyl)-υ-triazolo-[4,5-c]pyridine]. In fact, at the time there had been only a very limited amount of research conducted on the parent ring system, although there have been some recent reports[9,10] on a number of υ-triazolo[4,5-c]pyridine derivatives.



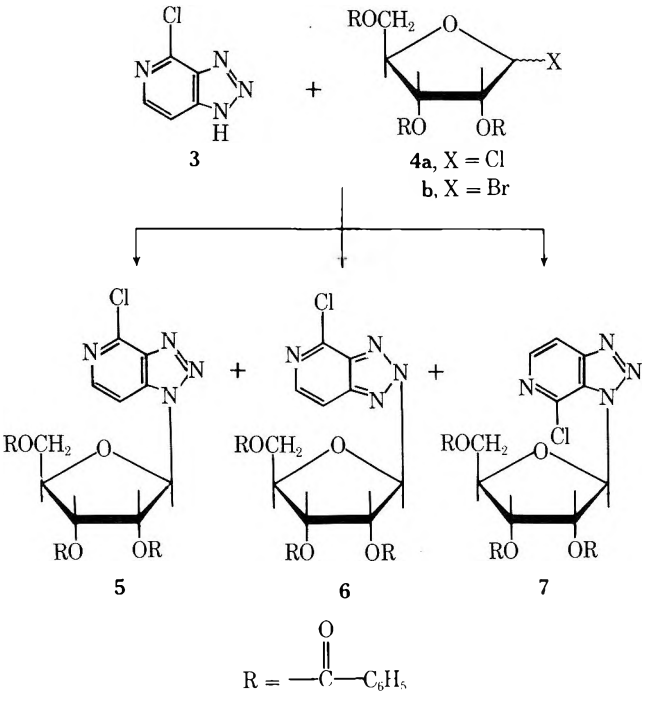
1



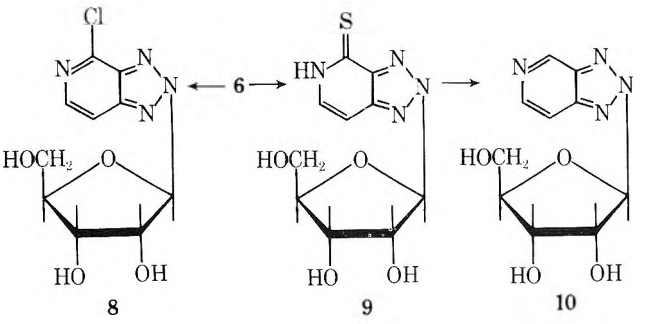
2

We elected to use 4-chloro-υ-triazolo[4,5-c]pyridine[11] (**3**) as our starting heterocycle in the glycosylation procedure[12,13] in an effort to obtain the 1-ribosyl derivative. The condensation of 4-chloro-υ-triazolo[4,5-c]pyridine (**3**) with 2,3,5-tri-O-benzoyl-D-ribofuranosyl chloride (**4a**) gave a mixture of nucleosides. This isomeric mixture was resolved by extensive column chromatography to give three nucleoside products, the structures of which were subsequently established as 4-chloro-1-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)-υ-triazolo[4,5-c]pyridine (**5**), 4-chloro-2-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)-υ-triazolo[4,5-c]pyridine (**6**), and 4-chloro-3-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)-υ-triazolo[4,5-c]pyridine (**7**) in 11, 15, and 8% yield, respectively, for a total nucleoside yield of 34% (Scheme I). However, since the desired isomer (**5**) was obtained in only minor quantities, this emphasized the need for a more suitable glycosylation procedure. A variety of standard glycosylation procedures (e.g., Wittenberg, silyl fusion, and acid-catalyzed fusion)[14] and modifications were investigated; however, no significant change in the product distribution or yield was observed. A nitrogen to nitrogen glycosyl migration has been recently reported[15] for the conversion of 7-methylthio-2-(2,3,5-tri-O-acetyl-β-D-ribofuranosyl)-υ-triazolo[4,5-d]pyrimidine to the desired 3-glycosyl derivative. Unfortunately, attempts to obtain a similar glycosyl migration with 7-amino-2-(2,3,5-tri-O-acetyl-β-D-ribofuranosyl)-υ-triazolo[4,5-d]pyrimidine were unsuccessful,[15] indicating that such migrations may not be very general in scope. Iodine has been reported to be an effective catalyst in promoting glycosyl migrations with certain indazole[16] and pyrazolo[3,4-b]pyrazine[17] glycosides. These observations prompted us to try this approach with a mixture of **5**, **6**, and **7**. When this mixture was heated in toluene at reflux temperature in the presence of molecular sieve, no change in the isomeric content was observed. A variety of other

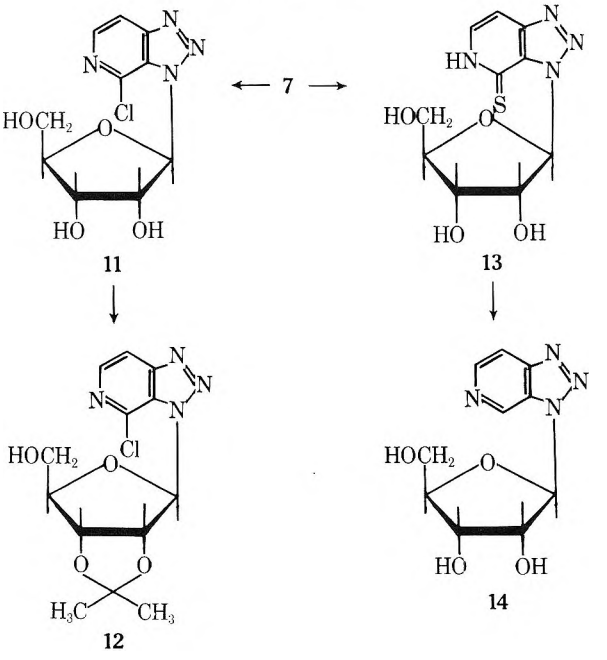
Scheme I



Scheme II



Scheme III



solvents were investigated with no glycosyl migration being observed. Treatment of a melt of the isomeric mixture with iodine resulted in extensive decomposition with no apparent glycosyl migration.

It was assumed that the monosilyl product used for glycosylation was actually a mixture of the 1-, 2-, and 3-trimethylsilyl derivatives of **3**. It was further assumed, based on proposed glycosylation mechanisms,[18] that if a trimethylsilyl derivative of higher integrity could be obtained, the isomer ratio of the nucleoside products could possibly be altered to provide **5** as the major nucleoside product.

A suspension of **3** in xylene was silylated with *N,O*-bis(trimethylsilyl)acetamide at 40 °C. The resulting solution was then heated (110 °C) with the solvent and excess silylating agent being removed at this temperature to provide a crystalline silyl derivative. This silyl derivative was glycosylated with 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl bromide (**4b**) in acetonitrile in the presence of mercuric cyanide at reflux temperature to give the three isomeric nucleosides, **5, 6,** and **7,** in a distribution which was much more favorable for our specific interests (**5,** 25%; **6,** 12%; and **7,** 4%). When this procedure was followed without heating the silylation mixture at an elevated temperature, the yield and isomeric distribution of the nucleoside products was similar to previous results (vide supra). This would indicate that the thermodynamically more stable monosilyl derivative of **3** was formed and that this species favored the formation of **5.** The structure of this monosilyl derivative and the dependence of the increased yield of **5** on the solvent and glycosylation procedure used is currently under investigation.

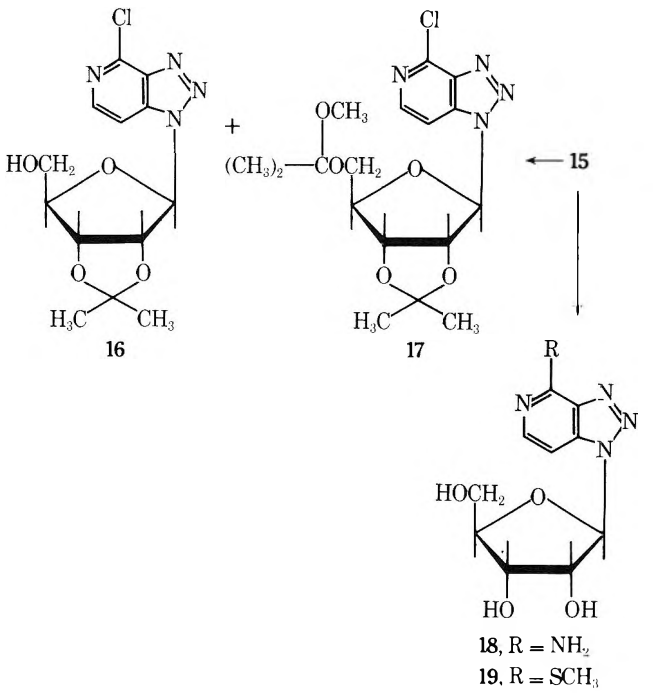
We then initiated studies designed to provide unequivocal assignments for the anomeric configuration and site of ribosylation for **5, 6,** and **7.** The nucleoside **6** was assigned the β configuration on the basis of a $J_{H_{1'},H_{2'}} = 0$ Hz, at δ 6.86 for the anomeric proton. Treatment of **6** with methanolic sodium methoxide provided 4-chloro-2-(β-D-ribofuranosyl)-*v*-triazolo[4,5-*c*]pyridine (**8**) (Scheme II). Thiation and deprotection of **6** with sodium hydrogen sulfide gave 2-(β-D-ribofuranosyl)-*v*-triazolo[4,5-*c*]pyridine-4-thione (**9**). Dethiation of **9** with Raney nickel provided 2-(β-D-ribofuranosyl)-*v*-triazolo[4,5-*c*]pyridine (**10**) [λ_{max} (pH 1) 296 nm (ϵ 6400), 263 (9100); λ_{max} (pH 11) 279 nm (ϵ 6600), 263 (7900); $[\alpha]^{33}D$ −83.5° (*c* 1.0, CH_3OH)] which compared favorably with the data reported previously[8] for **10** [λ_{max} (pH 1) 298 nm (ϵ 4300), 265 (6300); λ_{max} (pH 11) 280 nm (ϵ 5700), 268 (5800); $[\alpha]^{22}D$ −70° (*c* 1, CH_3OH)]. This established the actual site of ribosylation for **6** as N-2 and the anomeric configuration as β.

The coupling constant for the anomeric proton resonance of **7** was 1.0 Hz, which established the anomeric configuration of **7** as β. The nucleoside **7** was deprotected with methanolic sodium methoxide to give 4-chloro-3-β-D-ribofuranosyl)-*v*-triazolo[4,5-*c*]pyridine (**11**) (Scheme III). To further substantiate the configurational assignment for **7,** the nucleoside **11** was converted to 4-chloro-3-(2,3-*O*-isopropylidene-β-D-ribofuranosyl)-*v*-triazolo[4,5-*c*]pyridine (**12**).[19] The difference between the chemical shifts observed for the isopropylidene methyl groups of **12** was 0.23 ($\Delta\delta$) which is in agreement with the reported values for β-ribonucleosides.[20]

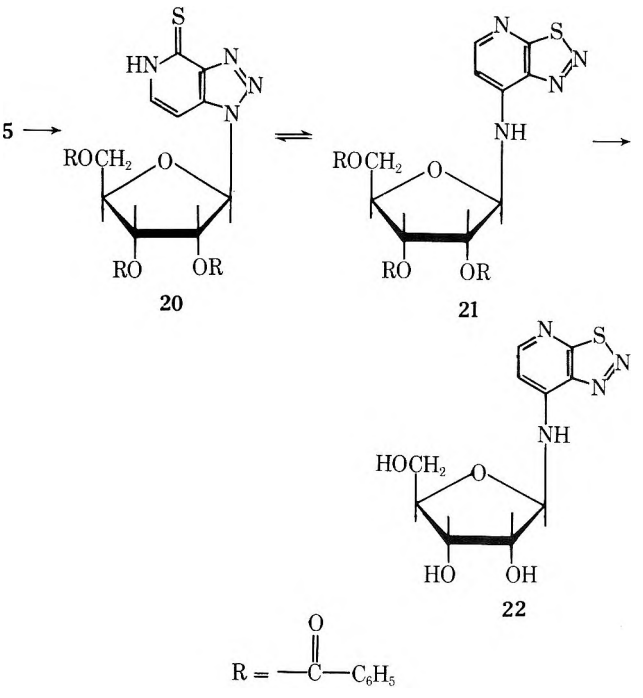
Thiation of **7** with sodium hydrogen sulfide effected a concomitant deblocking to give 3-(β-D-ribofuranosyl)-*v*-triazolo[4,5-*c*]pyridine-4-thione (**13**). The chemical shift for the anomeric proton of **13** appeared at δ 7.83, a significant downfield shift from the normal range. A downfield chemical shift of the anomeric proton resonance peak of a number of thionucleosides has been observed[21] when the ribosyl moiety was on a ring nitrogen atom adjacent to or in very close proximity to the carbon atom bearing the thione group. These observations would indicate that the site of glycosylation of **13** was at either position 3 or 5. Dethiation of **13** with Raney nickel provided 3-(β-D-ribofuranosyl)-*v*-triazolo[4,5-*c*]pyridine (**14**). The uv spectral data for **14** [λ_{max} (pH 1) 300 nm (ϵ 6700), 224 (3000); λ_{max} (pH 11) 290 nm (ϵ 5300), 240 (4100)] and 3-methyl-*v*-triazolo[4,5-*c*]pyridine[8] [λ_{max} (pH 1) 302 nm (ϵ 4500), 250 (1900); λ_{max} (pH 11) 290 nm (ϵ 4800), 248 (2400)] were comparable. This established the actual site of glycosylation for **7** as N-3 and the anomeric configuration as β.

The coupling constant observed for the anomeric proton resonance of **5** ($J_{1',2'} = 2.8$ Hz) was not sufficiently small to permit an unequivocal assignment of anomeric configuration. Treatment of **5** with methanolic sodium methoxide furnished 4-chloro-1-(β-D-ribofuranosyl)-*v*-triazolo[4,5-*c*]pyridine (**15**) which was converted to 4-chloro-1-(2,3-*O*-isopropylidene-β-D-ribofuranosyl)-*v*-triazolo[4,5-*c*]pyridine (**16**) (Scheme IV). The difference between the chemical shifts for the isopropylidene methyl groups of **16** was 0.23 ($\Delta\delta$) which is in agreement with the reported values for β-ribonucleosides.[20] This established the anomeric configuration of **16** and **5** as β. A second nucleoside product was obtained from the isopropylidenation of **15.** This product was shown to be 4-chloro-1-(2,3-*O*-isopropylidene-5-*O*-1′-methoxyisopropyl-β-D-ribofuranosyl)-*v*-triazolo[4,5-*c*]pyridine (**17**), based primarily on ^1H NMR data [δ 0.99 and 1.02 (2 s, 6, isopropyl methyls), 1.45 and 1.63 (2 s, 6, isopropylidene methyls), 2.91 (s, 3, OCH_3)]. As expected **17** was readily hydrolyzed to **16** by methanol at room temperature. To

Scheme IV



Scheme V



our knowledge this type of isopropylidenation intermediate has not been documented, most likely owing to its ease of hydrolysis, though surely encountered by others. A report[22] of the selective blocking of the 5′-hydroxyl of uridine by 2,2-dimethoxypropane has appeared. Although these authors report limited isopropylidene formation they did not observe an intermediate such as **17**. Treatment of **15** with liquid ammonia provided 4-amino-1-(β-D-ribofuranosyl)-υ-triazolo[4,5-c]pyridine (**18**, 3-deaza-8-azaadenosine). It is interesting to note that **18** showed a fluorescent emission maxima at 430 nm in water and may also be considered a deaza analogue of 8-azaadenosine which has shown some interesting biological properties. The reaction of **15** with the sodium salt of methanethiol provided 4-methylthio-1-(β-D-ribofuranosyl)-υ-triazolo[4,5-c]pyridine (**19**). Compound **19** is of interest since it can be considered an aza-deaza analogue of 6-methylthiopurine riboside which has shown some very interesting biological activity.[23]

Reaction of **5** with anhydrous dimethylformamide–sodium hydrogen sulfide resulted in thiation without concomitant deblocking to provide 1-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-υ-triazolo[4,5-c]pyridine-4-thione (**20**) (Scheme V). The chemical shift for the anomeric proton of **20** was observed at δ 7.17 while the resonance peak for the anomeric proton of **5** was observed at δ 7.28. The absence of any significant deshielding of the anomeric proton of **20** due to the magnetic anistropic effect of an adjacent thione group would indicate that the ribosyl moiety was residing at either N-1 or N-2. However, a complete dissimilarity between the uv spectral data for **20** and the uv spectral data for 2-(β-D-ribofuranosyl)-υ-triazolo[4,5-c]pyridine-4-thione (**9**) eliminated N-2 which established the actual site of glycosylation for **20** and **5** as N-1.

An equilibrium was established between **20** and 4-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)amino-1,2,3-thiadiazolo-[5,4-b]pyridine (**21**) when a solution of **20**, in a variety of solvents ranging in polarity from methanol to chloroform, was allowed to stand at room temperature. It was possible to shift the equilibrium in favor of **21** by heating the solution. Although this type of υ-triazole/1,2,3-thiadiazole rearrangement is well documented,[24,25] it appeared desirable to substantiate its occurrence in this situation.

A resonance for the anomeric proton of **20** appears as a doublet centered at δ 7.17 and a partially hidden doublet at δ 7.42 was assigned to the proton at C-7. Although a more complex and less well resolved spectrum was obtained after heating the ^{1}H NMR sample for a short time, the appearance of two well-resolved doublets at δ 7.24 and 8.61 was quite obvious. The Δδ (1.37) for these two doublets was indicative of the thiadiazolo[5,4-b]pyridine ring system. It became apparent during the course of this investigation, based on our findings and data from the literature,[9] that a difference in the chemical shifts between the doublets of the A:B pattern (H-6 and H-7) for the υ-triazolo[4,5-c]pyridine ring system is approximately 0.9 (Δδ) or less. By contrast, when the heteroatom resides in a position adjacent to the five-membered ring, e.g., the υ-triazolo[4,5-b]pyridine or thiadiazolo[5,4-b]pyridine ring systems, this difference is greater than 1.0 (Δδ).

Other studies designed to provide additional substantiation for the structure of **21** included treatment of **21** with sodium methoxide to give 4-(β-D-ribofuranosyl)amino-1,2,3-thiadiazolo[5,4-b]pyridine (**22**). The ^{1}H NMR spectrum of **22** revealed a signal for the anomeric proton as a quartet centered at δ 5.81, somewhat upfield from the normal range observed for υ-triazolo[4,5-c]pyridine nucleosides. The collapse of this quartet to a doublet centered at δ 5.81 upon the addition of deuterium oxide and the concomitant disappearance of the doublet centered at δ 8.00 upon deuterium exchange suggested that the anomeric proton was spin coupled with an exchangeable hydrogen. This relationship was established by spin decoupling of the doublet centered at δ 8.00 which caused the quartet at δ 5.81 to collapse to a doublet centered at δ 5.81. These data provide unequivocal proof for the structure of **22**.

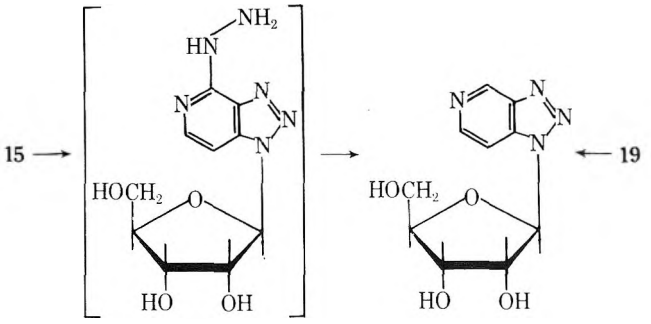
One technique generally employed for the determination of the site of glycosylation is to compare the ultraviolet spectra of the nucleoside product with that of the appropriate *N*-alkyl derivative of the aglycon. Since the uv spectral data for 1-methyl-υ-triazolo[4,5-c]pyridine (**23**) had been reported,[8] this prompted us to obtain additional corroboration for the actual site of ribosylation for **5** by dehalogenation of **15** to provide 1-(β-D-ribofuranosyl)-υ-triazolo[4,5-c]pyridine. Treatment of **15** with anhydrous hydrazine pro-

Table I. Ultraviolet Absorption Spectral Data for 23 and 25

	λ_{max} (pH 1), nm	λ_{max} (H_2O), nm	λ_{max} (pH 11), nm
25	274.5	265.5	264
23	265.5		
	257	259	258
Δ, nm	9.0	6.5	6.0

vided what we have assumed to be 4-hydrazino-1-(β-D-ribofuranosyl)-υ-triazolo[4,5-c]pyridine (24) which was treated (without purification) with silver oxide to give 1-(β-D-ribofuranosyl)-υ-triazolo[4,5-c]pyridine (25) (Scheme VI). A comparison of the uv spectral data obtained for 25

Scheme VI



24 25

and the uv spectral data reported[8] for 1-methyl-υ-triazolo-[4,5-c]pyridine (23) revealed a significant discrepancy. The authenticity of the published data[8] for 23 was established by the synthesis of 23 in our laboratory and the magnitude of the difference (see Table I) between the ultraviolet absorption spectral data of 25 and 23 was of concern since this difference between a nucleoside and the model methyl compound has been generally reported to be less than 5 nm.

We assumed that the observed discrepancy in the uv spectral data might arise from a structural modification of 15 during dehalogenation. However, the synthesis of 25 by an unrelated procedure, dethiation of 19 with Raney nickel, provided a product which was identical with 25 prepared via 24. This established that 25 was not the product of a rearrangement involving the hydrazino group. An infrared spectrum showed that 25 was not a ring-opened stabilized diazo compound[26] as established by the absence of a peak for a diazo band. The ^1H NMR spectrum and elemental analysis for 25 supported the structure indicated; however, these data could not unequivocally differentiate between 25 and 5-(β-D-ribofuranosyl)-υ-triazolo[4,5-c]pyridine, or the possibility of a dimeric structure. The formation of a dimer during dehalogenation was refuted by the mass spectral data which showed a molecular ion of *m/e* 252. However, the possibility remained that the ribosyl moiety was attached to position 5 of the aglycon rather than position 1. The lack of any deshielding of the anomeric proton of 20 and the data substantiating the υ-triazole–1,2,3-thiadiazole rearrangement observed for 20 and 21 established that the ribosyl moiety was at N-1 for 15 and 5. In view of the reaction conditions employed for the conversion of 15 to 25, it is reasonable to assume that the ribosyl group would be at N-1 of 25; however, an N-1–N-5 glycosyl migration or intermolecular transfer cannot be discounted, though both are very highly improbable.

An NMR technique which has been recently used to establish the glycosylation site of nucleosides[27,28] involves the use of ^{13}C nuclear magnetic resonance (^{13}C NMR). It has been shown for a number of heterocyclic systems that protonation of the anionic species resulted in an upfield chemical shift for the α carbons and a downfield chemical shift for the β carbons. It was further established that for N-methylation and N-glycosylation[27] these effects are qualitatively preserved. Furthermore, it was demonstrated[27] that the ^{13}C NMR shift data of the free base and the N-alkylated species were sufficient to establish the position of alkylation by a qualitative interpretation of the α and β substituent effects, not requiring a comparison with the corresponding anionic species.

Table II. Carbon-13 Chemical Shift Data for Certain υ-Triazolo[4,5-c]pyridine Derivatives[a,b]

No.	3a, 7a	4, 6	7
27	139.28	141.79	107.64
	140.11	142.48	
23	136.73	143.67	105.42
	142.49	144.16	
25	135.94	143.98	106.31
	142.99	144.57	

[a] Chemical shifts are in parts per million from Me_4Si. *p*-Dioxane was used as internal reference and converted to the Me_4Si scale using the relationship Me_4Si = dioxane − 17.5 × 10^{-4} *T* (°C) − 66.32. [b] All samples were dissolved in Me_2SO-d_6.

Inspection of the ^{13}C NMR spectrum of υ-triazolo[4,5-c]pyridine (27) showed a near degeneracy for the chemical shifts of C-3a and C-7a (see Table II) which precluded an unequivocal assignment of these two resonances. Although it was apparent from the ^{13}C NMR spectrum of 23 that one of these resonances shifted downfield while the other shifted upfield upon N-1 alkylation, it could not be readily determined which of the resonances of 27 shifted in which direction owing to the possibility of a crossover of resonance lines. It was obvious, however, that the C-4, C-6, and C-7 resonances of 27 showed no significant shift on N-1 methylation as expected. The spectrum of 25 was essentially identical with that of 23 (see Table II) and although it was not possible to unequivocally assign the ribosyl moiety of 25 to N-1 by this procedure owing to the inability to assign the C-3a and C-7a resonances, it was clearly evident that 25 was not the N-5 substituted compound. If the substituent were at N-5, an upfield shift would have been apparent for the C-4 and C-6 (α carbons) chemical shifts. Since these resonances for 25 occur at the same location as for 23 and 27 the possibility of N-5 substitution for 25 can be eliminated. This ^{13}C NMR procedure cannot differentiate between N-1, N-2, or N-3 substitution in this particular situation owing to the inability to assign the chemical shifts of the bridgehead carbons; however, previous data (vide supra) clearly indicate that 25 is not the N-2 or N-3 substituted compound.

Additional corroboration for the structure of 25 was pursued using the nuclear Overhauser effect (NOE). The conformational distribution (syn–anti) of various purine nucleosides in solution[29] as well as the determination of anomeric configuration for certain purine and pyrimidine nucleosides[30] has been investigated through the use of intramolecular nuclear Overhauser effect measurements.

Molecular models indicated that if the ribosyl moiety of 25 were to reside at N-1, the anomeric proton and H(7) would be in very close proximity. Hence, irradiation of the H(1′) proton would be expected to result in an enhancement in the integrated intensity of the H(7) signal. The H(6) and H(4) protons would show no enhancement on irradiation of the H(1′) proton since they are not in close proximity to the anomeric proton. Molecular models further indicated that if the ribosyl moiety were to reside at N-5, the anomeric proton would be in very close proximity

Table III. Nuclear Overhauser Effects Observed for 19 and 25

Compd	Proton irradiated	Proton observed	Enhancement
19	H(1′)	H(7)	0.22
	H(1′)	H(6)	0.0
25	H(1′)	H(7)	0.12
	H(1′)	H(6)	0.0
	H(1′)	H(4)	0.0

to both the H(6) and the H(4) protons. Therefore, irradiation of H(1′) in this situation would result in an enhancement in the intensity of both the H(6) and H(4) protons with no effect being observed on the H(7) proton. Irradiation of the anomeric proton signal of **19** and **25** produced the enhancements shown in Table III. These results clearly established that for **25** and **19**, the ribosyl moiety resides at N-1. Therefore, the identity of **25** as 1-(β-D-ribofuranosyl)-υ-triazolo[4,5-c]pyridine has been substantiated by chemical studies as well as ^{13}C NMR, NOE, and ^1H NMR spectroscopy.

To our knowledge this is the first report of an exception to the time-honored empirical model methyl procedure (uv) for assigning the glycosylation site of nucleosides. The reasons for this discrepancy between **25** and **23** are not readily apparent, and we are not prepared at this time to offer any explanation for this observation. However, it does serve to indicate that corroborative evidence may be beneficial when using model methyl compounds to establish the site of glycosylation. Furthermore, the use of ^{13}C NMR α and β substituent shifts may prove to be not only less time consuming but also more reliable, especially for those ring systems amenable toward this technique.

Experimental Section

Proton magnetic resonance (^1H NMR) spectra were obtained with Jeol C60H, Varian A56/60, and Varian XL-100/15 spectrometers (solutions in dimethyl sulfoxide-d_6 or deuteriochloroform with sodium 2,2-dimethyl-2-silapentane-5-sulfonate or tetramethylsilane, respectively, as internal standard) with chemical shift values reported in δ, parts per million, relative to the internal standard. Nuclear Overhauser experiments were performed at 100 MHz on ca. 0.50 M samples in dimethyl sulfoxide-d_6 alone or in combination with deuterium oxide where applicable to remove resonance peaks in close proximity to those of interest. The samples were prepared in coaxial tubes with hexamethyldisilizane in the annular space as external standard. Each resonance was integrated ten times with and without the saturating field present and the NOE was then calculated from the average areas. Carbon-13 magnetic resonance spectra were obtained with a Varian XL-100/15 spectrometer equipped with a 620-F computer. Ultraviolet spectra were recorded on Beckman DK-2 and Acta CIII spectrophotometers. Fluorescence spectra were determined with an Aminco-Bowman spectrophotofluorometer. Infrared spectra were recorded on a Beckman IR8 spectrophotometer. Optical rotations were determined with a Perkin-Elmer Model 141 automatic digital read-out polarimeter. Melting points were determined with a Thomas-Hoover capillary apparatus and are uncorrected. Mass spectra were recorded on a Hewlett-Packard 5930A instrument; ion source and direct inlet temperatures, 190 °C, ionizing energy 60 eV, samples were introduced by direct probe. Thin layer chromatography was run on glass plates coated (0.25 mm) with silica gel (SilicAR 7GF, Mallinckrodt) or aluminium oxide (HF_{254}, basic, type E, Merck). Compounds of interest were detected by either ultraviolet lamp (Mineralight, 254 nm), iodine vapors, or treatment with sulfuric acid followed by heating. Evaporations were performed under reduced pressure at 40 °C with a rotary evaporator unless otherwise stated.

4-Chloro-1-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-υ-triazolo[4,5-*c*]pyridine (5), 4-Chloro-2-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-υ-triazolo[4,5-*c*]pyridine (6), and 4-Chloro-3-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-υ-triazolo[4,5-*c*]pyridine (7). Method A. A solution of 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl chloride (prepared from 1-*O*-acetyl-2,3,5-tri-*C*-benzoyl-β-D-ribofuranose, 17.3 g, 33.0 mmol) in nitromethane (35 ml) was added to a suspension of 4-chloro-υ-triazolo[4,5-*c*]pyridine[11] (**3**, 4.7 g, 30 mmol) and potassium cyanide (2.14 g, 33 mmol) in nitromethane (300 ml), and the resulting mixture was heated at reflux temperature for 3 hr. The reaction mixture was cooled to room temperature, and the insoluble material was removed by filtration. The filtrate was evaporated to a dark syrup which was dissolved in chloroform (350 ml) and filtered. The filtrate was extracted with a saturated aqueous sodium bicarbonate solution (3 × 50 ml) and then with water (3 × 50 ml). The solution was dried over anhydrous sodium sulfate and concentrated to a syrup which was dissolved in a minimal amount of benzene and applied to the top of an aluminum oxide column (Merck, neutral, 4.5 × 50 cm) packed in benzene. The column was washed with benzene (2 l.) followed by elution with a mixture of benzene–ethyl acetate (9:1 v/v) to furnish partially resolved mixtures of the three isomeric nucleosides. The partially resolved isomers were combined into three fractions: (1) containing **6** and **7**; (2) containing **5, 6,** and **7** [R_f 0.39, 0.63, and 0.57, respectively, on Merck aluminum oxide developed with benzene–ethyl acetate (9:1 v/v)]; (3) containing **5** and **7**. The second fraction containing the three unresolved isomers was rechromatographed on a second aluminium oxide column (Merck, 3.5 × 35 cm) and eluted as above. The resulting partially resolved isomeric mixtures were combined with the similar mixture (fraction 1 or 3) from the initial column. Fraction 1 (containing **6** and **7**) was evaporated to an amber syrup which was dissolved in benzene (10 ml) and applied to an alumina column (Woelm, neutral, activity III, 3.5 × 20 cm) packed in benzene. The column was eluted with a mixture of benzene–ethyl acetate (19:1 v/v) to afford the resolved isomers. The first nucleoside to be eluted (**6**, R_f 0.63) was isolated as a light amber syrup after removal of eluent. Crystallization of this syrup from ethanol gave 2.7 g (15%) of **6** as white crystals: mp 114–116 °C; uv λ_{max} (pH 1) 246 nm (ε 33 600), 283 (sh) (19 100); λ_{max} (MeOH) 228 nm (ε 49 100), 265 (9900), 275 (9500), 282 (9600); ^1H NMR ($CDCl_3$) δ 6.86 (s, 1, $J_{1',2'}$ = 0.0 Hz, $H_{1'}$).

Anal. Calcd for $C_{31}H_{23}ClN_4O_7$: C, 62.15; H, 3.84; N, 9.36. Found: C, 62.20; H, 3.81; N, 9.20.

The second nucleoside to be eluted (**7**, R_f 0.57) was isolated as an amber syrup after removal of eluent. Crystallization of this syrup (after combination with **7** from fraction 3) from ethanol gave 1.4 g (8%) of **7** as thick needles: mp 147–149 °C; uv λ_{max} (pH 1) 248 nm (ε 28 200), 285 (sh) (17 100), 304 (sh) (15 300); λ_{max} (MeOH) 230 nm (ε 44 900), 277 (sh) (6900), 283 (7500), 294 (6900); ^1H NMR ($CDCl_3$) δ 7.19 (d, 1, $J_{1',2'}$ = 1.0 Hz, $H_{1'}$).

Anal. Calcd for $C_{31}H_{23}ClN_4O_7$: C, 62.15; H, 3.84; N, 9.36. Found: C, 62.25; H, 3.86; N, 9.25.

Fraction 3, containing **5** and **7**, was evaporated to an amber syrup which was dissolved in benzene (8 ml) and applied to an alumina column (Woelm, neutral, activity III, 3.5 × 20 cm) packed in benzene. The column was eluted with a mixture of benzene–ethyl acetate (9:1 v/v) to afford the resolved isomers. The first nucleoside to be eluted (**7**, R_f 0.57) was combined with that obtained from fraction 1 (vide supra). The second nucleoside to be eluted (**5**, R_f 0.39) was isolated as an amber syrup after removal of eluent. Crystallization of this syrup from methanol gave 2.0 g (11%) of **5** as white crystals: mp 135–136 °C; uv λ_{max} (pH 1) 245 nm (ε 35 400), 275 (sh) (23 900); λ_{max} (pH 11) 241 nm (ε 40 200), 274 (sh) (21 600); λ_{max} (MeOH) 230 nm (ε 44 300), 266 nm (ε 9900); ^1H NMR ($CDCl_3$) δ 7.31 (d, 1, $J_{1',2'}$ = 2.8 Hz, $H_{1'}$), 8.19 (d, 1, $J_{7,8}$ = 6.0 Hz, H_7), 8.48 (d, 1, $J_{6,7}$ = 6.0 Hz, H_6).

Anal. Calcd for $C_{31}H_{23}ClN_4O_7$: C, 62.15; H, 3.84; N, 9.36. Found: C, 62.09; H, 3.89; N, 9.53.

Method B. *N,O*-Bis(trimethylsilyl)acetamide (12 ml) was added to a suspension of **3** (5.0 g, 32 mmol) in xylene (50 ml) and the solution was heated at 40 °C for 1 h. The solvent and excess silylating agent were removed under reduced pressure at 110 °C to give a dark amber syrup. This syrup was heated at 110 °C for 1 h and then allowed to cool to room temperature, giving a dark solid. Mercuric cyanide (8.8 g, 39 mmol) was added to the silylation product and after acetonitrile (100 ml) was added, the mixture was brought to reflux temperature under a nitrogen atmosphere. A solution of 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl bromide (prepared from 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose, 16.4 g, 32 mmol) in acetonitrile (35 ml) was added to the reaction mixture and this was followed by an additional quantity of acetonitrile (30 ml). The resulting mixture was heated at reflux temperature for 1 h, cooled, and filtered and the filtrate was evaporated to a residue. The residue was then extracted with chloroform (4 × 100 ml) and filtered, and the filtrate was evaporated to a residue. The residue was ex-

tracted with chloroform (4 × 100 ml), filtered, and evaporated to a syrup. This syrup was dissolved in chloroform (300 ml) and extracted sequentially with a saturated aqueous sodium bicarbonate solution (3 × 50 ml), a 30% aqueous potassium iodide solution (3 × 50 ml), and water (3 × 60 ml). The chloroform solution was dried over anhydrous sodium sulfate and concentrated to a syrup (27 g). This syrup was dissolved in benzene (25 ml) and applied to an alumina column (J. T. Baker, 6.5 × 40 cm) which had been packed in benzene. The column was washed with 2.0 l. of benzene followed by elution with a mixture of benzene–ethyl acetate (9.25:0.75 v/v). The first nucleoside to be eluted was **6** (2.5 g of syrup) which was followed by an unresolved mixture (2.7 g of syrup) and then **5** (5.5 g of syrup). The mixture of unresolved nucleosides was rechromatographed as above to provide additional **5** and **6** as well as resolved **7**. The individual nucleosides were obtained in crystalline form as described in method A. The yields of each of the isomers obtained by this procedure follow: **6**, 2.0 g (12%); **7**, 0.9 g (4%); and **5**, 4.6 g (25%). The physical and spectral properties for **5**, **6**, and **7** prepared by this method was identical with those given in method A (melting point and ^{1}H NMR).

4-Chloro-2-(β-D-ribofuranosyl)-*v*-triazolo[4,5-*c*]pyridine (8). A solution of **6** (250 mg, 0.42 mmol) in methanol (35 ml) was cooled to 15 °C and sufficient sodium methoxide was added to adjust the pH of the solution to 10. The solution was stirred at 15 °C for 1 h and then at room temperature for 2.5 h. The reaction mixture was neutralized with Amberlite IRC-120 resin (H^+ form prewashed with methanol) and the resin removed by filtration. The filtrate was evaporated to afford a solid which was coevaporated with benzene and then triturated with benzene (25 ml). Recrystallization from a minimal amount of water provided 95 mg (79%) of **8**: mp 151–153 °C dec; uv λ_{max} (pH 1) 261 nm (ϵ 6500), 292 (6800); λ_{max} (pH 11) 260 nm (ϵ 6100), 292 (6300); λ_{max} (H_2O) 262 nm (ϵ 4600), 292 (5300); ^{1}H NMR (Me_2SO-d_6) δ 6.37 (d, 1, $J_{1',2'}$ = 3.0 Hz, $H_{1'}$), 8.16 (d, 1, $J_{7,6}$ = 6.0 Hz, H_7), 8.34 (d, 1, $J_{6,7}$ = 6.0 Hz, H_6).

Anal. Calcd for $C_{10}H_{11}ClN_4O_4$·0.5H_2O (verified by ^{1}H NMR): C, 40.61; H, 4.06; N, 18.95. Found: C, 40.77; H, 4.04; N, 18.86.

2-(β-D-Ribofuranosyl)-*v*-triazolo[4,5-*c*]pyridine-4-thione (9). A solution of **6** (1.5 g, 2.5 mmol) and sodium hydrogen sulfide (700 mg, 12.5 mmol) in methanol (100 ml) was heated at reflux temperature for 1.5 h. The solution was cooled to room temperature and neutralized with Amberlite IRC-120 resin (H^+ form, prewashed with methanol) and the resin was then removed by filtration. The filtrate was evaporated to a yellow residue which upon coevaporation with benzene gave a solid. The solid was then triturated at room temperature with benzene (45 ml). The resulting solid was dissolved in methanol and evaporated in the presence of silica gel (SilicAR CC7, 1 g) at reduced pressure. The resulting mixture was placed on top of a silica gel column (SilicAR CC7, 2.5 × 20 cm, dry packed), and the column was eluted with a chloroform–methanol mixture (5:1 v/v) to provide 570 mg (80%) of **9**. An analytical sample was prepared by recrystallization from ethyl acetate–methanol: mp 173–175 °C; uv λ_{max} (pH 1) 237 nm (ϵ 19 300), 365 (12 800); λ_{max} (pH 11) 236 nm (ϵ 22 700), 362 (9400); λ_{max} (MeOH) 240 nm (ϵ 17 900), 369 (13 400); ^{1}H NMR (Me_2SO-d_6) δ 6.27 (d, 1, $J_{1',2'}$ = 3.0 Hz, $H_{1'}$), 7.27 (d, 1, $J_{7,6}$ = 6.0 Hz, H_7), 7.57 (d, 1, $J_{6,7}$ = 6.0 Hz, H_6), 13.28 (broad singlet, 1, H_5).

Anal. Calcd for $C_{10}H_{12}N_4O_4S$: C. 42.25; H, 4.23; N, 19.71. Found: C, 42.08; H, 4.17; N, 19.56.

2-(β-D-Ribofuranosyl)-*v*-triazolo[4,5-*c*]pyridine (10). To a solution of **9** (200 mg, 0.7 mmol) in ethanol (20 ml) was added W2 Raney nickel (300 mg, prewashed with water until the pH of the aqueous suspension remained at 7 and this was followed by slurrying the catalyst in ethanol several times). This mixture was stirred vigorously at room temperature for 15 min, additional Raney nickel (200 mg) was added, and then stirring was continued for an additional 15 min. The catalyst was removed by filtration and the filtrate was evaporated at reduced pressure in the presence of silica gel (SilicAR CC7, 250 mg). The resulting mixture was placed on top of a silica gel column (SilicAR CC7, 2.5 × 15 cm) and elution with a mixture of chloroform–methanol (5:1 v/v) provided 105 mg (60%) of **10**. Recrystallization from ethanol gave fine yellow crystals: mp 183–184 °C (lit.[8] 167–168 °C); $[\alpha]^{33}D$ −83.5° (*c* 1, CH_3OH) [lit.[8] $[\alpha]^{22}D$ −70° (*c* 1, CH_3OH)]; uv λ_{max} (pH 1) 263 nm (ϵ 9100), 296 (6400); λ_{max} (pH 11) 263 nm (ϵ 7900), 279 (6600); λ_{max} (H_2O) 262 nm (ϵ 8100), 279 (sh) (6600) [lit.[8] λ_{max} (pH 1) 265 nm (ϵ 6300), 298 (4300); λ_{max} (pH 11) 268 nm (ϵ 5800), 280 (5700)]; ^{1}H NMR (Me_2SO-d_6) δ 6.37 (d, 1, $J_{1',2'}$ = 3.5 Hz, $H_{1'}$), 8.00 (dd, 1, $J_{7,6}$ = 6.0, $J_{7,4}$ = 1.5 Hz, H_7), 8.55 (d, 1, $J_{6,7}$ = 6.0 Hz, H_6), 9.58 (wide singlet, 1, H_4).

4-Chloro-3-(β-D-ribofuranosyl)-*v*-triazolo[4,5-*c*]pyridine (11). A solution of **7** (450 mg, 0.75 mmol) in methanol (50 ml) was adjusted to pH 9 by the addition of sodium methoxide. This solution was stirred at room temperature for 4 h and then neutralized to pH 7 with Amberlite IRC-120 resin (H^+ form, prewashed with methanol). The resin was removed by filtration. The filtrate was evaporated to a residue which was coevaporated with benzene to provide a solid. This solid was triturated with benzene (50 ml) and recrystallized from a minimal amount of water with charcoal treatment to give 150 mg (70%) of **11**: mp 158–160 °C dec; uv λ_{max} (pH 1) 232 nm (ϵ 4400), 295 (7200); λ_{max} (pH 11) 236 nm (ϵ 4300), 295 (7300); ^{1}H NMR (Me_2SO-d_6) δ 6.74 (d, 1, $J_{1',2'}$ = 3.4 Hz, $H_{1'}$), 8.20 (d, 1, $J_{7,6}$ = 5.5 Hz, H_7), 8.42 (d, 1, $J_{6,7}$ = 5.5 Hz, H_6).

Anal. Calcd for $C_{10}H_{11}ClN_4O_4$: C, 41.88; H, 3.84; N, 19.55. Found: C, 41.79; H, 3.98; N, 19.32.

4-Chloro-3-(2,3-*O*-isopropylidene-β-D-ribofuranosyl)-*v*-triazolo[4,5-*c*]pyridine (12). To a suspension of **11** (240 mg, 0.8 mmol) in acetone (15 ml) and 2,2-dimethoxypropane (2.5 ml) was added a 0.01% solution of sulfuric acid in acetone (24 ml). After stirring at room temperature for 1 h, a solution of saturated aqueous sodium bicarbonate (5 ml) was added. The resulting mixture was evaporated and the residual solid was extracted with chloroform (3 × 20 ml). The chloroform solution was concentrated to a small volume and applied to a silica gel column (SilicAR CC7, 2.5 × 20 cm, dry packed) and the column was eluted with chloroform–ethyl acetate (2:1 v/v). The fractions containing **12**, as indicated by TLC [R_f 0.28 on silica gel developed with chloroform–ethyl acetate (2:1 v/v)], were combined and evaporated to give a syrup. Coevaporation of the syrup three times with diethyl ether at 5 °C gave a white foam which readily reverted to a syrup (330 mg) upon warming to room temperature. Thin layer chromatography showed the presence of only one compound: ^{1}H NMR (C_6D_6–Me_2SO-d_6) δ 1.35 and 1.58 (2 s, 6, isopropylidene methyls), 6.86 (s, 1, $J_{1',2'}$ = 0.0 Hz, $H_{1'}$), 7.52 (d, 1, $J_{7,6}$ = 5.5 Hz, H_7), 7.89 (d, 1, $J_{6,7}$ = 5.5 Hz, H_6).

3-(β-D-Ribofuranosyl)-*v*-triazolo[4,5-*c*]pyridine-4-thione (13). To a solution of **7** (1.5 g, 2.5 mmol) in methanol (100 ml) was added 20 ml of a methanolic solution of sodium hydrogen sulfide (prepared by dissoloving 500 mg of sodium in 55 ml of methanol and then saturating this solution with hydrogen sulfide). This solution was heated at reflux temperature for 5 h. The reaction mixture was processed by the same procedure as that used for the synthesis of **9** and furnished 410 mg (58%) of **13**: mp 177–178°C; uv λ_{max} (pH 1) 266 nm (ϵ 17 400), 366 (13 200); λ_{max} (pH 11) 351 nm (ϵ 10 800); λ_{max} (H_2O) 226 nm (ϵ 15 400), 367 (11 800); ^{1}H NMR (Me_2SO-d_6) δ 7.44 (d, 1, $J_{7,6}$ = 7.0 Hz, H_7), 7.63 (d, 1, $J_{6,7}$ = 7.0 Hz, H_6), 7.84 (d, 1, $J_{1',2'}$ = 3.5 Hz, $H_{1'}$).

Anal. Calcd for $C_{10}H_{12}N_4O_4S$·0.5H_2O (verified by ^{1}H NMR): C, 40.96; H, 4.44; N, 19.11. Found: C, 40.90; H, 4.55; N, 19.27.

3-(β-D-Ribofuranosyl)-*v*-triazolo[4,5-*c*]pyridine (14). To a solution of **13** (110 mg, 0.38 mmol) in ethanol (20 ml) was added W2 Raney nickel (200 mg, prewashed with water until the pH of the aqueous slurry remained at 7 and this was followed by slurrying several times in ethanol). This mixture was stirred vigorously at room temperature for 15 min, additional catalyst (100 mg) was then added, and the stirring was continued for an additional 15 min. The mixture was filtered through a Celite pad which was then washed with ethanol. The filtrate was evaporated to a syrup which upon coevaporation with ethyl acetate gave a pale yellow solid. Recrystallization from ethanol with charcoal treatment gave 65 mg (67%) of **14** as pale yellow crystals: mp 166–168 °C; uv λ_{max} (pH 1) 224 nm (ϵ 3000), 300 (6700); λ_{max} (pH 11) 240 nm (ϵ 4100), 290 (5300); λ_{max} (H_2O) 240 nm (ϵ 4400), 289 (5600) ^{1}H NMR (Me_2SO-d_6) δ 6.53 (d, 1, $J_{1',2'}$ = 5.5 Hz, $H_{1'}$), 8.18 (d, 1, $J_{7,6}$ = 6.0 Hz, H_7), 8.62 (d, 1, $J_{6,7}$ = 6.0 Hz, H_6), 9.68 (s, 1, H_4).

Anal. Calcd for $C_{10}H_{12}N_4O_4$: C, 47.62; H, 4.76; N, 22.22. Found: C, 47.84; H, 4.82; N, 22.20.

4-Chloro-1-(β-D-ribofuranosyl)-*v*-triazolo[4,5-*c*]pyridine (15). A solution of **5** (1.0 g, 1.67 mmol) in methanol (60 ml) was treated by the same procedure as that used for the synthesis of **11** to furnish 450 mg (94%) of **15**: mp 171–172 °C; uv λ_{max} (pH 1) 268 nm (ϵ 7400); λ_{max} (pH 11) 268 nm (ϵ 8000); λ_{max} (H_2O) 267 nm (ϵ 7200); ^{1}H NMR (Me_2SO-d_6) δ 6.50 (d, 1, $J_{1',2'}$ = 5.0 Hz, $H_{1'}$), 8.31 (d, 1, $J_{7,8}$ = 5.5 Hz, H_7), 8.52 (d, 1, $J_{6,7}$ = 5.5 Hz, H_6).

Anal. Calcd for $C_{10}H_{11}ClN_4O_4$·1.0H_2O (verified by ^{1}H NMR): C, 39.41; H, 4.27; N, 18.39. Found: C, 39.68; H, 3.95; N, 18.02.

4-Chloro-1-(2,3-*O*-isopropylidene-β-D-ribofuranosyl)-*v*-triazolo[4,5-*c*]pyridine (16). To a suspension of **15** (240 mg, 0.8 mmol) in acetone (25 ml) and 2,2-dimethoxypropane (4.0 ml) was added a 0.05% solution of sulfuric acid in acetone (20 ml). After stirring at room temperature for 1 h, a solution of saturated aqueous sodium bicarbonate (8 ml) was added. The resulting mixture

was evaporated to dryness and the residual solid was extracted with chloroform (3 × 25 ml). Thin layer chromatography showed the presence of two nucleoside products [R_f 0.62 and 0.24 on SilicAR 7GF developed with chloroform–ethyl acetate (2:1 v/v)]. The chloroform solution was evaporated to a small volume and applied to the top of a silica gel column (SilicAR CC7, 2.5 × 20 cm, dry packed) and eluted with chloroform–ethyl acetate (2:1 v/v) to resolve the nucleoside mixture. The first nucleoside to be eluted, 4-chloro-1-(2,3-*O*-isopropylidene-5-*O*-1′-methoxyisopropyl-β-D-ribofuranosyl)-υ-triazolo[4,5-c]pyridine (**17**), resisted crystallization and remained a syrup: ^{1}H NMR ($CDCl_3$) δ 0.99 and 1.02 (2 s, 6, isopropyl methyls), 1.45 and 1.68 (2 s, 6, isopropylidene methyls), 2.91 (s, 3, OCH_3), 3.32 (d, 2, $H_{5'}$), 6.40 (d, 1, $J_{1',2'}$ = 1.5 Hz, $H_{1'}$), 7.68 (d, 1, $J_{7,6}$ = 6.0 Hz, H_7), 8.32 (d, 1, $J_{6,7}$ = 6.0 Hz, $H_{1'}$). Evaporation of the fractions containing **16** gave a syrup which crystallized to furnish 175 mg (67%) of the desired product: mp 120–121 °C; uv λ_{max} (pH 1) 270 nm (ε 9500); λ_{max} (pH 11) 268 nm (ε 9200); λ_{max} (MeOH) 267 nm (ε 9100); ^{1}H NMR (Me_2SO-d_6) δ 1.44 and 1.66 (2 s, 6, isopropylidene methyl), 6.87 (d, 1, $J_{1',2'}$ = 1.5 Hz, $H_{1'}$), 8.24 (d, 1, $J_{7,6}$ = 6.0 Hz, H_7), 8.53 (d, 1, $J_{6,7}$ = 6.0 Hz, H_6).

Anal. Calcd for $C_{13}H_{15}ClN_4O_4$: C, 47.74; H, 4.59; N, 17.15. Found: C, 47.82; H, 4.61; N, 17.02.

4-Amino-1-(β-D-ribofuranosyl)-υ-triazolo[4,5-c]pyridine (3-Deaza-8-azaadenosine, 18). A solution of **15** (1.0 g, 3.48 mmol) in liquid ammonia (40 ml) was heated in a steel reaction vessel at 85 °C for 6 h. The excess ammonia was removed to afford a solid which was dissolved in methanol (35 ml) and evaporated at reduced pressure in the presence of silica gel. This residue was applied to the top of a silica gel column (SilicAR CC7, 3.5 × 20 cm, dry packed) and eluted with a chloroform–methanol mixture (4:1 v/v). The fractions containing **18**, as indicated by TLC [R_f 0.45 on silica gel (SilicAR 7GF) developed with chloroform–ethanol (2:1 v/v)], were combined and evaporated to afford a white solid. Recrystallization from a minimal amount of water provided 475 mg (51%) of **18**: mp 212–215 °C dec; $[\alpha]^{26}$D −84.0° (*c* 1, H_2O); uv λ_{max} (pH 1) 274 nm (ε 12 100); λ_{max} (pH 11) 295 nm (ε 7500); λ_{max} (H_2O) 290 nm (ε 7800); ^{1}H NMR (Me_2SO-d_6) δ 3.65 (m, 2, $H_{5'}$), 4.10 (q, 1, $J_{3',4'}$ = 4.5, $J_{4',5'}$ = 7.5 Hz, $H_{4'}$), 4.32 (q, 1, $J_{3',2'}$ = 10.0, $J_{3',4'}$ = 4.5 Hz, $H_{3'}$), 4.75 (q, 1, $J_{2',1'}$ = 5.0, $J_{2',3'}$ = 10.0 Hz, $H_{2'}$), 5.05 (t, 1, $J_{5',O5'}$ = 5.0 Hz, 5′ OH), 5.40 (d, 1, $J_{3',O3'}$ = 6.0 Hz, 3′ OH), 5.67 (d, 1, $J_{2',O2'}$ = 6.0 Hz, 2′ OH), 6.13 (d, 1, $J_{1',2'}$ = 5.0 Hz, $H_{1'}$), 7.13 (d, 1, $J_{7,6}$ = 6.0 Hz, H_7), 7.24 (s, 2, 4-NH_2), 7.90 (d, 1, $J_{6,7}$ = 6.0 Hz, H_6).

Anal. Calcd for $C_{10}H_{13}N_5O_4$: C, 44.94; H, 4.78; N, 26.22. Found: C, 44.99; H, 5.06; N, 26.35.

Thin layer chromatography indicated the presence of a small quantity of a faster moving nucleoside which was not isolated [R_f 0.85 on SilicAR 7GF developed with chloroform–methanol (4:1 v/v)].

4-Methylthio-1-(β-D-ribofuranosyl)-υ-triazolo[4,5-c]pyridine (19). A solution of **15** (286 mg, 1.0 mmol) in ethanol (30 ml) containing sodium (50 mg) and methanethiol (0.2 ml) was heated at reflux temperature for 1 h. The reaction mixture was neutralized with Amberlite IRC-120 resin (H^+ form, prewashed with ethanol) and filtered and the filtrate evaporated to a solid which was triturated with chloroform (25 ml). This crude solid was dissolved in methanol and evaporated to dryness in the presence of silica gel (SilicAR CC7, 1 g). This mixture was then placed on top of a silica gel column (SilicAR CC7, 3.5 × 10 cm, dry packed). The column was eluted with chloroform–methanol (4.25:0.75 v/v) and the fractions containing **19**, as indicated by TLC [R_f 0.58 on silica gel (SilicAR 7GF) developed with chloroform–methanol (4:1 v/v)], were combined and allowed to slowly evaporate at room temperature to provide 205 mg (68%) of **19**: mp 174–175 °C; uv λ_{max} (pH 1) 312 nm (ε 20 700); λ_{max} (pH 11) 303 nm (ε 14 000); λ_{max} (MeOH) 299 nm (ε 15 700); ^{1}H NMR (Me_2SO-d_6) δ 2.78 (s, 3, SCH_3), 6.43 (d, 1, $J_{1',2'}$ = 5.0 Hz, $H_{1'}$), 7.92 (d, 1, $J_{7,6}$ = 6.0 Hz, H_7), 8.50 (d, 1, $J_{6,7}$ = 6.0 Hz, H_6); $[\alpha]^{25}$D −85.0° (*c* 0.96, CH_3OH).

Anal. Calcd for $C_{11}H_{14}N_4O_4S$: C, 44.29; H, 4.70; N, 18.79. Found: C, 44.16; H, 4.86; N, 18.36.

1-(2,3,5-Tri-*O*-benzoyl-β-D-ribofuranosyl)-υ-triazolo[4,5-c]pyridine-4-thione (20). Hydrogen sulfide (25 ml) was condensed into a reaction flask containing sodium (75 mg) which had been cooled to −75 °C in a dry ice–isopropyl alcohol bath and protected from moisture. Dimethylformamide (25 ml) was added in 5-ml portions over 1.5 h during which time the temperature was maintained at −75 °C. Following dimethylformamide addition the solution was stirred at −75 °C for 1 h and then allowed to slowly approach room temperature by a gradual warming of the dry ice–isopropyl alcohol bath. The dark blue dimethylformamide–sodium hydrogen sulfide solution was stirred at room temperature for 1.5 h. To this solution was added **5** (1.8 g, 3.0 mmol) and the resulting solution was stirred at room temperature for 2 h. The reaction mixture was filtered through a Celite pad. The filtrate was cooled to 0 °C and poured into cold water (125 ml at 5 °C) and a cream-colored precipitate formed. The pH of the aqueous suspension was adjusted to 7 with a solution of 1 N sodium hydroxide and then cooled to 0 °C. The solid was collected by filtration, washed with cold water (50 ml), and then dissolved in chloroform (350 ml). The aqueous layer was separated and washed with chloroform (3 × 25 ml). The combined chloroform solutions were dried over sodium sulfate at 10 °C for 12 h. The drying agent was removed and the filtrate evaporated at 0–5 °C in vacuo to furnish a yellowish syrup which was coevaporated with carbon tetrachloride (2 × 30 ml). The resulting solid was suspended in carbon tetrachloride (50 ml) and placed in a freezer at −25 °C for 24 h. The solid was collected by filtration, washed with carbon tetrachloride (50 ml), and air dried to furnish 1.55 g (86%) of **20**: mp 174–177 °C; uv λ_{max} ($CHCl_3$) 276 nm (ε 4800), 284 (4200), 334 (17 600); ^{1}H NMR (Me_2SO-d_6) δ 4.74 (s, 2, $H_{5'}$), 5.13 (m, 1, $H_{4'}$), 6.31 (t, 1, $H_{3'}$), 6.59 (q, 1, $H_{2'}$), 7.17 (d, 1, $J_{1',2'}$ = 2.2 Hz, $H_{1'}$), 7.42 (d, 1, $J_{7,6}$ = 6.0 Hz, H_7).

Anal. Calcd for $C_{31}H_{24}N_4O_7S$: C, 62.42; H, 4.03; N, 9.39. Found: C, 62.31; H, 4.16; N, 9.13.

4-(2,3,5-Tri-*O*-benzoyl-β-D-ribofuranosyl)amino-1,2,3-thiadiazolo[5,4-b]pyridine (21). A solution of **20** (1.25 g, 2.1 mmol) in ethanol (200 ml) was heated at reflux temperature for 2.5 h. The reaction mixture was evaporated to a syrup which resisted crystallization. The syrup was dissolved in ethanol (50 ml) and treated with charcoal and the filtrate was evaporated to provide **21** as a foam (1.05 g, 84%): uv λ_{max} (pH 1) 236 nm (ε 44 300), 275 (sh) (17 700), 327 (10 700); λ_{max} (pH 11) 237 nm (ε 44 900), 275 (sh) (17 600), 341 (10 400); λ_{max} (MeOH) 232 nm (ε 5300), 275 (10 600), 338 nm (ε 8400); ^{1}H NMR (Me_2SO-d_6) δ 6.25 (m, 2, $H_{1'}$, $H_{2'}$), 7.20 (d, 1, $J_{7,6}$ = 6.0 Hz, H_7), 8.59 (d, 1, $J_{6,7}$ = 6.0 Hz, H_6), 9.74 (d, 1, NH).

Anal. Calcd for $C_{31}H_{24}N_4O_7S$: C, 62.42; H, 4.03; N, 9.39. Found: C, 62.24; H, 4.24; N, 9.33.

4-(β-D-Ribofuranosyl)amino-1,2,3-thiadiazolo[5,4-b]pyridine (22). A solution of 21 (750 mg, 1.25 mmol) in methanol (50 ml) was adjusted to pH 9 by the addition of sodium methoxide. This solution was stirred at 15 °C for 1 h and then at room temperature for 5 h. The reaction mixture was allowed to stand at 4 °C for 2 days. The crystalline solid which had formed was collected by filtration and washed with methanol (10 ml) to furnish 190 mg of **22**. Treatment of the filtrate by the same procedure as that used for the isolation of **11** gave an additional 80 mg of **22** to provide a total of 270 mg (69%) of **22**. Recrystallization from a minimal amount of methanol provided an analytical sample: mp 202–204°; uv λ_{max} (pH 1) 252 nm (ε 11 900), 275 (8300), 322 (8700); λ_{max} (pH 11) 243 nm (ε 13 100), 272 (5600), 338 (5900); λ_{max} (MeOH) 234 nm (ε 13 900), 270 (5300), 339 (5700); ^{1}H NMR (Me_2SO-d_6) δ 4.83 (t, 1, $C_{5'}OH$), 5.80 (q, 1, $J_{1',2'}$ = 5.0, $J_{1',4}$ = 8.0 Hz, $H_{1'}$), 7.09 (d, 1, $J_{5,6}$ = 5.5 Hz, H_5), 7.99 (d, 1, $J_{4,1'}$ = 8.0 Hz, 4-NH), 8.57 (d, 1, $J_{6,5}$ = 5.5 Hz, H_6).

Anal. Calcd for $C_{10}H_{12}N_4O_4S{\cdot}0.5H_2O$: C, 40.96; H, 4.10; N, 19.11. Found: C, 41.09, H, 4.41; N, 19.12.

1-Methyl-υ-triazolo[4,5-c]pyridine (23). A solution of 3-amino-4-methylaminopyridine dihydrochloride[31] (250 mg, 1.25 mmol) in water (5 ml) containing 1.5 mequiv of hydrochloric acid was cooled to 3 °C. A precooled sodium nitrite solution (115 mg in 1 ml of H_2O) was added rapidly and the mixture was stirred at 3–5 °C for 1 h and then at room temperature for 1.5 h. The pH of the reaction mixture was adjusted to 7 with a 1 N aqueous sodium hydroxide solution and then evaporated to a solid which was coevaporated with ethanol. This solid was extracted with diethyl ether (5 × 15 ml) and the ether evaporated to give a solid which was vacuum sublimed (102 °C, 0.05 mmHg) to furnish 150 mg (90%) of **23**: mp 118–120 °C (lit.[32] 120 °C); uv λ_{max} (pH 1) 275 nm (ε 4600); λ_{max} (pH 11) 264 nm (ε 6000); λ_{max} (MeOH) 265 nm (ε 5800); ^{1}H NMR (Me_2SO-d_6) δ 4.45 (s, 3, NCH_3), 7.98 (dd, 1, $J_{7,6}$ = 6.0, $J_{7,4}$ = 1.0 Hz, H_7), 8.66 (d, 1, $J_{6,7}$ = 6.0 Hz, H_6), 9.54 (d, 1, $J_{4,7}$ = 1.0 Hz, H_4).

1-(β-D-Ribofuranosyl)-υ-triazolo[4,5-c]pyridine (25). A solution of **15** (500 mg, 1.75 mmol) in anhydrous hydrazine (10 ml) was heated at reflux temperature for 1 h. The reaction mixture was evaporated to afford an amber syrup which was coevaporated twice with ethanol. The resulting solid was dissolved in water (10 ml), treated with charcoal, and filtered and the filtrate was diluted with 10 ml of ethanol. Silver oxide (2.5 g) was added and the suspension was stirred with no external heating for 20 min. The solution was then heated on a steam bath for 1 h. The mixture was fil-

tered, the filtrate treated with charcoal and filtered, and the filtrate was evaporated to a dark syrup. This syrup was dissolved in methanol and evaporated in the presence of silica gel (SilicAR CC7, 1 g). This mixture was placed on the top of a silica gel column (SilicAR CC7, 2.5 × 10 cm, dry packed) and eluted with chloroform–methanol (4:1 v/v). The fractions containing **25,** as indicated by TLC [R_f 0.75 on silica gel (SilicAR 7GF) developed with chloroform–ethanol (2:3 v/v)], were combined and evaporated to an amber syrup which crystallized to provide 165 mg (38%) of **25:** mp 161–163 °C; uv λ_{max} (pH 1) 266 nm (ϵ 5400); λ_{max} (pH 11) 259 nm (ϵ 6600); λ_{max} (MeOH) 256 nm (ϵ 6700); ^{1}H NMR (Me_2SO-d_6) δ 6.48 (d, 1, $J_{1'2'}$ = 5.0 Hz, $H_{1'}$), 8.25 (d, 1, $J_{7,6}$ = 6.0 Hz, H_7), 8.70 (d, 1, $J_{6,7}$ = 6.0 Hz, H_6), 9.62 (s, 1, H_4).

Anal. Calcd for $C_{10}H_{12}N_4O_4$: C, 47.62; H, 4.76; N, 22.22. Found: C, 47.44; H, 4.58; N, 22.37.

3,4-Diaminopyridine (26). To a solution of 4-amino-2-chloro-3-nitropyridine[33] (1.74 g, 10 mmol) in ethanol containing 1 N sodium hydroxide (10 ml, 10 mequiv) was added 5% palladium on carbon (250 mg) and this mixture was hydrogenated at atmospheric pressure until hydrogen uptake had ceased. The resulting mixture was filtered and the filtrate evaporated to a residue which was dried in vacuo at 75 °C. The resulting solid was triturated briefly with cold water (5 ml) and the solid was collected by filtration. Recrystallization from water provided 725 mg (72%) of **26:** mp 217–219 °C (lit.[34] 218–219 °C); uv λ_{max} (pH 1) 285 nm (ϵ 7400); λ_{max} (pH 11) 246 nm (ϵ 5800), 283 (3500); λ_{max} (MeOH) 253 nm (ϵ 4100), 295 (5800); ^{1}H NMR (Me_2SO-d_6) δ 4.55 (s, 2, 3-NH_2), 5.38 (s, 2, 4-NH_2), 6.49 (d, 1, $J_{5,6}$ = 5 Hz, H_5), 7.56 (d, 1, $J_{6,5}$ = 5 Hz, H_6), 7.73 (s, 1, H_2).

***v*-Triazolo[4,5-*c*]pyridine (27).** A solution of 3,4-diaminopyridine (**26,** 725 mg, 6.6 mmol) in water (7 ml) containing hydrochloric acid (12 mequiv) was cooled to 3 °C. A solution of soium nitrite (530 mg in 1.5 ml of water) was added rapidly to this solution which was stirred at 5 °C for 1 h and then at 20 °C for an additional 1 h. The solution was filtered, neutralized with 6 N sodium hydroxide to pH 7, and then evaporated to dryness to afford a solid. This solid was triturated with cold water (3 ml), and the solid collected by filtration and recrystallized from water to give 595 mg (75%) of **27:** mp 243–245 °C (lit.[32] 240 °C); uv λ_{max} (pH 1) 261 nm (ϵ 4600); λ_{max} (pH 11) 264 nm (ϵ 4400), 279 (4600); λ_{max} (MeOH) 258 nm (ϵ 4300); ^{1}H NMR (Me_2SO-d_6) δ 7.96 (dd, 1, $J_{7,4}$ = 1.0, $J_{7,6}$ = 6.0 Hz, H_7), 8.57 (d, 1, $J_{6,7}$ = 6.0 Hz, H_6), 9.55 (d, 1, $J_{4,7}$ = 1.0 Hz, H_4), 15.00 (s, 1, H_1).

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Registry No.—**3,** 36258-82-9; **4a,** 5991-01-5; **4b,** 22860-91-9; **5,** 57680-35-0; **6,** 57680-36-1; **7,** 57680-37-2; **8,** 57680-38-3; **9,** 57680-39-4; **10,** 3969-28-6; **11,** 57680-40-7; **12,** 57680-41-8; **13,** 57680-42-9; **14,** 57680-43-0; **15,** 57680-44-1; **16,** 57680-45-2; **17,** 57680-46-3; **18,** 57680-47-4; **19,** 57680-48-5; **20,** 57680-49-6; **21,** 57680-50-9; **22,** 57680-51-0; **23,** 57680-52-1; **25,** 57680-53-2; **26,** 54-96-6; **27,** 273-05-2; 4-chloro-*v*-triazolo[4,5-*c*]pyridine, 36258-82-9; 2,2-dimethoxypropane, 77-76-9; methanethiol, 74-93-1; 3-amino-4-methylaminopyridine 2HCl, 57680-54-3; 4-amino-2-chloro-3-nitropyridine, 2789-25-5.

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Notes

Syn Selectivity in Diels-Alder Reactions of Isodicyclopentadiene

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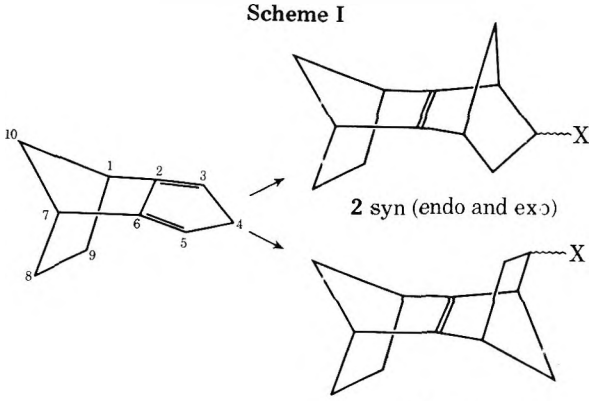
We have studied the stereochemistry of the Diels–Alder reactions of tricyclo[5.2.1.$0^{2,6}$]deca-2,5-diene (isodicyclopentadiene, **1**)[1] with methyl acrylate and propiolate. Conceivable for these reactions are the two stereochemical courses, syn and anti, which may be so termed according to the modes of attack from the ethano and methano sides of the norbornane framework, leading to the formation of **2** and **3**, respectively (Scheme I). These should be differentiated from the endo–exo isomerism possible for the stereochemical arrangement of dienophile substituents with respect to the cyclopentadiene moiety. (Note that the syn–anti isomerism corresponds exactly to the endo–exo terminology which is usually adopted for the stereochemistry of norbornenes.) Investigation of the syn–anti stereochemistry for **1** would also be interesting in connection with that for norbornenes.[2]

Scheme I

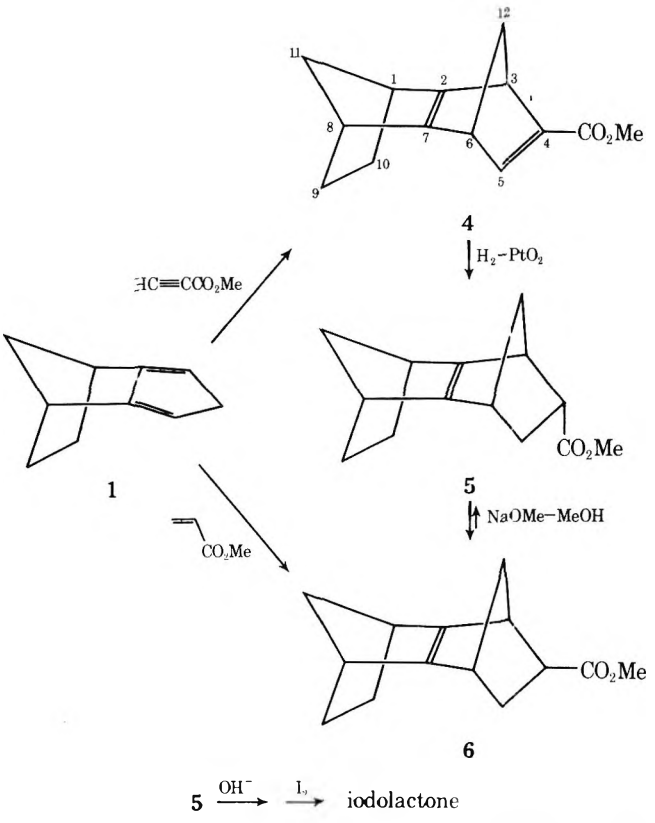


NMR spectroscopy, epimerization experiments, and chemical transformations of the adducts to a known compound have shown that the Diels–Alder adducts are exclusively of syn structure. The stereochemistry observed exhibits a sharp contrast to the preferential exo selection of norbornenes and seems to illuminate a potential importance of stereoelectronic effect and/or steric attraction in determining stereochemical courses of Diels–Alder reactions.

Diels–Alder reactions of **1** with methyl propiolate and acrylate were conducted in *n*-hexane at 40–50 °C. The products were isolated in a relatively high yield of 84 and 77%, respectively, after purification through column chromatography. Both adducts were homogeneous; no isomeric products were discernible on TLC and NMR spectra.

The product **4** from methyl propiolate was hydrogenated over platinum oxide at room temperature until an equimolar amount of hydrogen gas was absorbed. The central double bond remained unchanged under this condition. Since the hydrogenation of norbornene is established to occur exclusively from the exo side, the present hydrogenation product **5** is expected to have the endo configuration. This was supported by the coupling pattern of the exo proton at C_4 α to the carbomethoxy substituent[3] and ascertained by the successful transformation to a lactone via carboxylic acid. Isomerization of this *endo*-carbomethoxy derivative **5** in the presence of sodium methoxide in methanol at 100 °C gave an equilibrium mixture which contained more than 95% exo isomer **6** (Scheme II). NMR, ir, and VPC analyses identified this exo isomer with the original kinetic adduct **6** which resulted from methyl acrylate.

Scheme II

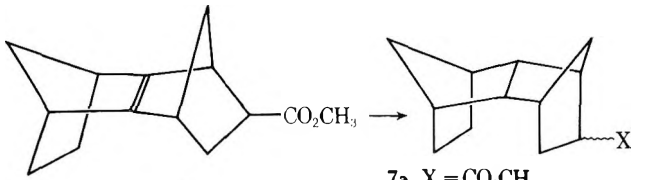


The above-described results clearly indicate that the syn–anti stereochemical selections of the propiolate and acrylate are identical. In order to determine the syn–anti configuration, we have first examined the NMR spectra of **4–6.** Although no signal was observed in the range higher than 0.5 ppm in the spectra of **5** or **6,** there were recorded multiplets at 0.26 ppm in the spectrum of compound **4.** These multiplets were assigned unequivocally to the endo protons of the ethano bridge (C_9–C_{10}) of **4** through decoupling as well as comparison with the spectrum of 9,10-exo,*exo*-dideuterio-**4.**[4] Thus it might be said that these endo protons suffer appreciable higher field shift in **4.** This might be best explained by the assumption that the endo protons of the ethano bridge in **4** face to the olefinic double bond (C_4–C_5) in the opposite norbornene skeleton. The situation is possible only when the syn addition is involved.

If the adducts have the syn structure, it would be possible to lead them to known cage compounds **7** by exo hydrogenation of the central double bond. Although this double bond is resistant to the catalytic hydrogenation as has been described above, it was found to be readily hydrogenated by diimide generated from potassium azodicarboxylate in

methanol.[5] The adduct **6** was transformed to a known bird cage alcohol **7e** by the sequential route via **7a** to **7d** as shown in Scheme III. Alkaline hydrolysis of **7a** followed by

Scheme III



6

7a, X = CO_2CH_3
b, X = CO_2H
c, X = COCl
d, X = *m*-ClC_6H_4COOCO
e, X = OH

the treatment with thionyl chloride gave an acid chloride **7c.** Treatment of **7c** with *m*-chloroperbenzoic acid in *n*-hexane at 0 °C for a few hours followed by reflux resulted in the formation of the acyl carbonate **7d** via carboxy inversion. Without isolation of **7d,** hydrolysis and chromatography gave rise to the hydroxy derivative **7e** in an overall yield of 17%. **7e** thus obtained was identified with the authentic cage alcohol.[6] During these reactions, no contamination by epimeric products was observed. These transformations firmly establish the syn configuration of the original kinetic adducts **4** and **6.** An alternative pathway to **7e** starting from the anti isomer **3** is no doubt a highly hedged possibility.[7]

The high stereoselectivity of isodicyclopentadiene (**1**) in favor of syn addition of dienophiles is rather surprising in comparison with the preferential exo addition of a wide variety of reagents to norbornene and its homologues.[2] Accordingly, the stereochemistry here observed can hardly be compromised with the ideas such as steric repulsion by the ethano bridge[2b] and torsional strain,[8] which have been invoked to explain the exo preference in the additions to norbornenes.

A similar syn preference in Diels–Alder reactions was observed for pentachlorocyclopentadiene and was interpreted in terms of the dipolar stabilizations.[9] However, such an interaction does not seem to be responsible for the syn selection here observed; the diene **1** is essentially nonpolar in nature.

Two explanations seem to be possible for the observed selectivity. One is a greater steric attraction by the ethano bridge which should stabilize the syn transition state. In previous papers we suggested the importance of steric attraction as well as dispersion forces in determining the endo–exo selectivity in Diels–Alder reactions of cyclopentadiene and norbornadiene.[10] The role of such a steric attraction has been stressed for several other types of reactions exhibiting contrathermodynamic stereoselectivities.[11] In the diene **1**, the reaction center is apart by one more carbon unit from the norbornane framework. This would allow steric attraction to outweigh steric repulsion which should diminish more sharply with the increase in distance.

The other explanation is a recourse to stereoelectronic effect. A greater development of π orbitals toward the exo side has been suggested to account for the exo preference of norbornene.[12] The relatively unstable filled σ orbitals of the norbornane skeleton would be so high lying as to permit its mixing with the π orbital. The mixing may well bias the spread of the π orbital in space above and below the cyclopentadiene plane of **1**. It is probable that such a spatial asymmetry of the π orbital should in effect favor the syn orientation of an attacking dienophile.

At present, it is not possible for us to decide which will be the more dominant factor to control the stereochemistry. Perhaps, the two factors combine to lead to the observed syn stereoselectivity. All that we can state at the present stage is that the syn predominance is not due to the steric repulsion.

Experimental Section

General. NMR spectra were measured on $CDCl_3$ solutions with Varian HA-100, T-60, and EM-360 spectrometers using tetramethylsilane as an internal standard. Infrared spectra were recorded on a Hitachi EPI-G spectrophotometer. Vapor phase chromatography was performed on a Perkin-Elmer F6-D instrument equipped with a capillary column, 45 m × 0.25 mm coated with Carbowax 20M. Tricyclo[5.2.1.$0^{2,6}$]deca-2,5-diene (**1**) was prepared according to the method of Alder et al.[1]

Diels–Alder Reaction of 1 with Methyl Acrylate. A solution of 1.00 g (7.58 mmol) of **1**, 2.00 g (23.3 mmol) of freshly distilled methyl acrylate, and a small amount of hydroquinone (ca. 10 mg) in 10 ml of *n*-hexane was maintained at 50 °C until **1** was consumed. The reaction was monitored by TLC (silica gel), and 1 day of heating was required. After evaporation of solvent and excess dienophile, the crude reaction mixture was chromatographed on silica gel using ether–petroleum ether (1:20) eluent. Evaporation of intermediate fractions gave 1.28 g (5.87 mmol) of 4-*exo*-carbomethoxy-*syn*-tetracyclo[6.2.1.1.^{3,6}.$0^{2,7}$]dodec-2-ene (**6**) (77% based on **1**): NMR 0.73–2.4 (10 H), 2.7–3.02 (br s, 1 H), 3.02 (br s, 3 H), 3.12 (br s, 1 H), 3.73 ppm (s, 3 H); ir (neat) 2950, 2875, 1733 (C=O), 1424, 1356, 1195, and 1043 cm^{-1}; mass spectrum *m/e* (rel intensity) 218 (1, M^+), 190 (1), 132 (18), 117 (12), 104 (75), 91 (10), 78 (9), and 55 (42).

Anal. Calcd for $C_{14}H_{18}O_2$: C, 77.03; H, 8.31; O, 14.66. Found: C, 77.27; H, 8.27; O, 14.86.

Diels–Alder Reaction of 1 with Methyl Propiolate. A similar procedure as described above was employed. A mixture of 2.00 g (15.2 mmol) of **1** and 1.00 g (11.9 mmol) of methyl propiolate in *n*-hexane was maintained at 40 °C for 24 h. There was isolated 2.16 g (10.0 mmol) of 4-carbomethoxy-*syn*-tetracyclo[6.2.1.1.^{3,6}.$0^{2,7}$]dodeca-2,5-diene (**4**) (84%) after chromatography on silica gel using ether–petroleum ether (1:10) eluent: NMR 0.26 (ddd, 2 H, J = 8, 3.5, 2 Hz), 1.10 (dt, 1 H, J = 8, 1.5 Hz), 1.42 (m, 3 H), 2.25 (dd, 1 H, J = 6.5 Hz), 2.99 (br d, 2 H), 3.45 (br s, 1 H), 3.70 (s, 3 H, and br, 1 H), 7.40 ppm (d, 1 H, J = 3 Hz); ir (neat) 2960, 2875, 1720, 1595, 1570, 1435, 1320 cm^{-1}; mass spectrum *m/e* (rel intensity) 216 (1, M^+), 200 (1), 198 (2), 173 (2.5), 172 (3).

Anal. Calcd for $C_{14}H_{16}O_2$: C, 77.75; H, 7.46; O, 14.79. Found: C, 77.35; H, 7.77; O, 15.22.

Catalytic Hydrogenation of 4. A solution of 0.553 g (2.54 mmol) of **4** and 15 mg of PtO_2 in 15 ml of ethyl acetate was pressured in a microbomb with hydrogen to 140 atm at room temperature and the mixture was shaken overnight. After removal of catalyst by filtration and of solvent under reduced pressure, the crude product was chromatographed on silica gel using ether–petroleum ether (1:20) eluent. By collecting early fractions, 0.465 g (2.13 mmol) of 4-*endo*-carbomethoxy-*syn*-tetracyclo[6.2.1.1.^{3,6}.$0^{2,7}$]dodec-2-ene (**5**) was obtained (84%): NMR 0.65 (m, 2 H), 0.85–2.2 (m, 8 H), 2.97 (br s, 4 H), 3.45 (dd, 1 H, J = 3, 5.5 Hz), 3.65 ppm (s, 3 H); ir (neat) 2960, 2865, 1740 (C=O), 1600, 1420, 1350, 1278, 1200, 793, and 770 cm^{-1}; mass spectrum *m/e* (rel intensity) 218 (1, M^+), 190 (0.7), 159 (1.1), 150 (1.1), 132 (5), 117 (4), 115 (3), 104 (15.4), 95 (5), 55 (7).

Iodolactonization of 5. A solution of 0.160 g (0.73 mmol) of **5** in 10 ml of 10% methanolic sodium hydroxide was maintained overnight at 50 °C. The reaction mixture was poured into 30 ml of water and the solution was acidified with dilute hydrochloric acid. The oily mixture was extracted with ether (30 ml × 2) and dried (Na_2SO_4). After evaporation of ether, 0.155 g of crude product was obtained. The crude product and 0.05 g of sodium hydroxide were dissolved in 30 ml of water, and 0.250 g (0.98 mmol) of iodine and 0.150 g (1.0 mmol) of sodium iodide were added and stirred at room temperature for 2 h. The solution turned to a dark brown slurry, and the reaction mixture was extracted twice with 30 ml each of chloroform. The combined chloroform solution was washed with aqueous sodium thiosulfate in order to remove excess iodine, and washed with water and dried (Na_2SO_4). After evaporation of solvent, the crude product where slight contamination was observed on TLC (silica gel) was chromatographed on silica gel using chloroform eluent. By totaling early fractions 0.110 g (0.33 mmol) of white solid was obtained (46% from **5**): NMR 1.0–3.0 ppm (br m); ir (KBr) 3055, 2950, 2875, 1775 (C=O), 1460, 1228, 1023, and

735 cm^{-1}; mass spectrum *m/e* (rel intensity) 203 (1, M − 1), 175 (1), 149 (2.5).

Isomerization of 5 to 6. Into 2.0 ml of methanol containing 0.20 g of sodium 0.07 g of **5** was dissolved and the solution was maintained at 100 °C in a sealed tube for 20 h. The solution was poured into 20 ml of water and acidified with dilute hydrochloric acid, and the oily mixture was extracted with ether (20 ml × 2). The combined extracts were washed with water (30 ml) and dried ($CaCl_2$). To this solution was added ethereal diazomethane solution generated from *N*-nitrosomethylurea until the solution remains yellow colored and the evolution of nitrogen ceases. After standing for 0.5 h at room temperature, a few drops of acetic acid were added to remove excess diazomethane and the solution was washed with saturated aqueous sodium bicarbonate, then with water and dried (Na_2SO_4). After evaporation the crude product was subjected to VPC analysis (Carbowax 20M, capillary tube 45 m × 0.25 mm, 140 °C), which exhibited the presence of **6** as a main component and the ratio over **5** to be 20.

Diimide Reduction of 6. To a stirred suspension of 4.05 g (20.9 mmol) of potassium azodicarboxylate in 20 ml of methanol containing 2.05 g (9.4 mmol) of **6** was added a solution of 3.15 g (52.5 mmol) of acetic acid in 5 ml of methanol during 0.5 h. After stirring was continued for an additional 0.5 h, 30 ml of water was added and the product was extracted with ether (30 ml × 2). The combined extracts were washed with water (30 ml) and dried (Na_2SO_4). After evaporation of solvent, the crude product (1.85 g) was chromatographed on silica gel using ether–petroleum ether (1:20) eluent. By collecting intermediate fractions, 1.433 g (6.51 mmol) of 4-*exo*-carbomethoxy-*endo,endo*-tetracyclo-[6.2.1.$1^{3,6}$.$0^{2,3}$]dodecane (**7a**) was isolated (69%): NMR 1.2–1.8 (m), 2.00 (br s), 2.36 (br s) (these signals were not separately recorded and total signal intensity in this region corresponds to 15 protons), 2.60 (br s, 1 H), 3.30 (ddd, 1 H, J = 1.5, 5.5, 9.0 Hz), 3.66 ppm (s, 3 H); ir (neat) 3020, 2950, 2885, 1738, 1420, 1355, 1303, 1195, 1173, and 1050 cm^{-1}; mass spectrum *m/e* (rel intensity) 220 (1, M^+), 193 (1.5), 180 (8), 161 (5), 134 (4), 121 (515), 119 (8), 104 (6), 93 (7.5), 91 (7.5), 87 (7.5).

Anal. Calcd for $C_{14}H_{20}O_2$: C, 76.33; H, 9.15; O, 14.52. Found: C, 76.05; H, 9.28; O, 14.29.

Transformation of 6 to 4-*exo*-Hydroxy-*endo,endo*-tetracyclo[6.2.1.$1^{3,6}$.$0^{2,7}$]dodecane (7e). To 10 ml of 10% methanolic potassium hydroxide, 1.205 g (5.48 mmol) of **7a** was dissolved and the solution was stirred overnight at room temperature. The reaction mixture was poured into 50 ml of water and acidified with dilute hydrochloric acid, and the product mixture was extracted with ether (30 ml × 3). The combined extracts were washed with water (30 ml) and dried (Na_2SO_4). Evaporation of ether afforded 1.08 g of crude carboxylic acid **7b**. The crude **7b** was heated under reflux with 10 ml of thionyl chloride and 0.50 ml of pyridine for 3 h. Excess thionyl chloride was removed by distillation, and the residue was further distilled under reduced pressure at 100–130 °C (0.1–0.5 mm) by using a Kugelrohr micro distilling apparatus to obtain 1.750 g of pale brown solid. This crude **7c** was used directly without further purification. A chilled stirred mixture of 1.750 g of crude **7c** and 1.583 g (7.78 mmol) of 85% *m*-chloroperbenzoic acid in 20 ml of *n*-hexane (dried over sodium) was treated dropwise with 0.615 g (7.78 mmol) of pyridine in 5 ml of *n*-hexane (5 min). The mixture was allowed to warm to room temperature with stirring and was left stand overnight. The solution was decanted from pyridine hydrochloride and the residue was washed with 5 ml of ether. The combined washings were evaporated and replaced with 30 ml of 10% methanolic potassium hydroxide. The solution was stirred at room temperature for 2 h followed by heating under reflux for 1 h. After cooling to room temperature, the solution was concentrated under reduced pressure, and the residue was treated with 30 ml of ether. The combined extracts were evaporated and the crude mixture was chromatographed on silica gel using ether–petroleum ether (1:5) eluent to isolate 0.165 g (0.93 mmol) of 4-*exo*-hydroxytetracyclo[6.2.1.$1^{3,6}$.$0^{2,7}$]dodecane (**7e**) (17% from **7a**). This material was confirmed to be identical with the authentic sample of **7e** by means of NMR, ir, and VPC.

Acknowledgment. We wish to thank Professor T. Fueno for helpful discussions.

Registry No.—**1**, 6675-72-5; **4**, 58240-70-3; **5**, 58240-71-4; **6**, 58267-54-2; **7a**, 58240-72-5; **7b**, 58240-73-6; **7c**, 58240-74-7; **7d**, 58240-75-8; **7e**, 7273-98-5; methyl acrylate, 96-33-3; methyl propiolate, 922-67-8.

References and Notes

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(3) P. Laszlo and P. v. R. Schleyer, *J. Am. Chem. Soc.*, **86**, 1171 (1964).
(4) The deuterated adduct 9,10-*exo,exo*-d_2-**4** was obtained by the Diels–Alder reaction of methyl propiolate with 8,9-*exo,exo*-d_2-**1**, where exo deuteriums were introduced by catalytic D_2 reduction of dicyclopentadiene at the first step of the preparation of **1**. The multiplets around 1.40 ppm disappeared while the signals at 0.26 ppm became sharp considerably owing to the decrease of geminal coupling and were assignable to endo protons at C_9 and C_{10}.
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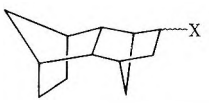
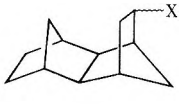
(7) Diimide reduction of **3** inevitably involves the reduction of a norbornene fragment from its endo side, a situation which is known to be seriously disfavored: W. C. Baird, Jr., B. Franzus, and J. H. Surrige, *J. Chem. Soc.*, **89**, 410 (1967). Even if the situation is overcome to produce **8**, some skeletal rearrangement is required in order for **8** to form **7e** during the transformation procedure. However, it has been calculated that



8a



8b

the parent hydrocarbon **7** is thermochemically less stable by 9.05 kcal/mol than its isomer **8** (X = H): E. M. Engler, J. D. Andose, and P. v. R. Schleyer, *ibid.*, **95**, 8005 (1973).
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Propellanes. XI. On the Mechanism of Oxygenation of Cyclopropyllithiums

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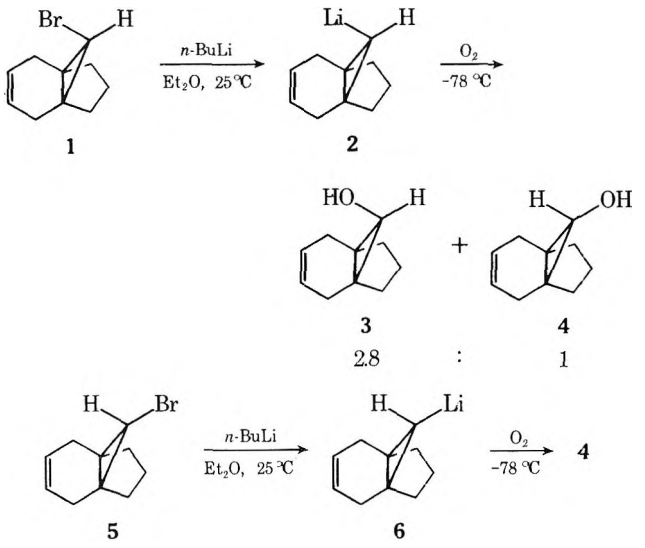
Some time ago, Longone[1] reported that the oxygenation of cyclopropyllithiums to give cyclopropanols was a synthetically useful reaction. However, the stereochemistry, and hence mechanism, of the oxygenation step was not elucidated. We now report results which strongly implicate an electron transfer process to give a superoxide intermediate.

Propellanes **1** and **5** were initially chosen as substrates, owing in part to our need to obtain the corresponding alcohols for another study.[2] We took advantage of the previously demonstrated[3,4] stereoretention of the *n*-BuLi exchange reaction in order to generate **2** and **6**. After cooling to −78 °C, O_2 was bubbled through the solution for ≥1 h. The resultant mixture of cyclopropanol(s) and 1-butanol (a tenfold excess of *n*-BuLi was normally used) was usually acetylated directly, followed by purification and separation of the epimeric acetates; **3** and **4** could then be regenerated by reaction with KOH in aqueous MeOH. A particularly distinguishing feature of **3**, not found for **4**, was an intramolecularly hydrogen-bound hydroxyl absorption in the ir spectrum.

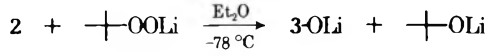
While the exclusive formation of **4** from **5** might lead one to consider direct collapse of **6** with O_2, the epimeric mix-



ture obtained from 1 strongly implies an electron transfer mechanism, which would proceed via an intermediate cyclopropyl radical–lithium superoxide ion pair; the lifetime of this radical pair would allow epimerization at C_{10}.[5] However, one must exclude the possibility that 4 arises via an SN2 displacement[6] by LiO_2^- (formed from the reaction of *n*-BuLi and O_2) on 1. To this end, a fivefold excess of *n*-BuLi and 1 were cooled to −78 °C and O_2 bubbled through; 1 was almost quantitatively recovered. Thus oxygenation of cyclopropyllithiums apparently occurs via the same electron transfer mechanism already observed for simpler alkylmagnesiums.[7]

Since the initial product formed from the collapse of a cyclopropyl radical with superoxide is a hydroperoxide salt, but the isolated product is an alcohol, a step involving the transformation of hydroperoxide to alkoxide salt must occur. This is well known to be the reaction of ROOLi with RLi to give two molecules of ROLi. In the cases we studied, the ratio of *n*-BuLi to cyclopropyllithium was 9:1; thus, assuming that the rates of oxygenation of *n*-BuLi, 2, and 6 are not much different, the secondary reactions of the peroxide salts from 2 and 6 were primarily with *n*-BuLi. If true, the stereochemistry observed was that of the primary step (see Scheme I). Nevertheless, it was of interest to determine the stereochemistry of the secondary step, as follows.

A solution of *t*-BuOOLi in ether, prepared by adding *n*-BuLi to dissolved *t*-BuOOH, was dropped into an ethereal solution of 2 (prepared as above) which was kept at −78 °C. Acetylation and analysis of the products showed that, to within the limits of NMR analysis, only 3-OAc was formed. Thus the carbanionic reduction of lithium hydroperoxides indeed appears to be an SN2 reaction, although an electron transfer process within a cage too tight to allow epimerization is, of course, not excludable.



Finally, within the context of Scheme I, we cannot tell whether 8 is more stable than 7, or whether 8 collapses to 10 more rapidly than 7 does to 9; note that the conversion of 7 to 8 involves more than simply inversion of a cyclopropyl radical.[5]

Experimental Section

10α-Bromotricyclo[4.3.1.0^{1,6}]dec-3-ene (1) and 10β-Bromotricyclo[4.3.1.0^{1,6}]dec-3-ene (5). The reduction of 10,10-dibromotricyclo[4.3.1.0^{1,6}]dec-3-ene[8] was achieved using 1 equiv of *n*-Bu_3SnH.[9] Typically, 5 g of the dibromide was placed in a flask, to which was added 5 g of *n*-Bu_3SnH. The reaction mixture became warm, and was allowed to stand for 2 h. Distillation of one or more such runs led to a ca. 85% yield of monobromides (bp 58–61 °C, 0.6 Torr).

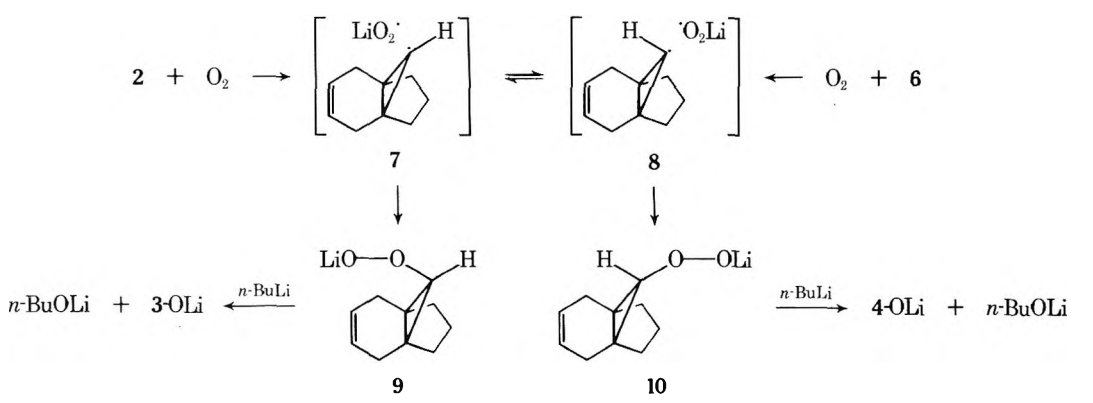
Anal. Calcd for $C_{10}H_{13}Br$: C, 56.36; H, 6.15. Found: C, 56.68; H, 6.23.

GLC analysis (2 m × 0.25 in. column of 20% Carbowax on 80/100 Chromosorb W) showed a 3.3:1 ratio of the isomers. Preparative separation was achieved via chromatography on activity I neutral Woelm alumina. Elution with hexane gave the minor isomer first (which was partly destroyed by the chromatography), followed by the major isomer. The identification of the major isomer as 1, and the minor isomer as 5, was based primarily on the NMR spectrum, and secondarily on the overall self-consistency of the observed chemistry (i.e., overall stereoretention in carbanionic reactions[4] and solvolytic reactivity of 5 but not 1[10]). The NMR of the major isomer (CCl_4) showed peaks at δ 5.44 (narrowly split multiplet, 2 olefinic H), 2.23 (broad s, 4 allylic H), 2.1–1.1 (multiplet, 6 aliphatic H), and 2.85 (s, cyclopropyl H). The minor isomer had peaks at δ 5.40 (narrowly split multiplet, 2 olefinic H), 2.5–1.6 (multiplet, 4 allylic + 6 aliphatic H), 3.16 (s, cyclopropyl H). The key difference between the spectra is that the major isomer shows a singlet for the allylic protons, whereas the minor isomer's allylic protons are broadly split up. Comparison with the NMR of the dibromide,[8] which has a singlet (δ 2.33, CCl_4) for the allylic protons, the NMR of 3-OAc (see below, singlet for allylic protons), and the NMR of 4-OAc (see below, broadly split up pattern for the allylic protons) confirms the identification of the major isomer as 1.

10α-Bromotricyclo[4.3.1.0^{1,6}]decane. To a solution of 100 mg of 1 in 50 ml of Et_2O was added a catalytic amount of 5% Pt/C. Room pressure hydrogenation was complete in less than 1 h. Filtration and evaporation of solvent gave a virtually quantitative yield of the saturated bromide: NMR (CCl_4) δ 2.86 (s, cyclopropyl H), 2.3–0.8 (m, 14 H). Anal. Calcd for $C_{10}H_{15}Br$: 214.03571. Found: 214.03533.

Oxygenation of 1. To a solution of 100 mg (0.47 mmol) of 1 in 10 ml of Et_2O contained in a flame-dried, N_2-swept 50-ml Schlenk flask was added a solution of 4.99 mmol of *n*-BuLi in 3 ml of hexane and 10 ml of Et_2O. The resulting mixture was allowed to stir for 0.75–1 h, after which it was cooled to −78 °C. O_2 was then bubbled into the solution (fritted glass bubbler) for 1 h. This was followed by addition of aqueous NH_4Cl to the reaction mixture (at ≥0 °C). After shaking in a separatory funnel, the layers were sepa-

Scheme I



rated and the aqueous layer further extracted with Et_2O. Combination of the ethereal layers was followed by drying (K_2CO_3) and solvent evaporation.

The crude mixture of **3**, **4**, and *n*-BuOH was then dissolved in ca. 5 ml of dry pyridine, to which was added ca. 1 ml of Ac_2O. The solution was heated to 75° for 1 h, followed by cooling, addition of H_2O, and extraction with Et_2O. The Et_2O extracts were then washed with 1 N HCl until the wash remained acidic. Drying of the ether layer was followed by rotoevaporation using a hot water bath (ca. 75 °C) to evaporate the *n*-BuOAc. The resulting crude oil was analyzed by NMR. The only methine peaks seen proved to be those for **3**-OAc and **4**-OAc in the ratio of 2.8:1. It was assumed that this ratio also applied to the alcohols **3** and **4**.

Separation and purification of **3**-OAc and **4**-OAc was achieved by chromatography on silica gel (of 355 mg of crude material). Both acetates were eluted with 4% Et_2O–96% hexane, with **4**-OAc coming through first. The total isolated yield of cyclopropyl acetates was 38%.

3-OAc: NMR ($CDCl_3$) δ 5.50 (narrowly split multiplet, olefinic H), 3.82 (s, cyclopropyl H), 2.13 (s, 4 allylic H), 2.1–1.2 (m, 6 aliphatic H), 1.90 (s, OAc); ir ($CDCl_3$) 3020 (m), 1740 (s), 1665 (w), 1250 cm^{-1} (s). Anal. Calcd for $C_{12}H_{16}O_2$: 192.1150. Found (70 eV): 192.1160.

4-OAc: NMR ($CDCl_3$) δ 5.50 (narrowly split multiplet, olefinic H), 3.95 (s, cyclopropyl H), 2.8–1.5 (m, 4 allylic + 6 aliphatic H), 2.07 (s, OAc); ir ($CDCl_3$) 3020 (m), 1735 (s), 1654 (w), 1245 cm^{-1} (s). Anal. Calcd for $C_{12}H_{16}O_2$: 192.1150. Found (70 eV): 192.1160.

Oxygenation of 5. In a manner exactly analogous to that described for **1**, 50 mg (0.23 mmol) of **5** was oxygenated and acetylated. To within the error limits of NMR analysis, the only detectable product was **4**-OAc.

10α-Hydroxytricyclo[4.3.1.0^{1,6}]dec-3-ene (3). In 1 ml of a 5% KOH in 25% aqueous MeOH solution was dissolved 16 mg of pure **3**-OAc. The mixture was heated for 2 h at 50 °C, followed by dilution with H_2O and extraction with Et_2O. After drying (K_2CO_3), filtering, and evaporating the solvent ca. 5 mg of solid white product was recovered. The ir ($CDCl_3$) showed peaks at 3590 (sharp, free OH), 3540 (sharp, intramolecularly hydrogen-bound OH), and 3430 cm^{-1} (broad, intermolecularly hydrogen-bound OH).

10β-Hydroxytricyclo[4.3.1.0^{1,6}]dec-3-ene(4). In the manner described above, a 50-mg sample of pure **4**-OAc was hydrolyzed (in 1 ml of the basic solution, and for only 40 min at 50 °C); 13 mg of product was recovered. The ir ($CDCl_3$) showed peaks at 3600 (sharp, free OH) and 3430 cm^{-1} (broad, intermolecularly hydrogen-bound OH).

Oxygenation of 10α-Bromotricyclo[4.3.1.0^{1,6}]decane. A variation of the procedure described above was tried, both to examine the effect on yield and mechanism (if any) of changing solvent. In a dried 100-ml Schlenk flask were placed 0.88 g (4.1 mmol) of 10α-bromotricyclo[4.3.1.0^{1,6}]decane and 6 ml of THF. To the resulting solution was added 26 ml of a 1.6 M hexane solution of *n*-BuLi (42 mmol), under N_2. After stirring for 1 h at room temperature (during which time the solution turned orange) the solution was cooled to −78 °C, and O_2 bubbled in for 1 h. The work-up of the reaction was carried out as described for the oxygenation of **1**. By pumping on the crude product at 1.5 Torr, it was possible to remove the *n*-BuOH; the resulting oil showed singlets at δ 2.98 and 3.17 (for cyclopropyl H) in a ca. 1:1 ratio.

Acetylation of the yellow oil was carried out as before (but at room temperature for 20 h). Chromatography of the products gave 0.34 g (43%) of an inseparable mixture of 10α-acetoxy- and 10β-acetoxytricyclo[4.3.1.0^{1,6}]decane in a 1:1 ratio. Analysis of a GLC-purified sample (20% DEGS on Chromosorb P column) gave the following.

Anal. Calcd for $C_{12}H_{18}O_2$: C, 74.18; H, 9.35. Found: C, 74.23; H, 9.23.

Spectral data for the mixture showed NMR peaks (CCl_4) at δ 3.72 (s, cyclopropyl H), 3.63 (s, cyclopropyl H), 2.00 (s, OAc), 1.96 (s, OAc), and 2.3–0.9 (m, aliphatics); ir (CCl_4) peaks at 3020 (w), 1754 (shoulder), 1740 (s), and 1235 cm^{-1} (s).

Catalytic hydrogenation (Et_2O, Pt/C) of a 25-mg sample of a 2.8:1 mixture of **3**-OAc and **4**-OAc served to establish that the peak at δ 3.63 belonged to the 10α-acetoxy- and that at δ 3.72 to the 10β-acetoxytricyclo[4.3.1.0^{1,6}]decane.

Reaction of 10α-Lithiotricyclo[4.3.1.0^{1,6}]dec-3-ene (2) with Lithium *tert*-Butylhydroperoxide. **1** (100 mg) was converted to the corresponding organolithium (**2**) exactly as described for the oxygenation of **1**. Subsequently, an addition funnel above the Schlenk flask containing **2** was charged with 5 mmol of *n*-BuLi in 3 ml of hexane and 5 ml of Et_2O. To this were cautiously added 5 mmol (90 mg) of *t*-BuOOH (previously dried, over K_2CO_3, in pentane) in 5 ml of Et_2O (a syringe was utilized). The resulting ethereal solution of LiOO-*t*-Bu was then added dropwise to the solution of **2** (which had been cooled to −78 °C). Thus the only way **3** and/or **4** could form would be via reaction with *t*-BuOOLi. The work-up and subsequent acetylation of the product mixture was performed as described for the oxygenation of **1**. To within the error of NMR analysis, the only cyclopropyl acetate formed was **3**-OAc.

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Registry No.—**1**, 58191-00-7; **2**, 58191-01-8; **3**, 58191-02-9; **3**-OAc, 58191-03-0; **4**, 58239-38-6; **4**-OAc, 58239-39-7; **5**, 58239-40-0; 10,10-dibromotricyclo[4.3.1.0^{1,6}]dec-3-ene, 38749-47-2; 10α-bromotricyclo[4.3.1.0^{1,6}]decane, 58191-04-1; 10α-acetoxytricyclo[4.3.1.0^{1,6}]decane, 58191-05-2; 10β-acetoxytricyclo[4.3.1.0^{1,6}]decane, 58239-41-1; lithium *tert*-butylhydroperoxide, 14680-31-0.

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(1) D. T. Longone and W. D. Wright, *Tetrahedron Lett.*, 2859 (1969).
(2) The saturated alcohols corresponding to **3** and **4** were also required. In addition to their synthesis via reduction of **3** and **4**, the saturated bromide analogue of **1** was lithiated (*n*-BuLi) in THF and oxygenated to give a ca. 1:1 mixture of the epimeric saturated alcohols. This provides independent evidence for the involvement of electron transfer in the oxygenation. Details are given in the Experimental Section.
(3) (a) A literature precedent for stereoretentive lithiation–deuteration is C. P. Lewis and M. Brookhart, *J. Am. Chem. Soc.*, **97**, 621 (1975); (b) E. Vogel, A. Vogel, H.-K. Kübbeler, and W. Sturm, *Angew. Chem., Int. Ed. Engl.*, **9**, 514 (1970), reported a possible case of nonstereoretention in a lithiation–carboxylation sequence. However, since they started with a mixture of epimers, and the overall yield was low, one cannot be sure that selective loss of one isomer was not occurring.
(4) We have established the overall stereoretention of the lithiation–deuteration and lithiation–carboxylation sequences (using *n*-BuLi). These sequences were carried out on **1**, at room temperature or below, with invariant stereochemical results. In the latter case, the stereochemistry was proven by iodolactonization of the acid. We also showed that loss of the epimeric acid was not occurring, since when the reaction was carried out with Mg, followed by CO_2, both acids resulted. Details of these experiments will be published soon.
(5) Of course we realize that some or all of the reaction may proceed via a radical chain mechanism, wherein the inversion of the cyclopropyl center (e.g., **7** → **8**) may be more complicated. There seems to be some evidence for cage reactions in oxygenations of Grignards, but other cases definitely involve chains. A good summary of this point is given by G. A. Russell, E. G. Janzen, A. G. Bemis, E. J. Geels, A. J. Moye, S. Mak, and E. T. Strom, "Selective Oxidation Processes", *Adv. Chem. Ser.*, **No. 51** (1965), and by A. G. Bemis, Ph.D. Dissertation, Iowa State University, Ames, Iowa, 1966.
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Base-Promoted Elimination Reactions in the 2-Aza-5-norbornene System. Stereospecific Ring Opening of 2-(*p*-Toluenesulfonyl)-*exo*-3-(trichloromethyl)-2-azabicyclo[2.2.1]hept-5-ene by Lithium Alkyls[1]

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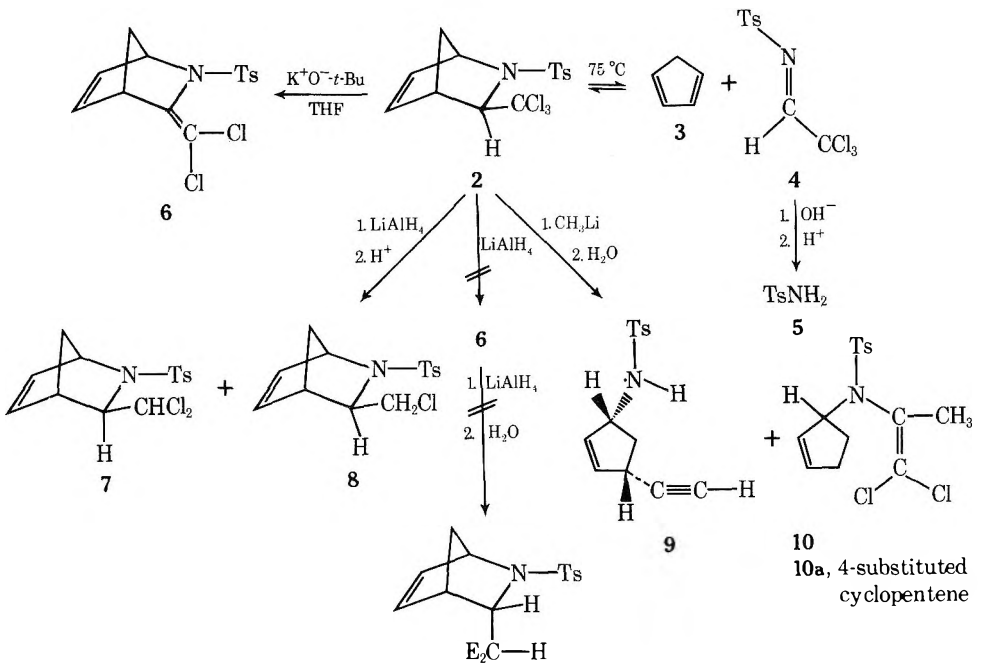
An ongoing interest in aza-aromatic and -antiaromatic character[2] has stimulated our curiosity as to the nature of

Chart I



heterocyclic analogues of homoaromatic and -antiaromatic ring systems, such as the recently synthesized 2-azabicyclo-[2.2.1]hepta-2,5-diene nucleus[3] (**1**). In a survey of possible routes to this system, we have examined the utility of base-promoted elimination reactions on 2-aza-5-norbornene derivatives. The action of various bases on 2-(*p*-toluenesulfonyl)-*exo*-3-(trichloromethyl)-2-azabicyclo[2.2.1]hept-5-ene[4] (**2**) has indeed shown some promise as a route to **1** and its derivatives. In addition, however, lithium alkyls have been found to effect a series of interesting elimination processes leading to a stereospecific ring opening of the 2-aza-5-norbornene nucleus (Chart I). The present report on this novel reaction would seem to be timely, in view of the current interest in the rearrangements of 2-halonorbornenes that are induced by lithium alkyls.[5]

Unfortunately, heating **2** with aqueous, alcoholic sodium or potassium hydroxide led to profound decomposition and the isolation of only *p*-toluenesulfonamide (**5**). This product seemed to have arisen from a retro-Diels–Alder reaction, for when **2** was heated at 75 °C in anhydrous pyridine-d_5, cyclopentadiene (**3**) was clearly discernible in the NMR spectrum at that temperature. In the presence of aqueous base, the liberated *N*-tosylimine (**4**) would undergo rapid hydrolysis to **5**. In agreement with a recent report,[6] however, the action of potassium *tert*-butoxide in anhydrous tetrahydrofuran on **2** gave smooth dehydrohalogenation and a high yield of 3-(dichloromethylene)-2-(*p*-toluenesulfonyl)-2-azabicyclo[2.2.1]hept-5-ene (**6**).

Lithium aluminum hydride in anhydrous tetrahydrofuran, on the other hand, caused both mono- and didechlorination of **2**. The formation of **7** and **8** could have occurred either by nucleophilic substitution of complex hydride on the trichloromethyl group, or by hydride base-promoted elimination to yield **6**, followed by hydralumination of such an enamine.[7] If the latter pathway were involved, **6** would be expected to undergo exo attack and hydrolysis would then lead to *endo*-chloromethyl and *endo*-dichloromethyl derivatives (**7a** and **8a**). However, examination of the NMR spectra of **7** and **8** shows that the C_3 proton is split only by the protons on the $ClCH_2$ and Cl_2CH groups, respectively. If the C_3 protons were exo, they would also be split by the C_4 proton.[6] Since they are not, the C_3 proton in **7** and **8** must be endo and, therefore, the hydride must have replaced the chlorine by a direct nucleophilic substitution.

By contrast, good yields of *cis*-3-*p*-toluenesulfonamido-5-ethynylcyclopentene (**9**) were realized by treating **2** with 4 equiv of either *n*-butyllithium in hexane or methyllithium in ethyl ether. Quenching such a reaction mixture with deuterium oxide led to **7** deuterated only on the N–H and C≡C–H sites. This finding supports the lack of proton abstraction at the C_3-H and C_5-H sites and, hence, the retention of the cis relation of the tosylamido and ethynyl groups on the cyclopentene ring. From the reaction of **2** with methyllithium, a small amount of an unstable substance was isolated whose spectral data are in good accord with the structure of 3-[(*N*-2,2-dichloro-2-propenyl)-*p*-toluenesulfonamido]cyclopentene (**10**) admixed with the 4-sulfonamide isomer (**10a**).

The formation of **9** and **10** from **2** and methyllithium can be rationalized as proceeding in the following steps (Chart II): (a) base-promoted elimination to yield **6**; (b) chlorine–lithium exchange to form **11**;[8] (c) ring opening by syn or anti elimination of the sulfonamide anion; (d) chlorine–lithium exchange leading to **9**; and (e) as an alternative to step b, the addition of methyllithium to **6**, followed rupture at the C_3–C_4 bond (**12**).

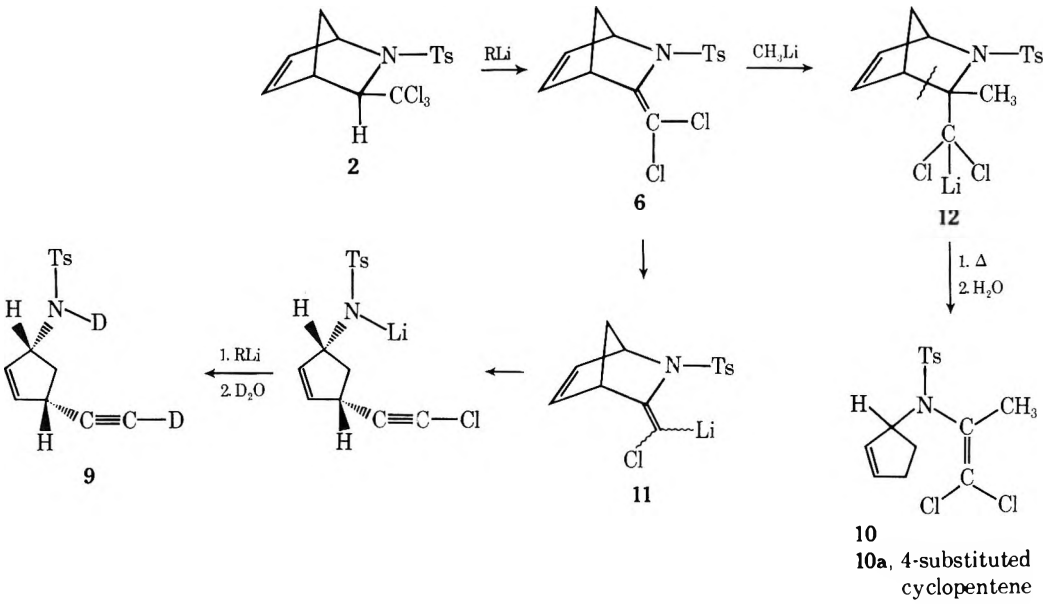
In continuing research, the suitability of the *exo*-chloromethyl-3-aza-5-norbornene derivative (**8**) for the synthesis of the enamine of 2-methyl-2-azabicyclo[2.2.1]hepta-2,5-diene is being explored. It should also be noted that the accessibility of cis-3,5-disubstituted cyclopentenes, such as **9**, from **2** may prove to be of value in the synthesis of prostaglandins.

Experimental Section[9]

Treatment of 2-(*p*-Toluenesulfonyl)-*exo*-3-(trichloromethyl)-2-azabicyclo[2.2.1]hept-5-ene (2) with Various Bases. A. Metal Alkoxides. Heating a solution of 1.0 g (3.0 mmol) of **2** in 20 ml of ethanolic potassium hydroxide solution, which contained 5 equiv of base, yielded, after 4 h at reflux and acidification with hydrochloric acid, *p*-toluenesulfonamide (**5**) as the only identifiable product.

In agreement with a recent report,[6] the treatment of **2** in tetra-

Chart II



hydrofuran solution with potassium *tert*-butoxide yielded 3-(dichloromethylene)-2-(*p*-toluenesulfonyl)-2-azabicyclo[2.2.1]hept-5-ene (**6**): ir (additional to published bands) strong bands at 696, 746, 765, 838, 900, and 993 cm^{-1}.

However, a solution of 1.0 g of **2** dissolved in 50 ml of a solution of methanol and deuterium oxide (1:1) which contained 3 equiv of sodium methoxide underwent no reaction upon standing at 25 °C for 8 h. Examination of the NMR spectrum also showed that the endo C_3 hydrogen had not undergone any exchange for deuterium.

B. Lithium Aluminum Hydride. A solution of 2.7 g (7.3 mmol) of **2** dissolved in 30 ml of anhydrous tetrahydrofuran was added dropwise to 600 mg (16 mmol) of the hydride dissolved in 30 ml of the same solvent. After a 6-h reflux period the excess of the hydride was destroyed by the cautious addition of an aqueous ammonium chloride solution. The suspension was filtered and the organic layer was separated and then dried over anhydrous magnesium sulfate. Removal of the solvent from the organic extract left a pale yellow oil, which turned semisolid A TLC analysis of the product on silica gel with a developing solvent of hexane–ethyl ether (v/v 2:1) showed ca. 10% of **2**, two major components, **7** and **8**, and four minor ones. Recrystallization from 95% ethanol gave 1.2 g of a colorless solid containing only the major components (ca. 60% yield of a 70:30 mixture of **7** and **8**). These two components could be separated by chromatography on a 2.0 × 75 cm column of silica gel with benzene used as the eluent.

The first component to be eluted was 2-(*p*-toluenesulfonyl-*exo*-3-(dichloromethyl)-2-azabicyclo[2.2.1]hept-5-ene (**7**), mp 123–124 °C, from 95% ethanol: NMR ($CDCl_3$) 1.40 (br d, J = 9 Hz, H_7 syn to C=C), 2.42 (s, CH_3, sh d, H_7 anti to C=C), 3.1 (d, J = 3.0 Hz, endo H_3), 3.42 (br m, H_4), 4.57 (m, H_1), 5.88 (d of d, H_5), 6.25 (m, H_6), 6.47 (d, J = 3.0 Hz, $HCCl_2$), and 7.5 ppm (m, C_6H_4); MS (70 eV) peaks at *m/e* 335, 333, and 331.

Anal. Calcd for $C_{14}H_{15}Cl_2NO_2S$: C, 50.58; H, 4.55; N, 4.22. Found: C, 50.58; H, 4.76; N, 4.33.

The second component was 2-(*p*-toluenesulfonyl)-*exo*-3-(chloromethyl)-2-azabicyclo[2.2.1]hept-5-ene (**8**), mp 154–155 °C, from 95% ethanol: NMR ($CDCl_3$) 1.46 (br d, J = 9 Hz, H_7 syn to C=C), 1.80 (br d, J = 9 Hz, H_7 anti to C=C), 2.42 (s, CH_3), 2.82 (d of d, J = 10.5, J' = 3.0 Hz, HCHCl anti to N-Ts), 3.30 (br m, H_4), 3.40 (t, J = 10.5 Hz, H_3), 4.27 (d of d, J = 10.5, J = 3.0 Hz, HCHCl syn to N-Ts), 4.58 (br m, H_1), 5.77 (d of d, H_5), 6.08 (m, H_6), and 7.47 ppm (m, C_6H_4); MS (70 eV) peaks at *m/e* 299, 297, and 248.

Anal. Calcd for $C_{14}H_{16}ClNO_2S$: C, 56.64; H, 5.42; N, 4.70. Found: C, 56.41; H, 5.38; N, 4.77.

C. Pyridine-d_5. The NMR spectrum of **2** in pyridine-d_5 showed the following absorptions: 1.32 (d, J = 9.0 Hz), 2.18 (s, CH_3), 2.57 (d, J = 9.0 Hz), 3.58 (m), 4.27 (s), 5.02 (m), 6.43 (m), 6.79 (d of d), 7.20 (d, J = 8.5 Hz), and 7.93 ppm (d, J = 8.5 Hz). After a 4-h heating period at 75 °C new spectral peaks appeared at 2.87 (q, J = 1.5 Hz) and 6.46 ppm (br m), the distinct doublets at 7.20 and 7.93 ppm were now blurred by the emergence of new doublets at 7.23 and 8.17 ppm, and a shoulder developed on the methyl signal. The integrated ratios of the protons at H_7, H_1, H_3, and H_4, however, maintained their proper values for **2**. The new peaks are in good agreement with those expected for the re-formation of cyclopentadiene (**3**), apparently by a retro-Diels–Alder reaction [lit. NMR data for C_5H_6 (in C_6H_6): 2.97 (q, apparent J = 1.4 Hz) and 6.53 (m)]. Eventually heating led to a precipitation of pyridine hydrochloride (peak at 8.72 ppm).

D. Alkyllithium. Under a nitrogen atmosphere a solution of 730 mg (2.0 mmol) of **2** in 50 ml of anhydrous benzene was treated at 25–30 °C with 4.0 equiv of 1.5 M *n*-butyllithium (or methyllithium in ether) in heptane. After a 3-h stirring period the solution was quenched with water, the benzene layer separated, and the aqueous layer extracted twice with ether. After the combined organic extracts were dried over anhydrous magnesium sulfate and the solvent removed, the NMR spectrum of the crude product showed one component to comprise ca. 70% of the mixture. Column chromatography on silica gel with a benzene eluent gave this pure compound **9** as colorless plates: mp 93–94° from 95% ethanol; negative test for halogen; NMR ($CDCl_3$) 1.48 (t, J = 6 Hz) and 1.70 (t, J = 6 Hz; components of a doublet of triplets, J = 13 Hz, H_4 anti to N-Ts and C≡C–H), 2.13 (d, J = 2.4 Hz, C≡C–H), 2.41 (s, CH_3), 2.54 (d of d, J = 8 and 13 Hz, H_4 syn to N-Ts and C≡C–H), 3.30 (m, H_5), 4.35 (br q, J = 9 and ~2–3 Hz, H_3), 5.15 (br d, J = 9 Hz, NH), 5.65 (m, H_1 and H_2), 7.30 (d) and 7.80 ppm (d); ir ($CHCl_3$, NaCl) 3375 (sh), 3330 (br, s, NH), 2125 (m, C≡C), 1600 (C=C), 1345 and 1150 (N–SO_2); MS (70 eV) prominent peaks at *m/e* 261 (P), 196, 106, and 78. These data are in accord with **9** being 3-*p*-toluenesulfonamido-5-ethynylcyclopentene.

Anal. Calcd for $C_{14}H_{15}NO_2S$: C, 64.32; H, 5.78; N, 5.36. Found: C, 64.40; H, 5.76; N, 5.15.

From the reaction of **2** with methyllithium in ethyl ether solution, a small amount of a labile component (**10**, ca. 10%) was isolated by a laborious thin layer chromatographic separation on silica gel employing a hexane–ethyl ether eluent (2:1 v/v). This component, which moved faster than **2** and slower than **9**, contained chlorine and decomposed in moist air. The spectral data are in accord with the structure of this substance **10** being a mixture of 3- and 4-[(*N*-2,2-dichloro-2-propenyl-*p*-toluenesulfonamido]cyclopentene: (a) ir (CCl_4, NaCl) no bands indicative of N–H, O–H, or C≡C–H groups, but a band of moderate intensity at 1625 cm^{-1}, suggestive of the C=C–N group (absent in the spectrum of **2**); and (b) NMR (C_6D_6), total of 17 protons, 0.82–1.6 (m, 2 H, C_4 protons), 1.7–2.1 (m, 1 H, C_5 proton), 2.1 (s, CH_3 of tolyl), 2.4–2.5 (d, 3 H, isomeric CH_3 groups due to 3- and 4-positional isomers), 2.9–3.25 (m, 1 H, C_5 proton), 4.9–5.5 (m, 3 H, C_1, C_2, and C_3 H), 7.1 (d, 2 H), and 7.7 ppm (d, 2 H).

In order to search for sites of metalation in this product, the reaction between **2** and *n*-butyllithium was repeated in benzene solution, as described above, except that the reaction mixture was worked up with deuterium oxide. After the isolation of pure prod-

uct by column chromatography, it was dissolved in $CDCl_3$ and shaken repeatedly with deuterium oxide to ensure N-deuteration. The NMR spectrum of the resulting product no longer displayed any signals at 2.1 and 5.15 ppm, but the position and intensity of the other bands for **9** were unchanged. The results confirm that the acetylenic and amide protons of **9** were abstracted during the reaction with *n*-butyllithium, but that the allylic and vinylene protons were not. Consequently, no epimerization had occurred at the allylic C_3 and C_5 positions of the cyclopentene ring and, therefore, the sulfonamido and ethynyl groups in **9** are cis to each other.

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Registry No.—**2**, 42082-52-0; **6**, 53112-02-0; **7**, 58191-30-3; **8**, 58191-31-4; **9**, 58191-32-5; **10**, 58191-33-6; potassium *tert*-butoxide, 865-47-4; lithium aluminum hydride, 16853-85-3; pyridine-d_5, 7291-22-7; butyllithium, 109-72-8; methyllithium, 917-54-4.

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Carbene Multiplicity in Decompositions of 2-Methyl-2-phenyldiazopropane

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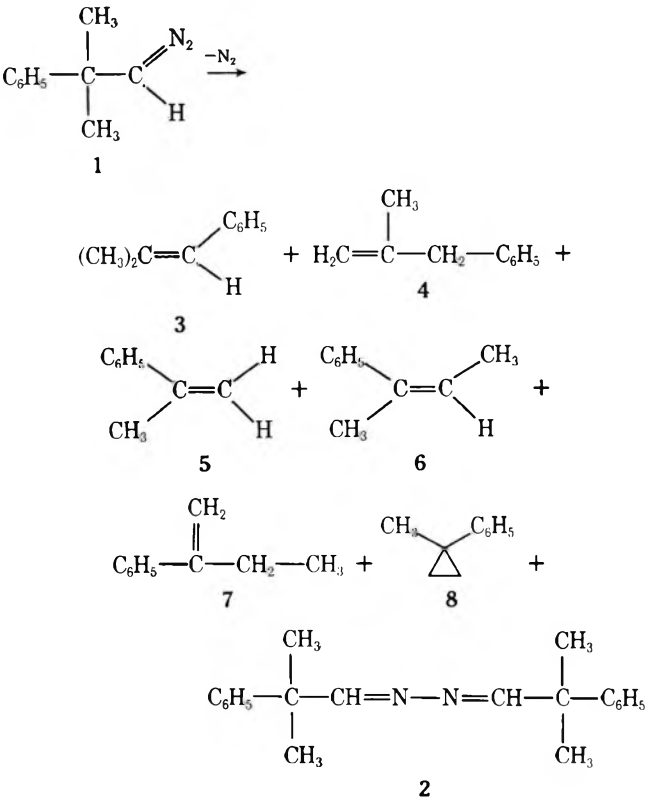
The literature of chemistry contains many examples of carbenes whose singlet and triplet states exhibit different chemical reactions.[1] A classical example of this phenomenon is seen in the addition of carbenes to cis or trans olefins. Singlet carbenes add predominantly stereospecifically, whereas triplet carbenes form cyclopropanes in a nonstereospecific manner.[2]

Some intramolecular carbene reactions are also dependent upon carbene multiplicity. When competing reactions are available, the rearrangements of hydrogen atoms[3] and phenyl groups[4] proceed more favorably to singlet rather than triplet carbenes. However, the experimental evidence does not exclude some triplet contribution to these rearrangement processes.

The carbene produced by the decomposition of 2-methyl-2-phenyldiazopropane (**1**) is suited to the study of three competing intramolecular reactions: phenyl rearrangement, methyl rearrangement, and C–H insertion. The thermal decomposition of **1** in dry hexane at 59 °C has been reported[5] to yield an azine ($C_{20}H_{24}N_2$), **2**, and six products of formula $C_{10}H_{12}$: 2-methyl-1-phenylpropene (**3**); 2-methyl-3-phenylpropene (**4**); *cis*-2-phenyl-2-butene (**5**); *trans*-2-phenyl-2-butene (**6**); 2-phenyl-1-butene (**7**); and 1-methyl-1-phenylcyclopropane (**8**). Products **3** and **4** are formed by phenyl rearrangement; olefins **5**, **6**, and **7** are methyl migration products; and cyclopropane **8** is a product of intramolecular C–H insertion. The object of the present study was to determine how the relative yields of these products might be affected by reaction conditions which would selectively favor carbene reaction from either the singlet or triplet state.



The ground state of alkylcarbenes appears to be the triplet.[6] However, the thermal or direct photochemical decomposition of diazoalkanes initially produces the excited singlet state of the carbene.[1] Methods of inducing triplet behavior in the carbene include the use of triplet photosensitizers to directly produce the triplet carbene, and the use of heavy atom solvents to quench the initially formed singlet to the ground state triplet.[7] The products of the decomposition of **1** under varying reaction conditions are summarized in Tables I and II.

While the origins of individual products in Table II are open to speculation, certain trends in migratory aptitudes and C–H insertion are evident. In comparing thermal decompositions I and II with reaction III, it is seen that the use of a heavy atom solvent decreases the relative amounts of methyl rearrangement and cyclopropane formation. The same trend is noted when comparing direct photolysis IV with photosensitized decompositions V and VI. Triplet sensitization increases phenyl migration at the expense of the competing intramolecular processes.

It is possible that phenyl rearrangement, methyl rearrangement, and C–H insertion all proceed to both the singlet and triplet states of the carbene. In any case, reaction conditions which favor triplet carbene production decrease the relative rates of methyl migration and C–H insertion while increasing the relative rate of phenyl rearrangement. The distinction between singlet and triplet behavior may be blurred by rapid intersystem crossing.[4b]

Tetraphenylethylene-catalyzed diazo decompositions have recently been reported by Ho, Conlin, and Gaspar.[8] The relative product yields of the tetraphenylethylene-catalyzed decomposition of **1** (reactions VII and VIII) resemble product yields from triplet carbene reactions (III, V, and VI) more closely than they resemble singlet carbene product yields (I, II, and IV). An explanation for this obser-

Table I. Reaction Conditions and Product Yields from Decompositions of 2-Methyl-2-phenyldiazopropane

Reaction no.[a]	Solvent	Temp, °C	Additive	Mode of decomposition	% N_2[b]	% $C_{10}H_{12}$[b]	% azine[b]
I	Hexane	69	None	Thermal	67	52	30
II	Benzene	69	None	Thermal	70	56	37
III	1-Bromonaphthalene	69	None	Thermal	78	57	*c*
IV	Benzene	25–29	None	Photolytic	64	54	38
V	Benzene	25–29	500% benzil	Photosensitized	66	48	*c*
VI	Benzene	25–29	500% fluorenone	Photosensitized	60	51	*c*
VII[d]	Hexane	−196 to 25	5% tetraphenylethylene	Catalytic	*c*	66	*c*
VIII[d]	Benzene	−196 to 25	10% tetraphenylethylene	Catalytic	*c*	62	*c*

[a] Averages of three to five reactions. Internal consistency among reactions was high. [b] Based on the amount of urethan used to prepare the diazo. [c] Not determined. [d] Degassed six times by freeze–pump–thaw.

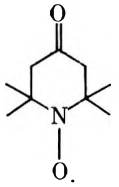
Table II. Relative Hydrocarbon Yields from Decompositions of 2-Methyl-2-phenyldiazopropane

Reaction no.	Relative yield, % 3	4	5	6	7	8	Ph∼/Me∼	Σ olefins/ cyclopropane
I	32.4	10.4	3.6	2.5	2.4	48.6	10.1	1.1
II	42.4	12.5	6.1	2.3	2.5	34.2	10.1	1.9
III	56.8	20.9	4.1	1.9	1.6	14.7	20.4	5.8
IV	25.7	25.6	9.7	6.3	4.4	28.3	5.0	2.5
V	49.9	22.1	2.9	2.3	2.8	20.0	18.0	4.0
VI	66.4	19.2	1.9	2.4	3.3	6.8	22.5	13.7
VII	66.0	6.8	3.7	1.5	1.3	20.7	22.4	3.8
VIII	51.0	12.8	4.8	2.0	1.7	27.7	15.0	2.6

[a] Ph∼/Me∼ = (3 + 4)/(5 + 6 + 7) ÷ 2.

vation may lie in the initial formation of a diazo–tetraphenylethylene charge-transfer complex, which subsequently dissociates to nitrogen, the triplet carbene, and triplet tetraphenylethylene (a spin conserving process). Tetraphenylethylene is an efficient triplet quencher (effective E_T = 45.4–47.3 kcal).[9]

Another method which was used to attempt to induce triplet carbene behavior was thermolysis of 1 in hexane at 69 °C in the presence of 10 mol % of the stable free radical, 4-oxo-2,2,6,6-tetramethylpiperidinooxy (9). It was expected



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that the stable free radical would promote spin inversion to form the ground state triplet carbene. Experimentally, the presence of the free radical had no effect upon absolute product yields or relative hydrocarbon yields (reaction I).

Experimental Section

2-Methyl-2-phenyldiazopropane (1) was prepared by the reaction sequence outlined by Hogan and Keating (urethane → *N*-nitrosourethane → diazo).[5,10] Diazo solutions were approximately 0.1 M for all decompositions. The NMR spectrum of the diazo solution (in benzene) shows no absorptions due to vinyl or cyclopropyl protons. NMR and ir spectroscopy indicate that conversion of the *N*-nitrosourethane to the diazo is quantitative. Reactions were performed under nitrogen in rigorously dried solvents. Photolytic and photosensitized reactions were carried out according to the procedures of Pomerantz and Witherup.[7] The tetraphenylethylene-catalyzed decomposition was induced by degassing through six freeze–pump–thaw cycles.[8]

In general, reactions were worked up by rotary evaporation of most of the solvent, removal of $C_{10}H_{12}$ materials under high vacuum, and recrystallization of the residual azine, 2, from hexane (mp 68–70 °C). Authentic samples of olefinic products 3–7 were prepared by dehydration of appropriate alcohols. Cyclopropane 8 was prepared by the Simmons–Smith procedure.[11] All products were stable to the conditions of reactions and analysis.

Hydrocarbon products were analyzed by VPC on a 15-ft column of 20% diethylene glycol succinate at 110 °C. Known amounts of isopropylbenzene were added to the hydrocarbon product mixtures as an external standard for determination of $C_{10}H_{12}$ yields. Retention times of the standard and products follow: isopropylbenzene, 7.3 min; 6, 10.5; 4, 11.6; 8, 12.6; 7, 13.9; 3, 16.1; and 5, 20.2. The relative molar VPC response of each $C_{10}H_{12}$ product was determined by VPC collection of the individual products and reinjection of each product as a mixture of known composition with isopropylbenzene. The relative molar VPC responses of all $C_{10}H_{12}$ products were nearly identical (1.05 ± 0.01 vs. isopropylbenzene standard as 1.00).

In several control experiments, a known amount of isopropylbenzene was added to a crude reaction mixture before work-up. VPC analysis before solvent removal, after solvent removal, and after high vacuum pumping showed that no appreciable changes in $C_{10}H_{12}$ absolute or relative yields occurred during work-up.

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Registry No.—1, 19217-61-9; 2, 58208-01-8; 3, 768-49-0; 4, 3290-53-7; 5, 768-00-3; 6, 767-99-7; 7, 2039-93-2; 8, 2214-14-4.

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Formation of Styrylglycine and Derivatives from Cyclopropylogs of Phenylalanine and Dihydroxyphenylalanine. Authentic Styrylglycine

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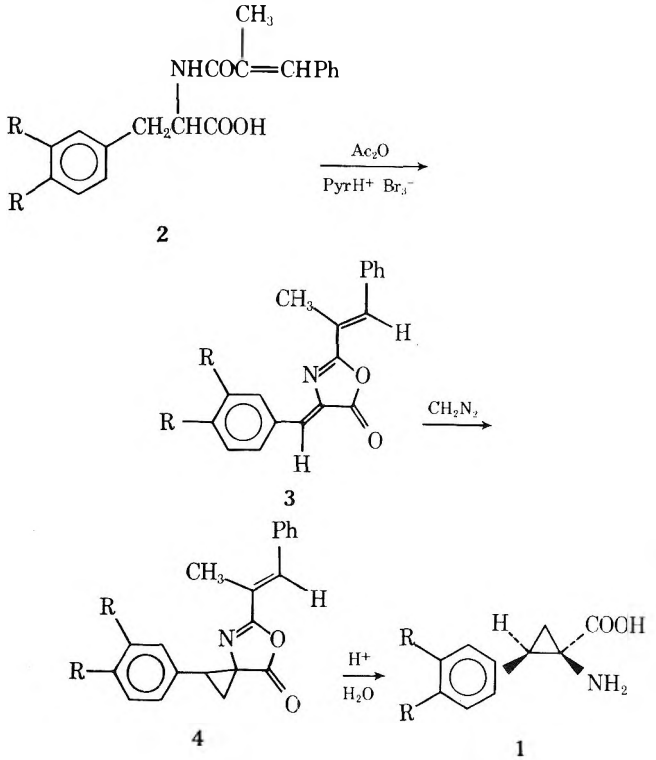
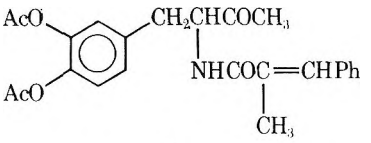
Much research has been devoted to the synthesis of compounds capable of inhibiting the enzymes associated with the biosynthesis of catecholamines. α-Methyldihydroxyphenylalanine (α-methyl-Dopa) is a potent Dopa decarboxylase inhibitor[3] while cyclopropane derivatives of metabolites such as histidine[4] and phenethylamine[5] are also enzyme inhibitors. In view of our recent work[6] on α,β-unsaturated azlactones and the fact that these may serve as intermediates[4,7] in the synthesis of "cyclopropylogs" of amino acids, we investigated an approach to the synthesis of "cyclopropyl Dopa" (**1a**). Our reaction sequence (Scheme I)

Scheme I



a, R = OH
b, R = H
c, R = OAc

was much shorter than that described in a 1965 patent by Kaiser[8] in that we were to obtain **1** directly from Dopa rather than by the complex process described by Kaiser. Our procedure gave the azlactone **3c** in 45% overall yield from Dopa and, in the second stage, **3c** was cyclopropylated with diazomethane giving **4c** in 45% yield. The structure of **4c** was secured by the presence of the cyclopropyl proton absorptions[7] at δ 3.04 (1 H) and 2.10 (2 H) and the styryl methyl group absorption at δ 2.08 (3 H) in its NMR spectrum. Interestingly, a by-product of the oxidation procedure was isolated by high-pressure liquid chromatography and proved to be ketone **5**, formed, apparently, by a Dakin–West[9] acetylation–decarboxylation reaction. We had not previously observed products of this type in our development of this oxidation procedure but, in 1968, Steglich[10]



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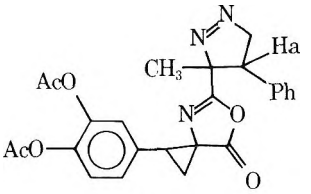

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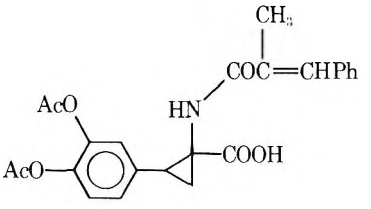
did report the conversion of an alanine azlactone into a ketone at ambient temperatures under conditions similar to those which led to the formation of **5**. Apparently, the Dakin–West reaction competes successfully, in some cases, with the double dehydrohalogenation which leads to **3**. From the cyclopropylation step, a crystalline by-product was also isolated in small yield by HPLC. This material proved to be the result of the addition of diazomethane to the styryl group in **4c** forming a pyrazoline ring. Of the two possible isomeric pyrazolines, **6** was established as the correct structure by the fact that the benzylic proton (H_a) appeared as a triplet due to coupling with the adjacent methylene group. ^{13}C spectroscopy established the purity of this compound even though it might be expected to be a mixture of diastereomers and did show a very broad melting point, apparently owing to thermolysis. It was interesting that only small amounts of **6** were formed even though a large excess of diazomethane was used. The methylenation reaction was much more selective than expected.

In spite of the careful exclusion of oxygen, all attempts to hydrolyze **4c** under basic conditions gave colored complex mixtures even though the literature[4,7] reports that similar cyclopropanes had been obtained this way. Long refluxing of a solution of **4c** in acidic aqueous acetone afforded only a 38% yield of the expected acid (**7**), the remainder



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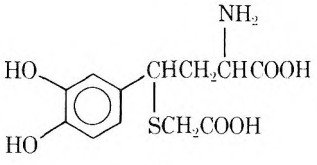

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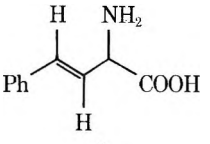
of the starting azlactone being recovered unchanged. This extreme resistance to hydrolysis of the azlactone ring was apparently due to steric hindrance exhibited by the trisubstituted a-carbon atom. Attempts to hydrolyze **4c** to the cyclopropyl amino acid in refluxing 6 N HCl led to complete decomposition as shown by TLC and NMR spectroscopy. When the hydrolysis was carried out in the presence of the antioxidant mercaptoacetic acid, a high-melting substance was obtained which, by elemental and spectral analysis, appeared to be a 1:1 combination of mercaptoacetic acid and **1**. The NMR spectrum indicated the presence of four different kinds of aliphatic protons consistent with structure **8**

in which the cyclopropane ring had been destroyed by reaction with the mercaptan.

Since oxidative decomposition is always a complicating factor in the synthesis of Dopa derivatives, we undertook the synthesis of cyclopropylphenylalanine (**1b**) in order to further investigate the hydrolysis in the absence of this complication. In 1964, Awad[7] reported the synthesis of *N*-benzoylcyclopropylphenylalanine but did not report its conversion into the free amino acid. By methods analogous to those just described, **2b** was converted into the unsaturated azlactone **3b** which was cyclopropanated to give the spiroazlactone **4b** in 39% yield. Using 6 N HCl, we hydrolyzed **4b** and obtained a small yield of an amino acid which was clearly not cyclopropylphenylalanine. This product was isomeric with the expected product, ninhydrin positive, and showed two coupled vinyl protons in its NMR spectrum. All the physical data were consistent with this product being styrylglycine (**9**), which had been reported by Pinner[11a] in 1889 and by later workers[11b] to have a melting point in the range of 240–250 °C. Since our product melted at 196–199 ° C, we synthesized authentic **9** by a new procedure which confirmed the melting point and the spectral data obtained for **9**.

The key intermediate in the Pinner synthesis of **9** was the hydantoin **10a** which was prepared by acid-catalyzed ring closure of the ureidonitrile **11**. Workers in the penicillin field[11b] reported that direct hydrolysis of **11** also gave **9**.



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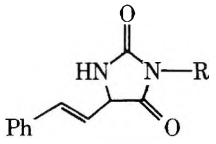
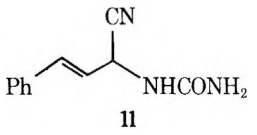


10a, R = H
b, R = C_2H_5



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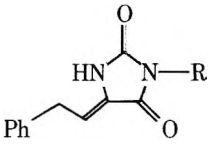
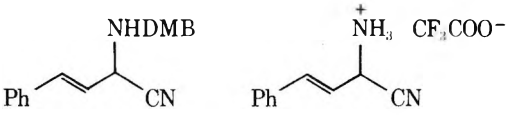


12a, R = H
b, R = C_2H_5

In our hands, the latter procedure gave an amino acid, mp 216–218 °C, which, by NMR spectroscopy, could not be **9**. We showed that this product was actually γ-phenyl-α-aminobutyric acid by comparison with an authentic sample prepared by hydrogenation of our styrylglycine (**9**). Pinner had obtained **9** by basic hydrolysis of what he thought was the *N*-ethylhydantoin, **10b**. He obtained **10b** by ethylation of either hydantoin **10a**, mp 172 °C, or its "cis isomer", mp 198 °C. We found that the "cis isomer" of **10a** was actually the conjugated isomer, **12a**, and that the N-ethylated compound was the conjugated isomer, **12b**. The treatment of **10a** with base during ethylation had rearranged the double bond into the more conjugated position. In our hands, basic hydrolysis of either **12a** or **12b** gave no amino acid of melting point 240–250 °C as reported by Pinner, and this approach to **9** was not further investigated.

Our synthesis of DL-styrylglycine is outlined below. Cinnamaldehyde, on treatment with 2,4-dimethoxybenzylamine and sodium cyanide, gave an excellent yield of the oily cyano amine **13** which was converted to a crystalline hydrochloride for characterization. Direct hydrolysis of **13** in concentrated hydrochloric acid gave **9** in an overall yield from the aldehyde of 13%. However, when **13** was treated with trifluoroacetic acid in the presence of dimethoxybenzene as scavenger, the nitrile salt **14** was obtained in 67% yield and **14** was hydrolyzed to **9** in 39% yield. Further de-



13 **14**

DMB = 2,4-dimethoxybenzyl

velopment showed that when **14** was first converted to an imino ester, hydrolysis of this compound afforded **9** in 70% yield. The pure DL-styrylglycine obtained by our procedure showed a melting point of 198–200 °C, in disagreement with all previous reports, and showed the required spectral characteristics.

The formation of DL-styrylglycine (**9**) during the hydrolysis of **4b** and the formation of the sulfide **8** from **4c** are an indication of the acid lability of 1-aminocyclopropanecarboxylic acids. Even though earlier workers[4] have not observed this, our work indicates that these compounds are not always readily accessible by acid hydrolysis of their *N*-acyl derivatives.

Experimental Section

Instrumentation. Melting points were determined on a Nalge Model Y6 micro hot stage and are uncorrected. Infrared spectra (Nujol mull and KBr pellet) were taken on a Perkin-Elmer 257 recording spectrophotometer with polystyrene as the standard, and proton NMR spectra were obtained on Perkin-Elmer R-20 and Varian HA-100 spectrometers with Me_4Si as the internal standard. Carbon-13 NMR spectra were obtained on a JEOL PFT-100 spectrometer with Me_4Si as the internal standard. Elemental analyses were carried out by Atlantic Microlabs, Atlanta, Ga.

Materials. β-3,4-Dihydroxy-DL-phenylalanine was purchased from Sigma Chemical Co., and used as received. (*E*)-α-Methylcinnamic acid was prepared according to Johnson[12] and converted to the acid chloride by refluxing in thionyl chloride.

***N*-[(*E*)-α-Methylcinnamoyl]-β-3,4-dihydroxy-DL-phenylalanine (2a).** A suspension of sodium metaborate (44.5 g, 116.6 mmol) in 100 ml of water in a 2-l. three-necked round-bottomed flask fitted with a magnetic stirrer, delivery funnel with nitrogen inlet, and an electrode connected to a Corning Model 10C pH control unit was stirred under nitrogen for 20 min. β-3,4-Dihydroxy-DL-phenylalanine (25.0 g, 126.7 mmol) was added and the mixture stirred for 30 min under nitrogen at room temperature. The mixture was then cooled in an ice bath, sodium dithionite (1.0 g) and 200 ml of 1,2-dimethoxyethane (DME) added, and the pH brought to 10 with 1.0 N NaOH. A solution of (*E*)-α-methylcinnamoyl chloride (21.0 g, 116 mmol) in 200 ml of DME was added dropwise over a period of 30 min while the pH was maintained at 10 by the addition of 1.0 N NaOH. The reaction mixture was stirred for 3 h at room temperature and filtered, and the yellow filtrate was acidified with concentrated HCl to pH 1. The acidic solution was extracted with five 200-ml portions of ethyl acetate, and the combined extracts were dried ($MgSO_4$) and concentrated in vacuo to yield a sticky solid. The solid was stirred with 100 ml of fresh ethyl acetate and filtered, and the resulting white solid was dried under vacuum to yield 32.2 g (81%) of crude **2**. The crude material was recrystallized from acetone–hexane to yield 28.7 g (72%) of **2a**: mp 196–198 °C; ir (Nujol) 3510 (OH), 3360 (NH), 1710 (acid C=O), 1650 and 1600 cm^{-1} (amide C=O and C=C); uv (95% ethanol) 264 nm (ε 19 350); NMR (acetone-d_6) δ 7.16–8.00 (3 H, broad, NH and OH), 7.36 (5 H, s, C_6H_5), 7.24 (1 H, m, PhCH=), 6.81–6.64 [3 H, m, Ar**H**$(OH)_2$], 4.78 (1 H, m, CHNH), 3.04 (2 H, m, ArCH_2), 2.04 ppm (3 H, d, CH_3C=).

Anal. Calcd for $C_{19}H_{19}NO_5$: C, 66.85; H, 5.61; N, 4.10. Found: C, 66.79; H, 5.73; N, 4.16.

2-[(*E*)-1-Methylstyryl]-4-(3,4-diacetoxybenzylidene)-5-oxazolone (3c). A solution of **2a** (25.0 g, 73.24 mmol) in 100 ml of

acetic anhydride and 1 ml of pyridine in a 250-ml round-bottomed flask fitted with a drying tube was stirred for 1 h in an ice bath. Pyridine hydrobromide perbromide (20.0 g, 83.71 mmol) was added and the mixture stirred for 2 h. Pyridine (20 ml) was then added and the mixture stirred for an additional 2 h at room temperature. The solvents were removed in vacuo to yield a yellow semisolid which was rinsed into ice–water with a small amount of acetone and rapidly stirred for 1.5 h. The resulting amorphous yellow solid was filtered, dried under vacuum, and crystallized from absolute ethanol to yield 18.3 g (62%) of **3a**, mp 148–152 °C. An analytical sample was recrystallized from benzene–hexane: mp 150.5–151.5 °C; ir (Nujol) 1805 (oxazolone C=O), 1765 and 1755 (acetoxy C=O), 1650 (C=N), 1610 and 1600 cm^{-1} (C=C); uv (CH_2Cl_2) 291 nm (ϵ 11 900), 377 (45 900); NMR ($CDCl_3$) δ 8.02–7.22 (8 H, m, aromatic), 7.63 (1 H, m, styryl), 7.00 (1 H, s, benzylidene), 2.32 (3 H, d, CH_3 C=), 2.30 (3 H, s, CH_3COO), 2.27 (3 H, s, CH_3COO); ^{13}C NMR ($CDCl_3$) 166.9 and 166.7 (CH_3COO), 166.2 and 164.9 (oxazolone C=O and C=N), 143.2, 141.5, 139.0, 134.7, 133.6, 131.5, 129.9, 129.4, 128.3, 127.8, 126.0, 123.0, and 122.6 (aromatic and vinyl), 20.4 (CH_3COO), 13.5 ppm (CH_3C=).

Anal. Calcd for $C_{23}H_{19}NO_6$: C, 68.14; H, 4.72; N, 3.45. Found: C, 68.01; H, 4.77; N, 3.40.

Isolation of 3-[(*E*)-α-Methylcinnamamido]-4-(3,4-diacetoxyphenyl)-2-butanone (5). A mixture of **2a** (15.0 g, 43.9 mmol) in 50 ml of acetic anhydride and 5 ml of pyridine in a 200-ml round-bottomed flask fitted with a drying tube was stirred for 1 h at room temperature. The solution was filtered, the filtrate was cooled in an ice bath, and pyridine hydrobromide perbromide (10.5 g, 43.9 mmol) added. The mixture was stirred for 1.5 h, 20 ml of pyridine was added, and the mixture stirred for an additional 1 h at room temperature. The mixture was then filtered, and the filtrate was concentrated in vacuo to yield a yellow semisolid. The residue was rinsed into ice–water with a small amount of acetone and the mixture was rapidly stirred for 1 h. The amorphous yellow solid was filtered, dried under vacuum, and crystallized from absolute ethanol to yield 8.3 g (47%) of **3c**. Evaporation of the mother liquor gave a yellow oil which partially crystallized on standing. The oil was triturated with a small amount of acetone and filtered to give 3.1 g (23%) of crude **5**. Recrystallization of the crude material several times from ethyl acetate–hexane gave 1.7 g (13%) of pure **5**: mp 136.5–137.5 °C; ir (Nujol) 3345 and 3290 (NH), 1765 (acetoxy C=O), 1725 (ketone C=O), 1645 (amide C=O), 1620 (C=C), 1515 cm^{-1} (amide II); NMR ($CDCl_3$) δ 7.46–6.94 (10 H, m, NH, PhC**H**=, aromatic), 4.85 (1 H, m, C**H**NH), 3.11 (2 H, m, ArCH_2), 2.24, 2.20, and 2.18 (9 H, 3 s, CH_3COO and CH_3CO), 2.02 (3 H, d, CH_3C=).

Anal. Calcd for $C_{24}H_{25}NO_6$: C, 68.07; H, 5.95; N, 3.31. Found: C, 68.36; H, 5.56; N, 3.32.

Cyclopropanation of 3c. Synthesis of 1-(3,4-Diacetoxyphenyl)-5-[(*E*)-1-methylstyryl]-6-oxa-4-azaspiro[2.4]hept-4-en-7-one (4c) and 1-(3,4-Diacetoxyphenyl)-5-(*cis*-3-methyl-4-phenyl-1-pyrazolin-3-yl)-6-oxa-4-azaspiro[2.4]hept-4-en-7-one (6). A solution of **3c** (8.0 g, 19.7 mmol) in 250 ml of $CHCl_3$ was treated with a solution of diazomethane in 250 ml of ether, prepared from 21.5 g (0.1 mol) of Diazald (Aldrich Chemical Co.), in a 1-l. Erlenmeyer flask fitted with a rubber stopper and drying tube. After the reaction mixture was stirred for 16 h at room temperature, the excess diazomethane was removed under a stream of dry nitrogen, and the solvents were evaporated in vacuo to yield a yellow oil. The oil was crystallized from ethyl acetate–hexane to yield 3.7 g (45%) of **4c**, mp 137–140 °C. An analytical sample was prepared by several recrystallizations from ethyl acetate–hexane: mp 142–144 °C; ir (Nujol) 1805 (oxazolone C=O), 1770 (acetoxy C=O), 1635 (C=N), 1610 cm^{-1} (C=C); uv (CH_2Cl_2) 291 nm (ϵ 28 860); NMR ($CDCl_3$) δ 7.46–6.96 [9 H, m, PhC**H**=, Ph, Ar**H**(OH)$_2$], 3.18 (1 H, m, cyclopropyl CH), 2.40 (2 H, m, cyclopropyl CH_2), 2.21 (6 H, s, CH_3COO), 2.08 (3 H, s, CH_3C=).

Anal. Calcd for $C_{24}H_{21}NO_6$: C, 68.72; H, 5.05; N, 3.34. Found: C, 68.82; H, 5.09; N, 3.31.

High-pressure liquid chromatography of the mother liquor on an 8 ft × 0.375 in. silica gel (18–32 μ) column eluting with 2:3 ethyl acetate–hexane gave an additional 1.7 g (total yield 54%) of **4c** as the first component. The second component was collected and rechromatographed on a 4 ft × 0.375 in. Porasil B (37–75 μ) column eluting with 2:3 $CHCl_3$–hexane. The second component was collected and the solvents evaporated in vacuo to yield a colorless oil which crystallized on standing. This material was recrystallized from ethyl acetate–hexane to yield 0.107 g (1.6%) of **6**: mp 116–140 °C; ir (KBr) 1815 (oxazolone C=O), 1770 (acetoxy C=O), 1640 cm^{-1} (C=N); NMR ($CDCl_3$) δ 7.28–6.78 [8 H, m, Ph and Ar**H**(OH)$_2$], 4.91 (2 H, m, pyrazoline CH_2), 3.70 (1 H, m, pyrazoline CH), 3.10 (1 H, m, cyclopropyl CH), 2.28 (6 H, s, CH_3COO), 2.23 (2 H, m cyclopropyl CH_2), 1.20 (3 H, d, pyrazoline CH_3).

Anal. Calcd for $C_{25}H_{23}NO_6$: C, 65.06; H, 5.02; N, 9.10. Found: C, 64.74; H, 5.02; N, 8.94.

1-[(*E*)-α-Methylcinnamamido]-2-(3,4-diacetoxyphenyl)cyclopropanecarboxylic Acid (7). A suspension of **4c** (0.5 g, 1.2 mmol) in 30 ml of acetone containing 10 ml of water and a few drops of trifluoroacetic acid was refluxed for 5 days in a 50-ml round-bottomed flask fitted with a condenser. The acetone was evaporated in vacuo, and the resulting mixture extracted with two 50-ml portions of ethyl acetate. The combined extracts were dried ($MgSO_4$) and the solvent evaporated in vacuo to yield a glass. The residue was recrystallized from acetone–hexane to give 200 mg (38%) of **7**, mp 186–195 °C. An analytical sample was prepared by several recrystallizations from acetone–hexane: mp 194–197 °C; ir (KBr) 3330 (NH), 3440–2300 (carboxyl OH), 1765 (acetoxy C=O), 1705 (acid C=O), 1650 (amide C=O), 1625 (C=C), 1505 cm^{-1} (amide II); NMR (Me_2SO-d_6) δ 7.48–6.82 [10 H, m, Ph, CH=, NH, Ar**H**(OH)$_2$], 3.01 (1 H, m, cyclopropyl CH), 2.45 (2 H, m, cyclopropyl CH_2), 2.21 (6 H, s, CH_3COO), 1.78 (3 H, s, CH_3C=).

Anal. Calcd for $C_{24}H_{23}NO_7$: C, 65.89; H, 5.30; N, 3.20. Found: C, 65.95; H, 5.31; N, 3.18.

2-Amino-4-(carboxymethylthio)-4-(3,4-dihydroxyphenyl)-butanoic Acid (8). A suspension of **4c** (1.0 g, 2.38 mmol) in 50 ml of 6.0 N HCl containing 2 ml of mercaptoacetic acid in a 100-ml round-bottomed flask was refluxed for 14 h under a nitrogen atmosphere. The clear yellow solution was cooled in an ice bath, and the resulting solid was filtered, 255 mg (67%) of (*E*)-α-methylcinnamic acid. The yellow filtrate was concentrated in vacuo at room temperature to yield a light brown oil. The oil was dissolved in 50 ml of water and the solution was extracted with six 50-ml portions of ether. The aqueous layer was again concentrated under high vacuum at room temperature to yield a viscous brown oil. The oil was dissolved in a minimum of absolute ethanol, and the solution was added dropwise with rapid stirring to 500 ml of anhydrous ether. The mixture was centrifuged, and the resulting hygroscopic solid was washed several times with anhydrous ether and dried in vacuo to yield 0.7 g (97%) of crude **8**. Chromatography of the crude material on a 1 × 80 cm column of Sephadex G-10 eluting with 0.001 M β-mercaptoethanol in water gave 415 mg (60%) of pure **8**: mp 300 °C dec; ir (Nujol) 3600–2300 (OH), 1720 (acid C=O), 1605 cm^{-1} (carboxylate); NMR (D_2O) δ 7.00–6.80 [3 H, m, Ar**H**(OH)$_2$], 4.06 (1 H, m, C**H**NH), 3.83 (1 H, m, PhC**H**), 3.18 (2 H, s, $-SCH_2COO$), 2.46 (2 H, m, CHCH_2CH).

Anal. Calcd for $C_{12}H_{15}NO_6S$: C, 47.83; H, 5.02; N, 4.65. Found: C, 47.71; H, 5.21; N, 4.61.

1-Phenyl-5-[(*E*)-1-methylstyryl]-6-oxa-4-azaspiro[2.4]-hept-4-en-7-one (4b). To a solution of 3.0 g (10.4 mmol) of **3b**[6] in 75 ml of chloroform was added 100 ml of ethereal diazomethane, prepared from 21.5 g (0.1 mol) of Diazald (Aldrich Chemical Co.), in a 250-ml Erlenmeyer flask fitted with a rubber stopper and a drying tube. After stirring at room temperature for 15 h, the excess diazomethane was removed in a stream of dry nitrogen. Evaporation of the solvents in vacuo gave a yellow, oily residue. Preparative chromatography of part of the oily residue on 3-mm silica gel plates in a 3:2 *n*-hexane–chloroform system followed by crystallization from 1:1 *n*-hexane–ethyl acetate gave pure **4b**, mp 93–97 °C. Using a seed crystal a total of 1.22 g (39%) of **4b** was obtained: mp 95–98 °C; ir (Nujol) 1802, 1780 (C=O), 1630 (C=N), 1603 cm^{-1} (C=C); NMR ($CDCl_3$) δ 2.11 (s, 3 H, CH_3C=), 2.00–2.31 (m, 2 H, CH_2), 3.00–3.22 (m, 1 H, cyclopropyl CH), 7.10–7.38 (m, 10 H, ArH), 7.45 ppm (m, 1 H, C_6H_5CH=C).

Anal. Calcd for $C_{20}H_{17}NO_2$: C, 79.17; H, 5.65; N, 4.62. Found: C, 79.19; H, 5.66; N, 4.57.

5-(2-Phenylethylidine)hydantoin (12a). One-half gram of **10a**[11a] (mp 172 °C) was dissolved in 10 ml of 10% NaOH. After a few minutes the solution was acidified with dilute HCl and the precipitate was collected, washed with H_2O, and dried to give 0.47 g (94%) of colorless **12a**: mp 198–200 °C; ir (Nujol) 3220 (NH), 1790 (C=O), 1735 (C=O), 1685 cm^{-1} (C=C); NMR (Me_2SO-d_6) δ 3.50 (2 H, d, J = 8 Hz, $-CH_2-$), 5.62 (1 H, t, J = 8 Hz, $-CH$=), 7.24 (5 H, s, Ph), 10.36 (1 H, s, NH), 10.96 ppm (1 H, s, NH).

Anal. Calcd for $C_{11}H_{10}N_2O_2$: C, 65.34; H, 4.98; N, 13.85. Found: C, 65.42; H, 4.99; N, 13.89.

3-Ethyl-5-(2-phenylethylidene)hydantoin (12b). Using the literature[11a] procedure, 13.5 g of **10a** was ethylated to give 3 g of colorless prisms (**12b**): mp 166–168 °C; ir (Nujol) 3220 (NH), 1780 (C=O), 1720 (C=O), 1680 cm^{-1} (C=C); NMR ($CDCl_3$) δ 1.19 (3 H, t, J = 7 Hz, CH_2CH_3), 3.54 (2 H, d, J = 8 Hz, $-CH_2CH$=), 3.58

(2 H, q, J = 7 Hz, $-CH_2CH_3$), 6.04 (1 H, t, J = 8 Hz, -CH=), 7.22 (5 H, s, Ph), 9.15 (1 H, s, NH).

Anal. Calcd for $C_{13}H_{14}N_2O_2$: C, 67.81; H, 6.13; N, 12.17. Found: C, 67.77; H, 6.18; N, 12.11.

2-(2,4-Dimethoxybenzylamino)-4-phenyl-3-butenonitrile (13). To an ice-cold stirred solution of cinnamaldehyde (2.64 g) and 2,4-dimethoxybenzylamine hydrochloride (4.07 g) in 40 ml of MeOH, a solution of NaCN (1.0 g) in 10 ml of H_2O was added. The mixture was stirred for an additional 45 min at 5–10 °C, diluted with H_2O, and extracted with CH_2Cl_2. The organic layer was washed with H_2O, dried over anhydrous $MgSO_4$, and evaporated in vacuo to give 5.9 (96%) of crude **13** as a colorless oil: ir (neat) 3340 (NH), 2240 (C=N), 1620 cm^{-1} (C=C); NMR ($CDCl_3$) δ 2.1 (NH), 3.77 (3 H, s, OCH_3), 3.79 (3 H, s, OCH_3), 3.66–4.12 (2 H, d, $-NHCH_2$), 4.36 (1 H, d, d, J = 5, 2 Hz, NHCHCH=), 6.14 (1 H, d, d, J = 5, 15 Hz, =CHCHN), 6.3–7.5 ppm [9 H, m, $C_6H_3(OCH_3)_2$, C_6H_5, and PhCH=CH–). A small portion of the crude oil was dissolved in hexane–dry ether (1:1) and dry HCl was passed into the solution to precipitate **13** HCl. Recrystallization from absolute ethanol–hexane gave colorless crystals, mp 113–115 °C dec.

Anal. Calcd for $C_{19}H_{21}N_2O_2Cl$: C, 66.17; H, 6.14; N, 8.12. Found: C, 65.93; H, 6.19; N, 8.00.

2-Amino-4-phenyl-3-butenonitrile Trifluoroacetate (14). Crude **13** (5.54 g) and m-dimethoxybenzene (5 g) were dissolved in 40 ml of CF_3COOH with ice cooling, and the mixture was allowed to stand at room temperature for 15 h. After evaporation of CF_3COOH in vacuo, 20 ml of MeOH was added to the residue and the mixture was evaporated in vacuo. The residual oil was washed with petroleum ether and crystallized from benzene–hexane. The crystal were collected and washed with benzene to give 3.5 g (67%) of **14** as pale yellow prisms, mp 122–125 °C. Recrystallization from EtOAc–hexane gave an analytical sample: mp 122–124 °C dec; ir (KBr) 2260 cm^{-1} (C=N); NMR (CF_3COOH) δ 5.23 (1 H, d, J = 6 Hz, –CHNH), 6.15 (1 H, d, d, J = 6, 15 Hz, =CHCH), 7.02 (1 H, d, J = 15 Hz, PhCH=), 7.22 ppm (5 H, m, C_6H_5).

Anal. Calcd for $C_{12}H_{11}N_2O_2F_3$: C, 52.94; H, 4.07; N, 10.29. Found: C, 52.79; H, 4.12; N, 10.45.

Styrylglycine (9). A. Direct Hydrolysis of 13. Crude aminonitrile **13**, prepared from 264 mg of cinnamaldehyde, was dissolved in 5 ml of MeOH and added to 30 ml of concentrated HCl and the solution was refluxed for 3 h. The reaction mixture was filtered to remove some resinous product, washed twice with $CHCl_3$, and evaporated to dryness giving a crystalline residue. The crude product was dissolved in a minimum amount of H_2O, and the pH was adjusted to 6.5 with dilute NaOH. After cooling, the precipitate was collected, washed with a small amount of H_2O and EtOH, successively, and dried to give 50 mg (overall yield 13%) of **9** as pale orange crystals, mp 178–183 °C dec. Recrystallization from H_2O gave colorless leaves: mp 198–200 °C dec; ir (Nujol) 3050–2650 (NH_3^+), 1655 cm^{-1} (COO^-); NMR (CF_3COOH) δ 5.06 (m, 1 H, –CHCOOH), 6.25 (1 H, d, d, J = 16, 6 Hz, PhCH=CH–), 7.06 (1 H, d, J = 16 Hz, PhCH=), 7.40 (5 H, s, C_6H_5–), 7.58 ppm (3 H, broad s, NH_3^+).

Anal. Calcd for $C_{10}H_{11}NO_2$: C, 67.78; H, 6.26; N, 7.90. Found: C, 67.87; H, 6.37; N, 7.84.

B. Hydrolysis of 14. Three hundred milligrams of **14** was dissolved in 15 ml of concentrated HCl and the solution was refluxed for 3 h. Evaporation of the reaction mixture gave a solid which was dissolved in H_2O. The solution was filtered to remove insoluble material and neutralized with dilute NaOH. After cooling, the precipitate was collected, washed with H_2O and EtOH, successively, and dried to give 75 mg (35%) of **9** as colorless crystals, mp 180–185 °C dec. The ir spectrum was identical with that of the product obtained by method A.

C. Hydrolysis of 14 via the Imino Ester. A solution of **14** (2.91 g) in 30 ml of absolute MeOH was saturated with dry HCl at 0 °C. After 2 h at room temperature, the reaction mixture was diluted with 300 ml of concentrated HCl and refluxed for 2 h. Using the same work-up procedure, 1.31 g (70%) of **9** as colorless crystals was obtained, mp 185–190 °C. The spectrum was identical with that of **9** obtained by method A.

D. From 4b. A solution of 0.92 g (3 mmol) of **4b** in 35 ml of glacial acetic acid and 35 ml of 6 N HCl was refluxed for 24 h. The dark reaction mixture was extracted with three 20-ml portions of diethyl ether and the aqueous solution was concentrated to 4–6 ml on a vacuum pump. After diluting with 20 ml of water, the aqueous solution was clarified with Norit and again evaporated in vacuo giving an extremely hygroscopic residue. The residue was redissolved in 15 ml of water, and the solution was adjusted to pH 5.0–6.0 with 10% ammonium hydroxide solution. After cooling to 0 °C, the precipitated amino acid was filtered and dried in vacuo, giving 0.215 g (41%) of crude product, mp 155–168 °C. Recrystallization from an ammonium acetate buffered solution gave 0.13 g (24%) of **9**, mp 181–190 °C dec (recrystallization raised the melting point to 196–199 °C), identical in all respects with authentic sample.

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Registry No.—**2a**, 58117-73-0; **3b**, 58117-74-1; **3c**, 58117-75-2; **4b**, 58117-76-3; **4c**, 58117-77-4; **5**, 58117-78-5; **6**, 58117-79-6; **7**, 58117-80-9; **8**, 58117-81-0; **9**, 58207-08-2; **10a**, 58117-82-1; **12a**, 58117-83-2; **12b**, 58117-84-3; **13**, 58117-85-4; **13** HCl, 58117-86-5; **14**, 58117-88-7; β-3,4-dihydroxy-DL-phenylalanine, 63-84-3; (*E*)-α-methylcinnamoyl chloride, 38449-13-7; (*E*)-cinnamaldehyde, 14371-10-9; 2,4-dimethoxybenzylamine hydrochloride, 6967-51-7.

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A Facile Preparation of Highly Fluorinated Diamines

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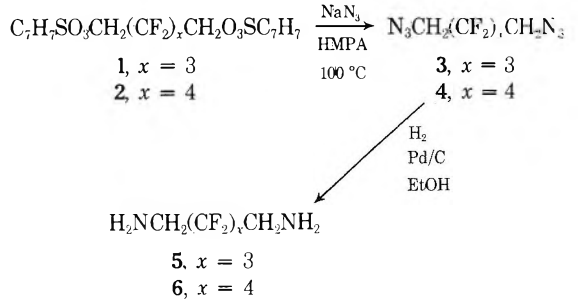
Most highly fluorinated amines and diamines are prepared by lithium aluminum hydride reduction of the corresponding amides[1] or by high-pressure (1000 psi) catalytic hydrogenation of nitriles.[2] The former class of compounds often gives highly explosive reaction mixtures,[1] while the latter reaction is inconvenient and involves an additional dehydration step in the synthesis. Both methods proceed in only moderate yield. Previous attempts to employ the easily obtained 2,2,3,3,4,4-hexafluoropentane 1,5-di-*p*-toluenesulfonate (**1**) with ammonia, methylamine, or diethylamine gave only tarry mixtures from which no amine could be isolated.[1] In one instance,[3] reaction of 1,1-di-*H*-heptafluorobutyl *p*-toluenesulfonate with aniline at 230 °C for 24 h gave a 68% yield of the desired amine, but reaction with ammonia gave only tars.

It has now been found that reaction of **1** with an excess of sodium azide takes place readily to give an almost quantitative yield of diazide **3** when hexamethylphosphoric triamide (HMPA) is employed as solvent. Azide formation was not observed when DMF was used as solvent. The

crude diazide was reduced directly to the diamine **5** in 82–90% yield by catalytic hydrogenation in ethanol at 3 atm using 10% Pd/C catalyst.[4] A similar sequence of reactions led to 2,2,3,3,4,4,5,5-octafluorohexane-1,6-diamine (**6**).



Experimental Section[5]

2,2,3,3,4,4-Hexafluoropentane-1,5-diazide (3). A mixture of 20.0 g (0.038 mol) of ditosylate 1,[1] 10.0 g (0.15 mol) of sodium azide, and 70 ml of HMPA was stirred and heated in an oil bath[6] at 100–110 °C for 19 h. The mixture was cooled and ca. 300 ml of water was added. The aqueous mixture was extracted three times with ether, washed twice with water, dried over $MgSO_4$, and evaporated in vacuo to leave 10.2 g (99%) of product as a pale yellow oil: ν_{max} (neat) 2100 (s), 2150 (sh), 2210 cm^{-1} (sh); NMR ($CDCl_3$) δ 2.4–4.0 (m). The purity of **3** was estimated by integrating the CH_2 multiplet against a small amount of aromatic resonance still present from unreacted tosylate, and was of the order of 90 ± 3%.

2,2,3,3,4,4,5,5-Octafluorohexane 1,6-Di-*p*-toluenesulfonate (2). To a solution of 100 g (0.38 mol) of 2,2,3,3,4,4,5,5-octafluoro-1,6-hexanediol[7] in 500 ml of dry pyridine cooled in an ice bath was added 195.0 g (1.0 mol) of *p*-toluenesulfonyl chloride in several portions with strong stirring. The temperature of the reaction was maintained at 30 °C or less until the end of the addition. After the reaction mixture was kept chilled for a further 2 h, it was allowed to equilibrate to room temperature and left overnight. The mixture was poured into 2 l. of cold 1 N HCl and the precipitate collected. Trituration of the moist solid with methanol gave 188.2 g (87%) of white solid, mp 134–136 °C.

Anal. Calcd for $C_{20}H_{18}F_8O_6S_2$: C, 42.08; H, 3.18; F, 26.67. Found: C, 41.65; H, 2.87; F, 26.48.

2,2,3,3,4,4,5,5-Octafluorohexane-1,6-diazide (4). This was prepared in a like manner as **3** from the ditosylate **2** in 92 ± 3% crude yield.

2,2,3,3,4,4-Hexafluoropentane-1,5-diamine (5). To a solution of 10.7 g of diazide **3** in 60 ml of absolute ethanol was added 1–2 g of 10% palladium on carbon. The mixture was hydrogenated at 48 psi for 5 h and filtered, and the solvent evaporated under reduced pressure. Distillation of the residual oil gave 8.1 g (90%) of colorless oil, bp 65–67 °C (0.7 mm),[8] $n^{25}D$ 1.373, which darkened slightly on standing. A sample in ethanol was treated with ethereal HCl and the precipitate recrystallized from ethanol–ether, mp 305–310 °C dec.

Anal. Calcd for $C_5H_8F_6N_2 \cdot 2HCl$: C, 21.22; H, 2.81; N, 9.90. Found: C, 21.37; H, 3.46; N, 9.91.

2,2,3,3,4,4,5,5-Octafluorohexane-1,6-diamine (6). This compound was prepared similarly as described for **5** in 87% yield, bp 95–98 °C (0.6 mm), mp 44–45 °C (reported[2] 44–45 °C).

Registry No.—**1**, 632-01-9; **2**, 58191-47-2; **3**, 58191-48-3; **4**, 58191-49-4; **5**, 336-33-4; **5** 2HCl, 58191-50-7; 2,2,3,3,4,4,5,5-octafluoro-1,6-hexanediol, 355-74-8.

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(5) Boiling points and melting points are uncorrected. Infrared spectra were recorded on a Perkin-Elmer Model 137 Infracord spectrophotometer. NMR spectra were measured on a Varian Associates T-60 spectrophotometer using Me_4Si as an internal standard. Combustion analyses were done by Galbraith Laboratories, Knoxville, Tenn.
(6) The use of a heating mantle is not advisable. In one experiment employing a mantle, superheating occurred which led to a vigorous reaction with concomitant decomposition to dark tarry materials.
(7) E. T. McBee, W. F. Marzluff, and O. R. Pierce, *J. Am. Chem. Soc.*, **74**, 444 (1952).
(8) R. Gosnell and J. Hollander, *J. Macromol. Sci., Phys.*, **1**, 831 (1967), report this compound, apparently erroneously, as having mp 52–53 °C, bp 40–45 °C (1.0 mm).

Synthesis and Reactions of Perfluorodialdehydes

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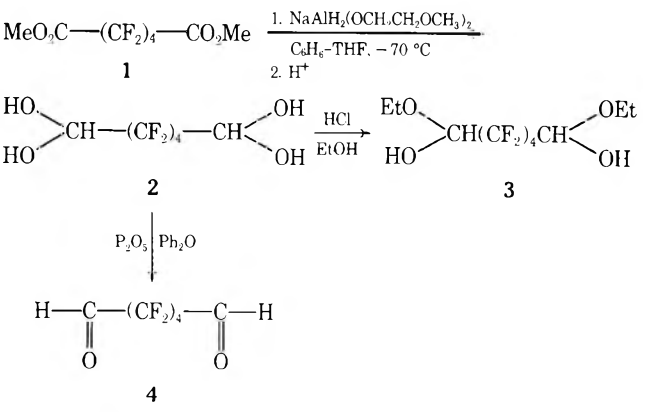
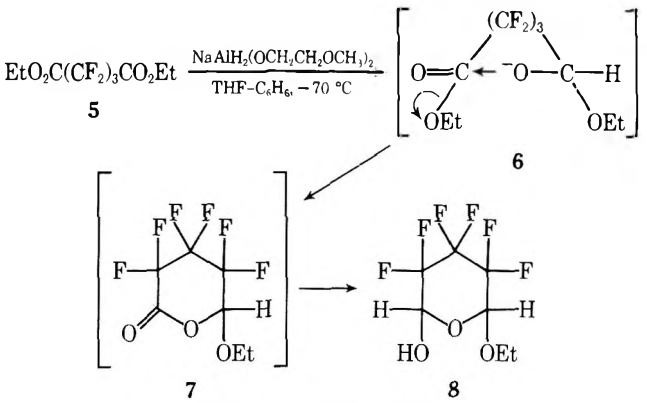
The synthesis of perfluoroaldehydes has generally been accomplished by the lithium aluminum hydride ($LiAlH_4$) reduction of the corresponding esters at low temperatures.[1] Inverse addition has been reported to improve yields.[2,3] Although there have been no reports of perfluorodialdehydes in the literature, we anticipated no difficulty in their preparation by the standard methods described above. However, only traces of the desired product could be detected from the $LiAlH_4$ reduction of dimethyl perfluoroadipate in ether at either 0 °C or −70 °C. Equally unsuccessful was the attempted reduction of perfluoroadipoyl chloride in tetrahydrofuran using lithium tri-*tert*-butoxyaluminum hydride.

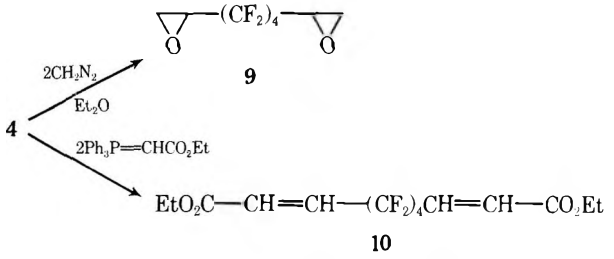
Successful synthesis of the desired dialdehyde (as the dihydrate) was achieved in good yield by employing commercially available sodium bis(methoxyethoxy)aluminum hydride (Vitride, 70% in benzene) in tetrahydrofuran solution at −70 °C. The dihydrate **2** reacted with 2,4-dinitrophenylhydrazine in acid solution to give a crystalline yellow bis-2,4-dinitrophenylhydrazone. Treatment of **2** with HCl in ethanol afforded the hemiacetal **3**, while dehydration of **2** to the free dialdehyde **4** was most conveniently carried out using phosphorus pentoxide in diphenyl ether.



When the Vitride reduction of diethyl perfluoroglutarate was effected under similar conditions, the dialdehyde was obtained in the form of the cyclic hemiacetal **8**, formation of which seems best explained by intramolecular cyclization of the initial reduction product **6** to **7** followed by further reduction to **8**. Reaction of perfluoro diesters with Vitride at room temperature afforded consistent yields of greater than 90% of perfluoro diols. Although $LiAlH_4$ reductions were also satisfactory in providing diols,[4] the convenience and greater safety margin of Vitride makes it the reagent of choice—especially in those cases where large quantities of material are required.



The dialdehyde **4** underwent reaction with diazomethane to give the diepoxide **9** and afforded the diolefin **10** via a Wittig reaction using carbethoxymethylenetriphenylphosphorane.



The importance of difunctional perfluorinated compounds has been extensively reviewed.[5] Consequently, the ready accessibility of the synthetically versatile perfluorinated dialdehydes should provide a valuable addition to the chemistry of highly fluorinated compounds.

Experimental Section

General. Infrared spectra were recorded on a Perkin-Elmer Model 137 spectrophotometer. NMR spectra were obtained with a Varian Associates T-60 instrument. Combustion analyses were performed by Galbraith Laboratories, Knoxville, Tenn. Vitride reagent was obtained from Eastman Organic Chemicals Co.; dimethyl perfluoroadipate was obtained from PoChemco Chemical Co.; and diethyl perfluoroglutarate was purchased from PCR Inc.

2,2,3,3,4,4,5,5-Octafluorohexane-1,6-dialdehyde (4). In a 3-l. three-neck round-bottom flask fitted with a mechanical stirrer, dropping funnel equipped with a drying tube, and low-temperature thermometer was placed a solution of 50.0 g (0.158 mol) of dimethyl perfluoroadipate in 450 ml of dry tetrahydrofuran. The reaction mixture was cooled to −70 °C (dry ice–acetone) and 67.5 ml (0.238 mol) of Vitride (70% in benzene) diluted with 50 ml of THF was added dropwise over 30 min with vigorous stirring. The temperature of the reaction was maintained at ≤−70 °C during the addition and at −70 °C for 2.5 h after addition was complete. To the viscous mixture 500 ml of 20% sulfuric acid previously chilled to 5 °C was added dropwise. The temperature of the reaction was allowed to rise to −50 °C and maintained until the excess Vitride had been decomposed. The mixture was then allowed to warm spontaneously to room temperature. Ether (400–600 ml) was added with vigorous stirring until a homogeneous two-phase system was obtained. The layers were separated and the aqueous phase extracted with an additional 200–300 ml of ether. The combined ether extracts were washed to neutrality with brine, dried over $MgSO_4$, and evaporated under reduced pressure. The dialdehyde dihydrate **2** was left as a thick syrup, 45.2 g (96%), ν_{max} (neat) 3600–2000 cm^{-1} (br).

Crude **2** from above was stirred with 3 equiv of phosphorus pentoxide in 60 ml of diphenyl ether[6] for 10 min and then the mixture was distilled through a 60-mm Vigreux column taking care to exclude moisture. The material so collected (28.1 g) was redistilled to give 26.5 g (65%) of **4** as a colorless liquid: bp 122–123 °C; $n^{26}D$ 1.3170; ν_{max} (neat) 2900, 2850 (sh), 1765 cm^{-1}; NMR ($CDCl_3$) δ 9.47 (m).

Because of the ease with which **4** underwent hydration, a sample was converted to the bis-2,4-dinitrophenylhydrazone for analysis, mp 228–230 °C (EtOH).

Anal. Calcd for $C_{18}H_{10}F_8N_8O_8$: C, 35.00; H, 1.62; N, 18.13. Found: C, 34.98; H, 1.62; N, 17.78.

2,2,3,3,4,4,5,5-Octafluoro-1,6-diethoxy-1,6-hexanediol (3). A solution of 5.0 g (0.017 mol) of crude **2** in 25 ml of absolute ethanol was saturated with HCl and allowed to remain overnight at room temperature. The precipitate was collected and washed with benzene to give 5.6 g (84%) of pure **3**: mp 110–111 °C; NMR (Me_2SO-d_6) δ 1.10 (t, 3 H, J = 6.5 Hz), 3.24–3.90 (m, 2 H), 4.94 (t, 1 H, J = 11 Hz), 7.34 (br s, 1 H, exchanges).

Anal. Calcd for $C_{10}H_{14}F_8O_4$: C, 34.30; H, 4.02. Found: C, 34.33; H, 4.04.

2-Ethoxy-6-hydroxy-3,3,4,4,5,5-hexafluoropyran (8). A solution of 30.3 g (0.105 mol) of Vitride (70% in benzene) in 30 ml of dry THF was added dropwise over 45 min to a stirred solution of 25.0 g (0.084 mol) of diethyl perfluoroglutarate in 200 ml of THF at −70 °C. The mixture was stirred for an additional 2 h at −70 °C followed by work-up as described for **4** to give 16.8 g (87%) of **8** as a pale yellow liquid. Distillation afforded a colorless oil [bp 65–70 °C (1.7 mm); $n^{26}D$ 1.3671; ν_{max} (neat) 3350 cm^{-1} (broad); NMR ($CDCl_3$) δ 1.20 (t, 3 H, J = 6.5 Hz), 3.46–4.10 (m, 2 H, J = 4 Hz), 5.07–5.26 (m, 2 H), 8.33 (br s, 1 H, exchanges)] which on prolonged storage (1 month) solidified to a white, crystalline product, mp 84–86 °C (C_6H_6).

Anal. Calcd for $C_7H_8F_6O_3$: C, 33.05; H, 3.17; F, 44.90. Found: C, 32.76; H, 3.01; F, 44.46.

A sample of **8** when treated with 2,4-dinitrophenylhydrazine gave a crystalline yellow bishydrazone, mp 214–216 °C (EtOH).

Anal. Calcd for $C_{17}H_{10}F_6N_8O_8$: C, 35.95; H, 1.76; N, 19.73, F, 20.10. Found: C, 36.12; H, 1.42; N, 19.46; F, 20.60.

1,2,7,8-Diepoxy-3,3,4,4,5,5,6,6-octafluorooctane (9). To a solution of diazomethane (ca. 120 mmol) in 200 ml of ether cooled to 5 °C in an ice bath was added 10.0 g (39.0 mmol) of **4** dropwise over 15 min. The solution was stirred for 30 min and then allowed to stand unstoppered at room temperature for 16 h at which time the yellow color indicative of diazomethane had been discharged. The solution was purged with nitrogen followed by evaporation in vacuo at ambient temperature to leave 11.0 g of viscous, pale yellow oil. Distillation afforded 5.5 g (49%) of colorless liquid: bp 70–75 °C (0.025 mm); $n^{26}D$ 1.3622; NMR ($CDCl_3$) δ 3.04 (m, 2 H), 3.53 (m, 1 H); ν_{max} (neat) 910 cm^{-1}.

Anal. Calcd for $C_8H_6F_8O_2$: C, 33.59; H, 2.11. Found: C, 34.01; H, 2.29.

Diethyl 4,4,5,5,6,6,7,7-Octafluorodecane-2,8-dienedioate (10). A mixture of 8.1 g (2.3 mmol) of carbethoxymethylenetriphenylphosphorane and 3.0 g (1.2 mmol) of **4** in 40 ml of toluene was heated at reflux for 18 h under an atmosphere of nitrogen. The solution was chilled in ice, and the precipitated triphenylphosphine oxide was collected. The filtrate was diluted with 200 ml of petroleum ether and a second crop of phosphine oxide removed. Evaporation of solvent under reduced pressure left an oil from which the residual phosphine oxide was removed by trituration with petroleum ether. Distillation of the evaporated petroleum ether supernatant gave 3.4 g (74%) of **10** as a colorless liquid, bp 148–153 °C (7.0 mm), $n^{25}D$ 1.450.

Anal. Calcd for $C_{14}H_{14}F_8O_4$: C, 42.25; H, 3.52; F, 38.19. Found: C, 42.66; H, 3.28; F, 37.91.

2,2,3,3,4,4,5,5-Octafluorohexane-1,6-diol. A solution of 100.7 g (0.316 mol) of dimethyl perflouroadipate in 100 ml of dry THF was added dropwise over 1 h to a mechanically stirred solution of 210 ml (0.750 mol) of Vitride (70% in benzene) dissolved in 300 ml of THF. A slow reflux was maintained throughout the addition. Following completion of the addition stirring was continued for 1 h at room temperature. The mixture was cooled in an ice bath and 500 ml of chilled 20% H_2SO_4 (v/v) was added dropwise, followed by 450 ml of ether. The mixture was allowed to warm to room temperature. The ether phase was decanted and 500 ml of water was added to the reaction vessel. Rapid stirring was continued until all of the pasty white solid had been dissolved. After the ether extraction was repeated, the combined ethereal extracts were washed to neutrality with cold water and dried over $MgSO_4$. Removal of solvent in vacuo gave an amber syrup which solidified readily upon cooling to give 78.5 g (95%) of diol as a tan solid, mp 63–66 °C (lit.[4] mp 68 °C). This material was found to be sufficiently pure for further conversions. When desirable, purification appears best effected by distillation: bp 100–110 °C (1.5 mm); mp 67–68 °C.

Registry No.—**1**, 3107-98-0; **2**, 58191-51-8; **3**, 58191-52-9; **4**, 58191-53-0; **4** bis-2,4-DNPH, 58191-54-1; **5**, 424-40-8; **8**, 58191-55-2; **8** bis-2,4-DNPH, 58191-56-3; **9**, 58191-57-4; **10**, 58191-58-5; 2,4-dinitrophenylhydrazine, 119-26-6; diazomethane, 334-88-3; (car-

bethoxymethylene)triphenylphosphorane, 1099-45-2; 2,2,3,3,4,4,5,5-octafluorohexane-1,6-diol, 355-74-8.

References and Notes

(1) D. R. Husted and A. H. Ahlbrecht, *J. Am. Chem. Soc.*, **74**, 5422 (1952).
(2) O. R. Pierce and T. G. Kane, *J. Am. Chem. Soc.*, **76**, 300 (1954).
(3) M. Braid, H. Iserson, and F. E. Lawlor, *J. Am. Chem. Soc.*, **76**, 4027 (1954).
(4) E. T. McBee, W. F. Marzluff, and O. R. Pierce, *J. Am. Chem. Soc.*, **74**, 444 (1952).
(5) I. L. Knunyants, L. Chih-Yuan, and V. V. Shokina, *Russ. Chem. Rev.*, **32**, 461 (1963).
(6) Previously dried by heating over phosphorus pentoxide so that no materials of bp <160 °C remained. Decantation of the clear supernatant from the dark residue was found to be satisfactory.

Solvolysis in Strong Acids. III. The Question of Alkyl–Oxygen Cleavage in Alkyl Tosylate Solvolysis[1]

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Simple primary alkyl *p*-toluenesulfonates solvolyze at markedly different rates in concentrated sulfuric acid. Mechanistic interpretations supported by investigations of first-formed products and kinetic isotope effects have been reported.[2] Recently, Harris has reviewed these and closely related studies within the general context of solvolytic substitution.[3,4] Our studies in this area have continued along several lines. One topic of interest has been the solvolytic behavior of some simple alkyl tosylates containing the trifluoromethyl group.[5]

Systems such as 2,2,2-trifluoroethyl tosylate and 1,1,1-trifluoro-2-propyl tosylate react most sluggishly under SN2-like conditions.[6] The remarkable stability of the 2,2,2-trifluoroethyldiazonium ion indicates that SN1-like reactions of these systems should also proceed with great reluctance.[7] Consequently, we were surprised to find that 2,2,2-trifluoroethyl tosylate and 1,1,1-trifluoro-2-propyl tosylate solvolyzed in the 85–100% sulfuric acid region at rates comparable to those of ethyl tosylate, but 3,3,3-trifluoro-1-propyl tosylate solvolyzed in sulfuric acid at rates significantly slower than those observed for methyl tosylate. Some of the relevant kinetic data are shown in Figure 1.[8] The fluorinated tosylates underwent solvolysis without rearrangement.

A consistent mechanistic representation that presumed alkyl–oxygen cleavage for the entire set of alkyl tosylates (Figure 1) was difficult to formulate. Further study of the seemingly aberrant fluorinated alkyl tosylates appeared necessary. We report here a correlated stereochemical and ^{18}O-labeling study which shows that solvolysis of 1,1,1-trifluoro-2-propyl tosylate in 98% sulfuric acid occurs with complete retention of configuration because solvolysis *does not* involve cleavage of the alkyl–oxygen bond.

An earlier survey study of asymmetric reductions with the lithium aluminum hydride–quinine complex indicated that a useful enantiomeric excess of (+)-1,1,1-trifluoro-2-propanol [(+)-1] could be produced by this reducing system.[9] After optimizing conditions, (+)-1 could be conveniently prepared in 30% enantiomeric excess by reduction of 1,1,1-trifluoroacetone at 25 °C with an ethereal slurry of the 1:1 complex. 1,1,1-Trifluoro-2-propanol-^{18}O (1-^{18}O) was prepared by hydration of anhydrous trifluoroacetone with 50 atom % $H_2{}^{18}O$ followed by acid-catalyzed dehydration and subsequent reduction with lithium aluminum hydride in diglyme.

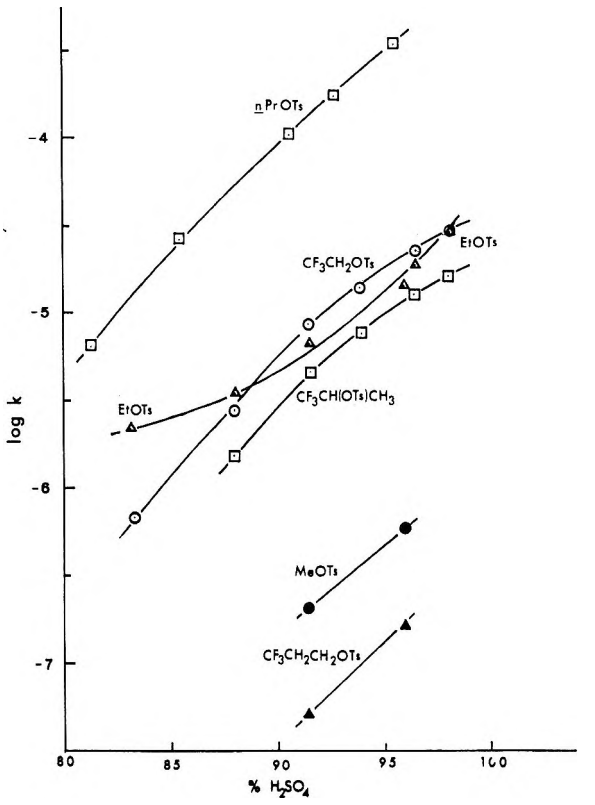
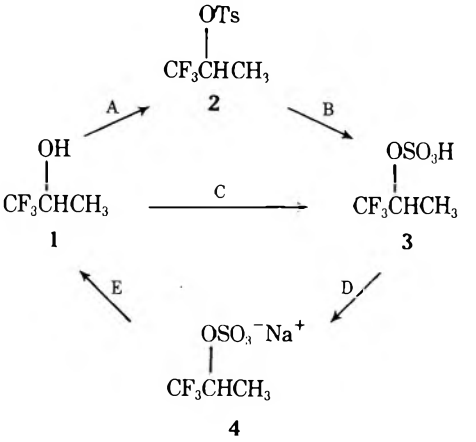


Figure 1. First-order rates (s^{-1}) of solvolysis of some simple alkyl tosylates in concentrated sulfuric acid solutions at 30 °C. A plot of log *k* vs. % H_2SO_4.

Samples of chiral and isotopically labeled **1** were carried through the reaction cycles depicted in Scheme I as steps

Scheme I[a]



[a] A, TsCl—pyridine, −5° C; B, 98% H_2SO_4, 30° C; C, 98% H_2SO_4, 30° C; D, NaOH (aqueous), evaporation, extraction with CH_3OH; E, moist Et_2O—H^+, reflux.

A, B, D, E and steps C, D, E. The rotation of (+)-1 before and after passing through the reaction cycles was found to be identical within experimental error (Table I). The rotations of intermediates **3** and **4** were also found to be path independent (Table II). Finally, the oxygen-18 content of 1-^{18}O was found to be unchanged after passage through the reaction cycles (Table III).

The conclusions are clear. No step in the cycles involves measurable cleavage of the alkyl–oxygen bond. Complete retention of configuration is a trivial consequence of this fact.

Table I. Specific Rotations of (+)-1 before and after Passage through Reaction Cycles (Scheme I)

	$[\alpha]_\lambda^{25}$		
λ, nm	1 st mat.	1 via ABDE	1 via CDE
584	0.872	0.870	0.868
578	0.913	0.913	0.938
546	1.036	1.036	1.042
436	1.756	1.740	1.789
365	2.682	2.692	2.679

Table II. Specific Rotations of Intermediates in Reaction Cycles (Scheme I)

	$[\alpha]_\lambda^{25}$			
λ, nm	3[a,b] via AB	3[a,b] via C	4[c] via CD	4[c] via AED
584	−3.21	−2.85	−1.78	−1.78
578	−3.34	−2.97	−1.84	−1.91
546	−3.78	−3.34	−2.19	−2.15
436	−6.36	−5.64	−3.69	−3.63

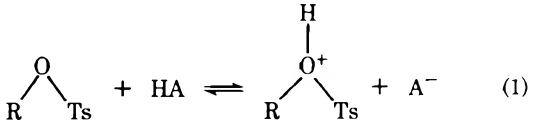
[a] $[\alpha]^{25}D$ of 1 used in these runs was +0.961. [b] In sulfuric acid reaction solution. Concentration uncertainties account for differences. [c] In aqueous solution.

Table III. ^{18}O Atom % of 1-^{18}O before and after Passage through Reaction Cycles (Scheme I)

	^{18}O atom %	
1 st mat.	1 via ABDE	1 via CDE
24.6 ± 0.3	24.4 ± 0.3	24.3 ± 0.3

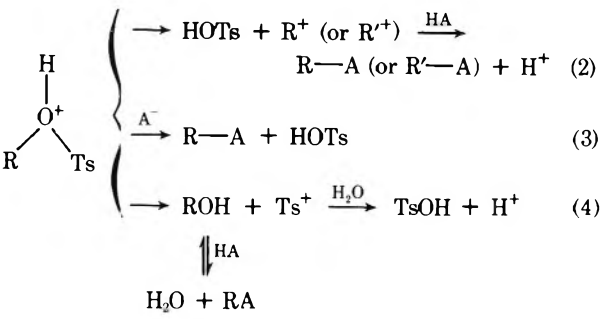
The implications of this result remain to be explored more fully. Previous discussions of solvolytic displacement of alkyl tosylates in strong acids have implicitly assumed alkyl–oxygen bond cleavage. In many cases this assumption appears to be required by product, label scrambling, and kinetic isotope effect data.[2-4] The solvolytic behavior of the 1,1,1-trifluoro-2-propyl system (and presumably the 2,2,2-trifluoroethyl system) shows that accessible, fundamentally different paths of solvolysis do exist. The dominance of one path over others seems to be a fairly sensitive function of alkyl group structure.

Since cleavage of the alkyl–oxygen bond does not occur in sulfuric acid solvolysis of 1,1,1-trifluoro-2-propyl tosylate, two possibilities remain, cleavage at the oxygen–sulfur bond or cleavage at the sulfur–aromatic carbon bond. The latter mode, presumably an electrophilic replacement of the alkoxysulfonylium cation ($ROSO_2^+$) by a proton, is discounted since no clear rationale is available to explain the sensitivity of solvolysis rate to alkyl group structure. Cleavage at the oxygen–sulfur bond could be accommodated within an expanded version of the mechanistic scheme previously suggested.[2a,3b] This scheme requires prior protonation of the substrate before cleavage.[10] For purposes of discussion the site of protonation is restricted to the alkyl oxygen atom, eq 1.



(1)

Given this, a partitioning among at least three paths can be proposed.



The first two paths, eq 2 and 3, represent conventional dissociative (SN1-like) and associative (SN2-like) solvolytic displacements. The third path, eq 4, is simply the complementary dissociative path that could occur when cleavage at the alkyl carbon–oxygen bond is very slow.[10b] Thus with the assumption that both sulfur–oxygen as well as alkyl–oxygen cleavages are slow for methyl tosylate and 3,3,3-trifluoro-1-propyl tosylate, the enhanced rates of solvolysis of 1,1,1-trifluoro-2-propyl tosylate and 2,2,2-trifluoroethyl tosylate might be rationalized in terms of leaving group tendencies of the respective alcohols. It seems reasonable to anticipate that the significantly higher K_A's of trifluoroethanol ($10^{-12.4}$) and 1,1,1-trifluoro-2-propanol ($10^{-11.8}$) with respect to methanol ($10^{-15.5}$) and 3,3,3-trifluoro-1-propanol would be reflected in better leaving group qualities for the former. Note, however, that this rationalization requires the implicit assumption that the K_A's of the alkyl tosylate conjugate acids are less influenced by alkyl group structure than are the rates of sulfur–oxygen cleavage.

If the assumptions made are valid, fairly conventional mechanistic arguments may explain the result reported within the larger context. However, a central question remains. Which tosylates of the set of fairly inert alkyl tosylates (methyl, ethyl, 3,3,3-trifluoro-1-propyl) solvolyze in whole or in part by paths other than alkyl–oxygen cleavage? The α-trifluoromethylalkyl systems may well be aberrant with respect to the previously assumed norm, but the issue remains open until studies in progress are completed.

This study points out the danger in tacit assumption of a given mode of bond cleavage in strong acid solvolysis, particularly when kinetic data are the sole indicators.

Experimental Section

Fluorinated alcohols and ketones were purchased from PCR, Inc., Gainesville, Fla. Water (50 atom % excess ^{18}O) was obtained from Bio-Rad Laboratories. NMR spectra were recorded on a Varian A-60 spectrometer. Rotation measurements were made with the use of a Perkin-Elmer 141 polarimeter. ^{18}O analyses were made with the use of a Perkin-Elmer Hitachi RMU 6D spectrometer.

(+)-1,1,1-Trifluoro-2-propanol. The preparation was patterned after the work of Cervinka and Belovsky.[11] A number of trials were made. The following conditions appeared to give the best yield and greatest enantiomeric excess.

Anhydrous (−)-quinine (52.8 g, 0.163 mol, dried by vacuum dehydration at 125°, 2 mm for 4 h) and lithium aluminum hydride (6.22 g, 0.164 mol) were added sequentially to 500 ml of anhydrous ether in a 2-l. flask equipped with a sealed mechanical stirrer and reflux condenser. The mixture was heated to reflux for 3 h to form a butter yellow suspension of the complex. The mixture was cooled to room temperature, the reflux condenser was replaced with a large dry ice cold finger condenser, and 1,1,1-trifluoroacetone (18.3 g, 0.163 mol) was distilled into the flask held at room temperature (ca. 25 °C). There was no color change although the reaction mixture appeared more homogeneous. After a period of 15 h, the reaction mixture was treated successively with water (150 ml, dropwise addition) and sulfuric acid (350 ml, 20 wt %). The clear yellow aqueous layer was separated from the colorless ether layer and the ether phase was extracted successively with three 50-ml portions of cold 20% sulfuric acid and three 50-ml portions of water. The dried (sodium sulfate) ether phase was concentrated by distillation

through a vacuum jacketed Vigreux column (300 × 15 mm). The residual liquid (ca. 50 ml) was transferred to a smaller flask and fractional distillation was continued to yield a fraction bp 75–75.9 °C, 13.14 g. NMR spectra of this fraction indicated the presence of water (1 wt %), ether (6 wt %), and trifluoroacetone (4 wt %, as hemiacetal and hydrate); crude yield 62%, α^{25}D (neat, uncorrected) 1.990. Redistillation afforded a sample with the following properties: bp 75.8–76.2 °C (726 mm); n^{25}D 1.3135; d_4^{25} 1.259; α^{25}D (neat) 2.165 [lit.[12] bp 77.7–77.9 °C (752 mm); n^{25}D 1.3130; d_4^{25} 1.263; α^{25}D −7.14].

Reduction by the procedure described above at various temperatures gave the following crude yields and enantiomeric excess values: −78 °C, 26%, 9.1% ee; −10 °C, 61%, 13.3% ee; 25 °C, 62%, 30% ee.

1,1,1-Trifluoroacetone-^{18}O. 1,1,1-Trifluoroacetone (9.5 g, 85 mmol) was distilled into a cooled 50-ml two-necked flask equipped with a dry ice condenser, drying tube, stir bar, and serum cap. Water (1.58 g, 50 atom % ^{18}O, 83 mmol) was added dropwise via a syringe. The first droplets of water added solidified. These were allowed to melt to globules of water on the surface, and a mildly exothermic reaction commenced. Crystallization started after addition of about 1.0 ml of labeled water, but continued addition caused solution and gentle refluxing. The system continued to reflux for about 15 min after addition of the last portion and then rapidly solidified to a mass of prisms. The solid was warmed to room temperature and volatiles were collected in a small trap cooled in dry ice–acetone. Less than 0.1 ml of volatile material was collected during a 3-h period. A vacuum jacketed Claisen-Vigreux still was attached to the reaction flask, sulfuric acid (0.5 ml, 96 wt %) was added, and the reaction mixture was heated to reflux. Distillate (7.0 ml, 8.8 g, bp 22–24 °C) was collected in a dry ice cooled graduated receiving tube. A mass spectrum indicated ca. 25% ^{18}O incorporation.

1,1,1-Trifluoro-2-propanol-^{18}O. 1,1,1-Trifluoroacetone-^{18}O (8.59 g, 76.4 mmol, ca. 25% ^{18}O) was slowly distilled into a stirred and cooled (−40 °C) 100-ml round-bottom flask containing a suspension of lithium aluminum hydride (1.53 g, 40 mmol) in 35 ml of diglyme (freshly distilled at 20 mm from $LiAlH_4$). The reaction flask was equipped with a dry ice condenser, serum cap, and stir bar. The reaction mixture was then brought to room temperature with the dry ice condenser charged and maintained during a 3-h period. Twelve hours later, the reaction mixture was treated with 25 ml of dry diethylene glycol. A vacuum jacketed Claisen-Vigreux still was attached and the labeled alcohol was distilled directly from the quenched reaction mixture to yield 6.99 g (5.8 ml, bp 74.5–78 °C) and 1.10 g (bp 78–120 °C). NMR analysis indicated that the first fraction was 95.6 wt % alcohol (76.4% yield) with diglyme the principal impurity. Preliminary mass spectral analysis indicated ca. 25% ^{18}O incorporation.

***p*-Toluenesulfonates of 1,1,1-Trifluoro-2-propanols.** The following procedure is representative. (+)-1,1,1-Trifluoro-2-propanol (10.1 g, 88 mmol, α^{25}D +1.101) was added slowly via a syringe to a cold (−7 °C), magnetically stirred solution of dry pyridine (60 ml) and *p*-toluenesulfonyl chloride (16.0 g, 84 mmol). The resulting mixture was stored in the freezer (−20 °C) for 2 weeks. The extent of conversion was monitored by NMR spectroscopy. The tosylate was isolated in the usual way, and purified by vacuum distillation to yield (−)-1,1,1-trifluoro-2-propyl tosylate, 13.1 g (56%), bp 97.5 °C (1 mm), α^{20}D −4.024, n^{25}D 1.4165. Unlabeled and ^{18}O-labeled tosylates were prepared by similar means in 50 and 80% isolated yields, respectively. NMR spectra and refractive indices were identical.

Solvolysis of 1,1,1-Trifluoro-2-propyl *p*-Toluenesulfonate-*ether*-^{18}O. A sample of the ^{18}O-labeled tosylate (0.4618 g, 1.72 mmol) was transferred to a 10-ml volumetric flask and 98 wt % sulfuric acid was added to the mark. The resulting solution was double sealed and held at 25 °C until the reaction was about 80% complete. The reaction mixture was quenched by pouring it on 80 g of crushed ice with magnetic stirring and external cooling, and the resulting acidic solution was neutralized with ca. 20 ml of 50% sodium hydroxide solution by dropwise addition with stirring and cooling so that the temperature did not exceed 15 °C. The solution was adjusted to pH 9, additional water was added to dissolve precipitated sodium sulfate, and the aqueous suspension was extracted with three 10-ml portions of methylene chloride. Thirty-seven milligrams of tosylate was recovered from the methylene chloride extracts. The NMR and mass spectra were identical with those of starting material.

The aqueous solution containing sodium sulfate, sodium 1,1,1-trifluoro-2-propyl sulfate, and sodium *p*-toluenesulfonate was rotary evaporated (temperature less than 35 °C) to yield a crystalline mass that was more thoroughly dried at the oil pump (1 mm, 25 °C, 24 h). The mixture of salts was triturated with two 15-ml portions of refluxing anhydrous methanol and the methanol filtrate evaporated to yield 0.97 g of hydrated crystalline residue. The NMR spectrum (D_2O) indicated a mole ratio sodium 1,1,1-trifluoro-2-propyl sulfate:sodium *p*-toluenesulfonate of 0.95:1.0.

Samples of unlabeled and chiral 1,1,1-trifluoro-2-propyl tosylate were solvolyzed in an identical manner. Products were isolated by the procedure described with similar results. Samples of 1,1,1-trifluoro-2-propyl hydrogen sulfate were prepared by direct esterification of labeled and chiral samples of 1,1,1-trifluoro-2-propanol with 98% sulfuric acid. The alkyl hydrogen sulfate was isolated as the sodium salt and purified by the method described above.

Hydrolyses of Sodium 1,1,1-Trifluoro-2-propyl Sulfates in Moist Ether. The procedure used is based on the known method most recently discussed by Groen and Kochansky.[13] The following is representative. The mixed salts, sodium (−)-1,1,1-trifluoro-2-propyl sulfate and sodium *p*-toluenesulfonate (4.68 g, 11.4 mmol of sulfate ester), obtained via steps ABD (Scheme I) were mixed with anhydrous ether (65 ml), water (0.5 ml), and 10% sulfuric acid (0.1 ml). The mixture was heated at reflux for 60 min and then titrated with standard base; 10.4 mequiv was consumed, 91% yield. The ether layer was separated. The aqueous layer was saturated with sodium sulfate and then extracted twice with ether. The combined, dried (sodium sulfate) ether layers were concentrated by distillation and the residue was distilled with the use of a one-piece vacuum-jacketed Vigreux microstill to yield 0.625 g, bp 72–76 °C, plus 0.200 g of hold-up in the still. NMR analysis indicated that the distilled fraction was 78.7 wt % alcohol (38%), contaminated with water and some ether. Rotation measurements and density measurements were made with this sample dissolved in 95% ethanol. A calibration chart was constructed with the use of standard solutions containing known amounts of the starting alcohol **1** in 95% ethanol. The observed rotations could then be converted to comparable specific rotations.

Samples of **1**-^{18}O obtained via steps ABDE and CDE were purified by GLC (Carbowax 20M) and analyzed by mass spectrometry. The intense CF_3CO^+H ion was used for these measurements.

Registry No.—(+)-**1**, 17628-73-8; (−)-**2**, 58219-97-9; (−)-**3**, 58219-98-0; (−)-**4**, 58219-99-1; *p*-toluenesulfonyl chloride, 95-59-9; sulfuric acid, 7664-93-9.

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HMO Calculation of the First Transition Energy of the Seleninium Cation and Its Benzologs[1]

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The uv spectra of the seleninium cation and its benzologs are very similar to those of their analogues in the thiapyr-

Table I. Regression Lines ($\tilde{\nu} = a\Delta m + b$) for Various Sets of Parameters h_{Se} and k_{C-Se}

h_{Se}	k_{C-Se}	a	b	S_ν, kcm^{-1}
0.9	0.6	27.06	−3.30	0.663
0.9	0.7	24.43	−2.15	0.658
0.9	0.8	22.15	−1.03	0.772
1.0	0.6	28.08	−4.13	0.836
1.0	0.7	25.54	−3.09	0.624
1.0	0.8	23.15	−1.90	0.675
1.1	0.6	28.71	−4.54	1.092
1.1	0.7	26.48	−3.83	0.698
1.1	0.8	24.06	−2.65	0.629
1.1	0.9	21.84	−1.37	0.714
1.2	0.8	24.88	−3.29	0.647
1.2	0.9	22.60	−1.99	0.662

Table II. Wavenumbers of the Longest Wavelength Electronic Bands and HMO Transition Energies (Δm) Based on Optimum Parameters (h_{Se} = 1.0, k_{C-Se} = 0.7)

Compd	$\tilde{\nu}$, kcm^{-1} [a]	Δm (β)
I	33.8	1.439
II	24.2	1.081
III	24.6	1.036
IV	18.2	0.823
V	21.3	0.974
VI	22.4	0.995
VII	22.5	1.033
VIII	21.7	0.962
IX	22.7	1.022

[a] All spectra were measured in H_2SO_4 (96%): I,[2a] 263 nm (log ε 3.92), 296 (3.60); II;[6] III;[7] IV,[8] 253 (3.97), 282 (4.87), 389 (4.44), 517 (3.64), 549 (3.57); V–VIII;[2e] IX.[2c]

ylium series, apart from a bathochromic shift attributable to the change in the heteroatom.[2a-e]

The present paper examines the longest wavelength uv spectrum band (assigned as the first $\pi \rightarrow \pi^*$ transition) of the only nine seleninium salts so far synthesized (Figure 1).

In the case of seleninium itself (I) (C_{2v} point group), this transition is $^1A_1 \rightarrow {}^1B_2^*$, which is allowed in the molecular plane and is perpendicular to the C_2 axis; in that of 9-selenaxanthylium (IV) (same point group), it is $^1A_1 \rightarrow {}^1A_1^*$, which is admitted parallel to the twofold axis. The other seven cations belong to the C_S group, whose first $\pi \rightarrow \pi^*$ transitions are $^1A' \rightarrow {}^1A'^*$; these are permitted in the molecular plane.

An attempt was made to relate the wavenumbers ($\tilde{\nu}$, kcm^{-1}) of these bands for all nine compounds, and the HMO transitions energies from the highest occupied (m) to the first virtual (m + 1) orbital, in accordance with the following formula (I)

$$h\nu = E_{m+1} - E_m$$

where

$$E_j = \alpha_c + \chi_j\beta_{cc}$$

This gives II

$$\tilde{\nu} = \Delta m \frac{\beta_{cc}}{hc}$$

with

$$\chi_{m+1} - \chi_m = \Delta m$$

Equation II represents a straight line with slope β_{cc}/hc and zero intercept.

The least-squares method was therefore used to determine a regression line in the form

$$\tilde{\nu} = a\Delta m + b$$

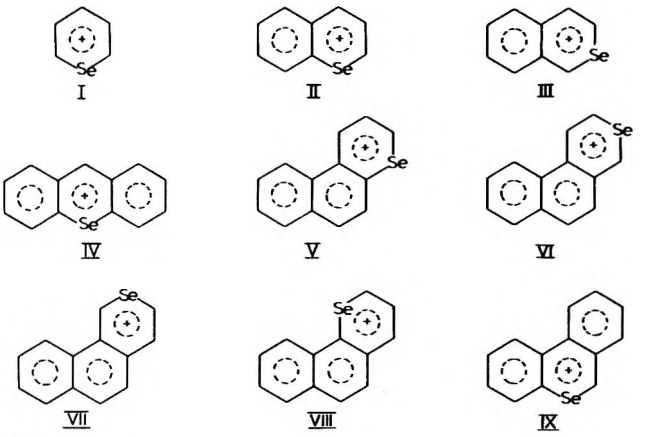

Figure 1.

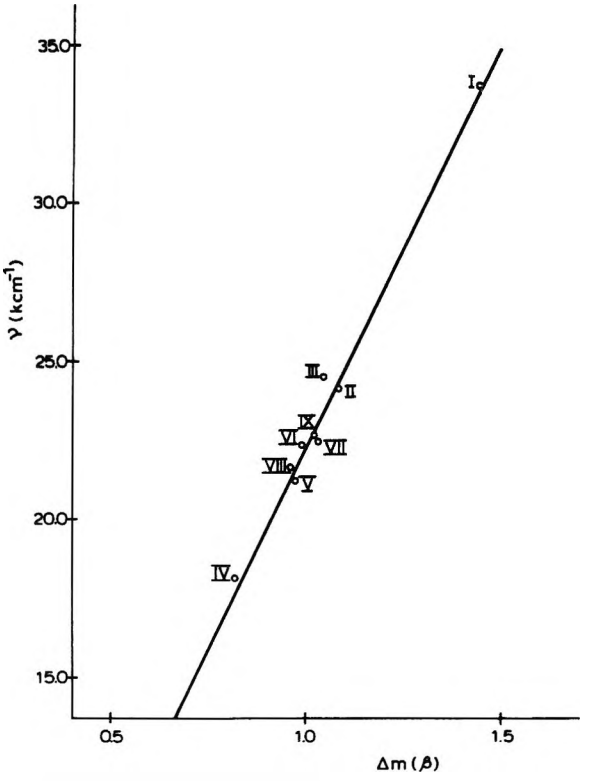

Figure 2. Final regression line of seleninium cations I–IX, correlating the longest wavelength uv spectrum bands with the $m \rightarrow m + 1$ HMO transition energies based on the parameters h_{Se} = 1.0 and k_{C-Se} = 0.7. Correlation coefficient r = 0.991; standard deviation $S_{\tilde{\nu}}$ = 0.624 kcm^{-1}.

For each h_{Se} and k_{C-Se} set, HMO gives a set of transition energies Δm (in β units), corresponding to a straight line with a given standard deviation (S_ν). The best regression line and parameters for the relation could thus be identified. Table I shows the regression line constants and standard deviations for a number of h_{Se} and k_{C-Se} values in the ranges 0.7–1.2 and 0.5–0.9, respectively. The best fit was obtained with h_{Se} = 1.0 and k_{C-Se} = 0.7 (values near those of sulfur[3a,b]), yielding a regression line $\tilde{\nu}$ = 25.5Δm − 3.09, standard deviation S_ν = 0.624, and correlation coefficient r = 0.991 (Figure 2). The data for this fit are shown in Table II.

The failure of this line to pass through the point of origin, often noted in other aromatic and heteroaromatic series,[3a,4a-d] is attributable to the approximative nature of the HMO method.[5]

Our results support assignment of the longest uv band for these cations to the lowest $\pi \rightarrow \pi^*$ transition.

As suggested by Boyd and Singer,[4c] the fact that differ-

ent slope values are observed for different series of compounds indicates that β_{cc} is an empiric quantity, rather than the constant required by eq II. This is yet another result of the many approximations used in the HMO method.

It is debatable whether Hückel's method can be applied to charged systems.[9] Its use here for a class of very similar compounds can, however, be justified by the linear relation between the HMO energies for the $m \rightarrow m + 1$ transition and the SCF–CI energies for the essentially similar transition observed for the thiapyrylium series.[10]

A more elaborate method is now being applied in the investigation of the electronic transitions of these nine cations.

Registry No.—I, 2567-17-1; II, 2567-18-2; III, 10352-19-9; IV, 2749-61-3; V, 53391-12-1; VI, 53391-14-3; VII, 53391-16-5; VIII, 53391-18-7; IX, 3541-46-6.

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Photooxidation of Benzophenone Oxime and Derivatives

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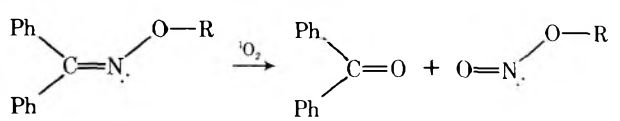
Singlet oxygen, generated by dye photosensitization of ground state triplet oxygen or by chemical reactions, has been shown to undergo a variety of reactions with organic compounds.[2] One of the more interesting of these reactions has been the [2 + 2] cycloaddition of singlet oxygen to electron-rich olefins, giving 1,2-dioxetanes which subsequently cleave to carbonyl products.[2,3] We have found that singlet oxygen reacts with benzophenone oxime and derivatives to give benzophenone and nitrite (Scheme I). To our knowledge, this represents the first report of a reaction of singlet oxygen with a π bond other than a C=C double bond.

Scheme I. Photooxidation of Benzophenone Oxime Derivatives



1a, R = H
b, R = CH_3
c, R = ⌐

Photooxidations were carried out in methanol solution, using rose bengal as sensitizer, keeping the solution saturated with oxygen, and irradiating with a 500-W projector bulb. Appropriate blank experiments indicated that the dye, the oxygen, and the light were all necessary for the photooxidation reaction. Further evidence that these are singlet oxygen reactions was the observation of specific quenching by 1,4-diazabicyclo[2.2.2]octane (Dabco), a singlet oxygen quencher.[4] Photooxidation of benzophenone oxime (**1a**), benzophenone oxime *O*-methyl ether (**1b**), or benzophenone oximate anion (**1c**) yielded benzophenone as the only product observable by gas chromatography. Benzophenone was isolated and characterized from the photooxidation of **1c**. The presence of nitrite ion was also detected in the photooxidations of **1a** and **1c**.

The addition of 2-methyl-2-butene, a singlet oxygen acceptor, decreased the rate of photooxidations. The rate of disappearance of 2-methyl-2-butene was taken to be 1.3×10^6 M^{-1} s^{-1}, using the reported relative reactivity[2] and the reported lifetime of singlet oxygen in methanol.[5] The rate of appearance of benzophenone from **1a**, **1b**, or **1c**, compared to the disappearance of 2-methyl-2-butene, thus allowed the absolute reactivities of the oxime derivatives to be determined (Table I). The order of reactivity is what would be expected for reaction with an electrophilic reagent such as singlet oxygen—reactivity is enhanced by electron donation to the π bond.[2]

Table I. Reaction Rate Constants for Singlet Oxygen Reactions

Substrate	Rate constant, M^{-1} s^{-1}	Substrate	Rate constant, M^{-1} s^{-1}
2-Methyl-2-butene	1.3×10^6	**1a**	7.7×10^4
1c	3.4×10^5	Acetone oxime	$<1 \times 10^4$
1b	2.0×10^5		

While we have obtained no direct evidence for a dioxetane intermediate in this reaction, we consider it highly probable, based upon analogies with similar reactions which involve cleavage of an electron-rich π bond by singlet oxygen.[2]

Experimental Section

Materials. Benzophenone oxime (**1a**) was prepared from benzophenone and hydroxylamine hydrochloride, mp 138–141 °C (lit. 142 °C).[6] Benzophenone oximate anion (**1c**) was prepared from **1a** and sodium in ether solution.[7] Benzophenone oxime *O*-methyl ether (**1b**) was prepared by refluxing **1c** with methyl iodide in ether solution, mp 97.5–100 °C (lit. 102 °C).[8] Acetone oxime was prepared from acetone and hydroxylamine hydrochloride, mp 54–57 °C (lit. 60–61 °C).[9] Dabco was from Eastman and was used as received.

Photooxidation Procedure. The light source was a 500-W quartz–iodine projector bulb (G.E. FBG), contained in a water-jacketed well and also cooled by air. A yellow glass filter was used to eliminate short-wavelength light (OD >2 for λ <390 nm). The sample to be irradiated was contained in a test tube cooled in ice in a clear Dewar flask, and was within several inches of the light source. Oxygen was presaturated with solvent and bubbled slowly into the reaction solution. Oxygen bubbling continued for 5 min before the light was turned on.

A typical reaction solution contained 1×10^{-4} M rose bengal as sensitizer and 0.1 M substrate in methanol solvent. Aliquots were removed at intervals and analyzed by GC, using a Hewlett-Packard Model 700 with a 6 ft × 0.125 in. column packed with 10% UC-W98. Benzophenone was the only product detectable as the photooxidation proceeded. By temperature programming, the disappearance of the oxime (**1a**) or the *O*-methyl ether (**1b**) could also be observed.

Detection of nitrite ion from the photooxidations of **1a** and **1c** was accomplished by testing with acidic ferrous sulfate;[10] a dark green-brown color indicated the presence of nitrite, even in the presence of the dye. A blank solution including all components of the reaction before irradiation gave no color change. Nitrate ion gave no color change.

Benzophenone was isolated after 7 h of photooxidation of **1c** by evaporating the solvent, washing with water to remove the dye, and recrystallizing the residue, yield 60%, mp 48–49.5 °C. It was identified by GC and mixture melting point comparison with an authentic sample.

Relative reactivities were obtained by inclusion of 0.1 M 2-methyl-2-butene (competitive singlet oxygen acceptor) and 0.1 M cyclohexane (internal standard) in the reaction solution. The appearance rate of the benzophenone and the disappearance rate of the 2-methyl-2-butene were monitored up to 50% conversion, during which time both were linear (zero order). The ratio of the slopes was taken to be the ratio of their absolute rate constants with singlet oxygen. Appropriate blank reactions were run: with oxygen bubbling and no irradiation, with irradiation and nitrogen bubbling, and with irradiation and oxygen bubbling but no dye. These blanks amounted to less than 10% of the photooxidation reaction and were simply subtracted from the reaction rates.

Quenching by Dabco was demonstrated by running two parallel photooxidations, containing 0.1 M **1c**, 0.1 M 2-methyl-2-butene, and 1×10^{-4} M rose bengal in methanol. One solution contained 1×10^{-3} M Dabco. After 3 h of irradiation, the solution with Dabco showed no detectable reaction, while in the other solution both **1c** and 2-methyl-2-butene showed substantial reaction.

Acknowledgments. We are pleased to acknowledge the donors of the Petroleum Research Fund, administered by the American Chemical Society, and the Research Corporation for generous financial support of this work.

Registry No.—**1a**, 574-66-3; **1b**, 3376-34-9; **1c**, 58074-11-6; 2-methyl-2-butene, 513-35-9; acetone oxime, 127-06-0.

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A Chromium(II)-Promoted Heterolytic Fragmentation Reaction. Application to the Synthesis of 1,5-Dienes[1]

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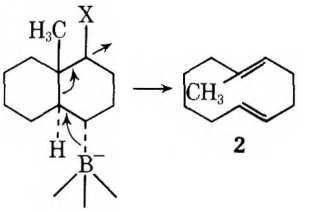
Interest in the stereoselective synthesis of 1,5-dienes has increased markedly in the last decade, as attested by the variety of methods[2] that have been developed for obtaining this class of compounds. Among the important natural products that possess two (or more) double bonds in a 1,5 relationship are a number of medium-ring sesquiterpenes[3] possessing the 1,5-cyclodecadiene skeleton as well as several important acyclic compounds such as squalene, farnesol, and the juvenile hormone of *Hyalophora cecropia*.[4]

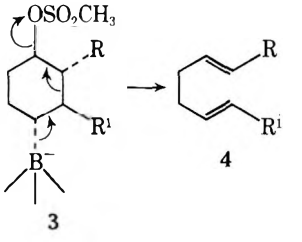
One of the more promising approaches to such systems involves the base-promoted heterolytic fragmentation[5] of appropriately substituted decalinboronate derivatives (e.g., **1** in eq 1) for the stereospecific synthesis[3] of 1,5-cyclodecadienes (**2**). Fragmentation of the corresponding cyclohexaneboronate (**3**) has been shown[6] likewise to yield in a stereospecific manner an acyclic 1,5-diene (**4**) (eq 2).



(1)

1

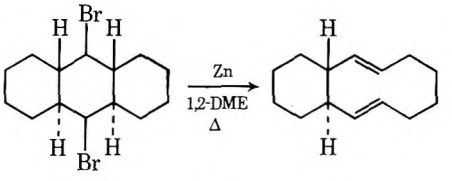
X = OSO_2CH_3, Br, etc.



(2)

3 **4**

The report[7] of a zinc-initiated fragmentation reaction of a cyclic 1,4-dibromide (**5**) (eq 3), together with studies of Kochi and Singleton[8] involving the reaction of ethylenediaminechromium(II)[9] with 1,2- and 1,3-dibromides (**6** and **7**, respectively) (eq 4), suggests that chromium(II) should also initiate fragmentation of an alicyclic bromide possessing a suitable nucleofugal group at the γ carbon.



(3)

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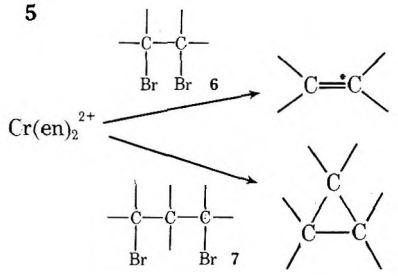
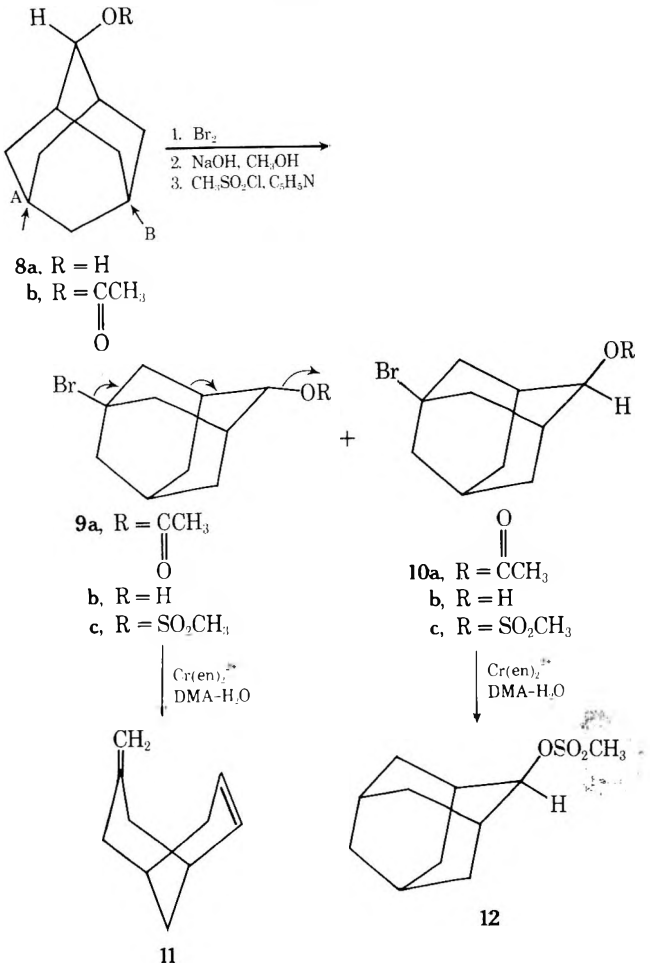


(4)

If successful, the use of chromium(II) may be advantageous over that of zinc since fragmentation reactions involving the latter are generally run at elevated temperature, conditions under which a Cope rearrangement of the 1,5-diene products can occur.[10]

The system selected for testing the feasibility of a Cr(II)-promoted fragmentation reaction directed toward the synthesis of 1,5-dienes was bromomesylate **9c**. The preparation of this substrate from the commercially available[11] 2-adamantanol (**8a**) is outlined in Scheme I. Acetylation of alcohol **8a** using acetic anhydride–pyridine afforded the corresponding acetate (**8b**)[12] in 94% yield. Ionic bromination of the latter (**8b**) afforded an undetermined mixture[13]

Scheme I



of bromoacetate epimers (**9a** and **10a**) in modest yield. Subsequent saponification followed by conversion of the alcohol product (**9b** and **10b**) to the corresponding mesylates (**9c** and **10c**) proceeded smoothly.

Treatment of this mixture of bromomesylates (**9c** and **10c**) with ethylenediaminechromium(II) in aqueous dimethylacetamide at room temperature for 1.5 h afforded the anticipated fragmentation product, 7-methylenebicyclo[3.3.1]non-2-ene (**11**), in 40% yield. The structure of the latter was verified by both elemental analysis as well as comparison of its ir and NMR spectral data with those previously reported[14] for this same diene. The other product on the basis of elemental analysis and its ir and NMR spectra was assigned structure **12**, and is presumed to have been formed by simple reduction of cis bromomesylate **10c**, which lacks the antiperiplanar relationship of the participant bonds required for a concerted fragmentation. Only in the trans isomer (**9c**) can the stereoelectronic requirement for concerted reaction be met.

Experimental Section[15]

2-Adamantanol Acetate (8b). A solution of 25.0 g of 2-adamantanol[11] (**8a**) in 250 ml of 1:1 acetic anhydride–pyridine was stirred overnight at room temperature. The mixture was subsequently poured onto 250 g of ice and acidified with concentrated hydrochloric acid. Extraction with ether afforded 30 g (94%) of acetate **8b**[12] as an oil: λ_{max} (film) 1735 (C=O), 1451, 1370, 1362, 1252, 1211, 1100 cm^{-1}; δ_{Me_4Si} ($CDCl_3$) 4.93 (m, CHOAc), 2.06 ppm [s, OC(=O)CH_3].

1-Bromo-4-adamantanol Acetate (9a and 10a). A solution of 25.0 g (129 mmol) of 2-adamantanol acetate (**8b**) in 100 ml of bromine was stirred at room temperature for 16 h, after which the reaction was quenched by pouring this mixture onto 500 g of ice and adding solid sodium bisulfite (and ice, to maintain the temperature below 25 °C) to destroy the excess bromine. Extraction of the product with ether followed by dissolution of the oily residue in 25 ml of pentane and chilling this mixture afforded 7.0 g (20%) of crystalline acetate mixture **9a** and **10a**: mp 75–79 °C; λ_{max} (KBr) 1741, 1378, 1364, 1350, 1041 cm^{-1}; δ_{Me_4Si} ($CDCl_3$) 4.88 (multiplet, CHOAc), 2.10 ppm [s, OC(=O)CH_3]. Anal. Calcd for $C_{12}H_{17}O_2Br$: C, 52.76; H, 6.27; Br, 29.25. Found: C, 52.40; H, 6.33; Br, 29.25.

1-Bromo-4-adamantanol (9b and 10b). A solution of 7.0 g of acetate mixture **9a** and **10a** in 75 ml of methanol containing 1 ml of 50% aqueous sodium hydroxide was stirred for 2 h at room temperature. The product was isolated by pouring this mixture onto 200 g of ice, followed by acidification with concentrated aqueous HCl and dilution to 500 ml by addition of water. The yield of crystalline alcohol mixture **9b** and **10b** was 5.6 g (95%): mp 130–140 °C; λ_{max} (KBr) 3270 (OH), 1051, 1011 cm^{-1}; δ_{Me_4Si} ($CDCl_3$) 3.85 (m, CHOH), 2.83 (m, 1 H), 2.03 ppm (m, 1 H). Anal. Calcd for $C_{10}H_{15}OBr$: C, 51.96; H, 6.54; Br, 34.57. Found: C, 52.34; H, 6.50; Br, 34.81.

1-Bromo-4-adamantanyl Methanesulfonate (9c and 10c). Methanesulfonyl chloride (10 ml) was added dropwise to a stirred solution of 5.6 g (24.2 mmol) of alcohol mixture **9b** and **10b** in 40 ml of dry pyridine. After this mixture was stirred at room temperature for 18 h, it was poured onto 200 g of ice and acidified with concentrated hydrochloric acid. Extraction with dichloromethane, followed by recrystallization from pentane, afforded 5.7 g (76%) of mesylate (**9c** and **10c**): mp 116–120 °C; λ_{max} (KBr) 1332, 1172, 915 cm^{-1}; δ_{Me_4Si} ($CDCl_3$) 4.82 (m, $CHOSO_2CH_3$), 3.05 ppm (s, CH_3SO_3). Anal. Calcd for $C_{11}H_{17}O_3BrS$: C, 42.72; H, 5.54; Br, 25.84; S, 10.37. Found: C, 42.79; H, 5.44; Br, 25.85; S, 10.75.

7-Methylenebicyclo[3.3.1]non-2-ene (11). Chromous chloride was prepared under a nitrogen atmosphere by mixing 10 g of granular zinc with a solution of 26.6 g of chromic chloride hexahydrate in 25 ml of deoxygenated water. After addition of 15 ml of concentrated hydrochloric acid to this system, as soon as the solution became light blue it was rapidly transferred to an addition funnel, into which was subsequently added 26 ml of deoxygenated ethylenediamine. This mixture was then added rapidly to a stirred solution of 5.5 g (17.8 mmol) of bromomesylate (**9c** and **10c**) in 200 ml of dimethylacetamide. The solution was stirred for 1.5 h at room temperature after which it was poured into 1600 ml of cold water. Extraction with ether, followed by removal of the solvent via distillation through a Vigreux column at atmospheric pressure, dissolution of the oily residue in hot pentane, and chilling of the latter solution, afforded 21% yield of mesylate **12**: mp 63–65 °C; λ_{max} (KBr) 1342, 1179, 990, 966, 930, 909 cm^{-1}; δ_{Me_4Si} ($CDCl_3$) 4.90 (m, CHOMs), 3.00 ppm (s, CH_3SO_3). Anal. Calcd for $C_{11}H_{18}O_3S$: C, 57.36; H, 7.88. Found: C, 57.08; H, 7.73. Diene **11** was recovered from the filtrate by placing it on a column of silica gel (100 ml) and elution with pentane. Removal of the pentane by distillation afforded 0.95 g (40%) of **11**: λ_{max} (film) 1649, 1431, 880, 730 cm^{-1}; δ_{Me_4Si} ($CDCl_3$) 5.67 (s, 2 H, CH=CH), 4.75 (s, 1 vinyl H), 4.57 ppm (s, 1 vinyl H). Anal. Calcd for $C_{10}H_{14}$: C, 89.49; H, 10.51. Found: C, 89.25; H, 10.60.

Acknowledgment. The authors wish to thank Searle Laboratories, a division of G. D. Searle & Co., for their support of this work. In particular, the service rendered by their Analytical Resources and Methods Department is gratefully acknowledged.

Registry No.—**8a**, 700-57-2; **8b**, 19066-22-9; **9a**, 58241-07-9; **9b**, 58241-08-0; **9c**, 58241-09-1; **10a**, 58267-56-4; **10b**, 58267-57-5; **10c**, 58267-58-6; **11**, 37439-70-6; **12**, 31616-68-9; bromine, 7726-95-6; methanesulfonyl chloride, 124-63-0.

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(2) For examples of recent methods used to synthesize 1,5-dienes, see Y. Kitagawa, K. Oshima, H. Yamamoto, and H. Nozaki, *Tetrahedron Lett.*, 1859 (1975); R. C. Cookson and N. W. Hughes, *J. Chem. Soc., Perkin Trans. 1*, 2738 (1973); J. A. Katzenellenbogen and R. S. Lenox, *Tetrahedron Lett.*, 1471 (1972); J. A. Marshall, *Synthesis*, 229 (1971); J. A. Marshall and J. H. Babler, *Tetrahedron Lett.*, 3861 (1970); E. H. Axelrod, G. M. Milne, and E. E. van Tamelen, *J. Am. Chem. Soc.*, **92**, 2139 (1970); J. F. Biellmann and J. B. Ducep, *Tetrahedron Lett.*, 3707 (1969); G. Stork, P. A. Grieco, and M. Gregson, *ibid.*, 1393 (1969); K. B. Sharpless, R. P. Hanzlik, and E. E. van Tamelen, *J. Am. Chem. Soc.*, **90**, 209 (1968); E. E. van Tamelen and M. A. Schwartz, *ibid.*, **87**, 3277 (1965).
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(8) J. K. Kochi and D. M. Singleton, *J. Org. Chem.*, **33**, 1027 (1968).
(9) For a review of the applications of chromium(II) salts in preparative organic chemistry, see J. R. Hanson, *Synthesis*, 1 (1974).
(10) C. A. Grob, H. Link, and P. W. Schiess, *Helv. Chim. Acta*, **46**, 483 (1963).
(11) Aldrich Chemical Co., Inc., Milwaukee, Wis.
(12) A. C. Udding, J. Strating, and H. Wynberg, *Tetrahedron Lett.*, 1345 (1968).
(13) Bromination of acetate **8b** is anticipated to be most favorable at the two bridgehead positions labeled A and B in structure **8** shown in Scheme I. Ionic attack of bromine at site A yields the trans isomer **9a**, whereas attack at site B affords the corresponding cis bromoacetate (**10a**). Since the two stereoisomers failed to separate on silica gel TLC and attempts to separate the mixture via fractional crystallization were unsuccessful at this stage as well as after subsequent reactions, no further attempt was made to determine the stereochemistry of the reaction products.
(14) J. H. Liu, G. A. Gauger, and P. Kovacic, *J. Org. Chem.*, **38**, 543 (1973).
(15) Reactions were carried out under a nitrogen atmosphere. The isolation of reaction products was accomplished by extracting the aqueous layer thoroughly with the specified solvent. Anhydrous sodium sulfate was used to dry the combined extracts, and the solvent was removed on a rotary evaporator under reduced pressure. Melting points were determined on a Fisher-Johns block and are corrected. The NMR spectra were recorded with a Varian A-60 NMR spectrometer and infrared spectra were obtained using a Beckman IR-12 spectrophotometer. Elemental analyses were performed by the Analytical Resources and Methods Department, Searle Laboratories, G. D. Searle & Co.

Oxidation of Trimethylsilyl Ethers via Hydride Abstraction. A New Method for Alcohol Oxidation

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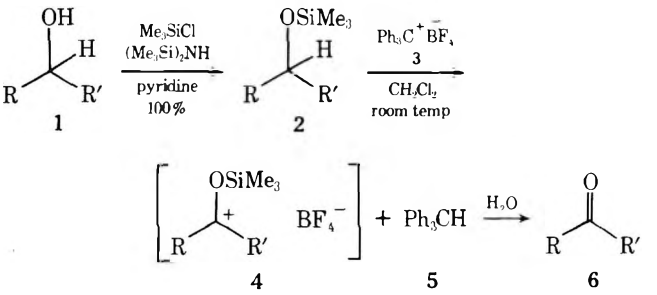
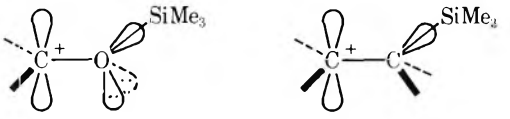
I wish to report a new method for the oxidation of alcohols to ketones and aldehydes under extremely mild conditions in nearly quantitative yields. The key step of this two-step procedure involves the treatment of the trimethylsilyl ethers **2** of the alcohols **1** with a triphenylcarbenium (trityl) salt **3** in methylene chloride at room temperature. The carbonyl compounds **6** are produced cleanly and can be easily isolated from the by-product, triphenylmethane (**5**), by simple distillation or chromatography. A variety of alcohols have been subjected to this new oxidation technique, the products and yields of which are listed in Table I.

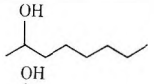
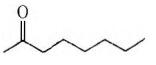
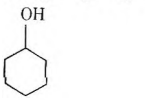
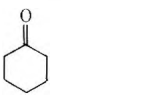
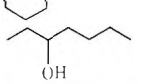
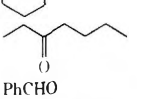
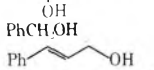
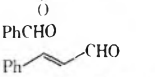
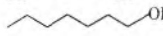


The oxidation of alkyl ethers to carbonyl compounds by trityl salts has been observed previously[1] but only recently has this become a useful synthetic method. Barton has used this technique in the oxidation of ketone acetals and in the deprotection of steroidal benzyl ethers and carbonates.[2] Doyle has also employed this oxidation in the disproportionation of trityl alkyl ethers by a cationic chain reaction process.[3] The trimethylsilyl ethers were chosen for the present study for several reasons. First, they could be quickly and easily prepared in quantitative yields. Secondly, the amount of simple complexation of the trityl salt and the ether oxygen could be lessened because of steric hindrance between the very bulky trimethylsilyl group and the trityl cation. Finally, it was anticipated that the trimethylsilyl group could provide additional stabilization to the carbonium ion β to it by a mechanism of vertical stabilization such as in **7**. This is completely analogous to the all-carbon case, **8**, which has been shown to offer a great deal



of stabilization.[4] For example, the Hammett electrophilic para-substitution constant, σ_p^+, for the trimethylsilylmethyl group (Me_3SiCH_2) is -0.66.[4] This very closely approximates the value for the methoxyl group (MeO), $\sigma_p^+ = -0.74$,[4] implying in a general sense that a trimethylsilyl group β to a carbonium ion stabilizes that ion to about the same extent as a methoxyl group α to it. Therefore it was anticipated that the stability of the carbonium ion, e.g., **4**, could be enhanced by changing the group attached to oxygen from alkyl to trimethylsilyl. In agreement with this expectation the silyl ether **9** is oxidized somewhat faster than the *tert*-butyl ether **10** under identical conditions, although **10** also gives cyclohexanone in reasonable yield. However, this result is not conclusive because the difference in rates may be due to other effects, e.g., steric effects, since the

Table I. Oxidation of Trimethylsilyl Ethers with $Ph_3C^+BF_4^-$[a]

Starting alcohol	Registry no.	Product[b]	Registry no.	% yield[c]
	123-96-6		111-13-7	95
	108-93-0		108-94-1	99 (92)
	589-82-2		106-35-4	98
	100-51-6		100-52-7	100
	104-54-1		104-55-2	100
	111-70-6		111-71-7	38

[a] All reactions were conducted in CH_2Cl_2 at 25 °C under a nitrogen atmosphere. [b] The products were identified by comparison (GC, NMR, ir) with authentic samples. [c] The yields were determined by gas chromatographic analysis through reference to an internal standard, normally mesitylene. The numbers in parentheses are isolated yields. The yields of triphenylmethane are all 100%.

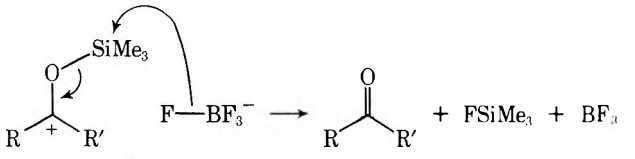
9 10

tert-butyl group is somewhat bulkier than the trimethylsilyl group.

The crude trimethylsilyl ether **2**, produced from the alcohol **1** by silylation in a few minutes at room temperature, is generally >95% pure and can be used directly in the oxidation step without further purification.

In all of the reported reactions trityl tetrafluoroborate (**3**) was employed as the hydride abstractor.[5] It is commercially available,[6] although it can be easily prepared in two steps from benzene and carbon tetrachloride by the method of Dauben.[7] The progress of the oxidation can be easily monitored by GC or NMR. Reaction times range from 1 min for the cinnamyl ether to 4 days for the 2-octyl ether. Thus far the reaction is not very useful for saturated aldehydes. The rate of oxidation is very slow and the aldehyde begins to decompose before the reaction is completed. All of these oxidations can be speeded up by using refluxing dichloroethane as solvent, but this causes some decomposition of the carbonyl products.[8]

Analysis of the crude reaction mixtures by NMR indicates the presence of the carbonyl compound before addition of water. This implies that the cation **4** probably decomposes by attack of a fluoride ion from BF_4^- to give the carbonyl compound and Me_3SiF directly. To support this



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hypothesis, when the reaction mixture is heated, one can detect the evolution of an acidic gas, probably BF_3 or Me_3SiF. It is postulated that hydride abstraction is a discrete step that precedes fluoride transfer to silicon. The alternative of a concerted pathway involving concomitant hydride abstraction and fluoride transfer is unlikely for entropy reasons, since it would require the correct alignment of three distinct species in the transition state, namely, the trityl cation, the silyl ether, and the tetrafluoroborate anion.

Since the ethers of primary alcohols oxidize slower than those of secondary alcohols (stability of a secondary vs. a tertiary carbonium ion), we are now pursuing the use of this procedure in oxidizing a primary, secondary diol to the primary hydroxy ketone. In addition, the oxidations of silylated amines to carbonyl compounds[9] and of silyl enol ethers to enones,[10] as well as other oxidations, are currently being investigated.

Experimental Section

The following is a typical experimental procedure.

Cyclohexanone. Cyclohexanol was converted into its trimethylsilyl ether **9** by stirring for a few hours at room temperature with a silylating solution consisting of pyridine, hexamethyldisilazane, and trimethylchlorosilane in the ratio of 10:2:1. A solution of the crude ether **9** (1.72 g, 10 mmol) and Ph_3CBF_4 (**3**, 4.95 g, 15 mmol) in 200 ml of CH_2Cl_2 was allowed to stir at room temperature under nitrogen. After 9 h, GC analysis of an aliquot showed completion of reaction. Addition of water, extraction, and distillation afforded 901 mg of cyclohexanone (92% yield).

Acknowledgment. The author wishes to acknowledge the donors of the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this research.

Registry No.—**2** (R = CH_3; R′ = C_6H_{13}), 18023-52-4; **2** (R = C_2H_5; R′ = C_4H_9), 18132-91-7; **2** (R = H; R′ = C_6H_5), 14642-79-6; **2** (R = H; R′ = PhCH=CH), 18042-41-8; 2 (R = H; R′ = C_6H_{13}), 18132-93-9; **3**, 341-02-6; **9**, 13871-89-1; Me_3SiCl, 75-77-4; $(Me_3Si)_2NH$, 999-97-3.

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(1) (a) J. F. Norris, "Organic Syntheses", Collect Vol. I Wiley, New York, N.Y., 1932, p 548; (b) P. D. Bartlett and J. D. McCollum, *J. Am. Chem. Soc.*, **78**, 1441 (1956); (c) N. C. Deno, G. Saines, and M. Spangler, *ibid.*, **84**, 3295 (1962).
(2) D. H. R. Barton, P. D. Magnus, G. Smith, G. Streckert, and D. Zurr, *J. Chem. Soc., Perkin Trans. 1*, 542 (1972).
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(4) W. Hanstein, H. J. Berwin, and T. G. Traylor, *J. Am. Chem. Soc.*, **92**, 829, 7476 (1970).
(5) Trityl salts with different counterions, e.g., PF_6^-, SbF_6^-, were also employed, as well as other hydride abstracting reagents. A comparison of the reactivities will be described elsewhere.
(6) Commercial samples from both the Aldrich Chemical Co. and Cationics, Inc. were used successfully.
(7) H. J. Dauben, L. R. Honnen, and K. M. Harmon, *J. Org. Chem.*, **25**, 1442 (1960).
(8) Solid Na_2CO_3 was added in an attempt to trap any acidic products which might be causing decomposition (e.g., BF_3), but without significant effects. Acetonitrile was also employed but the oxidation was very slow in this solvent.
(9) M. E. Jung and G. S. Tennyson, unpublished results.
(10) M. E. Jung and Y.-G. Pan, unpublished results.

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trans-β-Trimethylsilylvinyllithium

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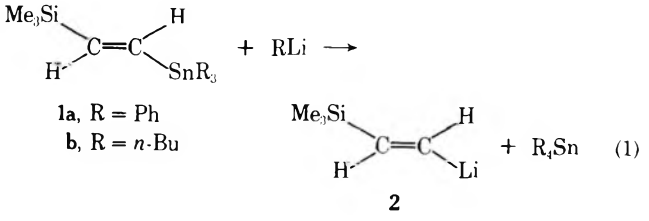
In connection with other investigations we required a synthetically useful preparation of *trans*-β-trimethylsilylvinyllithium (**2**). This reagent was unavailable at the time this work was begun, but has since been prepared by the reaction of *trans*-β-bromovinyltrimethylsilane with either lithium metal[1] or *tert*-butyllithium.[2] Synthetically useful yields of the reagent are realized by only the latter of these two methods. Our approach, different from either of these, but also affording excellent yields of **2**, is presented here.

The preparation of **2** involved the transmetalation reaction between organolithium reagents and vinyltin substrates developed by Seyferth and co-workers.[3] Thus, treatment of either *trans*-1-trimethylsilyl-2-triphenylstannylethylene (**1a**) or *trans*-1-trimethylsilyl-2-tri-*n*-butylstannylethylene (**1b**) with respectively phenyllithium or *n*-butyllithium led to high yields of **2**, as determined by subsequent derivatization (eq 1).

Although the transmetalation of **1a** with phenyllithium could be effected at 25 °C to afford, after trimethylchlorosilane derivatization, 84% of *trans*-1,2-bis(trimethylsilyl)ethylene (**3**), the reaction of **1b** with *n*-butyllithium gave better results at low temperature. Thus, **3** was obtained in only 53% yield from the transmetalation of **1b** at 25 °C, but 90% of **3** was afforded when transmetalation was effected at −70 °C.[4] The reaction of **2** with a variety of other electrophiles was examined in order to assess its utility in this regard. As shown in eq 1, *trans*-1-bromo-2-trimethylsilylethylene (**4**), *trans*-1-trimethylsilyl-1-hexene (**5**), and *trans*-3-trimethylsilylpropenoic acid (**6**) were all obtained in excellent yield. NMR and VPC analysis of these products indicated the absence of detectable amounts of corresponding cis isomers.

Of particular interest was the observation that the present procedure led to preparatively useful conversions

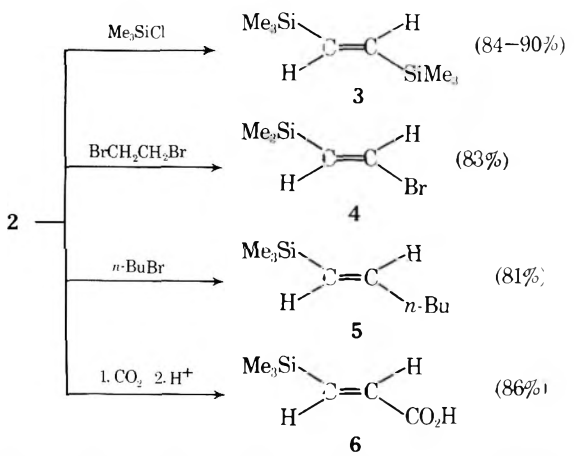
of **2** into **6**, as the approach to **6** via carbonation of *trans*-β-trimethylsilylvinylmagnesium bromide (**7**) affords only a moderate yield (46%) of acid.[5] The efficient coupling of **2**



1a, R = Ph
b, R = *n*-Bu

+ R_4Sn (1)

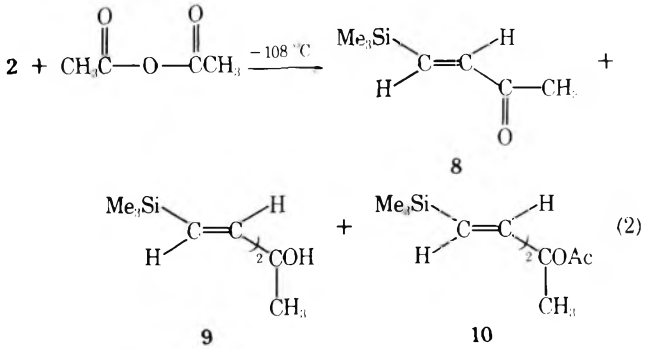
2



3 (84–90%)
4 (83%)
5 (81%)
6 (86%)

with *n*-butyl bromide is also worthy of note, as this reaction is representative of a new mode of entry to the 1-trimethylsilyl-1-alkene series, compounds which have potential for considerable synthetic utility.[6,7]

In an attempt to improve the yield (66%) of *trans*-4-trimethylsilyl-3-buten-2-one (**8**) reported from the low-temperature reaction of **7** with acetic anhydride,[8] the parallel reaction of **2** was examined (eq 2). However, these conditions led to the formation of **8** in only 30% yield accompanied by significant amounts of *trans,trans*-1,5-bis(trimethylsilyl)-3-methyl-1,4-pentadien-3-ol (**9**) and *trans,trans*-1,5-bis(trimethysilyl)-3-methyl-3-acetoxy-1,4-pentadiene (**10**).



8

(2)

9 **10**

Experimental Section

The normalities of solutions of *n*-butyllithium in hexane and phenyllithium in ether were determined by the double titration method using 1,2-dibromoethane.[9] Ether and tetrahydrofuran used as solvents were distilled from $LiAlH_4$. All experiments were carried out under a nitrogen atmosphere. NMR spectra (solvent, internal standard) were obtained with either Varian A-60A or JEOL PFT-100 spectrometers (chemical shift values are assigned from the center of a multiplet); infrared spectra (neat) were obtained with a Beckman IR-8 spectrophotometer. Elemental analyses were performed by Mr. J. Darby, Faraday Microanalytical Laboratory, Northern Illinois University, or Spang Laboratories, Ann Arbor, Mich.

Transmetalation of *trans*-1-Trimethylsilyl-2-triphenylstannylethylene (1a). A solution of 4.16 g (9.26 mmol) of **1a**[10] and 0.368 g of *o*-xylene (internal standard) in 20 ml of ether was treated with 11.7 ml (9.36 mmol) of 0.80 N phenyllithium in ether. A precipitate of tetraphenyltin appeared immediately. After 40 min at 25 °C, a 1-ml aliquot was withdrawn by syringe and injected into 4 ml of 1,2-dibromoethane. Chlorotrimethylsilane (3.0 ml, 23 mmol) was added to the remaining mixture and work-up carried out after overnight stirring. VPC analysis of the aliquot portion showed it to contain 1.37 g (83%) of **4** and 0.14 g (94%) bromobenzene. No *cis*-1-bromo-2-trimethylsilylethylene was present as determined by retention time check with an authentic sample.[11] Following $NaHCO_3$ hydrolysis, the solid was removed from the Me_3Si-Cl-derivatized mixture by filtration and sublimed to give 3.72 g (94%) of tetraphenyltin, mp 223–225 °C (lit.[12] mp 224–225 °C). Examination of the filtrate by VPC indicated the presence of 1.34 g (84%) **3** and 0.17 g (13%) of phenyltrimethylsilane. No *cis*-1,2-bis(trimethylsilyl)ethylene was detectable upon retention time check with an authentic sample.[13]

***trans*-1-Trimethylsilyl-2-tri-*n*-butylstannylethylene (1b).** A mixture of 58.3 g (0.20 mol) of tri-*n*-butyltin hydride and 24.5 g (0.25 mol) of ethynyltrimethylsilane[10] was heated to 100 °C for 83 h, affording 76.5 g (98%) of **1b**: bp 96–102 °C (0.5 mm); ir 6.50 μ (C=C); NMR ($CDCl_3$, CH_2Cl_2) δ 0.12 (9 H, s), 0.95 (9 H, t, J = 7 Hz), 1.41 (18 H, m), 6.65 and 7.08 (2 H, AB pattern, J = 23 Hz).

Anal. Calcd for $C_{17}H_{38}SiSn$: C, 52.45; H, 9.84. Found: C, 52.24; H, 9.57.

Transmetalation of *trans*-1-Trimethylsilyl-2-tri-*n*-butylstannylethylene (1b). The general procedure involved the addition of 1.50 N *n*-butyllithium to a precooled (−70 to −75 °C) solution of **1b** in THF or 1:1 THF–ether. After 1 h at this temperature, the mixture was allowed to warm to −30 °C over 30–40 min and then recooled to −75 °C prior to derivatization.

A. Chlorotrimethylsilane Derivatization. A solution of **2** prepared from 5.93 g (0.0154 mol) of **1b** and 0.0154 mol of *n*-butyllithium in 50 ml of THF–ether was treated with 1.89 g (0.017 mol) of chlorotrimethylsilane to afford 2.39 g (90%) of **3** and 0.037 g (2%) of *n*-butyltrimethylsilane, as determined by VPC (nonane internal standard).

B. Ethylene Bromide Derivatization. A 7-ml aliquot was removed from the solution of **2** generated in part A at −75 °C and added to 4.5 g (0.024 mol) of ethylene bromide in 10 ml of ether at −75 °C. VPC analysis indicated an 83% yield of **4** and 1% of *n*-butyl bromide.

C. Carbon Dioxide Derivatization. To a cooled (−110 °C) solution of **2** prepared from 14.4 g (0.0370 mol) of **1b** in 100 ml of THF and 1.1 equiv of *n*-butyllithium was added ca. 150 ml of pulverized dry ice which had been precooled to −100 °C. The reaction mixture was mechanically stirred at −110 °C for 0.5 h and then allowed to warm to 25 °C overnight. After extraction with aqueous NaOH, the organic phase afforded 12.4 g (97%) of tetrabutyltin, bp 84–87 °C (0.2 mm) [lit.[14] bp 94–96 °C (0.28 mm)] containing less than 1% unreacted **1b**, as determined by VPC. After acidification, the NaOH extracts yielded 4.90 g of material, bp 68–74 °C (0.5 mm), which NMR indicated contained 7% of *n*-pentanoic acid [86% yield of **6**; ir 3.4 s, 5.88 s, 6.17 w, 6.25 w, 7.08 s, 7.69 s, 7.97 s, 8.35 m, 10.00 m, 10.63 m, 10.87 m, 11.63 s, 11.90 s, 12.82 w, 13.16 w, 13.70 w, 14.37 μ; NMR (CCl_4, CH_2Cl_2) δ 0.28 (9 H, s), 6.33 and 7.49 (2 H, AB pattern, J = 18.5 Hz), 12.51 (1 H, s)].

No *cis*-3-trimethylsilylpropenoic acid could be detected by NMR analysis of a concentrated sample.

D. *n*-Butyl Bromide Derivatization. Addition of *n*-butyl bromide to a solution of **2** in THF gave an 86% yield of **5**, determined by using *n*-decane as internal VPC standard. In a larger scale reaction, 6.6 g (0.048 mol) of *n*-butyl bromide precooled to −50 °C was added to a solution of **2** prepared from 13.2 g (0.034 mol) of **1b** in 90 ml of THF and 1.1 equiv of *n*-butyllithium. This afforded 4.20 g (81%) of **5**, bp 94–97 °C (110 mm).

E. Acetic Anhydride Derivatization. A precooled (−90 °C) solution of 3.24 g (0.032 mol) of acetic anhydride in 10 ml of ether was added at −108 °C to a solution of **2** prepared from 6.13 g (0.0158 mol) of **1b** in 60 ml of THF and 1.1 equiv of *n*-butyllithium. After standing at 25 °C overnight, work-up afforded 0.66 g (30%) of **8**, 0.42 g (23%) of *trans,trans*-1-5-bis(trimethylsilyl)-3-methyl-1,4-pentadien-3-ol (**9**), and 0.29 g (14%) of *trans,trans*-1,5-bis(trimethylsilyl)-3-acetoxy-3-methyl-1,4-pentadiene (**10**), as determined by a combination of distillation and VPC analysis. Alcohol **9**, mp 47–49 °C, showed (melt) principal ir bands at 2.92 m, 3.36 s, 6.24 m, 8.04 s, 10.12 s, 11.85 vs, 13.52 m, 13.76 m, and 14.52 m μ; NMR ($CDCl_3$, CH_2Cl_2) δ 0.13 (18 H, s), 1.39 (3 H, s), 1.68 (1 H, broad s), 5.86 and 6.16 (4 H, AB pattern, J = 19 Hz).

Anal. Calcd for $C_{12}H_{26}OSi_2$: C, 59.43; H, 10.81. Found: C, 59.69; H, 10.94.

Ester **10** showed principal ir bands at 3.36 s, 5.78 s, 6.23 w, 7.32 m, 8.06 s, 8.50 m, 9.44 m, 10.15 m, 11.56 s, 11.98 s, 13.56 m, 13.75 m, and 14.50 μ m; NMR ($CDCl_3$) δ 0.06 (18 H, s) 1.56 (3 H, s), 2.02 (3 H, s), 5.73 and 6.12 (4 H, AB pattern, J = 19 Hz).

Anal. Calcd for $C_{14}H_{28}O_2Si_2$: C, 59.10; H, 9.92. Found: C, 58.86; H, 9.81.

Registry No.—**1a**, 17146-54-2; **1b**, 58207-97-9; **2**, 55339-31-6; **3**, 18178-60-4; **4**, 41309-43-7; **5**, 54731-58-7; **6**, 58207-98-0; **8**, 49750-09-6; **9**, 58207-99-1; **10**, 58208-00-7; phenyllithium, 591-51-5; chlorotrimethylsilane, 75-77-4; bromobenzene, 108-86-1; tetraphenyltin, 595-90-4; phenyltrimethylsilane, 768-32-1; tri-*n*-butyltin hydride, 688-73-3; ethynyltrimethylsilane, 1066-54-2; *n*-butyllithium, 109-72-8; *n*-butyltrimethylsilane, 1000-49-3; ethylene bromide, 106-93-4; *n*-butyl bromide, 109-65-9; carbon dioxide, 124-38-9; tetrabutyltin, 1461-25-2; *n*-pentanoic acid, 109-52-4; acetic anhydride, 108-24-7.

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A Novel Synthesis of Pyrrolo[1,2-*c*]pyrimidine-3-carboxylic Acid Esters[1]

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Pyrrolo[1,2-*c*]pyrimidine compounds are pharmaceutically interesting compounds[2] and several synthetic methods of the compounds have been reported.[3]

In the course of our studies on the reaction of isocyano compounds with various electrophiles,[4] we wish now to report the reaction of methyl isocyanoacetate (**1**) with pyrrole-2-carboxaldehydes (**2**) to afford pyrrolo[1,2-c]pyrimidine-3-carboxylic acid esters (**4**) as shown in Scheme I.

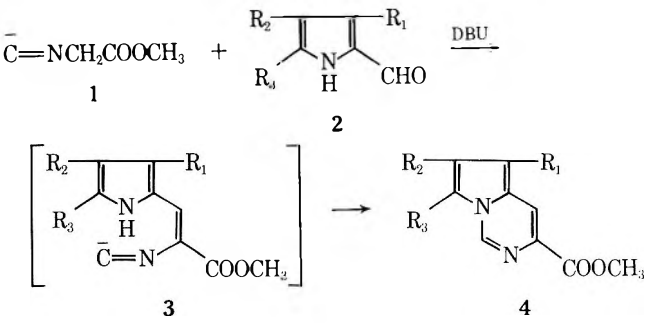
Condensation of the aldehydes (**2**) with isocyano compound **1** was carried out in THF solution, using 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as a base (Table I). The structure of the resulting products (**4**) was confirmed by spectral and analytical data. The formation of compounds **4** probably proceeds via intramolecular cycloaddition of the intermediates **3**.

Table I. Preparation of Methyl Pyrrolo[1,2-c]pyrimidine-3-carboxylates (4)

Registry no.	R_1	R_2	R_3	Mp, °C[a,b]	Yield, %
58298-71-8	H	H	H	78–80	69
58298-72-9	$COO-C_2H_5$	CH_3	$COO-C_2H_5$	144–145	59
58298-73-0	CH_3	$COO-CH_3$	CH_3	215–219	55
58298-74-1	3,4-Methylenedioxy Ph	H	H	199–200	57
58298-75-2	3-Methoxy Ph	H	H	162–164	50

[a] Recrystallization from ethyl acetate or methanol. [b] Satisfactory analytical values (±0.3% for C, H, N) for all compounds were submitted. Ed.

Scheme I



Experimental Section

Typical Procedure. To a solution of DBU (19.8 g, 0.13 mol) in THF (200 ml) was added dropwise a mixture of pyrrole-2-carboxaldehyde (12.4 g, 0.13 mol) and methyl isocyanoacetate (12.9 g, 0.13 mol) dissolved in THF (90 ml) at 40–45 °C for a period of 30 min with stirring. After stirring for 2 h at the same temperature, 10% acetic acid (70 ml) was added to the mixture and then the solvent was removed under reduced pressure. The resulting residue was extracted with ethyl acetate and the extract was further extracted with 5% hydrochloric acid (300 ml). The acidic solution was neutralized with sodium bicarbonate and the resulting products were sufficiently extracted with ethyl acetate. The extract was washed with saturated sodium chloride solution, dried, and then evaporated in vacuo. Methyl pyrrolo[1,2-c]pyrimidine-3-carboxylate (15.7 g), recrystallized from ethyl acetate, showed mp 78–80 °C; ir (Nujol) 3100 (CH), 1710 cm^{-1} ($COOCH_3$); NMR (Me_2SO-d_6) δ 9.20 (s, 1, C-1 H), 8.25 (s, 1, C-4 H), 7.90 (d, 1, C-7 H), 7.05 (double d, 1, C-6 H), 6.87 (d, 1, C-5 H), 3.87 (s, 3, OCH_3).

Registry No.—**1**, 39687-95-1; **2** (R_1 = R_2 = R_3 = H), 1003-29-8; **2** (R_1 = R_3 = $COOC_2H_5$; R_2 = CH_3), 2199-60-2; **2** (R_1 = R_3 = Me; R_2 = $COOCH_3$), 58298-68-3; **2** (R_1 = 3,4-methylenedioxy Ph; R_2 = R_3 = H), 58298-69-4; **2** (R_1 = 3-methoxy Ph; R_2 = R_3 = H), 58298-70-7.

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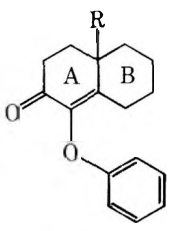
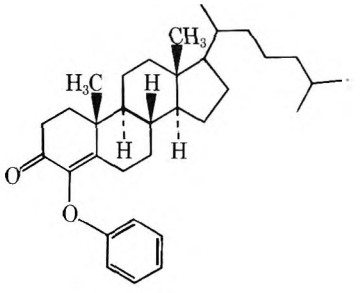
Heteroatom Directed Photoarylation. Stereochemistry of Aryloxyenone Photocyclization

Summary: Aryloxyenones **1a, 1b,** and **2** undergo high yield photocyclization–rearrangement to dihydrofurans **3, 8,** and **6,** with a *cis*-decalone ring fusion, via the relatively strain-free carbonyl ylide intermediate **7a.**

Sir: A structural feature common to the morphine, hasubanan, and aspidosperma alkaloids is the presence of an aryl nucleus at a ring junction carbon atom. A highly desirable tactic for synthesis of these alkaloids is the direct bonding of an aryl nucleus to a carbon atom already located at a ring junction. However, few pertinent synthetic methods presently exist, and with these, regiochemical and stereochemical problems can be anticipated. In this regard, photocyclization of aryl vinyl ethers seemed to possess considerable synthetic potential,[1] and our interest in the total synthesis of medicinally important alkaloids provided stimulus for investigation of the photochemistry of fused-ring aryloxyenones, e.g., **1a, 1b,** and **2.**[2]



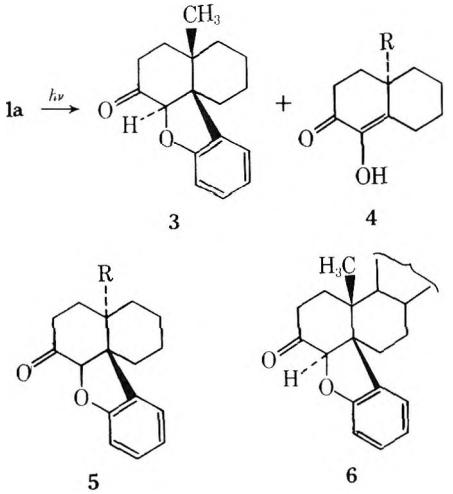
1a, R = CH_3
b, R = $CO_2CH_2CH_3$



2

Herein, we report the remarkable stereochemical control possible with aryl vinyl heteroatom photocyclization (heteroatom directed photoarylation)[3] and discuss factors responsible for observed stereoselectivity.

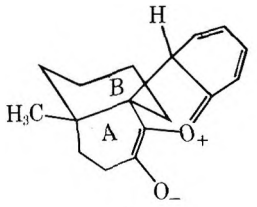
Pyrex-filtered irradiation of **1a** in degassed benzene solution saturated with *p*-toluenesulfonic acid gave two major photoproducts: dihydrofuran **3** (90% isolated yield) and diketone **4** (R = CH_3, 4–5%). VPC analysis indicated that three unidentified products also were present; however, none exceeded 1% of the total reaction components. Significantly, only dihydrofuran **3** possessing a *cis*-decalone ring system was isolated and none of the isomeric dihydrofuran **5** (R = CH_3) with a *trans*-decalone ring system could be detected; examination of NMR spectra of **1a** photoreactions indicated that formation of **5** could have been detected at a 1% level. Thus, the stereoselectivity of photocyclization of **1a** must be of the order of 90:1.



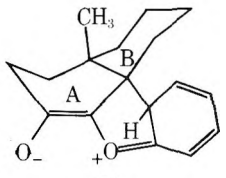
3 **4**

5 **6**

We feel that the origin of this remarkable stereoselectivity may be a result of relative ring strain in carbonyl ylides **7a** and **7b,** which are hypothetical intermediates in the conversions



7a

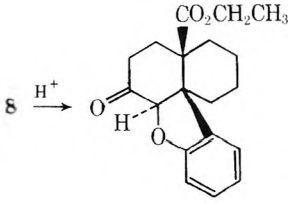


7b

1a → **3** and **1a** → **5,** respectively.[1] Conrotatory photocyclization[4] of **1a** via an orientation resulting from approach of the aryl nucleus toward the β face of the enone system would give **7a,** while conrotatory cyclization from an approach toward the α face would give **7b.** Clearly, existence of a planar π-electron system in **7** imposes a great deal of ring strain in configuration **7b,** but relatively little in **7a;** on the basis of unfavorable ring strain in **7b,** photocyclization of **1a** would be expected to preferentially lead to carbonyl ylide intermediate **7a,** the precursor of isolated *cis*-decalone **3.**

Having established a reasonable hypothesis for stereoselective control in photocyclization of **1a,** we sought to test the generality of control by structural modifications of **1a,** e.g., **1b** (steric alteration) and **2** (ring strain alteration).

Approach of the aryl nucleus toward the β face of the enone system during cyclization of **1a** results in little steric interaction with the angular methyl group. Replacement of the methyl group with an exceedingly bulky carbethoxy group (i.e., **1b**) might be expected to hinder β-face approach and result in a loss of the stereoselectivity encountered with **1a.** However, when **1b** was irradiated in benzene solution saturated with p-toluenesulfonic acid, no *trans*-fused decalone (i.e., **5,** R = $CO_2CH_2CH_3$) could be detected; *cis*-fused decalone **8** (40% yield), *cis*-fused decalone **9** (3%), and diketone **4** (R =



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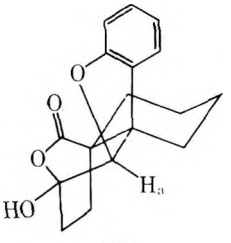

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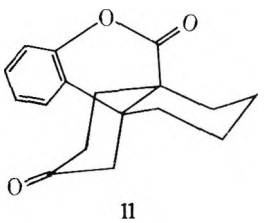

11

$CO_2CH_2CH_3$, 14%) were produced, together with a good deal of polymer.[5] Interestingly, polymer formation was eliminated in benzene–methanol–acetic acid solution (equal volumes of each solvent component);[1] formation of **8** (29%) and **9** (35%) and extensive ether cleavage (35%) was noted. Formation of *cis-fused decalone* **8** *(67% yield), with no evidence for formation* of **9** or **4** (R = $CO_2CH_2CH_3$), occurred when irradiation (366 nm) of **1b** was performed in benzene solution in the presence of the triplet sensitizer benzophenone.

Assignment of stereochemistry in **3, 6,** and **9** is based on NMR spectral data and chemical reactivity. Thus, in the NMR spectra of **3, 6,** and **9**, H_a appears as a sharp singlet at 4.43, 4.50, and 4.43 ppm, respectively. In that for **8**, H_a appears at 5.10 ppm and experiences W coupling (J_{ab} = 1.5 Hz). While **8** and **9** are not thermally interconvertible below 140 °C (refluxing xylene solution), **8** undergoes transformation into **9** in refluxing benzene solution saturated with *p*-toluenesulfonic acid (half-life ~5 h) or refluxing benzene–acetic acid solution (equal volumes of each solvent component, half-life ~14 h). Treatment of either **8** or **9** with 1 N potassium hydroxide in methanol followed by acidification gave a single lactol **10** (mp 232–233 °C).[5] NMR absorption for H_a in **10** appears as a sharp singlet at 4.25 ppm. Finally, **8** and **9** give lactone **11** (ir 5.69 and 5.80 μ) on treatment with zinc dust in refluxing propionic acid solution.[1]

In contrast to conversions **1** → **7a**, in which ring B may assume a chair conformation, conrotatory photocyclization of **2**, to give a cis-AB ring fusion, must result in a carbonyl ylide possessing a ring-B boat conformation. On the other hand, cyclization of **2**, to give a trans-AB ring fusion, would maintain the ring-B chair conformation present in **2**.[6] A carbonyl ylide derived from **2**, with a trans-AB ring fusion, would be expected to have approximately the same ring strain as hypothetical **7b**, while a carbonyl ylide with a cis-AB ring fusion should be somewhat more strained than **7a**. If the additional ring strain imposed on **7a** is significant, then photocyclization of **2** might be expected to be less stereoselective than that of **1a**. In fact, photolysis of **2** did not produce a dihydrofuran with a trans-AB ring fusion, but rather gave cis-fused **6** in high yield along with a small amount of ether cleavage.

Thus, our studies with **1b** indicate that, while replacement of the methyl group in **1a** with the bulky carbethoxy group does seem to make photocyclization less facile (note extensive ether cleavage in **1b**), this steric alteration does not lead to a detectable inversion in stereoselectivity of carbonyl ylide formation. Furthermore, the constraints imposed by the steroid framework in **2**, which would seem to operate in discord with formation of a cis-AB ring fusion, also do not alter stereoselectivity of carbonyl ylide formation. In general then, photocyclization–rearrangement of 1-aryloxy-$\Delta^{1(9)}$-octalone-2 systems should produce a dihydrofuran possessing a *cis*-decalone ring fusion. Application of the principles discussed here to the synthesis of complex organic molecules along with a detailed investigation of excited singlet and triplet state reactivity in aryloxyenones is currently being investigated.

Acknowledgment. This work was supported by the National Institutes of Health (Grant No. GM 21159-01). We thank Professor Albert Eschenmoser for a stimulating and helpful discussion during the early stages of this work. Assistance in the synthesis of **1b** and **2** by undergraduate research participants B. Gail Kurr and Cathy Stein is gratefully acknowledged.

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(1) A. G. Schultz and R. D. Lucci, *J. Org. Chem.*, **40**, 1371 (1975).
(2) Aryloxyenones **1a** (mp 71–73 °C) and **2** (mp 122–123 °C) were prepared from phenol and the corresponding epoxy ketone by a method previously reported,[1] while preparation of **1b** (mp 62–64 °C) followed an annelation approach from ethyl 2-cyclohexanonecarboxylate and 1-phenoxy-3-buten-2-one, the details of which will be described elsewhere.
(3) The methodological term heteroatom directed photoarylation is intended to characterize photochemically initiated electrocyclic reactions, which, by influence of an appropriate heteroatom, result in bond formation between two atoms at least one of which initially resides in an aromatic nucleus. In the present case, formation of a *carbon-carbon* bond is "directed" by an oxygen atom to give a dihydrobenzofuran. It should be noted that a variety of previously studied photoreactions may be considered to belong to this general reaction classification. To cite a few, the elegant investigation of "non-oxidative photocyclization" of *N*-aryl enamines [O. L. Chapman, G. L. Eian, A. Bloom, and J. Clardy, *J. Am. Chem. Soc.*, **93**, 2918 (1971)] and the photocyclization of benzoic acid anilides [B. S. Thyagarajan, N. Kharasch, H. B. Lewis, and W. Wolf, *Chem. Commun.*, 615 (1967)], acrylic acid anilides [P. G. Cleveland and O. L. Chapman, *ibid.*, 1064 (1967)], and biaryl isocyanates [J. S. Swenton, T. J. Ikeler, and G. LeRoy Smyser, *J. Org. Chem.*, **38**, 1157 (1973)] are well-known examples.
(4) A. G. Schultz and M. B. DeTar, *J. Am. Chem. Soc.*, **96**, 296 (1974).
(5) The acid- or base-catalyzed conversion of **8** to **9** must occur as a result of enolization at the carbon bearing H_a. We assume that tautomerization will occur to give the stable *cis*-dihydrofuran ring fusion in **9** as shown; see ref 1. Remaining stereochemical assignment in **8** must await further structural studies.
(6) Crystallographic studies with progesterone [H. Campsteyn, L. Dupont, and O. Dideberg, *Acta Crystallogr.*, **B28**, 3032 (1972)], testosterone [G. Precigouz et al., *Cryst. Struct. Commun.*, **2**, 435 (1973)], and 26-hydroxycholestenone *p*-bromobenzoate [E. Caspi et al., *J. Am. Chem. Soc.*, **93**, 6283 (1974)] demonstrate that ring B in all of these compounds assumes a chair conformation.
(7) Postdoctoral research associate 1973–1975.

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1,4,5,8-Tetrathiatetralin, a Tetrathiafulvalene Isomer

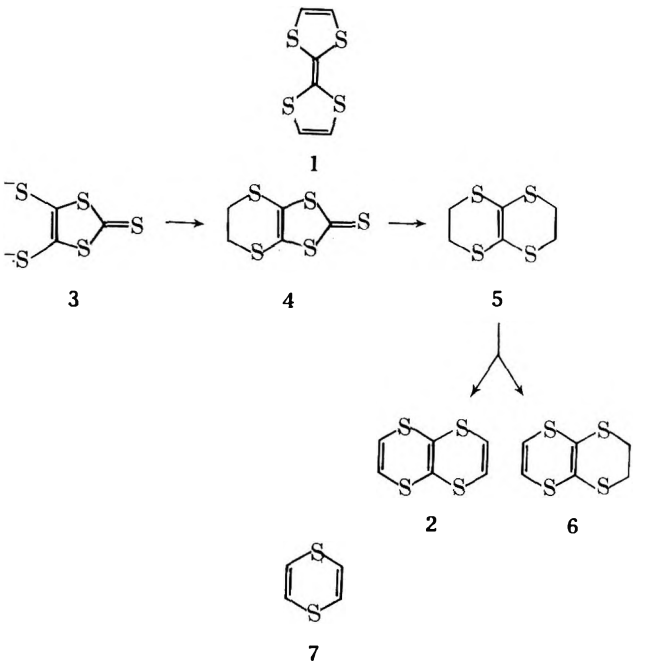
Summary: 1,4,5,8-Tetrathiatetralin (**2**) has been obtained by a four-step synthesis from carbon disulfide. Compound **2**, unlike the isomeric tetrathiafulvalene (**1**), is not readily oxidized to a cation radical.

Sir: Tetrathiafulvalene (**1**) and its selenium analogs have been the subject of great interest, since they are valuable π donors in the preparation of charge-transfer salts having metallic properties.[1] The hitherto unknown 1,4,5,8-tetrathiatetralin (**2**)[2] is an isomer of **1** which differs structurally from the latter only in the arrangement of the two ethyne bridges. We now report the first synthesis of **2** and some physical and electrochemical properties of this substance.

Electrochemical reduction of carbon disulfide to the dianion **3**,[3] followed by alkylation with 1,2-dibromoethane, gave (18%) trithiocarbonate **4** as golden plates, mp 121.5–122.5 °C. Hydrolysis of **4** by hot ethanolic potassium hydroxide, followed by alkylation with 1,2-dibromoethane, gave (70%) the tetrahydro derivative **5** of **2** as white needles, mp 154–156 °C. Compound **5** was dehydrogenated by refluxing overnight with DDQ in xylene to give, after silica chromatography, the dihydro derivative **6** of **2** (45%) as pale yellow needles, mp 80–81 °C, as well as **2** itself (37%) in the form of lemon yellow needles: mp 125–126 °C; $\lambda_{max}^{cyclohexane}$ 235 nm (ϵ 8000), 248 (sh, 6100), 270 (sh, 5000).

Although **2** may be viewed as a potentially aromatic 14-π-electron system, its NMR spectrum ($CDCl_3$) shows a singlet at δ 6.46 ppm, a position very close to that (6.55) of the olefinic protons of its dihydro derivative **6**. This observation suggests that **2**, like the parent monocyclic analog *p*-dithiin,[4] lacks aromatic stabilization and thus, may possess a nonplanar conformation.

Moreover, in sharp contrast to **1**, **2** is not readily oxidized by tetracyanoquinodimethane to give a radical ion charge-transfer salt. A quantitative measure of this difference in



oxidative behavior is directly provided by polarographic measurements. Whereas 1 is reversibly oxidized with values of 0.006 V and 0.385 V for $E_{1/2}^1$ and $E_{1/2}^2$, 2 is oxidized with corresponding values of 0.561 V and 0.965 V, where the second oxidation step occurs irreversibly.[5] This lack of relative ease to oxidize 2 hinders its use as a donor cation in highly conducting organic metals.

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(1) A. F. Garito and A. J. Heeger, *Acc. Chem. Res.*, **7**, 232 (1974).
(2) The more cumbersome systematic name of **2** is 1,4-dithiino[2,3-*b*]-1,4-dithiin. Satisfactory elemental analyses were obtained for compounds **2**, **4**, **5**, and **6**.
(3) S. Wawzonek and S. M. Heilmann, *J. Org. Chem.*, **39**, 511 (1974).
(4) W. E. Parham, H. Wynberg, W. R. Hasek, P. A. Howell, R. M. Curtis, and W. L. Lipscomb, *J. Am. Chem. Soc.*, **76**, 4957 (1954).
(5) Measured in CH_3CN with tetraethylammonium perchlorate (0.05 M) added vs. Ag/Ag^+ (0.1 N in CH_3CN) with a glassy carbon electrode (GCE) as the working electrode.
(6) (a) Department of Chemistry; (b) Department of Physics.

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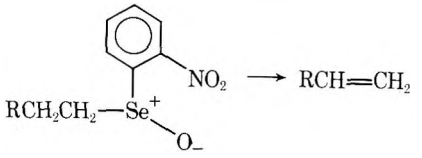
Organoselenium Chemistry. A Facile One-Step Synthesis of Alkyl Aryl Selenides from Alcohols

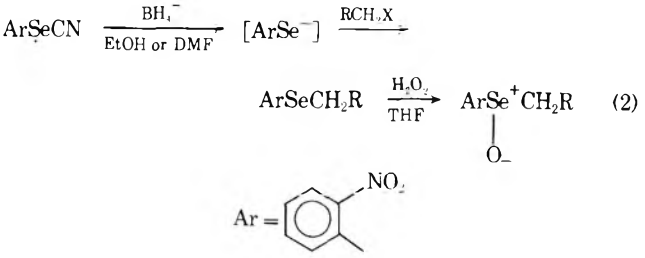
Summary: Treatment of alcohols with aryl selenocyanates in either tetrahydrofuran or pyridine containing tributylphosphine results in high yields of alkyl aryl selenides.

Sir: Substituents on the β and/or γ carbons of primary alkyl phenyl selenoxides result in low yields of terminal olefins. Recently it was demonstrated[1,2] that primary alkyl *o*-nitrophenyl selenoxides undergo facile elimination with formation of terminal olefins in high yield (eq 1). For example, the *o*-



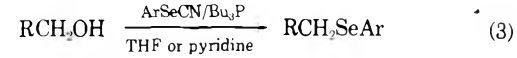
(1)

nitrophenyl selenoxide derived from cyclohexylmethanol provides a twofold increase in the yield of *exo*-methylenecyclohexane as compared to the corresponding phenyl selenoxide.[1] o-Nitrophenyl selenoxides are generated by oxidation of the corresponding alkyl *o*-nitrophenyl selenides which are prepared by displacement of alkyl tosylates, mesylates, or halides with the corresponding selenium anion (eq 2). The



(2)

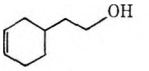
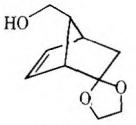
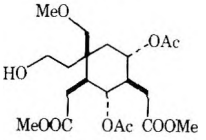
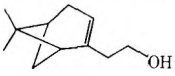
o-nitrophenyl selenium anion is generated by treatment of *o*-nitrophenyl selenocyanate with sodium borohydride in either absolute ethanol[1] or dimethylformamide[2b] (eq 2). We wish to describe in this communication the direct one-step conversion of alcohols to alkyl aryl selenides (eq 3).



(3)

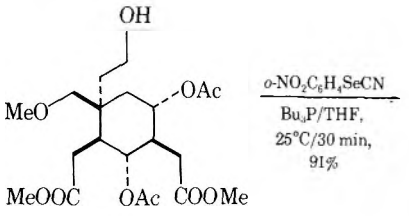
Treatment of a variety of primary alcohols with *o*-nitrophenyl selenocyanate[3] in tetrahydrofuran or pyridine at room

Table I. Conversion of Alcohols to Alkyl *o*-Nitrophenyl Selenides

Compound	% yield of selenide[a-c] in pyridine	% yield of selenide[a-c] in THF
1-Dodecanol	92	94
1-Heptanol	85	
3-Hexyn-1-ol	93	88
Benzyl alcohol	97	93
Cyclohexylmethanol	99	88
	98	95
	91	90
		91
	98	85
2-Propanol	93	
Cyclooctanol		63

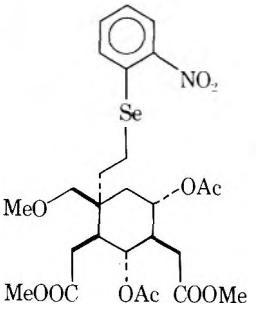
[a] All compounds were fully characterized by spectral methods. [b] Yields reported are for isolated, chromatographically pure substances. [c] All reactions were performed at room temperature in the presence of the indicated solvent.

temperature in the presence of tri-*n*-butylphosphine results in very high yields of primary alkyl selenides (see Table I). The method obviates the necessity of preforming the mesylate, tosylate, or halide and avoids the use of borohydride in ethanol or dimethylformamide to generate the selenium anion. The method is best illustrated by the conversion of the highly functionalized primary alcohol **1** to selenide **2** (eq 4) which results in a 91% yield of chromatographically pure material. It should be pointed out that the two-step procedure involving mesylation and displacement by selenium proceeds at best in only 77% yield.



1

o-$NO_2C_6H_4SeCN$, Bu_3P/THF, 25°C/30 min, 91%



2 (4)

The one-step conversion of alcohols to selenides by the above method was not successful with di-*o*-nitrophenyl diselenide,[4] diphenyl diselenide, or phenylselenenyl chloride. A reaction however does take place with phenyl selenocyanate. For example, treatment of dodecanol with phenyl selenocyanate[5] (1.2 equiv) in tetrahydrofuran containing tri-*n*-butylphosphine (1.2 equiv) resulted in a 92% yield of dodecyl phenyl selenide (eq 5).

$$CH_3(CH_2)_{10}CH_2OH \xrightarrow[THF]{PhSeCN/Bu_3P} CH_3(CH_2)_{10}CH_2SePh \quad (5)$$

The reaction of secondary alcohols with *o*-nitrophenyl selenocyanate to give secondary alkyl selenides can be performed in reasonable yield as illustrated in Table I for 2-propanol and cyclooctanol. Phenyl selenocyanate can be employed for the conversion of secondary alcohols to alkyl phenyl selenides; e.g., 2-propanol was converted in 85% yield to isopropyl phenyl selenide.

The above reactions can be rationalized as indicated in eq 6–8 by formation of a selenophosphonium salt which reacts with the alcohol providing an oxaphosphonium salt. Reaction of the aryl selenium anion with the oxaphosphonium species provides the corresponding alkyl aryl selenide plus tributylphosphine oxide. We cannot at this time rule out the intermediacy of $Bu_3P^+CN\ ArSe^-$.

$$ArSeCN + Bu_3P \rightarrow ArSe\overset{+}{P}Bu_3\ CN^- \quad (6)$$

$$ArSe\overset{+}{P}Bu_3\ CN^- + RCH_2OH \rightarrow RCH_2O\overset{+}{P}Bu_3 + HCN + ArSe^- \quad (7)$$

$$RCH_2O\overset{+}{P}Bu_3 + ArSe^- \rightarrow RCH_2SeAr + Bu_3P{=}O \quad (8)$$

The following experimental procedure indicates the simplicity of this convenient method. A solution of dodecanol (115 mg, 0.62 mmol) in 2.0 ml of tetrahydrofuran containing *o*-nitrophenyl selenocyanate (168 mg, 0.74 mmol) under nitrogen was treated dropwise with tri-*n*-butylphosphine (150 mg, 0.74 mmol) at room temperature. After the reaction was stirred for 30 min, the solvent was removed in vacuo. Chromatography of the residue on silica gel using hexane–ether (3:1) gave 214 mg (94%) of dodecyl o-nitrophenyl selenide as a yellow crystalline compound: mp 43–44 °C; ir ν_{CHCl_3} 1518, 1332 cm^{-1}; NMR δ_{CDCl_3} 0.88 (t, 3 H), 1.15–2.20 (m, 20 H), 2.91 (t, 2 H), 7.10–7.65 (m, 3 H), 8.27 (d, 1 H).

Acknowledgments. This investigation was supported by a Public Health Service Research Grant (CA 13689-04) from the National Cancer Institute.

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(1) K. B. Sharpless and M. W. Young, *J. Org. Chem.*, **40**, 947 (1975).
(2) For application of the *o*-nitrophenyl selenoxide elimination to natural product synthesis, see (a) P. A. Grieco, Y. Masaki, and D. Boxler, *J. Am. Chem. Soc.*, **97**, 1597 (1975); (b) P. A. Grieco, J. A. Noguez, and Y. Masaki, *Tetrahedron Lett.*, 4213 (1975).
(3) H. Bauer, *Ber.*, **46**, 92 (1913).
(4) Di-*o*-nitrophenyl diselenide is prepared from *o*-nitrophenyl selenocyanate which is readily available in one step from *o*-nitroaniline according to the procedure of Bauer.[3]
(5) O. Behaghel and H. Seibert, *Ber.*, **65**, 812 (1932).
(6) Fellow of the Alfred P. Sloan Foundation, 1974–1976.

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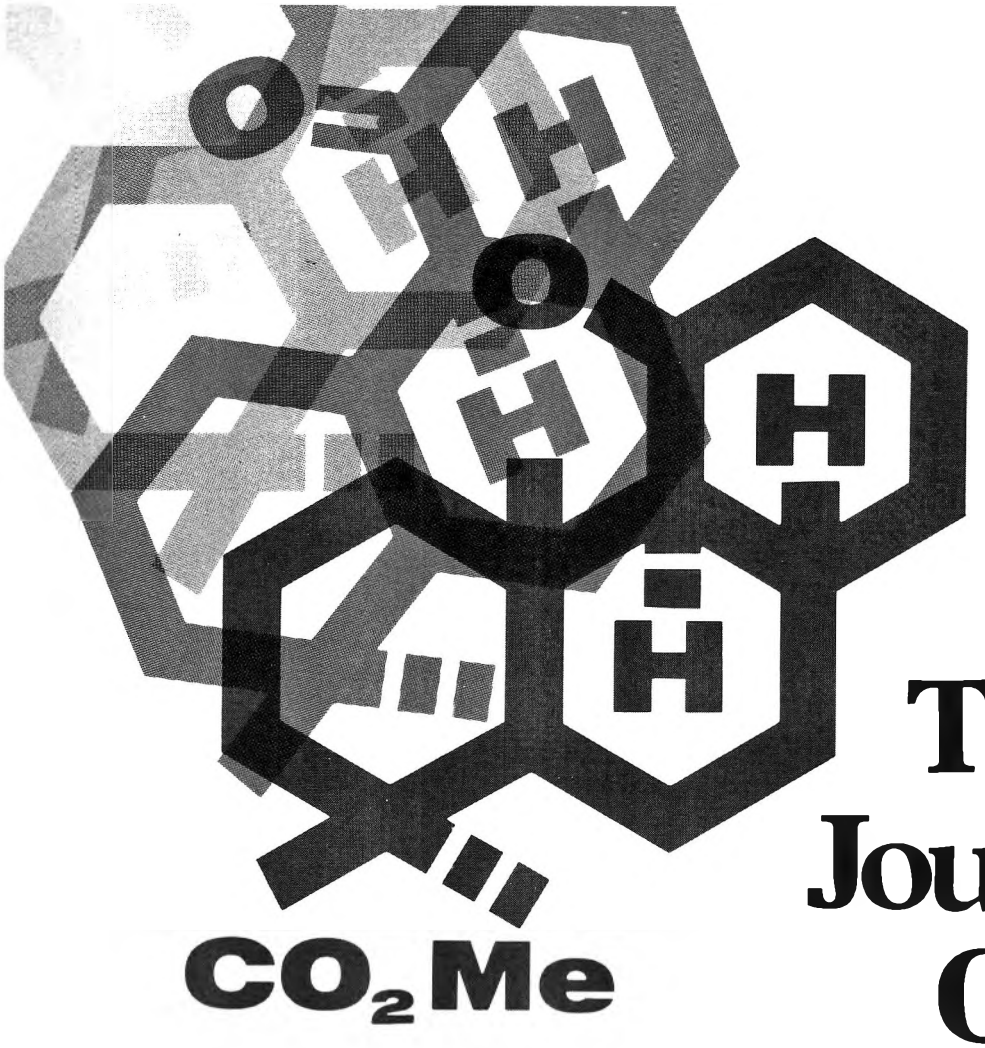

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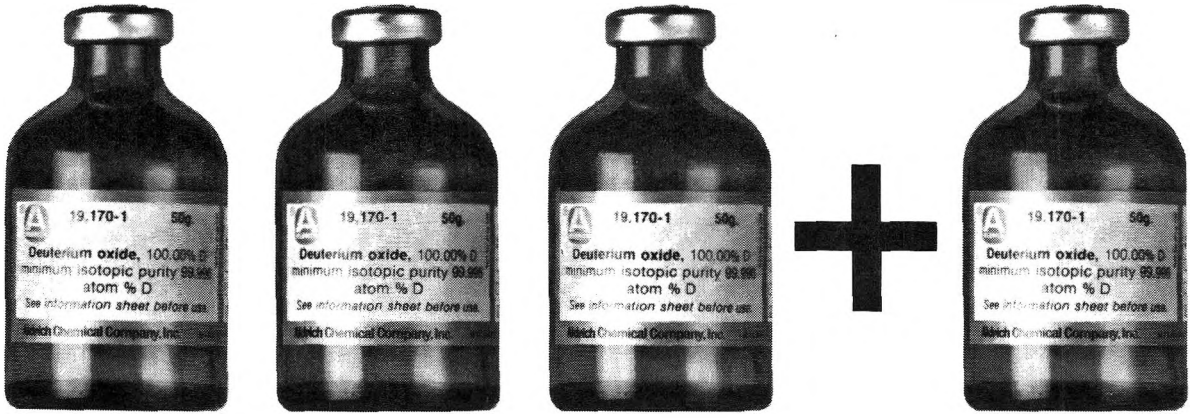

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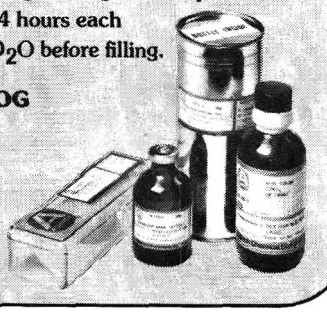

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