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NOTES

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SEPTEMBER 2, 1977

Synthesis of the Tricarboxylic Porphyrin Enzymically Formed from Coproporphyrinogen IV

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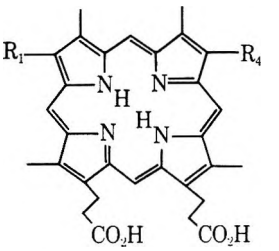
Received March 3, 1977

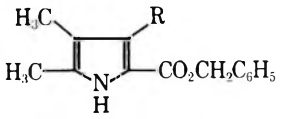
The synthesis of 1-vinyl-4,6,7-(β-methoxycarbonylethyl)-2,3,5,8-tetramethylporphyrin (**3**) was achieved; the product was identical with the tricarboxylic porphyrin isolated by the incubation of duck blood hemolysate with coproporphyrinogen IV. The precursor benzyl 2,3-dimethyl-4-(β-benzyloxycarbonylmethyl)-5-pyrrolecarboxylate was obtained by reductive C-methylation of the β-free pyrrole. It was reduced to the corresponding β-hydroxyethylpyrrole, which was transformed into the corresponding benzyl ester of the β-chloroethylpyrrole. The 2-acetoxymethyl derivative of the latter was condensed with the benzyl 4-methyl-3-(β-methoxycarbonylmethyl)-2-pyrrolecarboxylate and afforded the 5,5′-dibenzyloxycarbonyldipyrrylmethane. The latter was converted by hydrogenolysis into the corresponding 5,5′-dicarboxydipyrrylmethane, which was condensed with the 5,5′-diformyldipyrrylmethane **20** to afford 1-(β-chloroethyl)-4,6,7-(β-methoxycarbonylethyl)-2,3,5,8-tetramethylporphyrin (**19**). Treatment of the latter with potassium *tert*-butoxide afforded the tricarboxylic acid porphyrin **3** (as its trimethyl ester). The porphyrin can be distinguished from harderoporphyrin and from isoharderoporphyrin by its visible and NMR spectra.

We have recently shown[1] that coproporphyrinogen IV—the metabolically active hexahydro form of coproporphyrin IV (**1**)—was transformed by duck blood erythrocytes into a tricarboxylic acid porphyrin which was the main reaction product, and into a protoporphyrin isomeric with the natural protoporphyrin IX. The enzymatic transformation took place in high yields, higher even than the oxidative decarboxylation of the natural substrate coproporphyrinogen III to protoporphyrin IX. These results were at variance with previous results,[2] which reported that coproporphyrinogen IV underwent oxidative decarboxylation only one-tenth as fast as the natural isomer III, and that the reaction took place only to a slight extent.[3] The efficient enzymatic transformation of coproporphyrinogen IV into its reaction products added a new complexity to the studies on type III porphyrin biosynthesis.[4] These results found a prompt confirmation when the enzymatic reaction was carried out with chicken hemolysates,[5] and with beef liver mitochondria.[6] From biosynthetic considerations we reasoned that the protoporphyrin formed by the oxidative decarboxylation of coproporphyrinogen IV must be protoporphyrin XIII (**2**).[7] Jackson independently reached the same conclusion, and confirmed it by comparing the obtained product (as its dimethyl ester) with a synthetic sample of protoporphyrin XIII dimethyl ester.[5] Battersby lent support to this result by a study of the lanthanide shift of the meso protons in the NMR spectrum of the protoporphyrin isolated from beef liver mitochondria.[6] We now report the synthesis of the trimethyl ester of the tricarboxylic porphyrin **3**, which was found to be identical with the tricarboxylic trimethyl ester obtained by the esterification of the major reaction product formed during the enzymatic oxidation.[1]

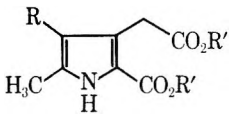


1, $R_1 = R_4 = CH_2CH_2CO_2H$
2, $R_1 = R_4 = CH{=}CH_2$
3, $R_1 = CH{=}CH_2$; $R_4 = CH_2CH_2CO_2H$
19, $R_1 = CH_2CH_2Cl$; $R_4 = CH_2CH_2CO_2H$ (trimethyl ester)

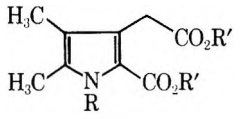
The visible absorption spectrum of the natural compound and its chromatographic mobility,[1] as well as biosynthetic considerations, suggested that **3** was its most probable structure. The synthetic sequence developed by Kenner and Jackson[8] to obtain vinylporphyrins—through β-chloroethylpyrroles—was adopted to prepare the synthetic precursors of ring A. This in turn required an efficient synthesis of pyrrole **4**. In our first attempts we made use of the Fischer–Fink method,[9] which was used[10] to prepare benzyl 2,3-dimethyl-5-pyrrolecarboxylate (**5a**)—a possible synthetic precursor of **4**—by condensation of (α-hydroxymethylenethyl) methyl ketone with the benzyl ester of 2-oximinoacetoacetate. However, the main reaction product was found to be **6a** (see also ref 11) and the purification of **5a** proved difficult. Hence the diethyl ester **5** was chosen as a starting product, and it was submitted to a reductive methylation with paraformaldehyde and hydriodic acid.[12] The unprotected NH group was found to be less reactive than the β carbon, and **6** was obtained in



4, R = $CH_2CO_2CH_2C_6H_5$
5a, R = H
6a, R = CH_3



5, R = H; R′ = C_2H_5
6, R = CH_3; R′ = C_2H_5
8, R = H; R′ = $CH_2C_6H_5$
9, R = H; R′ = H
11, R = CH_3; R′ = H



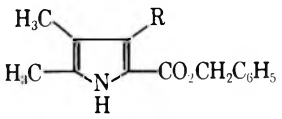
7, R = CH_3; R′ = C_2H_5
10, R = CH_2OH; R′ = $CH_2C_6H_5$

good yield. Only a small amount of the trimethyl derivative **7** was obtained, which could be easily separated from **6**.

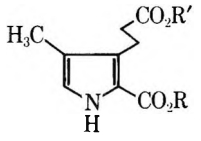
The dibenzyl ester **8** was then prepared by saponification of the diethyl ester **5** to the diacid **9**, followed by treatment of the latter with α-diazotoluene. Reductive methylation of **8** afforded the dibenzyl ester **4**, which was separated from a small amount of its *N*-hydroxymethyl derivative **10**. The dibenzyl ester **4** was also prepared from the diethyl ester **6** by saponification to **11**, followed by esterification of **11** with α-diazotoluene.

The dimethylpyrrole **4** was reduced with diborane,[8] and was transformed into the β-hydroxyethylpyrrole **12** in 83% yield; and by treatment of **12** with thionyl chloride the β-chloroethylpyrrole **13** was obtained.

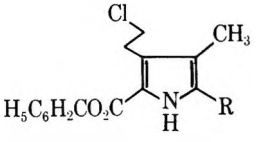
In a first attempt the benzyl ester was cleaved by hydrogenolysis, and the resulting acid **21** (65%) was treated with trifluoroacetic acid to give the 5,5′-free dipyrrylmethane. After an alkaline wash it was condensed with **20** in methylene chloride in the presence of *p*-toluenesulfonic acid.[8] An inseparable mixture of porphyrins was obtained. Hence, the dipyrrylmethane **18** was first treated with trifluoroacetic acid, and the resulting monobenzyl ester (87%) was transformed into its acid by hydrogenolysis and then condensed with **20** as mentioned above. Again a mixture of porphyrins was obtained; it was obvious that a randomization took place during the condensation process. The synthesis was then directed toward the preparation of the 5,5′-dibenzylcarbonyldipyrrylmethane **22**, which could be transformed into a 5,5′-dicarboxydipyrrylmethane **23**. The usefulness of this type of derivatives for the synthesis of uroporphyrins had already been noted.[14]



12, R = CH_2CH_2OH
13, R = CH_2CH_2Cl



17, R = $C(CH_3)_3$; R′ = C_2H_5
24, R = R′ = H
25, R = R′ = $CH_2C_6H_5$
26, R = $CH_2C_6H_5$; R′ = CH_3

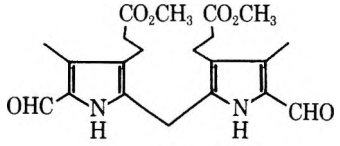


14, R = CH_2OOCCH_3
15, R = CHO
16, R = CH_2Cl

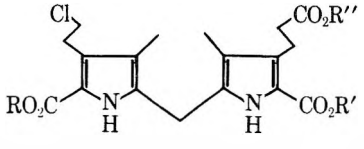
When **13** was treated with 1 equiv of lead tetraacetate in acetic acid to prepare the α-acetoxymethylpyrrole **14**, the latter was obtained in only 11% yield, since the major product (36%) was the aldehyde **15**. The pyrrole **13** was then transformed into its α-chloromethyl derivative **16** by treatment with sulfuryl chloride in carbon tetrachloride; and **16** was transformed into the desired α-acetoxymethyl **14** by treatment with sodium acetate in acetic acid.

The condensation of **14** and of the known[13] *tert*-butyloxycarbonylpyrrole **17** was carried out in acetic acid–*p*-toluenesulfonic acid,[8] and the dipyrrylmethane **18** was obtained (47%).

To prepare the porphyrin **19** the cleavage of the 5,5′ protecting groups of **18** was required in order to achieve its condensation with the known diformylpyrrylmethane **20**.[8]



20



18, R = $CH_2C_6H_5$; R′ = $C(CH_3)_3$; R″ = C_2H_5
21, R = H; R′ = $C(CH_3)_3$; R″ = C_2H_5
22, R = R′ = $CH_2C_6H_5$; R″ = CH_3
23, R = R′ = H; R″ = CH_3

The pyrrole **17** was saponified to the diacid **24**; the latter was treated with α-diazotoluene to afford the dibenzyl ester **25**, which was in turn transesterified with methanol–20% sulfuric acid.[14] The obtained methyl benzyl ester **26** was condensed with the acetate **14** and the dipyrrylmethane **22** was thus prepared (70%). Hydrogenolysis of **22** in acetic acid over Pd/C gave the diacid **23**, which was condensed with the diformyldipyrrylmethane **20** with the usual technique.[8,14] TLC analysis of the reaction mixture indicated the presence of a main porphyrin, which after isolation was found to be **19**. Vinylation of the β-chloroethyl side chain with potassium *tert*-butoxide gave a porphyrin in 65% yield which proved to be **3** (isolated as trimethyl ester). Its visible and NMR spectra were identical with those of the natural product, and different in several features from those of harderoporphyrin and isoharderoporphyrin.[15] A sample of the synthetic ester **3** was hydrolyzed to the triacid; the latter was reduced to its porphyrinogen, which was then incubated with duck blood hemolysate as described elsewhere.[1] It was transformed into protoporphyrin XIII at a rate similar to that of protoporphyrin XIII formation from coproporphyrinogen IV. Hence the rate-limiting step in the transformation of coproporphyrinogen IV into protoporphyrinogen XIII seems to be the decarboxylation of the tricarboxylic acid intermediate.

Experimental Section[16]

Benzyl 5-Methyl-3-(β-benzyloxycarbonylmethyl)-2-pyrrolecarboxylate (8). The diethyl ester **5**[17] (5 g) was dissolved in a solution containing 60 mL of ethanol and 60 mL of a 10% sodium hydroxide solution, and the mixture was evaporated to dryness in an open flask at 110 °C. The residue was dissolved in 60 mL of water, and

the solution was adjusted to pH 3 with concentrated hydrochloric acid. The precipitated acid **9** was filtered, dried (3.4 g, mp 148–150 °C), suspended in 300 mL of methanol, and esterified at 20 °C by a dropwise addition of freshly distilled α-diazotoluene.[18] A few drops of acetic acid were added to destroy the excess α-diazotoluene after Ehrlich's reaction was negative in the cold and all the acid had dissolved. The solution was evaporated to dryness in vacuo, and the residue was crystallized from cyclohexane, 6.7 g (90%), mp 92–94 °C.

Anal. Calcd for $C_{22}H_{21}O_4N$: C, 72.7; H, 5.9; N, 3.9. Found: C, 72.8; H, 5.8; N, 3.8.

Benzyl 2,3-Dimethyl-4-(β-benzyloxycarbonylmethyl)-5-pyrrolecarboxylate (4). Procedure A. Freshly distilled 57% hydriodic acid (85 mL) was dropwise added at 5 °C to a mixture of 85 mL of acetic anhydride and 35 mL of 50% hypophosphorous acid, and the mixture was kept at 20 °C during 10 min after the addition was completed. A solution of 2 g of paraformaldehyde in 300 mL of glacial acetic acid was then added, followed by 5 g of the dibenzyl ester **8**. The solution was further kept during 2 h at 20 °C, when 500 mL of ether and 500 mL of a cold saturated sodium carbonate solution were added, and the ethereal layer was separated after a thorough mixing. The aqueous solution was further extracted with ether (3 × 200 mL), and the ethereal extracts were pooled, washed with a 5% sodium carbonate solution (100 mL), then with a 2% sodium thiosulfate solution (100 mL), and finally with water. The dried (Na_2SO_4) extracts were evaporated to dryness, and the oily residue dissolved in a small volume of 2% methanol in benzene was adsorbed on a column (4.5 × 35 cm) of TLC silica gel packed and prewashed with the same solvent. The pyrrole **4** was eluted by applying a small pressure, and its complete elution was monitored by TLC (R_f, 0.60, 2% methanol in benzene). Evaporation in vacuo of the eluates afforded 2 g (38%) of **4**: mp 94–95 °C (cyclohexane); NMR ($CDCl_3$) 1.88 (s, 3, C_3CH_3), 2.15 (s, 3, C_2CH_3), 3.8 (s, 2, CH_2), 5.03, 5.2 (s, 4, CH_2Ph), 7.26 ppm (b, 10, C_6H_5).

Anal. Calcd for $C_{23}H_{23}O_4N$: C, 73.2; H, 6.1; N, 3.7. Found: C, 73.1; H, 6.1; N, 3.7.

Further elution of the column with the same solvent afforded the *N*-hydroxymethylpyrrole **10** (R_f, 0.50; 2% methanol in benzene): 0.45 g (9%); mp 57–58 °C (cyclohexane); NMR ($CDCl_3$) 2.0 (s, 3, C_3CH_3), 2.3 (s, 3, C_2CH_3), 3.8 (s, 2, CH_2), 4.85 (t, J = 9 Hz, OH, exchanges with D_2O), 5.12 (s, 2, CH_2OPh side chain), 5.30 (s, 2, CH_2OPh nucleus), 5.6 ppm (d, J = 9 Hz, 2, CH_2OH, was transformed into a s after exchange with D_2O); MS *m/e* 407 (M^+, 20).

Procedure B. A solution of 2.1 g of the 2,3-dimethylpyrrole **6** (see below) in 25 mL of ethanol and 25 mL of a 10% sodium hydroxide solution was saponified to the acid **11** following the procedure described for the diester **5**. The obtained acid (1.26 g, 75%) was esterified with α-diazotoluene as described for the preparation of **8**. The reaction product was filtered through a TLC silica gel column following procedure A, and 1.8 g (60%) of the dibenzyl ester **4** was thus obtained.

Ethyl 2,3-Dimethyl-4-(β-ethoxycarbonylmethyl)-5-pyrrolecarboxylate (6). A solution of 2 g of paraformaldehyde in 300 mL of acetic anhydride and 5 g of the diethyl ester **5** were added to a mixture of 85 mL of hydriodic acid (57%), 85 mL of acetic anhydride, and 35 mL of hypophosphorous acid as described for the preparation of **4**. Following the same working procedure as described for **4** except for the use of 2.5% methanol in benzene for the elution purposes, 2.1 g (39%) of **6** (R_f, 0.60, 2.5% methanol in benzene) was obtained: mp 113–114 °C (methanol); NMR ($CDCl_3$) 1.25 (m, 6, CH_3CH_2), 1.94 (s, 3, C_3CH_3), 2.2 (s, 3, C_2CH_3), 3.8 (s, 2, CH_2), 4.2 (m, 4, CH_2CH_3), 9.1 ppm (b, 1, NH).

Anal. Calcd for $C_{13}H_{19}O_4N_1$: C, 61.7; H, 7.5; N, 5.5. Found: C, 61.6; H, 7.6; N, 5.6.

During the elution of the column the eluates which preceded the fraction containing the diethyl ester **6** contained the minor reaction product **7** (R_f, 0.70, 2.5% methanol in benzene) which was recovered after evaporating the eluates in vacuo: 0.35 g (6%); mp 55–57 °C (methanol–water); NMR ($CDCl_3$) 1.2 (m, 6, CH_3CH_2), 1.9 (s, 3, C_3CH_3), 2.05 (s, 3, NCH_3), 2.2 (s, 3, C_4CH_3), 3.8 (s, 2, CH_2), 4.2 ppm (m, 4, CH_2CH_3).

Benzyl 2,3-Dimethyl-4-(β-hydroxyethyl)-5-pyrrolecarboxylate (12). By addition of 40 mL of boron trifluoride etherate to 12 g of sodium borohydride suspended in 40 mL of diglyme while the mixture was kept under a gentle nitrogen stream,[8] a diborane-carrying nitrogen flux was obtained and bubbled into a solution of 2 g of pyrrole **4** in 50 mL of dry tetrahydrofuran. After 3 h the reduction of the side chain was complete; methanol was added to the reaction mixture until the effervescence subsided, and the solution was evaporated to dryness. The residue was purified by filtration through a TLC silica gel column (3.5 × 30 cm) packed and eluted with 2% methanol in benzene. The eluates were evaporated to dryness and the residue was crystallized from benzene–petroleum ether (bp 60–80 °C): 1.2 g (83%); mp 84–85 °C; NMR ($CDCl_3$) 1.88 (s, 3, C_3CH_3), 2.1 (s, 3, C_2CH_3), 2.95 (t, J = 6 Hz, 2, CH_2OH), 3.7 (t, J = 6 Hz, 2, pyrr-CH_2), 4.6 (s, 1, OH), 5.25 (s, 2, CH_2Ph), 7.4 ppm (b, 5, C_6H_5).

Anal. Calcd for $C_{16}H_{19}O_3N$: C, 70.3; H, 6.9; N, 5.1. Found: C, 70.4; H, 7.0; N, 5.0.

Benzyl 2,3-Dimethyl-4-(β-chloroethyl)-5-pyrrolecarboxylate (13). To a solution of the β-hydroxyethylpyrrole **12** (1.76 g) in 20 mL of methylene chloride and 0.6 mL of dry pyridine was added 0.52 mL of freshly distilled thionyl chloride. The mixture was heated under nitrogen at 70 °C for 90 min, when 180 mL of methylene chloride was added and the solution was washed with 2 N hydrochloric acid, followed by a 5% sodium bicarbonate solution and then by water. The organic layer was evaporated to dryness and the residue was filtered through a TLC silica gel column with the usual technique using 2% methanol in benzene as eluent. The eluates were evaporated to dryness, and the residue crystallized from cyclohexane: 0.9 g (47%); mp 113–115 °C; NMR ($CDCl_3$) 1.94 (s, 3, C_3CH_3), 2.17 (s, 3, C; $_2CH_3$), 3.1 (m, 2, CH_2Cl), 3.6 (m, 2, pyrr-CH_2), 5.3 (b, 2, CH_2Ph), 7.4 ppm (b, 5, C_6H_5).

Anal. Calcd for $C_{16}H_{18}O_2NCl$: C, 65.9; H, 6.2; N, 4.8. Found: C, 65.8; H, 6.4; N, 4.7.

Benzyl 2-Chloromethyl-3-methyl-4-(β-chloroethyl)-5-pyrrolecarboxylate (16). To a solution of 900 mg of **13** in 100 mL of dry carbon tetrachloride was added 0.24 mL (1 mequiv) of freshly distilled sulfuryl chloride. The mixture was kept at 45 °C for 4 h, after which it was evaporated to dryness. The residue was crystallized from methylene chloride–petroleum ether (bp 60–80 °C): 1.0 g (100%); mp 118–120 °C; NMR ($CDCl_3$) 2.0 (s, 3, CH_3), 3.1 (m, 2, CH_2Cl), 3.56 (m, 2, pyrr-CH_2CH_2–), 4.5 (s, 2, CH_2), 5.3 (s, 2, CH_2Ph), 7.36 ppm (b, 5, C_6H_5).

Anal. Calcd for $C_{16}H_{17}O_2NCl_2$: C, 65.6; H, 4.4; N, 3.6. Found: C, 65.7; H, 4.5; N, 3.7.

Benzyl 2-Acetoxymethyl-3-methyl-4-(β-chloroethyl)-5-pyrrolecarboxylate (14). The 2-chloromethylpyrrole **16** (1.0 g) was dissolved in 30 mL of 1% sodium acetate in glacial acetic acid, and the mixture was kept at 20 °C for 1 h. It was then poured over 300 mL of ice–water, the aqueous solution was extracted with methylene chloride (2 × 50 mL), and the extracts were washed with a sodium bicarbonate solution followed by water, then dried (Na_2SO_4) and evaporated. The residue was crystallized from cyclohexane: 1.0 g (90%); mp 95 °C; NMR ($CDCl_3$) 1.98, 2.0 (s, 6, CH_3 and CH_3CO), 3.1 (m, 2, CHCl), 3.6 (m, 2, pyrr-CH_2), 5.0 (s, 2, $CH_2O.Ac$), 5.3 (s, 2, CH_2Ph), 7.4 ppm (b, 5, C_6H_5).

Anal. Calcd for $C_{18}H_{20}O_4NCl$: C, 61.8; H, 5.7; N, 4.0. Found: C, 62.0; H, 5.7; N, 4.0.

Benzyl 3-(β-Benzyloxycarbonylethyl)-4-methyl-2-pyrrolecarboxylate (25). *tert*-Butyl 3-(β-ethoxycarbonylethyl)-4-methyl-2-pyrrolecarboxylate (**17**, 2 g) was dissolved in 25 mL of ethanol and 25 mL of a 10% sodium hydroxide solution and saponified as described for **5**. The obtained acid **24** (0.91 g, 65%) was esterified with distilled α-diazotoluene as described for **8**. The product was filtered through a TLC silica gel column using the usual technique and 0.6% methanol in benzene as eluent. On evaporation of the eluates, the dibenzyl ester was obtained: 0.93 g (60%) (cyclohexane); mp 63–64 °C; NMR ($CDCl_3$) 2.0 (s, 3, CH_3), 2.8 (m, 4, CH_2CH_2), 5.1 (s, 2, CH_2Ph side chain), 5.25 (s, 2, CH_2Ph nucleus), 6.6 (b, 1, CH), 7.3 ppm (b, 10, C_6H_5).

Anal. Calcd for $C_{23}H_{23}O_4N$: C, 73.2; H, 6.1; N, 3.7. Found: C, 73.3; H, 6.2; N, 3.8.

Benzyl 3-(β-Methoxycarbonylethyl)-4-methyl-2-pyrrolecarboxylate (26). The dibenzyl ester **25** (2 g) was dissolved in a mixture of 500 mL of anhydrous methanol and 100 mL of concentrated sulfuric acid, and the solution was kept during 3 h at 20 °C. It was then poured over 2 L of ice–water, the aqueous solution was extracted with methylene chloride (3 × 200 mL), and the organic layer was washed with a saturated sodium bicarbonate solution, followed by a water wash, dried (Na_2SO_4), and evaporated to dryness. The residue was filtered through a TLC silica gel column using 0.6 methanol in benzene as eluent. The pooled eluates were evaporated, and the residue crystallized from cyclohexane: 1.2 g (75%); mp 62–63 °C; NMR ($CDCl_3$) 2.0 (s, 3, CH_3), 2.75 (m, 4, CH_2CH_2), 3.55 (s, 3, OCH_3), 5.2 (s, 2, CH_2Ph), 6.55 (b, 1, H), 7.3 ppm (b, 5, C_6H_5).

Anal. Calcd for $C_{17}H_{19}O_4N$: C, 67.8; H, 6.3; N, 4.6. Found: C, 68.0; H, 6.3; N, 4.6.

Dibenzyl 3,3′-Dimethyl-4-(β-chloroethyl)-4′-(β-methoxycarbonylethyl)-5,5′-dipyrrylmethanedicarboxylate (22). The acetate **14** (210 mg, 0.6 mequiv) and the pyrrole **26** (1.80 mg, 0.6 mequiv) were dissolved in 10 mL of glacial acetic acid containing 2.2% of *p*-toluenesulfonic acid. The mixture was heated under nitrogen at

43 °C for 3.5 h; it was then poured over 100 mL of ice water, and the precipitate was filtered, dried, and crystallized from methanol: 250 mg (70%); mp 121 °C (methanol); NMR ($CDCl_3$) 1.94, 1.96 (s, 6, CH_3), 2.7 (m, 8, CH_2CH_2), 3.57 (s, 3, OCH_3), 3.66 (s, 2, $-CH_2-$), 5.2 (s, 4, CH_2Ph), 7.2 ppm (b, 10, C_6H_5).

Anal. Calcd for $C_{33}H_{35}O_6N_2Cl$: C, 67.1; H, 5.9; N, 4.7. Found: C, 66.9; H, 6.0; N, 4.6.

Benzyl 3,3′-Dimethyl-4-(β-chloroethyl)-4′-(β-ethoxycarbonylethyl)-5′-*tert*-butyloxycarbonyl-5-dipyrrylmethanecarboxylate (18). A solution of the acetate **14** (170 mg, 0.5 mequiv) and the pyrrole **17** (160 mg, 0.5 mequiv plus 15%) were dissolved in 2.5 mL of glacial acetic acid containing 2.2% of *p*-toluenesulfonic acid and condensed as described for **22**. The reaction product was purified by filtration through a TLC silica gel column following the usual procedure and using 1% methanol in benzene as eluent. On evaporation of eluates, 136 mg (47%) of the dipyrrylmethane **18** was obtained: mp 113 °C (methanol–water); NMR ($CDCl_3$) 1.3 (t, J = 7 Hz, 3, CH_3CH_2), 1.6 [s, 9, $C(CH_3)_3$], 2.1 (b, 6, CH_3), 2.9 (m, 4, CH_2CH_2CO), 3.78 (m, 4, CH_2CH_2Cl), 4.0 (s, 2, pyrr-CH_2-pyrr), 4.3 (q, J = 7 Hz, 2, CH_2CH_3), 5.5 (s, 2, CH_2Ph), 7.7 (b, 5, C_6H_5).

Anal. Calcd for $C_{31}H_{39}O_6N_2Cl$: C, 65.3; H, 6.8; N, 4.9. Found: C, 65.2; H, 6.9; N, 5.0.

1-(β-Chloroethyl)-4,6,7-(β-methoxycarbonylethyl)-2,3,5,8-tetramethylporphyrin (19). A solution of 270 mg of the dibenzyl ester **22** in 100 mL of glacial acetic acid was reduced over 200 mg of 10% palladium on charcoal at 50 psi during 2 h. The catalyst was filtered and the solution evaporated to dryness in vacuo, affording 112 mg (0.27 nmol, 60%) of the diacid **23**. It was dissolved in a mixture of 80 mL of dry methylene chloride and 8 mL of methanol, 91 mg (0.27 nmol) of the dialdehyde **20** was added followed by 212 mg of *p*-toluenesulfonic acid, and the mixture was kept in the dark during 24 h at 20 °C. Methanol (8 mL) saturated with zinc acetate dihydrate was then added, and the mixture was kept for an additional 48 h; it was then evaporated to dryness at 40 °C, and the residue was dissolved in 60 mL of a 5% sulfuric acid in methanol solution. The solution was kept during 16 h at 20 °C in the dark; it was then diluted with 200 mL of chloroform and washed with water (80 mL), then with a 5% sodium carbonate solution (80 mL), and again with water (80 mL), dried (Na_2SO_4), and evaporated to dryness at 40 °C. The residue was dissolved in 1% methanol in benzene and filtered through a column (2 × 30 cm) of TLC silica gel, packed and prewashed with the same solvent. The eluates containing the main porphyrin fraction (as monitored by fluorescence) were collected and evaporated to dryness, and the residue dissolved in the above-mentioned solvent was adsorbed on a silica gel 60 prepacked column for liquid chromatography (Merck, Darmstadt, size B). Applying enough pressure to obtain a 0.6 mL/min flux of eluent, the porphyrin **19** was eluted separately from two satellite porphyrin bands. On evaporation of the eluent, porphyrin **19** was obtained in crystalline form and was crystallized from benzene–cyclohexane: 22 mg (23%); mp 193 °C; NMR (0.05 M $CDCl_3$) 3.27 (m, 6, $CH_2CO_2CH_3$), 3.50, 3.57 (b, 12, CH_3), 3.68 (s, 9, OCH_3), 4.27 (m, 10, pyrr-CH_2, CH_2CH_2Cl), 9.87, 9.92, 9.97, 10.07 ppm (s, 4, =CH); MS *m/e* 686.5 (M^+, 80%).

Anal. Calcd for $C_{38}H_{43}O_6N_4Cl$: C, 66.4; H, 6.3; N, 8.2. Found: C, 66.3; H, 6.2; N, 8.1.

1-Vinyl-4,6,7-(β-methoxycarbonylethyl)-2,3,5,8-tetramethylporphyrin (3) (Trimethyl Ester). Methanol saturated with zinc acetate dihydrate (4 mL) was added to a solution of the β-chloroethylporphyrin **19** (22 mg) in 10 mL of dry methylene chloride. The mixture was warmed to 35 °C for a while, and then poured over 50 mL of water. The organic layer was separated, washed with aqueous sodium acetate, then with water, dried (Na_2SO_4), and evaporated to dryness. The residue was dissolved in 3.5 mL of dry tetrahydrofuran, and 11 mL of 1 M solution of potassium *tert*-butoxide in *tert*-butyl alcohol was added. The mixture was kept in a sealed vessel under vacuum (50 μ) during 96 h at 20 °C. The vessel was then opened, the mixture was poured into water (100 mL), and the solution was adjusted to pH 6 with glacial acetic acid, then extracted with 1% pyridine in methylene chloride (3 × 30 mL). The organic extracts were dried (Na_2SO_4) and evaporated to dryness, and the residue was dissolved in 30 mL of 5% sulfuric acid in methanol. After keeping overnight at 20 °C in the dark, chloroform (150 mL) was added and the mixture was washed with aqueous sodium acetate, then with a sodium bicarbonate solution, and finally with water. The organic layer was dried (Na_2SO_4), evaporated to dryness, and purified by chromatography through a TLC silica gel column using 1% methanol in benzene as eluent. The eluates were evaporated to dryness and the residue was crystallized from benzene–cyclohexane: 14 mg (65%); mp 197–199 °C (the trimethyl ester of the porphyrin isolated by incubation of **1** had mp 197–198 °C; mmp 197–198 °C); R_f 0.40 (TLC, benzene–1% methanol); visible max spectrum ($CDCl_3$) 403 nm (ε 125 000), 502 (12 500), 536 (10 000), 573 (6670), 625 (4600) (see ref 1 for visible max of incubation product); NMR (0.05 M $CDCl_3$) 3.23 (m, 6, $CH_2CO_2CH_3$), 3.40 (s, 3, C_3CH_3), 3.50 (s, 6, C_5CH_3, C_8CH_3), 3.60 (s, 3, C_2CH_3), 3.7 (s, 9, OCH_3), 4.28 (m, 6, pyrr-CH_2), 6.26 (m, 2, $=CH_2$), 8.20 (m, 1, =CH), 9.77, 9.86, 9.92, 9.98 (s, 4, meso-CH); MS *m/e* 650 (M^+, 80%).

Anal. Calcd for $C_{38}H_{42}O_6N_4$: C, 70.1; H, 6.5; N, 8.6. Found: C, 70.0; H, 6.4; N, 8.5.

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Registry No.—**3** trimethyl ester, 60297-35-0; **4**, 62562-72-5; **5**, 53700-88-2; **6**, 54278-18-1; **7**, 62562-73-6; **8**, 62562-74-7; **9**, 62562-75-8; **10**, 62587-53-5; **11**, 54278-16-9; **12**, 62562-76-9; **13**, 62562-77-0; **14**, 62562-78-1; **16**, 62562-79-2; **17**, 62562-80-5; **18**, 62562-81-6; **19**, 62562-82-7; **20**, 4792-10-3; **22**, 62562-83-8; **23**, 62562-84-9; **24**, 62562-85-0; **25**, 51742-43-9; **26**, 51671-83-1; α-diazotoluene, 27457-43-8.

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(16) All melting points were taken on the Kofler block, and NMR spectra were taken as noted. Microanalyses were performed by the Alfred Bernhardt Mikroanalytisches Laboratorium (Elbach). The silica gel used for column chromatography was Kieselgel G (Fluka AG). TLC was performed on precoated silica gel 60 F-254 plaques (Merck, Darmstadt). The substances were spotted when necessary by spraying with Ehrlich's reagent (2% *p*-dimethylaminobenzaldehyde in 6 N HCl).
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Synthesis of Protoporphyrin XIII and Protoporphyrin III

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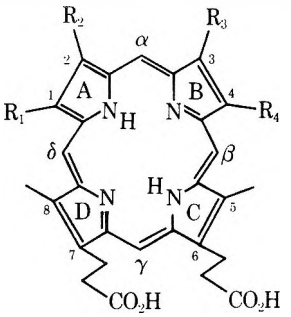
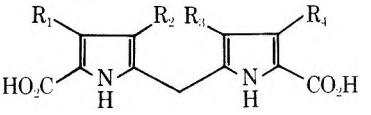
The synthesis of protoporphyrin XIII dimethyl ester [1,4-vinyl-2,3,5,8-tetramethyl-6,7-bis(β-methoxycarbonylethyl)porphine] and of protoporphyrin III dimethyl ester [1,4,5,8-tetramethyl-2,3-vinyl-6,7-bis(β-methoxycarbonylmethyl)porphine] was achieved. For the synthesis of protoporphyrin XIII the precursor ethyl 2,3-dimethyl-4-(β-ethoxycarbonylmethyl)-5-pyrrocarboxylate was obtained by the catalytic hydrogenation of the corresponding 3-formylpyrrole. The dimethylpyrrole was converted into its dimeric dipyrrylmethane through its acetate, and the former was reduced to the corresponding bis(β-hydroxethyl)dipyrrylmethane. Saponification with dilute potassium hydroxide afforded the 5,5′-dicarboxydipyrrylmethane, which was condensed with the 5,5′-diformyldipyrrylmethane **7** to give the 1,4-bis(β-hydroxyethyl)porphyrin. The latter was transformed into protoporphyrin XIII dimethyl ester through the β-chloroethyl intermediate. Protoporphyrin III was obtained either by a similar sequence, or from the benzyl 3,3′-bis(β-chloroethyl)-4,4′-dimethyl-5,5-dipyrrylmethanedicarboxylate.

Protoporphyrin IX (**1**) is the only natural divinylporphyrin involved in a major metabolism. Its iron chelate (heme)—the prosthetic group of hemoglobin—is an important metabolic factor for the in vivo induction of the synthesis of globin and other proteins,[1] and its regulatory properties in hemoglobin biosynthesis are firmly established.[2] It has no other natural analogues, since the specificity of the enzymes involved in the biosynthesis of protoporphyrin IX from coproporphyrinogen III preclude the formation of isomeric protoporphyrins from other coproporphyrinogen isomers.[3] We have found, however, that when coproporphyrinogen IV (**2**) was incubated with duck blood hemolysates, it was transformed in good yields into a protoporphyrin isomeric with protoporphyrin IX.[4] Similar results were obtained by Jackson and co-workers using chicken hemolysates,[5] and by Battersby and co-workers using been liver mitochondria.[6] Both reached the conclusion that the isomeric protoporphyrin was protoporphyrin XIII (**3**) (Fischer's notation[7]). The synthesis of **3** will be described in this paper. The synthetic product was also found by us to be identical with the product of the enzymatic reaction (see below). Since the enzyme spares the vicinal 6,7-β-carboxyethyl chains and only decarboxylates the propionic acid residues of rings A and B, the formal oxidative decarboxylation of coproporphyrinogen II (**4**) will afford protoporphyrin III)**5**).[8] Although protoporphyrin III was never isolated before as a natural product, its synthesis can make it available for further studies on hemoglobin biosynthesis. Protoporphyrin I—the formal decarboxylation product of coproporphyrinogen I—was recently prepared by synthesis.[9] Protoporphyrin IX (**1**) was also prepared by total synthesis.[10]

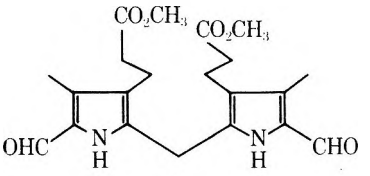


1, $R_1 = R_3 = CH_3$; $R_2 = R_4 = CH{=}CH_2$
2, $R_1 = R_4 = CH_2CH_2CO_2H$; $R_2 = R_3 = CH_3$ (hexahydro derivative)
3, $R_1 = R_4 = CH{=}CH_2$; $R_2 = R_3 = CH_3$ (dimethyl ester)
4, $R_1 = R_4 = CH_3$; $R_2 = R_3 = CH_2CH_2CO_2H$ (hexahydro derivative)
5, $R_1 = R_4 = CH_3$; $R_2 = R_3 = CH{=}CH_2$ (dimethyl ester)
16, $R_1 = R_4 = CH_2CH_2OH$; $R_2 = R_3 = CH_3$ (dimethyl ester)
17, $R_1 = R_4 = CH_2CH_2Cl$; $R_2 = R_3 = CH_3$ (dimethyl ester)
18, $R_1 = R_4 = CH_3$; $R_2 = R_3 = CHOHCH_3$
23, $R_1 = R_4 = CH_3$; $R_2 = R_3 = CH_2CH_2Cl$ (dimethyl ester)
29, $R_1 = R_4 = CH_3$; $R_2 = R_3 = CH_2CH_2OH$ (dimethyl ester)

The synthesis of **3** and **5** was carried out by condensation of a 5,5′-dicarboxydipyrrylmethane **6** containing the substituents of rings A and B with the known[10] diformyldipyrrylmethane **7**. The vinyl side chains in **3** and **5** were derived



6



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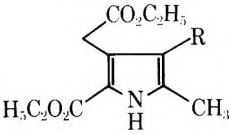
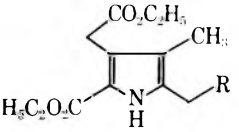
from a preformed β-chloroethyl residue.[10] The synthesis of protoporphyrin XIII (**3**) hence required a preparative synthesis of the 2,3-dimethylpyrrole **8**. We have recently prepared **8** by the reductive methylation of **9** with paraformaldehyde and hydriodic acid.[11] A new and very convenient method for the synthesis of **8** was found by the catalytic reduction of the readily available aldehyde **10** with hydrogen over 10% palladium on charcoal. The aldehyde **10** was in turn prepared by the Vilsmaier–Haak formylation of the easily available β-free pyrrole **9**. The 2,3-dimethylpyrrole **8** was transformed into its 2-acetoxymethyl derivative **11** by a prior treatment with sulfuryl chloride, followed by the reaction of the resulting 2-chloromethylpyrrole **12** with sodium acetate in acetic acid.

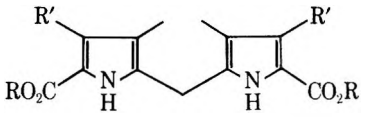


8, R = CH_3
9, R = H
10, R = CHO



11, R = $OCOCH_3$
12, R = Cl

The direct oxidation of **10** with lead tetraacetate gave poor yields of **11**. Dimerization of **11** afforded the dipyrrylmethane **13** in 80% yield. Treatment of **13** with diborane resulted in the

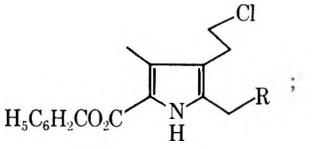


13, R = C_2H_5; R′ = $CH_2CO_2C_2H_5$
14, R = C_2H_5; R′ = CH_2CH_2OH
15, R = H; R′ = CH_2CH_2OH

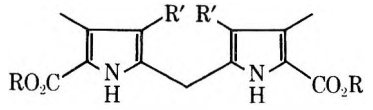
reduction of the side-chain esters and the dipyrrylmethane **14** was thus obtained. Saponification of **14** produced the 5,5′-dicarboxydipyrrylmethane **15** which was condensed without further purification with the aldehyde **7** in the presence of *p*-toluensulfonic acid.[10,12]

The porphyrin **16** was thus obtained in 26% yield; and by treatment with mesyl chloride in pyridine it was transformed into the β-chloroethylporphyrin **17**. Vinylation of **17** with potassium *tert*-butoxide afforded protoporphyrin XIII (**3**) which was isolated as its dimethyl ester. It was found to be identical in its spectral properties and melting point with the dimethyl ester of the protoporphyrin isolated by the enzymatic decarboxylation of coproporphyrinogen IV.[4,13]

Protoporphyrin III (**5**) dimethyl ester was prepared by Fischer[8] by dehydration of 1,4,5,8-tetramethyl-2,3-di(α-hydroxyethyl)-6,7-di(β-carboxyethyl)porphine (hematoporphyrin III) (**18**). The latter was in turn obtained by reduction of the corresponding 2,3-diacetylporphyrin prepared by acetylation of deuteroporphyrin III. When planning the total synthesis of **5**, we first made use of the known[14] 2-acetoxymethylpyrrole **19**. By dimerization of **19** in ethanol–hydrochloric acid the β-chloroethyldipyrrylmethane **20** was obtained in 33% yield. The yields were low owing to the ethanolysis of the acetoxymethyl residue of **19**, which resulted in the simultaneous formation of the ethyl ether **21**. The dimerization attempts of **21** were unsuccessful.



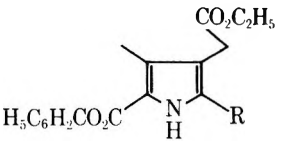
19, R = $OCOCH_3$
21, R = OC_2H_5



20, R = $CH_2C_6H_5$; R′ = CH_2CH_2Cl
22, R = H; R′ = CH_2CH_2Cl
26, R = $CH_2C_6H_5$; R′ = $CH_2CO_2C_2H_5$
27, R = $CH_2C_6H_5$; R′ = CH_2CH_2OH
28, R = H; R′ = CH_2CH_2OH

Hydrogenolysis of the benzyl ester group of **20** afforded the acid **22**, which was not purified but condensed directly with the usual technique with the diformyldipyrrylmethane **7** to give the bis(β-chloroethylporphyrin) **23** in 30% yield.

Due to the low yields obtained in the preparation of **20**, a second approach to **23** was developed analogous to the sequence used for the obtention of **17**. The readily available pyrrole **24** was transformed into its 2-acetoxymethylpyrrole **25** by treatment with lead tetraacetate. The dimerization of **25** afforded the dipyrrylmethane **26** in 59% yield. By reduction of **26** with diborane the bis(β-hydroxyethyl)dipyrrylmethane **27** was obtained in 90% yield. Hydrogenolysis of the benzyl esters of **27** and condensation of the crude diacid **28** with the diformyldipyrrylmethane **7** afforded the β-hydroxyethyl-



24, R = CH_3
25, R = CH_2OCOCH_3

porphyrin **29** in 32% yield. The latter was transformed into **23** by treatment with mesyl chloride. Vinylation of **23** with potassium *tert*-butoxide followed by esterification with methanol–sulfuric acid gave protoporphyrin III dimethyl ester (**5**) in 55% yield.

Although the dimethyl esters of both protoporphyrin XIII and protoporphyrin III markedly differ in their melting point and solubility properties, they could not be separated by TLC on silica gel, or by TLC on cellulose of the corresponding acids.

Experimental Section[15]

Ethyl 2-Methyl-4-(ethoxycarbonylmethyl)-3-formyl-5-pyrrolecarboxylate (10). Phosphorus oxychloride (43.2 mL, 0.48 mol) was added dropwise to 52 mL of dimethylformamide at 5 °C, and the mixture was kept during 15 min at 20 °C. A solution of 12 g (0.05 mol) of pyrrole **9**[16] in 100 mL of dimethylformamide was then slowly added to the former solution while the mixture was kept at 5 °C with continuous stirring under moisture exclusion conditions. The resulting solution was heated at 75 °C for 1 h and cooled, and a concentrated sodium hydroxide solution was added to adjust the mixture to pH 8. After a further heating at 75 °C during 15 min, the mixture was poured over 3 L of ice water and filtered, and the aldehyde **10** was recrystallized from methanol–water: 10.8 g (80%); mp 155–157 °C (lit.[17] mp 151–152 °C); NMR ($CDCl_3$) 1.35 (m, 6, CH_2CH_3), 2.5 (s, 3, CH_3), 4.3 (m, 6, CH_2CO, CH_2CH_3), 10.0 ppm (s, 1 CHO).

Anal. Calcd for $C_{13}H_{17}O_5N$: C, 58.4; H, 6.4; N, 5.2. Found: C, 58.4; H, 6.3; N, 5.1.

Ethyl 2,3-Dimethyl-4-(ethoxycarbonylmethyl)-5-pyrrolecarboxylate (8). The aldehyde **10** (3 g) was dissolved in 150 mL of ethanol and was reduced with hydrogen at 50 psi during 15 h over 3 g of 10% palladium on charcoal. The catalyst was filtered, the solution was evaporated to dryness, and the residue was crystallized from methanol–water: 2.35 g (85%); mp 113–114 °C (lit.[11] mp 113–114 °C); NMR ($CDCl_3$) 1.25 (m, 6, CH_3CH_2), 1.94 (s, 3, C_3CH_3), 2.2 (s, 3, C_2CH_3), 3.8 (s, 2, CH_2), 4.2 (m, 4, cH_2CH_3), 9.1 ppm (b, 1, NH).

Ethyl 2-Chloromethyl-3-methyl-4-ethoxycarbonylmethyl-5-pyrrolecarboxylate (12). To a solution of 1.5 g (6 mmol) of **8** in 50 mL of dry carbon tetrachloride was added 0.48 mL (6 mmol) of distilled sulfuryl chloride. The mixture was stirred and heated at 50 °C for 4 h, after which it was evaporated to dryness. The residue was crystallized from methylene chloride–hexane: 1.7 g (100%); mp 93–95 °C; NMR ($CDCl_3$) 1.3 (m, 6, CH_2CH_3), 2.0 (s, 3, CH_3), 3.8 (s, 2, CH_2CO), 4.14, 4.34 (m, 4, CH_2CH_3), 4.6 ppm (s, 2, CH_2Cl).

Anal. Calcd for $C_{13}H_{18}O_4NCl$: C, 54.2; H, 6.3; N, 4.9. Found: C, 54.3; H, 6.2; N, 4.8.

Diethyl 3,3′-Dimethyl-4,4′-(ethoxycarbonylmethyl)-5,5′-dipyrrylmethanedicarboxylate (13). The 2-chloromethylpyrrole **12** (1.7 g) was dissolved in 60 mL of glacial acetic acid containing 1% of anhydrous sodium acetate. After keeping the mixture for 1 h at 20 °C, it was evaporated to dryness and the dry solid residue of **11** was dissolved in 120 mL of absolute ethanol containing 6 mL of concentrated hydrochloric acid. The solution was heated at 100 °C during 4 h, after which it was cooled and poured into 500 mL of ice water. The aqueous mixture was extracted with chloroform (3 × 100 mL), and the pooled extracts were washed with a 5% bicarbonate solution (50 mL), then with water (100 mL), dried (Na_2SO_4), and evaporated to dryness. The residue was crystallized from methanol–water: 1.16 g (80%); mp 105–107 °C; NMR ($CDCl_3$) 1.27 (m, 12, CH_2CH_3), 1.97 (s, 6, CH_3), 3.78 (s, 4, CH_2CO), 3.89 (s, 2, $-CH_2-$), 4.22 ppm (m, 8, CH_2CH_3).

Anal. Calcd for $C_{25}H_{34}O_8N_2$: C, 61.2; H, 3.9; N, 5.7. Found: C, 61.1; H, 6.8; N, 5.9.

Benzyl 2-Acetoxymethyl-3-ethoxycarbonylmethyl-4-methyl-5-pyrrolecarboxylate (25). Lead tetraacetate (1.95 g) was added in small portions during 30 min to a stirred solution of 1.5 g of **24**[18] in 15 mL of glacial acetic acid. The solution was kept at 20 °C with constant stirring during a further 2 h. It was then poured into 500 mL of ice water, and the precipitate was filtered and crystallized from

ethanol–water: 1.24 g (70%); mp 112–114 °C; NMR ($CDCl_3$) 1.2 (t, J = 6 Hz, 3, CH_2CH_3), 2.0 (s, 3, CH_3), 2.3 (s, 3, CH_2CO), 3.5 (s, 2, CH_2COO), 4.1 (q, J = 6 Hz, 2, CH_2CH_3), 5.1 (s, 2, CH_2OCO), 5.3 (s, 2, $CH_2C_6H_5$), 7.4 ppm (b, 5, C_6H_5).

Anal. Calcd for $C_{20}H_{23}O_6N$: C, 64.3; H, 6.2; N, 3.7. Found: C, 64.2; H, 6.1; N, 3.6.

Dibenzyl 3,3′-(Ethoxycarbonylmethyl)-4,4′-dimethyl-5,5′-dipyrrylmethanedicarboxylate (26). The acetate **25** (1.19 g) was dissolved in 22 mL of absolute ethanol containing 1.1 mL of concentrated hydrochloric acid, and the mixture was heated under reflux during 6 h. The solution was cooled, and the precipitate was filtered and crystallized from ethanol: 575 mg (60%); mp 158–160 °C; NMR ($CDCl_3$) 1.25 (t, J = 6 Hz, 6 CH_2CH_3), 2.35 (s, 6, CH_3), 3.5 (s, 4, CH_2CO), 3.9 (s, 2, $-CH_2-$), 4.1 (q, J = 6 Hz, 4, CH_2CH_3), 5.3 (s, 4, $CH_2C_6H_5$), 7.4 ppm (s, 10, C_6H_5).

Anal. Calcd for $C_{35}H_{38}O_8N_2$: C, 68.4; H, 6.2; N, 4.6. Found: C, 68.3; H, 6.2; N, 4.5.

Dibenzyl 3,3′-(β-Chloroethyl)-4,4′-dimethyl-5,5′-dipyrrylmethanedicarboxylate (20). The β-chloroethyl acetate **19** (760 mg) was dissolved in a mixture of 50 mL of absolute ethanol and 2.5 mL of concentrated hydrochloric acid, and the solution was heated under reflux during 6 h. Methylene chloride (100 mL) was added to the cooled solution, and the mixture was washed with a 5% sodium bicarbonate solution, then with water, dried (Na_2SO_4), and evaporated to dryness. The dipyrrylmethane **20** was isolated by crystallization of the residue from methanol: 200 mg (33%); mp 133–135 °C; NMR ($CDCl_3$) 2.3 (s, 6, CH_3), 2.9 (t, J = 6 Hz, 4, CH_2Cl), 3.5 (t, J = 6 Hz, 4, CH_2CH_2Cl), 3.9 (s, 2, $-CH_2-$), 5.2 (4, s, $CH_2C_6H_5$), 7.3 ppm (s, 10, C_6H_5).-

Anal. Calcd for $C_{31}H_{32}O_4N_2Cl_2$: C, 65.7; H, 5.7; N, 4.9. Found: C, 65.7; H, 5.7; N, 5.0.

By addition of water to the methanolic crystallization liquors a second product precipitated, 72 mg (10%). It was identified as **21** by its NMR ($CDCl_3$): 1.27 (t, J = 7 Hz, 3, OCH_2CH_3), 2.35 (s, 3, CH_3), 2.9 (t, J = 6 Hz, 2, CH_2Cl), 3.4 (m, 4, OCH_2CH_3, CH_2CH_2Cl), 4.5 (s, 2, $-CH_2O$), 5.3 (s, 2, $CH_2C_6H_5$), 7.4 (b, 5, C_6H_5), 9.1 ppm (b, 1, NH).

Diethyl 3,3′-Dimethyl-4,4′-bis(β-hydroxyethyl)-5,5′-dipyrrylmethanedicarboxylate (14). A diborane-carrying nitrogen flux was obtained by addition of 40 mL of boron trifluoride etherate to 12 g of sodium borohydride suspended in 40 mL of diglyme while the mixture was kept under a gentle nitrogen stream. The diborane–nitrogen stream was bubbled through a solution of 1.2 g of dipyrrylmethane **13** in 50 mL of dry tetrahydrofuran. The reduction of the side chain esters was followed by TLC (8% methanol in benzene), until the tetraester (R_f 0.8) as well as the intermediate triester (R_f 0.5) disappeared. The desired diester **14** had R_f 0.3. Methanol was then added to the tetrahydrofuran solution until the effervescence subsided, and the solution was evaporated to dryness. The residue was purified by filtration through a TLC silica gel column (3.5 × 30 cm) packed and eluted with 10% methanol in benzene. The eluates were evaporated to dryness and the residue was crystallized from methanol–water: 450 mg (45%); mp 169–170 °C; NMR ($CDCl_3$) 1.3 (t, J = 7 Hz, 6, CH_2CH_3), 1.98, 2.0 (s, s, 8, OH, CH_3), 3.0 (t, J = 6 Hz, 4, CH_2OH), 3.8 (m, 6, $-CH_2-$, $-CH_2CH_2OH$), 4.25 ppm (q, J = 7 Hz, 4, CH_2CH_3).

Anal. Calcd for $C_{21}H_{30}O_6N_2$: C, 62.1; H, 7.4; N, 6.9. Found: C, 62.2; H, 7.5; N, 6.9.

Dibenzyl 3,3′-(β-Hydroxyethyl)-4,4′-dimethyl-5,5′-dipyrrylmethanedicarboxylate (27). The reduction of dipyrrylmethane **26** with diborane was carried out following the procedure described for **14**, except for the chromatographic purification, which was unnecessary. From 1 g of **26** was obtained 776 mg (90%) of the dialcohol **27**: mp 134–136 °C; NMR ($CDCl_3$) 1.8 (b, 2, OH), 2.2 (s, 6, CH_3), 2.6 (m, 4, CH_2OH), 3.65, 3.7 (m, 6, $-CH_2-$, CH_2CH_2OH), 5.2 (s, 4, $CH_2C_6H_5$), 7.4 ppm (b, 10, C_6H_5).

Anal. Calcd for $C_{31}H_{34}O_6N_2$: C, 70.2; H, 6.1; N, 5.3. Found: C, 70.1; H, 6.1; N, 5.2.

1,4-Bis(β-hydroxyethyl)-2,3,5,8-tetramethyl-6,7-bis(β-methoxycarbonylethyl)porphine (16). A solution of 410 mg of dipyrrylmethane **14** in 20 mL of ethanol and 20 mL of 4 N potassium hydroxide was kept at 20 °C during 48 h. The ethanol was then evaporated at 30 °C in vacuo, and the solution was adjusted to pH 4 with glacial acetic acid. The precipitated acid **15** was filtered and washed with cold water (180 mg, 0.51 mmol, 52%). The acid was dissolved in a mixture of 150 mL of dry methylene chloride, and 24 mL of methanol containing 222 mg (0.51 mmol) of the diformyldipyrrylmethane **7** added. The resulting solution was divided up into three equal portions, and 150 mg of p-toluenesulfonic acid was added to each portion. The mixtures were kept in the dark at 20 °C for 24 h, when 6.2 mL of methanol saturated with zinc acetate dihydrate was added to each portion. After a further period of 72 h at 20 °C in the dark the three batches were pooled and evaporated to dryness at 40 °C, and the residue was dissolved in 90 mL of a 5% sulfuric acid in methanol solution. The mixture was kept during 16 h at 20 °C in the dark; it was then diluted with 200 mL of chloroform, and washed with water (80 mL), then with a 5% sodium carbonate solution (80 mL), again with water (80 mL), dried (Na_2SO_4), and evaporated to dryness at 40 °C. The residue was dissolved in 4% methanol in benzene and filtered through a column (3.5 × 30 cm) of TLC silica gel, packed and prewashed with the same solvent. The eluates containing the main porphyrin band (monitored by its fluorescence) were collected and evaporated to dryness, and the residue of porphyrin **16** was crystallized from chloroform–hexane: 85 mg (26%); mp 219–221 °C; NMR ($CDCl_3$–CD_3OD, 1:1) 3.36 (m, 4, $CH_2CO_2CH_3$), 3.58, 3.53 (s, s, 12, CH_3), 3.66, 3.72 (s, b, 8, OCH_3, OH), 4.26 (m, 12, CH_2CH_2OH, CH_2CH_2CO), 10.06 ppm (s, 4, =CH); MS m/e 626 (M^+, 20%), 596 (M $-CH_2OH$, 15%), 566 (596 $-$ CH_2OH, 10%).

Anal. Calcd for $C_{36}H_{42}O_6N_4$: C, 69.0; H, 6.7; N, 8.9. Found: C, 68.9; H, 6.7; N, 8.8.

1,4,5,8-Tetramethyl-2,3-bis(β-hydroxyethyl)-6,7-bis(β-methoxycarbonylethyl)porphine (29). A solution of 700 mg of the dibenzyldipyrrylmethane **27** in 70 mL of dry tetrahydrofuran containing 20 drops of triethylamine was reduced with hydrogen at 50 psi during 15 h over 600 mg of 10% palladium on charcoal. The catalyst was filtered and washed with aqueous ammonia. The filtrate was evaporated to dryness in vacuo, and the residue was dissolved in the ammonia washings (100 mL). The solution was adjusted to pH 4 with 2 N acetic acid and cooled and the precipitated acid **28** was filtered and dried (420 mg, 90%). It was dissolved in 350 mL of methylene chloride and 280 mL of methanol and 520 mg of the dialdehyde **7** were added to the solution. The mixture was divided up in seven portions and 150 mg of p-toluenesulfonic acid was added to each one. The procedure described for the synthesis of **16** was then followed. The TLC silica gel column chromatography was performed by using 10% methanol in chloroform as solvent. Evaporation of the eluates afforded 240 mg (32%) of the β-hydroxyethylporphyrin **29**: mp >360 °C dec; NMR (TFA) 3.1 (m, 4, CH_2CO), 3.45, 3.5 (s, 5, 18, CH_3, OCH_3), 4.3 (m, 12, CH_2CH_2OH, CH_2CH_2CO), 10.2 ppm (b, 4, =CH); MS m/e 626 (M^+, 100%), 595 (M $-$ CH_2OH, 80%), 565 (595 $-$ CH_2OH, 30%), 553 (M $-$ $CH_2CO_2CH_3$, 30%), 491 (565 $-$ $CH_2CO_2CH_3$, 20%).

Anal. Calcd for $C_{36}H_{42}O_6N_4$: C, 69.0; H, 6.7; N, 8.9. Found: C, 69.1; H, 6.6; N, 8.8.

1,4,5,8-Tetramethyl-2,3-bis(β-chloroethyl)-6,7-bis(β-methoxycarbonylethyl)porphine (23). Procedure A. Dibenzyl ester **20** (140 mg) dissolved in 100 mL of glacial acetic acid was reduced with hydrogen at 50 psi during 2 h over 140 mg of 10% palladium on charcoal. The catalyst was filtered, the acetic acid was evaporated to dryness in vacuo, and the dry residue (96 mg) was condensed with 90 mg of the dipyrrylmethane aldehyde **7** in one batch following the procedure described for **16**. Final purification of the dimethyl ester **23** was achieved by purification through a TLC silica gel column (2.5 × 30 cm) using 0.5% methanol in chloroform as described above. The porphyrin was crystallized from methylene chloride–hexane: 50 mg (30%); mp 269–271 °C; NMR ($CDCl_3$) 3.25 (m, 4, $CH_2CO_2CH_3$), 3.64 (b, 18, OCH_3, CH_3), 4.40 (m, CH_2CH_2Cl, CH_2CH_2CO), 9.9 (b, 1, =CHα), 10.05 ppm (b, 3, =CH); MS m/e 663 (M^+, 100%), 628 (M $-$ Cl, 40%), 614 (M $-$ CH_2Cl, 40%), 590 (M $-$ $CH_2CO_2CH_3$, 30%).

Anal. Calcd for $C_{36}H_{40}O_4N_4Cl_2$: C, 65.2; H, 6.0; N, 8.4. Found: C, 65.1; H, 6.2; N, 8.3.

Procedure B. To a solution of β-hydroxyethylporphyrin **29** (240 mg) in 36 mL of pyridine was added 12 mL of mesyl chloride, and the mixture was heated at 75 °C for 35 min under nitrogen. The cooled solution was then diluted with 120 mL of water and extracted with methylene chloride (4 × 50 mL). The extracts were dried (Na_2SO_4) and evaporated to dryness in vacuo at 40 °C. The residue was dissolved in a 0.5% methanol in chloroform solution and was filtered through a TLC silica gel column as described above. The bisdichloroethylporphyrin **23** (128 mg, 50%) had mp 269–271 °C and was identical with the porphyrin obtained by procedure A.

1,4-Bis(β-chloroethyl)-2,3,5,8-tetramethyl-6,7-bis(β-methoxycarbonylethyl)porphine (17). The bis(β-hydroxyethyl)porphyrin **16** (80 mg) dissolved in 10 mL of pyridine was treated with 3.5 mL of mesyl chloride as described for the preparation of **23**. The bis(β-chloroethyl)porphyrin **17** was isolated after a purification by column chromatography following the procedure described for **17**: 45 mg (50%); mp 201–203 °C (chloroform–hexane); NMR ($CDCl_3$) 3.24 (m, 4, $CH_2CO_2CH_3$), 3.5, 3.6 (s, s, 12, CH_3), 3.7 (s, 6, OCH_3), 4.3 (m, 12, CH_2CH_2Cl, CH_2CH_2CO), 9.92, 9.97 (s, s, 3, =CH α, β, δ), 10.12 ppm (b, 1, =CHα); MS m/e 663 (M^+, 100%), 628 (M $-$ Cl, 80%), 614 (M $-$ CH_2Cl, 20%), 590 (M $-$ $CH_2CO_2CH_3$, 20%).

Anal. Calcd for $C_{36}H_{40}O_4N_4Cl_2$: C, 65.2; H, 6.0; N, 8.5. Found: C, 65.0; H, 6.1; N, 8.3.

1,4,5,8-Tetramethyl-2,3-vinyl-6,7-bis(β-methoxycarbonylethyl)porphine (Protoporphyrin III Dimethyl Ester) (5). Methanol saturated with zinc acetate (11 mL) was added to a solution of the β-chloroethylporphyrin **23** (64 mg) in 30 mL of dry methylene chloride. The mixture was warmed to 35 °C for a while, and then poured over 100 mL of water. The organic layer was separated, washed with aqueous sodium acetate, then with water, dried (Na_2SO_4), and evaporated to dryness. The residue was dissolved in 10 mL of dry tetrahydrofuran, and 30 mL of a 1 M solution of potassium *tert*-butoxide in *tert*-butyl alcohol was added. The mixture was kept in a sealed vessel under vacuum (50 μ) during 96 h at 20 °C. The vessel was then opened, the mixture was poured into water (200 mL), and the solution was adjusted to pH 6 with glacial acetic acid, then extracted with 1% pyridine in methylene chloride (3 × 60 mL). The organic extracts were dried (Na_2SO_4) and evaporated to dryness, and the residue was dissolved in 70 mL of 5% sulfuric acid in methanol. After keeping overnight at 20 °C in the dark, chloroform (300 mL) was added and the mixture was washed with aqueous sodium acetate, then with a sodium bicarbonate solution, and finally with water. The organic layer was dried (Na_2SO_4), evaporated to dryness, and purified by chromatography through a TLC silica gel column using 0.5% methanol in chloroform as eluent. The eluates were evaporated to dryness and the residue was crystallized from methylene chloride–hexane: 35 mg (60%); mp 262–264 °C (lit.[8] mp 276 °C); visible max spectrum ($CDCl_3$) 404 nm (ε 114 000), 502 (9500), 538 (6400), 574 (4000), 626 (2400); NMR (0.05 M, $CDCl_3$) 3.25 (m, 4, CH_2CO), 3.56 (b, 12, CH_3), 3.70 (s, 6, OCH_3), 4.35 (m, 4, CH_2CH_2CO), 6.3 (m, 4, $=CH_2$), 8.15 (m, 2, =CH), 9.93, 10.00 ppm (b, b, 4, meso =CH); MS *m/e* 590 (M^+, 100%), 517 ($M - CH_2CO_2CH_3$, 70%).

Anal. Calcd for $C_{36}H_{38}O_4N_4$; C, 73.2; H, 6.5; N, 9.5. Found: C, 73.1; H, 6.6; N, 9.4.

1,4-Vinyl-2,3,5,8-tetramethyl-6,7-bis(β-methoxycarbonylethyl)porphine (Porphyrin XIII Dimethyl Ester) (3). The bis(β-chloroethyl)porphyrin **17** (62 mg) was vinylated with potassium *tert*-butoxide as described in the preparation of **5**. After the purification by chromatography the protoporphyrin dimethyl ester **3** was crystallized from methylene chloride–hexane: 30 mg (55%); mp 208–210 °C (lit.[5] mp 198–200 °C); visible max ($CDCl_3$) 408 nm (ε 117 000), 506 (10 000), 540 (8000), 576 (4400), 630 (3500) (see ref 13 for visible max of the same product obtained by incubation of coproporphyrinogen IV with duck blood erythrocytes); NMR (0.05 M, $CDCl_3$) 3.35, 3.43 (s, s, 12, CH_3), 3.62 (s, 6, OCH_3), 3.12, 4.22 (t, t, 8, CH_2CH_2CO), 6.18, 8.20 (m, m, 6, $CH=CH_2$), 9.58, 9.76, 9.86 (s, s, s, 1, 1, 2, meso =CH). MS *m/e* 590 (M^+, 70%), 517 ($M - CH_2CO_2CH_3$, 50%), 416 ($M - 2CH_2CH_2CO_2CH_3$, 80%).

Anal. Calcd for $C_{36}H_{38}O_4N_4$: C, 73.2; H, 6.5; N, 9.5. Found: C, 73.1; H, 6.6; N, 9.3.

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Aldol Condensations of Regiospecific Penicillanate and Cephalosporanate Enolates. Hydroxyethylation at C-6 and C-7

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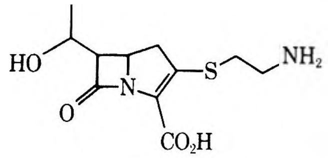
Enolates derived from 6α-bromo- or 6α-iodopenicillanates, 6,6-dibromopenicillanate, and 7α-iodocephalosporanate have been generated in situ by a metal–halogen exchange process at −78 °C using either *n*-butyllithium or methylmagnesium bromide and reacted with acetaldehyde to yield aldols. The condensations consistently provided diastereomeric mixtures of hydroxyethylated products at the α face of the β-lactam nucleus and a *single* diastereomer at the β face. The absolute configuration of one such diastereomer, benzyl 6α-bromo-6β-(1′-hydroxyethyl)penicillanate (**8a**), was determined by x-ray analysis of its *tert*-butyldimethylsilyl derivative **9**. Subsequent reduction of these bromohydrins with zinc–silver couple in methanol or methanolic acetic acid and GLC analysis of the resulting purified products as their trimethylsilyl ether derivatives lead to the absolute structures of benzyl 6-(1′-hydroxyethyl)penicillanates **4a–d**.

Thienamycin (**1**), a highly active β-lactam antibiotic recently discovered in these laboratories,[1] has several features which distinguish it from the more familiar penicillins **2** and cephalosporins **3**. In particular, the hydroxyethyl[2] side chain α to the lactam carbonyl at C-6 is unusual, as generally this substituent is an amide moiety in naturally occurring penicillins and cephalosporins.

We were therefore interested in preparing the hybrid



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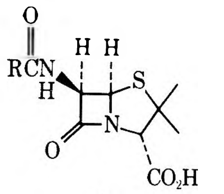

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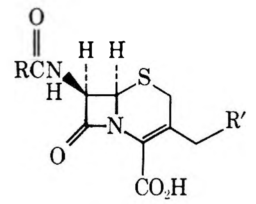
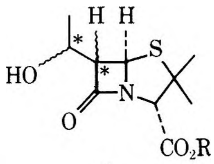
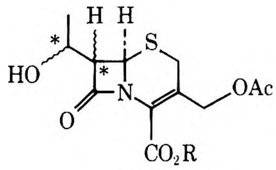


3

6(7)-hydroxyethyl substituted penicillins 4 and cephalosporins 5 to compare their chemical, physical, and antibacterial properties, and we report herein details of our findings.



4
R = CH_2Ph, H

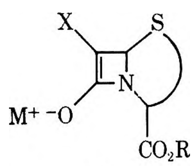


5
R = CMe_3, H

Results and Discussion

At the time this work was initiated, the relative stereochemistry of thienamycin was unknown. Accordingly, any solution to the introduction of the hydroxyethyl function should reflect the production of as many of the four possible stereoisomers at the designated centers.

Typically, β-hydroxycarbonyl systems are generated by use of an aldol or Reformatsky reaction, but few examples of the prerequisite penicillin and cephalosporin enolates 6 (wherein X = H or a reducible equivalent) have appeared in the literature.[3]

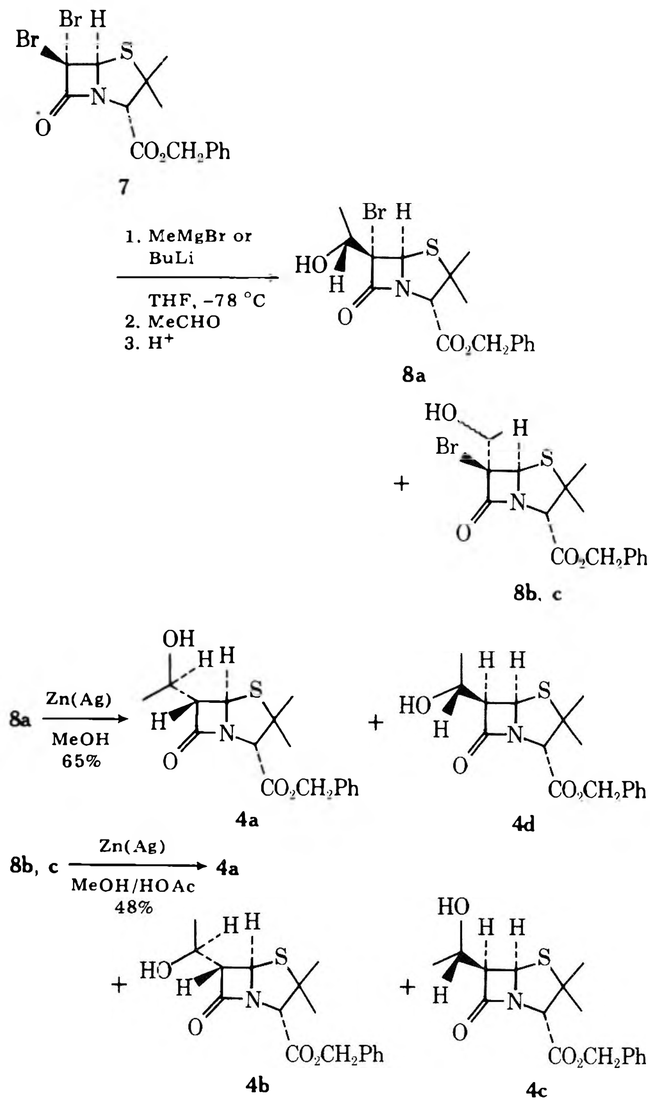


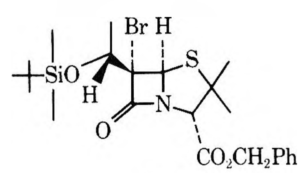
6

The mention[5] without comment or experimental detail that methyl 6-bromopenicillanate formed from methyl 6,6-dibromopenicillanate upon reaction with 1 equiv of butyllithium seemed to us to be a possible case of penicillin enolate formation.[6] We have exploited this idea of metal–halogen exchange as a first step in a sequence which leads to all four of the possible penicillin isomers 4 (R = CH_2Ph) (Scheme I).

Treatment of an anhydrous tetrahydrofuran solution of benzyl 6,6-dibromopenicillanate (7) with 1 equiv of either *n*-butyllithium in hexane or methylmagnesium bromide in ether gave upon reaction with excess acetaldehyde a mixture of three bromohydrins **8a–c**. Yields were 30–40% when produced with *n*-butyllithium and 95% with methylmagnesium bromide. The mixture was separable by multiple elution plate layer chromatography into **8a** and a mixture of **8b,c**. The configuration of the bromine atom of isomer **8a** was assigned as α based on the observed downfield shift of the C-5 proton in the NMR spectrum of **8a** as compared to diastereomers **8b** and **8c** using the argument previously advanced by Cama et al.[7] See Table I. Absolute confirmation of the structural assignment of **8a** was afforded by the single crystal x-ray analysis[8] of its *tert*-butyldimethylsilyl ether derivative 9 prepared by the method of Corey and Venkateswarlu.[9] A stereoview of this compound is depicted in Figure 1.

Scheme I



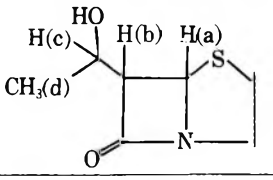


9

As depicted in Scheme I, removal of the bromine from **8a** and **8b,c** was accomplished with zinc-silver couple[10] in methanol or methanol–ccetic acid to provide the designated mixtures of isomers 4 (R = CH_2Ph).[11] Although not obvious by TLC, it was clear from NMR data that mixtures of isomers of 4 were present. Quantitative composition of each purified reduction sample could be determined by conversion of an aliquot with *N,O*-bis(trimethylsilyl)trifluoroacetamide (BSTFA) to the corresponding monotrimethylsilyl derivatives and analysis by gas–liquid chromatography wherein the four isomers **4a–d** had different retention times. Table II indicates the product ratios found.

When benzyl 6α-bromopenicillanate (**10a**) was substituted for dibromide 7 a mixture of isomers 4 (R = CH_2Ph) could be obtained directly in very low yield (Scheme II). Analogously, the use of the corresponding iodopenicillanate **10b** afforded yields of isomers 4 in the range of 0–21% when the metal–

Table I. Chemical Shift Data of β-Lactams[a]



Compd	H(a)	H(b)	H(c)	H(d)
8a	5.56 (s)		4.18 (m)	1.23 (d, J = 6 Hz)
8b, c	5.46 (s) 5.48 (sh)		4.18 (m)	1.46 (d, J = 6 Hz)
4a (R = CH_2Ph)	5.26 (d, J = 2 Hz)	3.26 (dd, J = 7, 2 Hz)	4.16 (m)	1.28 (d, J = 6 Hz)
4b (R = CH_2Ph)	5.23 (d, J = 2 Hz)	3.38 (dd, J = 6, 2 Hz)	4.18 (m)	1.33 (d, J = 6 Hz)
4c (R = CH_2Ph)	5.43 (d, J = 4 Hz)	3.50 (dd, J = 10, 4 Hz)	4.2 (m)	1.37 (d, J = 6 Hz)
4d (R = CH_2Ph)	5.35 (d, J = 4 Hz)	3.47 (dd, J = 9, 4 Hz)	4.18 (m)	1.20 (d, J = 6 Hz)
4a (R = H)[b]	5.29 (d, J = 2 Hz)	3.23 (dd, J = 7, 2 Hz)	4.13 (m)	1.26 (d, J = 6 Hz)
4b (R = H)	5.26 (d, J = 2 Hz)	3.38 (dd, J = 5, 2 Hz)	4.21 (m)	1.36 (d, J = 6 Hz)
4c (R = H)[b]	5.40 (d, J = 4 Hz)	3.51 (dd, J = 10, 4 Hz)	4.2 (m)	1.30 (d, J = 6 Hz)
4d (R = H)[b]	5.41 (d, J = 5 Hz)	3.53 (dd, J = 9, 5 Hz)	4.12 (m)	1.13 (d, J = 6 Hz)
9	5.46 (s)		4.16 (q, J = 6 Hz)	1.18 (d, J = 6 Hz)
5a (R = CMe_3)	4.67 (d, J = 3 Hz)	3.19 (dd, J = 6, 3 Hz)	4.26 (m)	1.35 (d, J = 6 Hz)
5b (R = CMe_3)	4.60 (d, J = 2 Hz)	3.26 (dd, J = 5, 2 Hz)	4.26 (m)	1.36 (d, J = 6 Hz)
5d (R = CMe_3)	4.90 (d, J = 5.4 Hz)	3.6 (dd, J = 9, 5.4 Hz)	4.36 (m)	1.31 (d, J = 6 Hz)

[a] All shifts are measured in $CDCl_3$ and are reported in δ ppm downfield from Me_4Si, followed by multiplicity and coupling constants J: s, singlet; d, doublet; dd, doublet of doublets; q, quartet; m, multiplet. [b] Measured in Me_2CO-d_6.

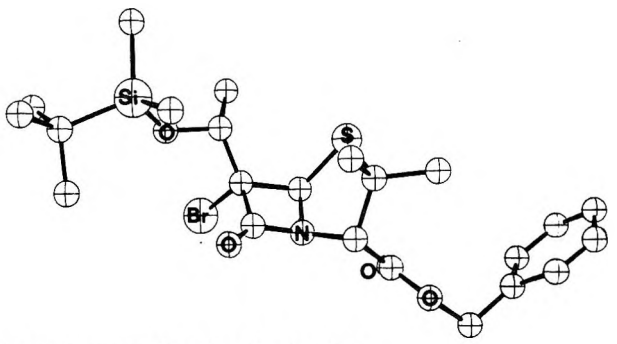
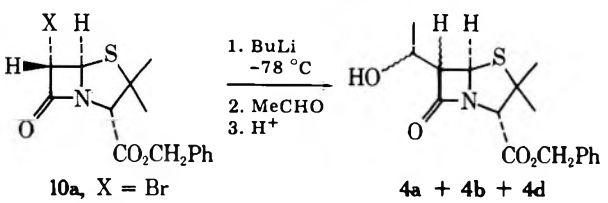


Figure 1. ORTEP drawing of molecule **9**.

halogen exchange reaction was conducted in THF. This situation was improved considerably when the solvent was changed to ethyl ether and **4a, 4b,** and **4d** could be obtained in consistent yields of about 50%. Optimally, this mixture could be produced in 80% yield by the action of methylmagnesium bromide instead of BuLi in THF solvent. See Table II for isomer composition.

Scheme II



10a, X = Br
b, X = I

4a + 4b + 4d

Table II. Isomer Distribution of Products 4

Starting material	Isomers	Yield, %
8a	**a:d** = 94:6	60
8b,c	**a:b:c** = 37:53:10	30
8b,c	**a:b:c** = 21:62:17[a]	55
8b,c	**a:b:c** = 20:41:39[b]	41
8b,c	**a:b:c** = 17:40:43[c]	48
10b	**a:b:d** = 32:47:21	0–21[d]
10b	**a:b:d** = 47:35:18	50[e]
10b	**a:b:d** = 24:49:27	80[f]

[a] 0.5 equiv of HOAc added. [b] 2.5 equiv of HOAc added. [c] 2.64 equiv of HOAc added. [d] Reactions carried out in THF; as reaction scale increased, yield decreased. [e] Reactions conducted in Et_2O. [f] Metal–halogen exchange performed with MeMgBr in THF.

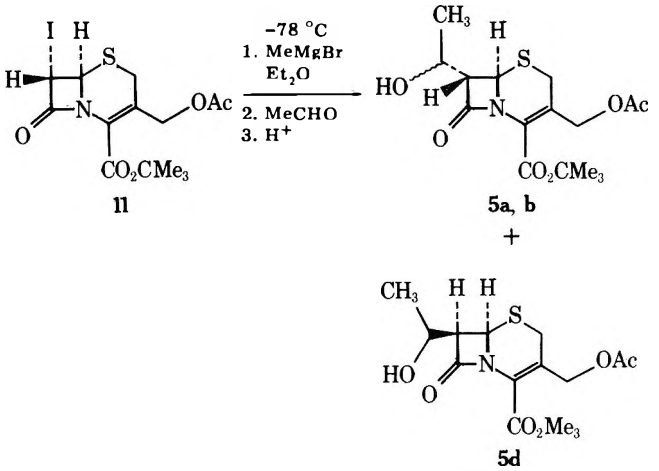
Having accomplished the objective of preparing all four isomers of penicillanate **4**, the problem of isomer separation was undertaken. In any TLC solvent system examined only a single spot was observed with every isomers **4** mixture. GC separation of the trimethylsilyl derivatives of **4** was satisfactory on an analytical scale but judged impractical on a preparative scale. However, through the use of high-pressure liquid chromatography (HPLC) a system was developed in which trans diastereomers **4a** and **4b** appeared as one peak and cis diastereomers **4c** and **4d** appeared as another. By using samples enriched in a given isomer together with the HPLC techniques of recycling and peak shaving, pure samples of each isomer were obtained. Table I contains the NMR data for the four individual isomers.

The separate benzyl ester isomers **4a–d** were smoothly

converted into the corresponding carboxylic acids **4a–d** (R = H) by hydrogenation over 10% palladium on carbon. Table I summarizes the pertinent NMR data of these antibiotics. Each isomer was tested as the sodium salt against a variety of bacteria. The two trans diastereomers **4a** and **4b** were essentially equiactive but substantially less active than the corresponding cis diastereomers **4c** and **4d** which were also essentially equiactive. All, however, were markedly less active than benzylpenicillin.

Finally, the cephalosporin derivatives **5** (R = CMe_3) were analogously obtained as outlined in Scheme III. Exposure of

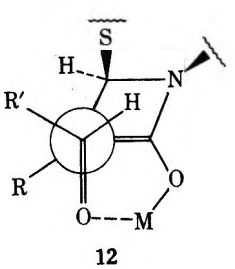
Scheme III



11 **5a, b** + **5d**

tert-butyl 7α-iodo-3-acetoxymethyl-Δ^3-cephalosporanate (**11**) to ethereal MeMgBr as before provided a 42% yield of a separable mixture of **5a,b** and **5d** in a respective ratio of 1.5:1.0. A pure sample of the major trans diastereomer **5a** could be obtained by fractional crystallization and subsequent HPLC. (See Table I for NMR data.) Isomers **5a** and **5d** were converted to the corresponding sodium salts by sequential treatment with trifluoroacetic acid and sodium bicarbonate. These materials were found to be almost completely devoid of antibacterial activity. Although no attempt was made to rigorously assign a configuration to the hydroxyethyl side chain of **5a** and **5d**, it is most probable by analogy to the penicillin examples and the argument that follows that both of these compounds possessed the *R* configuration.

In conclusion, it is noteworthy that in a variety of hydroxyalkylations[13] performed as depicted in Scheme II with aldehydic substrates, only a *single 6β-hydroxyalkyl penicillanate diastereomer* could be detected. This observation can be rationalized in terms of steric hindrance of substrate approach to the more sterically hindered face of the benzylpenicillanate with concomitant coordination of the aldehyde carbonyl oxygen atom to the metal of the enolate,[14] viz., **12**.



12

Molecular models clearly show a severe steric interaction of the aldehyde R′ group with the thiazolidine ring and the C-2β-Me group when it occupied the alternate conformation depicted in **12**. Such a postulate is also consistent with the observed (*R*) configuration of the 6β-hydroxyethylpenicillanates **4d** (R = CH_2Ph) and **8a** generated by **12** (R = H and Br, respectively). The demand of a rigid geometry for this β substituent is reflected by the magnitude of the coupling constant for the 6α proton and the methine proton of the ethanol group in compounds **4c** and **4d** (R = CH_2Ph). [Compare the analogous couplings in **4a** and **4b** (R = CH_2Ph) in Table I.] As a further test of this hypothesis, replacement of acetaldehyde by acetone as in Scheme II should then exclusively produce the 6α 2′-propanol adduct. Indeed, this was found to be the case in repetitive, carefully examined experiments.

Experimental Section

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were recorded in chloroform solution or as a thin film on a Perkin-Elmer 137 infrared spectrophotometer. Only selected absorptions are reported. The NMR spectra were recorded on either a Varian T-60 or HA-100 spectrometer. Tetramethylsilane was used as an internal standard and chemical shifts are reported in parts per million (δ) relative to Me_4Si. Deuteriochloroform was used as solvent unless indicated otherwise. Mass spectra were obtained on an LKB 9000 gas chromatograph–mass spectrometer at 70 eV. Only the most abundant and/or significant ions are given. Gas chromatographic analyses were performed on a Varian Aerograph Series 1200 instrument equipped with flame ionization detectors and helium was used as the carrier gas with a flow rate of 25 mL/min. Stainless steel columns (5 ft × 0.125 in.) packed with 5% SE-30 on 100/120 Variport were employed for analyses. High-pressure liquid chromatographic analyses were performed on a Waters Associates ALC/GPC 244 apparatus using Porosil A columns and Burdick and Jackson "distilled in glass" UV grade acetonitrile and chloroform. The progress of reactions was generally followed by TLC on Analtech silica gel GF 254 plates using UV and ceric sulfate spray followed by heating to detect spots. Plate layer chromatography (PLC) was performed on either Analtech silica gel GF 20 × 20 cm or 20 × 40 cm plates. Column chromatography was conducted with Baker silica gel 60–200 mesh. Tetrahydrofuran and diethyl ether were freshly distilled from benzophenone ketyl. Butyllithium (Ventron Corp.) was titrated periodically using the *sec*-butyl alcohol/biquinoline method. Methylmagnesium bromide in ether (2.9 M) was used as supplied by Ventron Corp. *N,O*-Bis(trimethylsilyl)trifluoroacetamide (BSTFA) was purchased from Supelco, Inc.

Preparation of Benzyl 6,6-Dibromopenicillanate (7).[7] To a stirred solution of freshly prepared benzyl diazopenicillanate[15] (9.9 g, 31 mmol) in 300 mL of methylene chloride at −40 °C under a nitrogen atmosphere was added dropwise a solution of bromine (5 g, 31 mmol) in 50 mL of methylene chloride over 55 min. The mixture was let warm to 0 °C over 45 min and evaporated under reduced pressure. The residue was purified by chromatography and eluted withbbenzene to give 6.2 g (44%) of **7**. Recrystallization from 2-propanol gave mp 78.5–79 °C dec: IR 1792, 1740 cm^{-1}; NMR δ 1.36 (s, 3 H), 1.6 (s, 3 H), 4.53 (s, 1 H), 5.16 (s, 2 H), 5.76 (s, 1 H), 7.33 (s, 5 H).

Anal. Calcd for $C_{15}H_{15}NO_3SBr_2$: C, 40.11; H, 3.37; N, 3.12; Br, 35.58. Found: C, 40.19; H, 3.27; N, 3.20; Br, 35.68.

Preparation of Benzyl 6α-Bromopenicillanate (10a). To a stirred mixture of freshly prepared benzyl diazopenicillanate[15] [derived from 1.59 g of (3 mmol) of benzyl 6-aminopenicillanate *p*-toluenesulfonic acid salt] and potassium bromide (1.0 g, 8.4 mmol) in 150 mL of acetone at 0 °C in an ice–water bath was added dropwise 10 mL of 1 N hydrobromic acid. The mixture was stirred at 0 °C for 40 min and 1.5 g of $NaHCO_3$ was added. This mixture was stirred at 0 °C for 20 min, filtered, and evaporated. The residue obtained was partitioned between water and benzene and the benzene extract dried over Na_2SO_4, filtered, and evaporated. Purification by column chromatography eluted with benzene provided 0.73 g (59%) of **10a**: pale yellow oil; NMR δ 1.38 (s, 3 H), 1.58 (s, 3 H), 4.52 (s, 1 H), 4.76 (d, J = 1.5 Hz, 1 H), 5.14 (s, 2 H), 5.38 (d, J = 1.5 Hz), 7.3 (s, 5 H).

Preparation of Benzyl 6α-Iodopenicillanate (10b). As described above, a solution of benzyl diazopenicillanate in 100 mL of acetone was stirred in an ice–water bath and treated dropwise with a solution of 2.0 g (13.1 mmol) of NaI, 1.3 mL of 57% HI, and 10 mL of water over 35 min. The mixture was stirred at 0 °C for 1 h, 2 g of $NaHCO_3$ was added, and the mixture was stirred for 15 min longer. The acetone was removed under reduced pressure and the residue was partitioned between benzene and H_2O. The benzene layer was separated, washed with aqueous sodium thiosulfate solution, dried over $MgSO_4$, and evaporated. The residue was chromatographed eluting with benzene to give 0.87 g (63%) of **10b** as a pale yellow oil: IR 1780, 1740 cm^{-1}; NMR δ 1.33 (s, 3 H), 1.53 (s, 3 H), 4.5 (s, 1 H), 4.92 (d, J = 1.5 Hz, 1 H),

5.12 (s, 2 H), 5.42 (d, J = 1.5 Hz, 1 H), 7.3 (s, 5 H); mass spectrum m/e 417 (M^+), 389, 250, 227.

Formation of Benzyl 6-Bromo-6-(1′-hydroxyethyl)penicillanates (8a and 8b,c). A. Reaction of 7 with MeMgBr. To a stirred solution of 449 mg (1.0 mmol) of benzyl 6,6-dibromopenicillanate (**7**) in 25 mL of dry THF at −78 °C under nitrogen was added dropwise 345 μL (1.0 mmol) of ethereal methylmagnesium bromide and the mixture was stirred for 20 min. To the stirred, colorless solution at −78 °C under N_2 was added 300 μL (5.3 mmol) of neat acetaldehyde and the solution was stirred for 20 min. The reaction was quenched at −78 °C with 2 mL of saturated aqueous NH_4Cl, and partitioned between Et_2O and H_2O. The organic phase was separated, washed with brine, dried with $MgSO_4$, filtered, and evaporated. Purification of the colorless, oily residue by PLC [one development, C_6H_6–EtOAc (4:1)] gave 80 mg of recovered dibromide (**7**) and 326.5 mg (96%) of a mixture of bromohydrins **8a–c**. Separation was effected by PLC [three developments, CH_2Cl_2–EtOAc (50:1)] to provide 230.5 mg of benzyl 6α-bromo-6β-[(*R*)-1′-hydroxyethyl]penicillanate (**8a**) which slowly crystallized [mp 63–64 °C; IR 3600–3200, 1783, 1748 cm^{-1}; NMR, see Table I; mass spectrum m/e 415, 413 (M^+), 334, 250, 225, 223, 166, 164, 114, 91] and 81 mg of a mixture of bromohydrins **8b,c** as a light yellow oil [IR 3600–3200, 1783, 1748 cm^{-1}; NMR, see Table I; mass spectrum m/e 415, 413 (M^+), 334, 250, 225, 223, 166, 154, 114, 91; GC–mass spectrum of separated Me_3Si derivatives in order of emergence m/e 487, 485 (16), 472, 470 (16), 406 (5), 250 (32), 222, 220 (32), 157 (21), 91 (100), and 487, 485 (12), 472, 470 (12), 406 (7), 250 (26), 222, 220 (26), 157 (17), 91 (100)].

B. Reaction of 7 with BuLi. To a stirred solution of **7** (3.5 g, 7.75 mmol) in 80 mL of anhydrous THF at −70 °C under nitrogen atmosphere was added dropwise 3.25 mL of a 2.38 M solution of butyllithium in hexane. The mixture was stirred for 10 min and a solution of acetaldehyde (0.36 g, 8.25 mmol) in 2.4 mL of anhydrous THF was added. The resulting mixture was stirred at −70 °C under nitrogen atmosphere for 15 min and the reaction was quenched with 10 mL of a saturated aqueous NH_4Cl solution. The cold solution was filtered and the filtrate was concentrated under reduced pressure. The concentrate was partitioned between chloroform and aqueous brine and the organic phase was separated, dried with $MgSO_4$, filtered, and evaporated. Purification by chromatography gave 1.3 g (41%) of **8a–c**. Separation as above gave 585 mg of **8a**[16] and 297 mg of **8b,c**.

Formation of Benzyl 6α-Bromo-6β-[(*R*)-1′-*tert*-butyldimethylsiloxyethyl]penicillanate (9). A mixture of crude **8a**[16] (133.5 mg, ca. 0.3 mmol) and 2 mL of a stock solution comprised of 10 mmol of *tert*-butyldimethylchlorosilane[9] and 25 mmol of imidazole in 10 mL of dry DMF was heated at 55 °C under N_2 for 5 h. The cooled mixture was poured into 25 mL of H_2O and 20 mL of Et_2O. The layers were separated and the aqueous phase further extracted with 20 mL of Et_2O. The ether extracts were combined, washed with H_2O (2 × 10 mL), dried ($MgSO_4$), filtered, and evaporated. Purification by PLC [one development, $CHCl_3$–hexane (1.5:1)] provided 92 mg (ca. 54%) of **9**: mp 89.5–90 °C (2-propanol); IR 1788, 1730 cm^{-1}; NMR δ 0.083 (s, 6 H), 0.92 (s, 9 H), 1.18 (d, J = 6 Hz, 3 H), 1.37 (s, 3 H), 1.57 (s, 3 H), 4.17 (q, J = 6 Hz, 1 H), 4.23 (s, 1 H), 5.17 (s, 2 H), 5.47 (s, 1 H), 7.33 (s, 5 H); mass spectrum m/e 514, 512, 472, 470, 422, 420, 392, 250, 241, 239, 221, 219, 91.

Anal. Calcd for $C_{23}H_{34}BrNO_4SSi$: C, 52.26; H, 6.48; N, 2.65; Br, 5.12. Found: C, 52.32; H, 6.18; N, 2.44; Br, 15.48.

Formation of Benzyl 6α- and 6β-[(*R*)-1′-Hydroxyethyl]penicillanates (4a and 4d). Reduction of 8a. To a stirred suspension of excess zinc–silver couple[10] in 0.5 mL of MeOH at room temperature was added a solution of **8a** (35 mg, 0.084 mmol) in 1 mL of MeOH. The mixture was stirred under an atmosphere of N_2 for 1.25 h. The excess couple was removed by filtration and the filtrate was evaporated. The residue was partitioned between EtOAc and dilute, aqueous HCl. The organic phase was separated, washed successively with brine and dilute, aqueous $NaHCO_3$, dried ($MgSO_4$), filtered, and evaporated. Purification by PLC [one development, C_6H_6–EtOAc (4:1)] yielded 18.5 mg (65%) of a mixture of **4a** and **4d**. See Table II for the isomer composition of this mixture, Table I for the NMR of the separated isomers, and below for further spectroscopic characterization and HPLC separation.

Formation of 4a, 4b, and 4c by Reduction of 8b,c. To a stirred suspension of excess Zn(Ag)[10] in 1 mL of MeOH were added in rapid succession 75.6 mg (1.26 mmol) of neat glacial HOAc and a solution of 197.7 mg (0.48 mmol) of **8b,c** in 1 mL of MeOH. The mixture was stirred under N_2 for 5 min and worked up as described above. PLC [one development, C_6H_6–EtOAc (3:1)] afforded 76 mg (48%) of a mixture of **4a, 4b,** and **4c**. See Tables I and II and below for HPLC separation and further characterization.

Analogous reductions of **8b,c** with 0.5 and 2.5 equiv of HOAc and without any HOAc gave the results depicted in Table II.

Formation of 4a, 4b, and 4d from Benzyl 6α-Iodopenicillanate (10b). To a stirred solution of 2.01 g (4.82 mmol) of **10b** in 50 mL of dry Et_2O at −73 °C under N_2 atmosphere was added 2 mL (4.82 mmol) of 2.4 M BuLi in hexane. After 20 min at −73 °C, 500 μL (8.9 mmol) of neat MeCHO was added. The mixture was stirred at −73 °C for 35 min and at −40 °C for 30 min. The reaction was quenched at −40 °C with 10 mL of saturated aqueous NH_4Cl solution. The layers were separated and the aqueous phase further extracted with CH_2Cl_2. The extracts were combined and evaporated. The residue was redissolved in CH_2Cl_2, dried over $MgSO_4$, filtered, and evaporated to give 2.04 g of residue. Purification by chromatography eluting with EtOAc (10–30%) in benzene yielded 811 mg (50%) of a mixture of **4a, 4b,** and **4d**. See Tables I and II and below for HPLC purification and characterization.

The analogous reaction conducted with either **10a** or **10b** in THF provided irreproducible results and diminished yields of **4** (R = CH_2Ph). See Table II.

Separation of Isomers 4 (R = CH_2Ph) by HPLC and Characterization. General. All separations were performed on two 2 ft × 0.375 in. columns of Porosil A using 2% acetonitrile in chloroform (0.65% EtOH content) at a flow rate of 6 mL/min unless specified otherwise. Each purified isomer possessed identical carbonyl and hydroxyl absorptions in the infrared and identical mass spectral fragmentation patterns. Accordingly, a single data set is provided for **4a**. Every isomer was obtained as a colorless oil. GC retention times of the trimethylsilyl derivative prepared from ca. 1–2 mg of material and 2 drops of BSTFA in 1 drop of DMF were recorded at 230 °C. Consult Table I for NMR data.

Isomer 4a. A sample of 197.5 mg of a mixture of **4a** and **4d** having a composition of 95:5, respectively, was divided into approximately four equal aliquots and separated as described above to yield 146 mg of **4a**: IR 3700–3200, 1776, 1754 cm^{-1} (sh); GC retention time 9.1 min; mass spectrum m/e 335 (M^+), 307, 250, 145, 114, 91; mass spectrum of Me_3Si derivative m/e 407 (M^+), 392, 379, 364, 250.

Isomer 4b. A sample of 126.0 mg of composition **4a:4b** 60:40 obtained by removing the isomer **4d** by HPLC from a sample of isomers **4a, 4b,** and **4d** was used to obtain isomer **4b**, the most difficult to obtain. The entire sample was injected into six 2 ft × 0.375 in. columns of Porosil A using 1.5% acetonitrile in chloroform (0.65% ethanol content) at a flow rate of 6 mL/min. All peaks were collected during cycle 1 except for the major peak, which was recycled through six columns a total of 22 times during 51 h. After seven cycles (with no evidence of peak asymmetry) small quantities were "shaved" from the front and back of the broad, large peak to obtain **4b** (front) and isomer **4a** (back). Five fractions obtained from shaving the front of the emerging peak at cycles 9, 10, 12, 17, and 22 were combined after GC analysis of their Me_3Si derivatives from aliquots to provide 22.9 mg of isomer **4b** (contained about 5% of isomer **4a**), GC retention time 9.8 min.

Isomer 4c. A sample of 107 mg of a mixture of composition **4a:4b:4c** 18.6:40.3:41.1 was separated as described to give 27 mg of **4c**, GC retention time 11.3 min.

Isomer 4d. A sample of 239 mg of mixture of composition **4a:4b:4d** 47:33:20 was divided into four equal portions and separated to provide 42 mg of **4d**, GC retention time 12.7 min.

General Procedure for the Formation of 6-(1′-Hydroxyethyl)penicillanic Acids 4a–d (R = H) and Their Sodium Salts 4 (R = Na). To a stirred mixture of 150 mg of prereduced 10% Pd/C, 2 mL of H_2O, 10 mL of MeOH, and 1 mL of 0.1 N $NaHPO_4$ buffer at room temperature was added a solution of a benzyl penicillanate in 3 mL of MeOH and the stirred mixture hydrogenated at atmospheric pressure for 0.5 h. The catalyst was removed by filtration through Solka-Floc and washed with MeOH. The filtrate was concentrated. The concentrate was diluted with H_2O, taken to pH 8.8 with dilute, aqueous $NaHCO_3$, and extracted thoroughly with EtOAc. The separated aqueous phase was acidified to pH 3 with 2.5 N HCl and extracted with EtOAc. The EtOAc extract was dried with $MgSO_4$, filtered, and evaporated to afford pure acids **4** (R = H) in yields of 70–80%. See Table I for NMR data.

The free acid was dissolved in acetone and treated with 1 equiv of aqueous $NaHCO_3$. The acetone was removed under reduced pressure and the aqueous solution lyophilized to give quantitative yields of **4** (R = Na).

Isomer 4a (R = H): mp 136–138 °C dec; IR (Nujol) 3400, 1780, 1774 cm^{-1}; mass spectrum m/e 245 (M^+), 217, 201, 159, 114; mass spectrum bis-Me_3Si m/e 374, 361, 346, 232, 143.

Isomer 4c (R = H): oil, IR 3700–3200, 1770, 1754 cm^{-1} (sh).

Isomer 4d (R = H): mp 150 °C dec.

Preparation of *tert*-Butyl 7α-Iodocephalosporanate (11). To

a stirred solution of *tert*-butyl 7-diazocephalosporanate from 2.7 g (8.4 mmol) of *tert*-butyl 7-aminocephalosporanate[17] by a modification of the procedure of Wiering and Wynberg[18] in 180 mL of acetone at 0–3 °C in an ice–H_2O bath was added dropwise a cold solution of 3.7 mL of 57% HI and 4.76 g (31.8 mmol) of NaI in 15 mL of H_2O over 25 min. To the cold mixture was added solid $NaHCO_3$ and the insoluble materials were removed by filtration. The filtrate was evaporated and the residue was partitioned between 150 mL of EtOAc and 125 mL of 5% aqueous $Na_2S_2O_3$. The organic phase was separated, dried over $MgSO_4$, filtered, and evaporated. Purification of the residue by column chromatography eluting initially with $CHCl_3$ and then C_6H_6–EtOAc (10:1) gave 1.0 g (27%) of **11** as an oil [IR 1778, 1717 cm^{-1}; NMR δ 1.6 (s, 9 H), 2.1(s, 3 H), 3.47 (bs, 2 H), 4.7 (d, J = 12 Hz, 1 H), 4.83 (s, 2 H), 5.07 (d, J = 12 Hz, 1 H); mass spectrum m/e 383, 323, 256, 196, 155] and 220 mg of a mixture of **11** and the corresponding β-iodo isomer. Separation of this mixture by PLC [three developments, C_6H_6–EtOAc (10:1)] gave 47 mg of **11** and 90 mg of *tert*-butyl 7β-iodocephalosporanate: mp 100–102 °C dec (Et_2O–petroleum ether); IR 1786, 1724 cm^{-1}; NMR δ 1.57 (s, 9 H), 2.07 (s, 3 H), 3.4 (bs, 2 H), 4.7 (d, J = 12 Hz, 1 H), 4.77 (d, J = 5 Hz, 1 H), 5.07 (d, J = 12 Hz, 1 H), 5.6 (d, J = 5 Hz, 1 H); mass spectrum m/e 383, 323, 256, 196, 155.

Formation of *tert*-Butyl 7α- and 7β-(1′-Hydroxyethyl)cephalosporanates 5a,b and 5d. To a stirred solution of **11** (137.5 mg, 0.3 mmol) in 10 mL of dry Et_2O at −70 °C under a N_2 atmosphere was added 108 μL (0.3 mmol) of 2.9 M MeMgBr in Et_2O. The mixture was stirred for 10 min and then exposed to a stream of anhydrous MeCHO for 15 min. The mixture was stirred at −70 °C for 45 min and quenched with 1 mL of saturated NH_4Cl solution. The mixture was partitioned between Et_2O and H_2O and the organic phase separated, dried ($MgSO_4$), filtered, and evaporated. Purification of the residue by PLC [two developments, C_6H_6–EtOAc (4:1)] gave 19.0 mg (17%) of **5d** [mp 154.5–155.5 °C (2-propanol); IR 3550 1770, 1732 cm^{-1}; NMR, see Table I; mass spectrum m/e 357 (M^+), 301, 241, 197, 155] and 27.5 mg (25%) of a mixture of **5a** and **5b.** Separation by fractional crystallization (2-propanol–petroleum ether) and HPLC gave a pure sample of the major trans diastereomer **5a:** mp 124 °C; IR 3400, 1778, 1724 cm^{-1}; NMR, see Table I; mass spectrum m/e 301, 241, 197, 155. No attempt was made to further purify the minor trans diastereomer **5b;** however, the NMR data provided in Table I for **5b** were obtained by a subtractive NMR comparison of pure **5a** and an enriched sample of **5b.**

General Procedure for the Conversion of *tert*-Butyl 7-(1′-Hydroxyethyl)cephalosporanates (5a and 5d) to the Free Acids 5a and 5d (R = H) and Their Sodium Salts (R = Na). The *tert*-butyl cephalosporanate (0.08–0.09 mmol) was dissolved in 1 mL of cold CF_3CO_2H (TFA) and stirred at 0 °C for 30 min. The TFA was removed under reduced pressure and the residue obtained partitioned between $CHCl_3$ and dilute, aqueous $NaHCO_3$ solution. The aqueous phase was separated and acidified to pH ca. 1–2 with 2.5 N HCl. The acidified mixture was thoroughly extracted with EtOAc. The combined EtOAc extracts were dried ($MgSO_4$), filtered, and evaporated to give the corresponding cephalosporanic acids which were characterized spectroscopically.

The cephalosporanic acid was dissolved in 3 mL of acetone and 1 mL of H_2O and treated with 1 equiv of $NaHCO_3$ in 0.5 mL of H_2O at room temperature for 5 min. The acetone was removed under reduced pressure and the aqueous solution lyophilized to yield the analogous sodium cephalosporanate.

Isomer 5d (R = H): IR 1763, 1739 cm^{-1}; NMR δ 1.27 (d, J = 6 Hz, 3 H), 2.03 (s, 3 H), 3.53 (bs, 2 H), 3.6 (m, 2 H), 4.6–5.23 (m, 3 H); mass spectrum (bis-Me_3Si) m/e 445 (M^+), 430, 385, 384, 215.

Isomer 5a (R = H): IR 3400, 1700, 1735 cm^{-1}; NMR δ 1.3 (d, J = 6 Hz, 3 H), 2.1 (s, 3 H), 3.36 (m, 3 H), 4.4 (m, 1 H), 5.97 (m, 3 H), 6.5 (bs, 2 H); mass spectrum (bis-Me_3Si) m/e 445 (M^+), 430, 385, 227, 117.

Acknowledgment. We wish to thank Mr. J. Smith, Mr. H. Flynn, and Dr. B. Arison for mass spectral and NMR measurements; Mr. J. P. Gilbert and staff for microanalytical determinations; Ms. J. Kahan for antibacterial evaluations; Dr. C. Shunk for the preparation of numerous starting materials; and Dr. Karst Hoogsteen and Mr. J. Hirshfield for the x-ray determination.

Registry No.—**4a** (R = CH_2Ph), 62263-73-4; **4a** (R = H), 62263-74-5; **4b** (R = CH_2Ph), 62263-75-6; **4b** (R = H), 62263-76-7; **4c** (R = CH_2Ph), 62263-77-8; **4c** (R = M), 62263-78-9; **4d** (R = CH_2Ph), 62263-79-0; **4d** (R = H), 62263-80-3; **5a** (R = CMe_3), 62279-92-9; **5a** (R = H), 62263-81-4; **5b** (R = CMe_3), 62263-82-5; **5d** (R = CMe_3), 62263-83-6; **5d** (R = H), 62263-84-7; **7,** 35564-99-9; **8a,** 62263-85-8; **8b,** 62263-86-9; **8c,** 62263-87-0; **9,** 62263-88-1; **10a,** 62263-89-2; **10b,** 62263-90-5; **11,** 62263-70-1; **11** β-iodo isomer, 62263-71-2; benzyl diazopenicillanate, 20097-92-1; *tert*-butyldimethylchlorosilane, 18162-48-6; benzyl penicillanate, 62263-72-3; *tert*-butyl 7-diazocephalosporanate, 58249-92-6.

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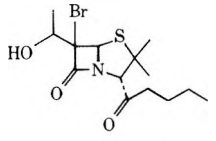

A

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Nucleophilic Addition of Amines to Benzo-Substituted Oxetenes. Formation of 6-Amino-2,4-cyclohexadienones and Their Ring Expansion

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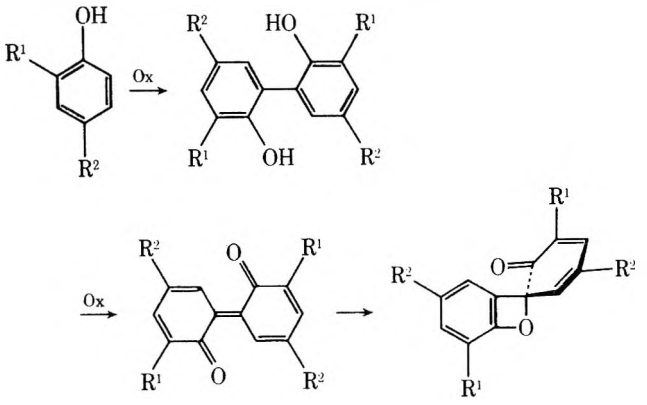
Benzo-substituted oxetenes have been found to react with primary and secondary amines to give 7-aryl-1,3-dihydro-2*H*-azepin-2-ones **3** and 6-amino-substituted 2,4-cyclohexadienones **10**, respectively. Upon direct irradiation through Pyrex, azepinones **3** and their oxidation products, benzofurano-annelated azepinones **4**, undergo isomerization to acetamido-substituted cyclobutenes.

The oxidative coupling of sterically hindered 2,4-substituted phenols smoothly leads to spiroquinol ethers **1** whose remarkable stability was first described in 1961 by Müller and his co-workers.[1]

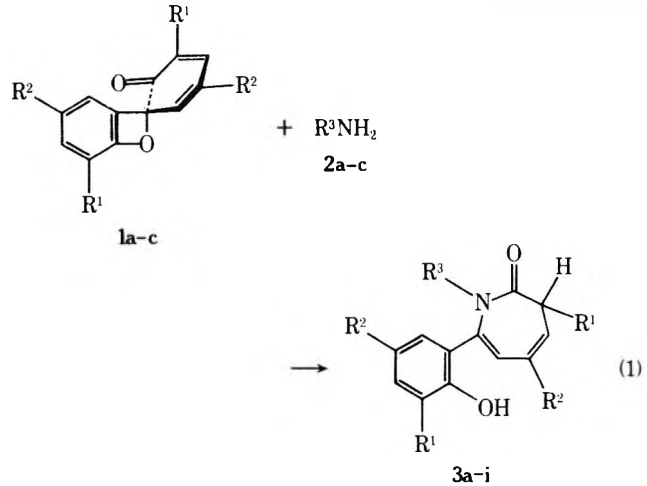


1

Outside the field of phenol oxidation, these spiroquinol ethers have attracted little attention and, consequently, their potential oxetene reactivity toward nucleophiles has not been investigated.[2] We deemed it worthwhile to consider spiroquinol ethers of structure **1** as easily available benzo-substituted representatives of otherwise hardly known oxetenes[3] and study their displacement reactions with amines. The present paper describes the formation of arylated azepinones by nucleophilic addition of primary amines to benzoxetes **1**.[4]

Results and Discussion

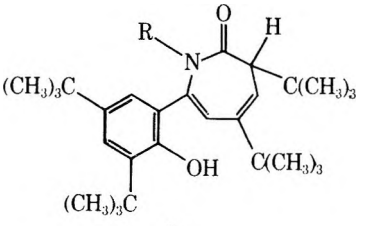
Benzoxetes **1a–c**, when suspended in methanol, readily react with primary amines **2a–c** to give colorless, crystalline 7-aryl-1,3-dihydro-2*H*-azepin-2-ones **3a–i** in good to excellent yields (reaction 1; see Table I). Depending on the degree of solubility of **1**, the reaction may be carried out at ambient or elevated temperature. As exemplified for **3a**, the azepinone structure is supported by the following data and reactions.



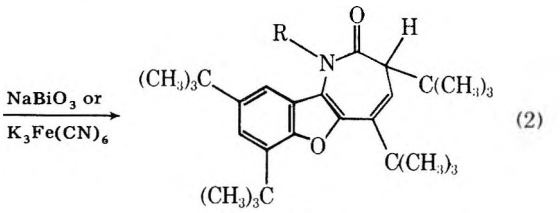
1a–c **2a–c** **3a–i** (1)

The mass spectrum of compound **3a** confirms the molecular weight of a 1:1 addition product by its molecular ion (M^+· 439).[5] The infrared spectrum of **3a** shows absorptions at 1680, 1655, and 1625 cm^{-1}, attributed to the seven-membered cyclic enamide structure. The phenolic hydroxyl gives rise to a sharp band at 3320 cm^{-1}. In its ^1H NMR spectrum, **3a** shows its aromatic hydrogens at 7.38 and 7.03 ppm (J = 2.5 Hz), and the hydrogens at the 3, 4, and 7 positions of the azepinone ring at 2.31, 5.62, and 6.43 ppm, respectively ($J_{3,4}$ = 6.5; $J_{3,6}$ = 1 Hz). In analogy to **3a**, the ^1H NMR spectra of azepinones **3b–i** exhibit the expected similar features of the cyclic enamide moiety (see Table II). Characteristically, H-3 and H-6 show long-range coupling ($J \leq 1$ Hz); however, coupling between H-4 and H-6 was not observed.[6]

In agreement with its hindered phenol structure, **3a** was found to undergo oxidation by potassium ferricyanide in alkaline solution to give a deep green colored radical which was slowly converted into the colorless benzofurano-annelated azepinone **4a** (reaction 2). As the ring closure resembles that



3a



4a (2)

of an electrophilic substitution,[7] the phenoxy radical conceivably is transformed, either by bimolecular disproportionation or by direct oxidation, into the phenoxonium ion. Under more stringent oxidation conditions, namely, by oxidation with sodium bismuthate in refluxing toluene, the conversion of **3** into **4** proceeds rapidly and in excellent yield.

Spectroscopic data of **4a** (and **4b,c**) are in agreement with the proposed structure (see Experimental Section). In particular, the ^1H NMR spectrum of **4a**, in general strikingly similar to that of **3a**, shows the disappearance of H-6 and, of

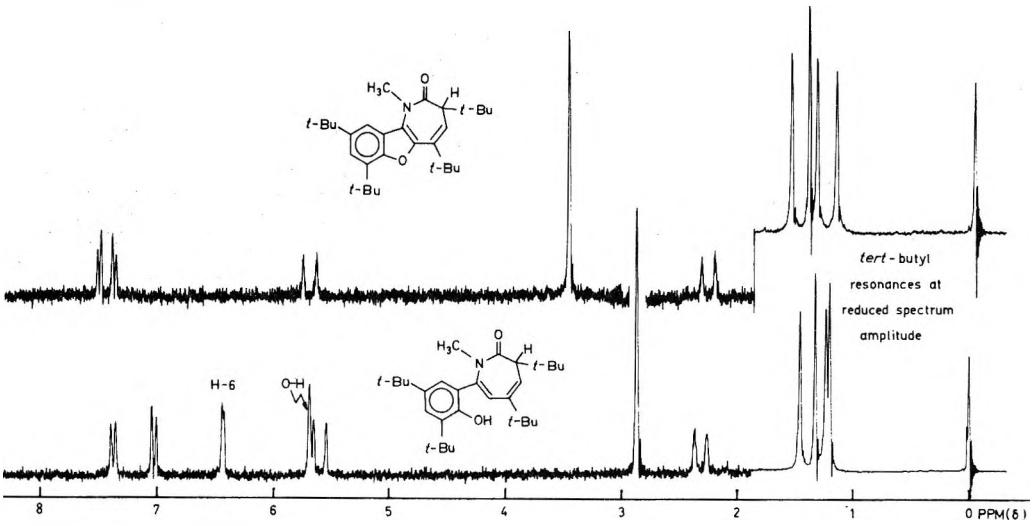


Figure 1. ^{1}H NMR spectra of azepinones **3a** and **4a**.

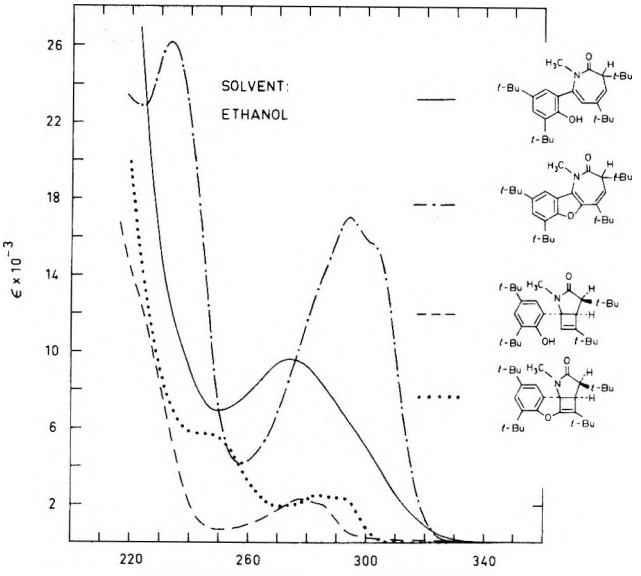


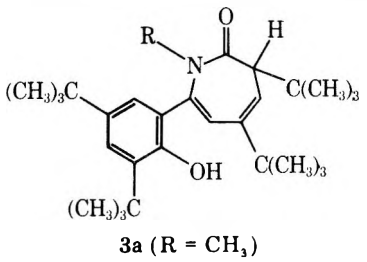
Figure 2. Electronic absorption spectra of azepinones **3a** and **4a**, and their photoproducts **5a** and **6a**.

Table I. Formation of Azepinones 3 from Benzoxetes 1

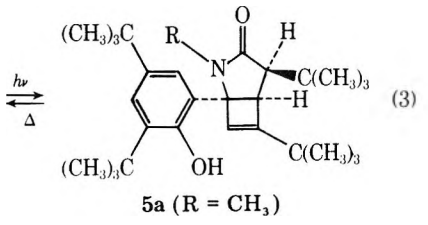
3a–i	R^1	R^2	R^3	Yield, %
a	*tert*-Butyl	*tert*-Butyl	Methyl	87
b	*tert*-Butyl	*tert*-Butyl	*n*-Propyl	76
c	*tert*-Butyl	*tert*-Butyl	Cyclohexyl	75
d	*tert*-Pentyl	*tert*-Pentyl	Methyl	72
e	*tert*-Pentyl	*tert*-Pentyl	*n*-Propyl	81
f	*tert*-Pentyl	*tert*-Pentyl	Cyclohexyl	41
g	*tert*-Butyl	Trityl	Methyl	83
h	*tert*-Butyl	Trityl	*n*-Propyl	90
i	*tert*-Butyl	Trityl	Cyclohexyl	86

course, the phenolic hydroxyl hydrogen (see Figure 1). The differences in the electronic absorption spectra of **3a** and **4a** are significant and revealing. Thus, nonplanar and nonrigid **3a** exhibits its longest wavelength maximum at 274 nm (ϵ 9500). More favorable π-orbital overlap of the 2-vinylbenzofuran chromophore in **4a** is associated with a bathochromic shift and a drastic enhancement of absorption (λ_{max} 294 nm, ϵ 17 000) (see Figure 2).

Support for the conjugated diene moiety in structures **3** and **4** was obtained by photochemical means. Thus, in accordance with the well-documented excited state reactivity of other seven-membered rings containing a conjugated diene moiety,[8] irradiation of **3a** and **4a** gave the acetamido-annelated cyclobutenes **5a** and **6a**, respectively (reactions 3 and 4, respectively). As the absorption of azepinones **3** and **4** at 300 nm is considerable (ϵ 5000 and 16 000 for **3a** and **4a**, respectively), irradiation through Pyrex was found to be most convenient from a preparative point of view, particularly in conjunction with the decrease of absorption in the photoproducts **5** and **6** (see Figure 2).

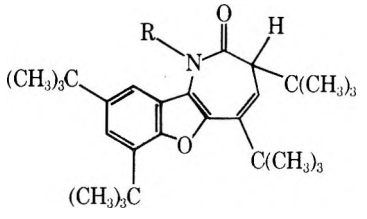


3a (R = CH_3)

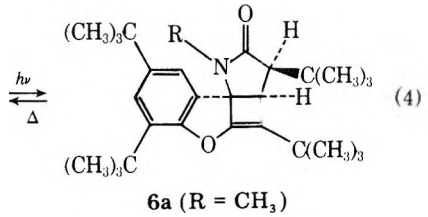


(3)

5a (R = CH_3)



4a (R = CH_3)



(4)

6a (R = CH_3)

Conceivable dimeric photoproducts[9] of **3** and **4** are excluded on the basis of an osmometric molecular weight determination and by the thermal reversibility of the photochemical isomerization.[10] In addition, oxidative cleavage of the cyclobutene

Table II. Chemical Shift Data of Azepinones 3a–i[a]

	3a	3b	3c	3d	3e	3f	3g	3h	3i
H-3	2.31	2.32	2.35	2.43	2.44	2.42	2.44	2.34	2.36
H-4	5.62	5.60	5.62	5.58	5.61	5.51	5.78	5.75	5.78
H-6	6.43	6.47	6.50	6.38	6.42	6.43	6.02	5.91	6.00
$J_{3,4}$	6.5	6.5	6.5	6.5	6.5	6.5	6.5	6.5	6.5
$J_{3,6}$	1	<1	1	<1	<1	<1	<1	<1	<1

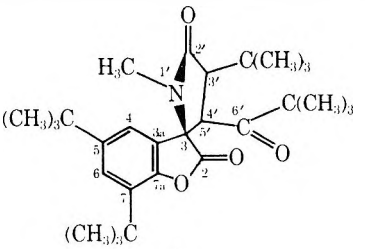
[a] Registry no.: **3a**, 62743-86-6; **3b**, 62778-07-8; **3c**, 62778-06-7; **3d**, 62778-05-6; **3e**, 62743-87-7; **3f**, 62743-88-8; **3g**, 62743-89-9; **3h**, 62743-90-2; **3i**, 62743-91-3.

Table III. ^{13}C Chemical Shifts of 7, 8a, 8b, and 8c[a,g]

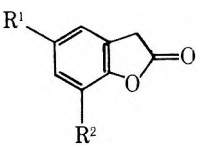
Carbon	7	8a	8b	8c
2	173.9[b]	174.0	173.5	174.1
3	69.8	32.5	33.5	32.7
3a	125.8[c]	123.3[b]	122.2	122.9[b]
4	117.7	122.4[b]	118.7	118.9
5	147.9	133.7[c]	147.1	146.8
5α	34.7[d]	21.0	34.4	34.6[c]
5β	31.3		31.5	31.5
6	125.0[c]	126.2	127.1	122.7[b]
7	134.3	133.1[c]	120.0	133.3
7α	34.2[d]	33.9	15.0	34.3[c]
7β	29.6[e]	29.4		29.6
7a	149.1	150.5	151.3	150.4
1′α	26.4			
2′	173.0[b]			
3′	56.5[f]			
3′α	34.0[d]			
3′β	29.3[e]			
4′	59.0[f]			
6′	212.8			
6′α	45.2			
6′β	25.7			

[a] In parts per million relative to internal Me_4Si. [b–f] Interchangeable assignments within any vertical column. [g] Registy no.: **7**, 60434-65-3; **8a**, 55510-86-6; **8b**, 62743-92-4; **8c**, 62743-93-5.

double bond in **6a** by potassium permanganate afforded the spiro-substituted benzofuranone **7**, exhibiting in its IR spectrum the characteristic[11] carbonyl absorption at about 1800 cm^{-1}. The presence of two strongly coupled hydrogens (J = 11 Hz) in the ^1H NMR spectrum of **7** is indicative of the cis arrangement of H-3′ and H-4′.[12] Comparison with the ^{13}C NMR spectra of model compounds **8a–c**, finally, facilitated



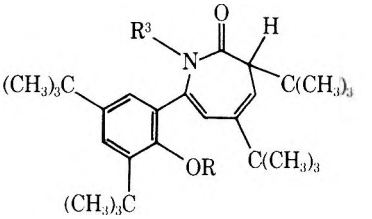
7



8a, $R^1 = CH_3$; $R^2 = C(CH_3)_3$
b, $R^1 = C(CH_3)_3$; $R^2 = CH_3$
c, $R^1 = R^2 = C(CH_3)_3$

complete assignment of the ^{13}C resonances in the NMR spectrum of **7** (see Table III).

In contrast to their excited state reactivity, azepinones **3** and **4** were found to be rather inert in ground state chemistry. Thus, anionic alkylation and acid-catalyzed acylation did not take place in the azepinone moiety but only affected the phenolic hydroxyl group. Thus, **3a** reacts with methylsulfinyl carbanion followed by treatment with methyl iodide to give methyl ether **9a**. Perchloric acid catalyzed reaction of acetic



9a, R = CH_3
b, R = $COCH_3$

anhydride with **3a** gave the acetate **9b**. Attempts to deuterate **9a** at C-3 by treatment with strong base and, subsequently, with deuterium oxide were unsuccessful. Likewise, azepinone **9a** was recovered unchanged after treatment with lithium aluminum hydride in refluxing ether. Attempts to hydrolyze the amido group in azepinones **3a**, **4a**, and **9a** failed. Thus, we have not been able to prove the presence of the amide function in **3** or **4** by chemical means.[14]

The formation of **3** from benzoxetes **1** and primary amines **2** can be rationalized by a nucleophilic displacement reaction leading to 6-amino-substituted 2,4-cyclohexadienones **10** (R^4 = H in Scheme I) which then spontaneously isomerize as

Scheme I

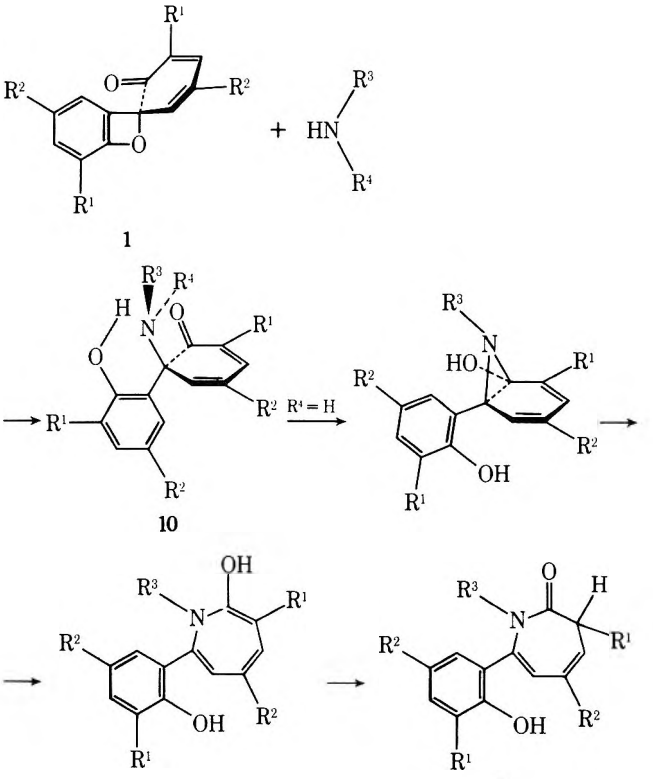


Table IV. Formation of 6-Amino-2,4-cyclohexadienones 10 from Benzoxetes 1

Registry no.	10a–f	R^1	R^2	R^3 R^4	Yield, %
62743-94-6	**a**	*tert*-Butyl	*tert*-Butyl	$-(CH_2)_2O(CH_2)_2-$	94
62743-95-7	**b**	*tert*-Butyl	*tert*-Butyl	$-(CH_2)_5-$	88
62743-96-8	**c**	*tert*-Pentyl	*tert*-Pentyl	$-(CH_2)_2O(CH_2)_2-$	80
62743-97-9	**d**	*tert*-Pentyl	*tert*-Pentyl	$-(CH_2)_5-$	91
62743-98-0	**e**	*tert*-Butyl	Trityl	$-(CH_2)_2O(CH_2)_2-$	97
62743-99-1	**f**	*tert*-Butyl	Trityl	$-(CH_2)_5-$	92

outlined in Scheme I, analogous to a mechanism suggested by Paquette for the reaction of chloramine with phenolate ion.[15] In support of the involvement of the heretofore hypothetical intermediacy of **10**, we have found that secondary amines, such as morpholine and piperidine, smoothly react with **1** in the presence of methanol, even at room temperature, to give 6-amino-2,4-cyclohexadienones **10a–f** in excellent yields (see Table IV). Compounds **10a–d** had been obtained previously in the copper–amine catalyzed autoxidation of the corresponding phenols. However, other structures had been assigned to these products, and they were believed to be formed by oxidative coupling.[17,30] The presence of methanol in the nucleophilic displacement reaction is quite essential,[16] as no **10a** was formed when benzoxete **1a** ($R^1 = R^2 =$ *tert*-butyl) was treated with neat morpholine.[17] Significantly, methanol is known to catalyze the valence isomerization of o-diphenoquinones to benzoxetes.[18] Thus, we believe that the formation of 6-amino-2,4-cyclohexadienones **10** from benzoxetes **1** described in this paper does involve a displacement reaction rather than a conceivable 1,4-addition to *o*-diphenoquinones in equilibrium with their thermodynamically favored valence isomers.

Experimental Section

Melting points (uncorrected) were determined on a hot-stage microscope. Infrared spectra, in KBr disks, and electronic absorption spectra were taken on Beckman IR9 and Beckman DK2 instruments, respectively. ^1H NMR spectra were obtained on a Varian A-60 or Bruker WH 270 spectrometer, using chloroform-*d* as solvent with Me_4Si as internal standard. Chemical shifts are reported in parts per million (δ). ^{13}C NMR spectra (in chloroform-*d*) with chemical shifts relative to internal Me_4Si were recorded at 67.88 MHz using a Bruker WH 270 instrument. Mass spectra were obtained at 70 eV ionizing voltage on an AEI MS9 instrument. Elemental analyses were performed by NOVO Microanalytical Laboratory, Bagsvaerd, Denmark.

Recrystallization of products in all cases involved filtration through Celite in order to remove trace amounts of insoluble material.

Materials. 2-*tert*-Butyl-4-tritylphenol was prepared according to the following modification of Shulgin's method.[19] Sulfuric acid (10 mL) was added to a stirred solution of 2-*tert*-butylphenol (30 g, 0.2 mol) and triphenylcarbinol (52 g) in glacial acetic acid (500 mL) at 45–50 °C. After stirring for 20 h at room temperature the precipitate formed was filtered off, washed with acetic acid and water, and then dried. Recrystallization from petroleum ether (bp 80–110 °C) gave 64 g (81%) of colorless crystals: mp 181–183 °C (lit.[19] 173–174 °C); IR 3540 cm^{-1}; NMR 7.20 (s, 15 H), 7.03 (d, J = 2.5 Hz, 1 H), 6.87 (dd, J = 8 and 2.5 Hz, 1 H), 6.45 (d, J = 8 Hz, 1 H), 4.37 (s, 1 H), 1.25 ppm (s, 9 H).

Anal. Calcd for $C_{29}H_{28}O$ (392.54): C, 88.73; H, 7.19. Found: C, 88.85; H, 7.28.

Benzoxetes **1a** ($R^1 = R^2 =$ *tert*-butyl)[20] and **1b** ($R^1 = R^2 =$ *tert*-pentyl)[21] were prepared according to the literature.

Benzoxete 1c. 2',6-Di-*tert*-butyl-4,4'-ditritylbenzoxete-2-spiro[6'-cyclohexa-2',4'-dien-1'-one].[22] A solution of potassium hydroxide (2 g) in anhydrous methanol (80 mL) and a solution of 2-*tert*-butyl-4-tritylphenol (see above, 15.7 g, 40 mmol) in methylene chloride (120 mL) were added to a stirred suspension of dichlorobis(pyridine)copper(II)[23] (8.5 g) in anhydrous methanol (80 mL) containing molecular sieve (25 g, 3 A). Dry oxygen was passed through the solution at 30–35 °C for 4 h; the reaction mixture was then diluted with ether and filtered and the residue was repeatedly washed with ether. The combined filtrates were thoroughly washed with water and dried (magnesium sulfate) and the solvent was removed in vacuo to give a residue which was dissolved in methylene chloride. Addition of a 3:2 mixture (75 mL) of methanol and 1-propanol to the boiling solution gave a pale yellow precipitate which was filtered off and recrystallized by dissolving in methylene chloride and adding ethanol to give 11.2 g (64%) of colorless crystals (containing 1 molar equiv of methylene chloride): mp 211–214 °C;[24] IR 1655 (m), 1625 (m),[25] 1600 cm^{-1} (s); UV (isooctane) λ ($\epsilon \times 10^{-3}$) 274 (sh, 10.4), 284 (sh, 8.9), 322 nm (sh, 2.5); NMR 7.18 (m, 30 H), 6.90 (d, J = 2 Hz, 1 H), 6.86 (d, J = 2 Hz, 1 H), 6.25 (s, 1 H), 5.25 (s, 2 H, CH_2Cl_2), 5.05 (s, 1 H), 1.27 (s, 9 H), 1.01 ppm (s, 9 H).

Anal. Calcd for $C_{58}H_{52}O_2 \cdot CH_2Cl_2$ (865.99): C, 81.83; H, 6.29. Found: C, 81.84; H, 6.36.

3,5 - Di - *tert*-butyl-7-(3,5-di-*tert*-butyl-2-hydroxyphenyl)-1-methyl-1,3-dihydro-2*H*-azepin-2-one (3a). A suspension of benzoxete **1a** (4.08 g, 10 mmol) in a 1:1:1 mixture of methylene chloride, methanol, and methylamine (40% aqueous solution) was refluxed for 2 h under nitrogen blanketing. Partial vacuum evaporation of solvent followed by addition of aqueous ethanol to the warm mixture gave a colorless crystalline precipitate. It was recrystallized from hot ethanol to give 3.82 g (87%) of colorless crystals: mp 153–155 °C; IR 3520 (m), 1680 (s), 1655 (s), 1625 cm^{-1} (m); UV (ethanol) λ ($\epsilon \times 10^{-3}$) 216 (33.4), 274 nm (9.5); NMR 7.38 (d, J = 2.5 Hz, 1 H), 7.03 (d, J = 2.5 Hz, 1 H), 6.43 (d, J = 1 Hz, 1 H), 5.68 (s, 1 H, OH), 5.62 (d, J = 6.5 Hz, 1 H), 2.87 (s, 3 H), 2.31 (d, J = 6.5 Hz, 1 H), 1.45 (s, 9 H), 1.32 (s, 9 H), 1.23 (s, 9 H), 1.19 ppm (s, 9 H); mass spectrum *m/e* 439 (3, $M^{+\cdot}$), 382 (100, M − 57), 354 (6, M − 57 − 28), 326 (7, M − 57 − 56), 242 (2, M − 57 − 56 − 84); ^{13}C NMR 167.9 (s), 148.9 (s), 145.8 (s), 142.0 (s), 139.0 (s), 135.6 (s), 124.1 (d), 123.7 (s), 123.1 (d), 120.0 (d), 120.0 (d), 53.8 (d), 34.5, 34.1, 33.6, 32.7, 31.2, 31.0, 29.5, 29.2, 27.4 ppm.

Anal. Calcd for $C_{29}H_{45}NO_2$ (439.68): C, 79.22; H, 10.32. Found: C, 79.33; H, 10.36.

3,5 - Di - *tert*-butyl-7-(3,5-di-*tert*-butyl-2-hydroxyphenyl)-1-*n*-propyl-1,3-dihydro-2*H*-azepin-2-one (3b). A suspension of benzoxete **1a** (4.08 g, 10 mmol) in methanol (25 mL) and *n*-propylamine (5 mL) was refluxed for 3 h under nitrogen blanketing. The precipitate obtained on cooling to room temperature was filtered off and recrystallized by precipitation with methanol from methylene chloride solution to give 3.55 g (76%) of colorless crystals: mp 162–164 °C; IR 3520 (m), 1675 (s), 1620 cm^{-1} (w); UV (ethanol) λ ($\epsilon \times 10^{-3}$) 216 (31.2), 273 nm (8.4); NMR 7.33 (d, J = 2 Hz, 1 H), 7.03 (d, J = 2 Hz, 1 H), 6.47 (s, 1 H), 5.68 (s, 1 H, OH), 5.60 (d, J = 6.5 Hz, 1 H), 4.16–3.46 (m, 1 H), 2.97–2.50 (m, 1 H), 2.32 (d, J = 6.5 Hz, 1 H), 1.67–0.90 ppm (m containing sharp peaks at 1.43, 1.33, and 1.22 ppm, 41 H).

Anal. Calcd for $C_{31}H_{49}NO_2$ (467.77): C, 79.60; H, 10.56. Found: C, 79.54; H, 10.80.

3,5-Di-*tert*-butyl-7-(3,5-*tert*-butyl-2-hydroxyphenyl)-1-cyclohexyl-1,3-dihydro-2*H*-azepin-2-one (3c). A suspension of benzoxete **1a** (4.08 g, 10 mmol) in methanol (25 mL) and cyclohexylamine (5 mL) was refluxed for 2 h under nitrogen. Addition of a few drops of water to the reaction mixture gave a precipitate which was filtered off and recrystallized by dissolving in methylene chloride and adding methanol: yield 3.80 g (75%) of colorless crystals, mp 209–211 °C; IR 3520 (m), 1675 (s), 1620 cm^{-1} (m); UV (ethanol) λ ($\epsilon \times 10^{-3}$) 216 (32.4), 274 nm (9.0); NMR 7.28 (d, J = 2.5 Hz, 1 H), 7.02 (d, J = 2.5 Hz, 1 H), 6.50 (d, J = 1 Hz, 1 H), 5.80 (s, 1 H, OH), 5.62 (d, J = 6.5 Hz, 1 H), 3.80–3.50 (hr m, 1 H), 2.35 (dd, J = 6.5 and 1 Hz, 1 H), 1.80–1.00 ppm (m containing sharp peaks at 1.43, 1.32, 1.28, and 1.17 ppm, 46 H); mass spectrum *m/e* 507 (11, $M^{+\cdot}$), 450 (70, M − 57), 368 (100, M − 57 − 82), 312 (17, M − 57 − 82 − 56).

Anal. Calcd for $C_{34}H_{53}NO_2$ (507.80): C, 80.42; H, 10.52. Found: C, 80.69; H, 10.71.

1-Methyl-3,5-di-*tert*-pentyl-7-(2-hydroxy-3,5-di-*tert*-pentylphenyl)-1,3-dihydro-2*H*-azepin-2-one (3d) was prepared as described for **3a** using benzoxete **1b** (2.33 g, 5 mmol) and refluxing for 4 h. The reaction mixture was diluted with ethanol (25 mL) and then concentrated by partial vacuum evaporation of solvent. The precipitate thus obtained was filtered off, washed with methanol, and

recrystallized from hot ethanol giving 1.78 g (72%) of colorless crystals: mp 144–146 °C; IR 3535 (m), 1675 (s), 1630 cm^{-1} (m); UV (ethanol) λ (ε × 10^{-3}) 275 nm (8.9); NMR 7.25 (d, J = 2.5 Hz, 1 H), 6.93 (d, J = 2.5 Hz, 1 H), 6.38 (s, 1 H), 5.70 (s, 1 H, OH), 5.58 (d, J = 6.5 Hz, 1 H), 2.83 (s, 3 H), 2.43 (d, J = 6.5 Hz, 1 H), 2.20–0.55 ppm (br m, 44 H).

Anal. Calcd for $C_{33}H_{53}NO_2$ (495.79): C, 79.94; H, 10.78. Found: C, 79.86; H, 10.69.

3,5-Di-*tert*-pentyl-7-(2-hydroxy-3,5-di-*tert*-pentylphenyl)-1-*n*-propyl-1,3-dihydro-2*H*-azepin-2-one (3e) was prepared as described for **3b** using benzoxete **1b** (2.33 g, 5 mmol) and refluxing for 1 h. The colorless precipitate thus obtained was washed with methanol and recrystallized by dissolving in methylene chloride and adding methanol to the hot solution: yield 2.12 g (81%) of colorless crystals, mp 180–182 °C; IR 3530 (m), 1670 (s), 1625 cm^{-1} (m); UV (ethanol) λ (ε × 10^{-3}) 275 nm (8.3); NMR 7.26 (d, J = 2.5 Hz, 1 H), 6.98 (d, J = 2.5 Hz, 1 H), 6.42 (s, 1 H), 5.73 (br s, 1 H, OH), 5.61 (d, J = 6.5 Hz, 1 H), 4.10–3.60 (m, 1 H), 2.98–2.63 (m, 1 H), 2.44 (d, J = 6.5 Hz, 1 H), 1.98–1.15 (m, 34 H), 0.98–0.54 ppm (m, 15 H).

Anal. Calcd for $C_{35}H_{57}NO_2$ (523.85): C, 80.25; H, 10.97. Found: C, 80.10; H, 11.06.

1-Cyclohexyl-3,5-di-*tert*-pentyl-7-(2-hydroxy-3,5-di-*tert*-pentylphenyl)-1,3-dihydro-2*H*-azepin-2-one (3f) was prepared as described for **3c** using benzoxete **1b** (2.33 g, 5 mmol) and refluxing for 15 h. The reaction mixture was concentrated by vacuum evaporation of solvent. Addition of a few drops of water gave a crystalline precipitate which was recrystallized from hot ethanol to give 1.15 g (41%) of colorless crystals: mp 153–156 °C; IR 3520 (m), 1680 (s), 1620 cm^{-1} (m); UV (ethanol) λ (ε × 10^{-3}) 276 nm (8.1); NMR 7.24 (d, J = 2.5 Hz, 1 H), 6.98 (d, J = 2.5 Hz, 1 H), 6.43 (s, 1 H), 5.87 (S= [H, OH), 5.51 (d, J = 6.5 Hz, 1 H), 3.67 (br m, 1 H), 2.42 (d, J = 6.5 Hz, 1 H), 2.13–0.52 ppm (m, 54 H).

Anal. Calcd for $C_{38}H_{61}NO_2$ (563.91): C, 80.94; H, 10.90. Found: C, 80.75; H, 10.99.

3-*tert*-Butyl-7-(3-*tert*-butyl-2-hydroxy-5-tritylphenyl)-1-methyl-5-trityl-1,3-dihydro-2*H*-azepin-2-one (3g). A suspension of benzoxete **1c** (500 mg, 0.58 mmol), methylamine hydrochloride (0.5 g), and sodium carbonate (1 g) in methanol (10 mL) was kept in an autoclave at 90–100 °C under nitrogen for 45 min. The suspension was then diluted with methylene chloride and washed with water. The organic layer was dried (magnesium sulfate), and solvent was evaporated in vacuo to give an oily residue which was dissolved in a little methylene chloride to give, after addition of methanol, a colorless, crystalline precipitate. It was recrystallized by dissolving in methylene chloride and adding 2-propanol to the boiling solution. The colorless needles obtained in this way contained (according to NMR and elemental analysis) 2 molar equiv of 2-propanol. Solvent-free azepinone **3g** was obtained by dissolving this material in methanol whereupon the substance dissolved, then formed a new precipitate which was dried at 130 °C for 1 h: yield 390 mg (83%) of colorless crystals, mp 143–145 °C; IR 3510 (m), 1685 (s), 1630 (m), 1600 cm^{-1} (m); UV (*n*-heptane) λ (ε × 10^{-3}) 274 (sh, 10.2), 284 (10.5), 301 nm (sh, 7.6); NMR 7.35–7.10 (m containing sharp peaks at 7.24 and 7.18 ppm, 31 H), 6.49 (d, J = 2.5 Hz, 1 H), 6.02 (s, 1 H), 5.78 (d, J = 6.5 Hz, 1 H), 4.86 (br s, 1 H), 2.68 (s, 3 H), 2.44 (d, J = 6.5 Hz, 1 H), 1.17 and 1.08 ppm (two s, 18 H).

Anal. Calcd for $C_{59}H_{57}NO_2$ (812.11): C, 87.26; H, 7.07. Found: C, 87.14; H, 7.13.

3-*tert*-Butyl-7-(3-*tert*-butyl-2-hydroxy-5-tritylphenyl)-1-*n*-propyl-5-trityl-1,3-dihydro-2*H*-azepin-2-one (3h). A suspension of benzoxete **1c** (500 mg, 0.58 mmol) in methanol (7 mL) and *n*-propylamine (3 mL) was kept in an autoclave at 120–130 °C under nitrogen for 15 min. The suspension obtained on cooling was dissolved in methylene chloride and the solution was concentrated by vacuum evaporation of solvent. Addition of acetonitrile gave a precipitate which was recrystallized by dissolving in a little methylene chloride and adding acetonitrile: yield 440 mg (90%) of colorless crystals, mp 211–214 °C after drying at 130 °C for 1 h; IR 3500 (m), 1675 (s), 1655 (s), 1620 (m), 1600 cm^{-1} (m); UV (*n*-heptane) λ (ε × 10^{-3}) 274 (sh, 9.8), 286 nm (11.0); NMR 7.19 (apparent s, 31 H), 6.55 (d, J = 2.5 Hz, 1 H), 5.91 (s, 1 H), 5.75 (d, J = 6.5 Hz, 1 H), 5.03 (br s, 1 H), 3.75 (br m, 1 H), 2.70 (m, 1 H), 2.34 (d, J = 6.5 Hz, 1 H), 1.45–0.87 (m containing sharp peaks at 1.19 and 1.09 ppm, 20 H), 0.62 ppm (m, 3 H).

Anal. Calcd for $C_{61}H_{61}NO_2$ (840.16): C, 87.21; H, 7.31. Found: C, 86.82; H, 7.26.

3-*tert*-Butyl-7-(3-*tert*-butyl-2-hydroxy-5-tritylphenyl)-1-cyclohexyl-5-trityl-1,3-dihydro-2*H*-azepin-2-one (3i). A suspension of benzoxete **1c** (500 mg, 0.58 mmol) in methanol (7 mL) and cyclohexylamine (3 mL) was kept in an autoclave at 130–140 °C under nitrogen for 15 min. The reaction mixture was filtered and organic solvents were removed in vacuo from the filtrate to give an oily residue which formed a precipitate upon treatment with methanol. Recrystallization from acetonitrile gave colorless crystals which were dried at 130 °C: yield 435 mg (86%); mp 188–191 °C; IR 3500 (m), 1685 (s), 1600 cm^{-1} (m); UV (*n*-heptane) λ (ε × 10^{-3}) 275 (sh, 9.7), 286 nm (10.7); NMR 7.19 (apparent s, 31 H), 6.62 (s, 1 H), 6.00 (s, 1 H), 5.78 (d, J = 6.5 Hz, 1 H), 5.07 (br s, 1 H), 3.41 (br m, 1 H), 2.36 (br m, 1 H), 1.75–0.88 ppm (m containing sharp peaks at 1.20 and 1.08 ppm, 28 H).

Anal. Calcd for $C_{64}H_{65}NO_2$ (880.23): C, 87.33; H, 7.44. Found: C, 87.46; H, 7.51.

3,5,7,9-Tetra-*tert*-butyl-1-methyl-1,3-dihydro-2*H*-benzofuro[2,3-*f*]azepin-2-one (4a). Method A. Oxidation of 3a with Potassium Ferricyanide. Azepinone **3a** (2.20 g, 5 mmol) in ether (100 mL) was oxidized with a solution of potassium ferricyanide (20 g) in water (100 mL) containing potassium hydroxide (4 g) under nitrogen for 20 h. The pale green organic layer was then washed with water and dried (magnesium sulfate) and ether was removed in vacuo to give an oil which crystallized upon treatment with methanol. Recrystallization from hot ethanol gave 1.25 g (57%) of colorless crystals: mp 167–168 or 182–183 °C (depending on the rate of crystallization);[26] IR 1675 cm^{-1} (s); UV (ethanol) λ (ε × 10^{-3}) 234 (26.1), 294 (17.0), 301 nm (sh, 15.7); NMR 7.55 (d, J = 2 Hz, 1 H), 7.43 (d, J = 2 Hz, 1 H), 5.73 (d, J = 7 Hz, 1 H), 3.50 (s, 3 H), 2.30 (d, J = 7 Hz, 1 H), 1.58 (s, 9 H), 1.43 (s, 9 H), 1.36 (s, 9 H), 1.19 ppm (s, 9 H); mass spectrum *m/e* 437 (6, $M^{+\cdot}$), 380 (100, M − 57), 324 (39, M − 57 − 56); ^{13}C NMR 168.1 (s), 149.5 (s), 146.9 (s), 145.9 (s), 140.2 (s), 134.4 (s), 124.9 (s), 123.1 (s), 122.5 (d), 120.1 (d), 113.5 (d), 53.2 (d), 35.1, 34.9, 34.4, 34.2, 32.0, 30.4, 29.9, 29.9, 27.9 ppm.

Anal. Calcd for $C_{29}H_{43}NO_2$ (437.67): C, 79.58; H, 9.90. Found: C, 79.54; H, 9.85.

Method B. Oxidation of 3a with Sodium Bismuthate. A suspension of sodium bismuthate (10 g) and azepinone **3a** (4.40 g, 10 mmol) in toluene (130 mL) was refluxed for 2 h under nitrogen. The cooled reaction mixture was filtered and the inorganic residue was washed with ether. Vacuum evaporation of solvent left an oily residue which crystallized when treated with ethanol. Recrystallization from hot ethanol gave 3.45 g (79%) of colorless crystals, mp 167–168 or 182–183 °C (see note above).

3,5,7,9-Tetra-*tert*-butyl-1-*n*-propyl-1,3-dihydro-2*H*-benzofuro[2,3-*f*]azepin-2-one (4b). Method A. **4b** was prepared as described for **4a** (method A). Recrystallization by dissolving in methylene chloride and adding ethanol to the boiling solution gave 1.82 g (78%) of colorless crystals: mp 190–193 °C; IR 1675 (s), 1610 cm^{-1} (w); UV (ethanol) λ (ε × 10^{-3}) 234 (24.8), 294 (16.0), 301 nm (sh, 14.8); NMR 7.51 (d, J = 2 Hz, 1 H), 7.42 (d, J = 2 Hz, 1 H), 5.77 (d, J = 7 Hz, 1 H), 4.50–3.40 (br m, 2 H), 2.30 (d, J = 7 Hz, 1 H), 2.00–0.60 ppm (br m containing sharp peaks at 1.58, 1.43, 1.35, and 1.17 ppm, 41 H).

Anal. Calcd for $C_{31}H_{47}NO_2$ (465.72): C, 79.95; H, 10.17. Found: C, 80.17; H, 10.15.

Preparation of **4b** according to method B (reaction time 1 h) afforded **4b** in 82% yield.

3,5,7,9-Tetra-*tert*-butyl-1-cyclohexyl-1,3-dihydro-2*H*-benzofuro[2,3-*f*]azepin-2-one (4c) was prepared as described for **4a** (method A). Recrystallization by dissolving in methylene chloride and adding ethanol to the boiling solution gave 2.45 g (97%) of colorless crystals: mp 237–238 °C; IR 1670 (s), 1610 cm^{-1} (w); uv λ (ε × 10^{-3}) 234 (24.8), 294 (15.7), 301 nm (sh, 14.7); NMR 7.48 (d, J = 2 Hz, 1 H), 7.40 (d, J = 2 Hz, 1 H), 5.78 (d, J = 7 Hz, 1 H), 4.13–3.58 (m, 1 H), 2.92–1.00 ppm (m containing a d at 2.33, J = 7 Hz, and sharp peaks at 1.58, 1.44, 1.36, and 1.16 ppm, 47 H).

Anal. Calcd for $C_{34}H_{51}NO_2$ (505.79): C, 80.74; H, 10.16. Found: C, 80.44; H, 10.08.

Preparation of **4c** by oxidation with sodium bismuthate (cf. **4a**) afforded **4c** in 96% yield.

4,6-Di-*tert*-butyl-1-(3,5-di-*tert*-butyl-2-hydroxyphenyl)-2-methyl-2-azabicyclo[3.2.0]hept-6-en-3-one (5a). A solution of azepinone **3a** (2.20 g, 5 mmol) in benzene (180 mL) was irradiated (Pyrex immersion well apparatus, 450-W medium-pressure mercury lamp) at 20 °C under nitrogen for 2.5 h. Vacuum evaporation of solvent gave a crystalline residue which was recrystallized by dissolving in methylene chloride and adding ethanol: yield 1.45 g (66%) of colorless crystals, mp 130–143 °C dec; IR 3310 (m), 1665 (s), 1605 cm^{-1} (w); UV (ethanol) λ (ε × 10^{-3}) 222 (sh, 13.4), 279 (2.1), 284 nm (sh, 1.9); NMR 7.33 (d, J = 2.5 Hz, 1 H), 7.03 (d, J = 2.5 Hz, 1 H), 6.75 (s, 1 H), 6.23 (s, 1 H), 3.59 (d, J = 9 Hz, 1 H), 2.97 (d, J = 9 Hz, 1 H), 2.73 (s, 3 H), 1.42 (s, 9 H), 1.28 (s, 9 H), 1.24 ppm (s, 18 H); ^{13}C NMR 174.2 (s), 164.1 (s), 152.0 (s), 141.7 (s), 136.3 (s), 134.6 (d), 123.9 (d), 123.0 (s), 122.8 (d), 64.5 (s), 57.3 (d), 52.4 (d), 34.8, 34.8, 34.2, 34.2, 31.5, 30.2, 29.9, 29.2, 25.7 ppm.

Anal. Calcd for $C_{29}H_{45}NO_2$ (439.68): C, 79.22; H, 10.32. Found: C, 79.02; H, 10.31.

4,6-Di-*tert*-butyl-1-(3,5-di-*tert*-butyl-2-hydroxyphenyl)-2-*n*-propyl-2-azabicyclo[3.2.0]hept-6-en-3-one (5b) was prepared as described for **5a** using azepinone **3b** (1.50 g, 3.2 mmol). The crude product was recrystallized as dissolving in methylene chloride, adding ethanol, and evaporation of methylene chloride: yield 1.40 g (93%) of colorless crystals, mp 133–153 °C dec; IR 3310 (m), 1670 cm^{-1} (s); UV (ethanol) λ ($\epsilon \times 10^{-3}$) 223 (sh, 13.4), 279 (2.4), 284 nm (sh, 2.2); NMR 7.34 (d, J = 2.5 Hz, 1 H), 7.07 (d, J = 2.5 Hz, 1 H), 6.71 (s, 1 H), 5.94 (s, 1 H), 3.56 (d, J = 10 Hz, 1 H), 3.32–2.85 (m, 2 H), 1.75–0.70 ppm (br m containing sharp peaks at 1.42, 1.30, 1.25, and 1.22 ppm, 42 H).

Anal. Calcd for $C_{31}H_{49}NO_2$ (467.74): C, 79.60; H, 10.56. Found: C, 79.70; H, 10.56.

4,6-Di-*tert*-butyl-1-(3,5-di-*tert*-butyl-2-hydroxyphenyl)-2-cyclohexyl-2-azabicyclo[3.2.0]hept-6-en-3-one (5c) was prepared as described for **5a** using azepinone **3c** (2.54 g, 5 mmol). Recrystallization by dissolving in methylene chloride and adding ethanol gave 2.10 g (83%) of colorless crystals: mp 138–155 °C dec; IR 3200 (m), 1675 (s), 1650 cm^{-1} (s); UV (ethanol) λ ($\epsilon \times 10^{-3}$) 225 (sh, 12.6), 279 (2.2), 284 nm (sh, 1.9); NMR 7.32 (d, J = 2.5 Hz, 1 H), 7.02 (d, J = 2.5 Hz, 1 H), 6.72 (s, 1 H), 5.88 (s, 1 H), 3.85–3.33 (br m containing a d at 3.47 ppm, J = 10 Hz, 2 H), 2.97 (d, J = 10 Hz, 1 H), 2.00–0.70 ppm (br m containing sharp peaks at 1.43, 1.32, 1.25, and 1.22 ppm, 46 H).

Anal. Calcd for $C_{34}H_{53}NO_2$ (507.80): C, 80.42; H, 10.52. Found: C, 80.39; H, 10.44; mol wt, 565 (in benzene).

4,6,9,11-Tetra-*tert*-butyl-2-methylbenzofuro[2,3-*g*]-2-azabicyclo[3.2.0]hept-6-en-3-one[22] (6a) was prepared as described for **5a** using azepinone **4a** (2.20 g, 5 mmol). The crude product was recrystallized by dissolving in methylene chloride and adding ethanol: yield 1.90 g (86%); mp 203–205 °C dec; IR 1690 (s), 1655 (m), 1605 cm^{-1} (w); UV (ethanol) λ ($\epsilon \times 10^{-3}$) 246 (sh, 5.6), 285 (2.5), 291 nm (sh, 2.4); NMR 7.35 (d, J = 2 Hz, 1 H), 7.17 (d, J = 2 Hz, 1 H), 3.56 (d, J = 9 Hz, 1 H), 2.72 (d, J = 9 Hz, 1 H), 2.42 (s, 3 H), 1.42 (s, 9H), 1.30 (s, 18 H), 1.26 ppm (s, 9 H); ^{13}C NMR 173.8 (s), 160.4 (s), 155.5 (s), 145.5 (s), 137.4 (s), 133.8 (s), 124.4 (d), 124.1 (s), 120.8 (d), 64.9 (s), 55.0 (d), 43.6 (d), 34.6, 34.4, 34.4, 32.0, 31.5, 30.2, 29.5, 29.0, 26.1 ppm.

Anal. Calcd for $C_{29}H_{43}NO_2$ (437.67): C, 79.58; H, 9.90. Found: C, 79.60; H, 9.96.

4,6,9,11-Tetra-*tert*-butyl-2-*n*-propylbenzofuro[2,3-*g*]-2-azabicyclo[3.2.0]hept-6-en-3-one[22] (6b) was prepared as described for **5a** using azepinone **4b** (1.17 g, 2.5 mmol) in ether (180 mL) and irradiation for 1.5 h. The crude product was recrystallized by dissolving in methylene chloride and adding methanol: yield 0.83 g (71%) of colorless crystals; mp 136–138 °C dec; IR [69] (s), 1655 (m), 1605 cm^{-1} (w); UV (ethanol) λ ($\epsilon \times 10^{-3}$) 246 (sh, 5.6), 285 (2.4), 291 nm (sh, 2.3); NMR 7.35 (d, J = 2.5 Hz, 1 H), 7.18 (d, J = 2.5 Hz, 1 H), 3.68–3.32 (m, 4 H), 2.70 (d, J = 9 Hz, 1 H), 2.40–1.93 (m, 2 H), 1.60–0.60 ppm (m containing sharp peaks at 1.42, 1.32, and 1.27 ppm, 38 H).

Anal. Calcd for $C_{31}H_{47}NO_2$ (465.72): C, 79.95; H, 10.17. Found: C, 79.54; H, 10.09.

4,6,9,11-Tetra-*tert*-butyl-2-cyclohexylbenzofuro[2,3-*g*]-2-azabicyclo[3.2.0]hept-6-en-3-one[22] (6c) was prepared as described for **5a** using azepinone **4c** (1.26 g, 2.5 mmol) in ether (180 mL) and irradiation for 1.5 h. The crude product was recrystallized by dissolving in methylene chloride and adding methanol: yield 1.20 g (95%); mp 181–183 °C dec; IR 1685 (s), 1650 (m), 1630 cm^{-1} (w); UV (ethanol) λ ($\epsilon \times 10^{-3}$) 246 (sh, 5.1), 285 (2.3), 291 nm (sh, 2.2); NMR 7.35 (d, J = 2.5 Hz, 1 H), 7.25 (d, J = 2.5 Hz, 1 H), 3.60–3.15 (br m containing a d at 3.45 ppm, J = 9 Hz, 2 H), 2.70 (d, J = 9 Hz, 1 H), 1.75–0.70 ppm (br m containing sharp peaks at 1.43, 1.32, and 1.26 ppm, 46 H).

Anal. Calcd for $C_{34}H_{51}NO_2$ (505.79); C, 80.74; H, 10.16. Found: C, 80.50; H, 10.19.

3′,5,7-Tri-*tert*-butyl-4′-(2,2-dimethylpropionyl)-1′-methyl-2(3*H*)-benzofuranone-3-spiro-5′-pyrrolidone(2′)[22] (7). Potassium permanganate (948 mg, 6 mmol) was added to a stirred solution of **6a** (1.31 g, 3 mmol) in acetone (300 mL) giving an immediate precipitation of manganese dioxide. After 30 min the reaction mixture was filtered and solvent was removed in vacuo from the filtrate to give a crystalline residue. This was washed with methanol and recrystallized by dissolving in methylene chloride and adding methanol: yield 1.30 g (92%) of colorless crystals; mp 234–235 °C; IR 1818 (s), 1807 (sh, s), 1698 (sh, s), 1687 cm^{-1} (s); UV (ethanol) λ ($\epsilon \times 10^{-3}$) 285 nm (1.9); NMR 7.38 (d, J = 2 Hz, 1 H), 7.08 (d, J = 2 Hz, 1 H), 4.07 (d, J = 11 Hz, 1 H), 2.98 (d, J = 11 Hz, 1 H), 2.72 (s, 3 H), 1.40 (s, 9 H), 1.35 (s, 9 H), 1.17 (s, 9 H), 0.83 ppm (s, 9 H).

Anal. Calcd for $C_{29}H_{43}NO_4$ (469.67): C, 74.16; H, 9.23. Found: C, 73.89; H, 9.09.

Preparation of 5,7-Disubstituted 2(3*H*)-Benzofuranones. The compounds were prepared according to a procedure described in the literature[11c] for **7-*tert*-butyl-5-methyl-2(3*H*)-benzofuranone (8a).**

5-*tert*-Butyl-7-methyl-2(3*H*)-benzofuranone (8b). A mixture of 4-*tert*-butyl-2-methylphenol (16.5 g, 0.1 mol), glyoxal (7.5 g, 0.05 mol of 40% aqueous solution), and concentrated hydrochloric acid (1 mL) in glacial acetic acid (50 mL) was refluxed for 16 h. The organic layer was washed with water and dried (magnesium sulfate) and solvent was vacuum evaporated giving an oily residue. This was dissolved in methanol and upon cooling (in dry ice–ethanol) a colorless, crystalline precipitate formed which was recrystallized from *n*-pentane to give 3.10 g (15%)[27] of **8b:** mp 101–102 °C; IR 1800 cm^{-1} (s); NMR 7.22 (s, 2 H), 3.73 (s, 2 H), 2.35 (s, 3 H), 1.35 ppm (s, 9 H).

Anal. Calcd for $C_{13}H_{16}O_2$ (204.27): C, 76.44; H, 7.90. Found: C, 76.41; H, 7.90.

5,7-Di-*tert*-butyl-2(3*H*)-benzofuranone (8c) was prepared from 2,4-di-*tert*-butylphenol as described for **8b.** The oily residue obtained after evaporation of methylene chloride crystallized when treated with cold methanol. Recrystallization by dissolving in *n*-hexane and cooling (in dry ice–ethanol) gave 4.85 g (20%)[27] of colorless crystals: mp 87–89 °C; IR 1795 cm^{-1} (s); NMR 7.33 (s, 1 H), 7.23 (s, 1 H), 3.72 (s, 2 H), 1.42 (s, 9 H), 1.33 ppm (s, 9 H).

Anal. Calcd for $C_{16}H_{22}O_2$ (246.35): C, 78.01; H, 9.00. Found: C, 77.77; H, 9.01.

3,5-Di-*tert*-butyl-7-(3,5-di-*tert*-butyl-2-methoxyphenyl)-1-methyl-1,3-dihydro-2*H*-azepin-2-one (9a). A solution of methylsulfinyl carbanion[28] (7.5 mL, ca. 12 mmol) was added to a stirred solution of azepinone **3a** (4.40 g, 10 mmol) in dimethyl sulfoxide (75 mL distilled from calcium hydride) under nitrogen. Methyl iodide (2 mL) was added and the resulting mixture was stirred for 20 min and then diluted with water. The precipitate thus obtained was washed with water and dried. Recrystallization from hot nitromethane gave 4.35 g (96%) of colorless crystals: mp 162–165 °C; IR 1670 (s), 1625 cm^{-1} (m); NMR 7.41 (d, J = 2.5 Hz, 1 H), 7.09 (d, J = 2.5 Hz, 1 H), 6.75 (d, J = 1 Hz, 1 H), 5.54 (d, J = 6.5 Hz, 1 H), 3.80 (s, 3 H), 2.93 (s, 3 H), 2.33 (d, J = 6.5 Hz, 1 H), 1.44 (s, 9 H), 1.33 (s, 9 H), 1.23 ppm (s, 18 H).

Anal. Calcd for $C_{30}H_{47}NO_2$ (453.71): C, 79.42; H, 10.44. Found: C, 79.20; H, 10.33.

3,5-Di-*tert*-butyl-7-(2-acetoxy-3,5-di-*tert*-butylphenyl)-1-methyl-1,3-dihydro-2*H*-azepin-2-one (9b). Azepinone **3a** (500 mg, 1.1 mmol) was dissolved in an acetic anhydride solution in ethyl acetate–perchloric acid[29] (20 mL). After stirring for 30 min the reaction mixture was poured into methanol (10 mL) and then concentrated by vacuum evaporation of solvent. Addition of methanol and a few drops of water gave a crystalline precipitate. It was recrystallized from ethanol to give 510 mg (93%) of colorless crystals: mp 187–190 °C; IR 1770 (s), 1675 (s), 1630 cm^{-1} (m); NMR 7.50 (d, J = 2.5 Hz, 1 H), 7.25 (br m, 1 H), 6.52 (s, 1 H), 5.54 (d, J = 6.5 Hz, 1 H), 2.88 (s, 3 H), 2.32 (s, 3 H), 2.22 (d, J = 6.5 Hz, 1 H), 1.40 (s, 9 H), 1.34 (s, 9 H), 1.22 (s, 9 H), 1.18 ppm (s, 9 H).

Anal. Calcd for $C_{31}H_{47}NO_3$ (481.72): C, 77.29; H, 9.84. Found: C, 77.20; H, 9.81.

2,4-Di-*tert*-butyl-6-(3,5-di-*tert*-butyl-2-hydroxyphenyl)-6-morpholino-2,4-cyclohexadien-1-one (10a). A suspension of benzoxete **1a** (4.08 g, 10 mmol) in methanol (50 mL) and morpholine (5 mL) was refluxed for 5 min. The yellow, crystalline precipitate obtained on cooling was filtered off, washed with methanol, and dried: yield 4.65 g (94%) of **10a;** mp 153–154 °C (lit.[30] 151–152 °C); IR 3400–2500 (m), 1675 (s), 1650 cm^{-1} (m); UV (methanol) λ ($\epsilon \times 10^{-3}$) 278 (3.7), 322 (2.5), 372 nm (sh, 1.5); NMR 11.25 (s, 1 H, OH), 7.25 (d, J = 2.5 Hz, 1 H), 6.98 (d, J = 2.5 Hz, 1 H), 6.65 (d, J = 2.5 Hz, 1 H), 6.25 (d, J = 2.5 Hz, 1 H), 3.88 (m, 4 H), 2.70 (m, 4 H), 1.38 (s, 9 H), 1.25 (s, 9 H), 1.20 (s, 9 H), 0.93 ppm (s, 9 H).

Anal. Calcd for $C_{32}H_{49}NO_3$ (495.75): C, 77.53; H, 9.96. Found: C, 77.26; H, 9.76.

2,4-Di-*tert*-butyl-6-(3,5-di-*tert*-butyl-2-hydroxyphenyl)-6-piperidino-2,4-cyclohexadien-1-one (10b) was prepared as described for **10a** using piperidine (5 mL) and refluxing for 10 min: yield 4.35 g (88%) of yellow crystals; mp 144–145 °C (lit.[30] 137–138 °C); IR 3400–2500 (m), 1675 (s), 1650 cm^{-1} (m); UV (ethanol) λ ($\epsilon \times 10^{-3}$) 280 (3.8), 321 (2.4), 370 nm (sh, 1.5); NMR 11.85 (s, 1 H, OH), 7.20 (d, J = 2.5 Hz, 1 H), 6.93 (d, J = 2.5 Hz, 1 H), 6.63 (d, J = 2.5 Hz, 1 H), 6.25 (d, J = 2.5 Hz, 1 H), 3.28–2.77 (m, 2 H), 2.63–1.56 (m, 8 H), 1.43 (s, 9 H), 1.33 (s, 9 H), 1.30 (s, 9 H), 1.05 ppm (s, 9 H).

Anal. Calcd for $C_{33}H_{51}NO_2$ (493.76): C, 80.27; H, 10.41. Found: C, 79.86; H, 10.93.

6-Morpholino-2,4-di-*tert*-pentyl-6-(2-hydroxy-3,5-*tert*-pentylphenyl)-2,4-cyclohexadien-1-one (10c). A suspension of benz-

oxete **1b** (1.17 g, 2.5 mmol) in methanol (25 mL) and morpholine (3 mL) was refluxed for 10 min. The yellow, crystalline precipitate obtained on cooling was filtered off, washed with methanol, and recrystallized from ethanol: yield 1.05 g (80%) of yellow crystals; mp 118–120 °C (lit.[30] 109–110 °C); IR 3300–2600 (m), 1675 cm^{-1} (s); UV (ethanol) λ ($\epsilon \times 10^{-3}$) 278 (3.4), 322 (2.2), 390 nm (2.0); NMR (11.15 (s, 1 H, OH), 7.10 (d, J = 2.5 Hz, 1 H), 6.90 (d, J = 2.5 Hz, 1 H), 6.59 (d, J = 2.5 Hz, 1 H), 6.18 (d, J = 2.5 Hz, 1 H), 3.90–3.70 (m, 4 H), 2.75–2.45 (m, 4 H), 2.10–0.20 ppm (m, 44 H).

Anal. Calcd for $C_{36}H_{57}NO_3$ (551.86): C, 78.35; H, 10.41. Found: C, 78.25; H, 10.37.

2,4-Di-*tert*-pentyl-6-(2-hydroxy-3,5-di-*tert*-pentylphenyl)-6-piperidino-2,4-cyclohexadien-1-one (10d) was prepared as described for **10c** using piperidine (3 mL). Recrystallization from ethanol gave 1.25 g (91%) of yellow crystals: mp 124–128 °C (lit.[30] 126–127 °C); IR 3300–2600 (m), 1680 cm^{-1} (s); UV (ethanol) λ ($\epsilon \times 10^{-3}$) 279 (4.4), 320 (2.5), 390 nm (2.0); NMR 11.70 (s, 1 H, OH), 7.06 (d, J = 2 Hz, 1 H), 6.85 (d, J = 2 Hz, 1 H), 6.58 (d, J = 2 Hz, 1 H), 6.18 (d, J = 2 Hz, 1 H), 3.10–2.70 (m, 5 H), 2.60–0.20 ppm (m, 49 H).

Anal. Calcd for $C_{37}H_{59}NO_2$ (549.88): C, 80.82; H, 10.82. Found: C, 80.73; H, 10.73.

2-*tert*-Butyl-6-(3-*tert*-butyl-2-hydroxy-5-tritylphenyl)-6-morpholino-4-trityl-2,4-cyclohexadien-1-one (10e). A suspension of benzoxete **1c** (500 mg, 0.59 mmol) in methanol (7 mL) and morpholine (3 mL) was kept in an autoclave at 140–150 °C under nitrogen for 10 min. After cooling the resulting suspension was dissolved in methylene chloride and filtered. The filtrate was concentrated by partial vacuum evaporation of solvent. Addition of methanol gave a yellowish precipitate which was recrystallized by dissolving in methylene chloride and addition of nitromethane followed by partial evaporation of methylene chloride: yield 485 mg (97%) of yellow crystals; mp 203–208 °C; IR 3100–2600 (m), 1675 cm^{-1} (s); UV (chloroform) λ ($\epsilon \times 10^{-3}$) 273 (sh, 7.9), 320 (2.7), 378 nm (sh, 1.8); NMR 11.13 (s, 1 H, OH), 7.25–6.85 (m, 32 H), 6.20 (d, J = 2 Hz, 1 H), 5.95 (d, J = 2 Hz, 1 H), 3.80–3.70 (m, 4 H), 2.80–1.95 (m, 4 H), 1.22 (s, 9 H), 0.92 ppm (s, 9 H).

Anal. Calcd for $C_{62}H_{61}NO_3$ (868.17): C, 85.78; H, 7.08. Found: C, 85.63; H, 7.02.

2-*tert*-Butyl-6-(3-*tert*-butyl-2-hydroxy-5-tritylphenyl)-6-piperidino-4-trityl-2,4-cyclohexadien-1-one (10f) was prepared as described for **10e** at 115–120 °C using piperidine (3 mL). The crude product was recrystallized by dissolving in methylene chloride and adding acetonitrile followed by partial evaporation of methylene chloride: yield 460 mg (92%); mp 195–197 °C; IR 3100–2600 (m), 1670 cm^{-1} (s); UV (chloroform) λ ($\epsilon \times 10^{-3}$) 280 (sh, 7.5), 320 (2.9), 382 nm (1.6); NMR 11.73 (s, 1 H, OH), 7.20–6.80 (m, 32 H), 6.18 (d, J = 2 Hz, 1 H), 5.91 (d, J = 2 Hz, 1 H), 3.00–2.50 (m, 2 H), 2.15–1.35 (m, 8 H), 1.21 (s, 9 H), 0.90 ppm (s, 9 H).

Anal. Calcd for $C_{63}H_{63}NO_2$ (866.20): C, 87.36; H, 7.33. Found: C, 86.97; H, 7.25.

Attempted Base-Catalyzed Deuterium Exchange of Azepinone 9a. Potassium *tert*-butoxide (600 mg) was added to a solution of azepinone **9a** (454 mg, 1 mmol) in hexamethylphosphoric triamide (15 mL, distilled from lithium aluminum hydride) under nitrogen. The deep purple suspension thus obtained was stirred for 30 min at room temperature and, in order to remove *tert*-butyl alcohol, it was then kept at 0.5 mmHg and 30 °C for 2 h. Addition of deuterium oxide (10 mL) under dry nitrogen gave a colorless, crystalline precipitate. It was dissolved in deuteriochloroform which then was washed with deuterium oxide. The organic layer was dried (magnesium sulfate) and solvent was vacuum evaporated to give an oily residue whose NMR spectrum was identical with that of the starting material and showed no incorporation of deuterium.

Attempted Reduction of Azepinone 9a with Lithium Aluminum Hydride. A solution of azepinone **9a** (454 mg, 1 mmol) in anhydrous ether (40 mL) was added to a suspension of lithium aluminum hydride (100 mg, 2.6 mmol) in anhydrous ether (20 mL) under nitrogen. The mixture was refluxed for 5 h and cooled in ice–water and excess lithium aluminum hydride was destroyed by dropwise addition of ethanol and water. The organic layer was washed with a saturated aqueous solution of ammonium chloride and, subsequently, with water. It was dried (magnesium sulfate) and solvent was removed in vacuo to give an oily residue which crystallized after addition of nitromethane, yield 440 mg (97%) of starting material as shown by melting point, TLC, and NMR.

Attempted Hydrolyses of Azepinones 3a, 4a, and 9a. A. A suspension of azepinone **3a** (200 mg) in methanol (15 mL) and concentrated hydrochloric acid (2 mL) was refluxed for 15 h. The crystalline precipitate obtained on cooling was filtered off, washed with water, and dried, yield 120 mg (60%), mp 153–155 °C (mixture melting point with starting material 153–155 °C). Likewise, no reaction was detectable (TLC) after keeping the reaction mixture at 150–160 °C (autoclave) for 60 min.

B. The sodium peroxide procedure of Vaughn and Robbins[31] was followed for hydrolysis of **4a.** The only detectable compound after 24 h was starting material (TLC and NMR).

C. Attempted hydrolysis of **9a** was performed using potassium *tert*-butoxide (6 equiv) and water (2 equiv) in refluxing tetrahydrofuran according to ref 32. Starting material (90%) was recovered after 40 h at reflux temperature.

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Registry No.—**1a,** 20026-75-9; **1b,** 20026-74-8; **1c,** 62778-04-5; **2a,** 74-89-5; **2a** HCl, 593-51-1; **2b,** 107-10-8; **2c,** 108-91-8; **4a,** 60434-67-5; **4b,** 60434-68-6; **4c,** 60434-69-7; **5a,** 60434-60-8; **5b,** 60434-61-9; **5c,** 60434-62-0; **6a,** 60434-70-0; **6b,** 60434-63-1; **6c,** 60434-64-2; **9a,** 62744-00-7; **9b,** 62744-01-8; 2-*tert*-butylphenol, 88-18-6; triphenylcarbinol, 76-84-6; 2-*tert*-butyl-4-tritylphenol, 60043-12-1; 4-*tert*-butyl-2-methylphenol, 98-27-1; glyoxal, 107-22-2; 2,4-di-*tert*-butylphenol, 96-76-4; morpholine, 110-91-8; piperidine, 110-89-4.

References and Notes

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(3) Cf. L. E. Friedrich and G. B. Schuster, *J. Am. Chem. Soc.*, **91,** 7204 (1969), and references cited therein.
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(5) Interestingly, in the mass spectrum of **3a,** the base peak (*m/e* 382, M − 57) results from loss of C_4H_9 rather than CH_3NCO. Accordingly, compound **3c** does not lose cyclohexyl isocyanate, but the base peak (*m/e* 368) results from the successive loss of C_4H_9 and cyclohexene from the molecular ion (see Experimental Section).
(6) In another azepinone system, however, a 1-Hz coupling between H-4 and H-6 was observed; see M. Ogata, H. Matsumoto, and H. Kano, *Tetrahedron*, **25,** 5205 (1969).
(7) The chlorination of 1,3-dihydro-2*H*-azepinones by *N*-chlorosuccinimide also occurs in the 6 position and has been explained in terms of an electrophilic substitution: L. A. Paquette and W. C. Farley, *J. Org. Chem.*, **32,** 2725 (1967).
(8) Cf. L. A. Paquette in "Nonbenzenoid Aromatics", Vol. I, J. P. Snyder, Ed., Academic Press, New York, N.Y., 1969, pp 249–310.
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(10) Cf. (a) O. L. Chapman and E. D. Hoganson, *J. Am. Chem. Soc.*, **86,** 498 (1964); (b) E. Vogel, R. Erb, G. Lenz and A. A. Bothner-By, *Justus Liebigs Ann. Chem.*, **682,** 1 (1965); F. R. Atherton and R. W. Lambert, *J. Chem. Soc., Perkin Trans. 1,* 1079 (1973).
(11) Cf. (a) W. H. Washburn, *Appl. Spectrosc.*, **18,** 61 (1964); (b) H. E. Holmquist, *J. Org. Chem.*, **34,** 4164 (1969); (c) R. W. Layer, *J. Heterocycl. Chem.*, **12,** 1067 (1975).
(12) This supports the previously suggested conformation at C-4 of acetamido-annelated cyclobutenes of structure **5** and **6;** see ref 10a and 13.
(13) L. A. Paquette, *J. Am. Chem. Soc.*, **86,** 500 (1964).
(14) Conceivably, the lack of reactivity may be attributable to steric overcrowding.
(15) (a) L. A. Paquette, *J. Am. Chem. Soc.*, **84,** 4987 (1964); (b) *ibid.*, **85,** 3288 (1963); (c) L. A. Paquette and W. C. Farley, *ibid.*, **89,** 3595 (1967).
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(17) D. G. Hewitt, *J. Chem. Soc. C,* 2967 (1971).
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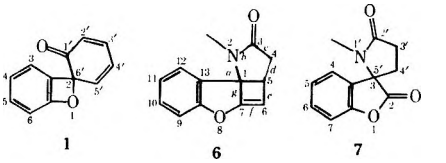
(22) The nomenclature used in this paper is based on the following skeletons:



1 6 7

(23) J. R. Allan, D. H. Brown, R. H. Nuttall, and D. W. A. Sharp, *J. Chem. Soc. A*, 1031 (1966).
(24) This compound melts around 150 °C, but resolidifies on further heating to give yellow crystals, mp 211–214 °C.
(25) This absorption disappears if the compound is dried at 120 °C for 70 min to give yellow-colored crystals, which, according to NMR, do not contain methylene chloride.
(26) The high-melting modification can be obtained from the low-melting modification by melting and resolidification.
(27) No attempts were made to optimize the yields.
(28) Cf. L. F. Fieser and M. Fieser "Reagents for Organic Synthesis", Vol. I, Wiley, New York, N.Y., 1967, p 310.
(29) J. S. Fritz and G. M. Schenk, *Anal. Chem.*, **31**, 1808 (1959).
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Anodic Cyanation of Tertiary Aliphatic and Heterocyclic Amines

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Electrochemical cyanation of tertiary aliphatic and heterocyclic amines in sodium cyanide–aqueous methanol solution using platinum electrodes was studied. Cyanation occurred at the carbon α to the nitrogen atom in each case to form corresponding α-cyano amines in reasonable yields. Some of the unsymmetrical aliphatic and heterocyclic amines gave two isomers. From the relative amounts of the isomers, it was found that the order of ease of the cyanation at the α position of the alkyl group is $(CH_2)_4 > (CH_2)_5 > CH_3 > C_2H_5 > n\text{-}C_3H_7 > i\text{-}C_3H_7$, and that the substitution occurs at the α-carbon situated in positions easily accessible to the electrode.

Electrochemical cyanation of organic compounds has been studied by various investigators,[1-3] but there are only a few reports on the anodic cyanation of amines. Previously, Andreades and Zahnow[4] found that the anodic oxidation of *N,N*-dialkylanilines and benzylamines gave rise to cyanation at the alkyl carbon atom α to the amino nitrogen. Yoshida and Fueno[5] pointed out that the anodic oxidation of diphenylamines in methanol containing sodium cyanide gave *p*-cyanodiphenylamines in good yields. However, no systematic reports are available on the cyanation of tertiary aliphatic amines. We have now studied anodic cyanation of tertiary aliphatic and heterocyclic amines in aqueous methanol containing sodium cyanide at a platinum electrode, and have examined whether this reaction could be used for the preparation of α-cyano amines on a macro scale.

Results

Prior to the preparative studies, current–potential measurements were carried out with triethylamine and α-diethylaminopropionitrile in 0.5 M sodium cyanide–aqueous methanol solution at a platinum anode.

As shown in Figure 1, triethylamine initiated a discharge at approximately 0.7 V (SCE) and then the current rose steeply at 0.9 V or over, whereas α-diethylaminopropionitrile was oxidized at about 0.3 V more anodic than triethylamine. Generally, oxidation potentials of the cyanated products are substantially higher than the values for the corresponding amines. In aqueous methanolic sodium cyanide without triethylamine, a deviation from the ohmic current was observed in the vicinity of 1.0 V, and the electrolytic current gradually increased through the potential of 1.7 V.[6-8] Despite the high concentration of cyanide ion, the degree of increase in the current was very low. Therefore, in the presence of amine, the oxidation of amine itself would be insignificantly affected below 1.4 V.

According to controlled potential electrolyses of triethylamine in 2.0 M sodium cyanide solution, the number of electrons, n, involved in the overall electrode reaction amounted to ca. 2 at 1.2 V.

In a similar manner, relative discharge potentials of other amines were read from the current–potential curves. Each amine employed, except for diisopropylmethylamine and *N-tert*-butylpyrrolidine, was significantly oxidized in a potential range from 0.97 to 1.05 V.

On the basis of the data, preparative constant current electrolyses were carried out under such conditions as to maintain the potential at a convenient range.

In Table I, representative results of anodic cyanation of several kinds of tertiary amines on a macro scale are summarized.

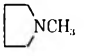
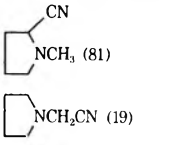
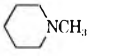
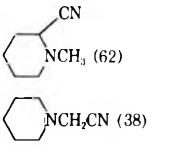
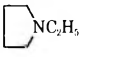
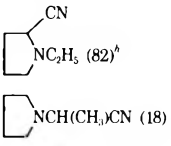
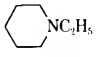
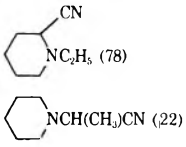
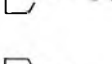
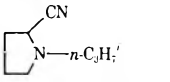
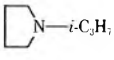
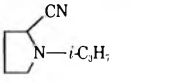
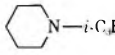
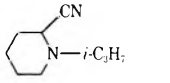
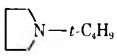
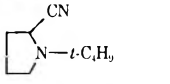
In each case, cyanation occurred exclusively at the carbon atom α to the nitrogen atom and the corresponding α-cyano amines were produced in reasonable yields. Unsymmetrical tertiary aliphatic amines with the methyl group were mainly cyanated at the methyl group, and the amount of cyanation at the methylene group decreased as the length of the alkyl group increased. No cyanated products at the methine group were obtained from dimethylisopropylamine and diisopropylmethylamine.

On the other hand, some of the *N*-alkylpiperidine and pyrrolidine derivatives gave two isomers, one of which was a product substituted at the ring and the other was a product cyanated at the side chain, and it was ascertained that the former product invariably formed in preference to the latter. For example, *N*-methylpiperidine gave *N*-methyl-2-cyanopiperidine in a yield of 41% and α-piperidineacetonitrile in a 25% yield according to GLC analysis (62:38). In the case of *N*-ethylpiperidine, the ratio of cyanation at the ring to the side chain was 78:22, and in *N*-isopropylpiperidine, no side chain substituted product was detected. A similar tendency was observed for *N*-alkylpyrrolidine derivatives, although the substitution showed more precedence to the ring α position than the corresponding piperidine derivatives. Apparently, the order of ease of the cyanation at the α position of the alkyl group is as follows: $(CH_2)_4 > (CH_2)_5 > CH_3 > C_2H_5 > n\text{-}C_3H_7 > i\text{-}C_3H_7 = 0$. This order is compatible with that of steric hindrance around the nitrogen atom of amine.

Table II shows the results of the constant potential electrolysis of *N*-methylpiperidine at various anode potentials.

The current efficiency for the formation of the cyanated products was about 95% even at a potential of 1.4 V. In addition, the relative amount of the isomers was hardly affected by the potentials.

Table I. Anodic Cyanation of Tertiary Aliphatic and Heterocyclic Amines[a]

Expt	Amine	Registry no.	Discharged[b] potential, V vs. SCE	Anode potential, V vs. SCE	Products[c]	Material[d] yield, %	Current[g] efficiency, %
1	$(CH_3)_3N$	75-50-3	1.03	1.2–1.4	$(CH_3)_2NCH_2CN$	[53]	[70]
2	$(C_2H_5)_3N$	121-44-8	0.97	1.1–1.2	$(C_2H_5)_2NCH(CH_3)CN$	36[e] [53][f]	48 [70]
3	$(CH_3)_2NC_2H_5$	598-56-1	1.02	1.0–1.3	$(C_2H_5)(CH_3)NCH_2CN$ (79) $(CH_3)_2NCH(CH_3)CN$ (21)	31 [44]	41 [58]
4	$(C_2H_5)_2NCH_3$	616-39-7	1.02	1.0–1.2	$(C_2H_5)_2NCH_2CN$ (57) $(C_2H_5)(CH_3)NCH(CH_3)CN$ (43)	32 [37]	43 [49]
5	n-$C_3H_7N(CH_3)_2$	926-63-6	1.02	1.1–1.3	(n-C_3H_7)$(CH_3)NCH_2CN$ (84) $(CH_3)_2NCH(C_2H_5)CN$ (16)	40 [53]	54 [70]
6	i-$C_3H_7N(CH_3)_2$	996-35-0	1.01	1.1–1.2	(i-C_3H_7)$(CH_3)NCH_2CN$	40 [54]	54 [73]
7	(i-C_3H_7)$_2NCH_3$	10342-97-9	0.90	0.9–1.1	(i-C_3H_7)$_2NCH_2CN$	43 [55]	57 [73]
8		120-94-5	0.99	1.0–1.3		46 [59]	62 [79]
9		626-67-5	1.05	1.1–1.4		57 [66]	76 [88]
10		7335-06-0	1.00	1.0–1.2		57	76
11		766-09-6	1.05	1.1–1.3		61	82
12		7335-07-1	0.98	1.0–1.2		59	79
13		17544-07-9	0.99	1.0–1.1		57	75
14		766-79-0	1.00	1.0–1.2		62	82
15		15185-01-0	0.92	0.9–1.0		63	84

[a] Anolyte: amine (0.10 mol) and NaCN (0.15 mol) in 75 mL of MeOH–H_2O (1:1). Constant current: 0.5 A. Consumed current: 0.15 Faraday. Temperature: 3 °C. [b] Read from the current–potential curve. [c] Identified either by direct comparison with authentic samples prepared by the Knoevenagel methods or by IR, NMR, and mass spectrum. Elemental analyses of α-aminonitriles are uncertain because they easily eliminated HCN upon combustion. Their picrates were analyzed. [d] Calculated by not considering recovery of unchanged amine. Theoretical yield is 75%. [e] Isolated yield. [f] According to GLC. [g] Assuming a 2e process. [h] The ratio was determined by NMR. [i] Very small amounts of α-pyrrolidinebutyronitrile were detected by NMR.

Discussion

The reaction mechanism for the present electrolysis appears to be analogous to that of anodic oxidation of tertiary amine, because amine is exclusively oxidized in preference to the cyanide ion. Anodic oxidation of aliphatic amines at a platinum electrode in nonaqueous media was studied extensively by Mann and his co-workers,[9] and Masui and Sayo[10] also investigated the electrochemical dealkylation of aliphatic tertiary amines in alkaline aqueous solution at a glassy carbon electrode. According to their reports, the generalized mechanism is as follows.

In the initial step, adsorbed amine undergoes one-electron transfer to form a cation radical (1), followed by deprotonation to give a neutral radical (2) which can undergo a second electron transfer to form the iminium cation (3), or can disproportionate to form the enamine (4). When a sufficient potential for a two-electron oxidation of amine is employed in the presence of sodium cyanide, the former reaction would be favorable and the produced iminium cation (3) would react with the cyanide ion to give α-cyano amine (5). Masui and Sayo[10] also described that the relative amount of dealkylation in unsymmetrical tertiary amines is predominantly governed by acidity and the number of α protons. Similar tendencies were recognized in our experimental results; namely, the order of increasing difficulty of the cyanation at the α carbon was

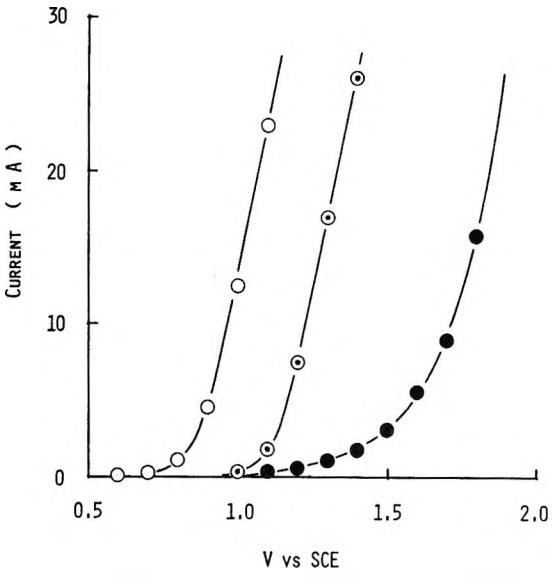
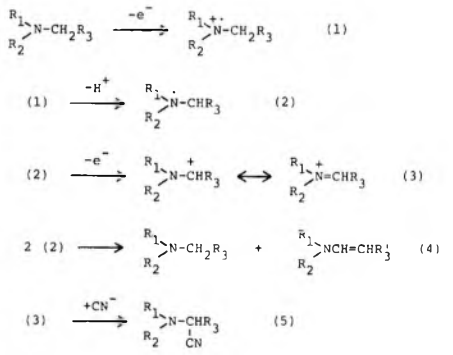


Figure 1. Current–potential curves: ●, 0.5 M NaCN MeOH–H_2O (1:1) solution; ○, in the presence of 0.1 M of $(C_2H_5)_3N$; ⊙, in the presence of 0.1 M of $(C_2H_5)_2NCH(CH_3)CN$ (at 25 °C).

Scheme I



methyl, ethyl, *n*-propyl, and isopropyl. However, it seems insufficient to explain the difference in the relative amount of isomers between five- and six-membered heterocyclic compounds, or in the reactivities of the alkyl group between the ring and the side chain.

It is known that amines are adsorbed through their lone pair of electrons of the nitrogen atom on an anode surface,[11] and that the degree of adsorption of an amine can affect its anodic oxidation.[12] Therefore, it is necessary to take into account the orientation of the amino molecule on the electrode surface. The steric configuration of the adsorbed amine must be appreciably restricted to the site of the electrode by interactions between the alkyl groups around the amino nitrogen and the electrode. As can be seen from the results in Table I, the cyanation at the alkyl groups with a greater steric hindrance was more difficult. Particularly, the isopropyl group should form a stable radical in a homogeneous system; however, the substituted products at the methine group could not be detected by NMR spectrum analysis of the crude product. (A strong singlet adsorption spectra arising from two isolated methyl groups at 1.4 ppm is expected.) Consequently, the deprotonation must occur at the α carbon situated in positions easily accessible to the electrode.

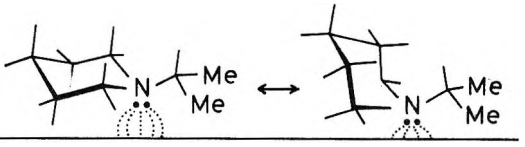
α carbons in the rings with limited free rotation can approach closer to the electrode than those of the side chain; especially it was noted that the five-membered ring has a nearly planar structure for access. Thus it would be preferable to make a substitution at the α carbon in the ring rather than in the side chain, and especially in a five-membered ring, the substitution would be strongly favored. On the contrary, for

Table II. Anodic Cyanation of *N*-Methylpiperidine at Various Potentials[a]

Applied potential, V vs. SCE	Conversion, %	Current[d] efficiency, %	Mol ratio of isomers 9a:9b
1.0	1.35	97.5	60[b]:40[c]
1.1	3.1	95.5	61:39
1.2	6.2	93.9	62:38
1.3	8.0	95.7	63:37
1.4	10.8	94.9	61:39

[a] Anolyte: amine (40 mmol) and NaCN (40 mmol) in 20 mL of MeOH–H_2O (1:1). Temperature: 3 °C. [b] *N*-Methyl-2-cyanopiperidine. [c] α-Piperidineacetonitrile. [d] According to GLC.

Scheme II



example, adsorbed *N*-isopropylpiperidine would be forced into such a configuration as to prevent access of the methine group to the electrode by a mutual repulsion between the two methyl groups and axial hydrogen atoms in the ring, and by a steric interaction between the alkyl groups and the electrode as shown in Scheme II.

It may be concluded that the chief determining factor of the end products is steric based on the actual configuration of the adsorbed amine on the electrode surface and the molecular structure itself, rather than the applied potential. This electrolytic method seems to be suitable for the introduction of the cyano group into the ring of heterocyclic amines even though other products are formed.

Experimental Section

Reagents. All amines except for trimethylamine and triethylamine were prepared by the usual methods[13–16] and their purities were checked by GLC analysis. Methanol was purified by fractional distillation. Reagent grade sodium cyanide was used without purification.

Analytical Methods. Gas chromatographic analyses were conducted with a Hitachi Model 163 gas chromatograph using glass columns packed with 20% Apiezon grease and 10% potassium hydroxide on 60–80 mesh Chromosorb W AW. Infrared spectra were recorded on a Hitachi EPI-G2 double beam recording spectrophotometer. Samples were prepared and scanned as a neat liquid between sodium chloride crystals. NMR spectra were recorded on a Hitachi 20-A recording spectrometer as an approximate 20% solution in carbon tetrachloride. Mass spectra were obtained with a Hitachi M-52 instrument.

Potentiostatic Electrolyses. All potentials were referred to a saturated calomel electrode. Controlled potential electrolyses and current–potential measurements were carried out in a H-type cell with a glass frit diaphragm separating two compartments. The anode compartment (25 mL) contained a smooth platinum plate (4.0 cm^2) and was rapidly stirred by a magnetic stirring bar. The cathode compartment (15 mL) contained a platinum wire. This cell was provided with a reference electrode. Anode potential was controlled by using a Nichia HP-500 type potentiostat.

A. Controlled Potential Electrolysis of *N*-Methylpiperidine. A solution consisting of 990 mg (40 mmol) of amine in 20 mL of 2.0 M sodium cyanide–aqueous methanol (1:1) solution was electrolyzed at various anode potentials at 3 °C. The consumed current was estimated from the current–time curve. After the electrolysis, the percent of the products was determined by GLC analysis.

B. Current–Anode Potential Relationships. Current–potential measurements were made in 20 mL of 0.5 M sodium cyanide–aqueous methanol (1:1) solution containing 2 mmol of reactant at 25 °C. Each discharge potential was read from the current–potential curve plotted from the current values after 1 min from adjustment of the potentials for each 10-mV rise from 0.4 to 2.0 V.

Constant Current Electrolyses for Preparative Studies. Large-scale electrolyses were carried out in a 100-mL separable flask shielded from the cathode compartment using a porous cup. A cylindrical platinum net (4.5 cm in height, 11.0 cm in circumference, 55 mesh) was used at the anode and the cathode was a coil of platinum wire (0.8 mm ϕ, 20 cm). A reference electrode was connected to the working electrode. The cell was thermostated at 3 °C, and was stirred by a magnetic stirring bar.

The experimental procedure is as follows. The anolyte contained 0.1 mol of amine and 0.15 mol of sodium cyanide dissolved in 75 mL of 1:1 methanol–water solution (for expt 7–15, 2:1 solution was used). The catholyte was an aqueous methanol solution of sodium cyanide. Electrolysis was carried out under a constant current at 0.5 A for 8 h. Total consumed current was 0.15 Faraday. During the electrolysis, the anode potential was gradualy increased up to 0.3 V above the initial potential. After completion of the reaction, the anolyte was concentrated under reduced pressure at 35 °C on a rotary evaporator, and the remaining crude liquid was saturated with 25 g of anhydrous potassium carbonate. The organic layer was separated, and the aqueous layer was extracted twice with 30-mL portions of ether. The combined extracts were dried with potassium carbonate, and then analyzed by GLC.

Trimethylamine (Expt 1). The anolyte (contained 4.4 g of *N,N*-dimethylaminoacetonitrile[17-19] according to the GLC analysis) was saturated with anhydrous potassium carbonate without evaporation. Then the oily layer was worked up as above and distilled. The portion collected at 35–67 °C (60 mm) was additionally dried and redistilled. The purified sample (bp 134–136 °C) was identical with an authentic sample as shown by IR and NMR. The nonvolatile residue in the first distillation was extracted with ether. The ether solution was decanted and concentrated to ½ volume. A small amount of white, needle crystals of α-dimethylaminoacetamide,[18] mp 94–96 °C, was obtained.

Triethylamine (Expt 2). The product was isolated by distillation. A colorless liquid of α-(*N,N*-dimethylamino)propionitrile[17,22] was obtained at 63–65 °C (17 mm) in a yield of 4.5 g. This was identified with an authentic sample by IR and NMR.

Dimethylethylamine (Expt 3). The crude undistilled liquid product was shown to be 3.3 g of *N*-methyl-*N*-ethylaminoacetonitrile (**3a**) and 1.0 g of α-dimethylaminopropionitrile (**3b**)[17] by GLC analysis (79:21). The aminonitriles were concentrated by distillation [3.0 g, bp 78–83 °C (74 mm)] and each nitrile for the analytical sample was isolated by preparative GLC. **3a**: IR ν 2220 cm^{-1} (CN); NMR δ 1.02 (t, 3 H), 2.30, 2.46 (s, q, 5 H), 3.42 ppm (s, 2 H); mass spectrum *m/e* (rel intensity) 98 (M^+, 15), 83 ($M^+ - 15$, 100), 71 ($M^+ - 27$, 9), 42 (38). Picrate of **3a**: yellowish needles from ethanol–acetone, mp 156–157.5 °C. Anal. Calcd for $C_{11}H_{13}N_5O_7$: C, 40.37; H, 4.00; N, 21.40. Found: C, 40.0; H, 3.9; N, 21.5. **3b** was identified with an authentic sample by IR and NMR.

Diethylmethylamine (Expt 4). After evaporation of the solvent, the remainder of the crude liquid exhibited two principal peaks arising from *N,N*-diethylaminoacetonitrile (**4a**)[17,19,20] and α-(*N*-methyl-*N*-ethylamino)propionitrile (**4b**) by GLC analysis. The mole ratio of the products was 57:43. The distillation of the mixture gave 3.6 g of colorless liquid at 64–67 °C (23 mm) and analytical samples were obtained by preparative GLC. The IR and NMR spectra of **4a** were identical with those of an authentic sample. **4b**: IR ν 2225 cm^{-1} (CN); NMR δ 1.05 (t, 3 H), 1.37 (d, 3 H), 2.21 (s, 3 H), 3.59 ppm (q, 1 H); mass spectrum *m/e* (rel intensity) 112 (M^+, 3), 97 ($M^+ - 15$, 11), 85 ($M^+ - 27$, 28), 70 ($M^+ - 42$, 82), 42 (100). Picrate of **4b**: yellowish prisms from ethanol–acetone, mp 120–122 °C dec. Anal. Calcd for $C_{12}H_{15}N_5O_7$: C, 42.23; H, 4.43; N, 20.52. Found: C, 42.1; H, 4.4; N, 20.6.

Dimethyl-*n*-propylamine (Expt 5). The distillation gave 4.5 g of colorless liquid at 55–64 °C (15 mm). GLC analysis showed 84% of *N*-methyl-*N*-*n*-propylaminoacetonitrile (**5a**) and 16% of α-dimethylaminobutylonitrile (**5b**).[17] Analytical samples were obtained by preparative GLC. **5a**: IR ν 2230 cm^{-1} (CN); NMR δ 0.94 (t, 3 H), 1.50 (sextet, 2 H), 2.33, 2.42 (s, t, 5 H), 3.45 ppm (s, 2 H); mass spectrum *m/e* (rel intensity) 112 (M^+, 7), 85 ($M^+ - 27$, 8), 84 ($M^+ - 28$, 14), 83 ($M^+ - 29$, 100), 42 (25). Picrate of **5a**: yellowish, rodlike crystals from ethanol–acetone, mp 97–98.5 °C. Anal. Calcd for $C_{12}H_{15}N_5O_7$: C, 42.23; H, 4.43; N, 20.52. Found: C, 42.5; H, 4.4; N, 20.9. **5b**: The IR and NMR spectrum were compared with those of an authentic sample, respectively.

Dimethylisopropylamine (Expt 6). The crude product was distilled. A fraction with bp 63–65 °C (15 mm) was obtained in a yield of 4.5 g. *N*-Methyl-*N*-isopropylaminoacetonitrile: IR ν 2225 cm^{-1} (CN); NMR δ 1.10 (d, 6 H), 2.35 (s, 3 H), 2.73 (sextet, 1 H), 3.52 ppm (s, 2 H); mass spectrum *m/e* (rel intensity) 112 (M^+, 9), 97 ($M^+ - 15$, 100), 85 ($M^+ - 27$, 12), 70 ($M^+ - 42$, 71), 42 (57). Picrate: yellowish leaflets from ethanol, mp 163.5–165.5 °C dec. Anal. Calcd for $C_{12}H_{15}N_5O_7$: C, 42.23; H, 4.43; N, 20.52. Found: C, 42.5; H, 4.4; N, 20.9. The NMR spectrum of the rough product was shown to be devoid of the cyanated isomer at the methine group.

Diisopropylmethylamine (Expt 7). Similarly, the combined ether layers were dried and distilled. *N,N*-Diisopropylaminoacetonitrile[17] was obtained in a yield of 6.0 g at 98–102 °C (35 mm). The isomer was not detected by NMR.

***N*-Methylpyrrolidine (Expt 8).** The crude product was concentrated by distillation. A fraction with bp 69–78 °C (18 mm) was obtained in a yield of 5.1 g. According to GLC analysis, the fraction consisted of 81% of *N*-methyl-2-cyanopyrrolidine (**8a**)[21] and 19% of 1-pyrrolidineacetonitrile (**8b**).[19,23] Each nitrile for analysis was isolated by fractional distillation and purified by preparative GLC. **8a**: bp 99–100 °C (64 mm); IR ν 2225 cm^{-1} (CN); NMR δ 2.42 (s, 3 H), 3.58 ppm (t, 1 H); mass spectrum *m/e* (rel intensity) 83 ($M^+ - 27$, 79), 82 ($M^+ - 28$, 100), 42 (45). **8b**: bp 74–76 °C (15 mm); IR ν 2230 cm^{-1} (CN); NMR δ 1.80 (m, 4 H), 2.59 (m, 4 H), 3.58 ppm (s, 2 H); mass spectrum *m/e* (rel intensity) 110 (M^+, 55), 109 ($M^+ - 1$, 84), 83 ($M^+ - 27$, 38), 82 (100), 42 (95). Picrate of **8a**: yellowish needles from ethanol–acetone, mp 134–137 °C dec. Anal. Calcd for $C_{12}H_{13}N_5O_7$: C, 42.48; H, 3.86; N, 20.64. Found: C, 42.4; H, 3.8; N, 20.4. Picrate of **8b**: yellowish prisms from ethanol–acetone, mp 156.5–157 °C dec. Anal. Found: C, 42.7; H, 3.8; N, 20.7.

***N*-Methylpiperidine (Expt 9).** The distillation of the products gave 7.1 g of colorless liquid at 104–120 °C (38 mm). The fraction was shown to be 62% of *N*-methyl-2-cyanopiperidine (**9a**)[21] and 38% of 1-piperidineacetonitrile (**9b**)[17,19,24,25] by GLC. Each nitrile was isolated by fractional distillation and was purified by preparative GLC. **9a**: bp 73.5–74 °C (12 mm); IR ν 2220 cm^{-1} (CN); NMR δ 2.28 (s, 3 H), 3.68 ppm (t, 1 H); mass spectrum *m/e* (rel intensity) 97 ($M^+ - 27$, 98), 96 ($M^+ - 28$, 100), 82 ($M^+ - 42$, 86), 42 (96). **9b**: bp 85 °C (12 mm); IR ν 2250 cm^{-1} (CN); NMR δ 3.37 ppm (s, 2 H); mass spectrum *m/e* (rel intensity) 124 (M^+, 45), 123 ($M^+ - 1$, 100), 97 ($M^+ - 27$, 39), 96 (62), 42 (58). Picrate of **9a**: yellowish crystal powder from ethanol–acetone, mp 153–155 °C dec. Anal. Calcd for $C_{13}H_{15}N_5O_7$: C, 44.19; H, 4.28; N, 19.83. Found: C, 43.9; H, 4.1; N, 19.7. Picrate of **9b**: yellowish crystal powder, mp 159.5–161 °C dec. Anal. Found: C, 44.1; H, 4.2; N, 20.2.

***N*-Ethylpyrrolidine (Expt 10).** The crude product was distilled. A fraction with bp 100–105 °C (39 mm) was obtained in a yield of 7.1 g. The gas chromatogram of the fraction showed a peak with a discernible shoulder. The chief product was *N*-ethyl-2-cyanopyrrolidine (**10a**). The retention time of the shoulder peak was checked against an authentic sample of α-pyrrolidinepropionitrile (**10b**)[26] and the identity of the product was confirmed by the peak enhancement method. NMR showed that the fraction was a mixture of 82% of **10a** and 18% of **10b**. **10a** could be isolated by preparative GLC but **10b** could not be purified. **10a**: IR ν 2220 cm^{-1} (CN); NMR δ 1.09 (t, 3 H), 3.84 ppm (t, 1 H); mass spectrum *m/e* (rel intensity) 97 ($M^+ - 27$, 97), 82 ($M^+ - 42$, 100). Picrate of **10a**: yellowish needles from ethanol, mp 114–116.5 °C dec. Anal. Calcd for $C_{13}H_{15}N_5O_7$: C, 44.19; H, 4.28; N, 19.83. Found: C, 44.3; H, 4.2; N, 19.9.

***N*-Ethylpiperidine (Expt 11).** The crude product was distilled. GLC analysis of the distillate [bp 116–121 °C (47 mm), 8.1 g] showed it to be 78% of *N*-ethyl-2-cyanopiperidine (**11a**) and 22% of α-piperidinepropionitrile (**11b**).[21] Analytical samples were obtained by preparative GLC. **11a**: IR ν 2220 cm^{-1} (CN); NMR δ 1.09 (t, 3 H), 3.84 ppm (t, 1 H); mass spectrum *m/e* (rel intensity) 111 ($M^+ - 27$, 54), 96 ($M^+ - 42$, 100). **11b**: IR ν 2220 cm^{-1} (CN); NMR δ 1.42, 1.56 (d, broad, 9 H), 3.47 (broad, 4 H), 3.53 ppm (q, 1 H); mass spectrum *m/e* (rel intensity) 111 ($M^+ - 27$, 100), 110 ($M^+ - 28$, 67), 96 ($M^+ - 42$, 82). Picrate of **11a**: yellowish prisms from ethanol–acetone, mp 124–128 °C dec. Anal. Calcd for $C_{14}H_{17}N_5O_7$: C, 45.77; H, 4.76; N, 19.07. Found: C, 45.5; H, 4.7; N, 19.2. Picrate of **11b**: yellowish prisms from ethanol–acetone, mp 121–125 °C dec. Anal. Found: C, 45.8; H, 4.6; N, 19.4.

***N*-*n*-Propylpyrrolidine (Expt 12).** The distillation of the crude product gave 8.2 g of colorless liquid at 114–119 °C (40 mm). Although the NMR spectrum of the distillate showed very weak signals which suggested the presence of α-pyrrolidinebutyronitrile, it consisted of almost pure *N*-*n*-propyl-2-cyanopyrrolidine: IR ν 2220 cm^{-1} (CN); NMR δ 0.91 (t, 3 H), 3.62 ppm (t, 1 H); mass spectrum *m/e* (rel intensity) 111 ($M^+ - 27$, 39), 82 (100). Picrate: yellowish, rodlike crystals from methanol, mp 103–104 °C dec. Anal. Calcd for $C_{14}H_{17}N_5O_7$: C, 45.77; H, 4.67; N, 19.07. Found: C, 45.9; H, 4.7; N, 19.4.

***N*-Isopropylpyrrolidine (Expt 13).** The distillation gave 7.8 g of *N*-isopropyl-2-cyanopyrrolidine at 95–98 °C (22 mm). NMR analysis showed that the distillate was free of the side-chain substi-

tuted product: IR ν 2220 cm^{-1} (CN); NMR δ 1.13 (d, 6 H), 3.91 ppm (t, 1 H); mass spectrum *m/e* (rel intensity) 111 ($M^+ - 27$, 43), 96 ($M^+ - 42$, 100). Picrate: yellowish leaflets from ethanol–acetone, mp 106–111 °C dec. Anal. Calcd for $C_{14}H_{17}N_5O_7$: C, 45.77; H, 4.67; N, 19.07. Found: C, 45.6; H, 4.6; N, 18.8.

***N*-Isopropylpiperidine (Expt 14).** The ether extracts were distilled. Unchanged amine (1.3 g) was recovered at about 55–60 °C (24 mm) and then 9.4 g of *N*-isopropyl-2-cyanopiperidine was obtained at 108–110 °C (24 mm): IR ν 2210 cm^{-1} (CN); NMR δ 1.10 (double d, 6 H, J = 6 Hz), 3.94 ppm (t, 1 H); mass spectrum *m/e* (rel intensity) 125 ($M^+ - 27$, 33), 110 ($M^+ - 42$, 100). Picrate: yellowish leaflets from ethanol–acetone, mp 105.5–109 °C dec. Anal. Calcd for $C_{15}H_{19}N_5O_7$: C, 47.24; H, 5.02; N, 18.37. Found: C, 47.0; H, 5.0; N, 18.0.

***N*-*tert*-Butylpyrrolidine (Expt 15).** The distillation gave 2.0 g of starting amine and 9.6 g of *N*-*tert*-butyl-2-cyanopyrrolidine [bp 98 °C (13 mm)]: IR ν 2225 cm^{-1} (CN); NMR δ 1.09 (s, 9 H), 1.95 (broad, 4 H), 2.75 (broad, 2 H), 3.73 ppm (broad, 1 H); mass spectrum *m/e* (rel intensity) 152 (M^+, 3), 137 ($M^+ - 15$, 85), 125 ($M^+ - 27$, 40), 110 ($M^+ - 42$, 100), 68 (74). Picrate: yellowish prisms from ethanol–acetone, mp 177–179 °C dec. Anal. Calcd for $C_{15}H_{19}N_5O_7$: C, 47.24; H, 5.02; N, 18.37. Found: C, 47.4; H, 5.0; N, 18.0.

Registry No.—**3a,** 62842-25-5; **3a** picrate, 62842-26-6; **4b,** 62842-27-7; **4b** picrate, 62842-28-8; **5a,** 62842-29-9; **5a** picrate, 62842-30-2; **6a,** 62842-31-3; **6a** picrate, 62842-32-4; **8a,** 20297-37-4; **8a** picrate, 18747-97-2; **8b,** 29134-29-0; **8b** picrate, 62842-33-5; **9a,** 18747-95-0; **9a** picrate, 18747-96-1; **9b,** 3010-03-5; **9b** picrate, 25283-66-3; **10a,** 62842-34-6; **10a** picrate, 62842-35-7; **11a,** 62842-36-8; **11a** picrate, 62842-37-9; **11b,** 62842-38-0; **11b** picrate, 62842-39-1; **12a,** 62842-40-4; **12a** picrate, 62842-41-5; **13a,** 62842-42-6; **13a** picrate, 62842-43-7; **14a,** 62842-44-8; **14a** picrate, 62842-45-9; **15a,** 62842-46-0; **15a** picrate, 62842-47-1; α-dimethylaminoacetamide, 6318-44-1; NaCN, 143-33-9; *N,N*-diisopropylaminoacetonitrile, 54714-49-7.

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The Mechanism of Indeno[1,2,3-*de*]quinolin-2-one Formation

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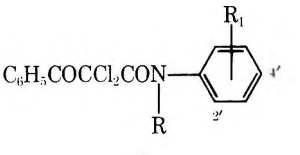
The unambiguous synthesis of 1,6-dichloro-3-ethylindeno[1,2,3-*de*]quinolin-2(3*H*)-one (**7**) was undertaken. Product **7** was found to be identical with that derived by sulfuric acid catalyzed cyclization of 2,2,4′-trichloro-*N*-ethylbenzoylacetanilide (**4**). This is evidence that **7** arises from **4** via a "direct" cyclization intermediate. A convenient modification of the Cook and Koelsch indenoquinolinone synthesis, which afforded **7** by a shorter route, is reported. The diagnostically useful anisotropic deshielding of the C-7 and C-10 protons by the halogen at C-1 and C-6 in the ^1H NMR spectrum of **7** is described.

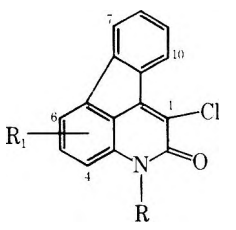
We report further developments relating to the mode of cyclization of 2,2-dichlorobenzoylacetanilides **1** to indeno[1,2,3-*de*]quinolin-2-ones **2.** In our earlier work,[1] a "direct" ring closure was tacitly assumed. The recent findings of Harcourt and Taylor[2] with 4′-methoxybenzylaminoacetonitrile prompted us to consider the intervention of a similar, appropriately modified "spiro" intermediate during the cyclization of **1,** in helping to explain the migrations encountered with certain methyl-substituted substrates.[1]

It is evident (Scheme I) that closure of the relatively uncomplicated **4** via a "spiro" intermediate i in which bond a breaks would lead to the 5-chloroindenoquinolinone **6,** whereas rearrangement of i to the "direct" intermediate ii,[3] and/or closure in a "direct" fashion, would result in the 6-chloroindenoquinolinone **7.** Competitive cleavage of both carbon and nitrogen bonds in related "spiro" species has been described by Hey; for example, treatment of the spirodienol **8** with acid gave a mixture of benzophenanthridinones in which the product of nitrogen migration, **9,** predominated.[4] The sole indenoquinolinone product derived from **4** has now been unequivocally identified as **7,** and accordingly, pathway 1 (Scheme I) for this cyclization can be discounted.



1

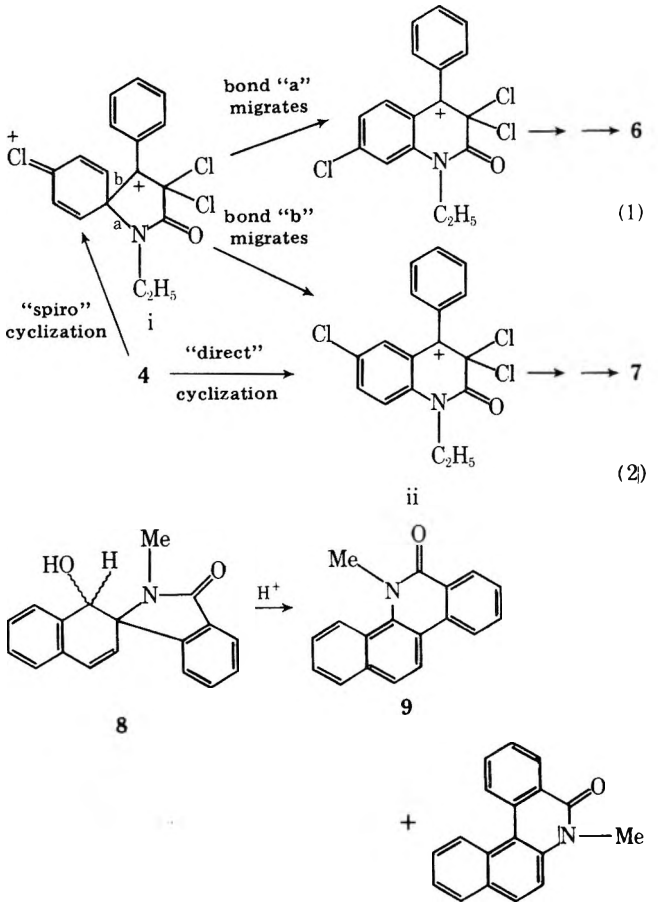
3, R = H; R_1 = 4′-Cl
4, R = C_2H_5; R_1 = 4′-Cl



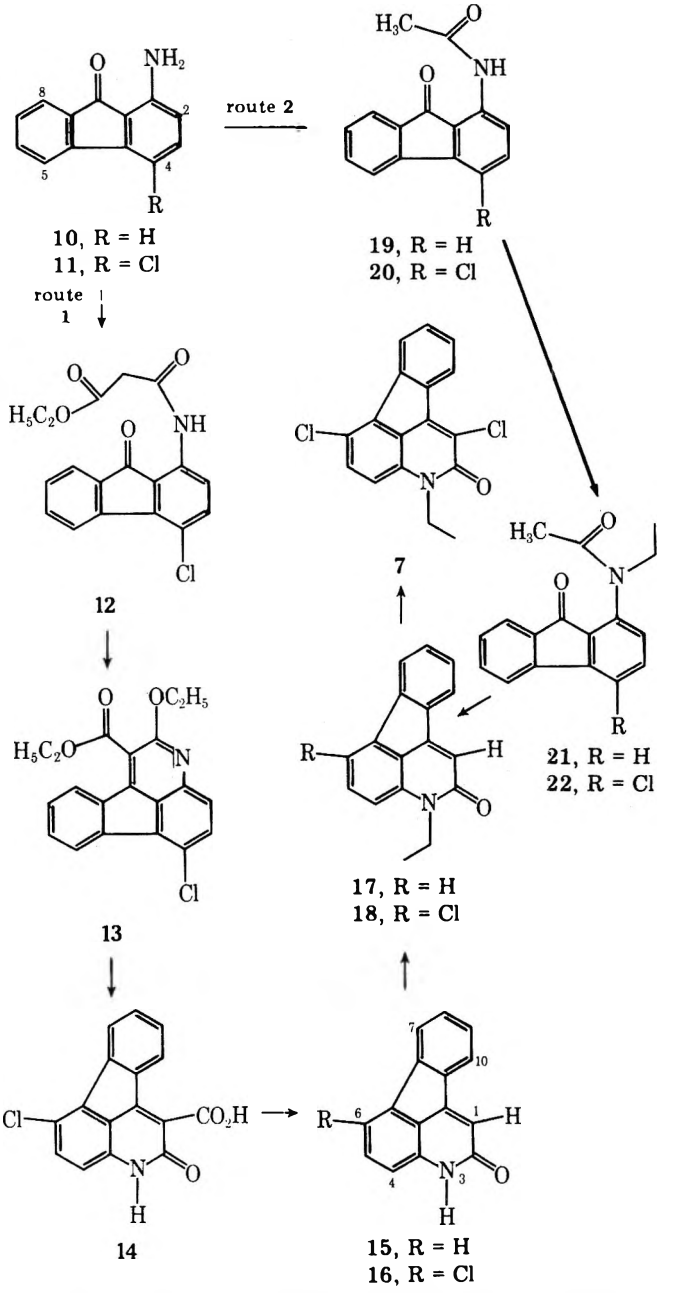
2

5, R = H; R_1 = 6-Cl
6, R = C_2H_5; R_1 = 5-Cl
7, R = C_2H_5; R_1 = 6-Cl

Scheme I



Scheme II

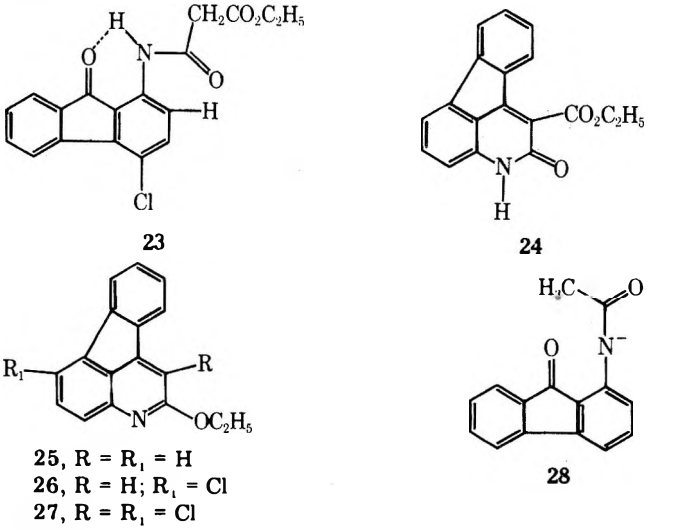


Anilides **3** and **4** were treated with concentrated sulfuric acid to afford the supposed **5** (60%) and **7** (88%), respectively. The structural relationship between these products was established by alkylating **5** with sodium hydride and ethyl bromide, to produce a mixture of *N*- and *O*-ethyl derivatives, which were separated and characterized from their spectral properties. The 3-ethylindenoquinolinone, **7**, so obtained proved to be identical with that derived from **4**, and confirmed a similar mode of cyclization for the substrates **3** and **4**.

In the absence of suitable crystals of either **5** or **7** for x-ray crystal structure determination, the preparation of authentic (chloroform-soluble) **7** was undertaken. Application of the unambiguous method of Koelsch and Steinhauer[5] furnished the intermediate product 6-chloroindeno[1,2,3-*de*]quinolin-2(3*H*)-one (**16**), and the complete synthesis of **7** is outlined in Scheme II (route 1). A modified and shorter approach (route 2) to **7** was subsequently developed.

Preparation of 7 via Route 1 (Scheme II). Chlorination of 1-aminofluoren-9-one (**10**) gave the 4-chloro derivative **11**.[6] The identity of this product, being central to the problem, was unequivocally confirmed from its NMR spectrum. The C-5 proton was anisotropically deshielded by the neighboring 4-Cl substituent and resonated downfield at δ 8.09 as a double doublet. The C-2 proton, shielded by the amino group, appeared as a doublet at δ 6.42; indeed, the spectrum was well resolved and the remaining protons could be assigned with confidence. In comparison, the NMR spectrum of **10** showed no deshielded protons.

Amine **11** was condensed with diethyl malonate to yield amide **12**. Hydrogen bonding in **12** may occur as indicated in **23**. In support,[7] **12** displayed a broad band near 3190 cm^{-1}. An interesting consequence of this suggested hydrogen bonding was revealed in the NMR spectrum of **12**. The deshielded proton ortho to the amide was further affected since it falls within the ambit of the deshielding cone of the amide carbonyl function; it thus appeared as a sharp doublet (J = 9 Hz) at δ 8.29. The NMR spectrum displayed the anisotropic deshielding of the C-5 proton as a broad doublet (J = 7.5 Hz) at δ 8.02.



Treatment of **12** with sodium ethoxide in ethanol gave the 1-carbethoxy-2-ethoxy derivative **13**. In contrast, Koelsch[5] obtained **24** from the corresponding amide, on neutralization of the reaction mixture with hydrochloric acid. Assignment **13** was supported by the IR spectrum [strong peak at 1730 cm^{-1} (ester CO); amide CO absent] and the mass spectrum, which showed the parent ion at *m/e* 353 and the expected fragmentations for **13**.

Hydrolysis of **13** to yield the corresponding 1-carboxyindenoquinolinone **14** was affected by refluxing with aqueous sodium hydroxide. In the final step of the Koelsch synthesis, thermal decarboxylation, by heating at 310 °C, gave the new 6-chloroindenoquinolinone **16** as a yellow sublimate. Spectral properties were in accord with structure **16**. A parallel series of reactions starting from **10** provided the known[5] parent indenoquinolinone **15**.

Sodium hydride abstraction of the amidic proton in **16**, followed by treatment of the ambident anion with ethyl bromide, yielded the desired 6-chloro-3-ethylindenoquinolinone **18** (51%) as well as the *O*-ethyl derivative **26** (11%). These were separated by chromatography and characterized from their spectra. Compound **15** was likewise alkylated and gave **17** (73%) and **25** (17%).

Completion of the synthesis (route 1) was effected by chlorination of the respective substrates, **17** and **18**, in chloroform with sulfuryl chloride. The two separate products proved to be the same, viz., the 1,6-dichloroindenoquinolinone **7**. The preferential electrophilic substitution at sites C-1 and C-6 in **17** was thus demonstrated.

Finally, comparison of this **7** with the product of cyclization of **4** showed them to be identical in all respects (IR, NMR, MS, mixture melting point, R_f). This finding supports the belief that **7** arises from **4** via a "direct" intermediate of type ii (Scheme I), notwithstanding the origin of the latter being in question.[3]

^1H NMR spectra were of particular diagnostic value in substantiating the various structural assignments. The protons at C-7 and C-10 in **7** were anisotropically deshielded by the chlorine substituents at C-6 and C-1, and this resulted in a two-proton multiplet (two juxtapositioned double doublets) centered at δ 7.95 ($CDCl_3$). In comparison, the monochloro compound **18** displayed only one deshielded proton (7-H) as a four-line multiplet (J_o = 7 and J_m = 2 Hz) centered at δ 8.06, while the unsubstituted **17** showed no deshielded protons. Closely related deshielding phenomena have been noted with certain 9,10-dihalogenated anthracenes.[8]

Synthesis of 7 via Route 2 (Scheme II). The acetyl derivatives **19** and **20** were readily obtained from the appropriate aminofluorenone and acetic anhydride. Cook[9] and Koelsch[5] had been unable to cyclize **19** using either sodium ethoxide or sodium hydroxide. This lack of success is here attributed to the monoanion **28**, formed by these relatively weak bases, being unable to cyclize. Alkylation of **19** and **20** with sodium hydride and ethyl bromide gave the *N*-ethyl derivatives **21** and **22**, respectively. This was evidence for the intermediacy of the anion **28**. Infrared analysis of **21** and **22** served to confirm that N-ethylation had occurred in preference to O-ethylation. Both compounds displayed the $\nu_{C=O}$ (amide) at 1650 cm^{-1}, while $\nu_{C=O}$ (keto) was near 1700 cm^{-1}. The mass spectra revealed (minor) McLafferty loss of C_2H_4, major elimination of ketene, and other fragmentations expected from the structures. Treatment of **21** and **22** with sodium hydride proved successful, and led to the cyclized products **17** (69%) and **18** (50%), respectively. This modification of the Koelsch[5] synthesis thus allowed for a more convenient approach to these heterocyclics.

Experimental Section

All melting points were determined with a Kofler hot-stage apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer Model 521 spectrophotometer using KBr disks (w = weak, m = medium, s = strong). Mass spectra were recorded on a Varian CH-5 spectrometer at 70 eV. Relative abundances, particularly in mixtures, were temperature dependent. In all cases, the correct isotope abundance ratios were observed in the MS of the various halogen-containing compounds reported. ^1H NMR spectra, taken on an Hitachi Perkin-Elmer R-20 spectrometer, are recorded in δ units relative to $(CH_3)_4Si$. Chemical shifts are reported as δ (multiplicity, coupling constant, number of protons, assignment). Silica gel 60 (particle size 0.063–0.2 mm, E. Merck) was used as adsorbent for column chromatography. The petroleum ether eluent had bp 60–80 °C. Organic solvents used for extraction of aqueous solutions were dried over anhydrous Na_2SO_4 and evaporated under reduced pressure.

1,6-Dichloroindeno[1,2,3-*de*]quinolin-2(3*H*)-one (5) was obtained in 60% (crude) yield from **3** (1 g) and concentrated H_2SO_4 (2 mL) at 95 °C for 15 min:[10] yellow crystals (from DMF); mp > 350 °C; mass spectrum *m/e* 286.992 (M^+, calcd for $C_{15}H_7Cl_2NO$, 286.991).

1,6-Dichloro-3-ethylindeno[1,2,3-*de*]quinolin-2-one (7) was similarly prepared from **4** (1 g) in 88% (crude) yield as yellow needles (from DMF): mp 204–205 °C (lit.[10] mp 198–201 °C); IR 2975 (m), 2850 (w), 1650 (s), 1630 (s), 1595 (m), 1480 (m), 1440 (m), 1120 (m), 1000 (m), 750 cm^{-1} (m); NMR ($CDCl_3$) δ 1.34 (t, J = 7 Hz, 3 H, CH_2CH_3), 4.18 (q, J = 7 Hz, 2 H, CH_2CH_3), 6.91 (d, J = 9 Hz, 1 H, ArH), 7.2–7.4 (m, 3 H, ArH), 7.84–8.06 (m, 2 H, 7-H and 10-H); mass spectrum *m/e* (rel intensity) 319 (M + 4, 7), 317 (M + 2, 41), 315 (M^+, 62), 289 (69), 287 ($M - C_2H_4$, 100).

Anal. Calcd for $C_{17}H_{11}Cl_2NO$: C, 64.58; H, 3.51; N, 4.43. Found: C, 64.29; H, 3.35; 4.39.

N- and O-Ethylation of 5. A mixture of **5** (0.421 g, 1.47 mmol) and NaH (0.168 g, 7.0 mmol, washed free of mineral oil) in dry DMF (15 mL) was stirred under a N_2 atmosphere for 30 min at 20 °C. Ethyl bromide (1.6 mL, 21 mmol) was added in one portion and stirring was continued for 3 h. After addition of water, extraction with $CHCl_3$ afforded a yellow solid. This was chromatographed on silica gel using petroleum ether–EtOAc (1.5:1) to give two products: (1) **1,6-Dichloro-3-ethylindeno[1,2,3-*de*]quinolin-2-one (7)**, mp 204–205 °C (0.164 g, 35.5%), identical (IR, NMR, MS, R_f, mixture melting point) with **7** derived from **4**, and (2) **1,6-dichloro-2-ethoxyindeno[1,2,3-*de*]quinoline (27)**, yellow crystals (from EtOH) [mp 153–154 °C (0.155 g, 33.6%); IR 2900 (w), 1620 (w), 1440 (s), 1370 (m), 1320 (s), 1280 (w), 1160 (w), 1060 (w), 810 (m), 740 cm^{-1} (s); NMR (CF_3COOD) δ 1.79 (t, J = 7 Hz, 3 H, CH_2CH_3), 4.89 (q, J = 7 Hz, 2 H, CH_2CH_3), 7.4–7.6 (m, 4 H, ArH), 8.04–8.35 (m, 2 H, 7-H and 10-H); mass spectrum *m/e* (rel intensity) 317 (M + 2, 38), 315 (M^+, 58), 300 ($M - CH_3$, 88), 287 ($M - C_2H_4$, 100), 271 ($M - C_2H_4 - O$, 52), 259 ($M - C_2H_4 - CO$, 12), 232 ($M - C_2H_4 - CO - HCN$, 10)].

1-Amino-4-chlorofluoren-9-one (11).[6] Dry Cl_2 was bubbled through a stirred solution of **10**[9] (2.0 g, 10 mmol) in glacial HOAc (100 mL). The reaction was monitored by TLC (petroleum ether–EtOAc, 6:1) and was terminated at the first sign of 1-amino-2,4-dichlorofluorenone. During the course of reaction **11** separated from solution. Filtration, followed by crystallization from EtOH, gave orange **11** (0.85 g, 36%): mp 178–179 °C (lit.[6] mp 186–187 °C); IR 3450 (s), 3340 (s), 1685 (s), 1640 (w), 1605 (w), 1570 (s), 1480 (m), 1450 (m), 1410 (w), 1290 (m), 1245 (m), 1190 (s), 1120 (s), 945 (m), 805 (m), 765 (m), 730 cm^{-1} (s); NMR ($CDCl_3$) δ 5.57 (bs, 2 H, NH_2), 6.42 (d, J = 9 Hz, 1 H, 2-H), 7.07 (d, J = 9 Hz, 1 H, 3-H), 7.28 (dt, J_o = 7.5, J_m = 1 Hz, 1 H, 6-H), 7.46 (dt, J_o = 7.5, J_m = 1.5 Hz, 1 H, 7-H), 7.62 (dd, J_o = 7.5, J_m = 1 Hz, 1 H, 8-H), 8.09 (dd, J_o = 7.5, J_m = 1.5 Hz, 1 H, 5-H); mass spectrum (65 °C) *m/e* (rel intensity) 231 (M + 2, 53), 229 (M^+, 100), 202 (54), 139 (36).

Anal. Calcd for $C_{13}H_8ClNO$: C, 67.99; H, 3.51; N, 6.10. Found: C, 67.71; H, 3.27; N, 6.00.

1-Carbethoxyacetamido-4-chlorofluoren-9-one (12). A mixture of **11** (0.723 g, 3.15 mmol) and diethyl malonate (10 mL, 65.5 mmol) was refluxed for 30 min. Excess ester was distilled under reduced pressure, and the resultant oil was triturated with 96% EtOH (6 mL) to yield **12**: yellow needles (from EtOH); mp 137–138 °C (0.619 g, 57%); IR 3230 (w), 3190 (w), 2981 (w), 2920 (w), 1730 (s), 1705 (s), 1690 (m), 1630 (w), 1605 (s), 1595 (m), 1575 (m), 1285 (m), 1185 (m), 930 (m), 820 (m), 770 (m), 745 cm^{-1} (m); NMR ($CDCl_3$) δ 1.31 (t, J = 7 Hz, 3 H, CH_2CH_3), 3.52 (s, 2 H, CH_2), 5.0 (q, J = 7 Hz, 2 H, CH_2CH_3), 7.25–7.59 (m, 4 H, ArH), 8.02 (bd, J = 7.5 Hz, 1 H, 5-H), 8.29 (d, J = 9 Hz, 1 H, 2-H); mass spectrum (110 °C) *m/e* (rel intensity) 345 (M + 2, 16), 343 (M^+, 47), 298 ($M - OC_2H_5$, 17), 256 ($M - CH_2CO_2C_2H_5$, 12), 229 ($M - C_2H_5CO_2CH{=}C{=}O$, 100).

Anal. Calcd for $C_{18}H_{14}ClNO_4$: C, 62.89; H, 4.10; N, 4.08. Found: C, 63.19; H, 4.10; N, 4.16.

1-Carbethoxy-6-chloro-2-ethoxyindeno[1,2,3-*de*]quinoline

(13). To a refluxing solution of 12 (0.568 g, 1.65 mmol) in absolute EtOH (20 mL) was added a solution of sodium ethoxide in EtOH (6 mL of 1.1 M, 6.6 mmol), and heating was continued for 45 min. Filtration of the cooled mixture afforded 13 (0.54 g, 93%): mp >200 °C; IR 1730 (s), 1645 (m), 1600 (s), 1580 (s), 1480 (s), 1440 (s), 1250 (m), 1155 (m), 1090 (s), 1075 cm^{-1} (s); mass spectrum *m/e* (rel intensity) 355 (M + 2, 35), 353 (M^+, 100), 325 (M − C_2H_4, 12), 308 (M − C_2H_5O, 25).

1-Carboxy-6-chloroindeno[1,2,3-*de*]quinolin-2(3*H*)-one (14). A mixture of 13 (0.575 g, 1.63 mmol) and 5% aqueous NaOH (100 mL) was refluxed for 3 h. The solution was filtered and added to boiling 6 M HCl to precipitate 14 as a yellow solid (0.267 g, 55%): mp >350 °C; IR 1740 (s), 1640 (w), 1630 (s), 1585 (w), 1475 (m), 1435 (s), 1400 (m), 1380 (m), 1150 (m), 1090 (m), 965 (w), 815 (w), 780 (m), 745 (m), 675 cm^{-1} (m); mass spectrum (223 °C) *m/e* (rel intensity) 299 (M + 2, 14), 297 (M^+, 37), 253 (M − CO_2, 100), 225 (M − CO_2 − CO, 33), 198 (M − CO_2 − CO − HCN, 44).

6-Chloroindeno[1,2,3-*de*]quinolin-2(3*H*)-one (16). Acid 14 (0.236 g, 0.794 mmol) was heated on a sand bath at 310 °C under a N_2 atmosphere. The product 16 was collected as a yellow sublimate (0.150 g, 74.6%): mp >300 °C; IR 3150 (w), 3010 (w), 2850 (w), 1660 (s), 1600 (m), 1585 (m), 1450 (m), 1435 (m), 1320 (m), 850 (m), 805 (m), 780 (m), 745 cm^{-1} (m); mass spectrum (165 °C) *m/e* (rel intensity) 255 (M + 2, 32), 253 (M^+, 100), 225 (M − CO, 8), 218 (M − Cl, 13), 198 (M − CO − HCN, 11).

Anal. Calcd for $C_{15}H_8ClNO$: C, 71.02; H, 3.18; N, 5.52. Found: C, 70.86; H, 3.00; N, 5.32.

The parent indenoquinolinone 15 was prepared in a parallel series of reactions starting from 10, and obtained as yellow crystals (from DMF): mp 275–278 °C (lit.[5] mp 277–279 °C); mass spectrum (157 °C) *m/e* (rel intensity) 219 (M^+, 100), 191 (M − CO, 16), 164 (M − CO − HCN, 31).

N- and O-Ethylation of 16. Alkylation of 16 (0.145 g, 0.572 mmol) with NaH (0.047 g, 1.95 mmol) and ethyl bromide (0.36 mL, 4.8 mmol) and subsequent chromatography, as for 6, afforded two products. (1) **6-Chloro-3-ethylindeno[1,2,3-*de*]quinolin-2-one (18),** yellow crystals (from DMF): mp 186–187 °C (lit.[11] mp 178–180 °C); 0.082 g (51%); IR 2970 (w), 1655 (s), 1610 (s), 1580 cm^{-1} (s); NMR ($CDCl_3$) δ 1.32 (t, *J* = 7 Hz, 3 H, CH_2CH_3), 4.21 (q, *J* = 7 Hz, 2 H, CH_2CH_3), 6.95 (s, 1 H, 1-H), 7.04–7.74 (m, 5 H, ArH), 8.06 (dd, J_o = 7, J_m = 2 Hz, 1 H, 7-H); mass spectrum (195 °C) *m/e* (rel intensity) 283 (M + 2, 27), 281 (M^+, 59), 253 (M − C_2H_4, 100). (2) **6-Chloro-2-ethoxyindeno[1,2,3-*de*]quinoline (26),** yellow needles (from petroleum ether): mp 128–130 °C; 0.018 g (11%); IR 2980 (w), 1630 (w), 1600 (w), 1440 (s), 1420 (w), 1370 (m), 1320 (s), 1200 (s), 1040 (w), 770 (m), 735 cm^{-1} (m); mass spectrum (150 °C) *m/e* (rel intensity) 283 (M + 2, 17), 281 (M^+, 42), 266 (M − CH_3, 94), 253 (M − C_2H_4, 100), 237 (M − C_2H_4 − O, 52), 225 (M − C_2H_4 − CO, 25), 198 (M − C_2H_4 − CO − HCN, 42).

The ethylation of 15 was similarly conducted and gave two products. (1) **3-Ethylindeno[1,2,3-*de*]quinolin-2-one (17):** 73% yield; yellow needles (from petroleum ether); mp 116–117 °C; IR 2970 (w), 1655 (s), 1620 (m), 1595 (s), 775 (s), 755 cm^{-1} (s); NMR ($CDCl_3$) δ 1.31 (t, *J* = 7 Hz, 3 H, CH_2CH_3), 4.19 (q, *J* = 7 Hz, 2 H, CH_2CH_3), 6.87 (s, 1 H, 1-H), 7.11 (dd, J_o = 7.5, J_m = 2 Hz, 1 H, ArH), 7.2–7.7 (m, 6 H, ArH); mass spectrum (162 °C) *m/e* (rel intensity) 247 (M^+, 95), 232 (M − CH_3, 17), 219 (M − C_2H_4, 100). (2) **2-Ethoxyindeno[1,2,3-*de*]quinoline (25)** (17%): yellow crystals (from EtOH); mp 72–74 °C (lit.[5] mp 76.5–77.5 °C); NMR ($CDCl_3$) δ 1.47 (t, *J* = 7 Hz, 3 H, CH_2CH_3), 4.56 (q, *J* = 7 Hz, 2 H, CH_2CH_3), 7.2–7.9 (m, 8 H, ArH); mass spectrum (33 °C) *m/e* (rel intensity) 247 (M^+, 43), 232 (M − CH_3, 100), 219 (M − C_2H_4, 84), 203 (M − C_2H_4 − O, 78), 191 (M − C_2H_4 − CO, 21), 164 (M − C_2H_4 − CO − HCN, 40).

Chlorination of 17 and 18 to 7. Substrate 17 (0.134 g, 0.54 mmol) was refluxed with SO_2Cl_2 (0.16 g, 1.2 mmol) in dry $CHCl_3$ (8 mL) for 4 h. Excess reagent and $CHCl_3$ were removed under reduced pressure and the residue was purified on a silica gel column using petroleum ether–EtOAc (1.5:1) as eluent. Crystallization from DMF gave yellow needles (90 mg, 53%), mp 204–205 °C, identical (IR, NMR, MS, R_f, mixture melting point) with the product derived from cyclization of 4. Compound 18 with a 2.2 molar proportion of SO_2Cl_2 gave the identical 7 in 74% yield.

1-Acetamido- (19) and 1-Acetamido-4-chlorofluoren-9-one (20). A mixture of 11 (0.05 g, 0.22 mmol) and acetic anhydride (2 mL) was refluxed for 1 h. Excess reagent was evaporated and the residue was extracted with Et_2O and crystallized (from EtOH) to give yellow 20 (0.046 g, 78%): mp 194–196 °C; mass spectrum (75 °C) *m/e* (rel intensity) 273 (M + 2, 11), 271 (M^+, 32), 229 (M − CH_2=C=O, 100).

Anal. Calcd for $C_{15}H_{10}ClNO_2$: C, 66.31; H, 3.71; N, 5.16. Found: C, 65.98; H, 3.52; N, 5.06.

Amide 19 was likewise formed from 10 in 36% yield: mp 139–140 °C (lit.[5] mp 136–137 °C); mass spectrum (88 °C) *m/e* (rel intensity) 238 (M + 1, 22), 237 (M^+, 67), 195 (M − CH_2=C=O, 100).

1-(*N*-Acetyl-*N*-ethyl)- (21) and 1-(*N*-Acetyl-*N*-ethyl)-4-chloroaminofluoren-9-one (22). The alkylation of 19 (0.100 g, 0.422 mmol) with NaH (0.030 g, 1.3 mmol) and ethyl bromide (0.20 mL, 2.6 mmol) was conducted as for 6. Chromatography on silica gel with petroleum ether–EtOAc (6:1) as eluent gave 21 (0.068 g, 61%): mp 99–100 °C; IR 2970 (w), 2930 (w), 1715 (s), 1710 (s), 1650 (s), 1615 (m), 1600 (s), 920 (s), 820 (m), 760 (s), 750 (m), 690 cm^{-1} (s); mass spectrum (84 °C) *m/e* (rel intensity) 266 (M + 1, 14), 265 (M^+, 71), 237 (M − C_2H_4, 5), 223 (M − CH_2CO, 100), 208 (M − CH_2CO − CH_3, 97). Product 22 was similarly obtained from 20 in 52% yield: mp 125–130 °C; IR 1700 (s), 1650 cm^{-1} (s); mass spectrum (86 °C) *m/e* (rel intensity) 301 (M + 2, 19), 299 (M^+, 43), 271 (M − C_2H_4, 4), 257 (M − CH_2CO, 71), 242 (M − CH_2CO − CH_3, 97).

3-Ethyl- (17) and 6-Chloro-3-ethylindeno[1,2,3-*de*]quinolin-2-one (18). A mixture of 21 (0.050 g, 0.19 mmol) and NaH (0.020 g, 0.83 mmol) in dry DMF(25 mL) was stirred at 18 °C for 2 h. Dilution with water (50 mL) and extraction into Et_2O yielded an orange oil (0.041 g) which was chromatographed on silica gel with petroleum ether–EtOAc (1.5:1) to afford 17 (32 mg, 69%), mp 116–117 °C, identical (IR, NMR, MS, mixture melting point, and R_f) with 17 derived from 15.

Compound 18 was likewise obtained from 22 in 50% yield, mp 185–188 °C, identical with the product from 16.

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Registry No.—3, 19359-40-1; 4, 19359-44-5; 5, 19359-53-6; 7, 19359-54-7; 10, 6344-62-3; 11, 5358-50-9; 12, 62743-42-4; 13, 62778-03-4; 14, 62743-43-5; 15, 25559-71-1; 16, 62743-44-6; 17, 62743-45-7; 18, 25559-79-9; 19, 6954-57-0; 20, 16304-68-0; 21, 62743-46-8; 22, 62743-47-9; 25, 62743-48-0; 26, 62743-49-1; 27, 62743-50-4; ethyl bromide, 74-96-4; diethyl malonate, 510-20-3.

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(3) (a) We thank a referee for helpful suggestions concerning the behavior of i. (b) An attempt to isolate a spirocyclodienone intermediate from 4′-methoxy-2,2-dichlorobenzoylacetanilide and sulfuric acid afforded instead a small yield of 3-chloro-6-methoxy-4-phenylquinolin-2(1*H*)-one and chlorinated derivatives (unpublished results). There is no compelling evidence at this stage for persevering with "spiro" intermediate i, and the simpler, "direct" pathway to ii is preferred.
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Synthesis of Adamantane Derivatives. 34.[1] Synthesis of 2,4-Methanoadamantane and 2,4-Methanoprotoadamantane

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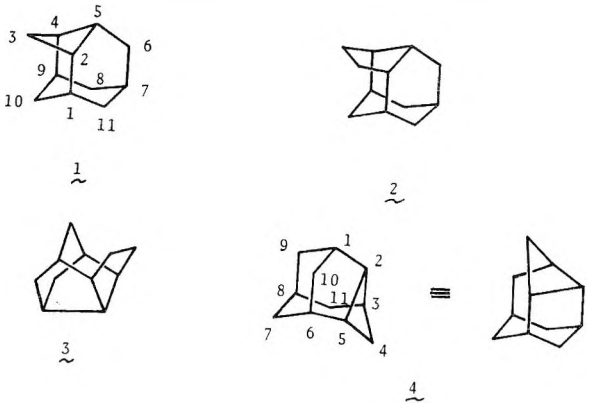
The ring contraction of 4-diazoethanoadamantan-3-one (**14**) gave 2,4-methanoadamantane-3-*endo*-carboxylic acid (**15n**) which on decarboxylation via *tert*-butyl perester (**17**) afforded 2,4-methanoadamantane (**1**). Attempted synthesis of **1** via C_4–H insertion of 2-adamantylcarbene (**5**) was unsuccessful because of occurrence of H migration and ring expansion affording methyleneadamantane (**11**) and 4-homoadamantene (**12**) as the major products. The intramolecular [2 + 2] cycloaddition of 7-*endo*-bicyclo[3.3.1]non-2-enylketene (**8**) proceeded to afford 2,4-methanoprotoadamantan-11-one (**20**) which was converted to 2,4-methanoprotoadamantane (**4**) via tosylhydrazone **21** or by the Wolff–Kishner reduction.

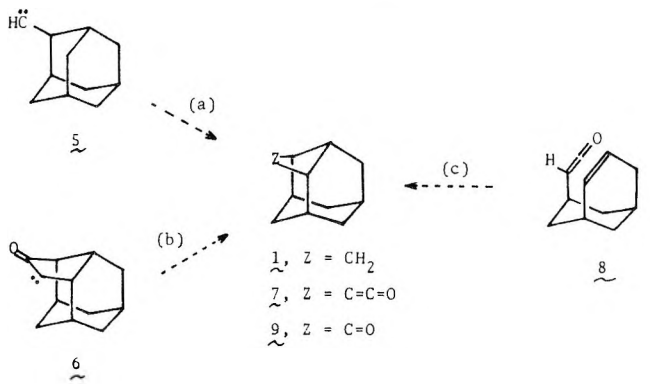
Although 2,4-methanoadamantane (tetracyclo[5.3.1.$0^{2,5}$.$0^{4,9}$]undecane, **1**) can be regarded as one of the lower homologues of 2,4-ethanoadamantane (**2**), the $C_{12}H_{18}$ tetracyclic stabilomer,[2] **1** must be a highly strained compound involving



a cyclobutane ring and a boat cyclohexane ring in the rigid tetracyclic system. Recently, Schleyer and his co-workers have shown that 2,4-ethanonoradamantane (**3**), another lower homologue of **2**, is the $C_{11}H_{16}$ stabilomer by rearrangement, synthesis, and empirical force field calculation studies.[3] The calculated strain energy of **1** is 46.22 (Engler force field)[4,5] or 46.56 kcal/mol (Allinger 1971 force field).[3,6]

We wish to report the synthesis of **1** and 2,4-methanoprotoadamantane (or 2,5-dehydrohomoadamantane, tetracyclo[4.3.1.$1^{3,8}$.$0^{2,5}$]undecane, **4**). The adamantane rearrangement method is obviously not applicable to the synthesis of such a thermodynamically unstable ring system[7] and we examined the following three routes (Scheme I): (a) the C–H insertion reaction of 2-adamantylcarbene (**5** → **1**); (b) the ring contraction of ketocarbene (**6** → **7** → **1**); (c) the intramolecular [2 + 2] cycloaddition of 7-*endo*-bicyclo[3.3.1]non-2-enylketene (**8** → **9** → **1**). Among the three routes, (b) was successful and (c) provided a facile route to **4**.

Scheme I



Results and Discussion

Intramolecular Reaction of 2-Adamantylcarbene (5). We have previously reported preparation of 2-adamantyldiazomethane by pyrolysis of the lithium salt (**10b**) of 2-adamantylcarboxaldehyde tosylhydrazone (**10a**) under reduced pressure.[8] However, 2-adamantyldiazomethane is very unstable at room temperature affording mainly the corresponding azine, and hence, thermal decompositions of **10b** in refluxing diglyme and at 160–170 °C without solvent were examined. Hydrocarbon mixtures obtained after sublimation were analyzed on GLC. The major products were methyleneadamantane (**11**), a hydrogen migration product, and 4-homoadamantene (**12**), a ring-expansion product based on the same retention times with authentic samples, though minor products could not be identified (Scheme II, Table I).[9] No trace amount of **1** could be detected by using the sample prepared from the ring-contraction route described below. Photodecomposition of **10c** by the method of Dauben and Willey[10] afforded also **11** as the major product. The absence of the C(4)–H insertion product **1** may be due to the somewhat longer distance between the C(4)–H bond and the carbenic center.[11] The distance measured on a Dreiding stereomodel (ca. 2.80 Å) is obviously longer than C–H- - -C: in the ring systems where the insertion is observed; the distance measured is ca. 2.5–2.55 Å.[12]

The Ring Contraction of Ethanoadamantan-3-one (13). Synthesis of 2,4-Methanoadamantane (1). Since ethanoadamantan-3-one (tetracyclo[6.3.1.$0^{2,6}$.$0^{5,10}$]dodecan-3-one, **13**) is now available readily from the insertion reaction of 2-adamantanecarbonylcarbene,[2] the ring contraction of **13** was carried out via diazotization followed by photolysis (Scheme III). The diazotization of **13** was carried out by the method of Wheeler and Meinwald,[13] i.e., treatment of **13** with isoamyl nitrite in the presence of *t*-BuOK gave the corresponding

Scheme II

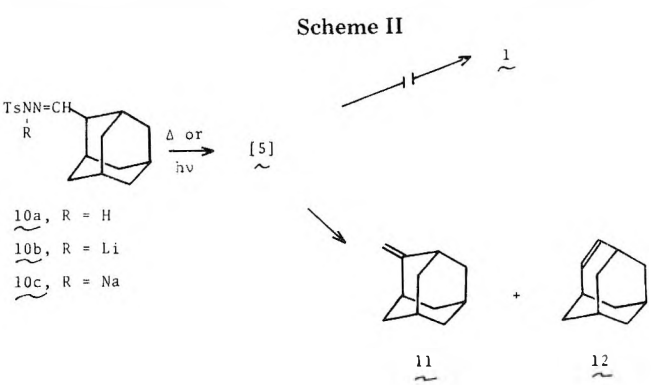


Table I. Thermal and Photodecompositions of 10b and 10c

Salt	Registry No.	Solvent	Decomposition method	Yield, %[a]	Products, %[b] 11	12	Others
10b	50782-16-6	Diglyme	Reflux	37.8	68.5	19.8	11.7[c]
10b		None[d]	160–170 °C	33.8	74.4	12.8	12.8[c]
10c	62881-86-1	0.1 N NaOMe–diglyme	Photolysis[e] (room temp)	20.3	77.6	0.5	21.9[f]

[a] The materials were sublimed at 70 °C (25 mm) and the yields are calculated as $C_{11}H_{16}$ hydrocarbons. [b] Relative peak area on GLC analysis. [c] No trace of 1 was involved. [d] Celite was used. [e] A 100-W high-pressure Hg lamp with quartz filter. [f] A trace amount of 1 was detectable.

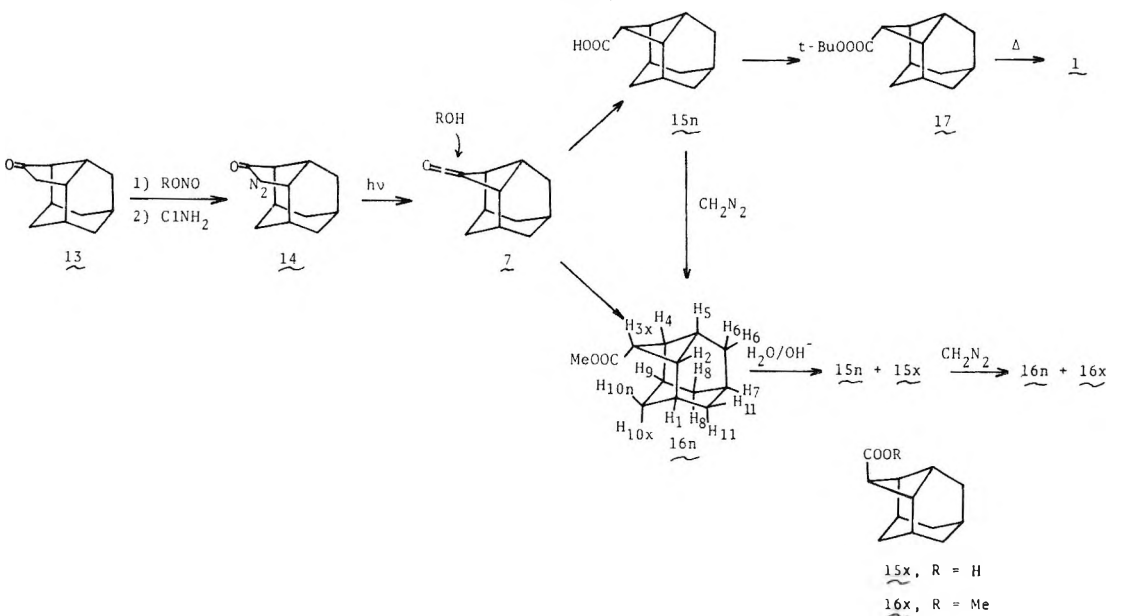
oximino ketone which was diazotized with chloramine to afford diazoketone **14** (49% from **13**) as yellowish prisms, mp 84–86 °C. The structure was supported by characteristic IR absorptions at 2070 and 1670 cm^{-1}. Photolysis of **14** in alkaline 70% aqueous tetrahydrofuran afforded 2,4-methanoadamantane-3-*endo*-carboxylic acid[14] (**15n**) (51%) as colorless crystals, mp 180–181 °C. The spectral data were compatible with the assigned structure. The endo stereochemistry of C_3–COOH was assigned based on the following facts: Treatment of **15n** with an excess amount of diazomethane afforded the corresponding methyl ester **16n** in 56% yield, which was also obtained by photolysis of **14** in methanol in 12% yield. Alkaline hydrolysis of **16n** gave a mixture of **15n** and **15x**, which afforded a 54:46 mixture of **16n** and **16x** on esterification with diazomethane as demonstrated by GLC and ^1H NMR analyses, indicating occurrence of epimerization at C(3) during the hydrolysis of **16n**. This means that photolytically produced **15n** and **16n** are thermodynamically less stable isomers, i.e., the C(3)-endo isomers where severe steric repulsion between C(3)–COOR (R = H or Me) and H(10n) should be relieved by the epimerization as suggested by stereomodel study and empirical force field calculations.[5,15] The ^1H NMR spectrum of **16n** in the presence of shift reagent, $Eu(dpm)_3$ [mole ratio of $Eu(dpm)_3$ to **16n** = 0.21], revealed signals at δ 7.28 (s, 3 H, COOMe) (the shift gradient G = 19.3),[16] 6.38 [broad d, J = 13 Hz, ca. 1 H, H(10n)] (22.0), 6.32 [t, J = 5.0 Hz, 1 H, H(3x)] (18.5), 4.30 [q, J = 5.0 Hz, 2 H, H(2), H(4)] (9.05), 3.94 [broad s, 2 H, H(1), H(9)] (9.15), 3.62 [s, 2 H, H(6) × 2] (1.10), 3.42 [s, 1 H, H(7)] (0.60), 2.96 [broad s, 1 H, H(5)] (5.75), 2.53 (d, J = 13 Hz, 1 H, H(10x)] (6.60), and 2.20 (broad m, ca. 4 H, other protons).[17] The presence of two protons having larger G values comparable to COOMe protons supported also the endo stereochemistry of **16n**. The exclusive formation of endo products rather than exo ones on the photodecomposition of **14** could be rationalyzed by addition of water or methanol to the intermediate ketene **7** from the less hindered exo side (Scheme III).

Decarboxylation of **15n** was successfully carried out via *tert*-butyl perester (**17**) followed by thermolysis in ethyl phenylacetate.[18] After chromatography and sublimations, 2,4-methanoadamantane (**1**) was obtained in 36% yield (from **15n**) as colorless crystals, mp 206–208 °C, which had correct mass spectral molecular weight and analysis. The structure of **1** was supported also by the ^{13}C NMR spectrum which revealed only eight lines due to the symmetry plane through C(3), C(5), C(6), C(7), and C(10) at δ 39.3 (d, 1 C), 38.5 (d, 2 C), 34.9 (t, 2 C), 33.7 (t, 1 C), 33.5 (t, 1 C), 29.9 (d, 2 C), 28.9 (t, 1 C), and 25.9 (d, 1 C).

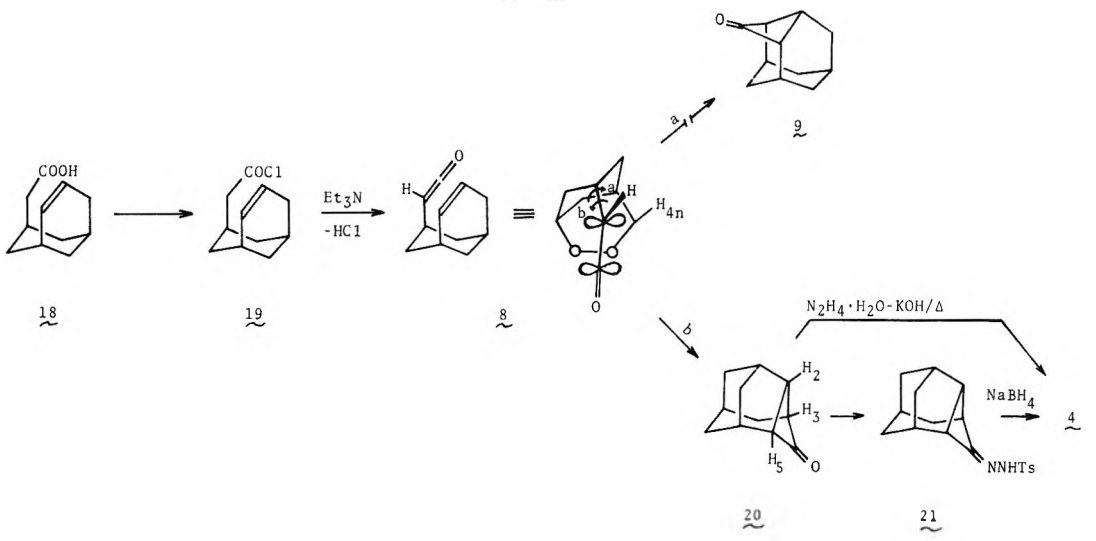
Intramolecular [2 + 2]Cycloaddition of 7-*endo*-Bicyclo[3.3.1]non-2-enylketene (8). Synthesis of 2,4-Methanoprotoadamantane (4). Thermally allowed $_\pi2_s + _\pi2_a$ cycloaddition of **8** has a possibility to afford 2,4-methanoadamantan-3-one (**9**) or 2,4-methanoprotoadamantan-11-one (**20**) depending on the rotation a or b (Scheme IV).[19,20] Bicyclo[3.3.1]non-6-ene-3-*endo*-acetic acid (**18**)[21] was converted to acid chloride (**19**) which on refluxing in benzene containing triethylamine afforded cyclobutanone derivatives, mp 224–227 °C, in 46% yield after chromatography. A strong IR absorption at 1780 cm^{-1} indicated the presence of a cyclobutanone moiety. The structure was assigned as 2,4-methanoprotoadamantan-11-one (tetracyclo[4.3.1.$1^{3,8}$.$0^{2,5}$]-undecan-4-one or 2,5-dehydrohomoadamantan-4-one, **20**) by appearance of characteristic ^1H NMR signals assignable to cyclobutanone ring protons at δ 3.58 [q, J = 7.5 Hz, 1 H, H(5)], 3.18 [d, q, J = 3.0 and 7.5 Hz, 1 H, H(3)], and 2.79 [q, J = 7.5 Hz, 1 H, H(2)]. The ^{13}C NMR data were also compatible with the assigned structure.

The selective formation of **20** via rotation b may be due to

Scheme III



Scheme IV



steric repulsion between ketene H and C(4)-*endo*-H on rotation a. In spite of considerable geometrical constraint in **8** for an ideal orthogonal approach of the two π moieties,[20] the formation of [2 + 2]cycloadduct **20** is of interest.

The ketone **20** gave the corresponding tosylhydrazone **21** which on reduction with $NaBH_4$ in refluxing ethanol[22] afforded tetracyclo[4.3.1.1^{3,8}.0^{2,5}]undecane (or trivial 2,4-methanoprotoadamantane or 2,5-dehydrohomoadamantane,[23] **4**) in 27% yield (from **20**) as sublimable crystals, mp 177–179 °C. The hydrocarbon **4** was also obtained by the Wolff–Kishner reduction of **20** in 64% yield. The spectral data (see Experimental Section) of **4** supported the assigned structure and furthermore different GLC retention times of **4** from 2,4-methanoadamantane (**1**) supported the structural assignment of **4** and **20**.

Experimental Section[24]

2-Adamantanecarboxaldehyde Tosylhydrazone (10a). This was prepared by refluxing crude 2-adamantanecarboxaldehyde[25] with a small excess amount of *p*-toluenesulfonylhydrazide in ethanol for 12 h. Repeated recrystallizations from methanol afforded an analytically pure sample of **10a**: mp 103–105 °C; IR (KBr) 3200, 1605, 1350, and 1160 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.81 (d, J = 8.0 Hz, 2 H), 7.48–6.85 (m, ca. 3 H), 2.51 (broad s, ca. 2 H, 1 H on shaking with D_2O), 2.42 (s, 3 H), and 2.15–0.85 (m, 14 H).

Anal. Calcd for $C_{18}H_{24}N_2O_2S$: C, 65.04; H, 7.28; N, 8.43. Found: C, 65.17; H, 7.29 N, 8.37.

Thermal Decomposition of Lithium Salt (10b) of 10a. (A). In Diglyme. To a stirred solution of **10a** (83 mg, 0.25 mmol) in tetrahydrofuran (2.0 mL) was added *n*-BuLi (0.11 mL of 15 wt % *n*-hexane solution, 0.26 mmol) at −78 °C. After stirring was continued for 0.5 h at −78 °C and for 0.5 h at 20 °C, the solvent was removed under reduced pressure (0.1 mm) to afford **10b** as a colorless solid which was further dried at ca. 45 °C for 6 h (0.1 mm). Thus, obtained **10b** was suspended in anhydrous diglyme (5 mL) and the mixture was refluxed for 2 h under an argon atmosphere. The cooled mixture was diluted with water (50 mL) and extracted with *n*-pentane (two 20-mL portions). The combined extracts were washed with water several times and dried (Na_2SO_4). Removal of the solvent gave crude products (42 mg) which were sublimed at 70 °C under an aspirator pressure (ca. 25 mm) to afford colorless solids (28 mg). The product composition was analyzed on GLC by using 2,4-methanoadamantane (**1**), methyleneadamantane (**11**),[26] and 4-homoadamantene (**12**).[27] The results are summarized in Table I.

(B) Without Solvent. The Li salt **10b** (from **10a**, 0.25 mmol) was mixed well with Celite (0.5 g) and was decomposed at 160–170 °C under reduced pressure (25 mm) by using a sublimation apparatus to afford crude products as colorless solids (25 mg) which were analyzed on GLC Table I).

Photodecomposition of Sodium Salt (10c). A suspension of **10a** (83 mg, 0.25 mmol) in 0.1 N NaOMe diglyme (10 mL) was irradiated with a 100-W high-pressure Hg lamp through a quartz filter under an argon atmosphere at room temperature for 6 h. Work-up as above gave a mixture of products (15 mg) after sublimation which was analyzed on GLC (Table I).

4-Diazotetracyclo[6.3.1.0^{2,6}.0^{5,10}]dodecan-3-one (**14**). To a stirred mixture of 2,4-ethanoadamantan-3-one[2,28] (**13**) (300 mg, 1.70 mmol) and potassium *tert*-butoxide (382 mg, 3.40 mmol) in *tert*-butyl alcohol (10 mL) was added a solution of isoamyl nitrite (398 mg, 3.40 mmol) in tetrahydrofuran (2.0 mL) over 0.5 h under an argon atmosphere at 20 °C. After the stirring was continued for 40 h, the mixture was diluted with water (10 mL), acidified with 10% hydrochloric acid, and extracted with ether (two 30-mL portions). The combined extracts were dried (Na_2SO_4) and evaporated to afford crude oximino ketone as an yellowish oil (0.55 g) which had IR absorptions at 3240, 1745, 1700, and 1635 cm^{-1}. The oximino ketone was dissolved in methanol (10 mL)–5% aqueous NaOH (10 mL) and filtered in order to remove a small amount of precipitate (60 mg) which was recovered **13**. To the stirred filtrate was added 28% aqueous ammonia (0.98 g) and then solid calcium hypochlorite (1.73 g of 60% purity chlorinated lime, ca. 7.2 mmol). After stirring was continued for 6 h at room temperature, the mixture was diluted with water (50 mL) and extracted with dichloromethane (two 20-mL portions). The combined extracts were washed with 20% aqueous sodium chloride and dried (Na_2SO_4). Removal of the solvent gave crude diazoketone (250 mg, ca. 72%) which was ca. 80% purity contaminated with unchanged **13**. On cooling the crude diazoketone crystallized; the crystals were washed with *n*-hexane to give an analytical sample of **14** as yellowish prisms (168 mg, 49%): mp 84–86 °C; IR (KBr) 2070 and 1670 cm^{-1}.

Anal. Calcd for $C_{12}H_{14}N_2O$: C, 71.26; H, 6.98; N, 13.85. Found: C, 71.01; H, 6.80; N, 13.76.

Tetracyclo[5.3.1.0^{2,5}.0^{4,9}]undecane-3-*endo*-carboxylic Acid (15n). A solution of the crude diazoketone (**14**) (170 mg, ca. 0.84 mmol) in tetrahydrofuran (250 mL)–0.5% aqueous sodium bicarbonate solution (100 mL) was irradiated under an argon atmosphere through a Pyrex filter with a 100-W high-pressure Hg lamp for 3 h at 25 °C. The irradiated mixture was concentrated to ca. 120 mL and diluted with 5% aqueous sodium hydroxide (30 mL) and washed with ether (20 mL). The aqueous layer was acidified with 10% hydrochloric acid and extracted with dichloromethane (five 20-mL portions). The combined extracts were dried (Na_2SO_4) and evaporated to afford crude carboxylic acid **15n** as a solid (110 mg) which was recrystallized from *n*-hexane–CH_2Cl_2 to give pure **15n** as colorless prisms (82 mg, 51%): mp 180–181 °C; IR (KBr) 3300–2300 (broad), 1680, 1615 (shoulder), 1400, 1240, and 870 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 9.20 (broad s, 1 H, disappeared on shaking with D_2O), 2.57 (unsymmetrical AB-q, J = ca. 5 Hz, 3 H), 2.30 (broad s, 2 H), 1.91 (broad s, ca. 2 H), 1.7–1.4 (m, 7 H), and 1.29 (unsymmetrical d, J = 13 Hz, ca. 1 H); ^{13}C NMR ($CDCl_3$) δ 181.5 (s, 1 C), 45.0 (d, 1 C), 42.0 (d, 2 C), 35.7 (d, 1 C), 35.0 (t, 1 C), 34.6 (t, 2 C), 32.9 (t, 1 C), 29.1 (d, 2 C), and 25.6 (d, 1 C); mass spectrum *m/e* (rel intensity) 193 (15.0), 192 (98.6, M$^+$), 174 (10.9, M − H_2O), 147 (20.4, M − CO_2H), 133 (29.3), 132 (40.8), 119 (20.4), 117 (17.7), 105 (40.8), 93 (54.3), 92 (40.8), 91 (76.2), 81 (22.4), 80 (37.4), 79 (100), 78 (27.2), 77 (47.6), 67 (32.7), 65 (23.8), 53 (24.5), 41 (47.6), and 39 (40.8).

Anal. Calcd for $C_{12}H_{16}O_2$: C, 74.97; H, 8.39. Found: C, 74.76; H, 8.41.

Methyl Tetracyclo[5.3.1.0^{2,5}.0^{4,9}]undecane-3-*endo*-carboxylate (16n). A solution of crude diazoketone (**14**) (172 mg, ca. 0.848 mmol)

in methanol (250 mL) was irradiated as above for 7.5 h. After concentration under reduced pressure to ca. 20 mL, the irradiated mixture was diluted with water (100 mL) and extracted with ether (five 30-mL portions). The combined extracts were washed with water and saturated aqueous sodium chloride and dried (Na_2SO_4). Removal of the solvent gave crude ester (**16n**) (45 mg) as an oil which was purified on a silica gel column eluting with *n*-hexane–CH_2Cl_2. Analytically pure 16n was obtained as a colorless oil (21 mg, 12%): $n^{18}D$ 1.5160; IR (neat) 1730, 1240, 1120, and 1025 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.68 (s, 3 H), 2.75–2.45 (m, 3 H), 2.29 (broad s, 2 H), 2.1–1.42 (m, 9 H), and 1.25 (unsymmetrical d, J = 13 Hz, 1 H).

Anal. Calcd for $C_{13}H_{18}O_2$: C, 75.69; H. 8.80. Found: C, 75.98; H, 8.58.

On treatment of the carboxylic acid **15n** (10 mg, 0.052 mmol) with diazomethane (ca. 30 mmol) in ether (50 mL) for 1 day at room temperature, the methyl ester **16n** was obtained also after chromatography on a silica gel column as an oil (6 mg, 56%) which was identical with the sample prepared from **14** by photolysis (GLC and IR spectral comparisons).

Hydrolysis of 16n and Esterification of 15n + 15x. A mixture of the endo ester **16n** (83 mg, 0.40 mmol) in ethanol (5 mL) and 51% aqueous potassium hydroxide (5 mL) was refluxed for 10 h under nitrogen atmosphere. The cooled mixture was concentrated under reduced pressure to ca. 7 mL and diluted with water (10 mL) and washed with *n*-hexane (10 mL). The aqueous layer was acidified with 10% hydrochloric acid and extracted with dichloromethane (four 10-mL portions). The combined extracts were dried (Na_2SO_4) and evaporated to afford crude carboxylic acid which was recrystallized from *n*-hexane–CH_2Cl_2 to afford a mixture of **15n** and **15x** (54:46 ratio estimated from the esterification described below) as colorless crystals (35 mg, 45%), mp 135–145 °C, with an IR spectrum (KBr) very similar to **15n** but with some extra absorptions observed at 1330, 1285, and 940 cm^{-1}.

On treatment with diazomethane (ca. 60 mmol) in ether (50 mL), the endo and exo carboxylic acid (35 mg, 0.18 mmol) afforded the corresponding methyl ester after chromatography (silica gel, *n*-hexane–CH_2Cl_2) as an oil (35 mg, 94%) which revealed two peaks in 54:46 ratio on GLC analysis (at 150 °C on a Silicone SE-30 column) and had an IR spectrum quite similar to **16n** except for bands at 990 and 745 cm^{-1}; ($CDCl_3$) δ 3.70 (s, 1.4 H, C(3x)–COOMe), 3.68 (s, 1.6 H, ^1H NMR C(3n)–COOMe), 2.83–2.1 (m, 5 H), and 2.1–1.06 (m, 10 H).

Anal. Calcd for $C_{13}H_{18}O_2$: C, 75.69; H, 8.80. Found: C, 75.83; H, 8.66.

Decarboxylation of 15n via the *tert*-Butyl Perester (17). Tetracyclo[5.3.1.0^{2,5}.0^{4,9}]undecane (1). To a stirred mixture of the acid **15n** (100 mg, 0.52 mmol) in 50% aqueous methanol (10 mL) was added 10% aqueous sodium hydroxide up to a phenolphthalein end point. After stirring for 0.5 h, the mixture was completely dried up at 80 °C under reduced pressure (0.2 mm) to afford the sodium salt of **15n**, which was suspended in benzene (6.5 mL) containing pyridine (80 mg). To the stirred suspension was added oxalyl chloride (0.2 mL, 2.4 mmol) under ice cooling and stirring was continued for 15 min at the same temperature and for 15 min at room temperature. The resulting precipitates were filtered and washed with benzene. The combined filtrate and washings were evaporated under reduced pressure to afford the corresponding acid chloride as an oil (110 mg): IR (neat) 1795 cm^{-1}.

To a stirred and ice-cooled mixture of *tert*-butyl hydroperoxide (70 mg, 0.78 mmol) and pyridine (63 mg, 0.78 mmol) in dichloromethane (5 mL) was added the acid chloride (110 mg) in dichloromethane (2 mL) and the stirring was continued for 1 h at the same temperature. After standing overnight in a refrigerator, the mixture was washed successively with cold water, 10% aqueous sulfuric acid, 5% aqueous sodium bicarbonate, and water and dried (Na_2SO_4). Removal of the solvent gave the *tert*-butyl perester **17** as an oil (170 mg), IR (neat) 1770, 1365, 1270, 1180, 1115, 980, and 800 cm^{-1}, which was pyrolyzed without further purifications.

The crude *tert*-butyl perester **17** (230 mg, from 135 mg of **15n**) was heated at 155 °C in ethyl phenylacetate (1 mL) for 2 h by the method of Ruechardt.[18] To the cooled mixture was added methanol (2 mL) and 45% aqueous sodium hydroxide, and the mixture was refluxed for 4 h under an argon atmosphere. The cooled mixture was diluted with water (10 mL) and extracted with *n*-pentane (three 10-mL portions). Crystals sublimed at the reflux condenser were washed with *n*-pentane (10 mL). The combined extracts and washings were washed with water and dried (Na_2SO_4). Removal of the solvent followed by chromatography (silica gel, *n*-pentane) and sublimation [80 °C (25 mm)] afforded **1** as colorless crystals (26 mg, 25%): mp 206–208 °C; IR (CCl_4) 2915, 2850, 1465, 1450, 1350, 1265, 1105, and 1020 cm^{-1}; ^1H NMR (CCl_4) δ 2.5–0.6 (m); ^{13}C NMR ($CDCl_3$) see text; mass spectrum *m/e* (rel intensity) 149 (10.0), 148 (62.2, M^+), 134 (13.9), 120 (11.1), 119 (23.3), 107 (16.7), 106 (23.3), 105 (30.0), 94 (14.4), 93 (24.4), 92 (44.4), 91 (52.2), 81 (20.0), 80 (44.4), 79 (100), 78 (23.3), 77 (36.7), 70 (13.3), 67 (16.7), 66 (16.6), 65 (16.5), 55 (10.0), 53 (16.7), 51 (13.3), 41 (33.3), and 39 (36.7).

Anal. Calcd for $C_{11}H_{16}$: C, 89.12; H, 10.88. Found: C, 89.09; H, 10.91.

Tetracyclo[4.3.1.1^{3,8}.0^{2,5}]undecan-4-one (20). To a suspension of the sodium salt prepared from bicyclo[3.3.1]non-6-ene-3-*endo*-acetic acid[21] (**18**) (300 mg, 1.66 mmol) as above in dry benzene (10 mL) and pyridine (0.24 mL) was added oxalyl chloride (0.42 mL, 4.96 mmol) with stirring under ice cooling. After the stirring was continued for 0.5 h at room temperature, the mixture was filtered in order to remove precipitates. The precipitates were washed with benzene (2 mL) and the combined washings and filtrate were evaporated under reduced pressure to afford acid chloride **19** as an oil (0.40 g): IR (neat) 1800 cm^{-1}.

To a refluxing mixture of triethylamine (200 mg, 1.97 mmol) and benzene (30 mL) was added the acid chloride (0.40 g) in benzene (10 mL) over 0.5 h and the refluxing was continued for 2 h. The cooled mixture was washed with water (two 10-mL portions) and dried (Na_2SO_4). Removal of the solvent gave an oily product which on purification on a silica gel column (*n*-hexane–CH_2Cl_2) afforded the ketone **20** as colorless crystals (125 mg, 46%): mp 224–227 °C (after one sublimation); IR (KBr) 1780, 1450, 1195, and 1130 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.58 (q, J = 7.5 Hz, 1 H), 3.18 (d, q, J = 3.0 and 7.5 Hz, 1 H), 2.79 (q, J = 7.5 Hz, 1 H), and 2.7–1.2 (m, 11 H); ^{13}C NMR ($CDCl_3$). Although carbonyl carbon chemical shift could not be determined, ten other carbons appeared at δ 70.9 (d), 54.6 (d), 46.3 (t), 36.1 (t), 35.2 (t), 33.8 (d), 33.7 (d), 31.9 (d), 31.0 (t), and 28.0 (d);[29] mass spectrum *m/e* (rel intensity) 162 (4.8, M^+), 135 (11.3), 134 (100), 119 (21.0), 105 (16.1), 93 (45.1), 92 (48.3), 91 (51.6), 80 (38.7), 79 (75.8), 78 (24.2), 77 (29.1), 66 (16.1), 41 (22.6), and 39 (22.5).

Anal. Calcd for $C_{11}H_{14}O$: C, 81.44; H, 8.70. Found: C, 81.40; H, 8.74.

As a by-product an oil (30 mg, 5.6%) supposed to be a ketene dimer was obtained: $n^{16}D$ 1.5313; IR (neat) 1820, 1745, and 1045 cm^{-1}.

Anal. Calcd for $C_{22}H_{28}O_2$: C, 81.44; H, 8.70. Found: C, 81.18; H, 8.96.

Tosylhydrazone of 20. A mixture of the ketone **20** (50 mg, 0.31 mmol) and *p*-toluenesulfonylhydrazide (100 mg, 0.54 mmol) in ethanol (5 mL) was heated under reflux for 2 h. Removal of the solvent gave a crude product which was purified by repeated recrystallizations from aqueous methanol to afford pure tosylhydrazone **21** as colorless crystals (80 mg, 79%): mp 170–172 °C; IR (KBr) 3200, 1670, 1603, 1340, and 1165 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.85 (d, J = 8.0 Hz, 2 H), 7.60 (m, 1 H, disappeared on shaking with D_2O), 7.30 (d, J = 8.0 Hz, 2 H), 3.55–3.0 (m, 2 H), 2.44 (s, 3 H), and 2.9–0.95 (m, 12 H).

Anal. Calcd for $C_{18}H_{22}N_2O_2S$: C, 65.44; H, 6.71; N, 8.48. Found: C, 65.20; H, 6.68; N, 8.50.

Tetracyclo[4.3.1.1^{3,8}.0^{2,5}]undecane (4). (A) From Tosylhydrazone (21). To a solution of crude tosylhydrazone (**21**) (from **20**, 125 mg, 0.771 mmol and *p*-toluenesulfonylhydrazide, 215 mg, 1.15 mmol) in ethanol (5 mL) was added sodium borohydride (875 mg, 23.1 mmol) and the mixture was refluxed for 6 h. The cooled mixture was diluted with water (30 mL) and extracted with *n*-pentane (10 mL × 4). The combined extracts were dried (Na_2SO_4) and evaporated to afford crude **4** (45 mg, 40%) which was purified by passing a short silica gel column (*n*-pentane), followed by sublimation at 80 °C (25 mm) to afford pure **4** as colorless crystals (30 mg, 27%): mp 177–179 °C; IR (CCl_4) 2930, 2860, 1455, 1155, and 1065 cm^{-1}; ^1H NMR (CCl_4) δ 2.9–0.7 (m); ^{13}C NMR ($CDCl_3$) δ 43.9 (t, 2 C), 38.3 (d, 1 C), 37.8 (t, 1 C), 36.7 (d, 1 C), 35.5 (t, 1 C), 33.4 (d, 1 C), 33.1 (d, 1 C), 31.5 (d, 1 C), 29.5 (d, 1 C), and 28.2 (t, 1 C); mass spectrum *m/e* (rel intensity) 149 (26.7), 148 (44.0, M^+), 133 (20.0), 119 (20.3), 107 (21.3), 106 (25.9), 105 (37.3), 97 (26.7), 93 (29.3), 92 (46.7), 91 (53.3), 85 (25.3), 83 (25.0), 81 (34.7), 80 (44.0), 79 (100), 78 (25.3), 77 (40.0), 71 (33.3), 70 (29.3), 69 (33.5), 67 (29.0), 66 (24.0), 57 (53.3), 55 (50.6), 43 (50.7), 41 (66.7), and 39 (40.0).

Anal. Calcd for $C_{11}H_{16}$: C, 89.12; H, 10.88. Found: C, 89.15; H, 10.85.

(B) From Ketone (20). A mixture of ketone (**20**) (162 mg, 1.00 mmol), hydrazine hydrochloride (126 mg, 1.20 mmol), and 100% hydrazine hydrate (500 mg, 10.0 mmol) in diethylene glycol (12 mL) was refluxed for 3 h. To the cooled mixture was added potassium hydroxide (285 mg) and the mixture was concentrated until the temperature rises to 230 °C and then refluxed for 4 h. The cooled mixture was diluted with water and extracted with *n*-pentane (two 10-mL portions). Sublimed crystals at the reflux condenser were washed with *n*-pentane. The combined extracts and washings were washed with

water, 5% hydrochloric acid, and water successively and dried (Na_2SO_4). Removal of the solvent and sublimation afforded the hydrocarbon 4 (95 mg, 64.1%) which was identical with the sample obtained via 21 on GLC analysis.

Acknowledgment. We are grateful to Professor Y. Hirata, Dr. K. Yamada, Mr. S. Manabe, and Mr. K. Wakamatsu (Department of Chemistry, Nagoya University) for obtaining the ^{13}C NMR spectra, and we are deeply indebted to them for their generosity. We are also grateful to Professors P. v. R. Schleyer and E. Osawa for a preprint of their manuscript (ref 3b) and the empirical force field calculation results on 1.

Registry No.—1, 59014-95-8; 4, 55638-02-3; **10a**, 50782-13-3; **13**, 41171-93-1; 13 oximino ketone, 62881-87-2; **14**, 62881-88-3; **15n**, 62881-89-4; **15n** Na salt, 62959-91-5; **15n** acid chloride, 62881-90-7; **15x**, 62959-92-6; **16n**, 62881-91-8; **17**, 62881-92-9; **18** Na salt, 62881-93-0; **19**, 62881-94-1; **20**, 62881-95-2; **20** ketene dimer, 62881-97-4; **21**, 62881-96-3; 2-adamantanecarboxaldehyde, 39750-93-1; *p*-toluenesulfonylhydrazide, 1576-35-8; isoamyl nitrite, 110-46-3; oxalyl chloride, 79-37-8; *tert*-butyl hydroperoxide, 75-91-2.

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Synthesis and Absolute Configuration of Optically Active C_2-Bishomocubane (Pentacyclo[5.3.0.0^{2,5}.0^{3,9}.0^{4,8}]decane)[1]

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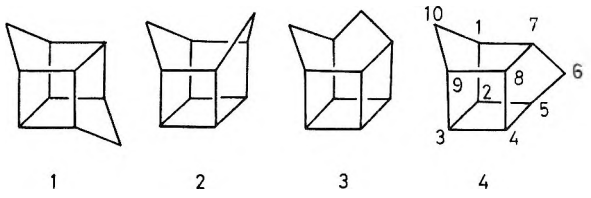
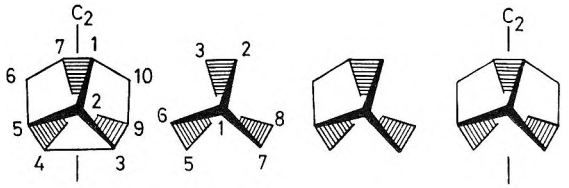
(−)-(1*S*,2*S*,3*S*,4*S*,5*R*,7*S*,8*S*,9*R*)-C_2-Bishomocubane (**4**) and (+)-(1*R*,2*R*,3*S*,4*R*,5*R*,7*S*,8*S*,9*S*)-C_2-bishomocuban-6-one (**14**) were prepared by photochemical ring closure of (+)-*endo*-dicyclopentadiene-1,8-dione 8-ethylene ketal (**12**) followed by successive removal of the substituent groups. Their absolute configurations were deduced from analyses of the CD spectra of (+)-C_2-bishomocuban-6-one (**14**) as well as other synthetic intermediates.

Theoretically, there are four ways to desymmetrize the highly symmetrical cubane molecule (O_h symmetry) furnishing bishomocubanes by insertion of each of two methylene groups between its eight methine groups situated on the eight corners. Among these four types of bishomocubanes (**1**,[2] **2**,[3] **3**, **4**[4]), only pentacyclo[5.3.0.0^{2,5}.0^{3,9}.0^{4,8}]decane (**4**) (C_2 symmetry) is chiral and hereafter we shall call this species C_2-bishomocubane[5] in this communication.



1 2 3 4

Inspection of the structure formula (**5**) of C_2-bishomocubane, which emphasizes the C_2 axis, reveals the presence of bicyclo[2.2.2]octane moiety **6** frozen in a twisted conformation, being held in position by two methylene groups and one single bond which respectively link 2–8, 3–6, and 5–7 positions of the bicyclo[2.2.2]octane. Also discernible in **5** are twist-brendane (**7**)[7] and di-twist-brendane (**8**)[8] frameworks, both of which



5 6 7 8

have been prepared in the optically active forms with known absolute configurations in our laboratory.

We have been interested in the syntheses and absolute configurations of high-symmetry chiral (gyrochiral)[11] cage-shaped molecules, and previous papers from our laboratory have reported the preparations and absolute configurations of various tricyclic cage-shaped compounds; e.g., (−)-twist-brendane (**7**),[7] (−)-brexane (**9**),[11] (+)-twistane (**10**).[12]

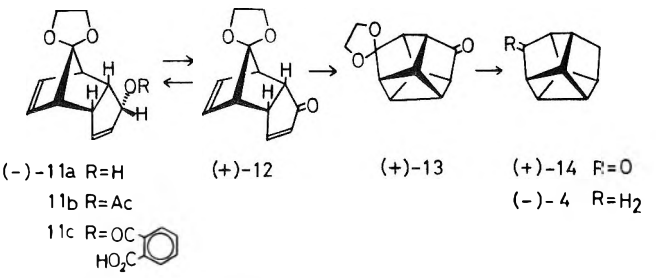
7 9 10

Our current interest concerning the absolute configuration determination of cage-shaped molecules by means of microbiological reduction[13] requires C_2-bishomocuban-6-one (pentacyclo[5.3.0.0^{2,5}.0^{3,9}.0^{4,8}]decan-6-one) (**14**) in the optically active form, and in this paper we report the preparations of (−)-C_2-bishomocubane (**4**) and (+)-C_2-bishomocuban-6-one (**14**) together with their chiroptical properties, which eventually established their absolute configurations.

Results and Discussion

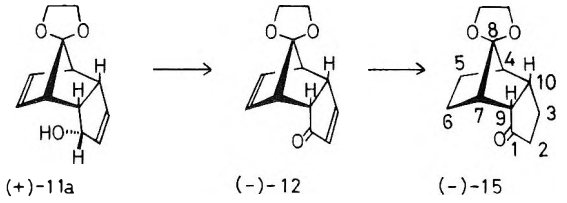
Syntheses of (+)-C_2-Bishomocuban-6-one (14) and (−)-C_2-Bishomocubane (4). Heating with sodium methoxide converted 2,5-dibromocyclopentanone ethylene ketal into *endo*-dicyclopentadiene-1,8-dione bisethylene ketal,[4] partial hydrolysis of which removed one of the protective groups to afford *endo*-dicyclopentadiene-1,8-dione 8-ethylene ketal (**12**). Photochemical ring closure[14] of this tricyclic α,β-unsaturated ketone was Chapman's[4] key strategy to secure the pentacyclic framework of C_2-bishomocubane (**13**). Of the various possible stages to accomplish the optical resolution, the stage at this compound was our choice, since we expected that the optically active unsaturated ketone **12** could be led to the *cis*-perhydroindanone derivative **15** (vide infra), whose CD spectrum could be compared with those of *cis*-perhydroindanone derivatives with known absolute configurations, furnishing informations indicative of the stereochemistry of the optically active precursor **12.**

Scheme I



(−)-11a R=H (+)-12 (+)-13 (+)-14 R=O
11b R=Ac (−)-4 R=H$_2$
11c R=OC(=O)C$_6$H$_4$CO$_2$H

Scheme II



(+)-11a (−)-12 (−)-15

Actual optical resolution was accomplished by working with the unsaturated alcohol **11a** secured by lithium aluminum hydride reduction of **12.** The oily unsaturated alcohol **11a** was converted to the crystalline acetate **11b** which was purified until it exhibited a single acetyl peak in the NMR spectrum corresponding to the endo-isomer **11b;** the stereochemistry was assumed on the basis of hydride attack from the less hindered side, which has been supported by ample examples in analogous tricyclic ketones.[15] Lithium aluminum hydride reduction of the purified acetate **11b** regenerated the endo-alcohol **11a** in crystalline form, which was converted to the hydrogen phthalate **11c.** Resolution was carried out by working with (+)-2-(1-aminoethyl)naphthalene as the resolving agent. Recrystallization of the salt from acetone resulted in complete resolution, as evidenced by the specific rotations of the isolated enantiomeric alcohols **11a:** (−)-isomer, $[\alpha]^{12}_D$ −142.2°; (+)-isomer, $[\alpha]^{15}_D$ +142.5°. Collins' oxidation of the (−)-alcohol **11a** afforded the (+)-unsaturated ketone **12,**[16] which was dissolved in ether and irradiated with a medium-pressure mercury lamp for 3 h to produce an 82% yield of (+)-pentacyclo[5.3.0.0^{2,5}.0^{3,9}.0^{4,8}]decane-6,10-dione 6-ethylene ketal (**13**): mp 60–62 °C; $[\alpha]^{14}_D$ +95.9°. Since attempts to hydrolyze the ketal protective group and thereby secure C_2-bishomocubane-6,10-dione (C_2 symmetry) were unsuccessful, removal of the functional groups to furnish C_2-bishomocubane was carried out in two steps. The Wolff–Kishner reduction followed by hydrolysis with 10% sulfuric acid converted the (+)-**13** into (+)-C_2-bishomocuban-6-one (**14**), $[\alpha]^{15}_D$ +11.0°, whose keto group was finally removed by the second Wolff–Kishner reduction to furnish (−)-C_2-bishomocubane (**4**): mp 136–138 °C; $[\alpha]^{19}_D$ −33.8°.

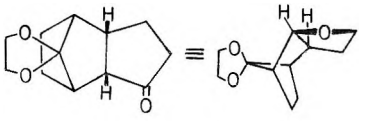
CD Spectra and Absolute Configurations. (−)-*endo*-Dicyclopentadiene-1,8-dione 8-ethylene ketal (**12**) (the enantiomer of the precursor of (−)-C_2-bishomocubane (**4**)) was prepared by Collins' oxidation of (+)-**11a.** (−)-Unsaturated ketone **12** was hydrogenated with the aid of 5% palladium-on-carbon catalyst affording the (−)-saturated ketone **15.**

A negative Cotton effect observed for the (−)-saturated tricyclic ketone **15** (Table I) is indicative of the (9*S*,10*S*) configuration for this ketone, as can be seen from the application of the octant rule to the octant projection (**16**). Furthermore, this assignment of absolute configuration was supported by the negative Cotton effects reported for *cis*-(8*R*,9*R*)-hexahydroindan-1-one (**17**)[17] and *cis*-(7*R*,8*S*)-3,3,6-trimethylbicyclo[3.3.0]octan-1-one (**18**),[18] both of which have closely related stereochemistry to the (−)-saturated tricyclic ketone **15.**

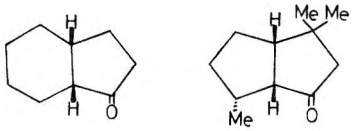
Table I. CD Spectra of (+)-C_2-Bishomocubane-6,10-dione Monoethylene Ketal (13), (+)-C_2-Bishomocuban-6-one (14), and (−)-Saturated Bicyclic Ketone (15) (in isooctane)

(+)-13[a]		(+)-14[a]		(−)-15[a]	
[θ]	nm	[θ]	nm	[θ]	nm
$+9.36 \times 10^3$ sh	297	$+1.22 \times 10^3$ sh	298	-3.70×10^3 sh	287.5
$+1.02 \times 10^4$	302	$+1.29 \times 10^3$	301.5	-5.95×10^3	296.5
$+1.00 \times 10^4$ sh	306	$+1.23 \times 10^3$ sh	304	-7.58×10^3	306.7
$+8.11 \times 10^3$ sh	312.5	$+9.48 \times 10^2$ sh	312	-6.75×10^3	318.3
				-3.10×10^3	330.5

[a] Registry no: (+)-**13**, 62928-73-8; (+)-**14**, 62928-74-9; (−)-**15**, 62851-16-5.

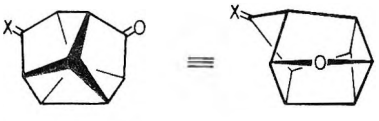


16



17 18

These conclusions suggest (1*R*,2*R*,3*R*,4*R*,5*S*,7*R*,8*R*,9*S*) and (1*R*,2*R*,3*S*,4*R*,5*R*,7*S*,8*S*,9*S*) configurations, respectively, to the pentacyclic intermediates, (+)-**13** and (+)-**14**, and this eventually assigns the (1*S*,2*S*,3*S*,4*S*,5*R*,7*S*,8*S*,9*R*) configuration to (−)-C_2-bishomocubane (**4**). Table I also records the Cotton effects of (+)-C_2-bishomocubane-6,10-dione monoethylene ketal (**13**) and (+)-C_2-bishomocuban-6-one (**14**). Examination of the octant projectons (**19**) given with the stereochemical representations of these pentacyclic ketones reveals that the groups (X) which should influence the Cotton effect fall in the positive octant region, predicting positive Cotton effects of these ketones. Observed positive Cotton effects (Table I) consistent with the octant projection (**19**) confirm our previous assignments of absolute configurations based on the CD spectrum of the tricyclic ketone **15**.



(+)-13 X= 

(+)-14 X=H_2

19

Experimental Section

Infrared spectral data were obtained from a Hitachi EPI-S2 spectrophotometer. Nuclear magnetic resonance spectra were obtained from a JNM-MH-100 spectrometer. Ultraviolet spectra were recorded on a Beckman DB spectrometer. Optical rotations were measured with a JASCO-DPI-SL automatic polarimeter. Circular dichroism data were measured on a JASCO-J-40 spectropolarimeter. Elemental analyses were performed on a Yanagimoto CHN-Corder type II. All melting points and boiling points are uncorrected.

***endo*-Dicyclopentadiene-1,8-dione 8-Ethylene Ketal (12).** A mixture of *endo*-dicyclopentadiene-1,8-dione bisethylene ketal[4] (mp 90–92 °C) (35.0 g, 0.141 mol), 35 mL of hydrochloric acid, and 350 mL of tetrahydrofuran was stirred for 1 h at room temperature and then diluted with 1.5 L of ether. The ethereal solution was washed with water, saturated sodium bicarbonate solution, and water, and dried over magnesium sulfate. Evaporation of the solvent gave a solid which was recrystallized from ethanol to yield 22.1 g of **12** (yield 77%): mp 94–95 °C (lit.[4] mp 93–94 °C).

Anal. Calcd for $C_{12}H_{12}O_3$: C, 70.57; H, 5.92. Found: C, 70.36; H, 5.90.

***endo*-1-Acetoxydicyclopentadien-8-one Ethylene Ketal (11b).** A solution of **12** (9.52 g, 0.0467 mol) in 200 mL of dry ether was added dropwise to a suspension of lithium aluminum hydride (1.20 g, 0.0316 mol) in 50 mL of dry ether, and the mixture was gently refluxed for 3 h. Saturated ammonium chloride solution was carefully added to the chilled reaction mixture. After an inorganic solid was filtered off, the filtrate was dried over magnesium sulfate. Evaporation of the solvent gave 9.00 g of an oily residue which was acetylated with 9.00 g of acetic anhydride and 25 mL of dry pyridine. The reaction mixture was stirred for 6 h at 0–5 °C, and then allowed to stand overnight at room temperature. The mixture was poured onto ice and the separated solid was collected. This was recrystallized from hexane to give 6.01 g of **11b** (yield 52% based on **12**): mp 72–73 °C; IR (KBr) 3025, 1725, 1298, 1245, 1090, 1038, 785, and 770 cm^{-1}; NMR ($CDCl_3$) δ 1.4–1.7 (m, 1 H), 2.04 (s, 3 H), 2.49–2.80 (m, 2 H), 2.90–3.46 (m, 2 H), 3.75–3.90 (m, 4 H), and 5.40–6.20 (m, 4 H).

Anal. Calcd for $C_{14}H_{16}O_4$: C, 67.73; H, 6.50. Found: C, 67.50; H, 6.59.

***endo*-1-Hydroxydicyclopentadiene-8-one Ethylene Ketal (11a).** A solution of **11b** (8.36 g, 0.0337 mol) in 200 mL of dry ether was added dropwise to a suspension of lithium aluminum hydride (2.00 g, 0.0526 mol) in 100 mL of dry ether, and the mixture was refluxed for 5 h. The reaction mixture was cooled with ice, and saturated ammonium chloride solution was added carefully to the chilled mixture. The precipitated inorganic solid was filtered, and the filtrate was dried over magnesium sulfate. Evaporation of the solvent gave a solid which was recrystallized from ether to yield 5.14 g of **11a** (yield 74%): mp 95–97 °C; IR (KBr) 3510, 3040, 1280, 1118, 1100, 1082, 1045, 1020, 1005, 785, and 770 cm^{-1}.

Anal. Calcd for $C_{12}H_{14}O_3$: C, 69.88; H, 6.84. Found: C, 69.85; H, 6.81.

Optical Resolution of 11a. Phthalic anhydride (22.6 g, 0.153 mol) was added to a chilled solution of **11a** (31.5 g, 0.153 mol) in 50 mL of pyridine, and the mixture was stirred for 5 h in an ice bath. After standing overnight at room temperature, the reaction mixture was poured onto ice. It was acidified with hydrochloric acid and extracted with ether. The extract was washed with water and dried over magnesium sulfate. Evaporation of the solvent gave a viscous oily product which, without further purification, was dissolved in 700 mL of acetone. To the solution was added (+)-2-(1-aminoethyl)naphthalene (24.0 g, 0.151 mol) with stirring at room temperature and then this mixture was boiled for 3 h. Standing overnight at room temperature deposited a solid which was collected to yield 56.5 g of the hydrogen phthalate salt: $[\alpha]^{13}_D$ +3.3° (c 0.144, $CHCl_3$). Fractional recrystallization of the salt from acetone (six times) yielded 30.2 g of the levorotatory salt; $[\alpha]^{12}_D$ −57.7° (c 0.147, $CHCl_3$). After this salt (29.0 g) was mixed with 300 mL of 5% aqueous potassium hydroxide solution, the mixture was stirred for 24 h at room temperature, and then extracted with ether. The extract was washed with 5% hydrochloric acid and water successively and dried over magnesium sulfate. Evaporation of the solvent gave 7.49 g of (−)-**11a** (yield 65%); $[\alpha]^{13}_D$ −123° (c 0.499, $CHCl_3$). Recrystallization of this from ether yielded 4.11 g of (−)-**11a**: mp 135–136 °C; $[\alpha]^{12}_D$ − 142.2° (c 0.449, $CHCl_3$). The specific rotation did not change with further recrystallization.

Anal. Calcd for $C_{12}H_{14}O_3$: C, 69.88; H, 6.84. Found: C, 69.68; H, 6.75.

Concentration of the combined mother liquors precipitated the dextrorotatory salt (8.91 g), $[\alpha]^{12}_D$ +61.3° (c 0.400, $CHCl_3$), which was treated with 5% aqueous potassium hydroxide solution. The same procedure described above for the enantiomer yielded 1.50 g of (+)-**11a** (yield 43%): $[\alpha]^{13}_D$ +139.4° (c 0.160, $CHCl_3$). Recrystallization of this from acetone afforded 1.37 g of (+)-**11a**: mp 135.5–136 °C; $[\alpha]^{15}_D$ +142.5° (c 0.175, $CHCl_3$).

Anal. Calcd for $C_{12}H_{14}O_3$: C, 69.88; H, 6.84. Found: C, 69.73; H, 6.81.

(+)-*endo*-Dicyclopentadiene-1,8-dione 8-Ethylene Ketal (12). A solution of (−)-**11a** (1.51 g, 7.40 mmol), $[\alpha]^{12}_D$ −142.2°, in 15 mL of dry methylene chloride was added to Collins' reagent, which was prepared from chromium trioxide (4.40 g, 44.0 mmol), dry pyridine (6.95 g, 87.9 mmol), and 140 mL of dry methylene chloride by the usual method.[19] After the mixture was stirred for 20 min at room temperature, the organic layer was separated by decantation. The residue was rinsed with methylene chloride. The combined methylene chloride solutions were washed successively with diluted hydrochloric acid, saturated sodium bicarbonate, and water. After drying over magnesium sulfate, the solvent was evaporated to give a solid which was recrystallized from ether to yield 1.33 g of **12** (yield 89%): mp 44.5–45.5 °C; $[\alpha]^{14}_D$ +117.6° (*c* 0.407, $CHCl_3$); IR (KBr) 3050, 1695, 1580, 1300, 1232, 1105, 1070, 795, and 780 cm^{-1}.

Anal. Calcd for $C_{12}H_{12}O_3$: C, 70.57; H, 5.92. Found: C, 70.34; H, 5.92.

(−)-*endo*-Dicyclopentadiene-1,8-dione 8-Ethylene Ketal (12). Oxidation of (+)-**11a** (1.00 g, 5.21 mmol), $[\alpha]^{12}_D$ −125.2°, was carried out by the same procedure described above and yielded 0.55 g of (−)-**12** (yield 55%): bp 130–133 °C (0.4 mm); $[\alpha]^{12}_D$ −102.7° (*c* 1.25, $CHCl_3$); CD (*c* 1.18×10^{-2}, isooctane) [θ] (nm) $+3.97 \times 10^4$ (213), 0 (265), -1.29×10^3 sh (304), -1.78×10^3 sh (310), -3.09×10^3 (323), -3.94×10^3 (347.5), -3.48×10^3 (353.5), -1.41×10^3 (372), and 0 (390).

Anal. Calcd for $C_{12}H_{12}O_3$: C, 70.57; H, 5.92. Found: C, 70.32; H, 5.91.

(−)-*endo*-Tetrahydrodicyclopentadiene-1,8-dione 8-Ethylene Ketal (15). A solution of (−)-**12** (500 mg, 2.45 mmol), $[\alpha]^{12}_D$ −102.7°, in 25 mL of ethyl acetate was shaken at room temperature in a hydrogenation flask with 80 mg of 5% palladium-on-carbon at 1 atm of hydrogen. After the hydrogen absorption had ceased, the catalyst was removed by filtration. The filtrate was condensed and the residue was distilled to give 450 mg of **15** (yield 89%): bp 115–118 °C (0.35 mm); $[\alpha]^{15}_D$ −189° (c 0.441, $CHCl_3$); IR (neat film) 1725, 1323, 1128, 1075, 1048, 1023, 1012, and 953 cm^{-1}; CD (c 1.00×10^{-2}, isooctane) [θ] (nm) 0 (235), -3.70×10^3 sh (287.5), -5.95×10^3 (296.5), -7.58×10^3 (306.7), -6.75×10^3 (318.3), -3.10×10^3 (330.5), and 0 (348).

Anal. Calcd for $C_{12}H_{16}O_3$: C, 69.21; H, 7.74. Found: C, 69.09; H, 7.71.

(+)-Pentacyclo[5.3.0.0^{2,5}.0^{3,9}.0^{4,8}]decane-6,10-dione 6-Ethylene Ketal (13). A solution of (+)-ketone ketal **12** (1.00 g, 4.90 mmol), $[\alpha]^{14}_D$ +117.6°, in 200 mL of dry ether was irradiated with a medium pressure mercury lamp (SHL-100UV, Toshiba) for 3 h at 5–6 °C. The ether was removed under reduced pressure, and the residue was chromatographed on neutral alumina (Woelm, activity III). Combined fractions eluted with benzene gave a solid, which was recrystallized from ether. Cooling at −78 °C furnished 817 mg of **13** (yield 82%): mp 60–62 °C (lit.[4] racemate, mp 58–60 °C); $[\alpha]^{14}_D$ +95.9° (*c* 0.323, $CHCl_3$); IR (KBr) 1755, 1720, 1325, 1105, 1090, 1055, 1010, and 945 cm^{-1}; CD (*c* 5.62×10^{-3}, isooctane) [θ] (nm) 0 (242), $+9.36 \times 10^3$ sh (297), $+1.02 \times 10^4$ (302), $+1.00 \times 10^4$ sh (306), $+8.11 \times 10^3$ sh (312.5), and 0 (340); λ_{max} (isooctane) 298 sh (ε 24.7), 302 (25.5), 306.5 sh (24.2), and 314 nm sh (18.6).

Anal. Calcd for $C_{12}H_{12}O_3$: C, 70.57; H, 5.92. Found: C, 70.42; H, 5.93.

(+)-Pentacyclo[5.3.0.0^{2,5}.0^{3,9}.0^{4,8}]decan-6-one (14). To a mixture of potassium hydroxide (0.42 g), 85% hydrazine hydrate, and triethylene glycol (7.4 mL) was added (+)-**13** (1.00 g, 4.90 mmol), $[\alpha]^{14}_D$ +95.9°, and the mixture was heated in an oil bath. When the bath temperature was raised to ca. 70 °C, the mixture gave a clear solution, which was stirred for 1.5 h at 150–160 °C and then for an additional 3 h at 200 °C. After cooling to room temperature, it was diluted with 10 mL of water and extracted with ether. The extract was washed successively with diluted hydrochloric acid, saturated sodium bicarbonate solution, and water. After drying over magnesium sulfate, the solvent was evaporated to give the residue, which was mixed with 10% sulfuric acid and stirred for 2 days at room temperature. The mixture was extracted with ether, and the extract was washed with saturated sodium bicarbonate solution and water and dried over magnesium sulfate. The solvent was evaporated and the residue was chromatographed on neutral alumina (Woelm, activity III). Elution with pentane yielded a solid, which was sublimed at 5 mmHg (60–70 °C bath temperature) to give 510 mg of **14** (yield 71%): mp 123–124 °C (in a sealed tube) (lit.[20] racemate, mp 111–112 °C); $[\alpha]^{15}_D$ +11°0 (*c* 0.519, $CHCl_3$); CD (c 4.89×10^{-2}, isooctane) [θ] (nm) 0 (256), $+1.22 \times 10^3$ sh (298), $+1.29 \times 10^3$ (301.5), $+1.23 \times 10^3$ sh (304), $+9.48 \times 10^2$ sh (312), and 0 (326); λ_{max} (isooctane) 292 sh (ε 13.1), 296 (13.8), 300 sh (13.6), and 306 nm sh (12.5).

Anal. Calcd for $C_{10}H_{10}O$: C, 82.16; H, 6.90. Found: C, 81.92; H, 6.93.

(−)-Pentacyclo[5.3.0.0^{2,5}.0^{3,9}.0^{4,8}]decane (4). To a mixture of potassium hydroxide (0.17 g), 80% hydrazine hydrate (0.3 mL), and triethylene glycol (3 mL) was added (+)-monoketone **14** (400 mg, 2.74 mmol), $[\alpha]^{15}_D$ +11.0°, and the mixture was heated in an oil bath. During 1.5 h, the bath temperature was gradually raised to 190 °C. When the temperature reached ca. 160 °C, a solid was observed to condense on the inner wall of the condenser. After cooling, this was washed with pentane, and the reaction mixture was diluted with water followed by extraction with pentane. Combined pentane solutions were washed with water and dried over magnesium sulfate. After evaporation of the solvent, the residue was sublimed at 70 °C (20 mm) to yield 240 mg of **4** (yield 64%): mp 136–138 °C (in a sealed tube) (lit.[4] racemate, mp 139–141 °C); $[\alpha]^{19}_D$ −33.8° (*c* 0.621, $CHCl_3$); IR (KBr) 1298, 1272, 1262, 948, 838, and 770 cm^{-1}; NMR ($CDCl_3$) δ 2.40–2.85 (m, 8 H), 1.64 (d, *J* = 10.5 Hz, 2 H), and 1.21 (d, *J* = 10.5 Hz, 2 H).

Anal. Calcd for $C_{10}H_{12}$: C, 90.85; H, 9.15. Found: C, 90.53; H, 9.05.

Registry No.—(−)-**4**, 62928-75-0; *endo*-**11a**, 62851-17-6; (−)-**11a**, 62928-76-1; (+)-**11a**, 62928-77-2; *endo*-**11b**, 62851,18,7; (−)-**11c**(+)-2-(1-aminoethyl)naphthalene, 62928-78-3; (+)-**11c** (+)-2-(1-aminoethyl)naphthalene, 62928-72-7; *endo*-**12**, 62929-25-3; (+)-**12**, 62928-79-4; (−)-**12**, 62928-80-7; *endo*-dicyclopentadiene-1,8-dione bisethylene ketal, 62929-26-4; (+)-2-(1-aminoethyl)naphthalene, 3906-16-9.

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A New Synthesis of Benzocyclobutenes. Thermal and Electron Impact Induced Decomposition of 3-Isochromanones

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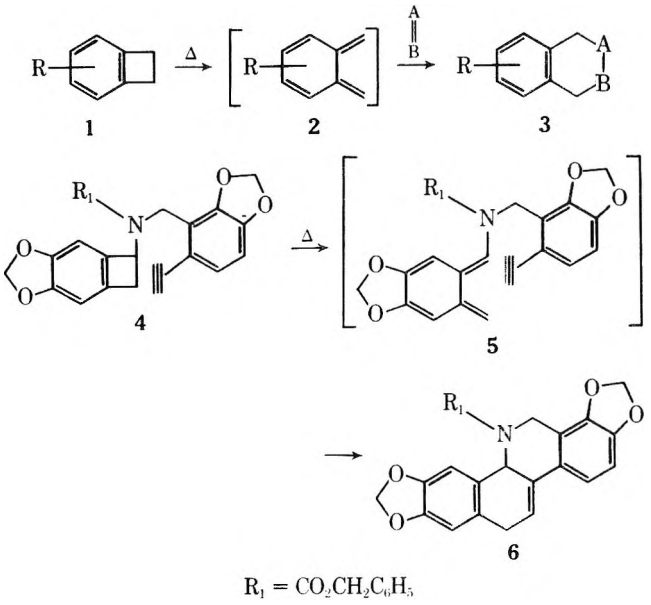
The gas-phase pyrolysis of 3-isochromanones provides a new synthesis of benzocyclobutenes, including the parent hydrocarbon, **21**, benzocyclobutenone (**8**), and several benzocyclobutenes with oxygenated substituents on the aryl ring, **25** and **28**; fulveneallene (**9**) is also prepared in high yield. The relationship between the thermal and electron impact induced decomposition of the isochromanones is described.

Although the development of benzocyclobutene chemistry began two decades ago,[1,2] and has received considerable attention since,[3] much interest in the chemistry of benzocyclobutenes prevails today. Theoretical calculations and physical studies of benzocyclobutenes, including their ^{13}C NMR spectra,[4] have been described in several recent reports.[5] The formation[6] and reactions[7] of numerous benzocyclobutenes are of continuing interest. 1,2-Dibromobenzocyclobutene was used as a precursor of benzocyclobutadiene in the first characterization of this elusive hydrocarbon.[8] Benzocyclobutenes are also useful intermediates in organic synthesis. These syntheses utilize the Diels–Alder reactivity of *o*-quinodimethanes (**2**) derived from benzocyclobutenes (**1**) by electrocyclic ring opening. Although the sequence **1** → **2** → **3** was recognized early in the development of benzocyclobutene chemistry,[3] it was not used synthetically until 1971 in the original synthesis of chelidonine (**4** → **5** → **6**).[9] Recent syntheses of berberines,[10] spirobenzylisoquinolines,[11] 3-arylisoquinolines,[12] benzocarbazoles,[13] yohimbanes,[14] and tetracyclines[15] have also utilized the Diels–Alder reactivity of dienes (**2**) derived by the thermolysis of benzocyclobutenes (**1**).[16] Because of their synthetic potential, intramolecular cyclizations similar to that used in the chelidonine synthesis have been examined in more detail,[17] the mechanisms of intermolecular cyclizations have been discussed,[18] the ease of electrocyclic ring openings of benzocyclobutenes have been correlated with their ^{13}C NMR chemical shifts,[19] and the Diels–Alder reactions of the *o*-quinodimethane (**24a**) generated by ring opening of 4-methoxybenzocyclobutene (**25a**) have been considered in terms of frontier orbital theory.[20] Simultaneous with the development of new synthetic methods using benzocyclobutenes as intermediates has been the appearance of a host of new syntheses of benzocyclobutene and its derivatives. Some of these have only been applied to the synthesis of the parent benzocyclobutene,[21] or a specific benzocyclobutene,[22] while others offer promise as a more general synthesis[23] of various benzocyclobutenes. We wish to describe the results of the pyrolysis of 3-isochromanones, a process which provides an efficient synthesis of benzocyclobutene (**21**), benzocyclobutenone (**8**), fulveneallene (**9**), and several benzocyclobutenes, **25** and **28**, with oxygenated substituents on the aryl ring. Furthermore, we report a relationship between the thermal and electron impact induced decomposition of the 3-isochromanones.[24]



Pyrolysis of Homophthalic Anhydride (7), 4,4-Dimethylhomophthalic Anhydride (18), and 1,2-Indandione (11). Homophthalic anhydride (**7**) was pyrolyzed by subliming **7** in a stream of nitrogen (22 mL/min) at 2 Torr over a heated nichrome wire. The pyrolysate, which was collected in a cold trap at −78 °C, consisted of a mixture of benzocyclobutenone (**8**) and fulveneallene (**9**); unreacted **7** solidified directly above the pyrolysis zone. When the cold trap was warmed to −25 °C at 1 mm, fulveneallene readily distilled to a second −78 °C trap. This process provided a simple means of obtaining pure **8** and **9**. In all cases the material balance was excellent and little carbonization occurred. No additional products were indicated by examination of the ^1H NMR spectra of the pyrolysates. The yields of pyrolysis products as a function of the pyrolysis temperature are shown in Figure 1. Ketone **8** was isolated pure in greater than 40% yield when the pyrolysis temperature was 515–545 °C. At 570 °C **9** was isolated pure in 71% yield. Thus the pyrolysis of homophthalic anhydride offers a convenient, one-step preparation of either **8**[25] or **9**.[26] Fulveneallene was also converted to the known tetracyanoethylene adduct **10**.[25a] When the neat adduct **10** was heated at 95–115 °C at 3 mm, **9** was regenerated and could be collected in a −78 °C cold trap. The overall process **9** → **10** → **9** proceeded in a 75% yield. Thus the unstable fulveneallene was stored in the form of the stable, solid adduct **10**, and was then easily regenerated later. This observation should facilitate the further study of this hydrocarbon.[27]

The thermal decomposition of homophthalic anhydride was very similar to that reported by Hedaya and Kent[25a] for 1,2-indandione (**11**), where **8** and **9** were also the major products. However, these authors found that benzocyclopropene (**12**) and ethynylcyclopentadiene (**13**) were produced as minor products. These products could not be detected in the ^1H NMR spectra of our pyrolysates from homophthalic anhydride. So that an exact comparison of the pyrolysis of homophthalic anhydride and 1,2-indandione could be made we pyrolyzed **11** under the same conditions used for the pyrolysis of **7**. Thus, the pyrolysis of **11** at 540 °C gave **8** in a 2.5% yield and **9** in a 2.5% yield. A considerable amount (94%) of the initial **11** remained unsublimed in the sample reservoir as a tarry residue. In contrast the pyrolysis of homophthalic anhydride under the same conditions gave **8** in 45% yield and **9**

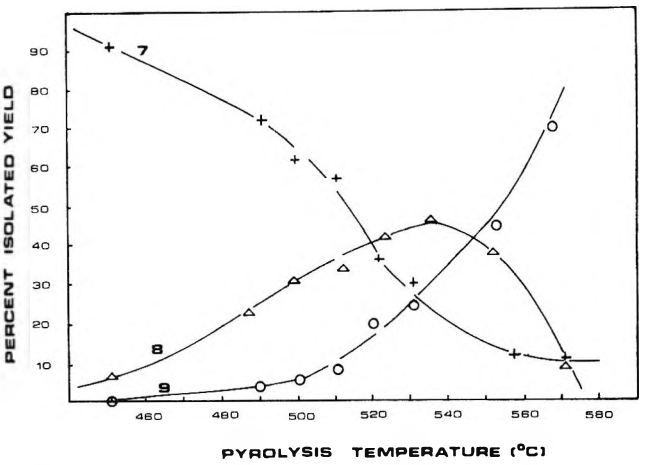
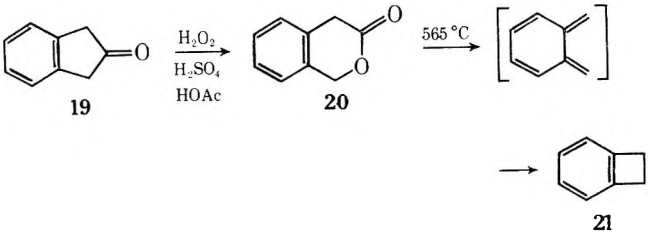


Figure 1. Pyrolysis of homophthalic anhydride (7).

mechanisms of these pyrolyses because reasonable ones have been proposed.[25a,27,28] Crow and Paddon-Row have suggested a common mechanism for the decomposition of **7** and **11**.[27] We propose that **14** and **18** also decompose by the same pathway. Brown and Butcher have suggested a likely mechanism for the decomposition of **14**.[28]

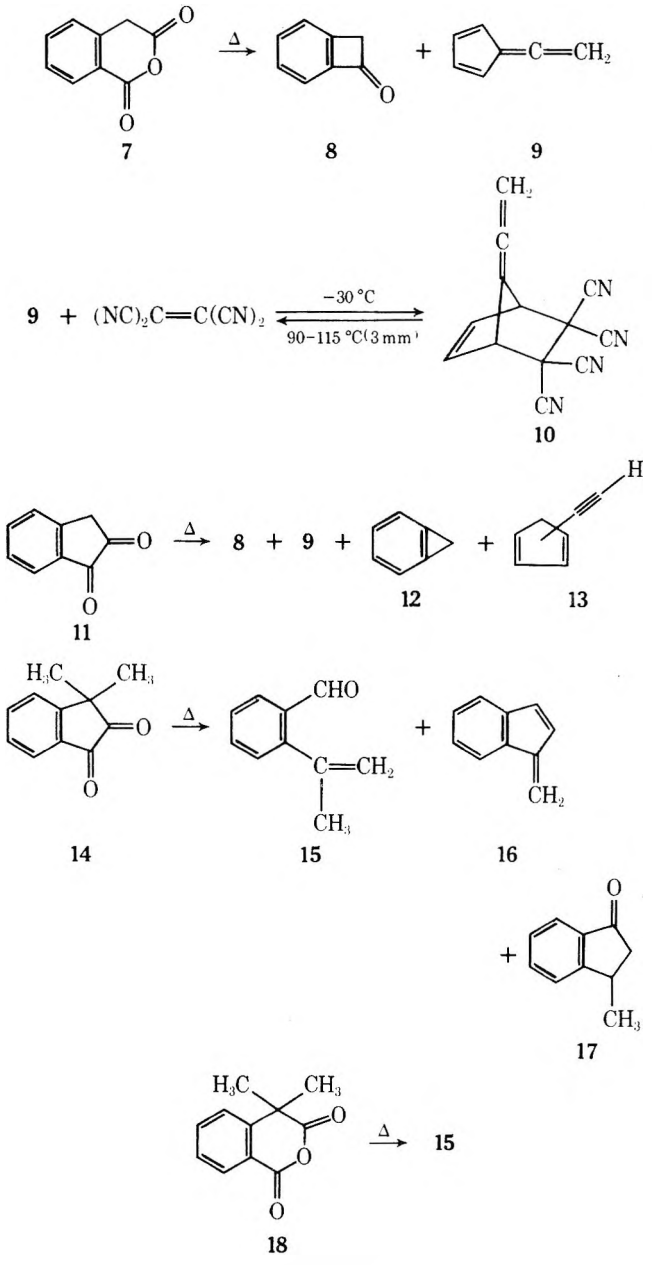
Synthesis of Benzocyclobutene (21) from 3-Isochromanone (20). 3-Isochromanone (**20**) was pyrolyzed by passing **20** vapor in a stream of nitrogen (20 mL/min) at 2 Torr over a heated, coiled nichrome wire; the crude pyrolysate was collected in a cold trap at −78 °C and was then vacuum distilled. The variation in the yield of distillate as a function of pyrolysis temperature is shown in Figure 2. At pyrolysis temperatures up to ca. 600 °C benzocyclobutene (**21**) was the sole component of the distillate (analysis by GC and ^{1}H NMR). At temperatures above ca. 600 °C the distillate had a light yellow color and traces of two additional volatile products were evident from the gas chromatogram. One of the minor products showed the same GC retention time as styrene, a known thermal decomposition product of benzocyclobutene,[29] but no further attempts were made to identify these minor products. An optimal 85% yield of pure benzocyclobutene was obtained at pyrolysis temperatures of 565–575 °C. 3-Isochromanone (**20**) was prepared in 70–80% yield by the Baeyer–Villiger oxidation of 2-indanone (**19**).[30] Thus this two-step sequence provides a simple and efficient synthesis of benzocyclobutene (**21**) from commercially available 2-



19 20 21

indanone (**19**)[31] in an overall yield of 60–65%. The good yield and brevity of the synthesis are advantages over other syntheses of benzocyclobutene.[3,21]

Pyrolysis of 3-Isochromanones with Oxygenated Substituents on the Aryl Ring. The pyrolyses of 6-methoxy-3-isochromanone (**23a**), 6,7-dimethoxy-3-isochromanone (**23b**), and 6,7-methylenedioxy-3-isochromanone (**23c**) gave 4-methoxybenzocyclobutene (**25a**) (70% yield), 4,5-dimethoxybenzocyclobutene (**25b**) (40% yield), and 4,5-methylenedioxybenzocyclobutene (**25c**) (90% yield), respectively. The optimum pyrolysis temperature for these isochromanones was found to be ca. 500 °C. 6,7-Dimethoxy-3-isochromanone (**23b**) was prepared in 80% yield by the reac-



in 36% yield and only 19% of recovered **7**. Peaks attributable to **12** and **13** were absent from the NMR spectrum of both pyrolysates. Thus under our conditions at 540 °C neither **7** nor **11** produced **12** or **13**. Only at considerably higher temperatures, such as used by Hedaya and Kent,[25a] were the latter hydrocarbons produced. Because **7** was stable and sublimed readily whereas **11** underwent tar formation at the temperature required for its sublimation, **7** is the superior precursor to **8** and **9**.

To compare further the pyrolysis of 1,2-indandiones with analogous homophthalic anhydrides, we examined the pyrolysis of 4,4-dimethylhomophthalic anhydride (**18**). Brown and Butcher[28] have reported that the pyrolysis of 3,3-dimethyl-1,2-indandione (**14**) gave o-(2-propenyl)benzaldehyde (**15**) as the major product and lesser amounts of benzofulvene (**16**) and 3-methyl-1-indanone (**17**); 2,2-dimethylbenzocyclobutenone was not found. Pyrolysis of anhydride **18** also gave **15** as the major product in 65% yield. Furthermore, the gas chromatogram of our crude pyrolysate was qualitatively similar to that reported for the crude pyrolysate of **14** except that no peaks corresponding to **16** or **17** were observed in our chromatogram. Thus, in these two comparisons, 1,2-indandiones and the analogous homophthalic anhydrides behaved in a similar manner upon pyrolysis. We did not examine the

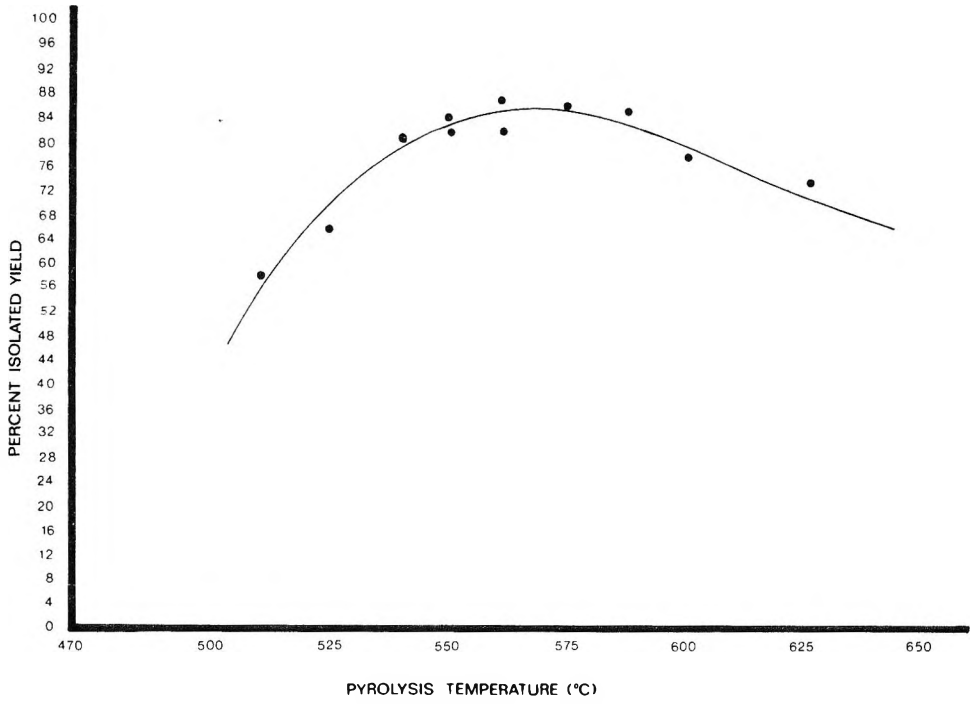
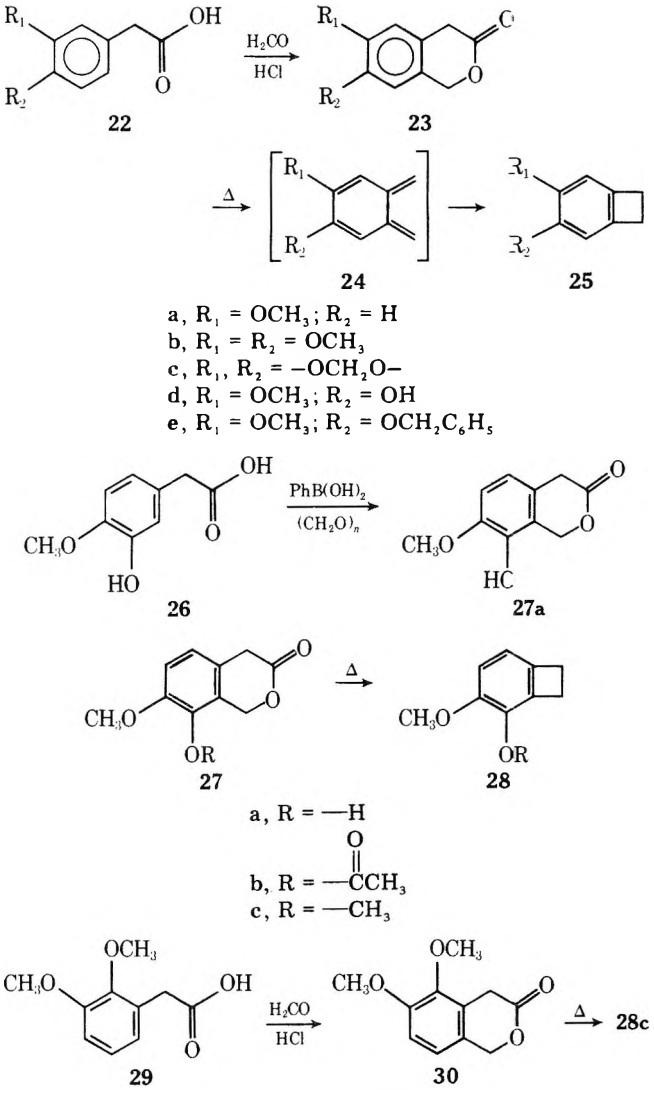


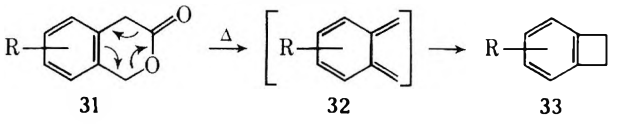
Figure 2. Pyrolysis of 3-isochromanone (**20**).

tion of commercially available 3,4-dimethoxyphenylacetic acid (**22b**) with formalin and hydrochloric acid in acetic acid.[32] Thus 4,5-dimethoxybenzocyclobutene (**25b**) is available in two synthetic steps with a 32% overall yield by this sequence. The only other reported synthesis of **25b** is a seven-step sequence proceeding in ca. 20% overall yield.[16,19] Isochromanones **23a** and **23c** were similarly prepared from the known phenylacetic acids, **22a** and **22c,** respectively. 4-Methoxybenzocyclobutene (**25a**) has been prepared previously by a six-step sequence from *p*-anisaldehyde[16] and from 4-nitrobenzocyclobutene.[20] Our work constitutes the first synthesis of 4,5-methylenedioxybenzocyclobutene (**25c**). Pyrolysis of **23d** gave only a 10% yield of impure 4-hydroxy-5-methoxybenzocyclobutene (**25d**) and a considerable amount of tar. The benzyl ether **23e** gave dibenzyl as the only volatile pyrolysate; the reaction again produced a large amount of tar. Thus the method appears to be unsuitable for the direct preparation of benzyloxy substituted or phenolic benzocyclobutenes. The 7,8-disubstituted isochromanones, **27a** and **27c,** were prepared from 3-hydroxy-4-methoxyphenylacetic acid by the procedure of Nagata et al.;[33] **27b** was prepared from **27a.** Pyrolysis of 7-methoxy-8-hydroxy-3-isochromanone (**27a**) gave none of the desired benzocyclobutene **28a,** pyrolysis of the acetate **27b** gave a 21% yield of 3-acetoxy-4-methoxybenzocyclobutene (**28b**), and pyrolysis of 7,8-dimethoxy-3-isochromanone (**27c**) gave a 10% yield of 3,4-dimethoxybenzocyclobutene (**28c**). 3,4-Dimethoxybenzocyclobutene was also obtained from 5,6-dimethoxy-3-isochromanone (**30**) in 21% yield. These reactions were accompanied by considerable tar formation. Thus as a method for the preparation of benzocyclobutenes with oxygenated substituents on the aryl ring, the pyrolysis of isochromanones is limited to methoxy and methylenedioxy substituents in the 4 and/or 5 positions of the benzocyclobutene ring system. Because this method for the preparation of **25a, 25b,** and **25c** is direct, it is advantageous over other known syntheses of these materials which involve multistep procedures.[16,19,20] This method complements other recent benzocyclobutene syntheses[21-23] which do not lend themselves as easily to the preparation of benzocyclobutenes with an oxygenated aryl ring. Such benzocyclobutenes are of increasing importance as intermediates in the synthesis of natural products.[16]

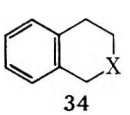


Thermal vs. Electron Impact Induced Decomposition of 3-Isochromanones. The relationship between the ions formed in electron impact mass spectrometry and the prod-

ucts of the pyrolysis of organic compounds has been of interest for some time.[34] Numerous examples have been reported in which the loss of a small neutral molecule (e.g., CO_2, C_2H_4, H_2CO, etc.) via a retro-Diels–Alder reaction was observed in the mass spectrum and also upon thermolysis of a compound. We have observed a qualitative similarity between the thermal and electron impact induced decomposition of the 3-isochromanones and homophthalic anhydrides described in this paper. The thermal formation of benzocyclobutenes from 3-isochromanones most likely occurs by a retro-Diels–Alder reaction with CO_2 expulsion followed by an electrocyclic ring closure (**31** → **32** → **33**). Analogously, all of the isochromanones except the 6-methoxy-7-benzyloxy (**23e**) and the 7-methoxy-8-acetoxy (**27b**) derivatives showed a prominent $M^+\cdot - 44$ ion in their mass spectra, arising from the loss of CO_2 by a retro-Diels–Alder reaction of the molecular ion. This relationship was best observed by comparing the yield obtained in the thermal reactions with the intensity of the $M^+\cdot - 44$ ion, expressed as % Σ_{50} (see Table II). 6-Methoxy-7-benzyloxy-3-isochromanone (**23e**) showed no $M^+\cdot - 44$ ion in its mass spectrum and produced none of the expected benzocyclobutene (**25e**) upon pyrolysis. Both the thermal reaction and the mass spectral fragmentation occurred at the benzyl group in that the mass spectrum of **23e** showed a large *m/e* 91 ($C_7H_7^+$) and pyrolysis gave dibenzyl as the only volatile product. The acetate (**27b**) also had no $M^+\cdot - 44$ ion in its mass spectrum (the base peak corresponded to ketene loss) but did produce a low yield of the benzocyclobutene (**28b**) upon pyrolysis. Increasing the number of methoxy groups on the aromatic ring decreased both the yield of benzocyclobutene and the intensity of the $M^+\cdot - 44$ ion. When the methoxy groups were adjacent to the lactone ring a further decrease in yield and $M^+\cdot - 44$ ion intensity were observed. The phenolic isochromanones **23d** and **27a** were anomalous in that both had intense $M^+\cdot - 44$ ions in their mass spectra but they gave little or none of the benzocyclobutenes **25d** and **28a** upon pyrolysis. With the exception of the phenolic isochromanones, the intensity of the $M^+\cdot - 44$ ion in the mass spectrum served as a rough guide to the yield of benzocyclobutene which could be expected upon pyrolysis. Loudon has similarly compared the mass spectrum and gas-phase pyrolysis of several compounds, **34**, structurally similar to the isochromanones **31** described here.[35] He has shown that the high-temperature thermolysis of **34** led to products analogous to the fragment ions observed in the mass spectra of these compounds. A retro-Diels–Alder reaction with loss of $CH_2{=}X$ was observed in all cases but was especially prominent in both the mass spectrum and thermolysis of isochroman (**34b**). Thus, 80% of **34b** decomposed thermally to benzocyclobutene.



31 32 33



34

a, X = CH_2
b, X = O
c, X = S
d, X = NH

We also examined the mass spectra of the isochromanones for the presence of metastable peaks corresponding to the loss of CO_2. The isochromanones **23a, 23d, 23e,** and **27b** showed no metastable peak for CO_2 loss whereas isochromanones **20, 23c, 27a, 27c,** and **30** showed a weak metastable peak; only **23b** showed a strong metastable peak. Thus the presence or absence of a metastable peak for CO_2 loss had no relationship to the yields of benzocyclobutenes obtained upon pyrolysis.

Experimental Section

General. Melting points were obtained on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Nuclear magnetic resonance (NMR) spectra were obtained using a Varian Anaspect EM360 spectrometer in $CDCl_3$ with tetramethylsilane as internal standard. Low-resolution mass spectra were obtained at 70 eV using a Hitachi Perkin-Elmer RMU-6E mass spectrometer; only ions with a relative intensity greater than 10% are reported. Elemental analyses were performed at the University of Idaho with a Perkin-Elmer 240 analyzer. Infrared (IR) spectra were obtained with a Perkin-Elmer 621 spectrometer. Analytical thin layer chromatography (TLC) employed precoated sheets of silica gel (F-254, 0.25 mm thick) on aluminum (E. Merck, Darmstadt, Germany).

6,7-Methylenedioxy-3-isochromanone (23c). A mixture of 2-phenyl-4-(4,5-methylenedioxybenzal)-5-oxazalone[36] (25 g, 85.5 mmol) in 10% sodium hydroxide (250 mL) was refluxed until no more ammonia was given off (8 h). To the cooled solution, 40% sodium hydroxide (15 mL) was added while maintaining the temperature below 15 °C and the solution was then allowed to stand at room temperature for 8 h. The mixture was then acidified with dilute hydrochloric acid (90 mL) and extracted with chloroform (3 × 100 mL); the extracts were dried ($MgSO_4$) and the solvent was evaporated to yield a mixture of benzoic acid and 3,4-methylenedioxyphenylacetic acid (**22c**) (22.5 g). A solution of the acids (10 g), 37% formalin (25 mL), concentrated hydrochloric acid (25 mL), and glacial acetic acid (75 mL) was heated on a steam bath for 1 h. The cooled solution was poured into water (750 mL) and extracted with chloroform (3 × 100 mL). The extracts were washed with 5% sodium bicarbonate (2 × 250 mL) and dried ($MgSO_4$), and the solvent was evaporated to yield a dark oil. This oil was sublimed at 0.25 mm with mild heating, and the sublimate was then recrystallized from 95% ethanol to yield white crystals of 3,4-methylenedioxy-3-isochromanone (**23c,** 1.85 g, 25%): mp 130.5–132 °C (lit.[37] mp 137 °C); IR (KBr) 1750, 1485, 1475, 1246, 1233, 1138, 1022, and 915 cm^{-1}; NMR δ 3.63 (s, 2 H), 5.23 (s, 2 H), 6.02 (s, 2 H), and 6.75 (s, 2 H); mass spectrum *m/e* (rel intensity) 192 (95), 163 (15), 149 (18), 148 (100), 147 (43), 135 (15), 91 (10), 90 (13), 89 (23), 77 (15), 74 (11), 63 (13), 51 (20), and 50 (15).

Anal. Calcd for $C_{10}H_8O_4$: C, 62.50; H, 4.17. Found: C, 62.24; H, 4.23.

6-Methoxy-3-isochromanone (23a). A solution of 3-methoxyphenylacetic acid[38] (**22a,** 10 g, 66.3 mmol), glacial acetic acid (45 mL), 37% formalin (15 mL), and concentrated hydrochloric acid (3 mL) was stirred at room temperature for 5 days. The solution was poured into water (250 mL) and extracted with chloroform (3 × 75 mL). The extracts were washed with 5% sodium bicarbonate and dried ($MgSO_4$) and the solvent was evaporated to give an oil (8.2 g). Vacuum distillation gave **23a,**[39] bp 125–145 °C (0.04 mm), as a white solid (5.1 g, 43%), which was recrystallized from 95% ethanol: mp 74–78 °C; IR (KBr) 2960, 2900, 1737, 1618, 1592, 1503, 1382, 1265, 1245, 1142, 1125, 1024, 954, 878, 815, and 694 cm^{-1}; NMR δ 3.61 (s, 2 H), 3.74 (s, 3 H), 5.20 (s, 2 H), and 6.54–7.34 (m, 3 H); mass spectrum *m/e* (rel intensity) 178 (90), 149 (25), 135 (15), 134 (100), 122 (15), 121 (15), 91 (41), 78 (12), 77 (17), 65 (15), 63 (15), 62 (45), 61 (15), 51 (21), 50 (10), 45 (100), and 44 (50).

Anal. Calcd for $C_{10}H_{10}O_3$: C, 67.40; H, 5.62. Found: C, 67.32; H, 5.72.

5,6-Dimethoxy-3-isochromanone (30). A solution of 2,3-dimethoxyphenylacetic acid (**29,**[40] 3.04 g, 11.5 mmol), glacial acetic acid (15 mL), 37% formalin (5 mL), and concentrated hydrochloric acid (5 mL) was stirred at room temperature for 21 h. The solution was poured into water (75 mL) and extracted with chloroform (3 × 25 mL). The extracts were washed with 5% sodium bicarbonate (2 × 50 mL), dried ($MgSO_4$), and evaporated to leave an oil. Vacuum distillation yielded a white solid, bp 118–121 °C (0.025 mm) (1.028 g, 43%), which was recrystallized from 95% ethanol to yield white crystals of **30:** mp 59.5–62 °C; IR (KBr) 2940, 2830, 1735, 1495, 1465, 1388, 1287, 1215, 1154, 1090, 1003, 965, 805, and 690 cm^{-1}; NMR δ 3.69 (s, 2 H), 3.80 (s, 3 H), 3.83 (s, 3 H), 5.20 (s, 2 H), and 6.87 (s, 2 H); mass spectrum *m/e* (rel intensity) 208 (100), 164 (25), 149 (64), 121 (28), 104 (15), 91 (20), 78 (16), 77 (22), 65 (15), 63 (15), and 50 (19).

Anal. Calcd for $C_{11}H_{12}O_4$: C, 63.46; H, 5.77. Found: C, 63.51; H, 5.84.

6-Methoxy-7-benzyloxy-3-isochromanone (23e). A solution of 3-methoxy-4-benzyloxyphenylacetic acid (**22e,**[41] 4.8 g, 17.6 mmol), glacial acetic acid (60 mL), 37% formalin (15 mL), and concentrated hydrochloric acid (3 mL) was stirred at room temperature for 44 h. The solution was poured into water (250 mL) and extracted with chloroform (3 × 75 mL). The extracts were washed with 5% sodium bicarbonate (2 × 100 mL), dried ($MgSO_4$), and evaporated to yield a white solid (4.6 g). Recrystallization from 95% ethanol gave white

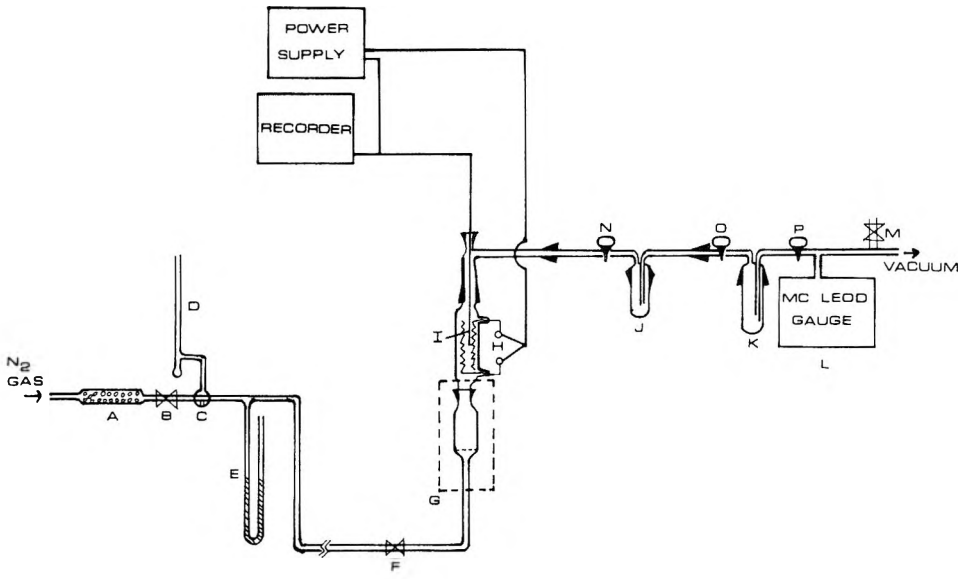


Figure 3. Pyrolysis apparatus.

crystals of **23e** (1.68 g), second crop (0.35 g), overall yield 90%: mp 137–138.5 °C; IR (KBr) 1740, 1512, 1447, 1370, 1342, 1302, 1244, 1223, 1112, 1015, 870, 744, and 698 cm^{-1}; NMR δ 3.60 (s, 2 H), 3.87 (s, 3 H), 5.11 (s, 2 H), 5.13 (s, 2 H), 6.73 (s, 2 H), 7.36 (s, 5 H); mass spectrum *m/e* (rel intensity) 284 (12), 91 (100), and 65 (11).

Anal. Calcd for $C_{17}H_{16}O_4$: C, 71.83; H, 5.63. Found: C, 72.08; H, 5.77.

6-Methoxy-7-hydroxy-3-isochromanone (23d). A mixture of 6-methoxy-7-benzyloxy-3-isochromanone (**23e**, 637 mg, 2.2 mmol), 10% Pd on carbon (300 mg), 95% ethanol (50 mL), and tetrahydro-

Table I. Physical Properties of Pyrolysis Products

Registry no.	Compd	Mp, °C	IR, cm^{-1}	NMR, δ	MS, *m/e* (rel intensity)
694-87-1	Benzocyclobutene (**21**)[3]	Oil	(neat) 3065, 2965, 2930, 2830, 1459, 1420, 1278, 1207, 1192, 1000	2.94 (s, 4 H), 6.77–7.24 (m, 4 H)	104 (100), 103 (45), 78 (35)
53995-96-3	4,5-Dimethoxybenzocyclobutene (**25b**)[19]	103–104	(KBr) 2920, 2840, 1487, 1468, 1305, 1208, 1180, 1168, 1066, 970	2.96 (s, 4 H), 3.72 (s, 6 H), 6.54 (s, 2 H)	164 (100), 149 (23), 121 (40), 78 (20), 77 (24)
56437-04-8	4-Methoxybenzocyclobutene (**25a**)[19,20]	Oil	(neat) 2920, 2826, 1600, 1588, 1473, 1271, 1248, 1165, 1075, 1025	2.80 (s, 4 H), 3.43 (s, 3 H), 6.27–6.80 (m, 3 H)	134 (100), 104 (15), 103 (12), 91 (47), 54 (15)
61099-23-8	4,5-Methylenedioxybenzocyclobutene (**25c**)[a]	62–63	(KBr) 2880, 2830, 1445, 1296, 1126, 1033, 936	2.91 (s, 4 H), 5.73 (s, 2 H), 6.50 (s, 2 H)	148 (51), 147 (37), 91 (55), 90 (42), 89 (100), 65 (19), 64 (30), 63 (70)
62726-48-1	3,4-Dimethoxybenzocyclobutene (**28c**)[a]	49–51	(KBr) 1575, 1475, 1425, 1245, 1200, 1165, 1060, 800	3.97–3.48 (m, 4 H), 3.80 (s, 3 H), 3.98 (s, 3 H), 6.44–7.90 (m, 2 H)	164 (85), 149 (100), 121 (43), 104 (14), 91 (29), 78 (35)
62726-49-2	4-Hydroxy-5-methoxybenzocyclobutene (**25d**)[b]	Oil	(neat) 3400, 2905, 1590, (1480, 1310, 1195, 1135, 1055, 860, 825	3.07 (s, 4 H), 3.84 (s, 3 H), 5.98 (broad s, 1 H), 6.58–6.71 (m, 2 H)	150 (100), 135 (36), 107 (36)
103-29-7	Bibenzyl[38]	49–51 (lit.[38] 52.5)	(KBr) 3040, 3010, 2900, 2840, 1590, 1485, 1440, 1055, 1020, 685	2.77 (s, 4 H), 7.03 (s, 10 H)	182 (100), 92 (27), 91 (82), 77 (15), 63 (11)
62726-50-5	3-Acetoxy-4-methoxybenzocyclobutene (**28b**)[a]	Oil	(neat) 2920, 1752, 1475, 1362, 1328, 1257, 1205, 1165, 1067, 1020	2.29 (s, 3 H), 3.07 (s, 4 H), 3.78 (s, 3 H) 6.80 (s, 2 H)	192 (25), 150 (100), 135 (41), 107 (18), 77 (14)
3469-06-5	Benzocyclobutenone (**8**)[25]	Oil	(neat) 1780, 1757, 1580, 1463, 1410, 1348, 1280, 1192, 1092, 1080, 955, 755	3.81 (s, 2 H), 7.07–7.68 (m, 4 H)	118 (99), 90 (100), 89 (92), 63 (13), 62 (34), 61 (15), 39 (19)
23417-79-0	*o*-Isopropenylbenzaldehyde (**15**)[28]	Oil	(neat) 3078, 2843, 2746, 1990, 1598, 1267, 1196, 906, 828, 769, 639	2.16 (m, 3 H), 4.90 (m, 1 H), 5.36 (m, 1 H), 7.1–7.5 (m, 3 H), 7.7–8.0 (m, 1 H), 10.1 (s, 1 H)	146 (8), 129 (12), 128 (100), 127 (15), 102 (12)
27041-32-3	Fulveneallene (**9**)[c,26]	Oil	(vapor) 3130, 3090, 1978, 1962, 1958, 1949, 1930, 1922, 1496, 1482, 1388, 1082, 1072, 898, 891, 883, 853, 842, 758	5.25 (s, 2 H), 6.40 (s, 4 H)	

[a] Satisfactory analytical data for this compound were submitted for review. [b] Anal. Calcd for $C_9H_{10}O_2$: C, 72.00; H, 6.67. Found: C, 71.39; H, 7.36. [c] 5-Ethenylidene-1,3-cyclopentadiene.

Table II. Pyrolysis of Isochromanones

Registry no.	Compd pyrolyzed	Mass spectrum of compd pyrolyzed: %Σ_{50} ($M^{+\cdot}$ − 44)	Mass spectrum of compd pyrolyzed: M* ($M^{+\cdot} \rightarrow M^{+\cdot} - 44$)	Pyrolysis chamber, H, temp, °C	Sublimation chamber, G, temp, °C	Product	% isolated yield
4385-35-7	3-Isochromanone (**20**)[30]	28	Weak	575	125	Benzocyclobutene (**21**)	88 (see Figure 2)
16135-41-4	6,7-Dimethoxy-3-isochromanone (**23b**)[32]	20	Strong	490	165	4,5-Dimethoxybenzocyclobutene (**25b**)	40
43088-72-8	6-Methoxy-3-isochromanone (**23a**)[39]	15	Absent	505	150	4-Methoxybenzocyclobutene (**25a**)	70
34140-20-0	6,7-Methylenedioxy-3-isochromanone (**23c**)[37]	21	Weak	505	150	4,5-Methylenedioxybenzocyclobutene (**25c**)	90
62726-51-6	5,6-Dimethoxy-3-isochromanone (**30**)	5	Weak	505	140	3,4-Dimethoxybenzocyclobutene (**28c**)	21
62726-52-7	6-Methoxy-7-hydroxy-3-isochromanone (**23d**)	22	Absent	480	180	4-Hydroxy-5-methoxybenzocyclobutene (**25d**)	10
62726-53-8	6-Methoxy-7-benzyloxy-3-isochromanone (**23e**)	0	Absent	450	190	Bibenzyl	26
56201-87-7	7-Methoxy-8-hydroxy-3-isochromanone (**27a**)[33]	16	Weak	505	140		
4697-59-0	7,8-Dimethoxy-3-isochromanone (**27c**)[33]	7	Weak	505	140	3,4-Dimethoxybenzocyclobutene (**28c**)	10
62726-54-9	7-Methoxy-8-acetoxy-3-isochromanone (**27b**)		Absent	505	150	3-Acetoxy-4-methoxybenzocyclobutene (**28b**)	21
703-59-3	Homophthalic anhydride (**7**)[38]	26	Absent	530	150	Benzocyclobutenone (**8**)	43
						Fulveneallene (**9**)	23 (see Figure 1)
31952-55-3	4,4-Dimethylhomophthalic anhydride (**18**)[44]	14	Absent	560	130	*o*-Isopropenylbenzaldehyde (**15**)	65

furan (50 mL) was hydrogenated at atmospheric pressure until the theoretical amount of hydrogen (50 mL) had been absorbed. The solvent was evaporated leaving a black solid. Vacuum sublimation (150 °C, 0.04 mm) yielded a light yellow solid which was recrystallized from 95% ethanol to give white crystals of **23d** (310 mg, 71%): mp 174–177 °C; IR (KBr) 3300, 1715, 1505, 1355, 1275, 1235, 1105, 1025, 1005, and 940 cm^{-1}; NMR δ 3.60 (s, 2 H), 3.90 (s, 3 H), 5.17 (s, 2 H), 5.67 (broad s, 1 H), 6.63 (s, 1 H), and 6.74 (s, 1 H); mass spectrum *m/e* (rel intensity) 194 (100), 151 (13), 150 (89), 137 (17), 135 (32), 107 (42), 77 (14), 67 (14), and 51 (12).

Anal. Calcd for $C_{10}H_{10}O_4$: C, 61.86; H, 5.16. Found: C, 61.72; H, 5.10.

7-Methoxy-8-acetoxy-3-isochromanone (27b). A solution of 7-methoxy-8-hydroxy-3-isochromanone (**27a**,[33] 362 mg, 1.86 mmol), acetic anhydride (1 mL), and pyridine (2 mL) was stirred for 5 h. The solution was cautiously diluted with ice water (10 mL) and made acidic with dilute hydrochloric acid. Extraction of the solution with chloroform (2 × 40 mL) and evaporation of the solvent yielded a white solid. Recrystallization from 95% ethanol gave **27b** as white crystals (368 mg, 83%): mp 133–135 °C; IR (KBr) 1720, 1490, 1435, 1360, 1275, 1235, 1180, 1145, 1085, 1025, 1000, 915, and 790 cm^{-1}; NMR δ 2.37 (s, 3 H), 3.69 (s, 2 H), 3.82 (s, 3 H), 5.22 (s, 2 H), and 6.92–7.08 (m, 2 H); mass spectrum *m/e* (rel intensity) 236 (17), 195 (13), 194 (100), 150 (50), and 135 (20).

Anal. Calcd for $C_{12}H_{12}O_5$: C, 61.02; H, 5.09. Found: C, 60.83; H, 5.09.

Pyrolysis Apparatus. A diagram of the pyrolysis apparatus is shown in Figure 3. Nitrogen gas was dried by passage through a tower A filled with molecular sieves. The flow rate of the nitrogen carrier gas from the cylinder was controlled by means of needle valve B and was measured with three-way stopcock C open to bubble flowmeter D. After obtaining the desired flow rate, stopcock C was turned to isolate bubble flowmeter D and to allow the carrier gas to enter the pyrolysis system. A Hewlett-Packard Model 5080-6710 gas chromatography flow controller valve F was adjusted so as to maintain the pressure gauge E at atmospheric pressure. Reactant sublimation chamber G contained a porous glass disk upon which the reactant was placed and was heated by an oil bath. The pyrolysis chamber H contained a multiple strand coiled nichrome wire. The wire was prepared by first close winding BS gauge 26 nichrome wire on a $\frac{3}{32}$ in. × 36 cm steel bar. Two turns of the coil were pulled out every 5 cm and a loop twisted in the stretched-out portion. In this way the wire was shaped into seven 5-cm coils, each separated by a twisted loop with hooks at each end. These strands of coil were stretched by hanging each loop from a glass hook inside the pyrolysis chamber H and by hanging the two ends to leads extending through the glass wall. The resistance of the installed coil was 54 ohm.[42] The pyrolysis temperature was determined with a chromel–alumel thermocouple I placed in the center of the pyrolysis chamber H and connected to a −0.68 to 36.19 mV strip chart recorder. The temperature of the pyrolysis chamber H was controlled by an electronic power supply using the thermocouple as a sensor. The pyrolysate was collected in cold trap J and could be trap to trap distilled to cold trap K. The pressure of the system was regulated with needle valve M and measured with a McLeod gauge L.

Pyrolysis of 3-Isochromanone (20). Using the apparatus described in the previous section, sublimation chamber G was charged with **20**[30] (1 g, 7.45 mmol), stopcock C was opened to the bubble flowmeter D, and the nitrogen flow rate was adjusted with valve B to 20 mL/min. The pressure of the system was then reduced to the minimum obtainable, stopcock C was then closed to the flowmeter and opened to the system, and valve F was adjusted to maintain the pressure gauge E at atmospheric pressure. The vacuum of the system

was 2.1 mm measured at the McLeod gauge L. The pyrolysis chamber H was heated to 570 °C and then sublimation chamber G was heated with an oil bath to ca. 130 °C. The pyrolysate was collected in cold trap J. When all of the isochromanone **20** had disappeared from sublimation chamber G the power to the pyrolysis chamber was turned off, stopcock N was closed, stopcock C was opened to the flowmeter, and the pressure was reduced to the minimum obtainable, ca. 1 mm. Stopcock P was then closed and the pyrolysate was distilled to cold trap K by warming cold trap J to 25 °C to yield pure benzocyclobutene (**21**, 588 mg, 85%). The properties of the benzocyclobutene thus obtained are shown in Table I. Figure 2 shows the relationship between the yield of pyrolysate and the pyrolysis temperature. The different points were obtained by using the above procedure and changing only the pyrolysis temperature.

Pyrolysis of Substituted 3-Isochromanones, 23, 27, and 30. The apparatus and procedure used were the same as those used for the pyrolysis of 3-isochromanone (**20**) with the following exceptions. The pressure of the system was maintained at 3 mm with needle valve M; the pyrolysis and oil bath temperatures were adjusted for each isochromanone (see Table II); the glass tubing between pyrolysis chamber H and cold trap J was heated with heat tape to ca. 200 °C; the pyrolysate was removed from cold trap J and washed with base to remove any unreacted starting material in every case except **23d** and **27a**; the pyrolysate was then recrystallized and/or distilled to yield pure products. The pyrolysis temperatures used and the results of these pyrolyses are summarized in Table II and properties of the purified pyrolysis products are shown in Table I.

Pyrolysis of Homophthalic Anhydride (7). The apparatus and procedure used were the same as those used for the pyrolysis of **20.** The sublimation chamber G was filled with **7**[38] (2.88 g, 17.75 mmol). The pressure of the system was maintained at 2.3 mm with needle valve M; the flow rate was 21 mL/min. The pyrolysis chamber and sublimation chamber were heated to 530 and 133–156 °C, respectively. When the pyrolysis was complete stopcock N was closed and the pressure reduced to 1 mm. The more volatile fulveneallene (**9**) was distilled to cold trap K by warming cold trap J to −25 °C. Benzocyclobutenone (**8**, 0.98 g, 46.7%) was obtained as a colorless oil in trap J, and fulveneallene (0.38 g, 23.6%) was obtained as a yellow liquid in trap K. Unpyrolyzed but sublimed **7** (0.83 g, 28.8%) was recovered from the arm between pyrolysis chamber H and cold trap J. No visible tar was formed during the reaction. The percent yields of **7**, **8**, and **9** as a function of the pyrolysis temperature are shown in Figure 1; the different points were obtained by using the above procedure and changing only the pyrolysis temperature. The properties of **8** and **9** are shown in Table I. Fulveneallene was converted to its tetracyanoethylene adduct (**10**) using the literature procedure.[26b] After five recrystallizations from acetone–water, adduct **10** was obtained as colorless crystals in 49% yield: mp 116–124 °C dec (lit. mp[26b] 115 °C decomp); IR (KBr) 3097, 3080, 3035, 3000, 2252, 2002, 1957, 1780, 1442, 1316, 1233, 1187, 1158, 1105, 1087, 1016, 940, 910, 899, 833, 749, and 740 cm^{-1}; NMR (acetone-d_6) δ 4.80 (t, 2 H), 5.40 (s, 2 H), 6.90 (t, 2 H);[43] mass spectrum *m/e* (rel intensity) 128 (96), 90 (100), 89 (100), 76 (61), 64 (22), 63 (39), 62 (20), 51 (11), 50 (15), 39 (13), and 38 (24).

Adduct **10** was reconverted to fulveneallene by heating the adduct in vacuo. Thus to a 5-mL round-bottom flask equipped with a 2 × 10 cm cold trap which was in turn connected to a vacuum pump was added 1.6 g of unpurified TCNE adduct **10**. The pressure of the entire apparatus was then reduced to 3 mm while cooling the cold trap with dry ice–acetone. Heating the flask at 90–115 °C for 2 h resulted in the condensation of 540 mg of regenerated **9** on the cold finger. The overall process **9** → **10** → **9** proceeded in 75% yield.

Pyrolysis of 4,4-Dimethylhomophthalic Anhydride (18). The pyrolysis was carried out with the same apparatus and in the same manner as the pyrolysis of the homophthalic anhydride (**11**). Thus **18**[44] (3.1 g, 16.3 mmol) was pyrolyzed at 560 °C with a flow rate of 20 mL/min and a vacuum of 4.5 mm. The sublimation chamber was heated at 82–130 °C. When the pyrolysis was complete the pyrolysate on the side arm leading to trap J was removed by washing with small amounts of acetone and combined with the pyrolysate in trap J. The solvent was evaporated and the solid was washed with petroleum ether (25 mL) and filtered to give unpyrolyzed **18** (0.59 g). The washings were evaporated to yield crude *o*-isopropenylbenzaldehyde (**15**, 1.25 g, 65%). The temperature programmed gas chromatogram (12 ft × 0.125 in. column packed with 20% QF-1 on 80/100 mesh Chromosorb W/AW DMCS; column temperature 115–145 °C, programmed at 10 °C/min) of crude **15** was similar to that reported for the pyrolysate of 3,3-dimethylindan-1,2-dione (**14**) except that peaks comparable to those reported for benzofulvene (**16**) and 3-methylindan-1-one (**17**) were absent. Pure **15** could be obtained by distillation (bp 42–44 °C, 0.25 mm). The spectral properties (see Table I) were identical with the literature values.[28]

Pyrolysis of 1,2-Indandione (11). The pyrolysis of **11** (3.0 g, 20.5 mmol) was carried out as described for 3-isochromanone. The pyrolysis chamber and sublimation chamber were heated to 540 and 91–97 °C, respectively. The nitrogen flow rate was 20 mL/min and the vacuum was 2.1 mm. After pyrolysis for 4.5 h, 2.82 g of unsublimed tar remained in the sublimation chamber. Trap J contained 110 mg of a yellow oil, which was a mixture of **8** (63 mg, 2.5%) and **9** (48 mg, 2.5%) as determined by integration of the NMR spectrum of the mixture and comparison of the spectrum with those of pure **8** and **9**.

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Registry No.—**10**, 27820-25-3; **11**, 16214-27-0; **22a**, 1798-09-0; **22c**, 2861-28-1; **22e**, 29973-91-9; **29**, 90-53-9; 2-phenyl-4-(4,5-methylenedioxybenzal)-5-oxazalone, 6412-89-1; benzoic acid, 65-85-0.

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Selective Reductions. 23. Asymmetric Reduction of Representative Ketones with Diisopinocampheylborane of High Optical Purity

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Diisopinocampheylborane of high optical purity, in tetrahydrofuran, diglyme, ethyl ether, methylene chloride, and *n*-pentane, was used to reduce a representative group of ketones, $RCOCH_3$ (R = Et, *i*-Pr, *t*-Bu, Ph). Asymmetric induction in the alcohol products in the range of 9 to 37% was observed. In contrast to earlier studies in which the reagent evidently contained small amounts of sodium borohydride and other minor constituents, the present results are consistent and reproducible. It was demonstrated that small quantities of sodium borohydride in the reagent can considerably diminish the optical purities of the product alcohols.

The asymmetric reduction of representative ketones, $RCOCH_3$ (R = Et, *i*-Pr, *t*-Bu, Ph), with optically active (−)-diisopinocampheylborane (from (+)-α-pinene) (IPC_2BH) was first reported in 1961.[2] The products obtained exhibited significant asymmetric induction (11 to 30%).

In a later study we attempted to carry out a related reduction of these ketones with (+)-IPC_2BH (from (−)-α-pinene).[3] Here also we realized optically active products with optical purities in the range of 9.5 to 12.8%. Unfortunately, there appeared a serious disagreement in the absolute configuration of the product from pinacolone, as well as major differences in the magnitudes of the rotations realized (Table I).

At that time, the IPC_2BH was a relatively crude product synthesized from α-pinene by hydroboration in diglyme with sodium borohydride (used in ~10% excess) and boron trifluoride etherate.[4] We felt that the discrepancy might be the result of minor components present in the crude product but deferred further study until such a time as we could develop an improved synthesis of IPC_2BH.

Recently, Varma and Caspi examined the reduction of these and other ketones and aldehydes by IPC_2BH.[5] They utilized borane–THF for the synthesis of their reagent.[4] They realized still different results (Table I). These authors also proposed a model to predict the absolute configuration of the major isomer produced.

We have recently developed an improved synthesis of IPC_2BH based on hydroboration of α-pinene with borane–THF, a procedure which makes available IPC_2BH in very high purity.[6] This new reagent achieves the asymmetric hydroboration of *cis*-2-butene to give after oxidation 2-butanol in an optical purity as high as 98.4%.[6] Consequently, we decided to utilize this reagent for the asymmetric reduction of the series of four ketones in the hope of resolving the conflicting results of the three earlier studies.

We have recently established that high-purity IPC_2BH can also be synthesized in THF and other solvents[7] by utilizing the readily available hydroborating agent, borane–methyl sulfide.[8] Accordingly, we extended the study to (−)-IPC_2BH prepared in this manner in several solvents.

Results and Discussion

(−)-IPC_2BH was prepared in THF at 0 °C (72 h) using a 15% excess of (+)-α-pinene, following the published procedure.[6] In all experiments the ketone was added to the suspension of the reagent in THF at 0 °C.

The reduction of 2-butanone required about 9 h at −30 °C but was complete within 1 h at 0 °C. The reductions of 3-methyl-2-butanone and acetophenone were complete within 2 h at 0 °C. However, the reduction of pinacolone was much more sluggish, the reaction being incomplete after 11 h at 0 °C with a further 12 h at 25 °C necessary to achieve near completion.

Table I. Asymmetric Reduction of Ketones by Diisopinocampheylborane[a]

Ketone, $RCOCH_3$, R =	Registry No.	Bigley[b] % opt purity[f]	Bigley[b] Config	Munekata[c] % opt purity[f]	Munekata[c] Config	Caspi and Varma[d] % opt purity[f]	Caspi and Varma[d] Config	Present study[e] % opt purity[f]	Present study[e] Config
Ethyl	78-93-3	11	*R*	9.5	*R*	7	*S*	16.5	*S*
Isopropyl	563-80-4	17	*R*	4	*R*	20	*S*	37	*S*
tert-Butyl	75-97-8	30	*S*	8.9	*R*	12.4	*S*	19.8	*S*
Phenyl	98-86-2	14	*R*	12.8	*R*			9	*R*

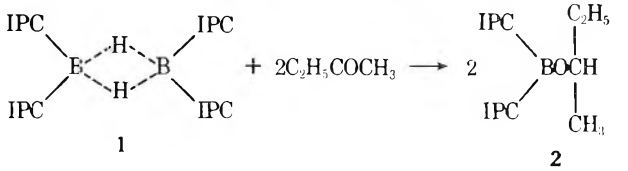
[a] All results translated to (−)-IPC_2BH from (+)-α-pinene to facilitate comparison. [b] (−)-IPC_2BH in diglyme from (+)-α-pinene, $NaBH_4$, and BF_3·OEt_2 (ref 2). [c] (+)-IPC_2BH in diglyme from (−)-α-pinene, $NaBH_4$, and BF_3·OEt_2 (ref 3). [d] (−)-IPC_2BH in THF from (+)-α-pinene and borane–THF. [e] (−)-IPC_2BH in THF from (+)-α-pinene and borane–THF, using the latest improved synthesis (ref 6). [f] Based on the following $[\alpha]_D$ values for 100%: 2-butanol, *R* −13.5°, P. J. Leroux and H. J. Lucas, *J. Am. Chem. Soc.*, **73**, 41 (1951); 3-methyl-2-butanol, *S* +5.34°, R. H. Pickard and J. Kenyon, *J. Chem. Soc.*, **103**, 1957 (1913); 3,3-dimethyl-2-butanol, *S* +8.1°, P. Newman, P. Lutkin, and K. Mislow, *J. Am. Chem. Soc.*, **80**, 465 (1958); 1-phenylethanol, *R* +42.85°, R. H. Pickard and J. Kenyon, *J. Chem. Soc.*, **99**, 45 (1911). Absolute configuration from W. Klyne and J. Buckingham, "Atlas of Stereochemistry", Oxford University Press, New York, N.Y., 1974.

Table II. Reduction of Ketones with High Purity (−)-Diisopinocampheylborane in THF

Ketone, $RCOCH_3$, R =, and mmol[a]	Reaction condition	H_2 on hydrolysis, mmol	α-Pinene displaced, mmol	After the reaction ROH Yield,[b,c] %	ROH $[\alpha]^{25}_D$	ROH Opt purity, %	ROH Config	Unreacted ketone, mmol
Ethyl, 50	0 °C, 1 h			95 (72)	+1.80°	13.4	*S*	
Ethyl, 50	−30 °C, 9 h			92 (73)	+2.23°	16.5	*S*	
Isopropyl, 50	0 °C, 2 h	13.5	15.8	97.5 (72)	+1.98°	37.0	*S*	
tert-Butyl, 50	0 °C, 11 h and 25 °C, 12 h	19.6	20.5	94 (78)	+1.61°	19.8	*S*	1.87
Phenyl, 50	0 °C, 2 h	13.2	13.3	89 (65)	+3.96°	9	*R*	

[a] In each case, reactants for the synthesis of IPC_2BH were: 115 mmol of α-pinene, 50 mmol of BH_3, and 50 mmol of IPC_2BH. [b] Analyzed by GC using *n*-dodecane as an internal standard. [c] Figures in the parentheses indicate isolated yield.

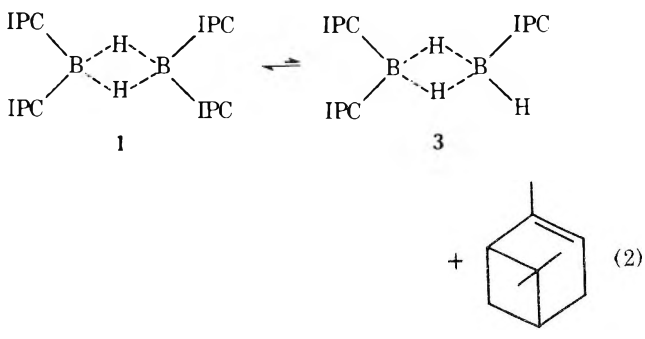
In the case of 2-butanone, the reaction appears to be a simple reduction, involving addition of the B–H bond to the carbonyl group to give the borinic ester **2** (eq 1). (Diisopinocampheylborane actually exists as the dimer **1**, *sym*-tetraisopinocampheyldiborane,[9] as shown in eq 1.)



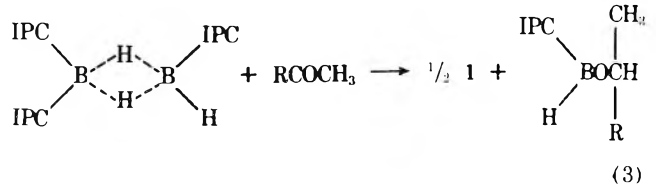
1 2 (1)

However, in the case of the other three ketones, a significant amount of α-pinene appeared in the reaction mixture during the reduction. Following completion of the reduction, hydrolysis of the reaction mixture produced hydrogen in amounts equivalent to the α-pinene formed.

We attribute the formation of α-pinene to a small equilibrium dissociation of the reagent, *sym*-tetraisopinocampheyldiborane, **1**, into α-pinene and triisopinocampheyldiborane[10,11] (**3**) (eq 2). Thus, in cases where the reaction of the ketone with the simple dimer (eq 1) is relatively slow, a significant amount of the reaction can proceed through **3** (eq 3).



1 3 (2)



(3)

This proposed mechanism is consistent with the displacement of α-pinene previously observed in the hydroboration of trans and hindered olefins[11] and nicely accounts for the appearance of α-pinene in the reduction of the more hindered ketones and the formation of an equivalent amount of hydrolyzable hydride in the reaction product.

Two procedures were utilized for the isolation of the products. For ketones other than acetophenone, the reaction mixtures, following the reduction, were oxidized with alkaline hydrogen peroxide (converting the borinic acid moiety into boric acid and isopinocampheol). The alcohol products from the ketones were then isolated by distillation. In the case of acetophenone, the similarity in the bp of isopinocampheol and 1-phenylethanol led to a modified procedure. In this case, the alcohol was distilled from the diisopinocampheylborinic intermediate following hydrolysis, without oxidation of the intermediate. Finally, the alcohol products from both procedures were subjected to preparative GC. The optical rotations and optical purities are summarized in Table II.

The results reveal that 2-butanone, 3-methyl-2-butanone, and 3,3-dimethyl-2-butanone with (−)-IPC_2BH yield the corresponding *S* alcohols in 16.5, 37, and 19.7% optical purity, respectively. The values are significantly higher than those reported by Caspi and Varma, presumably a consequence of

the higher optical purity of the present reagent. The configurations realized agree with those achieved by Caspi and Varma but disagree with our earlier results.

For these three ketones the observed configuration agrees with the model they proposed. However, acetophenone, reduced by (−)-IPC_2BH, provided *R*-1-phenylethanol. The formation of this isomer is contrary to that predicted from their model.

Their model assumes a mechanistically simple reduction by IPC_2BH or its dimer **1**. However, of the ketones studied, this is true only for methyl ethyl ketone. Reduction of the more hindered ketones apparently proceeds in part through **1** (eq 1) and in part through **3** (eq 3). Evidently it is too much to hope that a single model can handle such different processes.

We have recently developed a simple synthesis of monoisopinocampheylborane. Its use in the reduction of ketones appears to be mechanistically simple and its application may provide a definitive test of the utility of the Caspi–Varma model.

We briefly explored the question as to whether the presence of excess sodium borohydride, present in the product from the earlier synthetic procedure for IPC_2BH in diglyme, could have influenced the earlier results.[2,3] The reaction of sodium borohydride with ketones in diglyme is very slow, if not negligible, at these temperatures.[12] However, we observed that the presence of 10% sodium borohydride in a reaction mixture of 3-methyl-2-butanone and (−)-IPC_2BH speeded up the reaction of the latter two components and lowered drastically the optical purity of the *S*-3-methyl-2-butanol produced to 2%. This could account for the lower optical rotations observed in the earlier studies but not for the variations in the sign. The presence of variable amounts of **3** in the crude reagents then used could affect the sign of rotation, although we cannot at this time say that this was indeed the responsible factor.

In any event, it is gratifying that our present results agree so well with those realized by Caspi and Varma.

Borane–methyl sulfide (BMS) is finding increasing application as a hydroborating agent because of a number of advantages over BH_3·THF.[7] Recently we demonstrated the versatility of this readily available reagent for the convenient preparation of a number of valuable borane reagents.[7] Thus we prepared very pure (−)-IPC_2BH in a wide variety of solvents using BMS as the hydroborating agent. Hence it seemed desirable to explore the utilization of this reagent for the asymmetric reduction of this ketone in representative solvents and to compare the optical purities of the alcohol produced with those realized with the high optical purity reagent in THF.

The solvents utilized were THF, ethyl ether (EE), CH_2Cl_2, pentane, and diglyme (DG). 3-Methyl-2-butanone was taken as a representative ketone. (−)-IPC_2BH in THF, EE, CH_2Cl_2, pentane, and DG were prepared from BMS following the procedure reported earlier.[7] The reductions were carried out as before and the optical purities of the *S*-3-methyl-2-butanol obtained were in the range of 29–30.5%, irrespective of the particular solvent utilized. The reductions by this reagent of 2-butanone, 3,3-dimethyl-2-butanone, and acetophenone in THF were also carried out. The products, *S*-2-butanol, *S*-3,3-dimethyl-2-butanol, and *R*-1-phenylethanol, were obtained in 12, 17, and 9.8% optical purity, respectively. As before, α-pinene was displaced in all of the cases, except for 2-butanone.

These results are comparable to those realized with the high optical purity reagent in THF reported in the present study. The BMS procedure thus offers an advantage over the BH_3·THF procedure in that the preparation of IPC_2BH and its utilization for reduction is more convenient, utilizing a commercially available reagent, and is complete in less time (48 h, compared to 96 h in the case of the BH_3·THF procedure) with comparable optical purities of the product alcohols produced.

Experimental Section

Materials. THF, diglyme, EE, CH_2Cl_2, pentane, and BF_3·OEt_2 were purified by standard procedures.[13] Borane in THF was prepared from $NaBH_4$ and BF_3·OEt_2.[13] The borane·THF solution was standardized by hydrolyzing an aliquot of the solution with glycerine–water–THF mixture and measuring the hydrogen evolved.[13] BMS (Aldrich) was analyzed for hydride concentration as in the case of borane·THF and used directly. The commercial ketones were purified by distillation and kept under nitrogen. (+)-α-Pinene (Dragoco Co.) was used after distillation from LAH, which showed an optical rotation of $[\alpha]^{26.5}_D$ +48.7° and an optical purity of 95.2%.[14] The optical rotations were measured in a Zeiss polarimeter.

Reduction of 3-Methyl-2-butanone with (−)-IPC_2BH in THF. An oven-dried, 250-mL flask, equipped with a septum inlet, a magnetic stirring bar, and a stopcock, connected to a mercury bubbler was cooled in an ice bath under a slow stream of nitrogen. The flask was charged with 17 mL of 2.94 M borane in THF (50 mmol), 5.67 mL of *n*-dodecane (25 mmol), an internal standard for GC, and 4 mL of THF. (+)-α-Pinene (18 mL) (115 mmol) was then added in 10 min. The reaction mixture was stirred at 0 °C for 2 h and then kept in the cold room (−2 °C) for 70 h. An aliquot of the supernatant liquid was then oxidized and analyzed for α-pinene by GC using a 12 ft × 0.25 in. column packed with 10% Carbowax 20M on Chromosorb W containing 0.5% Armac. 3-Methyl-2-butanone (5.35 mL) (50 mmol) was then added at 0 °C, and the reaction mixture was stirred for 2 h at 0 °C, at which time the heavy white precipitate lightened considerably. Water (5 mL) was added and the volume of hydrogen was noted. Oxidation was effected by adding 20 mL of 3 M NaOH and 13.5 mL of 30% aqueous H_2O_2 (1 h, 40 °C). The aqueous phase was saturated with anhydrous K_2CO_3 and the THF layer separated. The aqueous phase was extracted with three 30-mL portions of ether. The combined extract was washed once with saturated brine solution and then dried over anhydrous magnesium sulfate for 4 h. An aliquot of this solution was then analyzed for α-pinene and 3-methyl-2-butanol. The results are summarized in Table II. 3-Methyl-2-butanol was then isolated in 72% yield by distillation using a 30-cm Widmer column. It was further purified through preparative GC using a 5 ft 20% SE-30 column (75 °C): n^{20}_D 1.4118, $[\alpha]^{25}_D$ +1.98°, and an optical purity of 37%.

Reduction of Acetophenone with (−)-IPC_2BH in THF. With the usual experimental setup, (−)-IPC_2BH in THF (50 mmol) was prepared as described earlier. To this reagent at 0 °C was added 5.83 mL of acetophenone (50 mmol). The reaction mixture assumes a pale yellow color. The heavy white precipitate of IPC_2BH lightens considerably within 15–30 min. The reaction mixture was stirred at 0 °C for 2 h, in which time the yellow color faded completely. It was methanolyzed (volume of H_2 noted) and then stirred with 10 mL of saturated aqueous potassium carbonate solution for 1 h. The organic layer was dried over anhydrous potassium carbonate overnight. THF and most of the α-pinene were removed under aspirator vacuum (15 mm, 3 h) and 1-phenylethanol was distilled from the diisopinocampheylborinic intermediate under high vacuum (0.5 mm). The distillate, bp 55–6 °C (0.5 mm) (4.035 g, 65%), was collected. This still contained a little amount of α-pinene. 1-Phenylethanol was purified from the α-pinene by preparative GC, using a 5 ft Carbowax 20M column (150 °C): n^{20}_D 1.5265, $[\alpha]^{22}_D$ +3.96°, and an optical purity of 9%.

Reduction of 3-Methyl-2-butanone with (−)-IPC_2BH (Made from (+)-α-Pinene and BMS) in THF. (−)-IPC_2BH in THF (50 mmol) was prepared following the procedure described earlier.[7] To this reagent at 0 °C was added 5.35 mL of 3-methyl-2-butanone (50 mmol) and the reaction mixture was stirred at 0 °C for 2 h as before. Oxidation and workup procedure were similar to that described in the earlier section. Distillation using a 30 cm Widmer column afforded 3.53 g (70%) of 3-methyl-2-butanol. It was further purified through preparative GC using a 20% SE-30 column: n^{20}_D 1.4117, $[\alpha]^{25}_D$ +1.63°, and an optical purity of 30.5%.

Acknowledgment. We are deeply indebted to Dr. E. Klein of the Dragoco Co., Holzminden, West Germany, for a generous gift of high purity α-pinene.

Registry No.—Diisopinocampheylborane, 62929-17-3; borane, 13283-31-3; (+)-α-pinene, 7785-70-8; 3-methyl-2-butanol, 598-75-4; 1-phenylethanol, 60-12-8.

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Nitrogen-15 Nuclear Magnetic Resonance Spectroscopy. Natural-Abundance Nitrogen-15 Chemical Shifts of Ring-Methylated *N,N*-Dimethylanilines. Effect of Inhibition of Conjugation

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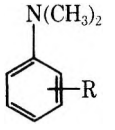
The ^{15}N chemical shifts of *N*-methylaniline, *N,N*-dimethylaniline, several ring-alkylated *N,N*-dimethylanilines, and their conjugate acids have been measured at the natural abundance level. Relative to aniline, N-methylation induces upfield shifts, in contrast to the downfield shifts expected on α-substitution. The influence of ring methyl substitution on the resonance position of dimethylaniline is the same as that reported for aniline, except for ortho substitution. Under these conditions, considerably larger upfield shifts are exhibited. In contrast, the chemical shifts of the conjugate acids of the dimethylanilines all lie within a 2-ppm range. The large diamagnetic shifts induced by ortho methyl substitution are attributed to the torsional distortion of the dimethylamino group from the optimum conformation for nitrogen lone-pair localization. The results correlate with appropriate aniline ^{13}C chemical shifts and, especially, with the ionization potentials of the corresponding aniline π orbitals, which are a measure of nitrogen lone-pair π delocalization. The diamagnetic α effects also may be rationalized by this means. The nitrogen shifts of 2,6-diethyl- and 2,6-diisopropyl-*N,N*-dimethylaniline have been used to estimate torsional angles of 77 and 80°, respectively.

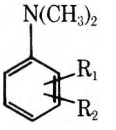
Correlations between the behavior of substituted anilines and extent of nitrogen lone-pair delocalization have been explored by investigation of myriad physical and chemical properties. The several relationships between nuclear magnetic resonance (NMR) properties and various functions of electron distribution make NMR spectroscopy eminently suitable for this type of study. Particularly when the NMR behavior of the nitrogen nucleus itself is affected, nitrogen NMR spectroscopy has been a useful probe of these phenomena. The first studies exploiting this possibility using substituted ^{15}N-enriched anilines,[1] as well as prior work with ^{14}N NMR,[2] demonstrated the direct relationship between nitrogen resonance positions and substituent conjugative electronic properties. Subsequently, the nonconjugative methyl group was shown also to influence aniline nitrogen chemical shifts[3] in a systematic, additive manner which could be related to polarization in the σ framework.[4] Because nitrogen lone-pair delocalization is possible with both types of substituents, it is of interest to determine the behavior of the nitrogen resonances when delocalization is in fact inhibited. Several lines of evidence[5-9] indicate that this is the case with ortho-methyl-substituted *N,N*-dimethylanilines. Consequently, we have determined the natural-abundance ^{15}N chemical shifts of a selected group of these compounds, represented in **1a–5**, in order to assess the influence of sterically inhibited conjugation on the resonance positions.

Experimental Section

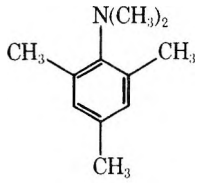
Compounds **1–5** were either commercially available or were prepared by methylation of the primary amine with trimethyl phosphate.[10] Infrared and ^{1}H NMR spectra were consistent with the structures, and boiling points agreed with reported values.[11]



1a, R = H
b, R = 2-CH_3
c, R = 3-CH_3
d, R = 4-CH_3



2a, R_1 = 2-CH_3; R_2 = 3-CH_3
b, R_1 = 2-CH_3; R_2 = 6-CH_3



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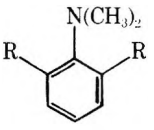


4, R = C_2H_5
5, R = *i*-C_3H_7

Spectra were determined on a JEOL PS/PFT-100 spectrometer as described elsewhere.[12] Initially, the free bases were run using 10–15% deuteriobenzene as internal lock in solution, and were referenced to an external capillary of 2.9 M enriched ammonium chloride in 1 M HCl. Subsequently, we noted that the resonance positions were somewhat solvent sensitive. For example, the resonance position of **1a** as a pure liquid (see below) differs by 1.5 ppm from that arising from a 25 vol % solution in cyclohexane. On the other hand, **3** remains unaffected upon dilution of the pure liquid to 25% in cyclohexane, yet moves 4 ppm downfield when 15% deuteriobenzene is used as internal

Table I. Nitrogen-15 Chemical Shifts of *N,N*-Dimethylanilines[a]

Registry no.		δ_N[b]	$\Delta\delta_N$[c]	$\Delta\delta_N'$[d]	δ_{NH^+}[b,e]	$\Delta\delta_{NH^+}$[f]	pK_a[g]	IP_{π_4}[h]	IP_{π_2}[h]
62-53-3	Aniline	31.5[i]	0	11.9	26.1	−5.4	4.26	8.05	10.81
100-61-8	*N*-Methylaniline	27.8	−3.7	8.2	19.6	−8.2	4.29	7.65	10.20
121-69-7	**1a**	19.6	−11.9	0	22.6	3.0	4.39	7.37	9.80
609-72-3	**1b**	8.9 (−20.3)[k]	−22.6	−10.7	21.1	12.2	5.15	7.92	9.51
121-72-2	**1c**	18.7 (−12.0)	−12.8	−0.9	22.6	3.9	4.66	7.24	9.61
99-97-8	**1d**	17.0 (−12.0)	−14.5	−2.6	21.7	4.7	4.94	7.27	9.55
24226-35-5	**2a**	8.4 (−19.5)	−23.1	−11.2	20.8	12.4	5.25		
769-06-2	**2b**	−7.9 (−33.9)	−39.4	−27.5	21.4	29.3	4.81	7.85	8.85
13021-15-3	**3**	−9.6 (−32.2)[l]	−41.1	−29.2	20.7	30.3	5.15[m]		
2909-78-6	**4**	−11.9 (−35.1)[n]	−43.4	−31.5	20.8	32.7			
2909-77-5	**5**	−14.6 (−37.0)[n]	−46.1	−34.2	19.2	33.8			

[a] Chemical shifts and differences in parts per million. [b] With respect to $^{15}NH_4Cl$; see Experimental Section. Positive values denote downfield shifts. [c] $\Delta\delta_{N_i} = \delta_i - \delta_{aniline}$. [d] $\Delta\delta'_{N_i} = \delta_i - \delta_{1a}$. [e] Chemical shifts of anilinium ions. [f] $\Delta\delta_{NH^+} = \delta_{ion} - \delta_{amine}$ = change in chemical shift on protonation. [g] Reference 6b, in 50% ethanol. [h] Vertical ionization potentials (eV), ref 9a,c. [i] Reference 4a. [j] Reference 4b. [k] Parenthesized values are differences between the substituted *N,N*-dimethylanilines and the corresponding anilines, ref 3. [l] $\delta_{mesidine}$ = 22.6 ppm. [m] Reference 13. [n] The chemical shifts of 2,6-diethyl- and 2,6-diisopropylaniline are 23.2 and 22.4 ppm, respectively.

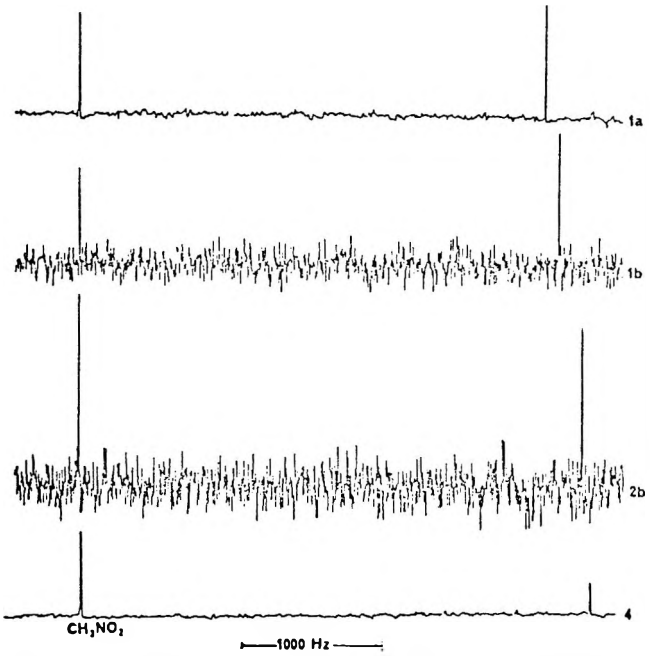


Figure 1. Natural-abundance ^{15}N spectra of *N,N*-dimethylanilines. The spectra were obtained at 1-s repetition rates for total accumulations ranging from 8800 (**1b**) to 61 800 (**1a**). The numbers on the spectra correspond to compound numbers in Table I.

lock. Hence, to circumvent this uncertainty, all free bases were run as pure liquids containing 10–20 mg of chromium tris(acetylacetonate) to shorten T_1 values, and a reference signal was derived from a concentric capillary of ca. 20% enriched nitromethane in deuteriobenzene, which provided the field frequency lock. Under these conditions the resonance of 2.9 M ammonium chloride lies 351.85 ppm to higher field. The experimental measurement uncertainty is estimated to be ±0.2 ppm or better.

The amine trifluoroacetates were prepared by dissolving the amines in 2 equiv of trifluoroacetic acid in deuteriobenzene. Final concentrations were 1–2 M, but the effect of concentration on the resonance positions was not determined.

Results and Discussion

The chemical shifts of **1–5** and their protonated forms are given in Table I, which also includes literature values for the pK_as of some of the bases[6,13] and photoelectron vertical ionization potentials.[9a,c] Table I also includes various chemical shift differences which will be useful in the ensuing discussion.

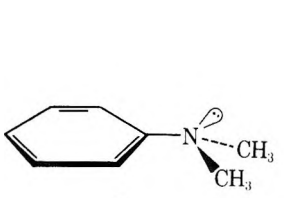
Several trends may be noted at the outset. First, successive methylation at nitrogen (aniline → *N*-methylaniline → **1a**) displaces the nitrogen resonance positions *upfield* by 5.3 and 11.9 ppm, respectively. While the direction of the change persists in going from anilinium to *N*-methylanilinium ion, protonated **1a** reverses the pattern. These changes stand in marked contrast to the effects of α-substitution on the ^{13}C chemical shifts of structurally analogous alkylbenzenes, where downfield shifts of ~9 ppm arise.[14] Similarly, α-substitution of aliphatic amines is reported to deshield nitrogen nuclei, although the magnitude of the shift (~9 ppm) was derived by multiple regression analysis of primary amine data rather than by direct measurements.[15] Isolated examples of upfield α effects have been reported. Thus, the nitrogen resonance of 1,1,3,3-tetramethylurea lies 14.2 ppm upfield from that of urea,[15b] and the resonances of several *N*-methyldecahydroquinolines lie ~5 ppm upfield of those of the unsubstituted compounds.[16] In a related manner, the nitrogen chemical shift of *N*-methylpiperidine is only 0.3 ppm downfield from that of piperidine. Similarly, an upfield shift on methylation of an aminoglycoside was reported very recently.[17] Because of the disparate nature and paucity of examples, a general rationalization of this behavior is not apparent.

Second, as in the anilines, ring methyl substitution of *N,N*-dimethylaniline shifts the nitrogen resonances to higher fields. Indeed, the effect of 3- and 4-methyl substitution (**1c** and **1d**, respectively) compares with that found in the anilines.[3] However, 2-methyl substitution (**1b** and **2a**) induces an additional 7–8 ppm change over that found in **1c** and **1d**. This is apparent from the parenthesized values in column 2 of Table I, which are expected to partially correct for effects of the methyl group common to both the anilines and the *N,N*-dimethylanilines. Further substitution at the ortho position (**2b** and **3**) augments the change. Thus, the nitrogen shift of **2b**, 34 ppm higher than that of 2,6-xylidine, is almost 40 ppm higher field than that of aniline itself, lying in a range characteristic of aliphatic amines.[15] As demonstrated by **4** and **5**, the upfield displacement is enhanced by increasing the size of the 2,6-dialkyl groups. These trends may be discerned easily in Figure 1.

Third, while changes of the aniline nitrogen positions on protonation are consistently upfield,[4b] those displayed by **1–5** are all downfield. Indeed, with the exception of **5**, the chemical shifts of the ions in this series differ by amounts, just outside experimental error, averaging 21.5 ppm with a standard deviation of 0.8 ppm. While effects of solvent, concentration, and nature of the anion are likely to influence the shifts of the cations,[18] nonetheless the relative constancy of the values probably reflects structural factors to a large extent. It is in-

teresting that, with the exception of **2b,** all the resonances lie at higher field than those of the corresponding primary anilinium ions.[4b] This appears to be another example of an upfield α effect, although the absence of detailed concentration studies makes such an observation speculative. The resonance positions of the first three cations in Table I (column 5) do not parallel those of the carbons of the isoelectronic toluene, ethylbenzene, and cumene, respectively.[14]

The upfield displacements induced by ortho alkyl substitution are most readily interpreted in terms of the well-established distortion of the dimethylamino group from the optimum conformation (**6**) for nitrogen lone-pair interaction with the benzene π system. In this case, the pyramidal nitrogen is still oriented such that the axis of the lone-pair orbital makes a dihedral angle of 90° with respect to the plane of the



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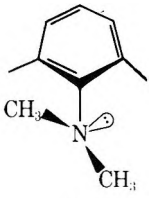

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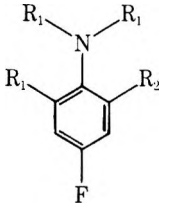
ring. Distortions from this geometry have been correlated with changes in basicity,[5,6] UV absorption intensities,[6] pK_as of substituted benzoic acids,[8] chemical shifts of ^{13}C[7a] and ^{19}F,[7b] and changes in ^{13}C–H coupling constants.[20] Thus, the increased basicity of **1b, 2a,** and **3** *relative* to **1a, 1c,** and **1d,** is attributable *in part* to greater localization of electron density at nitrogen in a twisted conformation (**7**). Similarly the lower field ^{19}F shift of **8** relative to that of **9** is attributable to reduced nitrogen delocalization, hence greater fluorine delocalization in the former, so that the fluorine is deshielded.[7b] Qualitatively, the change in the ^{19}F chemical shifts in the series **8–11**



8, $R_1 = R_2 = CH_3$
9, $R_1 = CH_3$; $R_2 = H$
10, $R_1 = R_2 = H$
11, $R_1 = H$; $R_2 = CH_3$

parallels that displayed by **2b, 1a,** aniline, and 2,6-xylidine, respectively, but there is no direct correlation. Similarly, if the ^{19}F and ^{15}N chemical shift differences between corresponding nonmethylated and dimethylanilines are compared, a qualitative but not quantitative parallelism exists. The absence of a direct correlation probably reflects the different degrees to which inductive and mesomeric effects contribute to the shifts in the disubstituted compounds compared to the monosubstituted.[7b]

A more fruitful comparison arises with the ^{13}C shifts of the anilines.[7a] To the extent that the same factors influence both sets of resonances, the differences between δ_{C4} of the dialkyl-*N,N*-dimethylanilines relative to the primary anilines are expected to reflect largely the electronic effect of the nitrogen. Hence literature values[7a] for the carbon shifts of the series, supplemented by new measurements for **2b, 4,** and **5,** were plotted against the nitrogen shifts (Figure 2). The scatter exhibited by these points may arise from two sources. First, steric and electronic factors are likely to influence the nitrogen shifts in the less hindered primary amines to a different extent than in the tertiary compounds, and this difference may be

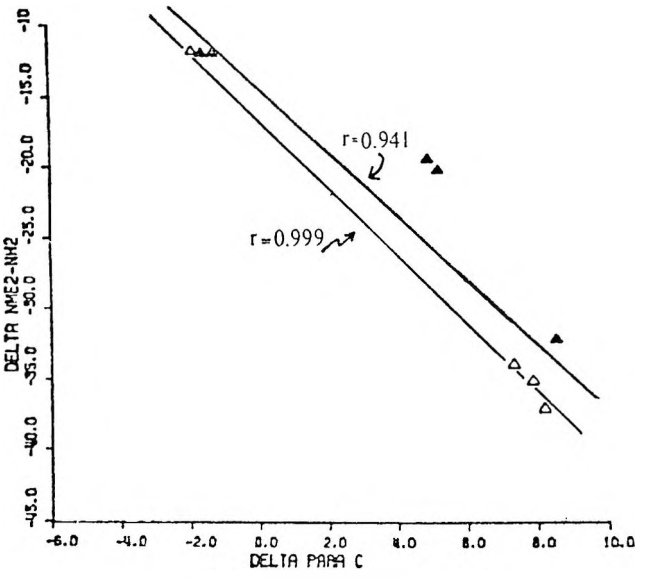


Figure 2. Plot of nitrogen shifts of dialkylanilines vs. carbon shifts of C_4. The upper line represents the least-squares correlation of all points, while the lower line (open triangles) represents the correlation within the 2,6-dialkyl-substituted series **1a, 2b, 4,** and **5.**

compensated only partially by taking the chemical shift differences (parenthesized values in column 2, Table I). Second, the positional influence of the ring alkyl substituents on the ^{13}C and ^{15}N resonances is likely to be different. Thus, in **2a,** the methyl group at C-3 is ortho to C-4, but meta to C-1, which bears the amino group; nothing requires that the responses of the two positionally different nuclei to the same substituent parallel each other exactly. Given these several possibilities, the moderate correlation displayed in Figure 2 (r = 0.941, slope = −2.3 ppm H/ppm C) is encouraging. To limit the number of variables influencing the shifts, the series **1a, 2b, 4,** and **5** may be examined, where only the nature of the alkyl substituents at C-2 and C-6 is changed. Here, electronic perturbations at C-4 and the nitrogen are expected to vary little throughout the series, and the correlation, admittedly with a smaller number of points, is much improved (r = 0.999, slope = −2.4 ppm N/ppm C). Hence it is reasonable to suggest that both the nitrogen and the C-4 resonance positions are primarily influenced by common factors, of which the torsional distortion of the dimethylamino group is likely to be dominant.[21,22]

That the nitrogen resonance positions move upfield as delocalization is inhibited is consistent with an increase in electron density as well as a decrease in the C_1–N π bond character. Within the qualitative Karplus–Pople treatment of chemical shifts an increase in the latter parameter is expected to increase the paramagnetic part of the chemical shift and deshield the nitrogen.[23] An approach of this type has been used to rationalize the nitrogen shifts of conjugatively substituted anilines.[1-3] A measure of the validity of this argument may be obtained by examination of vertical ionization potentials of the anilines, obtained from photoelectron spectroscopy.[9] Delocalization of the nitrogen lone pair results in splitting of one of the degenerate highest occupied molecular orbitals (HOMO) of benzene with the correct symmetry (b_1). The other is shifted only slightly, presumably because of an inductive effect. These interactions are indicated schematically in Figure 3. Calculations[24] indicate that the first and third ionization bands, labeled π_4 and π_2, respectively,[9a] may be assigned to those arising by interaction with the nitrogen lone pair; furthermore, from overlap populations[24] π_2 has a considerably higher degree of lone-pair character. Hence the difference between the π_4 and π_2 ionization potentials, ΔIP,

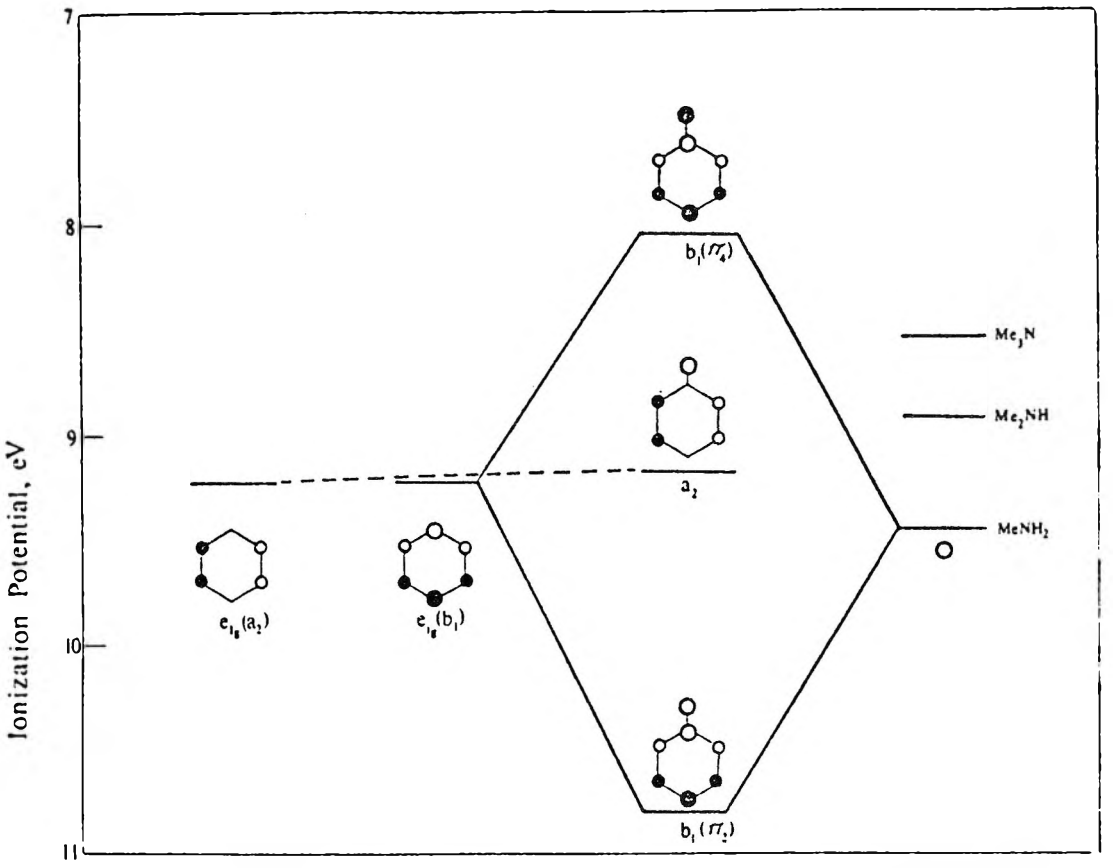


Figure 3. Schematic representation of the interaction between the 2p orbital of an amine nitrogen and the HOMOs of benzene.

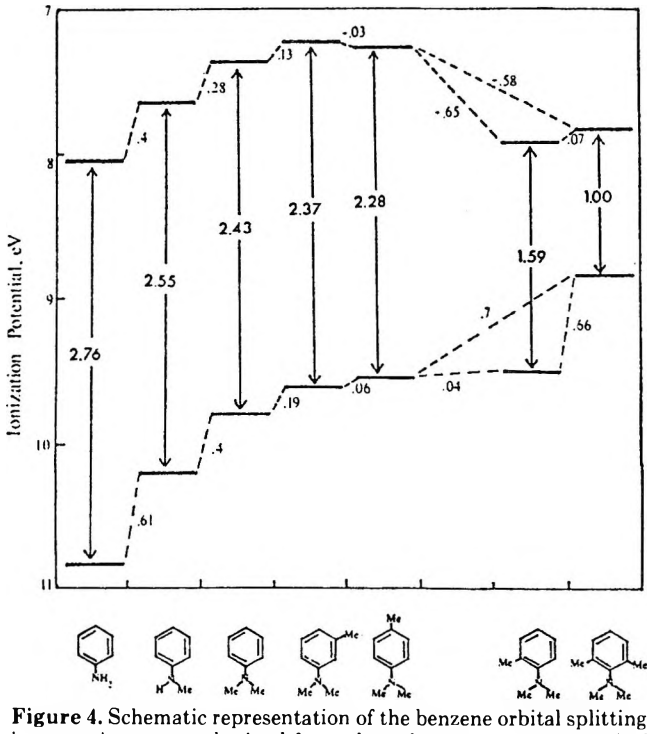


Figure 4. Schematic representation of the benzene orbital splitting by an amino group, obtained from photoelectron spectroscopy (ref 9c).

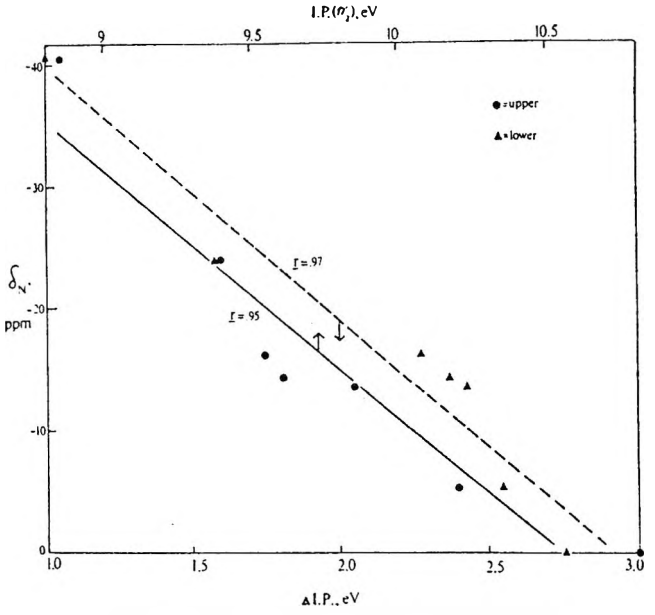


Figure 5. Plot of nitrogen chemical shifts of dimethylanilines vs. photoelectron ionization potentials and differences. The upper scale represents the π_2 ionization potential, while the lower gives the difference between the π_2 and π_4 ionization potentials.

reflects the extent of lone-pair delocalization; this is represented in Figure 4, where it is apparent that both ionization bands undergo similar changes in all compounds which do not bear ortho methyl groups. Indeed, the changes are comparable to those displayed in the series ammonia → methylamine → dimethylamine. On the other hand, substitution in the ortho position decreases ΔIP progressively, and a plot of δ_N vs. ΔIP yields a straight line with a least-squares correlation coefficient of 0.97 and a slope of 20.6 ppm/eV (Figure 5, lower scale, dotted line). Similarly, δ_N correlates[9] moderately well with the π_2 ionization potential, correlation coefficient = 0.95, slope = 20.2 ppm/eV.[25] While the correlations displayed in Figure 5 suggest that both the ΔIPs and the nitrogen shifts reflect the same changes in nitrogen lone-pair delocalization, it may not be immediately apparent why the correlation should be nearly

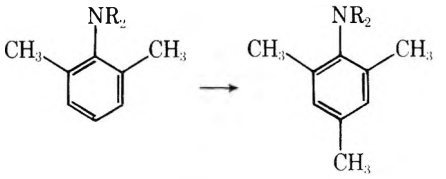
linear. This derives, however, from the relationship between the nitrogen 2p–π interaction and the C=N π bond order, whose role in influencing the nitrogen shifts was summarized above. Hence, preponderance of these factors may account for the high linearity exhibited.

The progression of IPs also rationalizes the upfield shifts in the series aniline → **1a**. Evidently, increasing methyl substitution reduces lone pair interaction with the ring. The influence is larger on π_2, which has the higher lone pair character. This may reflect an increase in the energy difference between the hypothetical nitrogen lone pair and the benzene b_1 orbitals as a function of methyl substitution. The change in δ_N parallels both ΔIP as well as the IP of π_2. It is likely that an effect of this type may also account for the nitrogen chemical shift difference between urea and tetramethylurea, cited above. It should also be noted that the change in ΔIP displayed by **1b** reflects a much larger change in π_4; only with the second methyl substitution is π_2 affected. Possibly, more extensive geometrical changes arise in the dimethylamino group itself in **2b** than in **1b**.

The decrease in ΔIP has been correlated with the torsional angle about the C_1–N bond, with values (55 and 69° for **1b** and **2b**, respectively) in good agreement with those estimated from UV data[6b] and from pK_a values of substituted benzoic acids.[8] Changes in photoelectron ionization potentials have been applied to geometrical studies of nitrobenzenes,[9c] phenols,[9a] anisoles,[9c] and disulfides.[26] In all cases the splitting between orbitals of appropriate symmetry is reduced when the geometry is perturbed from that which optimizes orbital overlap. Because the ionization potentials have been related to the cosine of the dimethylamino torsional angle,[9a,b] it is possible to use the chemical shifts to estimate these angles for other related compounds. Indeed, values of δ_N (Table I) for **1a**, **1b**, and **2b** correlate (r = 0.95) with cos θ, giving a slope of −0.022 ppm^{-1} and an intercept of 0.929. Applying these results to δ_N of **4** and **5**, values of 77 and 80° for the torsional angles are obtained. If the parenthesized δ_N values (column 2 of Table I) are used instead, in order to partially compensate for steric interactions in the primary amines themselves, values of 74 and 77° are obtained for **4** and **5**, respectively. Since the experimental θ values for **1a**, **1b**, and **2b** are estimated to have an uncertainty of ±5°, both sets of calculated torsional angles are in reasonable agreement with each other. It should be noted that geometrical changes other than in the torsional angle may be anticipated. The C–N–C bond angles are particularly susceptible to sterically induced distortion, and this would be expected to influence the shifts. However, the correlation of the nitrogen shifts with other data which are interpretable in terms of torsional angle distortion makes this structural factor highly likely to exert the major influence. Clearly, further studies on the effects of changes in bond angles on the nitrogen shifts would be welcome.

The other points deserve additional comment. In general, to the extent that the lone pair exerts a major paramagnetic influence on nitrogen resonance positions, its removal by protonation is expected to result in an upfield displacement of the nitrogen resonance position. This may be seen in the protonation-induced changes of pyridine (−110 ppm) and azobenzene (−150 ppm).[27] Thus the −5.4-ppm change exhibited by aniline may be attributed to the compensating influence of removal of the nitrogen lone pair (upfield shift) and generation of a positive charge. The effect of the latter is seen in the 24-ppm downfield shift of the ammonium ion relative to ammonia,[27] which has been shown[28] to arise from a change in the diamagnetic part of the chemical shift associated with the presence of the positive charge. That *N*-methylaniline also moves to higher field would seem to suggest that its lone pair is comparably delocalized, while the downfield shift exhibited by **1a** suggests that delocalization is partially reduced. The larger protonation shifts displayed by the remainder of the series are all consistent with successive attenuation of nitrogen lone-pair delocalization. The apparent anomalous behavior of *N*-methylaniline, in view of the correlation with the ionization potential data, must remain without explanation.

Finally, the previously reported substituent effects on the chemical shifts of the anilines themselves[1-3] assume that nitrogen lone-pair delocalization is influenced only by the degree of electronic interaction involving the substituent. It is reasonable to expect that these effects will differ if the nitrogen is sterically inhibited from conjugation. The nitrogen shift of **3** relative to **2b** supports this expectation. The 1.7-ppm upfield shift arising in the change **2b** → **3** is only half that characterizing the change 2,6-xylidine → mesidine. Preliminary results



R = CH_3: $\Delta\delta$ = − 1.7 ppm
R = H: $\Delta\delta$ = − 3.4 ppm

with 4-substituted 2,6,*N*,*N*-tetramethylanilines reveal similar differences.[29] Further studies are in progress to characterize this behavior.

Acknowledgments. This work was supported by the U.S. Public Health Service, Grant GM-21148 from the Division of General Medical Sciences, by the CUNY Faculty Research Award Program, the Research Corporation, and Eli Lilly and Co. Funds for the spectrometer were provided in part by National Science Foundation Instrument Grant GP-37025.

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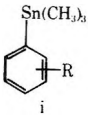

i

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Molecular Orbital Theory of the Electronic Structure of Molecules. 36. A Theoretical Study of Several α-Substituted Vinyl Cations[1a]

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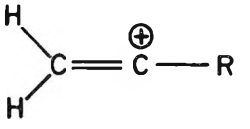
The α-ethynylvinyl (**4**), α-ethenylvinyl (**5**), α-cyclopropylvinyl (**6**), and α-phenylvinyl (**7**) cations have been investigated by SCF-MO ab initio methods, using both the STO-3G and the 4-31G basis sets. The cations **5**, **6**, and **7** are more stable in perpendicular conformations (**5a**, **6a**, and **7a**, respectively) where the interaction between the "empty" cationic orbital and the HOMO of the substituent is maximized. The calculated rotation barriers around the C^+–substituent bonds are 22.2, 15.8, and 24.7 kcal/mol for **5**, **6**, and **7**, respectively, approximately half the barrier in the corresponding primary alkyl cations. The efficiency of the α substituent in stabilizing the vinyl cation follows the order $C_6H_5 > c\text{-}C_3H_5 \simeq HC{=}CH_2 \gg C{\equiv}CH \simeq CH_3 \gg H$. The ability of the substituents to donate electrons to the empty cationic orbital follows the order $C_6H_5 > CH{=}CH_2 > C{\equiv}CH > c\text{-}C_3H_5 > CH_3 > H$. No correlation is found between the total charge at the cationic center or the corresponding populations of the formally empty p orbital and the stability of the cation. The cations vinyl (**2**), α-methylvinyl (**3**), and **6** have stabilities which are intermediate between those of the corresponding primary and secondary alkyl cations. However, the π-stabilized cations **4**, **5**, and **7** are of comparable stability to the corresponding primary alkyl cations. Corresponding substituted ethyl cations are 12–17 kcal/mol more stable than the vinyl cations, suggesting that, for the groups examined here, substituent effects are inherently similar for alkenyl and for alkyl cations. The proton affinities of substituted acetylenes and olefins are comparable, with the olefins being 1–5 kcal/mol more basic.

Vinyl cations are by now well-established reaction intermediates in solvolytic reactions.[2] Despite active research in the field over the last 10 years, very little is known about their inherent stabilities, their structures, or their charge distributions. The use of solvolysis rates to deduce the relative stability of resulting cations is complicated by ground state and solvation effects.[2] Observation of stable vinyl cations in superacid media has been claimed but not fully substantiated.[3a,b] Related experimental data in the gas phase are rare, although some heats of formation are known. These are for the parent vinyl cation (**2**),[3c] the propenyl cation (**3**),[3c-e] and $C_4H_3^+$ and $C_4H_5^+$ cations of unknown structure.[3b]

Extensive research has established that ab initio molecular orbital calculations even with minimal basis sets are a powerful, accurate, and inexpensive tool for the study of organic molecules.[4] Many theoretical studies of carbocations have been made,[5] but the vinylic cation family has received only little attention, with most of the emphasis devoted to the structure of the parent, **2**.[5a,6] The only other α-substituted vinylic cation which has been investigated in detail by ab initio methods is the 2-propenyl cation **3**.[7a] The energies of several other alkyl-substituted vinyl cations (**1**, R = Et, *i*-Pr, *t*-Bu) have been reported but not discussed in detail.[7b] We reported recently a systematic study of α-substituted vinyl cations **1** where R is varied along the whole series of first short period substituents, Li, BeH, BH_2, CH_3, NH_2, OH, and F.[8] In the present paper we use standard MO–SCF ab initio procedures to study the effect of substituents which are frequently used in solvolysis reactions (i.e., **1**, R = ethynyl, vinyl, phenyl, and cyclopropyl).[2]

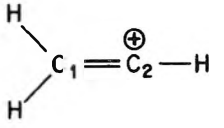


1

2, R = H
3, R = CH_3
4, R = C≡CH
5, R = CH=CH_2
6, R = c-C_3H_5 (cyclopropyl)
7, R = C_6H_5

Method, Geometrical Models, and Results

Calculations were carried out at the restricted Hartree-Fock (RHF) level using the ab initio SCF-MO Gaussian 70 series of programs.[9] The structures were fully or partially optimized using the minimal basis RHF/STO-3G method,[10a] followed by single-point calculations at the split-valence basis RHF/4-31G level.[10b] This procedure has been used previously for **2**[6d] and **3**.[7a]



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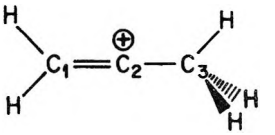


3

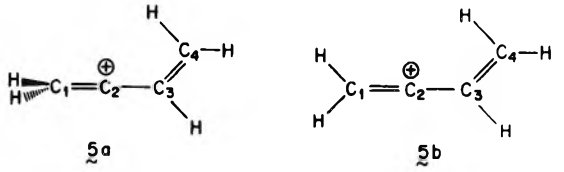
The structure of **4** was fully optimized (Figure 1). In the

Table I. Optimized Geometrical Parameters of Several α-Substituted Vinyl Cations (1)[a,b]

R	Structure and symmetry	C_1–C_2, Å	C_2–C_3, Å	C_3–C_4, Å	C_4–C_5, Å
CH=CH_2	**5a**, C_s	1.285	1.379	1.366	
c-C_3H_5	**6a**, C_s	1.281[c]	1.424	1.551	1.488
c-C_3H_5	**6b**, C_s	1.281[c]	1.468	1.521	1.511
C_6H_5	**7a**, C_{2v}	1.281[c]	1.380	*d*	*d*
C_6H_5	**7b**, C_{2v}	1.281[c]	1.450	*d*	*d*

[a] At RHF/STO-3G. For a detailed discussion of the parameters optimized and those held constant see text. [b] Numbering of atoms according to structures **5, 6, 7.** [c] Vinyl cation value without reoptimization. [d] Standard value used, see text.

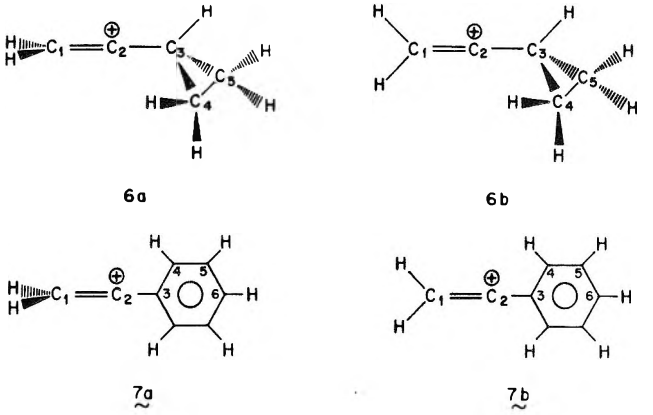
remaining cations, only the parameters that are expected to affect the energy considerably were optimized. **5** was examined most fully in the nonplanar form **5a** which is expected to be



5a **5b**

most stable. All CC bond lengths were optimized but CH bond lengths were kept at the standard value (1.08 Å).[11] All bond angles were fixed at standard values (120° at C_1, C_3, C_4, and 180° at C_2). Only one structure of **5b** was examined, obtained from **5a** by 90° rigid rotation about the C_1C_2 bond.

In **6** and **7**, the vinyl cation moiety was assumed to have



6a **6b**

7a **7b**

standard CH lengths (1.08 Å) and angles (120° at C_1, 180° at C_2) and a fixed C=C^+ length of 1.281 Å, taken from the RHF/STO-3G optimized structure of **2**.[6d,12] In **6**, both the C^+–R bond and the CC bonds of the cyclopropyl ring were optimized, while keeping the CH lengths and the HCH and HCC^+ angles as in cyclopropane.[13] The HCH and HCC^+ planes were taken to bisect the ring CC angles. In **7**, only optimization of C^+–R was carried out with standard geometry for the phenyl ring. To investigate rotation about the C^+–R bond, these geometrical optimizations were carried out for the conformers **6a, 6b** of the α-cyclopropylvinyl cation and **7a, 7b** of the α-phenylvinyl cation. The resulting parameters are listed in Table I.

For the neutral substituted ethylenes (**9**–**14**), two conformations differing by 90° rotation about the substituent bond were examined where appropriate (**12a, 12b, 13a, 13b, 14a, 14b**). Fully optimized RHF/STO-3G geometries[4] were used for **9**–**11** and **12b**. Rigid rotation about the single bond was used for **12a**. In cyclopropylethylene (**13a** and **13b**), standard

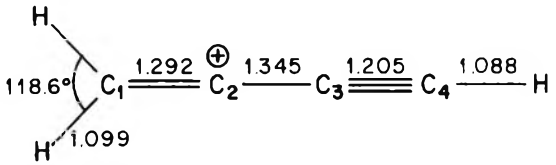
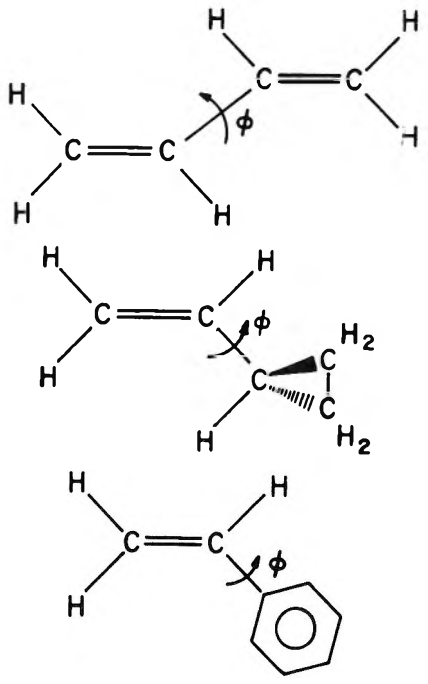


Figure 1. RHF/STO-3G structure of α-ethnylvinyl cation (**4**).



geometry was used for CH_2=CH– and the cyclopropyl ring was taken to be identical with that calculated for cyclopropane.[13] Standard geometry was used for styrene (**14a** and **14b**).

H_2C=CHR

8

9, R = H
10, R = CH_3
11, R = C≡CH
12, R = CH=CH_2
13, R = c-C_3H_5 (cyclopropyl)
14, R = phenyl

12a, $\varphi = 90°$; **b**, $\varphi = 0°$

13a, $\varphi = 90°$; **b**, $\varphi = 0°$

14a, $\varphi = 90°$; **b**, $\varphi = 0°$

The calculated total energies of the cations (**1**) and of the corresponding neutral molecules (**8**) are presented in Table II.

Discussion

The isodesmic[14a] hydride-transfer reaction 1 compares the stabilities of different vinyl cations **1** with that of the 2-propenyl cation **2**. The energies of reaction 1, derived from Table II using the most stable conformations for all species, are listed in Table III. A positive energy indicates a greater stabilization by the substituent (relative to methyl) in the cation than in the corresponding neutral molecule. Previous experience shows that the energies of such isodesmic reactions are well described even at the RHF/STO-3G level, and the estimated error limit is of the order of 2–5 kcal/mol.[4,14]

$$H_2C{=}\overset{+}{C}R + CH_2{=}CHCH_3 \rightarrow H_2C{=}\overset{+}{C}CH_3 + H_2C{=}CHR \quad (1)$$

Table II. Total Energies (hartrees) of α-Substituted Vinyl Cations 1 and the Corresponding Neutral Molecules 8

Substituent	Structures 1	Structures 8	Cations (1) RHF/STO-3G	Cations (1) RHF/4-31G	Neutral Molecules (8) RHF/STO-3G	Neutral Molecules (8) RHF/4-31G
H	**2**	**9**	−76.16540[a,b]	−76.97753[a,b]	−77.07396[a,b]	−77.92188[a,b]
CH_3	**3**	**10**	−114.79296[a,c]	−116.00048[a,c]	−115.66030[a,d]	−116.90459[a,d]
HC≡C	**4**	**11**	−150.94215[a]	−152.58574[a]	−151.80626[a,e]	−153.48995[a,e]
H_2C=CH perpendicular	**5a**	**12a**	−152.17709[f]	−153.81767[f]	−153.00592[g,h]	
H_2C=CH planar	**5b**	**12b**	−152.13931[i]	−153.78234[i]	−153.02036[a,e,j]	−154.69906[a,e]
c-C_3H_5 perpendicular	**6a**	**13a**	−190.76019[f]	−192.77680[f]	−191.59801[k]	
c-C_3H_5 bisected	**6b**	**13b**	−190.73856[f]	−192.75155[f]	−191.60234[k,o]	−193.65341[p]
C_6H_5 perpendicular	**7a**	**14a**	−303.01200[f]		−303.82176[k,l,m]	
C_6H_5 planar	**7b**	**14b**	−302.97268[f]		−303.82479[k,m,n]	

[a] Fully optimized RHF/STO-3G geometry. [b] From ref 12. [c] From ref 7a. [d] From ref 17. [e] From ref 4. [f] Partially optimized; see text for specification of the parameters optimized. [g] Rigid rotation of **12b** (standard geometry). [h] From L. Radom and J. A. Pople, *J. Am. Chem. Soc.*, **92**, 4786 (1970). [i] Rigid rotation of **5a**. [j] With the standard geometry the energy is −153.01661 hartrees (2.35 kcal/mol higher). [k] Standard geometry. [l] Optimization of the CCC angle lowers the energy by 0.62 kcal/mol. [m] From ref 28. [n] Optimization of the CCC angle lowers the energy by 3.14 kcal/mol. [o] Reference 27a gives −191.60520 for a slightly different geometry. [p] From Ref 27a.

Table III. Calculated Energies[a] (kcal/mol) for Reaction 1[b]

Substituent	RHF/STO-3G	RHF/4-31G
H	−25.9	−25.2
CH_3	0.0	0.0
C≡CH	2.0	−0.1
CH=CH_2	15.1	14.3
c-C_3H_5	15.8	17.3
C_6H_5	34.2	

[a] Using the total energies from Table II. [b] For each substituent the most stable conformation of both the cation 1 and the olefin 8 was used.

The results of Table III show that effectiveness of the substituents in stabilizing the vinyl cation follows the order $C_6H_5 \gg$ c-$C_3H_5 \simeq$ HC=$CH_2 \gg$ C≡CH $\simeq$ $CH_3 \gg$ H. Our results are, of course, pertinent only to the isolated cations in the gas phase where unfortunately little experimental data are available. Comparison with available solvolytic data should be done with circumspection, keeping in mind that solvation reduces the magnitude of electronic and polarization effects, and may change the relative stabilities of cations which have different sizes and charge distributions.[15] The RHF/4-31G results should be more reliable for energy comparisons. For cations **5**–**7** where geometry optimization is not complete, further optimization should produce only small changes in the energies of reaction 1.[16]

α-Ethenyl and α-Ethynyl Substituents. Both ethenyl and ethynyl substituents possess π electrons which can stabilize the cationic center by allylic-type conjugation, as represented by the resonance forms **4** ↔ **4′** and **5** ↔ **5′** below.

CH_2=C(+)—C≡CH(—) **4** $\quad$ CH_2=C=C=C(+)H **4′**

CH_2=C(+)—CH=CH_2(—) **5** $\quad$ CH_2=C=CH—C(+)H_2 **5′**

This conjugation is reflected in both the structures and the charge distributions of these cations. The calculated bond lengths (Figure 1 and Table I) of **4** and **5a** lie between those expected for the contributing resonance structures. The C_2C_3 bond length has an intermediate value between those of a single C_2C_3 bond (1.288 Å in 1,3-butadiene and 1.459 Å in but-1-yn-3-ene[4]) and a C_2C_3 double bond (1.288 Å in allene[17] and 1.257 Å in butatriene[4]). As expected, the C_3C_4 bonds are longer in the cations than in the corresponding hydrocarbons (1.171 Å in but-1-yn-3-ene and 1.313 Å in 1,3-butadiene), but the changes are smaller than in the C_2C_3 bonds. Similar bond lengths to **4** and **5a** were found in the analogous propargyl[18] and allyl cations.[7a] The calculated charge distributions (which are discussed in detail below) show that the positive charge is shared by C_2 and C_4 as expected if p–π conjugation is important. The allylic conjugation in **5** is possible only if the two double bonds are perpendicular; conformation **5a** is indeed 22.2 kcal/mol more stable than the planar conformer **5b** (RHF/4-31G, rigid rotation around the C_2C_3 bond). The lower stability of planar conformations of systems related to **5** was shown experimentally by Grob and Pfaendler.[19a]

An α-ethenyl substituent stabilizes the vinyl cation by 14.3 kcal/mol (RHF/4-31G) more than a methyl group (Table III). This is in agreement with the experimental result that 2-butadienyl derivatives solvolyze (in 80% EtOH) roughly 2000[19b,20] times faster (corresponding to a free-energy difference of 4.5 kcal/mol) than 2-propenyl derivatives. A larger substituent effect is expected in the gas phase than in solution.[15]

Ground-state effects, such as the energy associated with the π conjugation of butadiene, are included in reaction 1 as the neutral molecules are considered in their preferred conformation. As the preferred conformations of butadiene (**12b**) and of the butadienyl cation (**5a**) are different, a higher energy for reaction 1 results if perpendicular butadiene (**12a**) is used as the basis for comparison. The rotational barrier in butadiene (roughly **12b** vs. **12a**) is 6.7 kcal/mol at RHF/STO-3G[21a] (5.0 kcal/mol experimentally[21b]). The solvolysis of butadienylic systems where the double bonds are constrained in nonplanar conformations is indeed faster than normal.[19a] In addition, as the leaving group in **8** is a hydrogen, no account is taken of energy effects involving the double bond and other leaving groups, such as halogens or sulfonic esters.[7a]

In contrast to the large stabilizing effect of the conjugated α-double bond in **5a**, the triple bond in **4** provides stabilization which is only comparable to that of a methyl group. The failure of a triple bond to provide higher stabilization does not arise from ineffective charge delocalization, as the charge in the "empty" orbital on C_2 is almost the same in both cations (see Table VII and latter discussion). The low stabilization probably reflects cancellation between a stabilizing π conjugation and a destabilizing σ withdrawal by the acetylenic group, as previously suggested for the propargyl cation.[18] Derivatives of **4** have not yet been solvolyzed and our results suggest (assuming that solvation and leaving-group effects are similar for both cations) that their reactivity should be comparable to that of 2-propenyl derivatives.

α-Phenyl and α-Cyclopropyl Substituents. The ability of phenyl and cyclopropyl rings to stabilize an adjacent carbenium center is well known,[22] but the question of their relative efficiencies has been in dispute. Solvolysis rates[23a] and fluorine shielding constants[23b] suggest that an α-cyclopropyl is superior, while the ^{13}C shielding constants of the cation point to the opposite conclusion.[24] Taft, Hehre, and their co-workers[25] have recently applied ICR and ab initio computational techniques to this problem and showed that in the gas phase a phenyl substituent is superior to cyclopropyl in stabilizing both primary and secondary carbenium ions.

The results in Table III show that this is also the case for the vinyl cation, where the phenyl group is 18.4 kcal/mol more stabilizing than the α-cyclopropyl group (RHF/STO-3G). The excellent agreement between the corresponding calculations and the ICR measurements of Taft and Hehre[25] suggest that our results also should be close to experimental values. The 18.4 kcal/mol difference in the stabilizing abilities of phenyl and cyclopropyl is close to that in the corresponding primary saturated cations.[25] A much lower difference was observed by Taft and Hehre[25] for the saturated secondary cations, and both groups have comparable stabilizing effects on a tertiary carbenium ion. As in the saturated analogues,[23] α-cyclopropylvinyl derivatives solvolyze roughly 500 times faster than α-phenylvinyl derivatives.[26] The discrepancy between the gas-phase and solvolysis data probably results from preferential solvation of the smaller and less polarizable cation **6**.[15,25] Very large solvation effects (up to 10^{25} in equilibrium constants) were recently reported for proton-transfer reactions between small, highly solvated cations and large electron-delocalized cations.[15c] The gap between the gas phase and the solution results is much larger in the vinylic than in the corresponding alkyl cations. Thus, while the α-cyclopropyl/α-phenyl solvolysis rate ratio is 500 in both families,[23,26] the calculated energy difference between the corresponding cations is only 2.4 kcal/mol (phenyl favored) for the alkyl tertiary cations[25] compared to 18.4 kcal/mol for the vinylic cations. This points to differential solvation effects.

α-Cyclopropylethylene (**13**) and styrene (**14**) are included in reaction 1 in their most stable conformations, i.e., bisected (**13b**) for the first and planar (**14b**) for the second. The preference of a bisected conformation (**13b**) for **13**, in which the antisymmetric Walsh orbital of cyclopropane can interact with the π double bond, is analogous to the preferred planar arrangement for butadiene.[27] The conformation of the substituent relative to the double bond is reversed in the neutral molecule and in the cation (see below), and the double-bond conjugation of both **13b** and **14b** is therefore lost on ionization. The rotation barriers in **13** and **14** (2.7 and 4.4[28] kcal/mol, respectively) are good estimates of this conjugation energy.

The high stabilizing effect of the phenyl and cyclopropyl substituents arises mainly from the interaction between the empty cationic 2p (C^+) orbital and the highest occupied molecular orbital (HOMO) of the ring. For this interaction to be effective, the ring must be oriented appropriately. Similar effects have been discussed previously for benzyl[5b] and cyclopropylcarbinyl cations.[5b,29] Using the axes shown in Figure 2, the HOMO of the rings should have a node in the *xz* plane for effective stabilization. Thus, for α-phenylvinyl (**7**), 2p (C^+)–π (ring) overlap is possible only when the vinyl fragment and the phenyl ring are perpendicular; conformation **7a** is therefore most stable. Similarly, the perpendicular[30] conformation (**6a**), where interaction with the antisymmetric Walsh orbital of cyclopropane[29] takes place, is preferred in the α-cyclopropylvinyl cation **6**.

The 2p–HOMO interactions (Figure 2) are reflected in the cationic structures. The transfer of electrons from the ring to the empty 2p (C^+) orbital produces a shortening of the C_2C_3 bond by 0.044 and 0.070 Å (Table I) in **6a** and **7a**, respectively,

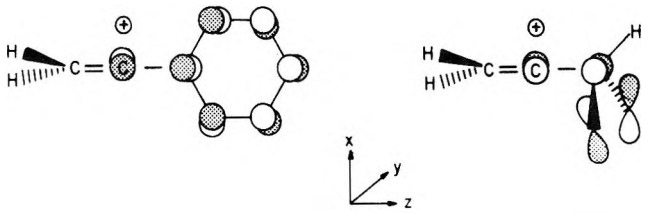


Figure 2. Formally vacant $2p_x$ (C^+) orbital of a vinyl cation interacting with the HOMO of phenyl (**7a**) and cyclopropyl (**6a**) substituents.

relative to the bond lengths in **6b** and **7b**. Similar, but even larger, results were reported for the benzyl and cyclopropyl carbinyl cations.[5b,29b] In **6a**, electrons are withdrawn from the antisymmetric Walsh orbital of the cyclopropyl ring, resulting in elongation of the C_3C_4 and the C_3C_5 bonds (1.551 Å) and shortening of the C_4C_5 bond (1.488 Å) relative to cyclopropane (1.50 Å).[13] Much weaker interactions are expected in the bisected conformation **6b** and the resulting geometrical changes (elongation of all the cyclopropyl ring bonds) are small (Table I).

Another consequence of the interaction between the cationic 2p orbital and the ring HOMO (Figure 2) is the high rotation barrier around the C_2C_3 bonds, 24.7 kcal/mol (RHF/STO-3G) in the α-phenylvinyl cation (**7**) and 13.6 (RHF/STO-3G) and 15.8 kcal/mol (RHF/4-31G) in the α-cyclopropylvinyl cation (**6**).[31] A similar relationship with even higher rotation barriers was found for the benzyl and cyclopropylcarbinyl cations,[5b,29b] respectively. Both **6b** and **7b** are stabilized by conjugation between the double bond and the cyclopropyl or the phenyl rings. A part of the higher rotation barriers in the saturated cations is therefore due to the absence of such stabilization in the perpendicular benzyl or cyclopropylvinyl cations.

Comparison with Alkyl Cations. The stability of the vinylic cations (**1**) may be compared to that of the corresponding primary or secondary alkyl cations by means of reactions 2 and 3, respectively (Table IV). These reactions provide a direct comparison of the stabilities of the cations, uncomplicated by ground-state and solvation effects as are the relative solvolysis rates of vinyl and alkyl derivatives.[2,7a]

$$H_2C{=}\overset{+}{C}R + RCH_3 \rightarrow RCH_2^+ + H_2C{=}CHR \qquad (2)$$

$$H_2C{=}\overset{+}{C}R + RCH_2CH_3 \rightarrow \overset{+}{R}CHCH_3 + H_2C{=}CHR \qquad (3)$$

Comparing the RHF/STO-3G and RHF/4-31G results in Table IV, one finds that the minimal basis set gives larger estimates of stability of the vinyl cations by 3–9 kcal/mol. RHF/4-31G results for reactions 2 and 3 (R = H, CH_3) were found earlier to be in good agreement with both experimental and theoretical results using a more extensive basis set (RHF/6-31G*).[7a] The RHF/4-31G energies can therefore be used with some confidence and, when not available (for **6** and **7**), 3–9 kcal/mol should probably be subtracted from the RHF/STO-3G energies.

The parent vinyl cation is 14.7 kcal/mol less stable than the ethyl cation, but 15.1 kcal/mol more stable than the methyl cation[7a] (Table IV). Similarly, the stability of the 2-propenyl cation (**3**) is intermediate between those of the ethyl (+10.5 kcal/mol) and propyl (−12.0 kcal/mol) cations. The preference of the vinylic cation over the primary alkyl cation (reaction 2) is, however, much smaller (or disappears) with the other substituents. Thus, the allyl cation is calculated to be 1.2 kcal/mol more stable than **5**, and the propargyl, cyclopropylcarbinyl, and benzyl cations are only slightly less stable than **4**, **6a**, and **7a**. (The STO-3G value for **7a** should be even

Table IV. Calculated Energies (kcal/mol) for Reactions 2 and 3[a,b]

Substituent	ΔE for reaction 2		ΔE for reaction 3	
	RHF/STO-3G	RHF/4-31G	RHF/STO-3G	RHF/4-31G
H	24.4[c]	15.1[c]	−6.6[c]	−14.7[c]
CH_3	19.3[c]	10.5[c]	−5.4[c]	−12.0[c]
C≡CH	13.1[d]	3.9[d]	−12.1	−13.5
CH=CH_2	4.7[f]	−1.2[f]	−13.3[g]	−17.2[g]
c-C_3H_5	7.2[g]	3.9[g]	−8.7	*e*
C_6H_5	5.5[h]		−13.0[h]	

[a] For each substituent the most stable conformation of both the cation and the hydrocarbon was used. [b] For the vinylic compounds the total energies from Table I were used. [c] From ref 7a. [d] Energies for the substituted alkanes and alkyl cations are taken from ref 17 and 18, respectively. [e] Energies for the saturated molecules are not available. [f] Energies for the substituted alkanes and alkyl cations are from ref 17 and 7a, respectively. [g] Energies for the substituted alkanes and alkyl cations from ref 4, 5a, and W. J. Hehre, unpublished results. [h] Energies for the saturated hydrocarbons and cations from W. J. Hehre, unpublished results, and from ref 45b, respectively.

Table V. Calculated Energies (kcal/mol) for Reactions 6, 7, and 8, and of the Relative Proton Affinities (PA) of Acetylenes and Ethylenes[a,b]

Substituent R	Reaction 6		Reaction 7		Reaction 8		Relative PAs[c]	
	RHF/STO-3G	RHF/4-31G	RHF/STO-3G	RHF/4-31G	RHF/STO-3G	RHF/4-31G	RHF/STO-3G	RHF/4-31G
H	15.6[d]	3.5[d,e]	0.0	0.0	0.0	0.0	5.0[i]	5.0[i]
CH_3	14.7[d]	2.1[d,f]	21.8	20.9[g]	20.8	19.4[h]	4.0	3.5[j]
C≡CH	13.2	2.3	23.4	21.6	21.0	20.4	2.6	3.4
CH=CH_2	15.3	0.1	38.7	37.8	38.4	34.3	4.7	1.5
c-C_3H_5	17.4		38.2		39.9		6.7	
C_6H_5	15.1		52.2		48.5		1.2	

[a] For each substituent the most stable conformation of both the cation and the hydrocarbon was used. [b] The total energies for the vinylic hydrocarbons and cations are taken from Table II, those for the acetylenes from ref 12, 17, and 45b, and for the saturated cations from the corresponding footnotes in Table IV. [c] Based on the difference between the calculated energies of reaction 7 and 8 and the experimental[3d] relative PA of acetylene and ethylene. [d] From ref 7a. [e] 4.1 kcal/mol at RHF/6-31G*. [f] 3.3 kcal/mol at RHF/6-31G*. [g] 19.8 kcal/mol at RHF/6-31G*. [h] 18.9 kcal/mol at RHF/6-31G*. [i] Experimental value, see ref 7a and references therein. [j] 4.1 kcal/mol at RHF/6-31G*.

smaller at 4-31G.) However, the values given by reaction 2 are influenced by the change in the relative sizes (polarizabilities) of the methyl and vinyl systems. A more representative comparison of substituent effects is provided by eq 3, where both vinyl and ethyl systems have the same number of carbon atoms. The values (12–17 kcal/mol, RHF/4-31G) are almost constant,[33] suggesting that substituent effects for the groups examined here are inherently similar for alkenyl and for alkyl cations. This is not general behavior, however. In a comparable study of a range of α substituents of widely differing electronegativity, it was found that σ donors, like lithium, preferentially stabilize the vinyl cation, but σ acceptors, like fluorine, favor the ethyl cation.[8]

Proton Affinities (PA) of Several Acetylenes and Ethylenes. The proton affinities (PA) of acetylenes and ethylenes are defined as the negative of the standard enthalpy change in reactions 4 and 5, respectively.

$$RC{\equiv}CH + H^+ \rightarrow RC^+{=}CH_2 \quad (4)$$

$$RCH{=}CH_2 + H^+ \rightarrow \overset{+}{R}CHCH_3 \quad (5)$$

These reactions, however, are not isodesmic[14a] and the theoretical energies are, therefore, subject to greater error.[5a,34] Thus, the PA of both acetylene and ethylene are overestimated by 10–13 kcal/mol even when the 6-31G* basis set is used.[35] The difference, however (reaction 6, R = H), is reasonably well reproduced with the 4-31G basis set (3.5 kcal/mol compared to the experimental value of 5.0 kcal/mol[3d]). The RHF/STO-3G energy difference (15.6 kcal/mol) is, however, far too high.

$$\overset{+}{R}C{=}CH_2 + RCH{=}CH_2 \rightarrow RC{\equiv}CH + \overset{+}{R}CHCH_3 \quad (6)$$

Only RHF/STO-3G energies are available for some of the molecules discussed here, and we therefore use the isodesmic reactions 7 and 8, which compare the proton affinities of substituted acetylenes and ethylenes with those of acetylene and ethylene respectively.

$$\overset{+}{R}C{=}CH_2 + HC{\equiv}CH \rightarrow RC{\equiv}CH + CH_2{=}\overset{+}{C}H \quad (7)$$

$$\overset{+}{R}CHCH_3 + H_2C{=}CH_2 \rightarrow RCH{=}CH_2 + C_2H_5^+ \quad (8)$$

The calculated energies for reactions 6, 7 and 8 are presented in Table V. The RHF/STO-3G and RHF/4-31G energies for reactions 7 and 8 are indeed very similar. If R is CH_3, the RHF/6-31G* and the RHF/STO-3G results differ by only 2 kcal/mol, supporting the reliability of the minimal basis set for obtaining energies of these isodesmic reactions. Furthermore, the experimental PA of propene is 19 kcal/mol higher than that of ethylene[35c] in excellent agreement with the calculations.

The proton affinities of acetylene and ethylene increase markedly upon substitution. Thus, phenylacetylene and styrene are ~50 kcal/mol more basic than their parent hydrocarbons, acetylene and ethylene, and have comparable proton affinities to ammonia.[15a] As expected, the order parallels that of the stabilizing effect of R on the corresponding cations.

The relative PA of the substituted acetylenes and ethylenes are given directly by the RHF/4-31G energies of reaction 6, or can be computed from the energies of reaction 7 and 8 and the experimentally known relative PA of acetylene and ethylene (see Table V).[36] The PA of ethylene is only 5 kcal/mol[3d,35c] higher than that of acetylene, while the difference

Table VI. Mulliken Atomic Charges (RHF/STO-3G) for Vinylic Cations 2–7[a]

Substituent	Structure	C_1	C_2	C_3	C_4	C_5	C_6	H (C_1)	H (C_2)	H (C_3)	H (C_4)	H (C_5)	H (C_6)
H	**2**	−0.060	+0.283					+0.250	+0.277				
CH_3	**3**	−0.096	+0.320	−0.193				+0.226		+0.172			
C≡CH	**4**	−0.056	+0.262	−0.008	+0.149			+0.214			+0.225		
CH=C-H_2	**5a**	−0.101	+0.235[b]	−0.092	+0.073			+0.196		+0.152	+0.171		
c-C_3H_5	**6a**	−0.107	+0.276[c]	−0.113	−0.079	−0.079		+0.206		+0.150	+0.134		
C_6H_5	**7a**	−0.107	+0.213[d]	−0.038	−0.023	−0.054	+0.028	+0.183			+0.121	+0.114	+0.130

[a] The carbon numbering according to structures **2–7**. Hydrogen charges are averaged over all hydrogens attached to the same carbon. [b] +0.336 in **5b**. [c] +0.328 in **6b**. [d] +0.326 in **7b**.

Table VII. Mulliken Gross Orbital Populations (RHF/STO-3G) in the Vinylic Cations 2–7[a]

Substituent	Structure	p_x (2)[b]	p_x (3)	p_x (4)	p_x (5)	p_x (6)	p_y (1)	p_y (2)	p_y (3)	p_y (4)
H	**2**	0.136					0.788	1.212		
CH_3	**3**	0.211					0.862	1.157		
C≡CH	**4**	0.295	1.151	0.550			0.816	1.177	0.941	1.066
$CH=CH_2$	**5a**	0.427[c]	1.116	0.546			0.886	1.122		
c-C_3H_5	**6a**	0.334[d]					0.885	1.130		
C_6H_5	**7a**	0.474[e]	1.133	0.838	1.005	0.791	0.910	1.039		

[a] The numbering of the atoms and the specification of the axes are given in Figure 2 and structures **2–7**. [b] The p_x orbital of carbon 2, etc. [c] The population is 0.206 in **5b**. [d] The population is 0.208 in **6b**. [e] The population is 0.192 in **7b**.

in the stabilities of the ethyl and vinyl cations is 15 kcal/mol. This apparent inconsistency is clarified if one remembers that acetylenes are more "strained" than olefins,[37] compensating for the lower stability of the vinyl cation.[7a] The relative PA are lower for all the substituted derivatives (except for cyclopropyl) than for the parent hydrocarbons (Table V), so that, in general, additions of protons to double and triple bonds should be comparably easy. The data in solution, although solvent dependent, also point to comparable rates of protonic additions to a variety of substituted ethylenes and acetylenes.[38,39]

The available experimental data in the gas phase are generally in good agreement with our calculations. Thus, propene and styrene are 19[35c] and 3.6 kcal/mol[15a,25] more basic than ethylene and cyclopropylethylene, respectively (calculated: 19.4 and 8.6 kcal/mol, respectively; Table V). A considerable discrepancy exists, however, between the experimental[3d] and calculated values for the relative PAs of propene and propyne, e.g., ~9 and 4.1 kcal/mol, respectively.

Charge Distributions. The calculated total atomic charges and the gross populations[40] in orbitals of particular interest in the cations **2–7** are reported in Tables VI and VII respectively. The data for the p_x(2) orbital (Table VII) show that the relative efficiency of the different substituents in donating electrons to the formally empty 2p (C^+) orbital follows the order C_6H_5 > $CH=CH_2$ > c-C_3H_5 > C≡CH > CH_3 > H. All the π donors investigated are therefore superior to the π-type cyclopropyl MOs in delocalizing the positive charge. In particular, a phenyl substituent donates 0.140 electron more than a cyclopropyl ring to the 2p (C^+) orbital. From the ^{13}C chemical shifts of phenyl- and cyclopropyl-substituted cations Olah[24b] concluded that: "Phenyl and cyclopropyl groups can show comparable ability to conjugatively delocalize positive charge, and steric interactions within a particular system may determine the relative order". Other workers have concluded from the fluorine chemical shifts of several cations that a cyclopropyl ring delocalizes the positive charge better than a phenyl.[23b] Our results suggest that, at least for the vinyl cation, phenyl is superior to cyclopropyl. A similar conclusion has been reached for the corresponding substituted alkyl cations (i.e., the benzyl and the cyclopropylcarbinyl cations), although the superiority of phenyl is smaller (0.137 electrons).[25] Among the π donors, phenyl delocalizes the charge better than a double bond in contrast with Olah's conclusions for alkyl cations;[24] the triple bond is the poorest π donor. The positive charge in **4** and **5** is divided between the p_x (2) and p_x (4) orbitals, pointing to almost equal contributions from the resonance structures **4** ↔ **4′** and **5** ↔ **5′**. On the basis of ^{13}C chemical shifts it was argued that in the analogous alkynoyl cation ($HC{\equiv}CC^+{=}O$) charge delocalization by the triple bond is unimportant.[41a] This conclusion was recently questioned by Pittman et al. who found considerable charge in the δ position of several alkynoyl cations by INDO calculations.[41b] The substantial delocalization by the triple bond in **4** supports Pittman's results.[41b] In **7a** the charge is delocalized mostly to the para (+0.209) and ortho (+0.162) positions, while some negative π charge (−0.005) is found in the meta position.

An α-methyl substituent can supply electrons to the 2p (C^+) orbital by hyperconjugation. The p–π (CH_2) hyperconjugation is however less effective than p–π or p–cyclopropane conjugation and the 2p (C^+) orbital in **3** is less populated than in **4**, **5a**, **6a**, or **7a**. In **5b**, **6b**, and **7b**, however, where conjugation with the substituent is excluded, the 2p (C^+) charge is similar to that in **3** (Table VII). The fact that alkyl groups are the poorest π-electron donors is well established.[5,24] The population is the lowest in the parent vinyl cation (**2**) and only 0.14 electron is transferred to the 2p (C^+) orbital by hyperconjugation with the two β-hydrogens.

An interesting result (see the p_y orbitals in Table VII) is the considerable polarization of the vinylic double bond (the C_1C_2 bond). In the extreme case (cation **2**), 1.2 of the vinylic π double-bond electrons are located at the α carbon and only 0.8 at the β carbon, pointing to a contribution from the resonance form H_2C^+–CH.[42] The polarization is smaller for the other cations, although significant (0.1 electron) even in the phenylvinyl cation (**7a**). Thus, although the cationic 2p (C^+) orbital and the C_1C_2 π electrons occupy two perpendicular planes and cannot interact directly, they are strongly coupled through polarization effects. An analogous interaction between the π and the σ frameworks was found for phenyl cation systems.[43]

The total charges in Table VI reflect both the inductive effect and π donation by the substituent. The total charge on C_2 parallels (except for methyl) the charge in the 2p (C^+) or-

bital, although the variations are smaller. Exclusion of the conjugation (by rotation) between the 2p (C^+) orbital and the substituent causes a sharp increase in the total charge at C_2 in **5**, **6**, and **7** (Table VI). The C_2 charge in **5b**, **6b**, and **7b** is higher than in **2**, reflecting the inductive electron-withdrawing nature (relative to hydrogen) of a double bond, a cyclopropyl group, or a phenyl group. An interesting result is that the total charge at C_2 is significantly more positive in the 2-propenyl cation (**3**) than in the vinyl cation (**2**), even though the 2p (C^+) orbital in the latter has a lower population. This suggests that relative to hydrogen a methyl group withdraws electrons inductively from an sp-hybridized carbon. Olah recently reached a similar conclusion regarding trigonal sp^2 cationic centers.[44]

In all the cations most of the unit positive charge is transferred to the hydrogens, with a relatively small fraction remaining on the cationic and the conjugating carbons. Some charge alteration is found in both the total (Table VI) and π charges (Table VII), a phenomenon well documented for both cationic and neutral species.[44,45]

Charge Distribution and Stability. It is often assumed that electron donation to a cationic center is of benefit energetically and that, in conjugated systems, better charge dispersal (or additional resonance structures) leads to a more stable cation.[46] It was shown recently, however, that the charge in the 2p (C^+) orbital, which correlates with the measured ^{13}C chemical shifts,[25,44b,47] does not necessarily reflect the stability of the cation.[25,48] Our study, which includes both σ and π donors and which covers cations of a wide range of stabilities, is suitable for the evaluation of this assumption.[46]

Neither the charge in the 2p (C^+) orbital (Table VII) nor the total charge (Table VI) at the cationic center correlates well with the stabilization provided by the substituents (Table III). Vinyl and cyclopropyl substituents, for example, stabilize the cation to a comparable degree but the 2p (C^+) population in the two cations (+0.43 in **5a** and +0.33 in **6a**) differ considerably. Similarly, α triple bond and methyl substituents have comparable stabilizing effects (Table III), but the triple bond is more efficient in delocalizing the positive charge (Table VI). The 2-propenyl cation (**3**) is 25.2 kcal/mol (RHF/4-31G, Table III) more stable than the parent vinyl cation (**2**), but the total charge at C_2 in **3** is higher than **2**. When only the π donors are compared, a gradual decrease in the 2p (C^+) charge with increasing stability of the cation is found, suggesting that with closely related substituents a correlation between charge and stability may exist. We conclude that it might be misleading to deduce the stability of cations from their charge densities (or from their NMR shielding constants[25,44b,47,48]) especially when comparing cations with substituents of different types (such as π or σ donors).

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A Chemically Induced Dynamic Nuclear Polarization Study of the Neophyl Radical Rearrangement

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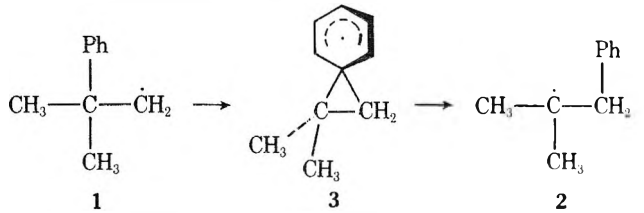
A CIDNP study of the thermolysis of benzoyl β-phenylisovaleryl peroxide and β-phenylisovaleryl peroxide has been carried out. Polarized signals in products resulting from both the 2-methyl-2-phenyl-1-propyl radical and from the rearranged 2-methyl-1-phenyl-2-propyl radical are observed. The CIDNP signals were consistent with a mechanism in which the majority of phenyl migration is not concerted with loss of CO_2 and occurs after diffusion from the cage. When β-phenylisovaleryl peroxide was decomposed, no polarization of aromatic ^1H signals was observed. Thus, if a phenyl-bridged intermediate is involved in the rearrangement, it does not have sufficient lifetime for spin selection and its consequent polarization to occur.

Although 1,2 migrations in free radicals are rather rare, they have been observed in a number of instances.[1] An extremely interesting example is the migration of a phenyl group in the 2-methyl-2-phenyl-1-propyl radical (**1**) which yields the 2-methyl-1-phenyl-2-propyl radical (**2**).[1,2] This rearrangement owes its thermodynamic driving force of approximately 8 kcal/mol[3] to the production of a tertiary radical from a primary radical. In addition, the kinetic barrier to rearrangement

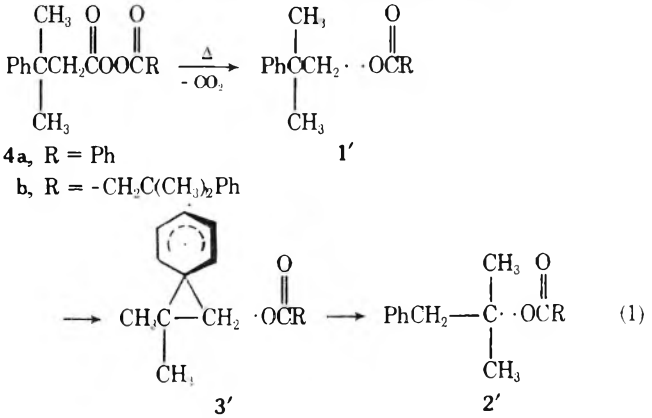


1 **3** **2**

is lowered by the known tendency for phenyl group rearrangement in radicals.[1] This propensity for phenyl migration has been ascribed to delocalization of the unpaired electron in an intermediate spiro radical such as **3**. Simple molecular-orbital calculations predict that, if **3** is involved, the energy of the transition state for this rearrangement will be lowered over that for a simple alkyl migration.[4]

ESR studies of both **1**[5] and **2**[6] and of the rearrangement of **1** to **2**[3,7] have been reported. However, in none of these investigations was the bridged structure **3** detected. These results indicate that, if **3** is an intermediate, it does not have sufficient lifetime to permit its detection by ESR. Hence, it is not clear at this time whether **3** is an intermediate, lying in a shallow minimum on the energy surface between **1** and **2**, or simply a transition state for this rearrangement.

NMR–CIDNP studies have become an important means of detecting short-lived radical intermediates.[8] If an intermediate radical lives longer than $\sim 10^{-10}$ s as a member of a radical pair, spin selection and its consequent nuclear polarization can result.[9] In the rearrangement of **1** to **2**, CIDNP has the potential of providing a means for the detection of **3** if it is a short-lived intermediate. This is illustrated in eq 1 for the decomposition of a β-phenylisovaleryl peroxide (**4**).



4a, R = Ph
b, R = $-CH_2C(CH_3)_2Ph$

1′ **3′** **2′** (1)

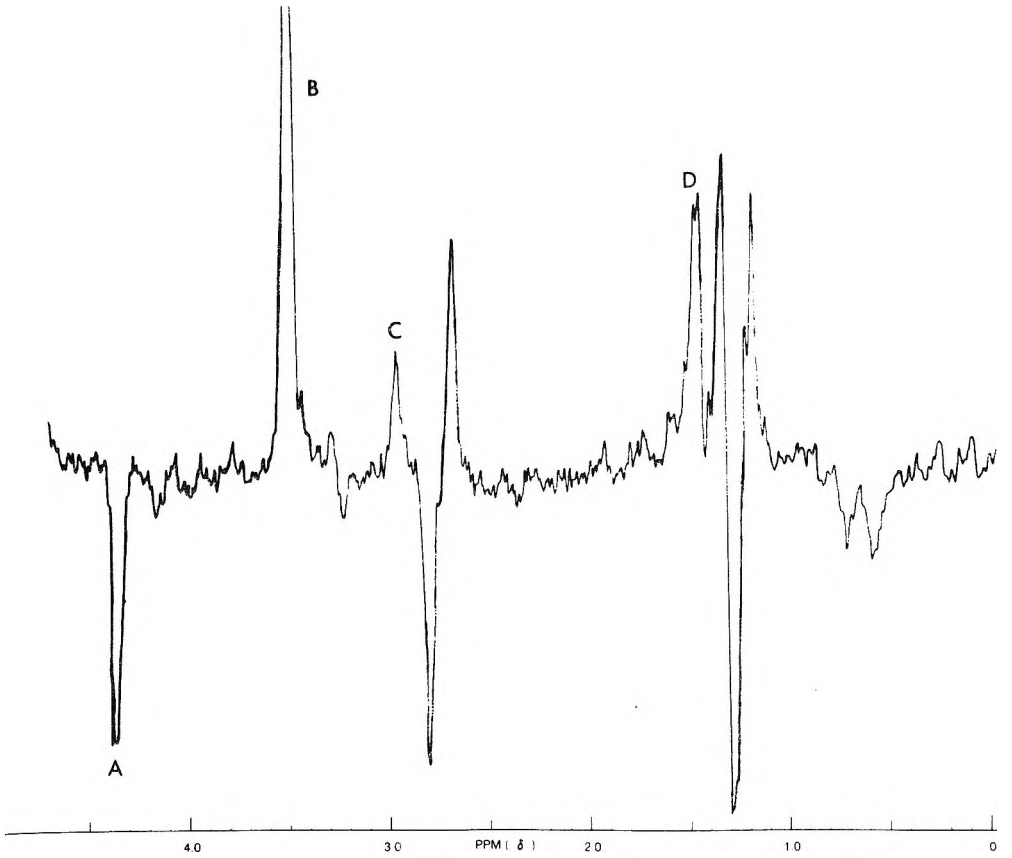
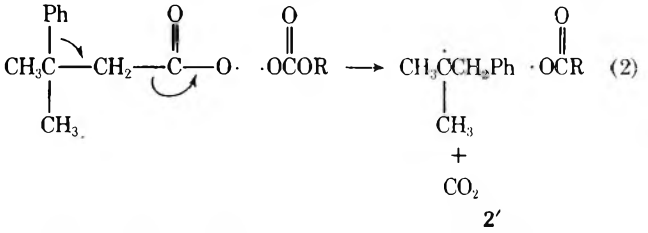


Figure 1. ^{1}H NMR spectrum recorded during the thermolysis of **4a** in HCA at 105 °C. Revelant assignments are: A, methylene protons in **7a**; B, methylene protons in **5**; C, methylene protons in **6**; D, methyl protons in **8a**.

Initial decomposition of **4** gives radical pair **1′** which will rearrange to pair **2′** via **3′**. In radical pair **3′**, unpaired spin is delocalized on the phenyl ring. Hence, phenyl protons in products resulting from **3′** are expected to be polarized if **3′** lives longer than 10^{-10} s.

In addition to providing information regarding the intermediacy of **3**, a CIDNP study of the decomposition of **4** can provide important information regarding the timing of phenyl migration with respect to decarboxylation. If decarboxylation is assisted by concerted phenyl migration (eq 2), all products



(2)

resulting from **2′** will show only polarization derived from spin selection in **2′** and none from **1′**.

In order to provide further information regarding the mode of decomposition of **4** and the mechanism of the rearrangement of **1** to **2**, we have conducted a CIDNP study of the thermolysis of **4**.

Results and Discussion

When the decomposition of **4b** was carried out in either hexachloroacetone (HCA) or *m*-dichlorobenzene, no polarization of any aromatic protons was observed. However, the polarizations observed in the aliphatic protons of rearranged cage product (vide infra) established that some rearrangement of **1′** to **2′** occurs. These results may be taken to indicate that the spiro radical pair **3′** does not have sufficient lifetime for spin selection and its consequent polarization of aromatic protons to occur.

However, a number of polarized signals were observed during the thermolysis of either **4a** or **4b**. Figure 1 shows the NMR spectrum taken during the 105 °C thermolysis of **4a**. Although the identity of all polarizations has not been established, a number of interesting points emerge from a consideration of the spectrum.

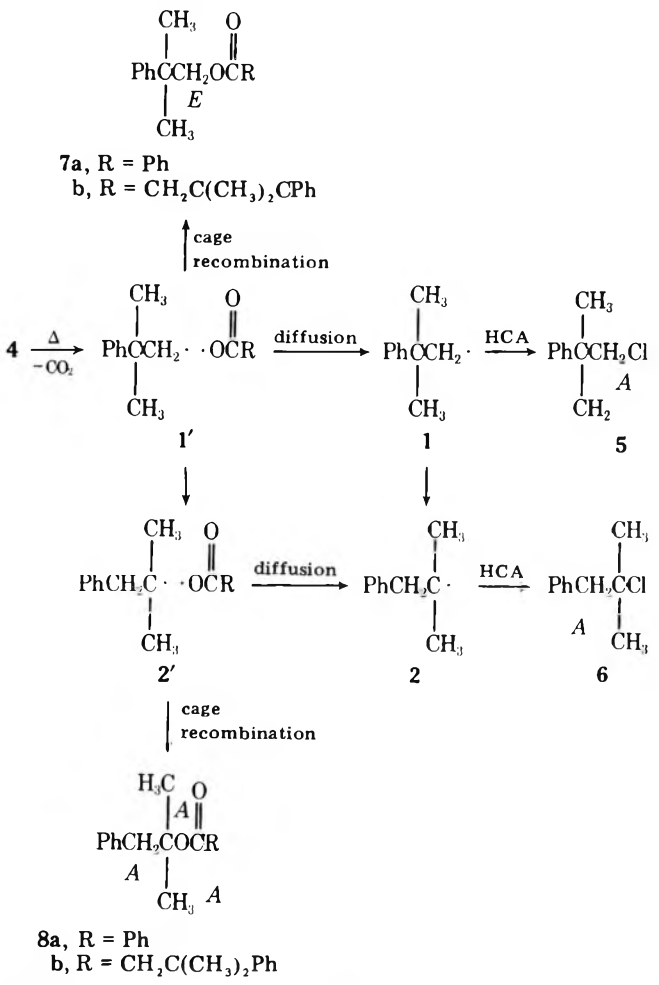
In the thermolysis of **4a** and **4b**, the products of initial interest were the unrearranged and rearranged cage recombination products and those products corresponding to diffusion of **1** and **2** from the cage. In order to simplify the product spectrum, the decomposition was initially carried out in hexachloroacetone (HCA), a solvent in which 1-chloro-2-phenyl-2-methylpropane (**5**) and 2-chloro-2-methyl-1-phenylpropane (**6**) are expected to be the major products of diffusion from the cage. The product of recombination within radical pair **1′** is the 2-phenyl-2-methyl-1-propyl ester **7**, while ester formation within pair **2′** will result in the 1-phenyl-2-methyl-2-propyl ester **8**.

These four products, **5**, **6**, **7**, and **8**, were detected in this study. The polarizations of the ^{1}H CIDNP signals resulting from them are shown in Scheme I, where *A* denotes enhanced absorption and *E* emission. Scheme I also depicts mechanisms of product formation consistent with the observed polarization.

Application of Kaptain's rules[10] to determine the polarization in unrearranged cage recombination product **7** and unrearranged diffusion product **5** is straightforward and leads to the conclusion that the methylene protons in **7** should exhibit emission while those in **5** should give enhanced absorption. These are the polarizations observed (Figure 1).

A prediction of the polarization expected for the methylene protons in rearranged cage product **8** is slightly more complicated. Kaptain's rules predict enhanced absorption for the methylene protons when **8** is produced from **2′** as the primary radical pair. In the present case, however, **2′** is a secondary

Scheme I



radical pair derived from the initial pair 1′. Since cage products from 1′ should exhibit methylene proton emission, the situation is ambiguous.

den Hollander[11] and Schwerzel, Lawler, and Evans[12] have recently examined systems in which secondary radical pairs are formed. Although these authors do not consider a case exactly analogous to the present system, they conclude that polarizations may be predicted using Kaptain's rules and summing the parameters for both primary and secondary radical pairs.

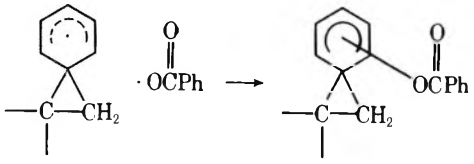
In the present case, only the values of the hyperfine splittings (a_H) in the two radical pairs differ. Since the sign of a_H in 1′ is opposite to that in 2′, the a_H values tend to cancel and little polarization of the methylene protons in 8 is expected. In fact, no polarized signal for these protons at δ 3.20 is observed in HCA (Figure 1). However, when the thermolysis of **4a** is carried out in *m*-dichlorobenzene, a weak enhanced absorbtion at δ 3.20 attributed to the methylene protons of **8a** is observed. The fact that a slight enhanced absorption actually occurs may reflect a longer lifetime of 2′ as compared to 1′.

Since a_{CH_3} is much larger in 2′ than in 1′,[3] a prediction of the polarization of methyl signals in 8 is unambiguous. The positive sign of a_{CH_3} in 2′ leads one to predict the enhanced absorption for the methyl protons in 8 which is observed in the spectrum (Figure 1).

Scheme I shows that the polarization of CIDNP signals from rearranged chloride, **6**, can be used to deduce the sequence of events leading to its formation. If **6** results mainly from a sequence involving 1′ → 2′ → 2 → **6**, its methylene protons should show a net emission as spin selection will occur in pair 2′. However, the fact that the methylene protons in **6** show enhanced absorption implies that the major pathway leading to **6** is 1′ → 1 → 2 → **6**. That is, most of the rearrangement of 1 to 2 occurs after diffusion from cage 1′. This must be true as the polarization observed in **6** is that predicted to be the result of diffusion from pair 1′ rather than from pair 2′.

The polarization of the methylene protons in **6** also establishes that the majority of the rearrangement cannot be concerted with decarboxylation, as this process would lead directly to 2′ which would yield **6** with methylene protons polarized oppositely to that observed.

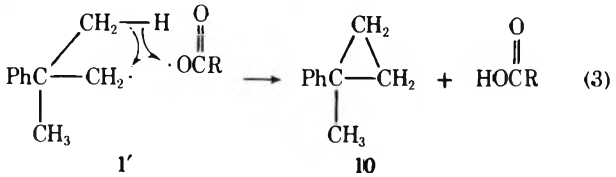
When the pyrolysis of **4a** was carried out in HCA, a CIDNP emission consisting of a multiplet centered at δ 0.67 was observed. Since this chemical shift is that expected for cyclopropyl protons, we first thought that this emission resulted from a structure such as **9** in which the spiro radical **3** is captured by benzoyloxy radical.



3′ 9

However, it was subsequently found that the *E* at δ 0.67 was identical with the multiplet for the cyclopropane protons in 1-methyl-1-phenylcyclopropane (**10**). Rickatson and Stevens[2c] have reported that **10** is produced when **4b** is decomposed in refluxing benzene. It is interesting that **10** is not reported when radical 1 is produced by other methods.[2a,b,d]

The most probable mechanism for the formation of **10** is via the radical disproportionation shown in eq 3. This process would produce **10** with the observed polarization of the cyclopropane protons. Polarization of either the phenyl or methyl protons in **10** is not observed nor is it expected, since there is little hyperfine splitting by these protons in radical **1**.[3,5]



(3)

1′ 10

Conclusion

This CIDNP study of the decomposition of **4** has established that phenyl migration in the intermediate neophyl radical is not concerted with the loss of carbon dioxide. Furthermore, phenyl migration has been found to occur both within the cage and after diffusion of the neophyl radical from the cage. ESR studies have failed to produce evidence for a spiro radical intermediate in this rearrangement.[3,5-7] Likewise our search for this intermediate using the CIDNP technique has provided no evidence for its existence. Hence, we conclude that, if a spiro radical intermediate exists, it must live less than 10^{-10} s.

Experimental Section

Procedure for Obtaining CIDNP Spectra. All CIDNP spectra were obtained on a Varian A-60 NMR spectrometer. The appropriate peroxide, **4a** or **4b**, was weighed and dissolved in 0.4 mL of solvent, hexachloroacetone or *m*-dichlorobenzene, to give a 0.43 M solution. The probe of the spectrometer was heated to 105 °C and allowed to equilibrate, and the tube containing the solution of the peroxide was introduced. The CIDNP signals were observed while sweeping the field with a sweep time of 100 s. After completion of the reaction, a small amount of *o*-xylene was added to the solution as an internal standard. The positions of the CIDNP signals were obtained in ppm relative to the methyl signals in *o*-xylene at 105 °C. The identity of the signals was established by adding a small amount of each product to the hot solution and observing the growth of signal intensity. Al-

though NMR signals from **10** were not present at the conclusion of the reaction, addition of authentic **10** to the reaction mixture produced signals identical with the emissions assigned to **10**. In order to further confirm the identity of the products, the reaction mixtures were analyzed by gas chromatography on an 8-ft 3% SE-30 on 60/80 Supelcopert column. The GC analysis consisted of coinjection with known samples of **5**, **6**, **7**, and **8** and observing peak uniformity.

Benzoyl β-Phenylisovaleryl Peroxide (4a). Perbenzoic acid (108 mL, 54.3 mmol in chloroform) was placed in an ice-cooled 200-mL three-necked flask. β-Phenylisovaleryl chloride (10.7 g, 54.3 mmol) was then added all at once with stirring. A solution of 50 mL of methylene chloride and 4.4 mL of pyridine was added dropwise over a period of 1 h and the stirring continued for an additional hour. The reaction mixture was washed with four 50-mL portions of saturated sodium bicarbonate solution. The organic layer was dried over anhydrous sodium sulfate and the solvent removed on a rotary evaporator at room temperature. Upon cooling in a dry ice–acetone slush (−78 °C) and adding a small amount of petrolium ether, the oil crystallized. After repeated recrystallizations from methylene chloride–petroleum ether, then from petroleum ether, the pure peroxide was obtained, 6.5 g (40%): mp 65.5 °C; NMR (CCl_3D) δ 7.25–8.2 (m, 10 H, ArH), 2.86 (s, 2 H, CH_2), 1.6 (s, 6 H, CH_3); IR (CCl_3H cm^{-1} 3100–3010 (ArH), 2980 (CH_3), 1805, 1770 (C=O), 1060–1000 (COO).

β-Phenylisovaleryl Peroxide (4b). The symmetric peroxide was prepared according to the general procedure of Price and Krebs:[13] mp 42.5–43.8 °C, dec 75 °C; NMR (CCl_3D) δ 7.49 (s, 10, Ar–H), 2.72 (s, 4 H, CH_2), 1.5 (s, 12 H, CH_3); IR (CCl_3H) cm^{-1} 3030, 3060, 3090 (t, Ar–H), 1810, 1780 (C=O), 1055 (COO).

Reaction Products. The ester products of the peroxide decompositions (**7a**, **7b**, **8a**, and **8b**) were prepared by dissolving x mL of the alcohol in $3x$ mL of pyridine and adding $0.5x$ mL of the acid chloride. This solution was refluxed for 1 h, washed with 5% sodium carbonate, then with 1 N sulfuric acid, dried, and distilled through a small distillation apparatus with a Claison head.

2-Methyl-1-phenylprop-2-yl benzoate (8a): bp 105 °C (0.15 Torr); NMR (CCl_4) δ 7.08–8.14 (m, 10 H, ArH), 3.22 (s, 2 H, CH_2), 1.57 (s, 6 H, CH_3); IR (CCl_4) cm^{-1} 3040, 3070, 3090 (ArH), 2980 (CH_3), 1715 (C=O), 1115 (CO).

2-Methyl-2-phenylprop-1-yl benzoate (7a): bp 105 °C (0.15 Torr); NMR (CCl_4) δ 7.08–8.12 (m, 10 H, ArH), 4.35 (s, 2 H, CH_2), 1.42 (s, 6 H, CH_3); IR (CCl_4) cm^{-1} 3040, 3060, 3090 (ArH), 2970 (CH_3), 2930 (CH_2), 1740 (C=O), 1110 (CO).

2-Methyl-1-phenylprop-2-yl 3-methyl-3-phenylbutanoate (8b): bp 110 °C (0.15 Torr); NMR (CCl_4) δ 7.16–7.6 (m, 10 H, ArH), 2.91 (s, 2 H, CH_2), 2.52 (s, 2 H, CH_2), 1.46 (s, 6 H, CH_3), 1.24 (s, 6 H, CH_3); IR (CCl_4) cm^{-1} 3030, 3060, 3080 (ArH), 2970 (CH_3), 2930 (CH_2), 1720 (C=O(= [[[] (CO).

2-Methyl-2-phenylprop-1-yl 3-methyl-3-phenylbutanoate (7b): bp 110 °C (0.15 Torr); NMR (CCl_4) δ 7.26 (s, 10 H, ArH), 4.0 (s, 2 H, CH_2), 2.52 (s, 2 H, CH_2), 1.27 (s, 6 H, CH_3), 1.2 (s, 6 H, CH_3); IR (CCl_4) cm^{-1} 3020, 3060, 3080 (ArH), 1720 (C=O), 1110 (CO).

1-Chloro-2-methyl-2-phenylpropane (5) was prepared by the procedure of Whitmore, Weisgerber, and Shabica.[14]

2-Chloro-2-methyl-1-phenylpropane (6). This chloride was synthesized by refluxing 2-methyl-3-phenylpropan-2-ol with a molar excess of thionyl chloride. The thionyl chloride was removed by distillation under reduced pressure. The residue was washed with water, dried over sodium sulfate, and used without further purification: NMR (CCl_4) δ 7.25 (s, 5 H, ArHO), 3.01 (s, 2 H, CH_2), 1.5 (s, 6 H, CH_3); IR (CCl_4) cm^{-1} 3030, 3060, 3080 (ArH), 2970 (CH_3), 2920 (CH_2).

1-Methyl-1-phenylcyclopropane (15) was prepared by dechlorination of the adduct of dichlorocarbene with α-methylstyrene according to literature procedures.[15]

Acknowledgment. We express our appreciation to Professor James W. Wilt for an extremely helpful correspondence.

Registry No.—**4a**, 62698-29-7; **4b**, 62726-47-0; **5**, 515-40-2; **6**, 1754-74-1; **7a**, 19284-03-8; **7b**, 62698-30-0; **8a**, 16737-31-8; **8b**, 62698-31-1; perbenzoic acid, 93-59-4; β-phenylisovaleryl chloride, 4094-64-8; 2-phenyl-2-methylpropan-1-ol, 2173-69-5; benzoyl chloride, 98-88-4; 3-methyl-3-phenylbutanoyl chloride, 4094-64-8; 1-phenyl-2-methylpropan-2-ol, 100-86-7; thionyl chloride, 7719-09-7.

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Rates and Products of Solvolysis of Arylmethylcyclobutylcarbinyl p-Nitrobenzoates. Increasing Stabilization with Increasing Electron Demand[1]

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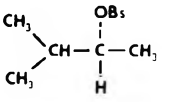
Increasing the electron demand at the carbonium ion center by varying the substituent on the aryl group results in small increases in rates of solvolysis for the arylmethylcyclobutylcarbinyl p-nitrobenzoates, as compared with the corresponding arylmethylisopropylcarbinyl derivatives. The rate increases must reflect increases in the electron supply by the cyclobutyl group under increasing demand of the cationic center. This is the lowest level of stabilization by strained bonds detected by this approach, a factor of 86 for the secondary cyclobutylcarbinyl system, and demonstrates the sensitivity and usefulness in evaluating neighboring group effects by this approach.

A basic tenet of neighboring group effects is that the more stable the carbonium ion center, the less demand that center will make on neighboring groups for additional stabilization through participation.[2] Use of the Hammett–Brown relationship permits one to vary the electron demand at a carbonium ion center over a wide range while maintaining the steric effects around that center essentially constant. This approach can provide definite evidence for the presence or absence of neighboring group participation, e.g., in the 7-*anti*-norbornenyl,[3] 2-norbornenyl,[4] 5-methyl-2-norbornenyl,[5] and the benzonorbornenyl[6] systems.

Unlike π participation, which has been well established,[7] σ participation has been the subject of extensive debate. In particular, the 2-norbornyl system has been the center of controversy.[8,9] The study of the solvolysis of 2-aryl-2-norbornyl p-nitrobenzoates failed to detect any σ participation.[10] It was suggested that this approach may not be sensitive to σ stabilization (σ participation and/or conjugation). Therefore this approach was tested on the strained σ bonds in cyclopropylcarbinyl systems and found to be valid.[11] However, it was argued that cyclopropylcarbinyl systems are too reactive and that results in this system should not be extrapolated to the 2-norbornyl system.[8a] Moreover, there are large differences in the hybridization of the carbon atoms of cyclopropane compared to norbornane. Thus a much less reactive system is needed in order to demonstrate the ability of the approach of varying the electron demand to detect small amounts of stabilization by strained σ bonds.

The cyclobutylcarbinyl system offers such a route. For example, methylcyclobutylcarbinyl brosylate (**2**) undergoes acetolysis 86 times faster than a model system, **1**.[12] This rate enhancement is attributable to stabilization of the developing carbonium ion by the strained σ bonds in the adjacent cyclobutyl group.



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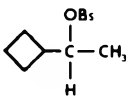


2

	1	2
rel rate (25 °C)	1.0	85.5

Accordingly, the arylmethylcyclobutylcarbinyl p-nitrobenzoates (**3**) were synthesized and their rates and products of solvolysis in 80% acetone determined. The rates of **3** were compared with a model system which solvolyzes without unusual stabilization, the arylmethylisopropylcarbinyl p-nitrobenzoates (**4**).[11a]

Results

Synthesis. The arylmethylcyclobutylcarbinols (**5**) were prepared by the addition of the appropriate Grignard reagent to cyclobutyl methyl ketone. These alcohols were converted into the p-nitrobenzoates by the lithium alkoxide method.[11b]

Kinetic Studies. The rate constants for the solvolysis of **3** in 80% aqueous acetone are listed in Table I. The data reveal an excellent linear correlation with σ^+ constants with a ρ^+ value of −3.94 (correlation coefficient 0.999).

Product Studies. The products of solvolysis were determined in buffered aqueous acetone and analyzed by NMR.

Discussion

The cyclobutylcarbinyl system has been the subject of theoretical and experimental studies,[12–14] and it is generally agreed that the cyclobutyl group stabilizes an adjacent cationic center much less than a cyclopropyl group. Thus the cyclobutylcarbinyl system allows one to test for much smaller amounts of stabilization by strained σ bonds, and should provide a critical test for the ability to detect small levels of neighboring group stabilization by increasing the electron demand.

If neighboring group stabilization is significant in a given system, the rate of solvolysis must be greater than the rate of solvolysis in the absence of such stabilization.[15] Problems can arise in defining an analogous system which reacts without neighboring group stabilization.[11b] In order to accurately address this problem one has to consider numerous factors before choosing an appropriate model. Ground state energies and steric effects (B strain, steric hinderance to ionization, and resonance) are critical. Their neglect can lead to an erroneous assessment of neighboring group effects.[9,11b] For example, **4** has been suggested as a model system for 2-norbornyl.[16] However, it does not appear to be very prudent to compare an aliphatic system with a bicyclic system. Steric effects are much greater in rigid bicyclic systems than in the more flexible aliphatic systems.[17] Moreover, the bond angle strain at the reaction center in 2-norbornyl is greater than in a simple aliphatic system.[18]

However, this is not a problem with **3** and **4**. The bond angle strain at the reaction site should be quite similar. Molecular models show that the isopropyl group has about the same steric requirements as a cyclobutyl group. Hence there should not be any significant differences in steric effects during the solvolysis of **3** and **4**. Therefore, the best possible model system for **3** which reacts without any neighboring group stabilization is clearly **4**.

Indeed it was observed that with increasing electron demand at the cationic center the rate of solvolysis of the arylmethylcyclobutylcarbinyl derivatives (**3**) increases slightly, as compared to the arylmethylisopropylcarbinyl derivatives (**4**).[11a]

Table I. Solvolysis of Arylmethylcyclobutylcarbinyl *p*-Nitrobenzoates in 80% Aqueous Acetone

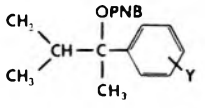
Substituent on aryl group	Registry no.	Temp, °C	$k_1 \times 10^6$, s^{-1}	$\Delta H^{\ddagger}$, kcal mol^{-1}	$\Delta S^{\ddagger}$, eu
p-CH_3O	62861-28-3	25.0	63.2[a]		
p-H	62861-29-4	100.0	389		
		75.0	30.9		
		25.0	5.45×10^{-2} [b]	27.4	−6.0
p-CF_3	62861-30-7	150.0	422		
		125.0	44.3		
		25.0	1.23×10^{-4} [b]	31.0	−4.6
m,m'-$(CF_3)_2$	62861-31-8	150.0	44.1		
		125.0	3.97		
		25.0	4.60×10^{-6} [b]	32.9	−4.3

[a] Rate constant was estimated by multiplying the rate constant for the benzoate by the factor 20.8: H. C. Brown and K. Takeuchi, *J. Am. Chem. Soc.*, **90**, 2691 (1968). [b] Calculated from data at higher temperatures.

Table II. Products of Solvolysis of Arylmethylcyclobutylcarbinyl *p*-Nibrobenzoates[a]

Substituent	Products of solvolysis[b] 5	6	7	8
p-CH_3O[c]	(75) (62861-32-9)	(10) (62861-36-3)	(15) (62861-39-6)	(0)
p-H	63 (62861-33-0)	23 (4747-36-8)	14 (4413-14-3)	0
p-CF_3	50 (62861-34-1)	30 (62861-37-4)	15 (62861-40-9)	5 (62861-42-1)
m,m'-$(CF_3)_2$[d]	37 (62861-35-2)	40 (62861-38-5)	12 (62861-41-0)	11 (62861-43-2)

[a] Determined in 80% acetone at 125.0 °C with 10 mol % excess sodium acetate. [b] Analyzed by NMR; values are ±2% unless otherwise noted. Registry numbers are in parentheses. [c] Products of benzoate ester; because of purity of this ester (92%) the product may be in error by more than ±2%, except for 8. [d] Products determined in 50% acetone at 125.0 °C with 10 mol % excess sodium acetate.



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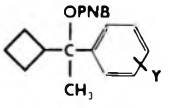


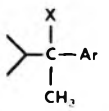
3

Y	rel rates 4	3
p-CH_3O	1.0	1.0
p-H	1.0	5.7
p-CF_3	1.0	9.0
m,m'-$(CF_3)_2$	1.0	17.6

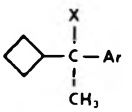
Clearly the approach is valid for the small electron supply from the carbon–carbon bonds of the cyclobutyl ring. Thus small levels of stabilization (~86) in secondary derivatives can be detected in their analogous tertiary benzylic derivatives.

Let us examine the sensitivity of ρ^+ values to neighboring group effects. The available data reveal that ρ^+ values are very sensitive to neighboring group stabilization. Such stabilization can be classified by their $\Delta\rho^+$ when compared to a suitable model system. For example, large amounts of stabilization found in cyclopropylcarbinyl,[3,11b,19] allylic,[20] and benzylic systems[21] and the π participation found in 7-norbornenyl have $\Delta\rho^+$ between 1.4 and 2.95. Systems with small levels of stabilization such as the 1-(*p*-cyclopropylphenyl)-1-arylethyl,[23] 6-methoxybenzonorbornenyl,[6] and the 5-methyl-2-norbornenyl systems[22] are characterized by $\Delta\rho^+$ of 0.3–0.9. Systems which undergo solvolysis with no significant neighboring group stabilization as in tertiary benzonorbornenyl,[6] 2-norbornyl,[10] 2-norbornenyl,[24] and Δ^3-cyclopentenyl systems[25] have no difference in $\Delta\rho^+$ (0.01 to −0.08).

Let us now examine the cyclobutylcarbinyl system. **4** has a ρ^+ of −4.65, while **3** has a ρ^+ of −3.94. The change in ρ^+ ($\Delta\rho^+$ = 0.71) is in the direction anticipated for a small amount of neighboring group stabilization.



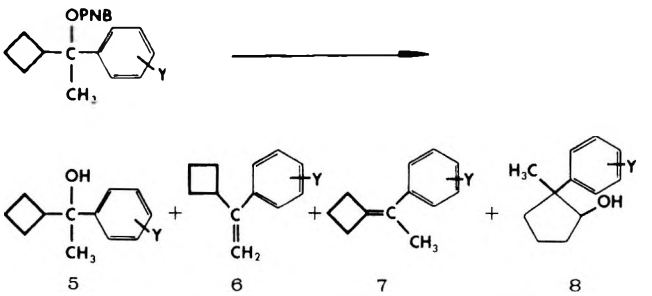
ρ^+ −4.65



−3.94 $\Delta\rho^+$ = 0.71

The amount of σ stabilization by the 1,6 carbon–carbon bond of 2-*exo*-norbornyl brosylate is reported to be 350. Since the approach of varying the electron demand can detect the factor of 86 attributable to σ stabilization in the cyclobutylcarbinyl system, it is of major importance that this approach reveals no significant stabilization by the 1,6 carbon–carbon bonds in the tertiary arylnorbornyl derivatives. Consequently, the high exo/endo rate ratio in the solvolysis of 2-norbornyl must be due to some factor other than participation. Steric hindrance to ionization has been suggested as an alternative explanation.[9a]

The products of solvolysis of **3** were determined in buffered aqueous acetone at 125.0 °C and appear in Table II. The predominant products are those with no skeleton rearrangement **5, 6,** and **7**. The derivatives with increased electron demand [*p*-CF_3 and *m,m'*-$(CF_3)_2$] exhibit a small amount of rearranged product **8**. These results are consistant with the kinetic arguments.



5 6 7 8

The fact that the phenyl derivative reacts with a rate enhancement of almost six but gives no rearranged product suggests that the formation of **8** in the *p*-trifluoromethylphenyl and *m,m'*-bis(trifluoromethyl)phenyl derivatives occurs after the rate determining step.

In conclusion, neighboring group stabilization by carbon–carbon bonds in the cyclobutylcarbinyl system is a linear function of the electron demand of the carbonium ion center. Moreover, the technique of increasing the electron demand of a cationic center was able to detect the small amount of σ

Table III. Preparation of Arylmethylcyclobutylcarbinols[a]

Aryl group	% yield	Bp, °C	$n^{20}D$
p-Anisyl	82	75–76 (0.001 mm)	1.5332
Phenyl	89	94–96 (1 mm)	1.5381
p-Trifluoromethylphenyl	85	67–70 (0.05 mm)	1.4814
3,5-Bis(trifluoromethyl)-phenyl	87	64–66 (0.03 mm)	1.4460

[a] Boiling points are uncorrected; all new compounds gave spectral and microanalytical data (±0.4% for C, H. F) consistent with the proposed structure.

Table IV. Preparation of Arylmethylcyclobutylcarbinyl p-Nitrobenzoates[a]

Aryl group	% yield	Mp, °C
p-Anisyl	b	b
Phenyl	89	107.0–107.5
p-Trifluoromethylphenyl	91	124.8–126.0
3,5-Bis(trifluoromethyl)phenyl	85	95.5–96.5

[a] Melting points are uncorrected; all new compounds gave spectral and microanalytical data (±0.4% C, H, N, F) consistent with the proposed structure, except the p-anisyl derivative which was not pure enough for microanalysis. [b] This p-nitrobenzoate was too unstable to isolate. The benzoate would not solidify. The NMR indicates that this ester was about 92% pure.

stabilization, a factor of 86, in the cyclobutylmethylcarbinyl system. Clearly, this approach is sensitive in detecting small amounts of π and σ participation and/or conjugation and is a valuable tool for the physical organic chemist.

Experimental Section

Cyclobutyl methyl ketone was prepared from cyclobutylcarboxylic acid in 90% yield following the general procedure for the preparation of methyl ketones from carboxylic acids:[27] bp 134–136 °C (lit. bp 137 °C).[28]

General Procedure for the Preparation of Arylmethylcyclobutylcarbinols. The Grignard reagents of p-bromoanisole, bromobenzene, p-bromobenzotrifluoride, and 3,5-bis(trifluoromethyl)-bromobenzene were prepared by the reaction of the respective bromides with magnesium in anhydrous ether under nitrogen. A solution of cyclobutyl methyl ketone in ether was added to a stirred solution of the Grignard reagent (10 mol % excess) at 0 °C. After hydrolysis of the reaction mixture with saturated ammonium chloride solution, the organic layer was separated and the aqueous layer extracted twice with ether. The combined ether extracts were dried over anhydrous magnesium sulfate and filtered, and solvent was evaporated. The resultant arylmethylcyclobutylcarbinols were purified by distillation and characterized by NMR and IR; properties are listed in Table III.

Preparation of p-Nitrobenzoates. The arylmethylcyclobutylcarbinyl p-nitrobenzoates were prepared from the lithium alkoxide and p-nitrobenzoyl chloride as described by Brown and Peters.[11] The benzoate of p-anisylmethylcyclobutylcarbinol was obtained in a similar manner. The properties of these derivatives are listed in Table IV.

Kinetic Procedure. The procedure utilized for the determination of rate constants was similar to that previously reported by Brown and Peters.[11]

Registry No.—2, 62861-44-3; p-bromoanisole, 104-92-7; bromobenzene, 108-86-1; p-bromobenzotrifluoride, 402-43-7; 3,5-bis(trifluoromethyl)bromobenzene, 328-70-1; cyclobutyl methyl ketone, 3019-25-8.

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Comparative Capabilities of 1-Phenylpropane-*1*-^{13}C and 1-Phenylbutane-*1*-^{13}C toward the Alkylbenzene Automerization[1]

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1-Phenylbutane-*1*-^{13}C failed to undergo rearrangement of the isotopic label from C-1 to C-2 of the side chain (automerization) when heated with $AlCl_3$ or $AlBr_3$ under conditions which produce complete equilibration of isotopic carbon between C-1 and C-2 in labeled 1-phenylpropane (*n*-propylbenzene). When equimolar mixtures of 1-phenylbutane-*1*-^{13}C and 1-phenylpropane-*1*-^{13}C were treated with $AlCl_3$ and $AlBr_3$, neither hydrocarbon underwent automerization when the usual concentration of catalysts was used; with a much higher concentration of $AlBr_3$, 1-phenylpropane-*1*-^{13}C showed isotopic automerization but 1-phenylbutane-*1*-^{13}C could not be recovered. Various compounds, known to be produced from 1-phenylbutane under the conditions of the reaction, were tested as potential inhibitors of the isotopic automerization. Di- and tri-*n*-butylbenzenes appeared to be the most likely candidates. The failure of 1-phenylbutane-*1*-^{13}C to undergo isotopic automerization may be ascribed partly to alternative reactions which it undergoes but which are not available to 1-phenylpropane-*1*-^{13}C. These alternative reactions are cyclialkylations to indan and indene derivatives via the secondary carbocation produced by hydride abstraction at the 3 position in the side chain of 1-phenylbutane. In accord with this explanation, significant amounts of indans and indenes have been identified among the products from 1-phenylbutane. A second factor in the failure of 1-phenylbutane-*1*-^{13}C to undergo automerization is the lesser tendency of a 1,2-ethyl shift in an intermediate carbocation compared with a 1,2-methyl shift. This was demonstrated in the reaction of 1,2-diphenylbutane-*2*-^{13}C with aluminum chloride, which gave only 8–10% isotopic rearrangement in recovered 1,2-diphenylbutane and the 1-phenylbutane produced from it.

In 1957 a surprising isotopic rearrangement (automerization) was observed in *n*-propylbenzene (1-phenylpropane-*1*-^{14}C), induced by heating the hydrocarbon with aluminum chloride.[2] The isotope became equilibrated between C-1 and C-2 of the 1-phenylpropane, but none was introduced into C-3. Subsequently other structural, nonisotopic rearrangements of several alkylbenzenes were discovered and correlated with the isotopic *n*-propylbenzene automerization. These included *sec*-butylbenzene, isobutylbenzene, and some pentylbenzenes.[3] A mechanism proposed independently by Streitwieser and Reif[4] and by us[3c] for the isotopic automerization of 1-phenylpropane has been given additional support from results of experiments with ^{13}C-labeled molecules.[5] An isotopic automerization of 1-phenylbutane-*1*-^{14}C might be expected to follow an analogous mechanism in which the only differences would be the intermediacy of 1,2-diphenylbutane instead of 1,2-diphenylpropane, and the 1,2 shift of an ethyl group instead of a methyl group (Scheme I).

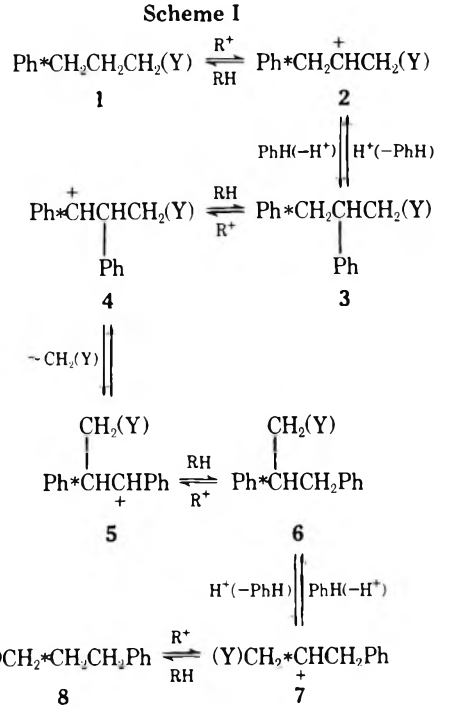
Early tests on ^{14}C-labeled *n*-butylbenzene showed an unexpectedly small amount of automerization, compared to that of the lower homologue.[6] However, these experiments were carried out before the optimum conditions for automerization of *n*-propylbenzene were worked out. It was found later that the extent of automerization was highly dependent on the nature of the catalyst (e.g., $AlCl_3$ or $AlBr_3$), the concentration of the catalyst, the presence of a cocatalyst (H_2O, HCl or HBr, etc.), and the choice of solvent, if any.[3c,7] Because of the subtlety of the influence of these factors, we felt that a reexamination of the possible isotopic automerization of *n*-butylbenzene under a variety of experimental conditions was justified, especially since the use of ^{13}C instead of ^{14}C would simplify the gathering of experimental data.

Results and Discussion

Samples of 1-phenylbutane-*1*-^{13}C were treated with water-activated aluminum chloride or bromide, usually in the presence of benzene, at 85–95 °C. The recovered 1-phenylbutane was investigated by mass spectrometry and in some cases by ^1H NMR spectroscopy in order to determine the position and percentage of the isotopic carbon label within the molecules.

In order to determine the percentage of monolabeled molecules and the position of the label in samples of 1-phenylbutane-*1*-^{13}C before and after treatment with aluminum chloride, mass spectra of (1) unlabeled 1-phenylbutane, (2) 1-phenylbutane-*1*-^{13}C, and (3) 1-phenylbutane-*1*-^{13}C recovered after treatment with aluminum halide were obtained. The mass spectrometric analysis of ^{13}C-labeled 1-phenylbutane samples was performed by the same process as that described for labeled 1-phenylpropane[5] except that the P (parent) and P + 1 peaks for the labeled 1-phenylbutane are found at *m/e* 134 and 135, respectively. The method of Biemann[8] was used to calculate the mole percentage of ^{13}C-singly labeled molecules (*m/e* 135) and unlabeled molecules (*m/e* 134), and the mole percentage of molecules labeled in C-1 of the side chain (*m/e* 92) and those not labeled in C-1 (*m/e* 91),[9] as in the case of labeled 1-phenylpropane.[5]

Scheme I



a, Y = H
b, Y = CH_3

The results of experiments in which samples of 1-phenylbutane-*1*-^{13}C were treated with aluminum chloride or aluminum bromide are given in Table I. Comparison of the mole percentage of labeled molecules before and after reaction (columns 2 and 3) showed no loss of ^{13}C from the phenylbutane molecules, and comparison of the mole percentage of molecules labeled in C-1 before and after reaction (columns 3 and 4) indicated no change within experimental error in the distribution of the ^{13}C label in any sample of 1-phenylbutane-*1*-^{13}C. This complete lack of rearrangement in 1-phenylbutane-*1*-^{13}C was confirmed by ^1H NMR analysis. The integrals of the triplet at δ 2.61 ppm and its ^{13}C-satellite triplet at δ 3.66 ppm showed the same ratio before and after reaction in all of the experiments of Table I except expt 2 and 6, in which no NMR analysis was applied. It should be noted that the reaction conditions of catalyst concentration, temperature, solvent, and reaction time employed in the experiments of Table I were those which produced complete automerization of isotopic carbon between C-1 and C-2 of the *n*-propylbenzene side chain.[3c,5]

Although these new experiments with 1-phenylbutane-*1*-^{13}C confirmed and extended the earlier evidence that *n*-butylbenzene was much less susceptible to isotopic automerization than *n*-propylbenzene, it occurred to us that the best opportunity for a direct comparison of the behavior of the two homologous alkylbenzenes would be afforded by heating a mixture of 1-phenylpropane-*1*-^{13}C and 1-phenylbutane-*1*-^{13}C with aluminum halide, recovering and separating the alkylbenzenes by gas chromatography, and determining the distribution of the ^{13}C in each of them. The results of such experiments are shown in Table II, as determined by mass spectrometry. Water-activated $AlCl_3$ at 85 °C for 6.5 or 12 h (expt 1 and 2) produced no isotopic automerization in either alkylbenzene. The result of expt 1 was confirmed by NMR analysis. The same lack of automerization was observed when the mixture of alkylbenzenes was heated with water-activated $AlBr_3$ and benzene in sealed tubes at 95 °C, using a molar ratio of combined alkylbenzenes:$AlBr_3$ = 1:0.5 (expt 3). However, when the molar ratio of catalyst to hydrocarbon was raised to 1:1 (expt 4), partial automerization of ^{13}C occurred in the 1-phenylpropane-*1*-^{13}C: 33.7/47.2 × 100 = 71% ^{13}C remained in C-1 after heating. Not enough 1-phenylbutane for analysis could be recovered from this reaction mixture. Experiment 5, in which the same reactant ratio was used, but a longer heating period, gave complete equilibration of the ^{13}C label in the 1-phenylpropane (23.6/47.2 × 100 = 50.1% ^{13}C remained in C-1), but the recovered material with the same GLC retention time as 1-phenylbutane was chiefly (ca. 80%) a side-reaction product with a molecular ion of *m/e* 132, presumably 1-methylindan. It has previously been demonstrated that heating 1-phenylbutane with aluminum chloride in benzene produces some 1,3-diphenylbutane, and the latter is converted to 1-methylindan.[3c,10]

The experiments on ^{13}C-labeled 1-phenylpropane and 1-phenylbutane separately and in mixtures clearly demonstrated three facts: (1) 1-phenylbutane is much less susceptible to isotopic automerization than is 1-phenylpropane; (2) 1-phenylbutane is much less resistant to structural modification by aluminum chloride than is 1-phenylpropane; (3) the presence of 1-phenylbutane has an inhibitory effect on the isotopic automerization of 1-phenylpropane. We shall now describe further studies designed to explain the basis of each of these facts and their possible interrelationships.

The first approach had as its aim discovery of the cause of the inhibitory effect of 1-phenylbutane on the automerization of 1-phenylpropane-*1*-^{13}C. Mixtures of 1-phenylpropane-*1*-^{13}C and unlabeled 1-phenylbutane in various proportions were treated with aluminum chloride in the presence of benzene and water cocatalyst. The recovered 1-phenylpropane samples were examined by mass spectrometry to determine the effect of the concentration of 1-phenylbutane in the reaction mixture on the extent of the rearrangement of ^{13}C label from C-1 to C-2. The crude reaction mixtures were also analyzed by GLC to observe changes in the composition of the mixture of starting materials during the reaction.

Table I. Mass Spectrometric Analysis of 1-Phenylbutane-*1*-^{13}C before and after Reaction with Aluminum Halides in Benzene Solution[a]

Expt[d]	Catalyst	Mol % ^{13}C-labeled Molecules[b] Before reaction	Mol % ^{13}C-labeled Molecules[b] After reaction	Mol % ^{13}C label in C-1[c] Before reaction	Mol % ^{13}C label in C-1[c] After reaction
1	$AlCl_3$	26.3	26.1	24.4	25.3
2	$AlCl_3$	26.3	26.2	24.4	25.1
3	$AlCl_3$	26.3	26.6	24.4	25.0
4	$AlCl_3$	40.9	40.8	37.6	37.9
5	$AlCl_3$	40.9	41.2	37.6	35.9
6	$AlCl_3$	40.9	41.9	37.6	39.4
7	$AlCl_3$	40.9	39.7	37.6	37.0
8	$AlBr_3$	40.2	39.5	37.3	36.2

[a] For molar ratios of reactants and reaction times see Experimental Section. [b] Mole % ^{13}C-labeled molecules was determined from *m/e* 135 ($C_9{}^{13}CH_{14}{}^+$) compared to *m/e* 134 ($C_{10}H_{14}{}^+$). [c] Mole % ^{13}C label in C-1 of 1-phenylbutane was determined from *m/e* 92 ($C_6{}^{13}CH_7{}^+$) compared to *m/e* 91 ($C_7H_7{}^+$). [d] Expt 1–3, CEC 21-110 mass spectrometer, ±2% uncertainty; expt 4–8, CEC 21-491 mass spectrometer, ±5% uncertainty.

As seen in Table III, there was complete or nearly complete scrambling of the label in 1-phenylpropane-*1*-^{13}C between C-1 and C-2 when the starting proportion of 1-phenylbutane in the reaction mixture was less than 0.8 mol of 1-phenylbutane per mol of 1-phenylpropane, and in these reaction mixtures only a small part of the added 1-phenylbutane remained after the treatment with aluminum chloride. The missing 1-phenylbutane was converted into 2-phenylbutane, 1-methylindan (major product), di-*n*-butylbenzenes, and diphenylbutanes, the same products observed when 1-phenylbutane was treated with aluminum chloride and benzene in the absence of 1-phenylpropane.

When the starting amount of 1-phenylbutane was more than 0.8 mol per mol of 1-phenylpropane-*1*-^{13}C, there occurred little or no rearrangement of the isotopic label in 1-phenylpropane-*1*-^{13}C (Table III). These results indicated that either 1-phenylbutane or products formed from it can, in fact, inhibit the isotopic automerization of 1-phenylpropane-*1*-^{13}C catalyzed by aluminum chloride.

Several of the hydrocarbons which are products of the treatment of 1-phenylbutane with aluminum chloride were tested for their effects on the isotopic automerization by adding them singly to reaction mixtures with 1-phenylpropane-*1*-^{13}C as was done with 1-phenylbutane in the preceding experiments. The mass spectrometric data from the recovered samples of 1-phenylpropane-*1*-^{13}C treated in the presence of the various hydrocarbons are presented in Table IV.

In four experiments, the presence of 1,3-diphenylbutane clearly did not inhibit the isotopic automerization of 1-phenylpropane-*1*-^{13}C, as smaller molar quantities of 1-phenylbutane did in the preceding experiments. The 1,3-diphenylbutane added to the reaction mixture actually appeared to *increase* the extent of the isotopic automerization, if it had any effect.

In expt 5 and 6, in which the mole ratio of 1-phenylpropane-*1*-^{13}C:1-methylindan was 1:0.2 and 1:0.8, respectively, complete scrambling of the ^{13}C label between C-1 and C-2 of the side chain in the labeled 1-phenylpropane was observed.

Table II. Treatment of Equimolar Mixtures of 1-Phenylpropane-*1*-^{13}C and 1-Phenylbutane-*1*-^{13}C in Benzene with Aluminum Chloride and Bromide[a]

Expt	Catalyst	Temp, °C	Time, h	1-Phenylpropane ^{13}C label in C-1, mol % Before reaction	1-Phenylpropane ^{13}C label in C-1, mol % After reaction	1-Phenylbutane ^{13}C label in C-1, mol % Before reaction	1-Phenylbutane ^{13}C label in C-1, mol % After reaction
1[b]	$AlCl_3$[c]	85	6.5	41.2	37.5	37.3	37.4
2	$AlCl_3$[c]	85	12	31.4	32.2	37.3	36.2
3	$AlBr_3$[d]	95	12	46.5	46.7	37.6	35.2
4	$AlBr_3$[e]	85	1.2	47.2	33.7	37.3	None recovered
5	$AlBr_3$[e]	95	2.5	47.2	23.6	37.3	None recovered

[a] Mole % ^{13}C label in C-1 of 1-phenylpropane or 1-phenylbutane was determined from *m/e* 92 ($C_6{}^{13}CH_7^+$) compared to *m/e* 91 ($C_7H_7^+$). In expt 2, 4, and 5, CEC 21-110 mass spectrometer was used (±2% uncertainty). [b] In these experiments, a CEC 21-491 mass spectrometer was used (±5% uncertainty). [c] Molar ratio alkylbenzenes:$AlCl_3$:benzene:water = 1:0.5:6:0.1. [d] Molar ratio alkylbenzenes:$AlBr_3$:benzene:water = 1:0.5:4:0.1. [e] Molar ratio alkylbenzenes:$AlBr_3$:benzene:water = 1:1:4:0.2.

Table III. Mass Spectrometric Analysis of 1-Phenylpropane-*1*-^{13}C before and after Reaction with Aluminum Chloride in the Presence of 1-Phenylbutane[a]

Expt	1-Phenylpropane-*1*-^{13}C: 1-phenylbutane, mole ratio of starting mixture	Percentage of ^{13}C in C-1 after reaction[b]
1	1:0	6.9
2	1:0	7.5
3	1:0	7.9
4	1:0.1	6.2
5	1:0.2	6.8
6	1:0.4	6.3
7	1:0.4	6.7
8	1:0.4	6.8
9	1:0.6	8.7
10	1:0.6	7.1
11	1:0.8	12.8
12	1:0.8	12.4
13	1:1.0	9.5
14	1:1.0	15.6
15	1:1.2	11.4
16	1:1.2	10.8
17	1:1.5	12.3
18	1:1.5	11.6

[a] % ^{13}C in C-1 obtained by comparing *m/e* 92 ($C_6{}^{13}CH_7^+$) with *m/e* 91 ($C_7H_7^+$) using the CEC 21-491, ±5% uncertainty. No change in the percentage of ^{13}C-labeled molecules ($C_9{}^{13}CH_{14}^+$) was observed. [b] The percentage of ^{13}C in C-1 in the starting material was 13.4 in all experiments.

The reaction mixture in expt 6 clearly contained more 1-methylindan than the amount formed in the preceding series of experiments with mixtures of 1-phenylpropane-*1*-^{13}C and 1-phenylbutane in which the isotopic rearrangement was completely blocked. This observation means that 1-methylindan is unlikely to be the cause of the inhibition of ^{13}C rearrangement in the presence of 1-phenylbutane. In expt 7, a massive amount of 1-methylindan (1.5 mol per mol of 1-phenylpropane-*1*-^{13}C) only caused partial inhibition of the isotopic automerization. A much smaller amount of 1-phenylbutane (1.0 mol per mol of 1-phenylpropane-*1*-^{13}C) was sufficient to completely block the ^{13}C rearrangement in the preceding experiments.

In a series of six experiments, a mixture of di- and tri-*n*-butylbenzenes (also containing 1-phenylbutane) was added to 1-phenylpropane-*1*-^{13}C and the mixture was treated with aluminum chloride as in the preceding experiments. By comparison of the total number of moles of the mono-, di-, and tributylbenzenes used in these experiments with the moles of 1-phenylbutane (without the others) used in the earlier series of experiments, it was found that the di- and tri-*n*-butylbenzenes inhibit the isotopic automerization in 1-phenylpropane-*1*-^{13}C more than an equal molar quantity of 1-phenylbutane does.[11]

An experiment similar to the preceding ones was performed except that the hydrocarbons added to 1-phenylpropane-*1*-^{13}C were a mixture containing unlabeled 1-phenylpropane, di-*n*-propylbenzenes, and tri-*n*-propylbenzenes. Comparison of the calculated value for the mole percent of monolabeled 1-phenylpropane-^{13}C molecules with the mole percent of molecules labeled in C-1 of the side chain indicated that complete automerization took place.

In an experiment similar to the preceding, except that 2-phenylbutane was the added hydrocarbon, complete rearrangement of the label in the recovered 1-phenylpropane-^{13}C within experimental error occurred.

The results of the experiments involving the treatment of mixtures of 1-phenylpropane-*1*-^{13}C and various hydrocarbons with aluminum chloride clearly indicated that the isotopic automerization was inhibited by the presence of 1-phenylbutane. The inhibition of this reaction required a 1-phenylbutane concentration of ≥0.8 mol per mol of 1-phenylpropane-*1*-^{13}C. The 1-phenylbutane was converted to 1-methylindan and other products. Among these products only the di- and tri-*n*-butylbenzenes were found to have a strong inhibiting effect on the isotopic automerization. In fact, adding di- and tri-*n*-butylbenzenes to the reaction mixture caused greater inhibition than adding the same molar quantity of 1-phenylbutane. Thus, the di- and tri-*n*-butylbenzenes, which are always formed from 1-phenylbutane in the presence of aluminum chloride, may be the major cause of the observed inhibition. An obvious explanation is the known ability of di- and trialkylbenzenes to form relatively unreactive complexes with aluminum halide catalysts. Why the di- and tri-*n*-*propyl*benzenes do not have a comparable inhibitory effect is not clear.

Although no completely satisfactory explanation of the inhibitory effect of 1-phenylbutane on the isotopic automerization of 1-phenylpropane was deduced, further consideration of the failure of 1-phenylbutane itself to undergo appreciable isotopic automerization was more successful. Referring to Scheme I again, in terms of this mechanism, one difference between an isotopic automerization of 1-phenylbutane and 1-phenylpropane would be the 1,2 shift of an *ethyl* group in the 1,2-diphenylalkane carbocations (**4b, 5b**) produced from the former instead of a 1,2-methyl shift in the analogous intermediates (**4a, 5a**) from the latter alkylbenzene. One could hardly expect the difference in the migratory aptitudes of methyl and ethyl groups to be great enough to be responsible for the wide discrepancy in the behavior of the homologous alkylbenzenes in reaction with aluminum halides.[13] However, an approach to ascertaining the magnitude of this difference for this particular system would be to pre-

Table IV. Rearrangement of 1-Phenylpropane-*1*-^{13}C after Treatment with Aluminum Chloride in the Presence of Various Hydrocarbons

Expt	1-Phenylpropane:HC, mole ratio of starting mixture	Hydrocarbon added	^{13}C label in C-1, mol %[a] Before reaction	After reaction
1	1:0.4	1,3-Diphenylbutane	13.4	6.7
2	1:0.6		13.4	8.1
3	1:1.0		13.4	6.1
4	1:1.2		13.4	6.4
5	1:0.2	1-Methylindan	13.4	6.3
6	1:0.8		13.4	6.4
7	1:1.5		13.4	9.2
8	1:0.2	Mixture of mono-, di-, and tri-*n*-butylbenzenes	19.8	11.2
9	1:0.2		19.8	10.1
10	1:0.5		19.8	18.3
11	1:0.5		19.8	22.7
12	1:0.5		19.8	20.9
13	1:0.8		19.8	18.8
14	1:1.2		19.8	22.0
15	1:1.0	Mixture of mono-, di-, and tri-*n*-propylbenzenes		4.4/10.3[b]
16	1:0.8	2-Phenylbutane	19.8	10.8

[a] Mass spectrometric analysis with CEC 21-491, ±2–5% uncertainty. [b] Mol % ^{13}C in C-1/mol % labeled molecules measured after reaction.

pare an isotopically labeled 1,2-diphenylbutane and compare its behavior with that of labeled 1,2-diphenylpropane. 1,2-Diphenylpropane-2-^{14}C has previously been shown to undergo equilibration of the isotope between C-1 and C-2 when treated with aluminum chloride even at room temperature (27 °C), and the 1-phenylpropane produced in the reaction also had the isotope evenly distributed between C-1 and C-2.[14]

1,2-Diphenylbutane-2-^{13}C was synthesized by conventional methods and the percentage of ^{13}C was determined to be 58% by the method of Biemann.[8] Treatment of the labeled diphenylbutane with aluminum chloride in benzene (molar ratio 1:0.5:6, respectively) at reflux for 1 h gave a mixture from which the starting material (mainly) and 1-phenylbutane were isolated by preparative gas chromatography. ^{13}C magnetic resonance analysis of the recovered 1,2-diphenylbutane indicated about 8% ^{13}C was at C-1 and 92% remained at C-2. Mass spectrometric analysis of the 1-phenylbutane produced showed 59% total ^{13}C, with only 10% of the isotope at C-1.[15] A second sample of 1,2-diphenylbutane-2-^{13}C was heated with aluminum chloride in benzene (in the same molar proportions as before) for 7 h. The 1-phenylbutane produced was separated and analyzed by mass spectrometry as before and found to have 8% of the ^{13}C at C-1.

These results showed that only 8–10% rearrangement of ^{13}C occurred in 1,2-diphenylbutane and in the 1-phenylbutane produced from it, whereas under much milder treatment 1,2-diphenylpropane-2-^{14}C gave complete equilibration of the isotopic label between C-1 and C-2 of the diphenylpropane and in the 1-phenylpropane produced from it.[14]

There is another significant factor to be considered in comparing the reaction of 1-phenylpropane and 1-phenylbutane with aluminum halides. In the first step of Scheme I, hydride abstraction from the β carbon opens the way for production of a 1,2-diphenylalkane intermediate, which is essential for allowing the 1,2 shift of a methyl or ethyl group without producing a primary carbocation. In the case of 1-phenylbutane, hydride abstraction may take place at either the 2 carbon or the 3 carbon, producing a secondary carbocation in either event (10 and 11 in Scheme II). The capability of forming the carbocation 11 by attack at the 3 position with subsequent production of a 1,3-diphenylalkane as well as indan and indene derivatives, as outlined in Scheme II, is of course not possible for 1-phenylpropane *except via a primary carbocation.* We proposed that this difference in the structure of 1-phenylpropane and 1-phenylbutane was mainly responsible for the lesser resistance of the higher homologue to structural modification by aluminum chloride, and indeed that the additional reaction capability of 1-phenylbutane might well be an important factor in its failure to show isotopic automerization comparable to that of 1-phenylpropane. Thus

Scheme II

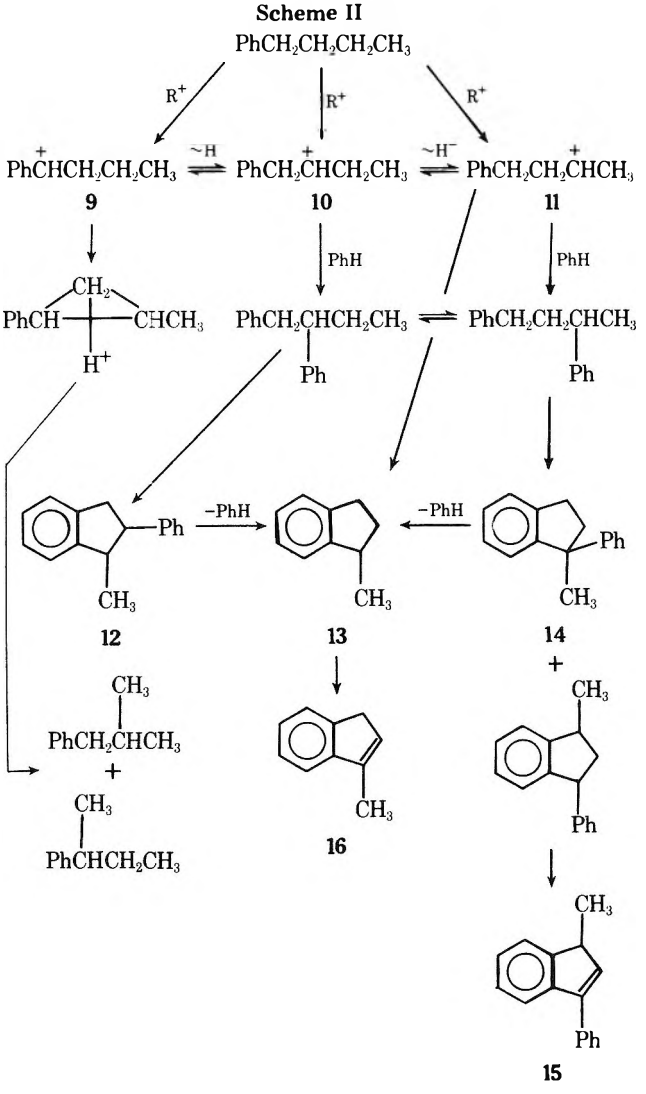


Table V. Products from the Reaction of 1-Phenylbutane in Benzene with Water-Activated Aluminum Chloride[a]

Temp, °C	24			52			81		
Time, h	1	6	13	1	2	4	0.5	1	2
Products	Relative distributions, wt %[b]								
1-Phenylbutane	84	54	50	84	65	60	43	51	50
2-Phenylbutane		Tr	0.5		1.5[c]	3[c]	8[c]	14[c]	14[c]
1-Methylindan							3	5	2
3-Methylindene		0.2	1		1	1	3	9	16
Dibutylbenzenes	16	45.5	48	16	31.5	33.5	39	15	6
Phenylcyclohexane									3
3-Methyl-6-butylindene							0.5	2	6
1,2-Diphenylbutane									0.5
1,3-Diphenylbutane		0.3	0.5	Tr	1	2	2	2	1
1-Methyl-3-phenylindene					Tr	0.5	1.5	2	1.5

[a] Molar ratios, 1-phenylbutane:benzene:aluminum chloride:water = 1:6:1:0.2. [b] Higher molecular weight compounds such as tributylbenzenes were not included in these distributions. [c] Assumed to contain isobutylbenzene, which is not separated by the GLC column.

Table VI. Treatment of 1,3-Diphenylbutane and 1,2-Diphenylbutane in Benzene

Products, %	Starting material 1,3-DPB	1,2-DPB
1-Phenylbutane	17	13
1-Methylindan	35	5
3-Methylindene	7	3
1,2-Diphenylpropane		3
1,2-Diphenylbutane	7	73
1,3-Diphenylbutane	34	3

a careful examination was made of the products formed from 1-phenylbutane and aluminum chloride.

Treatment of 1-phenylbutane with aluminum chloride in benzene at reflux temerature (ca. 82 °C) produced a variety of products that may be classified as (1) transalkylation products (di- and tributylbenzene); (2) rearrangement products (2-phenylbutane and isobutylbenzene); (3) cyclialkylation products (1-methylindan, 3-methylindene, 3-methyl-6-butylindene, 1-methyl-3-phenylindene); and (4) alkylation products (1,2- and 1,3-diphenylbutane). The progress of the reaction was monitored by withdrawing aliquots after various time intervals from reactions run at reflux and at lower temperatures, and analyzing the product aliquots by GLC and mass spectrometry. The results from samples taken after three reaction times at three different temperatures are shown in Table V.

Considering first the reaction at 24 °C, the initial products were dibutylbenzenes, formed by transalkylation (disproportionation).[15] After 13 h these were still the major products, with only traces of rearrangement, cyclialkylation, and alkylation products having appeared. The results of the reaction at 55 °C were similar, but the minor products appeared sooner, as might be expected. At 82 °C the rearrangement and cyclialkylation reactions became much more significant. 1,2-Diphenylbutane was detected for the first time after a 2-h reaction time and 1,3-diphenylbutane was present in slightly larger amount. No 1,1- or 1,4-diphenylbutane was detected.

All of the cyclialkylation products (indans and indenes) in the reaction mixture from the 2-h treatment at 82 °C can be rationalized as derived from the carbocation **11** produced from 1-phenylbutane by hydride abstraction at C-3. For example, 1-methylindan (**13**) and 3-methylindene (**16**) may be produced by the direct cyclization of **11**, or by its alkylation to 1,3-diphenylbutane followed by cyclization to 1-methyl-1-phenylindan (**14**) and dephenylation. 1,3-Diphenylbutane may also be formed from 1,2-diphenylbutane by a 1,2-phenyl shift. The facility of this latter route could be tested. If the two diphenylbutanes are readily interconverted, they should give the same product mixtures when treated separately and identically with aluminum chloride. In Table VI it may be seen that they were not readily interconverted and that they gave quite different mixtures of products when heated with aluminum chloride in benzene at 55 °C. Calculated on the basis of the diphenylbutane converted, 1,2-diphenylbutane gave 48% dealkylation to 1-phenylbutane and 30% cyclization (to 1-methylindan and 3-methylindene), whereas 1,3-diphenylbutane gave 26% dealkylation and 64% cyclization. Although these results did not rule out interconversion of the two diphenylbutanes, it showed that they do not reach an equilibrium composition before secondary reactions set in.

1-Methylindan (**13**) and 3-methylindene (**16**) might also be derived from carbocation **10** via 1,2-diphenylbutane and 1-methyl-2-phenylindan (**12**). However, the small extent of cyclialkylation of 1,2-diphenylbutane to **13** and **16** made this route appear less important than the route from **11** via 1,3-diphenylbutane and 1-methyl-1-phenylindan (**14**).

Conclusions

The difference in the degree of isotopic automerization which 1-phenylpropane-*1*-^{13}C and 1-phenylbutane-*1*-^{13}C undergo in reaction with aluminum chloride can reasonably be ascribed to two main factors. One is the ability of 1-phenylbutane to give a secondary carbocation at the 3 position of the side chain leading to 1,3-diphenylbutane and several indan and indene derivatives by cyclialkylation. Reaction of 1-phenylpropane with aluminum chloride gives 1,2-diphenylpropane, rather than 1,3-diphenylpropane, and subsequent methyl shifts in carbocations derived from the 1,2-diphenylpropane may lead to automerization of isotopic carbon between the 1 and 2 positions of 1-phenylpropane. The second factor is that even though some 1,2-diphenylbutane may be produced from 1-phenylbutane, the ethyl shifts which would lead to automerization do not take place readily, as has been demonstrated by the lack of automerization of 1,2-diphenylbutane-*2*-^{13}C.

Experimental Section

Synthesis of 1-Phenylbutane-*1*-^{13}C. 1-Phenylbutane-*1*-^{13}C was prepared by the method used to prepare 1-phenylpropane-*1*-^{14}C.[16] The reaction of the carbon dioxide produced from barium carbonate-^{13}C (6.4 g, 32 mmol, Monsanto Chemical Co., Mound Lab, A. E. C., 92.9 mol % ^{13}C) with *n*-propylmagnesium bromide gave sodium butanoate-*1*-^{13}C. Acylation of benzene with the sodium butanoate-*1*-^{13}C in the presence of aluminum chloride produced butyrophenone-*1*-^{13}C, which was catalytically (Pd/C) hydrogenated to 1-phenylbutane-*1*-^{13}C. When very vigorous conditions [hydrogen pressure 72 psig, 2.4 g of butyrophenone-*1*-^{13}C, 1.2 g of Pd/C (5%) in 80 mL of glacial acetic acid and 2 mL of perchloric acid (72%) reacting for 24 h] were used, a mixture containing about 75% 1-cyclohexylbutane and 25% 1-phenylbutane-*1*-^{13}C was produced. Better results were ob-

tained with more moderate conditions; no 1-cyclohexylbutane was formed using hydrogen pressure 72 psig, 2.5 g of butyrophenone-*1*-^{13}C, 0.80 g of Pd/C (5%) in 80 mL of glacial acetic acid, and 9 drops of perchloric acid (72%) shaken for 2 h (Parr hydrogenator). Preparative GLC (30% SE-30 on Chromosorb P) afforded the product in 30% yield based on ^{13}C.

Di- and Tri-*n*-propylbenzenes. A sample of 1-phenylpropane (4.0 g, 33 mmol) was treated with aluminum chloride (2.7 g, 20 mmol) at room temperature with stirring for 20 h. The reaction mixture was quenched with water, and the organic product mixture was distilled (boiling range 40–84 °C, 0.1 mm). Analysis of the product mixture (3.1 g) by GLC, using a Varian 600-D instrument with a 10 ft × 0.125 in. (5%) SE-30 column operating at 182 °C, indicated that the product mixture contained 39% (by weight) 1-phenylpropane, 33% di-*n*-propylbenzenes, and 28% tri-*n*-propylbenzenes.

Di- and Tri-*n*-butylbenzenes. A sample of 1-phenylbutane (4.2 g, 31 mmol) was treated with aluminum chloride (2.7 g, 20 mmol) at room temperature with stirring for 12 h. The reaction mixture was quenched with water, and the organic product mixture was distilled (boiling range 45–98 °C, 0.1 mm). Analysis of the product mixture (3.8 g) by GLC under the same conditions as described above indicated that the mixture contained 60% (by weight) 1-phenylbutane, 20% di-*n*-butylbenzenes, and 20% tri-*n*-butylbenzenes.

1,3-Diphenylbutane. A pure sample of 1,3-diphenylbutane prepared by Dr. Ali A. Khalaf[10] was used as the source of this compound.

1-Methylindan. 1-Methylindan was prepared by the method of Khalaf and Roberts.[17]

Treatment of 1-Phenylbutane-*1*-^{13}C with Aluminum Halides. Three samples of 1-phenylbutane-*1*-^{13}C (160 mg, 1.20 mmol, 26.3 mol % monolabeled) were treated with aluminum chloride in the presence of benzene and water in a 1.0:0.5:6.0:0.1 mole ratio, respectively, at reflux (heated by oil bath at 85 °C) for 7 h. The reaction conditions and workup were the same as those used for the 1-phenylpropane-*1*-^{13}C rearrangement.[5] The treated 1-phenylbutane-*1*-^{13}C was recovered by preparative GLC with a Varian Autoprep A-700 instrument on a 12 ft × 0.375 in. SE-52 column at 95 °C giving 78.2 mg (49%), 73.9 mg (46%), and 81.7 mg (51%) in expt 1, 2, and 3, respectively (Table I).

Experiments 4–7 were carried out similarly with samples of 1-phenylbutane-*1*-^{13}C which were 40.9 mol % labeled, and the mole ratios of $C_{10}H_{14}$:$AlCl_3$:C_6H_6:H_2O were varied as follows: expt 4, 1:0.5:6:0.1; expt 5, 1:0.75:6:0.15; expt 6, 1:0.5:6:0; expt 7, 1:0.5:6:0.2. The reaction time was 8 h in expt 5 and 6.5 h in the others. Experiment 8 was carried out in a sealed NMR tube with a 180-mg (1.3 mmol) sample of 1-phenylbutane-*1*-^{13}C, 40.9 mol % monolabeled, which was heated at 95 °C for 9 h with $AlBr_3$, benzene, and water in the mole ratio 1:0.5:4:0.1. The recovery of 1-phenylbutane in expt 4–7 ranged from 22 to 42%. The results of mass spectrometric analysis of expt 1–8 are given in Table I.

The 1-phenylbutane samples recovered from expt 1, 3, 4, 5, and 7 were examined in a Perkin-Elmer R-12 NMR spectrometer. The integrals of the ^1H triplet centered at δ 2.66 ppm and its ^{13}C satellite centered at δ 3.66 ppm showed the same ratio in samples before and after heating with aluminum chloride. The sample heated with aluminum bromide was monitored by NMR after 2.2, 6, and 9 h and showed no change.

Treatment of Mixtures of 1-Phenylpropane-*1*-^{13}C and 1-Phenylbutane-*1*-^{13}C with Aluminum Halides. These experiments were conducted as indicated in Table II.

Treatment of 1-Phenylpropane-*1*-^{13}C with Aluminum Chloride in the Presence of Various Hydrocarbons. These experiments were conducted as described in the text and in Tables III and IV.

Synthesis of 1,2-Diphenylbutane-*2*-^{13}C. Sodium propionate-*1*-^{13}C was prepared by carbonating ethylmagnesium bromide (70 mmol) with $^{13}CO_2$ produced from 5.92 g (30 mmol) of barium carbonate (92 mol % ^{13}C, Monsanto Chemical Co., Mound Lab, A. E. C.) and 20 mL of 85% phosphoric acid according to conventional procedures. The usual workup yielded 2.15 g (75%) of sodium propionate-*1*-^{13}C.

Propiophenone-*1*-^{13}C was synthesized by the reaction of the sodium propionate-*1*-^{13}C (2.15 g, 22 mmol) with benzene (50 mL) in the presence of anhydrous aluminum chloride (12 g, 90 mmol), heating under reflux with stirring for 10 h. The reaction mixture was cooled and decomposed with cold dilute hydrochloric acid and extracted with ether; the ether solution was washed with water and dried over $MgSO_4$. One gram of ordinary propiophenone was added to the ether solution, the ether was distilled at atmospheric pressure, and the residue was distilled to give 3.0 g of propiophenone-*1*-^{13}C, bp 64–65 °C (1 mm). Assuming the distilled product to contain all of the added ordinary propiophenone, the yield of labeled material was 68%.

Propiophenone-*1*-^{13}C (2.8 g, 21 mmol) was allowed to react with 40 mmol of benzylmagnesium chloride. Reduction of the resulting alcohol using hydrogen with Pd/C catalyst in 100 mL of glacial acetic acid and 0.5 mL of perchloric acid at a pressure of 60 psi gave 4.3 g (94%) of 1,2-diphenylbutane-*2*-^{13}C, bp 91–94 °C (0.2 mm). The product was further purified by preparative gas chromatography.

The pure 1,2-diphenylbutane-*2*-^{13}C was analyzed by mass spectrometry and ^{13}C NMR. By comparing the parent peak (P) at *m/e* 210 and the P + 1 peak at *m/e* 211 of the unlabeled compound with the same peaks in the mass spectrum of the labeled compound, and making calculations according to the method of Biemann,[8] the degree of ^{13}C labeling was found to be 58%. The ^{13}C NMR spectrum (Varian HA-100) of unlabeled 1,2-diphenylbutane in dioxane showed four equal peaks at 1.88 (C-2), 2.66 (C-1), 3.28 (C-3), and 6.14 ppm (C-4) relative to dioxane. The labeled product showed only one peak at 1.88 ppm (C-2).

Reaction of 1,2-Diphenylbutane-*2*-^{13}C with Aluminum Chloride. Treatment of the labeled hydrocarbon with anhydrous aluminum chloride in benzene (molar ratio 1:0.5:6, respectively) for 1 h at reflux temperature gave a mixture that consisted mainly of the starting material and 1-phenylbutane. These were separated by preparative GLC.

Recovered 1,2-diphenylbutane showed two peaks in the ^{13}C NMR spectrum with relative intensities corresponding to 92% at C-2 and 8% at C-1.

By comparing the P and P + 1 peaks in the mass spectrum of the 1-phenylbutane isolated from the reaction with the same peaks in the spectrum of ordinary (unlabeled) 1-phenylbutane, it was possible to determine that the total ^{13}C mol % was 59, and by comparing the *m/e* 91 and 92 peaks[9] it was shown that 5.7 mol % of ^{13}C was at C-1, corresponding to 9.7% rearrangement.

The experiment was repeated using the same proportion of 1,2-diphenylbutane-*2*-^{13}C, benzene, and aluminum chloride, but heating for 7 h under reflux. Using the same technique and calculations as before, the 1-phenylbutane produced was found to contain 4.5 mol % ^{13}C at C-1, corresponding to 7.6% rearrangement.

Reaction of 1-Phenylbutane with $AlCl_3$–H_2O in Benzene. 1-Phenylbutane (13.4 g, 0.10 mol), benzene (47 g, 0.60 mol), $AlCl_3$ (13.3 g, 0.10 mol), and water (0.36 mL, 0.020 mo) were heated and stirred under reflux for 8 h. The cooled reaction mixture was quenched with cold dilute hydrochloric acid and extracted with ether. The ether extract was dried over K_2CO_3 and distilled to remove the ether. The residue was distilled through a 2-cm Vigreux column. Three fractions were collected: (1) 0.7 g, bp 80–160 °C; (2) 6.2 g, bp 169–180 °C; (3) 0.5 g, bp 130–170 °C (0.2 mm); residue, 2.4 g. The distillate fractions were separated further by preparative GLC using a 6 ft × 0.25 in. 10% SE-30 silicone column and the components, identified by NMR and mass spectrometry, with approximate yields, were as follows: 1-phenylpropane (4%), 2-phenylbutane (9%), 1-phenylbutane (59%), 1-methylindan (8%), 3-methylindene (4%), phenylcyclohexane (4%), 1,2-diphenylbutane (1.5%), 1,3-diphenylbutane (3%), and 1-methyl-3-phenylindene (1.5%).

Experiments were then performed in which 2-mL aliquot samples were withdrawn from the reaction mixtures after stated time intervals and analyzed by GLC on a 6 ft × 0.125 in. 10% SE-30 and a 5 ft × 0.125 in. 10% UCON column. The results of reactions at three different temperatures are presented in Table V.

Registry No.—Barium carbonate-^{13}C, 51956-33-3; sodium butanoate-*1*-^{13}C, 62601-04-1; butyrophenone-*1*-^{13}C, 62601-05-2; sodium propionate-*1*-^{13}C, 62601-06-3; propiophenone-*1*-^{13}C, 62601-07-4; 1,2-diphenylbutane-*2*-^{13}C, 62601-08-5; 1-phenylbutane-*1*-^{13}C, 62601-09-6; 1-phenylpropane-*1*-^{13}C, 62601-10-9; 1-phenylbutane, 104-51-8; 1,3-diphenylbutane, 1520-44-1; 1,2-diphenylbutane, 5223-59-6.

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Nucleophilic Substitution in the Side Chain of Five-Membered Heterocycles. 3. Reactions of Heterocyclic Aldehydes with Aniline and with Benzoylmethylenetriphenylphosphorane

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The rate constants for the reactions of five-membered heteroaromatic aldehydes with aniline in acetonitrile (Schiff reaction) and with benzoylmethylenetriphenylphosphorane in methanol (Wittig reaction) were measured in order to attempt structure–reactivity correlations. The observed reactivity sequence (2-furyl > phenyl > 2-thienyl > 2-pyrrolyl) is the same as previously found in other substitutions at the carbonyl group. The electron-donating character of the heteroatoms in the Schiff reaction is proved by the Hammett treatment of the data. However, extension of this treatment to other reactions at the carbonyl group does not give constant σ_{het} values. Application of the Taft–Pavelich eqation points out a dependence of the rate of reaction on polar and steric effects of heteroaromatic rings. Information from Hammett and Taft–Pavelich equations, however, is not unequivocal owing to inherent features of both free-energy relationships.

In previous articles of this series kinetic data for the reactions of arylmethyl chlorides[1] and arenesulfonyl chlorides[2] with aniline were reported, in order to correlate the reactivity of five-membered heterocycles with that of benzene derivatives and to attempt structure–reactivity correlations. However, no generalization was drawn owing to different behavior of heterocyclic compounds in different kinds of reactions.

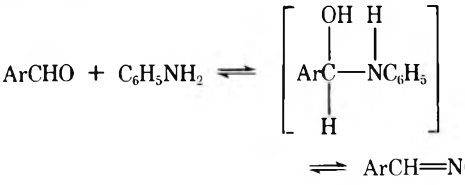
In fact, the reactivity sequence (2-furyl > 2-thienyl > phenyl) observed for the reaction of arylmethyl chlorides with aniline[1] appears to be in agreement with the polarity of heterocycles, given by σ^* values,[3] while the rate sequence for the reaction of arenesulfonyl chlorides with aniline[2] (phenyl > 2-furyl > 2-thienyl) suggests that the conjugative effect, described by σ^+ values, appears to be prevailing.[4,5]

Moreover, a different reactivity sequence (2-furyl > phenyl > 2-thienyl) is observed in some nucleophilic substitutions at the carbonyl group, as in the reaction of arylcarbonyl chlorides with aniline,[6] of aryl chloromethyl ketones with triethyl phosphite,[7] in the alkaline hydrolysis of esters[3] and in the reduction of aryl methyl ketones by sodium borohydride.[8] This fact might formally derive from the balance between the opposite electronic effects in the five-membered heterocycles (−I, +M), even if the role of steric factors in some of these reactions cannot be neglected.[3,9]

To verify the specificity of this sequence for reactions at the carbonyl group, we here report kinetic data relative to the reactions of heterocyclic aldehydes with aniline (Schiff reaction), and with benzoylmethylenetriphenylphosphorane (BMTPP) (Wittig reaction). In this paper we intend also to rationalize the data on nucleophilic substitutions at the carbonyl group in the side chain of five-membered heterocycles, using free-energy relationships.

Results

Reactions of Aldehydes with Anilines. The Schiff base formation from aromatic aldehydes and amines (reaction 1) is a well-known two-step addition–elimination reaction, in which the rate-determining step depends on the aromatic ring structure and on experimental conditions (solvent, pH).[10-12]



Ar = 2-C_4H_3S, 2-C_4H_3NH, *p*-$(CH_3)_2NC_6H_4$, *p*-$CH_3OC_6H_4$, *p*-$CH_3C_6H_4$, *p*-ClC_6H_4, *p*-$O_2NC_6H_4$

Acetonitrile was chosen as a solvent because, being dipolar, it allows an appreciably fast kinetics in the absence of catalyst; moreover, being aprotic, it prevents the hydrolysis of the Schiff bases, a phenomenon that would not give quantitative yields.[13]

The reaction was followed by monitoring the UV absorbance of the Schiff base (see Experimental Section). The kinetics is second order overall, first order with respect to each reactant, as expected for an uncatalyzed reaction, according to the simple rate law

$$\text{rate} = k_2[\text{aldehyde}][\text{nucleophile}] \quad (2)$$

Rate constants at 25 °C are reported in Table I, showing that the reactivity sequence is the following: phenyl > 2-thienyl > 2-pyrrolyl. The k_2 value for 2-furaldehyde is not re-

Table I. Second-Order Rate Constants for the Reactions of RCHO with Aniline in Acetonitrile at 25 °C

Registry no.	R	10^5k_2, L mol^{-1} s^{-1} [a]
100-52-7	C_6H_5	72.0
104-88-1	p-ClC_6H_4	45.8
104-87-0	p-$CH_3C_6H_4$	13.9
123-11-5	p-$CH_3OC_6H_4$	7.34
555-16-8	p-$O_2NC_6H_4$	4.49
98-03-3	2-C_4H_3S	2.64
1003-29-8	2-C_4H_3NH	0.0452
100-10-7	p-$(CH_3)_2NC_6H_4$	0.0254

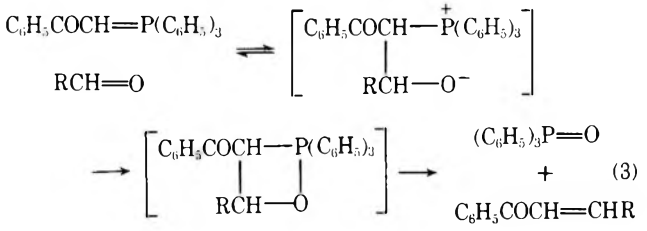
[a] Maximum error ±7%.

ported, as the Schiff base is not formed quantitatively, owing to the occurrence of competitive and consecutive reactions.[14]

The Hammett plot for para-substituted benzaldehydes is not linear, showing a rate maximum near the point for benzaldehyde (Figure 1).

This behavior, already observed for the reactions of benzaldehydes with n-butylamine in methanol,[10] with aniline in water (pH 6.1),[12] and with p-toluidine in ethanol and in benzene,[15] is due to the influence of substituents on both steps (reaction 1): electron-donating groups (ρ positive) decrease the nucleophilic attack rate (first step), while electron-withdrawing ones (ρ negative) reduce the carbinolamine dehydration (second step); thus, these effects cause a variation in the rate-limiting step.

Reactions of Aldehydes with BMTPP. The synthesis of olefins from carbonyl derivatives and phosphorus stable ylides (Wittig reaction) is a nucleophilic substitution in which the rate-determining step is the attack of a carbanion to the carbonyl carbon atom, followed by the stepwise formation of a betaine and a four-membered intermediate (eq. 3).[16]



(3)

R = 2-C_4H_3O, 2-C_4H_3S, 2-C_4H_3NH, C_6H_5, c-C_6H_{11}

BMTPP is a stable ylide, easily workable, and for this reason it was chosen as a reagent. The reaction, carried out in methanol, yields chalcone analogues quantitatively and was followed by titration of the residue ylide in the presence of an indicator (see Experimental Section). In all cases, an overall second-order kinetics, first order with respect to each reactant (eq 2), was observed. In Table II the rate constants and the activation parameters are reported.

The reactivity sequence (2-furyl > phenyl > 2-thienyl > 2-pyrrolyl) is analogous to that already observed for other nucleophilic reactions at the carbonyl group.[3,6-8]

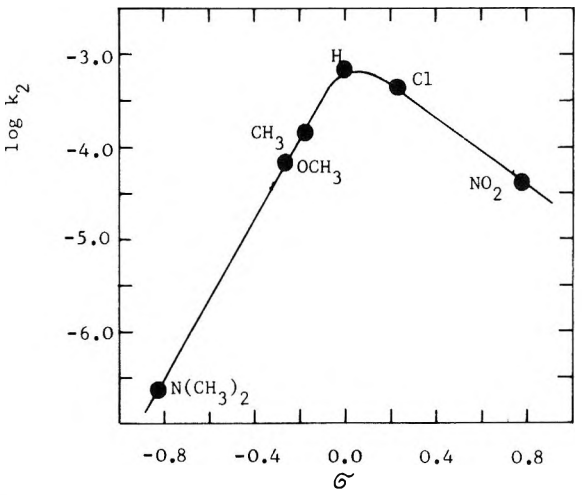


Figure 1. Hammett plot for the reactions of para-substituted benzaldehydes with aniline in acetonitrile at 25 °C.

Discussion

Application of the Hammett Equation. Application of the Hammett equation to equilibrium or reactivity data of five-membered heterocycles provides information on the electronic effects of heteroatoms.[5,17] In fact, if we consider the heterocycle as a substituted benzene, σ_{het} constants for the replacement of a CH=CH group in the benzene ring by the heteroatom can be calculated by eq 4, using the appropriate ρ and log k_0 values:

$$\sigma_{het} = (\log k - \log k_0)/\rho \quad (4)$$

The electron-donating effect of the heteroatom is evident in the Schiff reaction,[18] as shown by the negative $\sigma_{2\text{-}S}$ and $\sigma_{2\text{-}NH}$ values (Table III).

Actually, in the case of five-membered rings, variable σ_{het} values can be derived from other reaction systems,[19] while a high degree of consistency of σ_{het} from pyridine derivatives is observed.[5]

The Hammett treatment was also applied to the available data for nucleophilic substitutions at carbonyl group. Results reported in Table III show the variability of σ_{het} values, also in the case of reactions at the carbonyl group only. Particularly, the 2-furyl group acts as benzene ($\sigma_{2\text{-}O}$ zero) in reactions 2 and 5, and as an electron-withdrawing group in 3, 4, and 6; 3-furyl and 3-thienyl groups show strong resemblances with benzene, except in reaction 5; σ_{het} for 2- and 3-pyrrolyl groups, instead, appear to be more consistent.

The wide variability of σ_{het} can be ascribed to the polarizability of five-membered heterocycles, whose ability to induce through-conjugation is well known.[20] Hence some authors[8,21] used the Yukawa–Tsuno equation (5) to rationalize reactivity data:

$$\log k/k_0 = \rho[\sigma_{het} + r(\sigma^+_{het} - \sigma_{het})] \quad (5)$$

However, while σ^+_{het} values are constant, as is proven by extended selectivity treatment,[22] the choice of a particular set

Table II. Second-Order Rate Constants and Activation Parameters for the Reactions of RCHO with BMTPP in Methanol

Registry no.	R	10^3k_2, L mol^{-1} s^{-1} [a] 35 °C	45 °C	60 °C	$\Delta H^{\ddagger}$, kcal mol^{-1}	$-\Delta S^{\ddagger}$, cal mol^{-1} K^{-1}
98-01-1	2-C_4H_3O	2.90	5.14	9.95	9.4	39.7
	C_6H_5	1.04	2.06	4.26	10.8	37.3
	2-C_4H_3S	0.54	0.97	2.56	12.2	34.2
2043-61-0	c-C_6H_{11}	0.081	0.18	0.48	13.9	29.4
	2-C_4H_3NH	0.023	0.038	0.12	13.1	37.6

[a] Maximum error ±6%.

Table III. Application of the Hammett Equation to Reactions at the Carbonyl Group and Substituent Constants for Heteroatoms in Five-Membered Rings

Reaction or equilibrium	X[a]	r[b]	ρ[c]	Log k_0[c] (or pK_0)	σ_{het}[d] 2-O	3-O	2-S	3-S	2-NH	3-NH	Ref[e]
1. $XC_6H_4CHO + C_6H_5NH_2$[f] (acetonitrile, 25 °C)	1, 2, 3, 4	0.999	4.18 (0.14)	−3.11 (0.06)			−0.35		−0.83		*f*
2. $XC_6H_4CHO + OH^-$[g] (pK, water, 25 °C)	1, 2, 3, 5, 6, 7, 8, 9, 10, 11, 12	0.994	−2.76 (0.05)	14.98 (0.10)	0.08		−0.085		<−0.73		*h*
3. $XC_6H_4COCH_2Cl + (C_2H_5O)_3P$[i] (benzene, 40 °C)	1, 2, 3, 5, 6	0.997	1.88 (0.08)	−4.13 (0.03)	0.43	0.01	−0.16	−0.01			*j*
4. $XC_6H_4COCl + C_6H_5NH_2$[k] (benzene, 25 °C)	1, 2, 3, 5,7, 13, 14, 15	0.978	1.42 (0.12)	−1.31 (0.03)	0.31	−0.05	−0.20	−0.04			*l*
5. $XC_6H_4COCH_3 + NaBH_4$[m] (2-propanol, 30 °C)	1, 2, 3, 4, 5, 7, 9, 13, 14, 16, 17, 18	0.987	2.84 (0.15)	−2.75 (0.06)	0.06	−0.16	−0.16	−0.11	−0.79	−0.93	*n*
6. $XC_6H_4COOC_2H_5 + OH^-$[o] (62% aq acetone, 25 °C)	1, 2, 6, 7, 10, 16, 19	0.999	2.37 (0.06)	−2.51 (0.03)	0.27	0.03	0.01	0.00	−0.58[q]	−0.94[q]	*p*

[a] Key for X substituent: 1, H; 2, *p*-CH_3; 3, *p*-OCH_3; 4, *p*-$N(CH_3)_2$; 5, *p*-Cl; 6, *p*-NO_2; 7, *m*-CH_3; 8, *m*-OCH_3; 9, *m*-Cl; 10, *m*-NO_2; 11, *m*-CN; 12, *p*-CN; 13, *p*-Br; 14, *m*-Br; 15, *m*-I; 16, *p*-NH_2; 17, *p*-F; 18, *m*-F; 19, *m*-NH_2. [b] Correlation coefficient. [c] Standard deviation of the estimate in parentheses. [d] Standard deviation of σ_{het} ranges from 0.05 to 0.08. [e] References for reactivity data of heterocyclic compounds. [f] This work. [g] W. J. Bover and P. Zuman, *J. Chem. Soc., Perkin Trans. 2*, 786 (1973). [h] W. J. Scott, W. J. Bover, K. Breatin, and P. Zuman, *J. Org. Chem.*, **41**, 1952 (1976). [i] A. Arcoria and S. Fisichella, *Tetrahedron Lett.*, 3347 (1971). [j] Reference 7. [k] R. A. Benkeser, C. E. DeBoer, R. E. Robinson, and D. M. Sauve, *J. Am. Chem. Soc.*, **78**, 682 (1956). [l] Reference 6. [m] Reference 8, 9. [n] Reference 8. [o] E. Tommila and C. N. Hinshelwood, *J. Chem. Soc.*, 1801 (1938). [p] Reference 3; M. K. A. Khan and K. J. Morgan, *Tetrahedron*, **21**, 2197 (1965). [q] Reported from ref 8.

Table IV. Data Used and Results of Correlations with Equation 6

Equilibrium or reaction	X σ^*[c]	C_6H_5 0.60	2-C_4H_3O 1.08	3-C_4H_3O 0.65	2-C_4H_3S 0.93	3-C_4H_3S 0.65	r[a]	ρ[b]	Log k_0[b] (or pK_0)
pK_a XCOOH (water, 25 °C)[c]		4.21	3.16	3.95	3.53	4.10	0.988	−2.04 (0.18)	5.39 (0.15)
pK_a $XB(OH)_2$ (water, 25 °C)[d]		8.83	7.88	8.65	8.11	8.77	0.993	−2.00 (0.14)	10.0 (0.11)
pK_a XSO_2NHR (50% aq ethanol, 20 °C)[e]									
R = H		11.33	10.39		10.76	11.20	0.995	−1.87 (0.13)	12.44 (0.11)
R = C_6H_5[f]		9.98	9.02		9.41	9.83	0.982	−2.05 (0.16)	11.28 (0.18)
R = $CH_2C_6H_5$		12.53	11.54		11.93	12.47	0.997	−2.05 (0.12)	13.79 (0.10)
Rearrangement $XCH(OH)CH{=}CHCH_3$[g]									
(log k_2 rel, 60% aq dioxane, 30 °C)		0.00	1.95		1.54		0.994	4.16 (0.46)	−2.45 (0.41)
Isomerization *cis*-$XCH{=}CHC_6H_5$[h]									
(log k_1, decalin, 170 °C)		−2.21	−0.98		−1.32		0.999	2.58 (0.10)	−3.75 (0.09)
Reaction $XCH_2Cl + C_6H_5NH_2$[i]									
(log k_3, acetonitrile, 50 °C)		−4.39	−3.61		−3.75		0.990	1.68 (0.24)	−5.38 (0.21)
(log k_3, benzene, 50 °C)		−6.58	−4.78		−5.46		0.997	3.69 (0.27)	−8.82 (0.24)
Alkaline hydrolysis $XCONHC_6H_5$[j]									
(log k_1, 76% aq ethanol, 100 °C)		−4.59	−4.00	−4.56	−4.24	−4.51	0.994	1.19 (0.08)	−5.31 (0.06)
Rearrangement XCOCOY[k]									
(log k_2, 67% aq dioxane, 50 °C)			−4.00	−3.73	−3.43	−2.91	0.995	1.59 (0.11)	−5.85 (0.17)
($\sigma_X^* + \sigma_Y^*$)			(1.20)	(1.30)	(1.53)	(1.86)			

[a] Correlation coefficient. [b] Standard deviation of the estimate in parentheses. [c] Reference 3. [d] B. P. Roques, D. Florentin, and M. Callanquin, *J. Heterocycl. Chem.*, **12**, 195 (1975). [e] A. Ballistreri, E. Maccarone, and G. Musumarra, *J. Chem. Soc., Perkin Trans. 2*, 984 (1977). [f] The correlation includes pK_a of the following 5-Y-2-$C_4H_2SO_2NHC_6H_5$ (Y, pK_a,[e] σ^*[c]): CH_3, 9.65, 0.84; Cl, 8.84, 1.26; Br, 8.84, 1.29; NO_2, 7.68, 1.65. [g] E. A. Braude and J. S. Fawcett, *J. Chem. Soc.*, 4158 (1952). [h] G. Scarlata and M. Torre, *J. Heterocycl. Chem.*, **13**, 1193 (1976). [i] Reference 1. [j] Reference 26. [k] G. P. Nilles and R. D. Schuetz, *J. Org. Chem.*, **36**, 2489 (1971).

of σ_{het} values, which is of doubtful general validity, can undergo some criticism.[5]

For this reason, combination of electronic effects as in eq 5 does not appear to be formally appropriate in order to interpret the reactivity data, and we believe that a different approach is necessary to rationalize the behavior of five-membered heterocycles in nucleophilic substitutions at the carbonyl group.

Application of the Taft Equation. Ten Thije and Janssen[3] pointed out in 1965 that failure of the Hammett equation might be expected for 2-substituted five-membered rings, owing to the proximity of the substituent to the side chain. Consequently, they proposed to correlate the data by the Taft equation (6)

$$\log k/k_0 = \rho^*\sigma^* \quad (6)$$

and derived σ^* values for the heterocycles, following the standard conditions originally suggested by Taft.[23]

Recently, Tomasik and Johnson restricted the derivation of σ values for heteroatoms in such rings to cases where steric interactions with the reaction site appear to be absent.[5] The different geometry of five-membered rings can in fact influence differently the stability of the transition state. Specifically, in substitutions at the carbonyl group, the carbon atom which is sp^2 planar trigonal in the initial state becomes a sp^3 tetrahedral carbon atom in the transition state. The bond angles are drastically reduced from about 120° to about 109°, and the reaction rate will then be decreased because of the

Table V. Data Used and Results of Correlations with Equation 7

Reaction or equilibrium	X	C_6H_5	2-C_4H_3O	3-C_4H_3O	2-C_4H_3S	3-C_4H_3S	2-C_4H_3-NH	ρ^a	δ^a	Log k_0^a (or pK_0)
	σ^*[b]	0.60	1.08	0.65	0.93	0.65	0.46[c]			
	E_s[b]	−2.55	−3.16	−2.71	−3.39	−2.73	−3.88[d]			
1. XCHO + $C_6H_5NH_2$ (log k_2, acetonitrile, 25 °C)[e]		−3.14			−4.58		−6.34	1.39	2.26	1.79
2. XCHO + BMTPP (log k_2, methanol, 35 °C)[e,f]		−2.98	−2.54		−3.27		−4.64[g]	2.58 (0.30)	0.72 (0.14)	−3.03 (0.30)
3. XCHO + OH^- (pK, water, 25 °C)[h]		14.9	14.75		15.21		17	−2.28 (0.13)	−1.30 (0.09)	13.00 (0.20)
4. $XCOCH_2Cl$ + $(C_2H_5O)_3P$ (log k_2, benzene, 40 °C)[i]		−4.05	−3.31	−4.10	−4.43	−4.15		4.12 (0.09)	2.10 (0.06)	−1.09 (0.12)
5. XCOCl + $C_6H_5NH_2$ (log k_2, benzene, 25 °C)[j,k]		−1.20	−0.876	−1.39	−1.59	−1.36		1.52 (0.12)	1.03 (0.11)	0.49 (0.23)
6. XCOCl + m-$NO_2C_6H_4NH_2$ (log k_2, benzene, 20 °C)[l]		−3.49	−3.24[m,n]	−3.80[m,n]		−3.69[n,o]		1.18 (0.09)	1.01 (0.06)	−1.55 (0.10)
7. $XCOCH_3$ + $NaBH_4$ (log k_2, 2-propanol, 50 °C)[p,q]		−2.19	−1.99	−2.53	−2.51	−2.39	−4.45	2.55 (0.14)	0.98 (0.04)	−1.54 (0.09)

[a] Standard deviation of the estimate in parentheses. [b] Reference 3. [c] Obtained from the equation $\sigma^* = (pK_a - pK_{a_0})/\rho^* = (4.45 - 5.39)/-2.04$ (see Table IV). [d] Obtained by interpolation from the data of reaction 2 by the equation $E_s = (\log k_2 - \rho^*\sigma^* - \log k_0)/\delta$. [e] This work. [f] The correlation includes log k_2 for the reaction of c-$C_6H_{11}CHO$ (−4.09,[e] $\sigma^* = -0.15$, $E_s = -0.79$). [g] Not included in correlation. [h] W. J. Scott, W. J. Bover, K. Breatin, and P. Zuman, *J. Org. Chem.*, **41**, 1952 (1976); the correlation includes the pK of 5-Br-2-C_4H_2SCHO (14.64, $\sigma^* = 1.29$,[b] $E_s = -3.58$[b]). [i] Reference 7. [j] Reference 6. [k] The correlation includes log k_2 of the following 5-Y-2-C_4H_2SCOCl (Y, log k_2, σ^*[b], E_s[b]): CH_3, −1.99, 0.84, −3.58; Cl, −1.23, 1.26, −3.53; NO_2, −0.374, 1.65, −3.19. G. Alberghina, A. Arcoria, S. Fisichella, and G. Scarlata, *Gazz. Chim. Ital.*, **103**, 319 (1973). [l] The correlation includes log k_2 of the following XCOCl (X, log k_2, σ^*, E_s): CH_3, −1.91, 0.0, 0.0; n-C_3H_7, −2.02, −0.115, −0.36; n-C_4H_9, −2.17, −0.13, −0.39; i-C_4H_9, −2.42, −0.125, −0.93; $C_6H_5CH_2$, −1.68, 0.215, −0.38; $CH_3CH{=}CH$, −2.32, 0.36, −1.63; $ClCH_2$, −0.38, 1.05, −0.24; Cl_3C, −0.558, 2.65, −2.06. H. S. Venkataraman and C. N. Hinshelwood, *J. Chem. Soc.*, 4977 (1960). [m] A. Arcoria, S. Fisichella, G. Scarlata, and D. Sciotto, *J. Org. Chem.*, **39**, 3025 (1974). [n] Interpolated at 20 °C from activation parameters. [o] A. Arcoria and S. Fisichella, *J. Org. Chem.*, **38**, 3774 (1973). [p] Reference 8. [q] The correlation includes log k_2 of the following $XCOCH_3$ (X, log k_2, σ^*, E_s): CH_3, −1.68, 0.0, 0.0; C_2H_5, −1.95, −0.10, −0.07; i-C_3H_7, −2.27, −0.19, −0.47; $C_6H_5CH_2$, −1.49, 0.215, −0.37; $C_6H_5(CH_3)CH$, −2.32, 0.11, −1.19; $(C_6H_5)_2CH$, −2.40, 0.405, −1.76. H. C. Brown, R. Bernheimer, and K. J. Morgan, *J. Am. Chem. Soc.*, **87**, 1280 (1965); ref 9.

back strain in the transition state, due to the bulky adjacent group.

The Taft–Pavelich equation (7), which is widely used,[24] takes into account both polar (σ^*) and steric (E_s) effects, and appears to be a better model to relate the substrate structure to the carbonyl group reactivity:[25]

$$\log k/k_0 = \rho^*\sigma^* + \delta E_s \qquad (7)$$

Equation 6 was applied successfully to equilibria or reaction series in which steric hindrances are negligible, as dissociation of carboxylic acids,[3] alkaline hydrolysis of arylanilides,[26] and reactions of arylmethyl chlorides with aniline;[1] the reported results are shown in Table IV, together with other data elaborated by us.

The data for seven more reactions, for which eq 6 was unsuccessfully attempted, were satisfactorily interpreted according to eq 7, and, whenever homogeneous data were available, this equation was also successfully applied in the case of aliphatic and unsaturated compounds. Data used and results of correlations are reported in Table V.

As eq 7 correlates a wide range of data for reactions at the carbonyl group, the behavior of five-membered rings might be discussed in general terms on the basis of steric and polar effects.[27] The observed reactivities, separated from the contribution due to steric effect ($\log k_2 - \delta E_s$), are in agreement with the polar effect sequence (Figure 2).

In particular, the 2-thienyl ring, which seems to behave as an electron-donating group using the Hammett treatment, appears to be an electron-withdrawing group as suggested by its σ^* values. However, a limitation to this interpretation is due to the fact that E_s values for aromatic and unsaturated

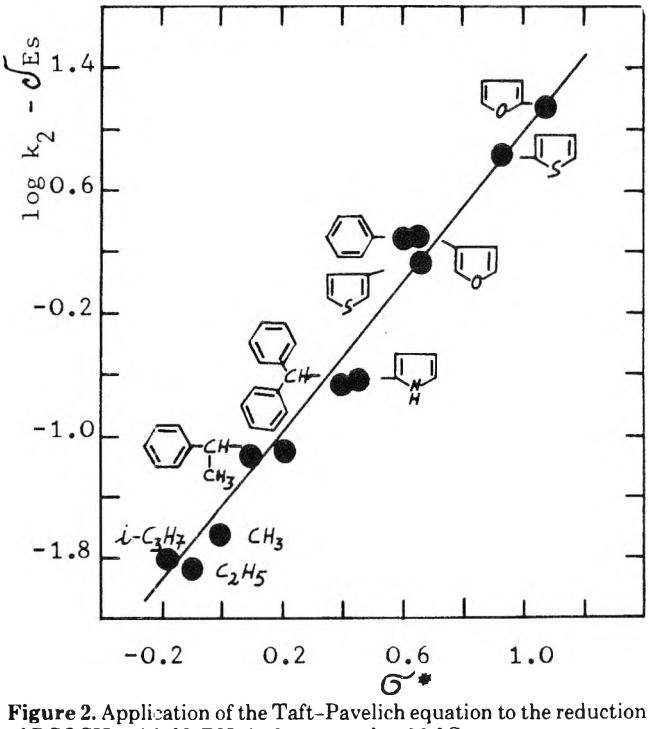


Figure 2. Application of the Taft–Pavelich equation to the reduction of $RCOCH_3$ with $NaBH_4$ in 2-propanol at 50 °C.

groups, as well as for heterocyclic five-membered rings, include a conjugative contribution, as pointed out by Taft.[23]

In conclusion the Hammett treatment neglects the contribution due to the steric effects, while the Taft–Pavelich equation, in this case, includes conjugative effects in the steric

parameter. A better model might be represented by Charton's equation (8),[25] which takes into account independent variations of inductive (σ_I), resonance (σ_R), and steric (υ) effects:

$$\log k = \alpha\sigma_I + \beta\sigma_R + \psi\upsilon + h \quad (8)$$

Unfortunately, its application, which might provide the "weight" of each effect on the observed reactivity, is not possible at the moment owing to the lack of appropriate σ_I, σ_R, and υ values for five-membered rings.

Experimental Section

Reagents and Solvents. Aldehydes and aniline were commercial products, purified by distillation or crystallization. Solvents (acetonitrile and methanol, RPE Carlo Erba) were used without further purification.

Benzoylmethylenetriphenylphosphorane (BMTPP) was obtained by treating phenacyltriphenylphosphonium bromide with 10% aqueous sodium carbonate following the procedure already described,[28] mp 178–180 °C.

Kinetic Procedure. A. Schiff Reaction. Standard solutions of aldehyde and aniline in acetonitrile (10 mL) were mixed at 25 °C. Initial concentrations varied in the range 0.025–0.50 mol L^{-1}. At intervals, 1 mL of the reaction solution was placed in a 100-mL volumetric flask and the volume made up with acetonitrile. The optical density and the molar extinction coefficient of the Schiff bases were measured at the appropriate wavelength[29] and their concentrations calculated. The reaction follows a second-order kinetics to at least 70% completion. k_2 constants reported in Table I are average values from at least four determinations at different reagent concentrations.

B. Wittig Reaction. Standard solutions (10 mL) of ylide (0.02 mol L^{-1}) and aldehyde (0.10 mol L^{-1}) in methanol were mixed in stoppered flasks and kept at constant temperature. At intervals the flask was cooled with an ice bath and part of hydrochloric acid necessary to titrate the residue ylide added. Some drops of bromophenol blue (1/1000 v/v alcohol solution) were then added and the ylide titrated with HCl until greenish color was observed. In all cases the reactions followed a second-order kinetics. The rate constants were calculated by

$$k_2 = 2.303/4at \log[(5a - x)/5(a - x)] \quad (9)$$

where a is the ylide concentration (0.02 mol L^{-1}) and x the reacted amount at time t.

Reaction Products. Schiff Bases. Equimolar amounts of aldehyde and aniline (0.10 mol) were allowed to react in acetonitrile (100 mL) at room temperature for 6–48 h, depending on the aldehyde reactivity. Acetonitrile was evaporated and the residue distilled under vacuum or crystallized from petroleum ether (bp 30–60 °C) or absolute ethanol, yield >90%. RCH=NC_6H_5 [R, bp (mmHg) or mp]: C_6H_5, 50–51 °C;[30] p-$CH_3C_6H_4$, 150 °C (0.2), 43 °C;[31] p-$CH_3OC_6H_4$, 176 °C (1.0), 63 °C;[31] p-$(CH_3)_2NC_6H_4$, 99 °C;[31] p-ClC_6H_4, 63 °C;[31,32] p-NO_2, 90 °C;[31,32] 2-C_4H_3S, 109–110 °C (0.1);[33] 2-C_4H_3NH, 92–93 °C.[34]

Chalcones. Solutions of BMTPP and aldehyde in methanol were allowed to react at 50 °C for about 24 h. After evaporation of the solvent the residue was distilled or crystallized from petroleum ether or absolute ethanol, yield > 80%. RCH=$CHCOC_6H_5$ [R, bp (mmHg) or mp]: C_6H_5, 57–58 °C;[35] 2-C_4H_3O, 171 °C (3);[36,37] 2-C_4H_3S, 58–59 °C;[37] 2-C_4H_3NH, 138–139 °C;[38] c-C_6H_{11}, 167–168 °C.[39]

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Registry No.—Aniline, 62-53-3; BMTPP, 859-65-4.

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Cyclizations to Lactones. ^{18}O Mechanism Study

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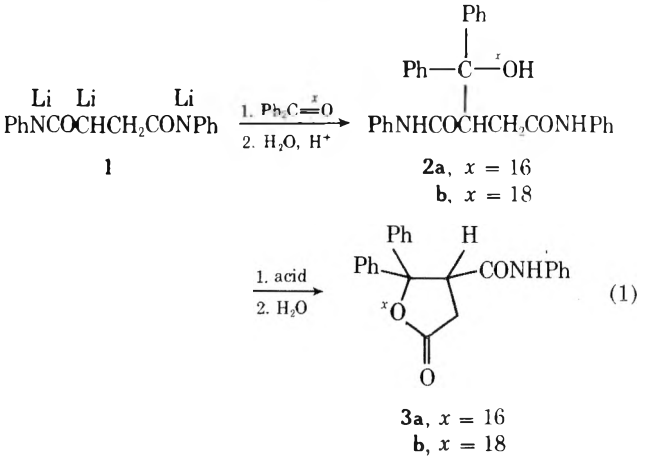
^{18}O was incorporated into the hydroxyl oxygen of 2-(1,1-diphenyl-1-hydroxymethyl)succinanilide (2), which was subsequently treated with concentrated sulfuric acid (a), refluxing acetic acid (b), and methanolic hydrogen chloride (c). The resulting cyclization product, 4,4-diphenyl-3-carboxanilidebutanolactone (3), exhibited complete elimination (a) or retention (b and c) of ^{18}O. These results indicate that both a carbonium ion mechanism (a) or an intramolecular (A-2) acyl substitution mechanism (b and c) can account for the formation of lactone 3.

Benzophenone and 1,3,6-trilithiosuccinanilide (**1**) were condensed to afford **2a**,[1] which was subsequently treated with refluxing acetic acid, methanolic hydrogen chloride, or cold concentrated sulfuric acid (eq 1). All three acid systems ef-



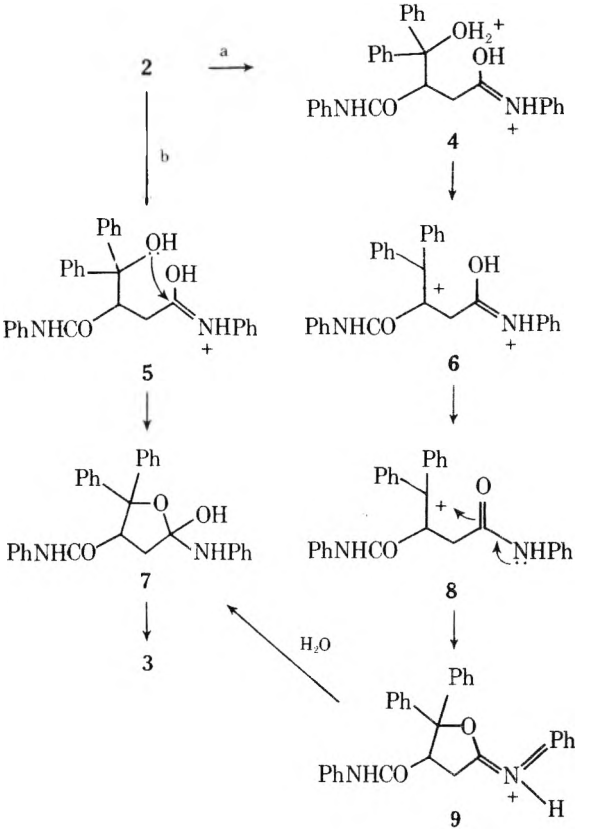
(1)

fected cyclization to 4,4-diphenyl-3-carboxanilidebutanolactone (**3a**) in high yield, 92, 89, and 91%, respectively. A single mechanism consistent with these results would be difficult to formulate considering the dehydrating properties of concentrated sulfuric acid vs. the proton donating characteristics of acetic acid or methanolic hydrogen chloride. Two basic mechanisms could be designed for these observations (Scheme I). One, path a, would entail carbonium ion formation (**6**) with its subsequent capture by the oxygen of the amide carbonyl[2] upon pouring the reaction mixture onto ice. The incipient water would then hydrolyze the resulting imino lactone (**9**) to give **3**.[3] An alternative mechanism, path b, is an intramolecular (A-2) acyl substitution.[4]

Distinguishing between these mechanisms could be effected by incorporation of an oxygen label in the hydroxyl of **2** with subsequent mass spectral analysis. Cyclization via path b would result in the oxygen label being located in the ether linkage of **3**, whereas the label would be lost via carbonium ion formation in path a.

Benzophenone-^{18}O (**11**), synthesized by hydrolyzing its imine hydrochloride (**10**) in water-^{18}O, was reacted with 1,3,6-trilithiosuccinanilide (**1**) to form the ^{18}O-carbinol **2b**. The resulting diphenylmethyl carbinol **2b**, with its hydroxyl oxygen containing 21.8% ^{18}O, was subsequently treated with the various acid systems, the lactone products being analyzed by mass spectrometry (Table I). No oxygen label was retained in the lactone when **2b** was treated with cold concentrated sulfuric acid. This reaction proceeded via a carbonium ion (**6**) as outlined in path a. In contrast, there was complete retention of the hydroxyl oxygen when the labeled carbinol **2b** was refluxed with acetic acid or treated with methanolic hydrogen chloride (Table I). These results demonstrate that acyl substitution (path b) is the mechanism of this cyclization reaction.

Scheme I



Mass Spectral Analysis. A fragmentation pathway as outlined in Scheme II demonstrated the presence of the oxygen label in the sets of peaks for *m/e* 183 (**12**) and *m/e* 105 (**13**). The oxygens of these species originated from the ether linkage of **3b** (Table II) and contained 91 (via acetic acid) and 87.2% (via methanolic hydrogen chloride) of the ^{18}O. The remaining 9 and 12.8%, respectively, of the oxygen label was contained in the set of ions at *m/e* 175, the base peak. This fragment contains the lactone carbonyl oxygen, and arises directly from the molecular ion by the loss of benzophenone ($M^+ - m/e$ 182).[5] For **3b**, it would be reasonable to expect that the oxygen

Scheme II

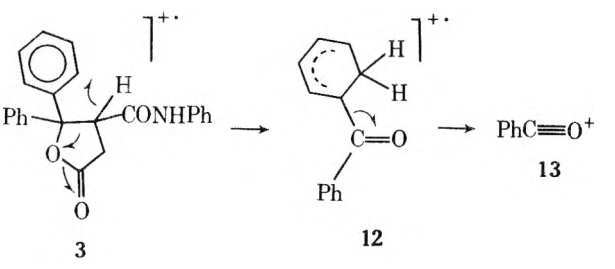
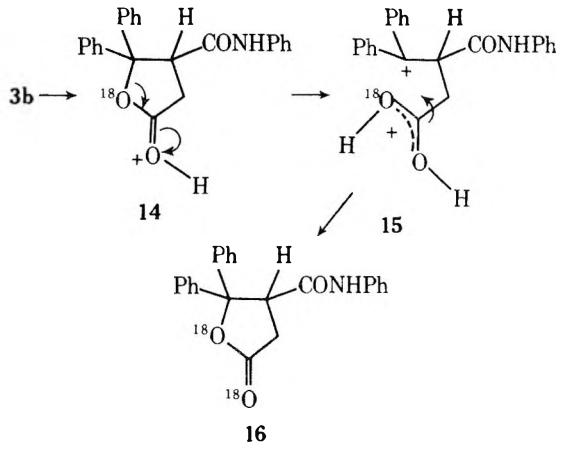


Table I. ^{18}O Analysis

	% ^{18}O[a]	% retention
^{18}O-carbinol **2b**	21.8	
Lactone via		
H_2SO_4 (**3a**)	0.0	0
CH_3COOH (**3b**)	21.8[b]	100
CH_3OH/HCl (**3b**)	21.7	>99

[a] The set of peaks containing the molecular ion was used for these calculations. [b] In the sequence **2b** (via acetic acid) to **3b** to **16**, the mass spectra of both **2b** and **16** analyze for 21.8% ^{18}O. It is therefore assumed that **3b** also contains the same amount of ^{18}O label, even though its mass spectra analyze for 21.4% ^{18}O.

Scheme III



label present in the set of ions at *m/e* 175 comes about by scrambling in the mass spectrometer.[6]

The mass spectrum of the product (**16**) resulting from the treatment of **3b** with concentrated sulfuric acid (Scheme III) gave corroborative evidence for the above fragmentation pathways. The peaks corresponding to *m/e* 175 and 105 analyze for 54.8 and 45.2% of the oxygen label, respectively. This indicates that the ether oxygen of **3b** equilibrated with the lactone carbonyl oxygen. That the oxygen label is not evenly distributed in the mass spectral fragments of **16** is indicative of about 9.6% scrambling in the mass spectrometer[6] and is consistent with the average of 10.9% scrambling in the mass spectra of **3b** (Table II).[7]

Mechanistic Analysis. The above reaction sequence (Scheme III) also provided insight into the reaction mechanism in sulfuric acid. The diphenylmethyl carbonium ion (**15**) should be analogous to the corresponding ion (**6**) of Scheme I. Upon quenching these carbonium ion intermediates by pouring onto ice, they are captured by the relatively nucleophilic carbonyl oxygens and not by the incipient water. This eliminates the possibility of carbonium ion **6** from capturing a molecule of water and cyclizing via path b. Cyclization with refluxing acetic acid or methanolic hydrogen chloride must occur via an intramolecular A-2 mechanism (path b), the reacting species being expected to be the oxygen-protonated anilide **5**.

Experimental Section

Melting points were recorded on a Thomas-Hoover melting point apparatus in open capillary tubes and are uncorrected. Tetrahydrofuran (THF) was distilled from lithium aluminum hydride immediately before use. Low resolution mass spectra were obtained by Mr. Fred Williams at the Research Triangle Institute for Mass Spectrometry, Research Triangle Park, N.C., on a MS-902 mass spectrometer. Elemental analysis were performed by M-H-W Laboratories, Garden City, Mich. and Janssen Pharmaceutica, Beerse, Belgium.

2-(1,1-Diphenyl-1-hydroxymethyl)succinanilide (2a). *N*-Butyllithium in hexane (28 mL, 63 mmol) was added dropwise over 30 min under nitrogen to a cooled (0–5 °C) suspension of 5.4 g (20 mmol) of succinanilide in 125 mL of THF. After stirring the clear yellow-orange solution for 10 min, the dropwise addition of 4.2 g (23 mmol) of benzophenone dissolved in 50 mL of THF was made over 5 min. The resulting dark blue mixture was stirred (0–5 °C) for 1 h before pouring it onto 100 mL of a 2 N HCl–ice mixture (1:1 by volume). The organic layer was separated and the aqueous phase saturated with NaCl before extraction with three 100-mL portions of ether. The combined organic extracts were dried (Na_2SO_4) and evaporated. The resulting solid was recrystallized from methanol, giving 4.4 g (49%) of **2a**, mp 218–219.5 °C. One recrystallization ($EtOH-H_2O$) gave an analytical sample, mp 218–219.5 °C; mass spectrum, *m/e* (relative intensity): 450 (4), 358 (5), 316 (69), 268 (18), 193 (35), 182 (69), 176 (100), 148 (35). Anal. Calcd for $C_{29}H_{26}N_2O_3$: C, 77.31; H, 5.81; N, 6.21. Found C, 77.23; H, 5.76; N, 6.22.

Benzophenone Imine Hydrochloride (10). To 120 mL of sodium-dried benzene at room temperature, a mixture of 10 g (100 mmol) of tetramethylethylenediamine and 45 mL (100 mmol) of *n*-butyllithium in hexane was added over 30 min. The yellow solution was stirred for 3 h, after which time it was assumed to contain 100 mmol of phenyllithium. To this solution was added 10 g (100 mmol) of benzonitrile in 25 mL of sodium-dried hexane, and the mixture was stirred for 1 h. The resulting dark brown solution was poured onto 200 mL of ice–water. The organic layer was separated, the aqueous layer being twice extracted with 100-mL portions of ether. The combined organic fractions were dried (Na_2SO_4) and evaporated to give an oil. The oil, as indicated by its infrared spectrum, was a mixture of benzophenone and the desired benzophenone imine. Separation was effected by pouring the oil into 100 mL of cold (0–5 °C) 2 N HCl. The resulting crystals of benzophenone imine hydrochloride (**10**) were filtered and dried, 14.7 g (68%), and used without further purification.

Benzophenone-^{18}O (11). A solution of 1.5 g (8.3 mmol) of benzophenone imine hydrochloride (**10**) in 5 mL of 20% water-^{18}O (obtained from Diaprep Inc., Atlanta, Ga.) was refluxed for 1.5 h. The resulting oil was repeatedly extracted with ether by pipet. This procedure was repeated several times upon addition of **10** to the water-^{18}O. The subsequent ether extracts were combined, dried (Na_2SO_4), and evaporated to an oil. Crystallization was effected by seeding to give **11**, mp 47–49 °C. Benzophenone-^{18}O obtained in this manner was used without further purification.

2-(1,1-Diphenyl-1-hydroxymethyl-^{18}O)succinanilide (2b). This reaction was performed on one-half scale as that of **2a**, 10 mmol of **1** in 75 mL of THF being formed before 2.1 g (11.5 mmol) of **11** in 25 mL of THF was added over 4 min. Stirring for 1 h preceded inverse neu-

Table II. Mass Spectral Data of ^{18}O Containing Fragments

	% ^{18}O		% M^+[c]		% norm[d]	
Fragment	*m/e* 175[a]	*m/e* 105[b]	*m/e* 175[a]	*m/e* 105[b]	*m/e* 175[a]	*m/e* 105[b]
Lactone **3b** via						
CH_3COOH	2.0	20.2	9.3	94.4	9.0	91.0
CH_3OH/HCl	2.6	17.7	12.0	81.6	12.8	87.2
Lactone **16**[e]	12.1	10.0	55.5	54.9	54.8	45.2

[a] The set of peaks for the base peak containing the lactone **3b** carbonyl oxygen. [b] The set of peaks for the benzoyl fragment containing the ether oxygen of **3b**. [c] Retention of the oxygen label relative to that in the molecular ion. [d] Normalization, as determined by totaling the ^{18}O of the set of peaks at *m/e* 175 and 105 and setting this equal to 100% ^{18}O. [e] From the molecular ion **16** was calculated to contain 21.8% ^{18}O.

tralization. Upon workup, the resulting solid was recrystallized (EtOH), affording the desired **2b**, 1.9 g (42%), mp 217–219 °C.

Cyclization of 2a and 2b with Sulfuric Acid. In a typical reaction, 1.0 g (2.22 mmol) of **2a** was dissolved by manipulation and stirring with a glass rod in 15 mL of cold (0–5 °C) concentrated sulfuric acid. Upon standing 1 h **3a** was precipitated from the resulting solution by pouring onto 100 g of ice. Melting allowed for collection of the precipitate, and gave 0.73 g (92%) of **3a**, mp 210–213 °C. One recrystallization (EtOH) gave the analytical sample, mp 220–222 °C: mass spectrum, *m/e* (relative intensity) 357 (15), 175 (100), 147 (34), 146 (30), 119 (18), 105 (36), 93 (50), 91 (15); *m*/e* 123.5, 121.8, 98.5, 85.7, 59.2, 56.5. Anal. Calcd for $C_{29}H_{19}NO_3$: C, 77.29; H, 5.36; N, 3.92. Found: C, 77.06; H, 5.43; N, 3.83. The yield of **3a** from **2b** was 81%.

Cyclization of 2a and 2b by Refluxing Acetic Acid. In a typical reaction, a mixture of 10 mL of acetic acid and 0.75 g (1.66 mmol) of **2b** was refluxed for 1 h. Upon cooling, **3b** was precipitated from the resulting solution by pouring onto 50 g of ice. The precipitate was collected to give 0.51 g (86%) of **3b**, mp 215–218 °C. One recrystallization (EtOH) gave a sample melting at 218–220 °C. The yield of **3a** from **2a** was 89%.

Cyclization of 2a and 2b by Methanolic Hydrogen Chloride. In a typical reaction, $HCl_{(g)}$ was bubbled into a stirred solution of 0.75 g (1.66 mmol) of **2b** in 100 mL of absolute methanol for about 30 min. The solution was evaporated to 25 mL before pouring onto an equal volume of cold (0–5 °C) water. The resulting precipitate was collected and recrystallized (EtOH) affording **3b**, 0.47 g (79%), mp 218–220 °C. The yield of **3a** from **2a** was 91%.

Treatment of 3b with Sulfuric Acid. In 2 mL of cold (0–5 °C) concentrated sulfuric acid, 30 mg (66.6 μmol) of **3b** was dissolved by stirring with a glass rod. After standing 5 min, **16** was precipitated from the solution by adding 20 g of crushed ice. The precipitate was collected and gave 28 mg (93%), mp 120–170 °C. One recrystallization ($EtOH–H_2O$) afforded pure **16**, mp 217–218 °C.

Acknowledgment. We wish to thank Professor Peter W. Jeffs for helpful discussions. This work was supported by Grant No. 2 R01 CA04455 from the United States Public Health Service and by a Traineeship from the National Aeronautic Space Administration (T.C.A.).

Registry No.—**2a**, 23105-20-6; **2b**, 62861-49-8; **3a**, 23105-22-8; **3b**, 62905-90-2; **10**, 5319-67-5; **13**, 62861-50-1; **16**, 62905-91-3; succinanilide, 15510-09-5; benzophenone, 119-61-9; tetramethylethylenediamine, 110-18-9; benzonitrile, 100-47-0.

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Stereochemistry of the Cycloaddition Reaction of Methylcarbenoid of Zinc to Cyclic Allylic Alcohols

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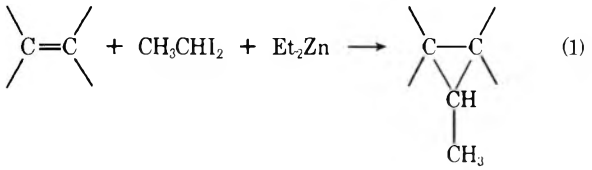
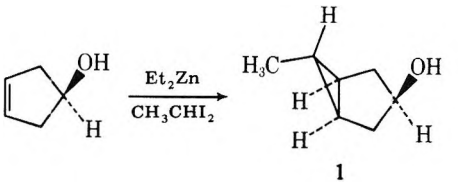
Stereochemistry of the cycloaddition reaction of the methylcarbenoid of zinc to 2-cyclohexen-1-ol, 2-cyclohepten-1-ol, and *cis*-2-cycloocten-1-ol was investigated under two conditions: (A) equimolar amounts of diethylzinc and cyclic allylic alcohol were used; and (B) twice as much diethylzinc as the alcohol by mole was used. Intramolecular ethylidene transfer reaction in an intermediate like **20**, and a quasi-intermolecular ethylidene transfer reaction in an intermediate like **22**, were considered to be predominant under the conditions A and B, respectively. However, with respect to the configuration of the cyclopropane ring with hydroxyl group in the products, highly syn- or anti-selective cycloadditions were observed independently of the two reaction conditions. On the other hand, with respect to the configuration of the methyl group introduced by the organozinc reagent, the stereoselectivity depended upon the two reaction conditions, and the steric restraint caused by the hydroxyl group on the configuration of the methyl group was concluded to be relatively loose under the condition of a quasi-intermolecular ethylidene transfer reaction in an intermediate like **22**.

In a previous paper,[1] we have demonstrated the synthesis of methylcyclopropane derivatives by the reaction of olefins with 1,1-diiodoethane and diethylzinc (eq 1). The reaction



(1)

proceeds stereospecifically, i.e., cis and trans olefins afford cyclopropane derivatives whose configurations with respect to the substituents from original olefins are cis and trans, respectively. With respect to the stereochemistry of the methyl group introduced by the organozinc reagent, the reaction generally yields the endo or cis isomers predominantly over the corresponding exo or trans isomers, respectively. For example, the reaction with cyclohexene gave a 1.5:1 mixture of *endo*- and *exo*-7-methylbicyclo[4.1.0]heptane. On the other hand, the exo or trans isomers were obtained predominantly over the corresponding endo or cis isomers, respectively, from olefins containing hydroxyl group such as allyl alcohol and 2-buten-1-ol. The stereochemistry of the reaction with 3-cyclopenten-1-ol was especially interesting, which gave exclusively *exo*-6-methyl-*cis*-3-hydroxybicyclo[3.1.0]hexane (**1**) among four possible stereoisomers. This work was aimed at



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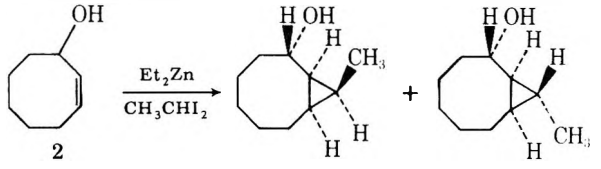
an investigation of the stereochemistry of the reaction 1 with olefins containing hydroxyl group to some detail.

In the Simmons–Smith reaction with cyclic allylic and homoallylic alcohols, the hydroxyl group plays an important role in not only the reactivity of the olefin, but also the stereospecificity of the reaction.[2] In most cases, the cyclopropane ring was exclusively cis to the hydroxyl group in the product. However, in the reaction with some larger and relatively complicated cyclic molecules, the cyclopropane ring was exclusively trans to the hydroxyl group in the product. For example, highly anti-selective addition[3] was observed with 2-cycloocten-1-ol and 2-cyclononen-1-ol, whereas syn-selective addition[3] was predominant for 2-cyclohepten-1-ol, 2-cyclohexen-1-ol, and 2-cyclopenten-1-ol.[2n] We studied the steric course of the cycloaddition of the methylcarbenoid of zinc to these cyclic allylic alcohols.

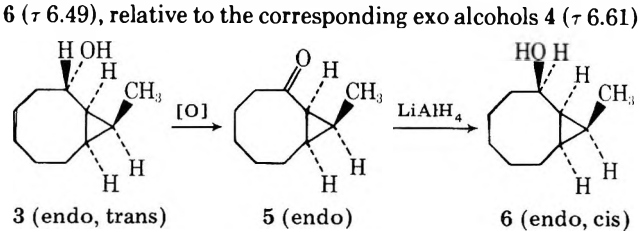
Results

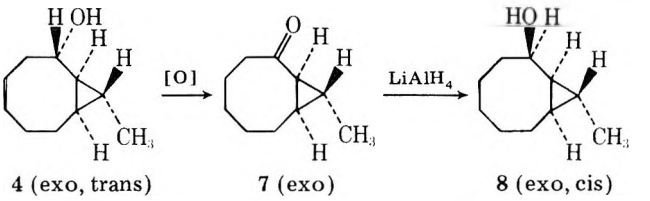
We found that, when equimolar amounts of diethylzinc and *cis*-2-cycloocten-1-ol (**2**) were used, reaction 1 gave *endo*-9-methyl-*trans*-2-hydroxy- (**3**) and *exo*-9-methyl-*trans*-2-hydroxy-*cis*-bicyclo[6.1.0]nonane (**4**) in 29 and 31% yields, respectively, with traces of *endo*-9-methyl-*cis*-2-hydroxy- (**6**) and *exo*-9-methyl-*cis*-2-hydroxy-*cis*-bicyclo[6.1.0]nonane (**8**). The isomer ratio of the endo,trans alcohol **3** to the exo,trans alcohol **4** was thus 0.9. In the case where twice as much diethylzinc as the cyclic allylic alcohol **2** by mole was used, the



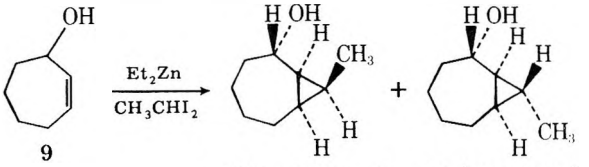
reaction gave the two trans alcohols **3** and **4** in 54 and 22% yields, respectively, with traces of the two cis alcohols **6** and **8**. The isomer ratio of **3** to **4** was thus 2.5 in this case. In both runs of experiments, the cyclopropane ring was exclusively trans to the hydroxyl group as in the corresponding Simmons–Smith reaction.[2n] The isomer ratio of the cyclopropylcarbinol was independent of the yield and the reaction time under our experimental conditions.

The relative configurations of these alcohols were assigned from the expected direction of hydride reduction of ketones **5** and **7** and by comparison of their ^{1}H NMR spectra.[2r] Jones oxidation[4] of the endo,trans alcohol **3** and the exo,trans alcohol **4** followed by reduction of the corresponding ketones **5** and **7** with lithium aluminum hydride gave the endo,cis alcohol **6** and the exo,cis alcohol **8**, respectively, contaminated with traces of the trans alcohols **3** and **4**, respectively. The protons in the geminal position to the hydroxyl group were observed at higher fields with broader bands in the endo,trans alcohol **3** (τ 6.78 with a width at half-height of 21 Hz) and the exo,trans alcohol **4** (τ 6.61 with a width at half-height of 21 Hz), relative to the endo,cis alcohol **6** (τ 6.49 with a width at half-height of 14 Hz) and the exo,cis alcohol **8** (τ 6.42 with a width at half-height of 14 Hz), in accord with the expected influence of a neighboring cyclopropane ring.[2c,2n] The protons in the geminal position to the hydroxyl group were observed at higher fields in the endo,trans alcohol **3** (τ 6.78) and the endo,cis alcohol **6** (τ 6.49), relative to the corresponding exo alcohols **4** (τ 6.61) and **8** (τ 6.42), respectively, in accord with the expected influence of the C–CH_3 bond.





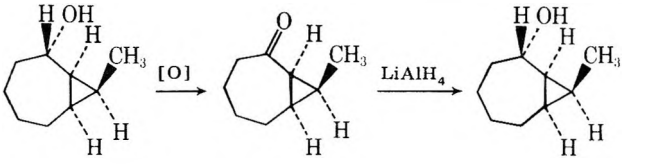
When equimolar amounts of diethylzinc and 2-cyclohepten-1-ol (**9**) were used, *endo*-8-methyl-*trans*-2-hydroxy- (**10**) and *exo*-8-methyl-*trans*-2-hydroxybicyclo[5.1.0]octane (**11**) were obtained in 38 and 36% yields, respectively. In the case where twice as much diethylzinc as the cyclic allylic alcohol **9** by mole was used, the reaction gave the two trans alcohols **10** and **11** in 38 and 41% yields, respectively. In both runs of

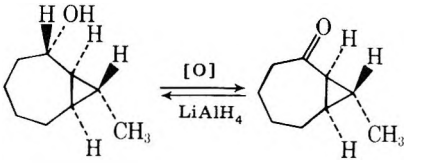


experiments, the cyclopropane ring was exclusively trans to the hydroxyl group, contrary to the corresponding Simmons–Smith reaction.[2n,5]

The relative configurations of these alcohols were assigned based on their ^{1}H NMR spectra. The endo,trans alcohol **10** and the exo,trans alcohol **11** showed the absorptions due to the protons in the geminal position to the hydroxyl group at τ 6.77 (with a width at half-height of 18 Hz) and τ 6.66 (with a width at half-height of 18 Hz), respectively. This result is consistent with the trans configuration of the cyclopropane ring to the hydroxyl group. In the case of 2-hydroxybicyclo[5.1.0]octanes, the peak due to the hydrogen atom in the geminal position to the hydroxyl group of the trans isomer was reported to appear at τ 6.7 with a width at half-height of 15 Hz, whereas the corresponding peak of the cis isomer was reported to appear at τ 5.8 with a width at half-height of 10 Hz.[2c]

Jones oxidation[4] of the endo,trans alcohol **10** and the exo,trans alcohol **11** followed by reduction of the ketones **12** and **13** with lithium aluminum hydride gave predominantly the trans alcohols **10** and **11**, respectively.[6]

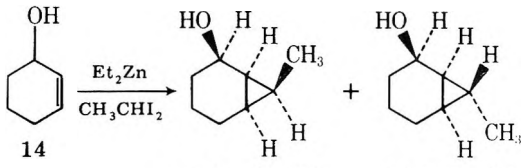




Reaction of equimolar amounts of diethylzinc and 2-cyclohexen-1-ol (**14**) with 1,1-diiodoethane gave *endo*-7-methyl-*cis*-2-hydroxy- (**15**) and *exo*-7-methyl-*cis*-2-hydroxybicyclo[4.1.0]heptane (**16**) in 79% yield. The isomer ratio of the exo,cis alcohol **16** to the endo,cis alcohol **15** was 1.6. When twice as much diethylzinc as the cyclic alcohol **14** by mole was used, the reaction gave the two cis alcohols **15** and **16** in 60% yield. The isomer ratio of **16** to **15** was 1.7 in this case.

In both runs of experiments, the cyclopropane ring was cis to the hydroxyl group as in the corresponding Simmons–Smith reaction.[2n]

The relative configurations of these alcohols were also determined based on their ^{1}H NMR spectra. Since **15** and **16** were thermally unstable, they were not separated. ^{1}H NMR spectra of mixtures of the endo,cis alcohol **15** and the exo,cis alcohol **16** showed the absorption of the protons in the geminal position to the hydroxyl group at τ 5.74. With the aid of a shift reagent Eu(dpm)$_3$, the absorption was separated into two multiplets, both of which showed the width at half-height of 11 Hz. These chemical shifts and widths at half-height are consistent with the cis configuration of the cyclopropane ring with the hydroxyl group.[2c] ^{1}H NMR spectra of mixtures of **15** and **16** showed two doublets at τ 8.89 (J = 5.7 Hz) and 8.92 (J = 6.3 Hz), in the intensity ratio of 1.6:1 and 1.7:1, respectively, for the two runs of experiments mentioned above. The former doublet was assigned to the exo,cis alcohol **16**, and the latter to the endo,cis alcohol **15**, respectively, based on the expected



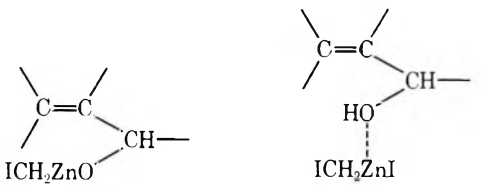
14 15 (endo, cis) 16 (exo, cis)

influence of cyclohexyl ring.[7] The predominant isomer was thus determined to be the exo,cis alcohol **16**. The coupling constants and the intensity ratio of the two doublets were determined with an aid of a shift reagent Eu(dpm)$_3$.

Results were summarized in Table I.

Discussion

Stereoselectivity with Respect to the Configuration of the Hydroxyl Group with the Cyclopropane Ring. Two mechanisms were proposed for the steric course of the Simmons–Smith reaction with cyclic allylic and homoallylic alcohols. One mechanism involves cleavage of the Simmons–Smith reagent by the hydroxyl group of the olefin to give a zinc compound like **17**, and stereospecific intramolecular methylene transfer would then yield the cyclopropylcarbinol after hydrolysis.[2f] Another mechanism includes the formation of a zinc complex like **18**, and the complex would undergo methylene transfer with stereospecificity.[2i] Since the cyclopropane ring was predominantly cis or trans to the hydroxyl group, methylene transfer reaction by a free zinc carbenoid without formation of these intermediates is not probable.



17 18

In the reaction 1 with cyclic allylic alcohols, the addition of 1,1-diiodoethane was carried out after the unsaturated alcohol was converted to the corresponding ethylzinc alkoxide **19**.

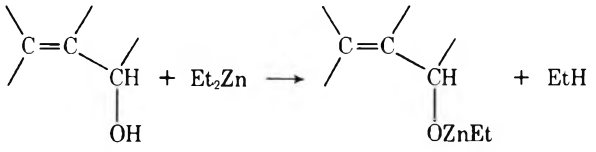


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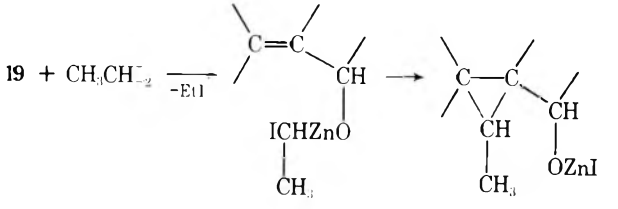
Table I. Product Distribution and Yields of Cyclopropylcarbinols

Cyclic allylic alcohol	Epimer distribution, % Endo, cis	Exo, cis	Endo, trans	Exo, trans	Total yield, %
Under condition A[a]					
2-Cyclohexen-1-ol **14**	38	62			79[c]
2-Cyclohepten-1-ol **9**			51	49	74[d]
cis-2-Cycloocten-1-ol **2**			48	52	60[d]
Under condition B[b]					
2-Cyclohexen-1-ol **14**	37	63			60[c]
2-Cyclohepten-1-ol **9**			48	52	79[d]
cis-2-Cycloocten-1-ol **2**			71	29	76[d]

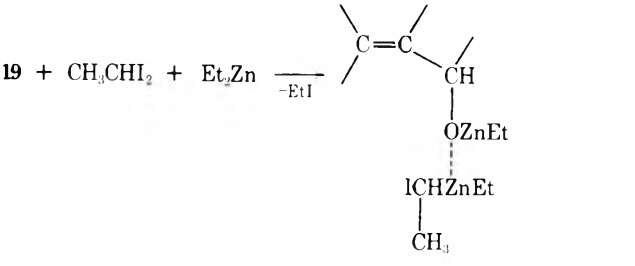
[a] Equimolar amounts of diethylzinc and the cyclic allylic alcohol were used. [b] Twice as much diethylzinc as the cyclic allylic alcohol by mole was used. [c] Isolated yield. [d] Determined by VPC analysis of the reaction mixture.

Thus intermediate **18** is not probable, but the following two types of intermediates **20** and **22** can be conceivable, which correspond to the intermediates **17** and **18**, respectively.

We carried out the reaction 1 with cyclic allylic alcohols under two conditions. (A) Equimolar amounts of diethylzinc and cyclic allylic alcohol were used. In this case, a stereospecific intramolecular ethylidene transfer reaction would occur in an intermediate like **20** and yield the corresponding cyclopropylcarbinol after hydrolysis of **21**. The formation of an



20 21



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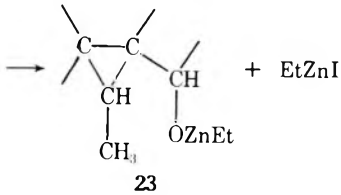

23

intermediate like **22** is very difficult to be conceived. (B) Twice as much diethylzinc as cyclic allylic alcohol by mole was used. In this case, ethylidene transfer reaction would principally occur in an intermediate like **22**. That is, intermolecular reaction of **19** with the methylcarbenoid of zinc would give a complex **22**, which undergoes a quasi-intermolecular ethylidene transfer reaction with stereospecificity to afford the corresponding cyclopropylcarbinol after hydrolysis of **23**. The formation of an intermediate like **20** is much less probable in this case, because diethylzinc is much more reactive than

ethylzinc alkoxide toward 1,1-diiodoethane.[8]

The exo/endo isomer ratio, i.e., the isomer ratio with respect to the configuration of the introduced methyl group, depended upon the reaction conditions A and B, especially in the reaction with cyclooctenol **2**. This fact also supports that the reaction proceeded via different intermediates under the two reaction conditions. However, the cyclopropane ring was exclusively cis or trans to the hydroxyl group in the products independently of the two reaction conditions. Therefore, both of the intermediates **20** and **22** would lead to the same steric configuration between the cyclopropane ring and hydroxyl group.

The reaction 1 with the cyclohexenol **14** and the cyclooctenol **2** showed exclusive syn- and anti-selective additions,[3] respectively, as in the corresponding Simmons–Smith reaction. On the other hand, the reaction 1 with the cycloheptenol **9** showed an exclusive anti-selective addition[3] contrary to the corresponding Simmons–Smith reaction, which was reported to give a 90:10 mixture of the cis and trans alcohols.[2n] The stereospecific syn- or anti-selective additions in the Simmons–Smith reaction with cyclic allylic alcohols were explained in terms of the attack of organozinc reagent on the nearest face of the neighboring double bond.[2n] Models of the cyclohexenol **14** indicate that the allylic hydroxyl group can only function as a syn director. Models of the cyclooctenol **2** shows that the anti-selective addition is favored. On the other hand, models of the cycloheptenol **9** are less helpful in determining which face of the double bond is more accessible. The energy difference between the transition states of syn- and anti-selective additions for the Simmons–Smith reaction was reported to be only 1.3 kcal/mol.[2n] In the transition states **20** or **22** for the reaction with the cycloheptenol **9**, the steric interference between the methyl group of the organozinc reagent and the cycloheptene ring would lead the carbenoid to the anti-selective addition.

Stereoselectivity with Respect to the Configuration of the Methyl Group Introduced by the Organozinc Reagent. Reaction 1 usually gives the endo or cis isomers predominantly over the corresponding exo or trans isomers, respectively.[1] However, the reversal of the stereoselectivity was observed in reaction 1 with olefins containing hydroxyl group,[1] which can be ascribable to the steric restraint in intermediates like **20** and/or **22**. In reaction 1 with the cyclohexenol **14**, the exo,cis alcohol **16** was obtained predominantly over the endo,cis alcohol **15**. In reaction 1 with cycloheptenol **9**, nearly equal amounts of the two trans alcohols **10** and **11** were obtained. In reaction 1 with cyclooctenol **2**, nearly equal amounts of the two trans alcohols **3** and **4** were obtained when equimolar amounts of diethylzinc and **2** were used. On the other hand, the endo,trans alcohol **3** was obtained predominantly over the exo,trans alcohol **4** when twice as much diethylzinc as **2** by mole was used. Based on these observations, we can conclude that the steric restraint on the configuration of the methyl group decreases with ring size of the cyclic allylic alcohols. The nonbonding interaction between the methyl group and the cycloalkane ring would become more significant than the steric restraint caused by the hydroxyl group as the ring size increases. The endo/exo isomer ratio in reaction 1 with the cyclooctenol **2** was 0.9 when equimolar amounts of diethylzinc and the cyclootenol **2** were used, while the ratio was 2.5 in the case where twice as much diethylzinc as the cyclooctenol **2** by mole was used. The endo/exo isomer ratio in the latter case was close to that observed in reaction 1 with *cis*-cyclooctene (see the Experimental Section for detail). This result indicates that the steric restraint caused by the hydroxyl group on the configuration of the methyl group is relatively loose in the reaction with larger cyclic alcohols especially under the condition of a quasi-intermolecular ethylidene transfer reaction in the intermediate like **22**.

Experimental Section

Microanalyses were performed at the Elementary Analyses Center of Kyoto University. ^{1}H NMR spectra were recorded on a Varian Model T-60-A or a Japan Electron Optics Model HA-100 spectrometer using carbon tetrachloride as solvent and tetramethylsilane as internal standard. Mass spectra were obtained on a Hitachi Model RMU-6 spectrometer. VPC analysis and separation were carried out on a Shimadzu GC-4A or GC-4B gas chromatograph.

Materials. Diethylzinc,[9] 1,1-diiodoethane,[10] 2-cyclohexen-1-ol,[2d] 2-cyclohepten-1-ol,[2d] *cis*-2-cycloocten-1-ol,[11] and chromium(VI) oxide[12] were prepared according to the literature methods. Solvents and nitrogen were purified as in a previous paper.[1] Other chemicals were commercially available and used without further purification.

Procedure. The reaction of cyclic allylic alcohols and other olefins with 1,1-diiodoethane and diethylzinc were carried out as in a previous paper.[1] Except for the reaction with cyclohexen-1-ol **14**, yields were determined by VPC analysis of the reaction mixture, and were based on the olefin. Jones oxidation[4] of alcohols was carried out in dry pyridine with the use of chromium(VI) oxide at room temperature as in a previous paper.[1] Reduction of ketones was carried out with use of lithium aluminum hydride in diethyl ether at room temperature.

Reaction of *cis*-2-Cycloocten-1-ol (2) with Diethylzinc and 1,1-Diiodoethane. *cis*-2-Cycloocten-1-ol (10.0 mmol, 1.36 g) was added dropwise to diethylzinc (10.0 mmol, 1.04 mL; or 20.0 mmol, 2.08 mL) in 10.0 mL of cyclohexane at room temperature. After gas evolution ceased, 1,1-diiodoethane (15.0 mmol, 1.70 mL) was added dropwise to the reaction mixture with stirring, and allowed to react at room temperature. After 15 h, the reaction mixture was poured into aqueous ammonium chloride. The aqueous layer was extracted several times with dry ether, and the combined organic solution was submitted for VPC analysis. In other runs of experiments, the organic solution was washed with methanolic sodium hydroxide. Solvents were removed by distillation. A sample of **3** collected from the residue by VPC was analyzed: ^{1}H NMR (CCl_4) τ 6.78 (m, 1 H, width at half-height = 21 Hz), 7.68 (s, 1 H), 7.8–9.8 [m, 16 H, including 8.92 (d, 3 H, J = 4.8 Hz)]; MS *m/e* (rel intensity) 155 (0.29), 154 (2.44 M^+), 71 (100), 55 (68), 41 (74). Anal. Calcd for $C_{10}H_{18}O$: C, 77.87; H, 11.76. Found: C, 77.64; H, 11.48. An isolated sample of **3** was oxidized to **5** with use of chromium(VI) oxide in pyridine. Reduction of **5** with lithium aluminum hydride in diethyl ether gave **6**. A sample of **6** collected by VPC was analyzed: ^{1}H NMR (CCl_4) τ 6.49 (m, 1 H, width at half-height = 13 Hz), 7.41 (s, 1 H), 7.7–9.4 [m, 16 H, including 8.95 (d, 3 H, J = 5.0 Hz)].

An isolated sample of **4** collected from the distillation residue by VPC was analyzed: ^{1}H NMR (CCl_4) τ 6.61 (m, 1 H, width at half-height = 21 Hz), 7.27 (s, 1 H), 7.8–9.8 [m, 16 H, including 8.93 (d, 3 H, J = 4.5 Hz)]; MS *m/e* (rel intensity) 155 (0.24), 154 (2.12, M^+), 71 (100), 55 (71), 41 (72). Anal. Calcd for $C_{10}H_{18}O$: C, 77.87; H, 11.76. Found: C, 77.95; H, 11.81. An isolated sample of **4** was oxidized to **7** and reduced to **8** in a similar manner. A sample of **8** collected by VPC was analyzed: ^{1}H NMR (CCl_4) τ 6.42 (m, 1 H, width at half-height = 14 Hz), 7.61 (s, 1 H), 7.7–9.4 [m, 16 H, including 9.10 (d, 3 H, J = 7.2 Hz)].

Reaction of 2-Cyclohepten-1-ol (9) with Diethylzinc and 1,1-Diiodoethane. 2-Cyclohepten-1-ol (5.0 mmol, 0.78 g), diethylzinc (5.0 mmol, 0.52 mL; or 10.0 mmol, 1.04 mL), and 1,1-diiodoethane (7.5 mmol, 0.85 mL) were allowed to react in 3.0 mL of diethyl ether at room temperature in a similar way. After solvents were removed by distillation, a sample of **10** was collected from the residue by VPC and analyzed: ^{1}H NMR (CCl_4) τ 6.77 (m, 1 H, width at half-height = 18 Hz), 7.5–9.7 [m, 15 H, including 7.93 (s, 1 H) and 8.93 (d, 3 H, J = 4.5 Hz)]; MS *m/e* (rel intensity) 141 (0.15), 140 (1.45, M^+), 71 (91), 67 (73), 55 (73), 43 (75), 41 (100). Anal. Calcd for $C_9H_{16}O$: C, 77.09; H, 11.50. Found: C, 77.03; H, 11.50. An isolated sample of **10** was oxidized with the use of chromium(VI) oxide. Reduction of the product by lithium aluminum hydride gave **10**.

A sample of **11** collected from the distillation residue by VPC was analyzed: ^{1}H NMR (CCl_4) τ 6.66 (m, 1 H, width at half-height = 18 Hz), 7.5–9.7 [m, 15 H, including 7.41 (s, 1 H) and 8.99 (d, 3 H, J = 4.5 Hz)]; MS *m/e* (rel intensity) 141 (0.10), 140 (0.96, M^+), 71 (97), 67 (66), 55 (74), 43 (85), 41 (100). Anal. Calcd for $C_9H_{16}O$: C, 77.09; H, 11.50. Found: C, 76.79; H, 11.50. An isolated sample of **11** was oxidized by chromium(VI) oxide. Reduction of the product with lithium aluminum hydride gave **11**.

Reaction of 2-Cyclohexen-1-ol (14) with Diethylzinc and 1,1-Diiodoethane. 2-Cyclohexen-1-ol (10.0 mmol, 0.97 g), diethylzinc (10.0 mmol, 1.04 mL), and 1,1-diiodoethane (15.0 mmol, 1.70 mL) were allowed to react in 10.0 mL of diethyl ether in a similar way at room

temperature. After solvents were removed under a reduced pressure, the residue was distilled at 44 °C (5 mmHg) to afford a mixture of **15** and **16** in 79% yield. Since **15** and **16** were thermally unstable, they were not separated, and the mixture was analyzed: ^{1}H NMR (CCl_4) τ 5.74 (m, 1 H), 7.89 (s, 1 H), 7.8–9.5 [m, 12 H, including 8.89 (d, J = 5.7 Hz) and 8.92 (d, J = 6.3 Hz)]. With the aid of a shift reagent Eu(dpm)$_3$, the absorption at τ 5.74 was separated into two multiplets with widths at half-height of 11 Hz, respectively. With the aid of the shift reagent, the two doublets were shown to include three protons, and the intensity ratio of the doublets at τ 8.89 and 8.92 to be 1.6:1. The coupling constants of the doublets were also determined with the aid of the shift reagent. Anal. Calcd for $C_8H_{14}O$: C, 76.14; H, 11.18. Found: C, 76.11; H, 11.20. When 20.0 mmol (2.08 mL) of diethylzinc was used, a mixture of **15** and **16** was obtained in 60% yield. ^{1}H NMR spectrum of the mixture showed the ratio of **15** to **16** to be 1:1.7.

Reaction of *cis*-Cyclooctene with Diethylzinc and 1,1-Diiodoethane. Reaction of *cis*-cyclooctene (1.2 mmol, 0.23 g) with diethylzinc (1.5 mmol, 0.15 mL) and 1,1-diiodoethane (2.4 mmol, 0.23 mL) in 3.0 mL of octane at 30 °C for 7 h gave a 1:2.6 mixture of *exo*- and *endo*-9-methyl-*cis*-bicyclo[6.1.0]nonane in 87% yield based on the olefin. The exo isomer: ^{1}H NMR (CCl_4) τ 7.8–10.2 [m, 18 H, including 8.99 (d, 3 H, J = 4.8 Hz)]. Anal. Calcd for $C_{10}H_{18}$: C, 86.88; H, 13.12. Found: C, 86.60; H, 13.23. The endo isomer: ^{1}H NMR (CCl_4) τ 7.9–9.8 [m, 18 H, including 9.09 (d, 3 H, J = 4.5 Hz)]. Anal. Calcd for $C_{10}H_{18}$: C, 86.88; H, 13.12. Found: C, 86.94; H, 13.02. In the case where 1.5 mmol of ethylzinc methoxide was used instead of diethylzinc, the yield of 9-methyl-*cis*-bicyclo[6.1.0]nonane was <1% when the reaction time was 7 h.

Registry No.—**2**, 14390-23-9; **3**, 62861-98-7; **4**, 62929-18-4; **5**, 62861-99-8; **6**, 62929-19-5; **7**, 62929-20-8; **8**, 62929-21-9; **9**, 4096-38-2; **10**, 62862-00-4; **11**, 62929-22-0; **12**, 62862-01-5; **13**, 62929-23-1; **14**, 822-67-3; **15**, 62862-02-6; **16**, 62862-03-7; diethylzinc, 557-20-0; 1,1-diiodoethane, 594-02-5; *cis*-cyclooctene, 931-87-3; *exo*-9-methyl-*cis*-bicyclo[6.1.0]nonane, 62862-04-8; *endo*-9-methyl-*cis*-bicyclo[6.1.0]nonane, 62929-24-2; ethylzinc methoxide, 15860-82-9.

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(6) Reduction of bicyclo[4.1.0]heptan-2-one with lithium aluminum hydride was reported to give predominantly the trans isomer of 2-hydroxybicyclo[4.1.0]heptane.[2d]
(7) The ^{1}H NMR spectra of *exo*- and *endo*-7-methylbicyclo[4.1.0]heptane showed the absorptions of the methyl protons at τ 9.03 and 9.06, respectively.[1]
(8) For example, the formation of 9-methyl-*cis*-bicyclo[6.1.0]nonanes was extremely slow when ethylzinc methoxide was used instead of diethylzinc in reaction 1 with *cis*-cyclooctene as is given in the Experimental Section.
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Synthesis of Steroidal [16α,17-*b*][1,4]Dioxanes

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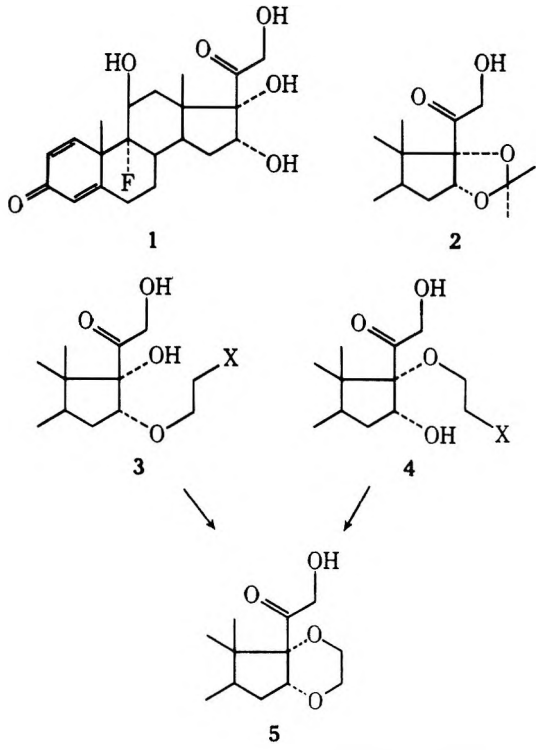
Steroidal [16α,17-*b*][1,4]dioxanes have been prepared for the first time. The key reaction involves the selective functionalization of polyhydroxylated steroids via interaction of 16,17-cycloborates and functionalized diazo compounds to give 16α-alkoxylated 17-hydroxy steroids. Conversion of these intermediates to a variety of substituted dioxanes and dioxins is described. ^{1}H NMR and CD spectra of the products are discussed.

The conversion of certain 16α,17α-dihydroxy steroids, such as triamcinolone[1] (**1**), to the corresponding "acetonides" [2′2′-dimethyl[16α,17-*d*][1,3]dioxolanes (**2**)] is accompanied by a marked increase in topical antiinflammatory activity.[2] A variety of other fused five-membered ring systems incorporating an additional boron, carbon, phosphorus, or sulfur atom[3–6] have been prepared from **1**; however, none of these modifications has led to a therapeutic agent. We decided to incorporate a second carbon atom into the moiety bridging the 16- and 17-oxygen atoms in **2** and prepare compounds of the type **5** in order to explore the effect on antiinflammatory activity.

One attractive approach to such compounds appeared to be the cyclization of intermediates of the type **3** or **4**. Conversion of **1** to the penultimate intermediate **3** requires selective functionalization of one of the two most reactive hydroxyl groups in **1**; for conversion to **4**, one of the two least reactive hydroxyls must be alkylated. A simple approach to 16α-alkoxy derivatives such as **3** is provided by the reaction of the 16,17-cycloborate esters of 11β,16α,17,21-tetrahydroxy steroids with diazoalkanes discovered by Fried and Thomas.[8] We have used the reaction of functionalized diazo compounds with cycloborate esters to prepare derivatives of **3** suitable for transformation to various dioxanes, including the parent ring system **5**. At this time, we wish to describe the synthesis of steroidal [16α,17-*b*][1,4]dioxanes; the biologic activity of these compounds will be reported separately.

Results

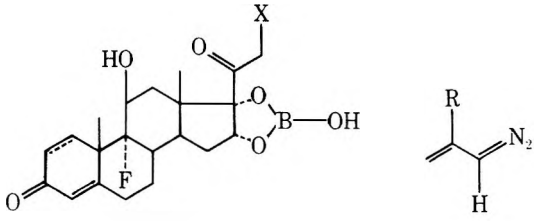
Reaction of 9-fluoro-11β,16α,17,21-tetrahydroxypregn-4-ene-3,20-dione with a large excess of boric oxide in methanol gives cycloborate **6** in excellent yield.[3] When powdered **6** is added to a well-stirred solution of diazoalkene **8a**[9] in ether–methanol at 0 °C nitrogen is evolved and the ether **9a** is produced in 78% yield. It is necessary to use a large excess of diazo compound, since the boron species that is liberated reacts



1 2 3 4 5

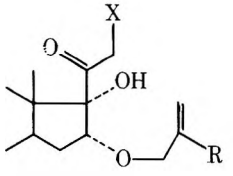
rapidly with diazo compounds. We have generally utilized 7–8 mol of the urethane or urea intermediate to the diazo compound for each mole of steroidal borate.

Epoxidation of acetate **10a** with *m*-chloroperbenzoic acid proceeded slowly to give epoxide **12a** (25.6% after 19 h at ambient temperature). Cleavage of **12a** with periodic acid in aqueous tetrahydrofuran gave aldehyde **15a** (53.2%), which existed as the corresponding lactol **21** both in the solid state and in solution (as evidenced by its IR spectrum in KBr and its ^{1}H NMR spectrum in Me_2SO, respectively). This material was converted to the dioxin **18a** (53%) when refluxed for 24 h in benzene with *p*-toluenesulfonic acid (TsOH).

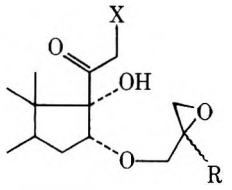


6, X = OH
7, X = Cl ($\Delta^{1,4}$-)

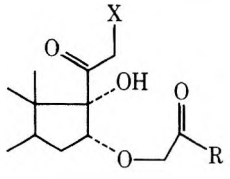
8



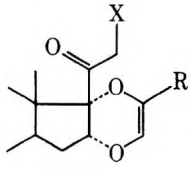
9, X = OH
10, X = OAc
11, X = Cl ($\Delta^{1,4}$-)



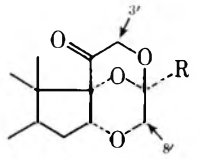
12, X = OAc
13, X = Cl ($\Delta^{1,4}$-)



14, X = OH
15, X = OAc
16, Cl ($\Delta^{1,4}$-)

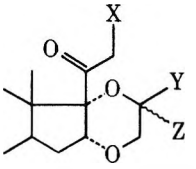


17, X = OH
18, X = OAc
19, X = Cl ($\Delta^{1,4}$-)

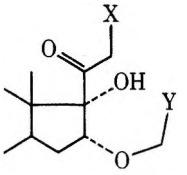


20
a, R = H
b, R = CH_3
c, R = C_6H_5
d, R = $(CH_3)_3C$

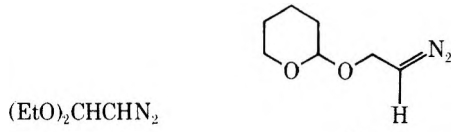
Similar sequences utilizing diazoalkenes **8b–d** provided the corresponding dioxins **18b–c** and **19a–d**. Interestingly, each step of the sequence **10** → **12** → **15** → **18** (21-acetate series) and **11** → **13** → **16** → **19** (21-chloro series) proceeded faster and in better yield with the methyl- and phenyl-substituted derivatives than in the unsubstituted series. This is undoubtedly due to the ability of these substituents to stabilize an adjacent positive charge. In the *tert*-butyl series, epoxidation proceeded rapidly, but the periodic acid cleavage and subsequent cyclization were slower than the unsubstituted case. Thus, the rate enhancement expected for an alkyl substituent is offset by the steric effect of the *tert*-butyl group on nucleophilic attack at the adjacent carbon atom.



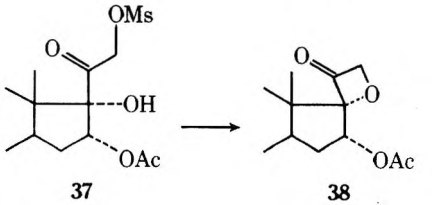
21, X = OAc; Y = OH; Z = H
22, X = OH; Y = OH; Z = H
23, X = OAc; Y = Z = =O
24, X = OH; Y = OEt; Z = H
25, X = OAc; Y = OAc; Z = H
26, X = OAc; Y = Z = H
27, X = Cl ($\Delta^{1,4}$-); Y = Z = H



28, X = OH; Y = $CH(OEt)_2$
29, X = OAc; Y = CH_2OH
30, X = OH; Y = CH_2OThp
31, X = OAc; Y = CH_2OMs
32, X = Cl ($\Delta^{1,4}$-); Y = CH_2OThp
33, X = Cl ($\Delta^{1,4}$-); Y = CH_2OH
34, X = Cl ($\Delta^{1,4}$-); Y = CH_2OMs



$(EtO)_2CHCHN_2$ 35 36



37 38

Ms = CH_3SO_2 Thp =

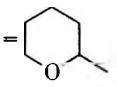


Table I

Registry no.	Compd	Mp, °C	Anal[a]	C-18	C-19	16α-(OCCCH$_3$)	Solvent
57331-56-3	**11b**	238–240	C, H, Cl, F	0.83	1.47	1.52	D[b]
	13b	193–236	C, H, Cl, F	0.95	1.51	1.27, 1.31[c]	C[d]
57331-58-5	**16b**	226–227	C, H, Cl, F	0.94	1.53	2.00	C
57331-26-7	**19b**	259–260	C, H, Cl, F	1.03	1.48	1.68	D
59648-62-3	**20b**	248–250	C, H, F	1.45	1.55	1.39	C
57331-37-0	**27**	320–321	C, H, Cl, F	0.82	1.45		D
57331-75-6	**33**	226–228	C, H, Cl, F	0.85	1.49		D
4524-39-4	**43**			0.94	1.53		C
	43			0.82	1.48		D

[a] Satisfactory analytical data (±0.4% for C, H, and halogens) reported for all new compounds listed in the table. [b] D = dimethyl-d_6 sulfoxide. [c] Diastereomeric mixture of epoxides. [d] C = chloroform.

Reaction of the 21-hydroxydioxins **17b–c** (prepared by saponification of the corresponding 21-acetates **18b–c**) with TsOH in refluxing benzene gave the internal ketals **20b–c.** Similar treatment of lactol **22** gave **20a.**

Aldehydes such as **14–16a** proved to be versatile intermediates to substituted dioxanes. Oxidation of **15a** with Fetizon's reagent[10] (Ag_2CO_3/Celite) slowly gave the lactone **23** with no oxidation of the 11β-hydroxyl group. A better preparation of such aldehydes is provided by reaction of borates with diazoacetal **35**[11] followed by acid hydrolysis. Reaction of borate **6** with diazo acetal **35** gave the acetal **28;** hydrolysis of **28** with aqueous acid gave lactol **22,** while treatment with TsOH in benzene gave the cyclic acetal **24.** Acetylation of **22** gave the lactol acetate **25** as a mixture of epimers.

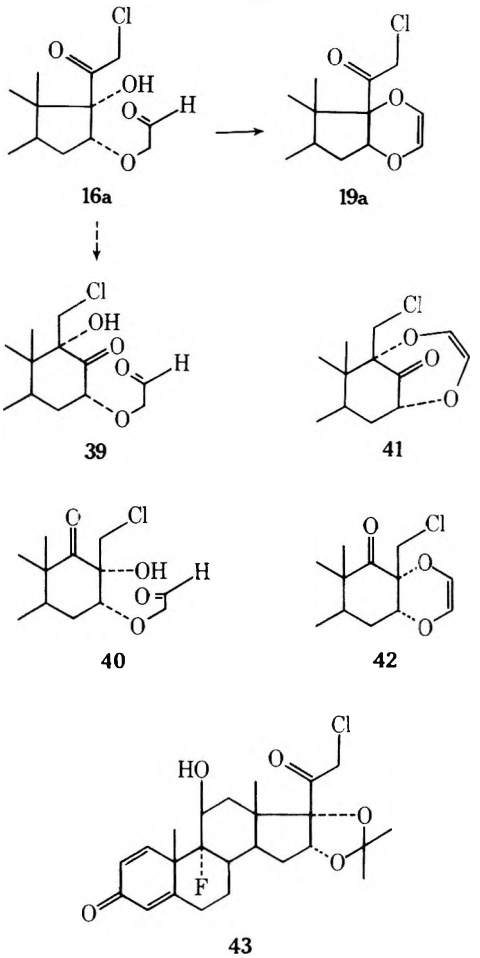
Reduction of **15a** with sodium borohydride in methanol gave the β-hydroxy ether **29** (30%). A better route to **29** involved diazo acetal **36,** prepared from glycolonitrile via the tetrahydropyranyl ether of ethanolamine.[12] Reaction of **6** with **36** gave the tetrahydropyranyl ether **30,** which could be converted to **29** by acetylation followed by hydrolysis with aqueous acetic acid. Treatment of the corresponding mesylate **31** with dry $NaHCO_3$ in Me_2SO[13] gave the parent dioxane **26.** A similar sequence proceeding from borate **7** gave the mesylate **34.** In view of the conversion of **37** to oxetanone **38** with $NaHCO_3$ in Me_2SO,[13] we were concerned that oxetanone formation might intervene in the case of **34** also; however, treatment of **34** smoothly gave dioxane **27.** Apparently the kinetic preference[14] for formation of six- vs. four-membered rings is responsible for this observation.

D-Ring Structure. D-Homoannelation of 17α-hydroxy-20-keto steroids under acidic or basic conditions is well documented.[15] All of the conditions utilized for ring closure in this work, therefore, had the potential for first D-homoannelating the steroid, as illustrated in Scheme I for **16a,** to eventually form either a dioxepin (**41**) or a rearranged dioxin (**42**), rather than the normal dioxin **19a.** The ^1H NMR spectrum of **19a** exhibits a coupling constant of 18 Hz between the magnetically nonequivalent C-21 methylene hydrogens (4.50 and 4.71 ppm), indicating that the C-20 carbonyl group is still adjacent to this methylene group[16] as it is in **16a** (J = 16 Hz, 4.28 and 4.99 ppm). The coupling constant anticipated for the C-21 methylene group of **41** or **42** is ca. 12 Hz; further, the chemical shift of this group would be expected ca. 0.6 ppm upfield[17] from that in normal 21-chloro-20-ketones. Similar coupling constants (16–18 Hz) are exhibited by **18c, 20b,** and **26.**

Further evidence for the normal D-ring structure of these compounds is provided by CD spectra. Compounds **19d** and **27** exhibit the expected[18] positive maxima at ca. 300 nm ($[\theta]_{306}$ = +15 900 and $[\theta]_{304}$ = +10 500, respectively). For comparison, dioxolane **43** exhibits $[\theta]_{300}$ = +12 080.

The IR, UV, and NMR spectra of these compounds were all in accord with the assigned structures. Table I illustrates

Scheme I



the effect of selected substitutions on C-18 and C-19 chemical shifts as compared with the dioxolane **43.** Only in the case of bicyclo[3.3.1]nonane derivatives such as **20b** is the C-18 resonance affected in any major way; the restricted conformation of the C-4′ carbonyl is responsible for this downfield shift of 0.51 ppm.

Summary

A novel class of annelated steroids has been prepared for the first time and characterized. The reaction of steroidal cycloborates with diazoalkanes discovered by Fried and Thomas has been utilized as the key step in a regioselective alkylation of 11β,16α,17,21-tetrahydroxy steroids. Conversion of these intermediates to steroidal [16α,17-b]dioxanes may be effected in a variety of ways. The integrity of the D ring of the resultant compounds was demonstrated by NMR and CD spectroscopy.

Experimental Section

All boiling points and melting points are uncorrected. Melting points were determined on a Thomas-Hoover capillary apparatus. NMR spectra were obtained on a Perkin-Elmer R-12B in either Me_2SO-d_6 or $CDCl_3$. CD spectra were determined on a Cary 60 in dioxane (c 0.022–0.066). IR spectra were determined on a Perkin-Elmer 621 in KBr. Column chromatography was performed with dry packed columns of J. T. Baker silica gel, 60–200 mesh.

21-Chloro-9-fluoro-11β,16α,17-trihydroxypregna-1,4-diene-3,20-dione 16,17-Cycloborate (7). A solution of 15.0 g of 21-chloro-9-fluoro-11β,16α,17-trihydroxypregna-1,4-diene-3,20-dione[10] and 60 g of boric oxide in 750 mL of methanol was refluxed for 1 h, cooled to 30 °C, and diluted with 1.5 L of water. The resulting solid was filtered and dried in vacuo to give 13.85 g (86.5%) of borate **7**.

Anal. Calcd for $C_{21}H_{25}BClFO_6$: B, 2.56. Found: B, 2.37.

3-Diazo-2-phenylpropene (8c) and 3-Diazo-2-*tert*-butylpropene (8d). Utilizing the general procedure of ref 9, 3-bromo-2-phenylpropene[20] and 2-bromomethyl-3,3-dimethyl-1-butene[21] were converted into **8c** and **8d**, respectively.

16α-(Allyloxy)-9-fluoro-11β,17,21-trihydroxypregn-4-ene-3,20-dione (9a). A total of 11.8 g (0.028 mol) of **6** was added in portions to a stirred solution of 3-diazopropene (**8a**) in 250 mL of ether (prepared from 0.22 mol of ethyl *N*-allylcarbamate[9]) to which 50 mL of methanol had been added at 0 °C. After nitrogen evolution ceased the solvent was removed in vacuo, the residue was dissolved in chloroform–hexane (4:1) and chromatographed on a 220-g silica gel column. Elution with chloroform gave 9.5 g (78%) of TLC pure **9a** after crystallization from acetone–hexane. Recrystallization of a similar sample from acetone–hexane gave the analytical sample, mp 199–201 °C.

Anal. Calcd for $C_{24}H_{33}FO_6$: C, 66.04; H, 7.62; F, 4.35. Found: C, 65.82; H, 7.83; F, 4.24.

21-(Acetyloxy)-9-fluoro-11β,17-dihydroxy-16α-(oxiranylmethoxy)pregn-4-ene-3,20-dione (12a). A solution of 6.44 g (0.013 mol) of **10a** (mp 189–191 °C, prepared by acetylation of **9a** with acetic anhydride–pyridine) in 150 mL of dichloromethane was stirred with 2.88 g (0.0143 mol) of *m*-chloroperbenzoic acid for 19 h at room temperature. The resulting solution was washed with a mixture of 10% potassium carbonate solution and 10% sodium sulfite solution, dried, and evaporated in vacuo. The residue was dissolved in dichloromethane and chromatographed on a 125-g silica gel column. Elution with chloroform and chloroform–ethyl acetate mixtures gave successively 3.5 g of unreacted starting material and 1.7 g (25.6%) of TLC pure **12a.** Two recrystallizations from acetone–hexane gave the analytical sample, mp 191–192.5 °C.

Anal. Calcd for $C_{26}H_{35}FO_8$: C, 63.15; H, 7.13; F, 3.84. Found: C, 63.17; H, 6.84; F, 3.64.

21-(Acetyloxy)-9-fluoro-5′ε,11β-dihydroxypregn-4-eno-[16α,17-*b*][1,4]dioxane-3,20-dione (21). A solution of 20.1 g of crude **12a** in 300 mL of tetrahydrofuran was stirred with a solution of 30 g of periodic acid in 75 mL of water for 6.75 h. The solution was diluted with water and extracted with chloroform. The chloroform extract was washed with 5% sodium bicarbonate solution, dried, and evaporated in vacuo to give 18.2 g of crude product. This material was dissolved in 60 mL of dichloromethane and chromatographed on a 450-g silica gel column. Fractions of 250 mL were collected as the column was eluted successively with 3 L each of dichloromethane, chloroform, and 19:1 chloroform–ethyl acetate. Fractions 17–21 were combined and evaporated in vacuo to give 4.4 g of recovered **10a.** Fractions 23–31 were combined and evaporated in vacuo to give 8.1 g of slightly impure **21** (53.2%). A portion of this material was recrystallized from acetone–hexane and then from acetonitrile to give the analytical sample, mp 205–208 °C.

Anal. Calcd for $C_{25}H_{33}FO_8$: C, 62.10; H. 7.50; F, 3.93. Found: C, 62.22; H, 7.28; F, 3.69.

21-(Acetyloxy)-9-fluoro-2′,3′-dihydro-11β-hydroxypregn-4-eno[16α,17-*b*][1,4]dioxin-3,20-dione (18a). A slurry of 100 mg of TsOH in 250 mL of benzene was distilled to a volume of 200 mL and 1.0 g (0.0021 mol) of **15a** added. The resulting solution was refluxed with a Dean–Stark trap filled with Linde 4A molecular sieves for 24 h under nitrogen. The solution was then cooled, diluted with chloroform, washed with 5% sodium bicarbonate solution, and dried. The residue obtained on solvent removal in vacuo was chromatographed on a 20-g silica gel column. Elution with 1:1 dichloromethane–chloroform gave 510 mg (53%) of TLC pure **18a.** Two recrystallizations from acetone–hexane gave the analytical sample, mp 231–240 °C dec.

Anal. Calcd for $C_{25}H_{31}FO_7$: C, 64.92; H, 6.76; F, 4.11. Found: C, 64.64; H, 6.54; F, 3.90.

9-Fluoro-11β-hydroxy-1′α-methylandrost-4-eno[17β,16α-*e*]-2,7,9-trioxabicyclo[3.3.1]nonane-3,4′-dione (20b). A slurry of 150 mg of TsOH in 600 mL of benzene was distilled to a volume of 500 mL, Linde 4A molecular sieves added to the trap, and the solution refluxed for 30 min. The solution was cooled and 775 mg of **17b** (prepared in 96% yield by hydrolysis of **18b** with 10% aqueous potassium carbonate in methanol) added. The resulting slurry was refluxed for 1 h and the benzene evaporated in vacuo. The residue was dissolved in chloroform, washed with 5% sodium bicarbonate solution and water, dried, and evaporated in vacuo. The residue was dissolved in chloroform and chromatographed on a 40- g silica gel column. Elution with chloroform gave 580 mg (74.8%) of material that was recrystallized twice from acetone–hexane to give the analytical sample of **20b** (375 mg), mp 248–256 °C dec.

Anal. Calcd for $C_{24}H_{31}FO_6$: C, 66.34; H, 7.19; F, 4.37. Found: C, 66.06; H, 7.18; F, 4.18.

9-Fluoro-5′ε,11β,21-trihydroxypregn-4-eno[16α,17-*b*][1,4]-dioxane-3,20-dione (22). A solution of 1.6 g (0.0031 mol) of **28** in 200 mL of tetrahydrofuran was refluxed with 20 mL of 1 N hydrochloric acid for 3 h. The solution was cooled, evaporated in vacuo to one-third the original volume, and diluted with water. The resulting solid was filtered and dried in vacuo to give 800 mg (58.9%) of product. Recrystallization from methanol gave 350 mg of **22,** mp 260–262 °C dec.

Anal. Calcd for $C_{23}H_{31}FO_7$: C, 63.00; H, 7.13; F, 4.33. Found: C, 62.96; H, 7.07; F, 4.48.

21-(Acetyloxy)-9-fluoro-11β-hydroxypregn-4-eno[16α,17-*b*][1,4]dioxane-3,5′,20-trione (23). A solution of 1.2 g (0.0025 mol) of **21** in 250 mL of toluene, slurried with 22 g of Fetizon's reagent,[10] was distilled to a volume of 200 mL. The resulting slurry was refluxed under nitrogen for 12.5 h, cooled, and filtered, and the solid washed well with chloroform. The filtrate and washings were combined and evaporated in vacuo, and the residue was chromatographed on a 40-g silica gel column. Elution with chloroform gave 270 mg (22.6%) of oil, which crystallized from acetone–hexane to give 181 mg of TLC pure solid. Recrystallization from acetone–hexane gave the analytical sample of **23,** mp 217–220 °C dec.

Anal. Calcd for $C_{25}H_{31}FO_8$: C, 62.75; H, 6.53; F, 3.97. Found: C, 62.61; H, 6.53; F, 3.73.

5′ε-Ethoxy-9-fluoro-11β,21-dihydroxypregn-4-eno[16α,17-*b*][1,4]dioxane-3,20-dione (24). A slurry of 100 mg of TsOH in 250 mL of benzene was distilled to 200 mL and Linde 4A molecular sieves added to the trap. After 30 min at reflux, the solution was cooled and 2 g (0.0039 mol) of **28** added. The resulting slurry was refluxed for 2 h under nitrogen, cooled, diluted with chloroform, washed with 5% sodium bicarbonate solution and water, dried, and evaporated. The crude residue (2.25 g) was dissolved in chloroform and chromatographed on a 100-g silica gel column. Elution with chloroform and 4:1 chloroform–ethyl acetate gave a total of 1.33 g (73.5%) of TLC pure material. Two recrystallizations from acetone–hexane (the last with charcoal) gave the analytical sample of **24,** mp 248–250 °C dec.

Anal. Calcd for $C_{25}H_{35}FO_7$: C, 64.64; H, 7.16; F, 4.10. Found: C, 64.75; H, 7.02; F, 3.95.

5′,21-Bis(acetyloxy)-9-fluoro-11β-hydroxypregn-4-eno[16α,17-*b*][1,4]dioxane-3,20-dione (25). A solution of 1.3 g of **22** in 10 mL of pyridine was kept for 4 h at ambient temperature with 5 mL of acetic anhydride. The solvent was removed in vacuo and the residue dissolved in chloroform, washed with dilute hydrochloric acid, and dried. The solvent was removed in vacuo and the residue dissolved in chloroform and chromatographed on a silica gel column. Elution with chloroform gave 506 mg of TLC pure material. Recrystallization from acetone–hexane gave the analytical sample of **25,** mp 195–197 °C.

Anal. Calcd for $C_{27}H_{35}FO_9$: C, 62.42; H, 6.21; F, 3.66. Found: C, 62.37; H, 6.44; F, 3.61.

21-(Acetyloxy)-9-fluoro-11β-hydroxypregn-4-eno[16α,17-*b*][1,4]dioxane-3,20-dione (26). A solution of 521 mg (0.000 93 mol) of **31** (prepared as described below for **34** by reaction of **6** with **36** followed by acetylation, hydrolysis, and mesylation) in 40 mL of dimethyl sulfoxide was stirred at 110 °C under nitrogen for 2 h with 600 mg of sodium bicarbonate (dried at 110 °C in vacuo). The solution was cooled, poured into 5% hydrochloric acid, and extracted with chloroform. The chloroform extract was washed twice with 2% hydrochloric acid, dried, and evaporated in vacuo to give 421 mg of oil. This material was chromatographed on a 20-g silica gel column. Elution with chloroform gave 331 mg (76.6%) of TLC pure material which solidified. Recrystallization from acetone–hexane gave 215 mg, mp 275–280 °C dec.

Anal. Calcd for $C_{25}H_{33}FO_7$: C, 64.64; H, 7.16; F, 4.09. Found: C, 64.59; H, 7.21; F, 3.98.

16α-(2,2-Diethoxyethoxy)-9-fluoro-11β,17,21-trihydroxy-

pregn-4-ene-3,20-dione (28). A solution of 2,2-diethoxy-1-diazoethane (prepared[11] from 0.0935 mol of *N*-2,2-diethoxyethylurea) in 300 mL of 3:2 ether–pentane was diluted with 100 mL of methanol and stirred at 0 °C. A total of 5.5 g (0.013 mol) of **6** was added in portions until nitrogen evolution stopped. The solvent was removed in vacuo and the residue recrystallized from methanol to give 3.4 g (51%) of slightly impure material. This was dissolved in chloroform and chromatographed on an 80-g silica gel column. Elution with chloroform gave 2.95 g, which was recrystallized from acetone–hexane to give the analytical sample (2.6 g), mp 208–210 °C.

Anal. Calcd for $C_{21}H_{41}FO_8$: C, 63.26; H, 8.07; F, 3.71. Found: C, 63.03; H, 7.86; F, 3.79.

21-Chloro-9-fluoro-11β,17-dihydroxy-16α-(2-mesyloxyethoxy)pregna-1,4-diene-3,20-dione (34). Reaction of **7** with **36** as described for **6** and **8a** gave **32** (mp 168–170 °C, 51.8%). Hydrolysis of **32** was effected by stirring a 5% solution in acetic acid–water (2:1) for 6 h, diluting with water, and recrystallizing the resulting solid from acetone–hexane to give the alcohol **33** (mp 226–228 °C, 53%).

A solution of 1.5 g (0.003 28 mol) of **33** in 25 mL of pyridine was cooled to 0 °C and 0.6 mL of methanesulfonyl chloride added. After 2 h the mixture was poured into cold dilute hydrochloric acid and extracted with chloroform. The chloroform solution was dried and evaporated in vacuo to 2.0 g of crude mesylate **34.**

21-Chloro-9-fluoro-11β-hydroxypregna-1,4-dieno[16α,17*b*][1,4]dioxane-3,20-dione (27). A solution of 2.0 g of crude **34** in 100 mL of dimethyl sulfoxide was stirred at 110 °C under nitrogen with 2.0 g of sodium bicarbonate (dried at 110 °C in vacuo). After 1 h the slurry was cooled, poured into 2 L of 2.5% hydrochloric acid, and extracted with chloroform. The chloroform solution was washed twice with dilute hydrochloric acid, dried, and evaporated in vacuo to give 1.4 g of crude product. This material was dissolved in chloroform and chromatographed on a 100-g silica gel column. Elution with chloroform gave 880 mg (62%) of material which crystallized from methanol–chloroform to give 405 mg of the analytical sample of **27**, mp 320–321 °C dec.

Anal. Calcd for $C_{23}H_{28}ClFO_5$: C, 62.94; H, 6.43; Cl, 8.08; F, 4.33. Found: C, 62.73; H, 6.20; Cl, 8.27; F, 4.27.

16α-(Acetyloxy)-9-fluoro-17,21-epoxy-11β-hydroxypregna-1,4-diene-3,20-dione (38). A solution of 3.0 g (0.0058 mol) of **37** (prepared by mesylation of triamcinolone 16-acetate[17]) in 70 mL of dimethyl sulfoxide was stirred at 130 °C under nitrogen for 2 h with 3.0 g of sodium bicarbonate (dried at 110 °C in vacuo). The reaction mixture was cooled, poured into cold 5% hydrochloric acid, and extracted with chloroform. The chloroform extract was dried and evaporated to give 4.2 g of oil. This was chromatographed on a 110-g silica gel column. Elution with 9:1 chloroform–hexane gave 1.1 g (45.2%) of TLC pure solid. Two recrystallizations from acetone–hexane gave the analytical sample of **38**, IR (KBr) 1810 cm^{-1}, mp 286–287 °C dec.

Anal. Calcd for $C_{23}H_{27}FO_6$: C, 66.01; H, 6.54; F, 4.54. Found: C, 65.78; H, 6.64; F, 4.33.

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Registry No.—**6**, 2795-82-6; **7**, 57331-55-2; **8a**, 2032-04-4; **9a**, 59648-65-6; **10a**, 57517-40-5; **12a**, 57331-44-9; **13b** epimer I, 63038-22-2; **13b** epimer II, 62990-39-0; **15a**, 62973-53-9; **17b**, 57331-22-3; **18a**, 57331-24-5; **18b**, 57331-21-2; **21**, 57372-75-5; **22**, 57331-30-3; **23**, 57331-35-8; **24**, 57331-27-8; **25**, 57331-31-4; **26**, 60882-09-9; **28**, 60882-11-3; **31**, 57331-68-7; **32**, 60882-13-5; **34**, 57331-76-7; **36**, 57331-64-3; **37**, 5168-33-2; **38**, 4982-55-2; 21-chloro-9-fluoro-11β,16α,17-trihydroxypregna-1,4-diene-3,20-dione, 805-95-8; boric oxide, 1303-86-2; 2,2-diethoxy-1-diazoethane, 3846-60-4; triamcinolone,16-acetate, 3925-42-6.

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Studies on the Syntheses of Heterocyclic Compounds. 715.[1] Stevens Rearrangement of *cis*-and *trans*-Berbine Methiodides by Sodium Bis(2-methoxyethoxy)aluminum Hydride

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Refluxing the *cis*- and *trans*-berbine methiodides in the presence of sodium bis(2-methoxyethoxy)aluminum hydride in dioxane gave rise to Stevens rearrangement to afford the spirobenzylisoquinolines and the 8-methylberbines. Studies using deuterium labeled substrates or optically active compounds have made clear the following matters. Quasi-axially oriented hydrogens at the C_8 and C_{14} positions of berbine methiodides were independently abstracted by the complex hydride. The *trans*-quinolizidinium methiodides gave the spirobenzylisoquinolines with retention of the stereochemistry at the C_8 and C_{14} positions and the 8-methylberbines with inversion at the C_8 position. On the other hand, the cis methiodides yielded the spirobenzylisoquinolines with retention at the C_8 and inversion at the C_{14} position, and the 8-methylberbines with retention at the C_8 position.

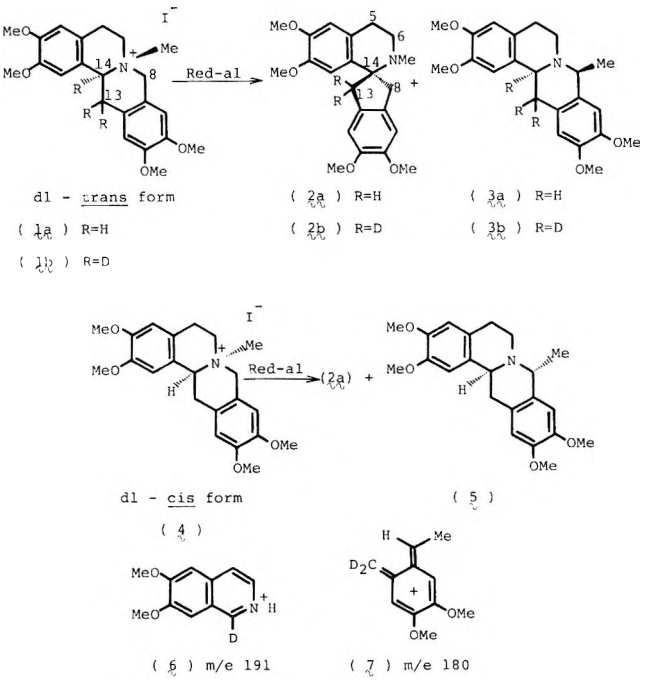
In the course of our investigation of the hydrogenolysis with sodium bis(2-methoxyethoxy)aluminum hydride (Red-al),[2] we found the Stevens type rearrangement of berbine methiodides yielding spirobenzylisoquinolines and 8-methylberbines.[3] The rearrangement of quaternary berbines to spirobenzylisoquinolines with strong bases has already been reported by two other groups.[4,5] Radical anion intermediate has been suggested for Stevens rearrangement.[6] Furthermore, the retention of the stereochemistry on the migrating group during the rearrangement was known.[3,7] However, the stereochemistry at the carbon anion formed has not yet been studied. It was hoped that the Stevens reaction of the quaternary quinolizidine would reveal the stereochemical requirement for the rearrangement. Therefore, we studied the relationship between the configuration of the quinolizidinium salt and the stereochemistry of the products and here wish to report our interesting findings.

(±)-Xylopinine was heated with methyl iodide in methanol to give a mixture of the methiodides, which were separated into the trans (**1a**) and cis (**4**) methiodides applying low solubility of the trans isomer in chloroform. The stereochemistry was determined by the comparison of the NMR spectra in Me_2SO-d_6;[3] the chemical shift of an *N*-methyl group of the quaternary trans isomer (**1a**) appeared at a higher field (δ 2.85) than that of the cis one (**4**) (δ 3.20). Refluxing the trans methiodide (**1**) with an excess of sodium bis(2-methoxyethoxy)aluminum hydride in dioxane for 24 h under nitrogen gave the spirobenzylisoquinoline (**2a**) in 77% yield and (±)-coralydine (**3a**)[8,9] in 6% yield. On the other hand, the cis isomer (**4**) yielded the spirobenzylisoquinoline (**2a**) in 51% yield and (±)-*O*-methylcorytenchirine (**5**)[9] in 20% yield under the same reaction conditions as above. These facts supported that the quaternary *N*-methyl groups shifted to the same side at the C_8 position to give the 8-methylberbines.

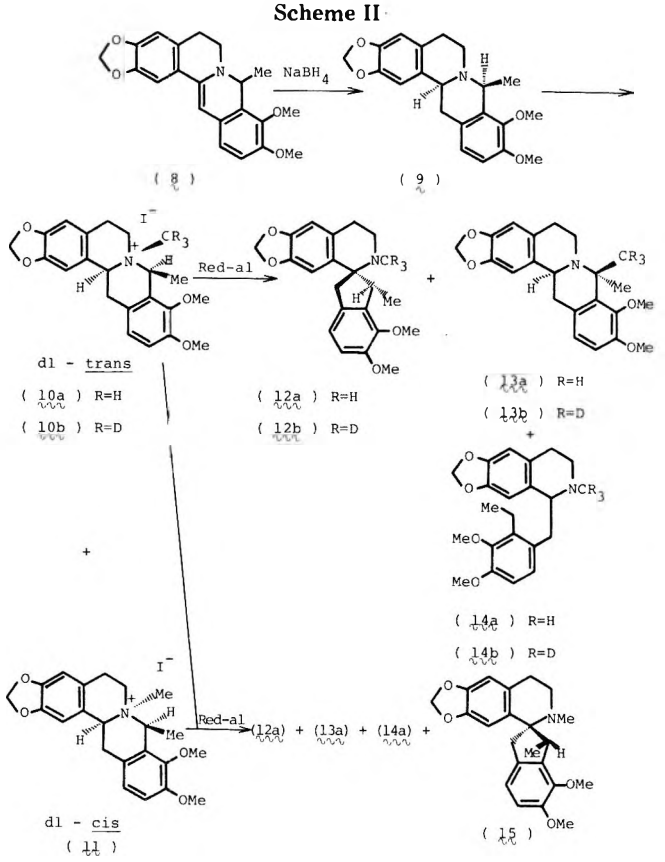
It was assumed that the anion first formed at the C_{14} position abstracted the α-hydrogen at the C_8 position and the anion at the C_8 position resulted in Stevens rearrangement yielding the 8-methylberbines. In order to examine this assumption the reaction of (±)-*trans*-[13,13,14-$^2H_3$]xylopinine methiodide (**1b**) was carried out under the same reaction conditions as above. This trideuterated compound (**1b**) was prepared from the corresponding free base.[10] Coralydine (**3b**) formed in 22.5% yield by the above reaction carried three deuterium atoms. The same spectrum showed a new parent ion at *m/e* 372, three mass units higher than that corresponding to the undeuterated authentic sample (**3a**), and the intensity was found to be more than 95% of trideuterio compound. Furthermore, the isoquinolinium ion (**6**) appeared at *m/e* 191, while the ion (**7**) formed by retro-Diels–Alder fragmentation was observed at *m/e* 180 as a base peak. The 13,13-dideuteriospirobenzylisoquinoline (**2b**) was obtained in 47% yield. The poorer yield of **2b** compared with the case of the nonlabeled compound would be partly due to the isotope effect of the deuterium at the C_{14} position. It was thus made clear that the anions were formed independently at the C_8 and C_{14} positions by the attack of the complex hydride.

Then, we presumed that abstraction of the quasi-axially oriented α hydrogen at the C_8 position of the trans isomer (**1a** and **1b**), followed by an inversion and an attack of the resulting anion at the C_8 position to the quaternary *N*-methyl group, gave the 8-methylberbine (**3a** and **3b**), since the antarafacial shift of the methyl group could not be expected. In order to clarify this assumption, the Stevens-type rearrangements of the trans [N-CD_3]methiodide (**10b**) of the 8β-methylberbine (**9**) and the trans methiodide (**18**) of the 8β-ethylberbine (**17**) were undertaken. (±)-8β-Methylcanadine (**9**), which was synthesized by reduction of the 8-methyldihydroberberine (**8**)[11] with sodium borohydride, was converted, on heating with methyl iodide in acetonitrile, into a 5:4 mixture of the trans (**10a**) and cis (**11**) methiodides. The trans methiodide (**10a**) showed the *N*-methyl group at δ 2.76 as a singlet and the 8-methyl group at δ 1.93 as a doublet with

Scheme I



Scheme II



J = 8 Hz, while the N-methyl and the 8-methyl groups of the cis isomer (**11**) appeared respectively at δ 3.15 as a singlet and δ 1.67 as a doublet with J = 8 Hz in the NMR spectra in Me_2SO-d_6. The trans one (**10a**), which was isolated as a pure form by recrystallization from methanol, was heated with the complex hydride under the same conditions as above for 24 h to furnish the spirobenzylisoquinoline (**12a**) in 9.4% yield, the 8,8-dimethylberbine (**13a**) in 22.5% yield, and 1-(2-ethyl-3,4-dimethoxybenzyl)-1,2,3,4-tetrahydro-2-methyl-6,7-methylenedioxyisoquinoline (**14a**) in 15% yield. The methyl group at the C_8 position of the spirobenzylisoquinoline (**12a**) was observed at δ 1.30 as a doublet with J = 7 Hz indicating that the methyl group exists syn to the nitrogen atom.[3] The structures of **13a** and **14a** were confirmed by analyses of the NMR and mass spectra. Then the trans [N-CD_3]methiodide (**10b**) was treated under the same conditions. The NMR spectrum ($CDCl_3$) of the 8,8-dimethylberbine (**13b**), which was formed together with **12b** and **14b**, exhibited one quaternary methyl group at δ 1.52 with a disappearance of the other methyl group, which was observed at δ 1.72 in that of the undeuterated sample (**13a**). The α-methyl group, oriented quasi-axially at the C_8 position of **13a**, was expected to resonate at a higher field than the β-methyl group oriented quasi-equatorially.[9] The above finding thus indicated the inversion of the stereochemistry at the C_8 position during the shift of the quaternary N-methyl group to the carbon at the C_8 position in the trans methiodides.

The above fact was further supported by the reaction of the methiodides (**18** and **19**) of the 8β-ethylberbines, which were prepared as follows. Sodium borohydride reduction of the sulfate (**16**)[12] in methanol yielded stereoselectively the 8β-ethylberbine (**17**), which was alternatively synthesized by photocyclization[13] of the enamide (**25**), followed by reduction with sodium borohydride of **26**, debenzylation of **27**, and methylation with diazomethane of the resulting phenol (**28**). The above enamide (**25**) obtained by condensation of the dihydroisoquinoline (**24**) hydrochloride with propionic anhydride in pyridine showed two maxima due to absorptions at 330 and 293 nm with log ϵ 4.14 and 3.97, respectively, indicating the Z form.[14]

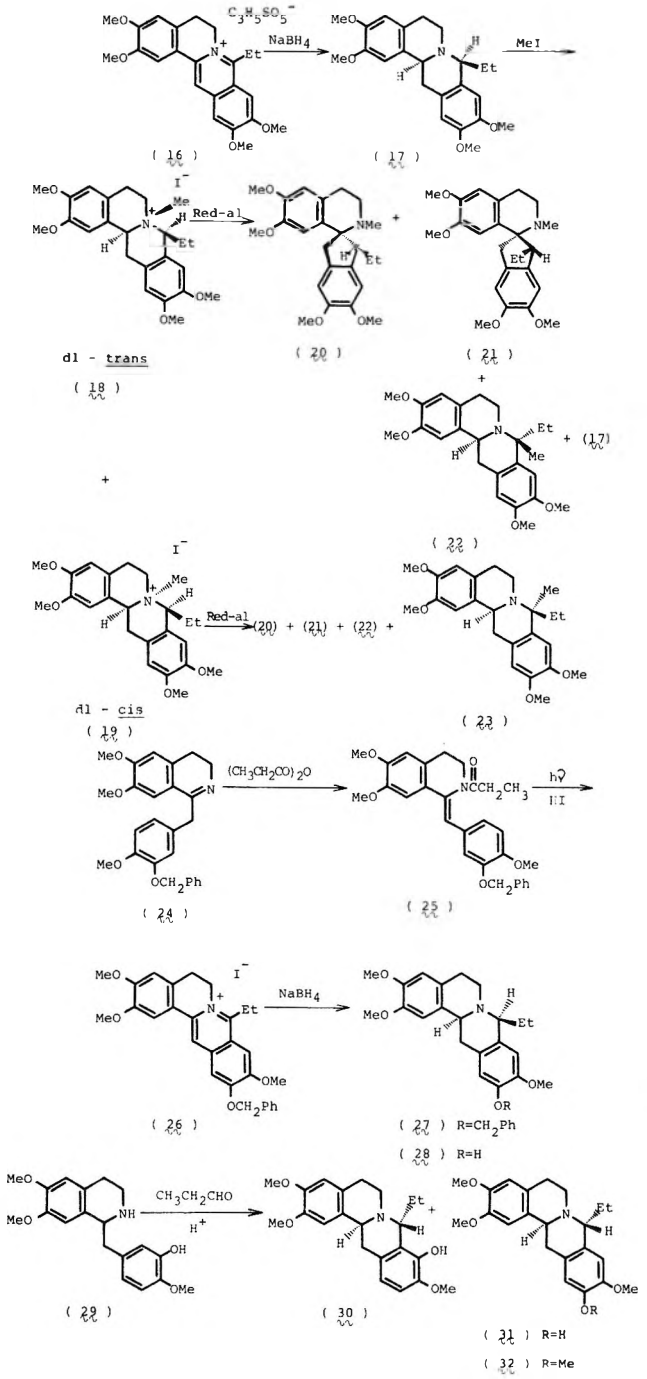
The stereochemistry of **17** was confirmed by the spectral comparison with the stereoisomer (**32**) synthesized as follows. Mannich reaction of the phenolic isoquinoline (**29**) hydrochloride with propionaldehyde in acetic acid gave a separable mixture of two positional isomers (**30** and **31**). The former compound (**30**), obtained in 47.8% yield, showed two aromatic protons at δ 6.48 and 6.77 with ortho coupling constant having J = 10 Hz in the NMR spectrum measured in Me_2SO-d_6 and a positive Gibbs indophenol test.[15] The latter (**31**), which was gained in 22.7% yield and showed a negative Gibbs indophenol test,[15] was transformed into **32** by a treatment with diazomethane. The above three compounds (**30, 31,** and **32**) exhibited no *trans*-quinolizidine bands in their IR spectra ($CHCl_3$) and the hydrogen of the C_{14} position at δ ca. 4.2 as a triplet, while **17** and **28** showed *trans*-quinolizidine bands at 2700–2800 cm^{-1} and the angular proton signal at a higher field than δ 3.8, which indicated the hydrogens at the C_8 and C_{14} positions of the compounds **17** and **28** to be cis to each other.[9]

Treatment of **17** with methyl iodide in acetonitrile for 3 days at room temperature afforded a mixture of the methiodides, recrystallization of which from methanol easily separated the trans (**18**) and cis (**19**) isomers in 41.6 and 50.5% yields, respectively. The former (**18**) showed the quaternary N-methyl group at δ 2.77, whereas the latter (**19**) exhibited it at δ 3.57 in the NMR spectra ($CDCl_3$).[3] Treatment of the trans methiodide (**18**) with the complex hydride for 24 h gave the spirobenzylisoquinolines (**20**), the 8α-ethyl-8β-methylberbine (**22**), and the N-demethylated product (**17**) in 31, 15.2, and 9.1% yield, respectively, in addition to a trace amount of the stereoisomer (**21**) of **20**. On the other hand, the cis isomer (**19**) afforded **21** and the stereoisomer (**23**) of **22** in 20.3 and 17.2% yield, respectively, together with a trace amount of **20** and **22**. The quaternary methyl group of **22** was observed at a more deshielded field at δ 1.52 than that of **23** at δ 1.37, supporting that the compound **22** has a quasi-equatorially oriented β-methyl group as shown in the structural formula. It was therefore revealed that the quasi-axially oriented α hydrogen at the C_8 position of the trans methiodides was attacked by the complex hydride and the resulting anion gave the 8-methylberbines with the inversion of the stereochemistry at the C_8 position, while the cis methiodides gave the 8-methylberbines without inversion.

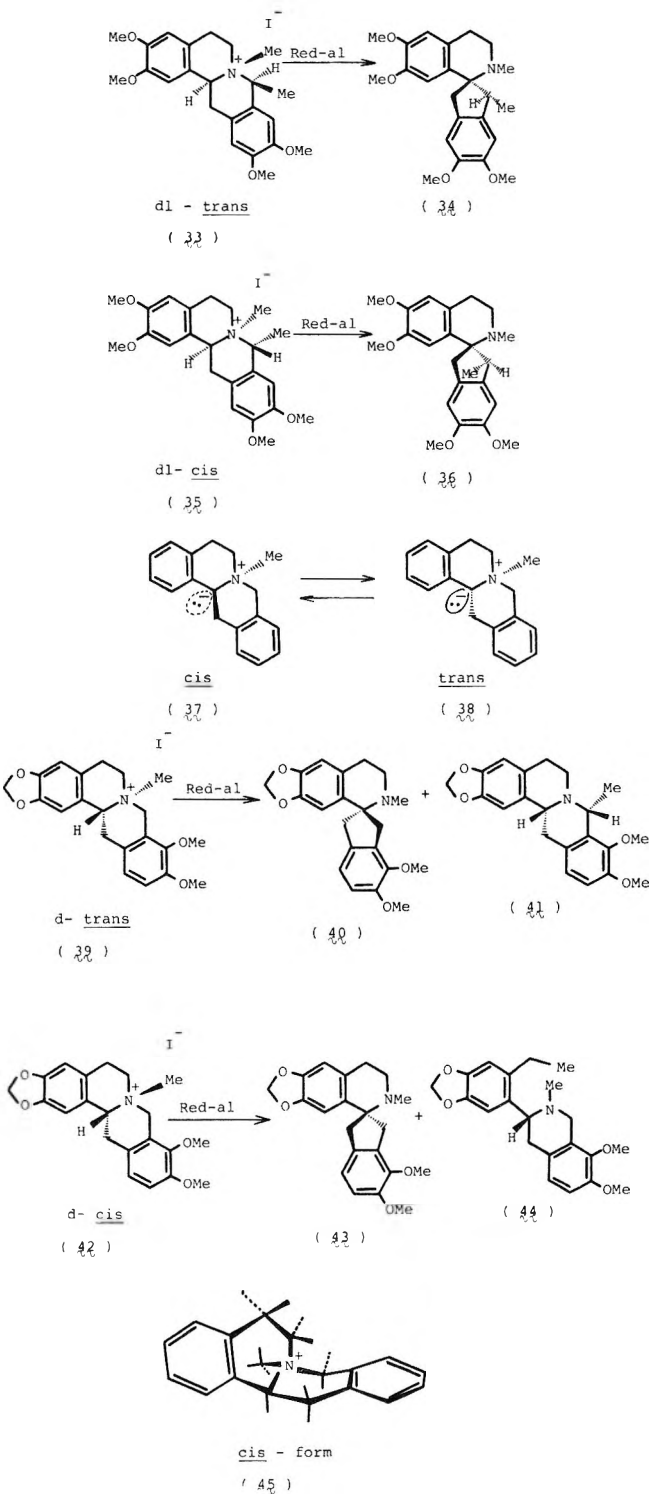
In the previous paper,[3] we deduced the retention of the configuration at the migrating atom in the Stevens rearrangement because the trans methiodides **33** and **35** afforded mainly the spirobenzylisoquinolines **34** and **36**, respectively. It was thus interesting that the stereoisomer **21** was obtained as one of the main products from the cis methiodide **19**. Furthermore, a 1:1 mixture of the trans and cis methiodides (**10a** and **11**) gave the stereoisomer (**15**) of **12a**, which was not obtained by the reaction using the pure trans methiodide (**10a**) as described above. We could account for this phenomenon as follows. The anion (**37**) formed at the C_{14} position of the cis methiodides would cause the inversion and the resulting *trans*-quinolizidinium ion (**38**) gave rise to the rearrangement to the spirobenzylisoquinolines.[16] Since the energy barrier for inversion of the anion is expected to be less than 6 kcal/mol,[17] the interchange of the betaines (**37** and **38**) would occur very easily as the case of the free bases of dibenzo[*a*,*g*]quinolizidines.[18]

Therefore the optically active (*R*)-(+)-canadine[19] was transformed into a mixture of the methiodides, fractional recrystallization of which furnished the trans isomer (**39**) in 51% yield and the cis one (**42**) in 20.7% yield. The former (**39**), which showed its quaternary N-methyl group at δ 2.83 in the NMR spectrum (Me_2SO-d_6),[3] gave the (−)-spirobenzyliso-

Scheme III



Scheme IV



quinoline (**40**)[5] and the (+)-8β-methylberbine (**41**) on refluxing with the complex hydride in dioxane. On the other hand, the latter (**42**), which exhibited the methyl group at δ 3.22 in the NMR spectrum (Me_2SO-d_6),[3] yielded the (+)-spirobenzylisoquinoline (**43**)[5] and (+)-3-(2-ethyl-4,5-methylenedioxyphenyl)-1,2,3,4-tetrahydro-7,8-dimethoxy-2-methylisoquinoline (**44**). The CD spectrum (methanol) of **40** showed two Davydov splittings centered at 276 and 205 nm, corresponding to the A → Lb and A → B bands, respectively, with negative first Cotton effects, whereas **43** showed a symmetrical curve of **40** as shown in Figure 1, indicating the absolute configurations of **40** and **43** to be 14*S* and 14*R*, respectively.[5,20]

On the consideration of the above findings, the conformation of the *cis*-quinolizidinium methiodides would exist in a more distorted form than a typical cis form (**45**)[21] having two half-chair conformations. It was thus estimated that the orientation of the anion at the C_{14} position of the cis methiodide is not favorable for the rearrangement.

Furthermore, we may again emphasize that the chemical shift of the quaternary *N*-methyl group in the NMR spectrum which is measured in Me_2SO-d_6 or $CDCl_3$ provides a good criterion to distinguish the *trans*- and *cis*-quinolizidinium iodides.

We can summarize the above Stevens rearrangement of berbine methiodides as follows. Quasi-axially oriented hydrogens at the C_8 and C_{14} positions of berbine methiodides were predominantly abstracted by sodium bis(2-methoxyethoxy)aluminum hydride in hot dioxane. In the case of the *trans*-quinolizidinium ions, the stereochemistry at the C_8 and C_{14} positions was retained during the conversion into the spirobenzylisoquinolines, and the 8-methylberbines were formed with the inversion of the configuration at the C_8 position. On the other hand, the *cis*-quinolizidinium ions gave

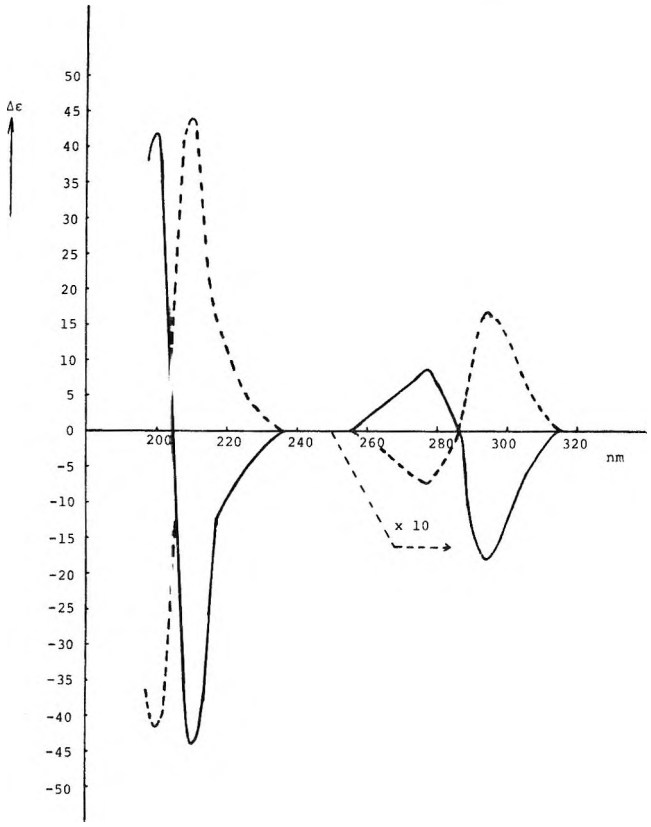


Figure 1. CD curves of the (−)-spirobenzylisoquinoline **40** (—) and (+)-**43** (- - - -) in methanol.

the spirobenzylisoquinolines with the retention of the stereochemistry at the C_8 position and the inversion at the C_{14} position, and the 8-methylberbines with the retention at the C_8 position.

Experimental Section

All melting points are uncorrected. UV spectra were taken with a Hitachi 124 spectrophotometer, IR spectra with a Hitachi 215 spectrophotometer, NMR spectra with a JNM-PMX-60 spectrometer (tetramethylsilane as an internal reference), and mass spectra with a Hitachi RMU-7 spectrometer. Optical rotations were measured with a JASCO-PIP-SL automatic polarimeter. CD curves were taken with a JASCO J-20 spectropolarimeter. A 70% solution of sodium bis(2-methoxyethoxy)aluminum hydride in benzene (Wako Chemicals) was used for the following reactions.

(±)-Xylopinine *trans*- and *cis*-Methiodides (1a and 4). A mixture (2.45 g) of (±)-xylopinine *trans*- and *cis*-methiodides prepared according to the known method[22] was washed with chloroform. The resulting mass, which was insoluble in chloroform, was recrystallized from methanol to give (±)-xylopinine *trans*-methiodide (**1a**, 1.25 g) as hygroscopic, colorless crystals: mp 250–252 °C; NMR (Me_2SO-d_6) δ 2.85 (3 H, s, NCH_3), 3.80 (12 H, s, 4 OCH_3), 6.83 (1 H, s, ArH), 6.87 (1 H, s, ArH), 6.95 (2 H, s, 2 ArH).

Anal. Calcd for $C_{22}H_{28}NO_4I{\cdot}0.2H_2O$: C, 52.74; H, 5.71; N, 2.80. Found: C, 52.46; H 5.45; N, 2.79. The chloroform-soluble portion was recrystallized repeatedly from methanol to give (±)-xylopinine *cis*-methiodide (**4**, 200 mg) as hygroscopic, pale yellowish crystals: mp 233–234 °C; NMR (Me_2SO-d_6) δ 3.20 (3 H, s, NCH_3), 3.73 (12 H, s, 4 OCH_3), 6.73 (1 H, s, ArH), 6.76 (1 H, s, ArH), 6.85 (2 H, s, 2 ArH).

Anal. Calcd for $C_{22}H_{28}NO_4I{\cdot}0.2H_2O$: C, 52.74; H, 5.71; N, 2.80. Found: C, 52.45; H, 5.62; N, 2.73.

(±)-[13,13,14-$^2H_3$]Xylopinine *trans*-Methiodide (1b). (±)-[13,13,14-$^2H_3$]Xylopinine, which was prepared by the known method,[10] was converted to its methiodide salts, from which the trans isomer, mp 250–252 °C, was separated in the same manner as above.

(±)-5,6,13,14α-Tetrahydro-9,10-dimethoxy-8β-methyl-2,3-methylenedioxyberbine (9). To a solution of 8-methyldihydroberberine (**8**,[11] 2 g, 5.7 mmol) in methanol (100 mL), sodium borohydride (0.5 g, 13.6 mmol) was added in small portions at 10 °C with stirring. After stirring for 2 h at room temperature, the solvent was evaporated in vacuo. The resulting residue was partitioned between benzene and water. The benzene layer was dried over anhydrous sodium sulfate and evaporated to give a solid, which was recrystallized from ethanol to afford **9** (1.7 g, 84.6%), mp 152–153 °C (lit.[3] mp 152–153 °C), whose spectral data were identical with those of the authentic sample.[3]

(±)-5,6,13,14α-Tetrahydro-9,10-dimethoxy-8β-methyl-2,3-methylenedioxyberbinium *trans*-Methiodide (10a). To a solution of (±)-8β-methylcanadine (**9**, 3.5 g, 9.9 mmol) in acetonitrile (80 mL) was added methyl iodide (10 mL), and the resulting mixture was allowed to stand overnight. After evaporation of the solvent, the resulting residue, which was estimated as a 5:4 mixture of the *trans*- and *cis*-methiodides by the NMR spectrum (Me_2SO-d_6), was washed with chloroform. The resulting mass, which was insoluble in chloroform, was repeatedly recrystallized from methanol to give **10a** (380 mg) as pale yellowish prisms: mp 240–242 °C; NMR (Me_2SO-d_6) δ 1.93 (3 H, d, J = 8 Hz, 8-CH_3), 2.76 (3 H, s, NCH_3), 3.79 (6 H, s, 2 OCH_3), 6.02 (2 H, s, OCH_2O), 6.85 (1 H, s, ArH), 7.09 (3 H, br s, 3 ArH).

Anal. Calcd for $C_{22}H_{26}NO_4I$: C, 53.34; H, 5.29; N, 2.83. Found: C, 53.11; H, 5.26; N, 2.78.

(±)-8β-Ethyl-2,3,10,11-tetramethoxy-14α*H*-berbine (17). To a solution of the sulfate **16**[12] (2 g) in methanol (500 mL) was added in portions sodium borohydride (2.5 g) below 10 °C with stirring and the mixture was stirred for 4 h at room temperature. After evaporation of the solvent, the residue was partitioned between water and benzene. The benzene layer was washed with water, dried over potassium carbonate, and evaporated to give a powder, recrystallization of which from methanol afforded **17** (960 mg, 66.8%) as colorless needles: mp 150–151 °C; IR ($CHCl_3$) 2820–2750 cm^{-1} (Bohlmann bands); NMR ($CDCl_3$) δ 0.70 (3 H, t, J = 7 Hz, CH_2CH_3), 1.50–2.20 (2 H, m, CH_2CH_3), 3.83 (12 H, s, 4 OCH_3), 6.55 (1 H, s, ArH), 6.58 (2 H, s, 2 ArH), 6.70 (1 H, s, ArH).

Anal. Calcd for $C_{23}H_{29}NO_4$: C, 72.03; H, 7.62; N, 3.65. Found: C, 71.94; H, 7.55; N, 3.69.

(*Z*)-1-(3-Benzyloxy-4-methoxybenzylidene)-1,2,3,4-tetrahydro-2-propionyl-6,7-dimethoxyisoquinoline (25). A mixture of the 3,4-dihydroisoquinoline (**24**)[23] hydrochloride (1 g) and propionic anhydride (2.5 mL) in pyridine (2.5 mL) was heated for 3 h on a steam bath. After evaporation of the reagents under reduced pressure, the residue was recrystallized from methanol to afford **25** (850 mg, 79.6%) as yellowish needles: mp 158–159 °C; UV (MeOH) λ_{max} (log ε) 330 (4.14), 293 nm (3.97); IR ($CHCl_3$) 1625 cm^{-1} (C=O); NMR ($CDCl_3$) δ 0.80 (3 H, t, J = 7 Hz, CH_2CH_3), 3.83 (3 H, s, OCH_3), 3.87 (3 H, s, OCH_3), 3.92 (3 H, s, OCH_3), 5.12 (2 H, s, OCH_2Ph), 6.52–7.38 (11 H, m, 10 ArH and >=CH–).

Anal. Calcd for $C_{29}H_{31}NO_5$: C, 73.55; H, 6.60; N, 2.96. Found: C, 73.41; H, 6.80; N, 2.95.

11-Benzyloxy-8-ethyl-5,6-dihydro-2,3,10-trimethoxydibenzo[*a*,*g*]quinolizinylium Iodide (26). A mixture of the above enamide **25** (733 mg), anhydrous methanol (290 mL), dioxane (250 mL), and 57% hydriodic acid (0.2 mL) was irradiated for 15 min with a 450-W high-pressure mercury lamp enclosed in a quartz well under cooling with ice. The resulting yellow crystals were recrystallized from methanol to give **26** (234 mg, 25.8%) as pale yellow crystals: mp 248–249 °C; UV (MeOH) λ_{max} (log ε) 339 sh (3.86), 308 (4.08), 288 sh (4.22), 266 sh nm (3.86).

Anal. Calcd for $C_{29}H_{30}NO_4I{\cdot}0.5H_2O$: C, 58.63; H, 5.26; N, 2.36. Found: C, 58.46; H, 5.27; N, 2.27.

(±)-11-Benzyloxy-8β-ethyl-2,3,10-trimethoxy-14α*H*-berbine (27). To a solution of the above iodide **26** (181 mg) in methanol (54 mL) was added in small portions sodium borohydride (181 mg) below 10 °C with stirring and, after addition, the mixture was stirred for 5 h at room temperature and then refluxed for 30 min. After evaporation of the solvent, the residue was partitioned between water and chloroform. The chloroform layer was washed with water, dried over potassium carbonate, and evaporated to leave a powder, which was recrystallized from methanol to give **27** (77.3 mg, 54.2%) as colorless needles: mp 157–158 °C; IR ($CHCl_3$) 2850–2750 cm^{-1} (Bohlmann bands); NMR ($CDCl_3$) δ 0.72 (3 H, t, J = 7 Hz, CH_2CH_3), 3.85 (9 H, s, 3 OCH_3), 5.10 (2 H, s, OCH_2Ph).

Anal. Calcd for $C_{29}H_{33}NO_4$: C, 75.79; H, 7.24; N, 3.05. Found: C, 75.19; H, 7.27; N, 2.93.

(±)-8β-Ethyl-2,3,10-trimethoxy-14α*H*-berbin-11-ol (28). A mixture of the above base **27** (58 mg) and concentrated hydrochloric acid (9 mL) in ethanol (9 mL) was refluxed for 4 h. After evaporation of the solvent and reagent, the residue was partitioned between 10% ammonia and chloroform. The chloroform layer was washed with water, dried over anhydrous sodium sulfate, and evaporated to leave

a powder, recrystallization of which from methanol afforded 28 (12 mg, 26%) as colorless plates: mp 169–170 °C; IR ($CHCl_3$) 3570 (OH), 2830–2750 cm^{-1} (Bohlmann bands); NMR ($CDCl_3$) δ 0.72 (3 H, t, J = 6.6 Hz, CH_2CH_3), 1.50–2.20 (2 H, m, CH_2CH_3), 3.85 (9 H, s, 3 OCH_3), 6.55 (3 H, s, 3 ArH), 6.70 (1 H, s, ArH).

Anal. Calcd for $C_{22}H_{27}NO_4$: C, 71.52; H, 7.37; N, 3.79. Found: C, 71.50; H, 7.60; N, 3.60.

Mannich Reaction of 1,2,3,4-Tetrahydro-1-(3-hydroxy-4-methoxybenzyl)-6,7-dimethoxyisoquinoline (29). A mixture of the phenolic isoquinoline (**29**)[23] hydrochloride (1.0 g) and propionaldehyde (2 mL) in glacial acetic acid (100 mL) was refluxed for 2.5 h. After evaporation of the reagents under reduced pressure, the residue was partitioned between 10% ammonia and chloroform. The chloroform extract was washed with water, dried over anhydrous sodium sulfate, and evaporated to leave a gum, which was purified by silica gel column chromatography with benzene–methanol (98:2 v/v). Evaporation of the eluate gave a gum, recrystallization of which from ethanol yielded (±)-8α-ethyl-2,3,10-trimethoxy-14α*H*-berbin-9-ol (**30**, 483 mg, 47.8%) as colorless prisms: mp 204.5–205.5 °C; IR ($CHCl_3$) 3550 cm^{-1} (OH); NMR ($CDCl_3$) δ 1.03 (3 H, t, J = 6 Hz, CH_2CH_3), 1.22–1.90 (2 H, m, CH_2CH_3), 3.80 (9 H, s, 3 OCH_3), 4.20 (1 H, t, J = 8.2 Hz, 14-H), 6.54 (4 H, s, 4 ArH); NMR (Me_2SO-d_6) δ 1.00 (3 H, t, J = 6 Hz, CH_2CH_3), 3.73 (6 H, s, 2 OCH_3), 3.75 (3 H, s, OCH_3), 6.48 (1 H, d, J = 10 Hz, ArH), 6.66 (1 H, s, ArH), 6.77 (1 H, d, J = 10 Hz, ArH), 6.78 (1, H, s, ArH), which gave a positive Gibbs indophenol test.[11]

Anal. Calcd for $C_{22}H_{27}NO_4 \cdot 0.5H_2O$: C, 69.89; H, 7.47; N, 3.71. Found: C, 70.26; H, 7.26; N, 3.68.

The mother liquor during the above recrystallization was evaporated to leave a gum, which was further chromatographed on silica gel in benzene. The resulting mass was recrystallized from ethanol to give (±)-8α-ethyl-2,3,10-trimethoxy-14α*H*-berbin-11-ol (**31**, 229 mg, 22.7%) as colorless scales: mp 137–138 °C; IR ($CHCl_3$) 3550 cm^{-1} (OH); NMR ($CDCl_3$) δ 1.08 (3 H, t, J = 6.2 Hz, CH_2CH_3), 1.50–1.90 (2 H, m, CH_2CH_3), 3.87 (9 H, s, 3 OCH_3), 4.22 (1 H, t, J = 8.4 Hz, 14-H), 6.55 (3 H, s, 3 ArH), 6.60 (1 H, s, 3 ArH); NMR (Me_2SO-d_6) δ 1.00 (3 H, t, J = 7 Hz, CH_2CH_3), 3.72 (9 H, s, 3 OCH_3), 6.43 (1 H, s, ArH), 6.60 (2 H, s, 2 ArH), 6.72 (1 H, s, ArH), which showed a negative Gibbs indophenol test.[11]

Anal. Calcd for $C_{22}H_{27}NO_4$: C, 71.52; H, 7.37; N, 3.79. Found: C, 71.70; H, 7.50; N, 3.50.

(±)-8α-Ethyl-2,3,10,11-tetramethoxy-14α*H*-berbine (32). To a solution of the above base **31** (256 mg) in methanol (10 mL) was added an excess of diazomethane in ether, which was prepared from *N*-nitrosomethylurea, and the mixture was allowed to stand overnight at room temperature. After evaporation of the solvents, the residue was dissolved in dilute hydrochloric acid, which was washed with ether. The acidic solution was then basified with 10% aqueous sodium hydroxide solution. Extraction with chloroform, followed by washing the extract with water, drying over anhydrous sodium sulfate, and evaporation of the chloroform extract, gave a powder, which was recrystallized from methanol to yield **32** (120 mg, 45%) as colorless crystals: mp 121–122.5 °C; NMR ($CDCl_3$) δ 1.06 (3 H, t, J = 7 Hz, CH_2CH_3), 1.40–1.90 (2 H, m, CH_2CH_3), 3.81 (3 H, s, OCH_3), 3.86 (9 H, s, 3 OCH_3), 4.25 (1 H, t, J = 8 Hz, 14-H), 6.52 (1 H, s, ArH), 6.58 (3 H, s, 3 ArH).

Anal. Calcd for $C_{23}H_{29}NO_4$: C, 72.04; H, 7.62; N, 3.65. Found: C, 72.00; H, 7.90; N, 3.30.

(±)-8β-Ethyl-2,3,10,11-tetramethoxy-14α*H*-berbinium *trans*- (18) and *cis*- (19) Methiodides. To a solution of the 8β-ethylberbine **17** (2.37 g) in acetonitrile (120 mL) was added methyl iodide (6 mL) and the mixture was allowed to stand for 3 days at room temperature in a dark place. After evaporation of the reagents, the residue was recrystallized from methanol to give the *trans*-methiodide (**18**, 1.35 g, 41.6%) as orange prisms: mp 244.5–246 °C; NMR ($CDCl_3$) δ 1.33 (3 H, t, J = 7 Hz, CH_2CH_3), 2.77 (3 H, s, NCH_3), 3.87 (6 H, s, 2 OCH_3), 3.89 (6, H, s, 2 OCH_3), 6.33, 6.70, 6.83, and 7.00 (each 1 H, each s, 4 ArH).

Anal. Calcd for $C_{24}H_{32}NO_4I \cdot 0.2H_2O$: C, 54.59; H, 5.99; N, 2.65. Found: C, 54.28; H, 6.25; N, 2.82.

The resulting mass from the mother liquor during the above recrystallization was recrystallized from methanol to give the *cis*-methiodide (**19**, 1.64 g, 50.5%) as colorless needles: mp 194–196 °C; NMR ($CDCl_3$) δ 1.37 (3 H, t, J = 6.2 Hz, CH_2CH_3), 3.57 (3 H, s, NCH_3), 3.85 (6 H, s, 2 OCH_3), 3.88 (6 H, s, 2 OCH_3), 6.53, 6.68, 6.80, and 6.88 (each 1 H, each s, 4 ArH).

Anal. Calcd for $C_{24}H_{32}NO_4I \cdot 0.2H_2O$: C, 54.59; H, 5.99; N, 2.65. Found: C, 54.30; H, 6.20; N, 2.40.

(*R*)-(+)-Canadine *trans*-(39) and *cis*- (42) Methiodides. To a solution of (+)-canadine[19] (580 mg, 1.71 mmol) in methanol (50 mL) was added methyl iodide (3 mL), and the mixture was allowed to stand overnight. After evaporation of the solvent, the resulting residue was washed with chloroform. The mass which was insoluble in chloroform was recrystallized from methanol to give (+)-canadine *trans*-methiodide (**39**, 420 mg, 51%): mp 252–254 °C (lit.[24] 252–254 °C); $[\alpha]^{18}_D$ +115.2° (c 0.13, MeOH) (lit.[24] $[\alpha]^{21}_D$ +124.5°); CD (MeOH) nm (Δε) 288 (−0.15), 267 (+0.07), 254 (−0.29), 236 (+6.79), 223 (+5.85), 215 (13.69). The above chloroform solution was evaporated and the resulting residue was recrystallized from methanol to give (+)-canadine *cis*-methiodide (**42**, 170 mg, 20.7%): mp 220 °C (lit.[25] 220 °C); $[\alpha]^{18}_D$ +100° (c 0.04, MeOH); CD (MeOH) nm (Δε) 287 (+0.61), 269 (+0.30), 266 (+0.37), 236 (+12.89), 266 (+6.56), 213 (+28.69).

Reaction of (±)-Xylopinine *trans*-Methiodide (1a) with Sodium Bis(2-methoxyethoxy)aluminum Hydride. A mixture of **1a** (1 g, 2.012 mmol) and 70% sodium bis(2-methoxyethoxy)aluminum hydride (5.8 g, 0.02 mol) in dry dioxane (100 mL) was refluxed for 24 h under a current of nitrogen. After evaporation of the solvent, the excess reagent was decomposed with 10% aqueous sodium hydroxide solution on cooling. The separated benzene layer was washed with water, dried over sodium sulfate, and evaporated to leave a brownish caramel, which was purified by silica gel column chromatography. The elution with benzene–methanol (99.5:0.5 v/v) afforded a solid, recrystallization of which from ethanol yielded (±)-3-coralydine (**3a**, 42 mg, 6%): mp 95–96 °C (lit.[3] 95–96 °C); mass spectrum *m/e* 369, 354, 192, 190, 178, 163. Further elution with benzene–methanol (99:1 v/v) gave a solid, recrystallization of which from ethanol afforded (±)-2,3,10,11-tetramethoxyochotensane (**2a**, 572 mg, 77%): mp 138–139 °C; NMR ($CDCl_3$) δ 2.26 (3 H, s, NCH_3), 2.77–2.95 (4 H, m, CH_2CH_2), 3.22 (2 H, br s, 8-H and 14-H), 3.33 (2 H, br s, 8-H and 14-H), 3.59 (3 H, s, OCH_3), 3.81 (3 H, s, OCH_3), 3.83 (6 H, s, 2 OCH_3), 6.43 (1 H, s, ArH), 6.47 (1 H, s, ArH), 6.69 (2 H, s, 2 ArH); mass spectrum *m/e* 369, 354, 204, 164.

Anal. Calcd for $C_{22}H_{27}NO_4$: C, 71.52; H, 7.37; N, 3.79. Found: C, 71.75; H, 7.28; N, 3.75.

Reaction of (±)-Xylopinine *cis*-Methiodide (4) with Sodium Bis(2-methoxyethoxy)aluminum Hydride. A mixture of **4** (100 mg, 0.2012 mmol) and 70% sodium bis(2-methoxyethoxy)aluminum hydride (580 mg, 2.012 mmol) in dry dioxane (10 mL) was refluxed for 24 h under the same conditions as above. The same workup as above gave a caramel, which was developed by preparative TLC on silica gel with methanol–chloroform (1:9 v/v) and then methanol–ethyl acetate–benzene (1:4:5 v/v). The part with R_f 0.75 was extracted with chloroform–methanol (9:1 v/v) to afford *O*-methylcorytenchirine (**5**, 15 mg, 20%), mp 86–88 °C (lit.[9] mp 86–88 °C), whose spectral data were identical with those of the authentic sample.[5] The part with R_f 0.5 was extracted with chloroform–methanol (9:1 v/v) to leave **2a** (38 mg, 51%), which was identical with the authentic sample prepared as above.

Reaction of (±)-[13,13,14-$^2H_3$]Xylopinine *trans*-Methiodide (1b) with Sodium Bis(2-methoxyethoxy)aluminum Hydride. A mixture of **1b** (330 mg, 0.66 mmol) and 70% sodium bis(2-methoxyethoxy)aluminum hydride (1.9 g, 6.6 mmol) in dry dioxane (30 mL) was refluxed for 24 h under the same conditions as above. The same workup as above gave a brownish caramel, which was purified by silica gel column chromatography. The elution with benzene–methanol (99.5:0.5 v/v) afforded a solid, recrystallization of which from ethanol gave (±)-[13,13,14-$^2H_3$]coralydine (**3b**, 55 mg, 22.5%): NMR ($CDCl_3$) δ 1.53 (3 H, d, J = 7 Hz, 8-CH_3), 3.83 (12 H, s, 4 OCH_3), 6.57 (1 H, s, ArH), 6.61 (1 H, s, ArH), 6.65 (1 H, s, ArH), 6.72 (1 H, s, ArH); mass spectrum *m/e* 372, 357, 193, 191, 180, 165. Further elution with benzene–methanol (99:1 v/v) gave a solid, which was recrystallized from ethanol to afford **2b** (115 mg, 47%): NMR ($CDCl_3$) δ 2.26 (3 H, s, NCH_3), 2.77–2.95 (4 H, m, CH_2CH_2), 3.22 (1 H, br s, 8-H), 3.33 (1 H, br s, 8-H), 3.81 (3 H, s, OCH_3), 3.83 (6 H, s, 2 OCH_3) 6.43 (1 H, s, ArH), 6.47 (1 H, s, ArH), 6.69 (2 H, s, 2 ArH); mass spectrum *m/e* 371, 356, 206, 204, 166.

Reaction of (±)-5,6,13,14-Tetrahydro-9,10-dimethoxy-8β-methyl-2,3-methylenedioxyberbinium *trans*-Methiodide (10a) with Sodium Bis(2-methoxyethoxy)aluminum Hydride. A solution of **10a** (360 mg, 0.727 mmol) and 70% sodium bis(2-methoxyethoxy)aluminum hydride (2.1 g, 7.27 mmol) in dry dioxane (40 mL) was refluxed for 24 h under the same conditions as above, followed by the workup as above, to afford a brownish caramel, which was purified by silica gel column chromatography with benzene–methanol (99.5:0.5 v/v) as eluent. The first fraction afforded a solid, recrystallization of which from ethanol gave (±)-5,6,13,14-tetrahydro-9,10-dimethoxy-8,8-dimethyl-2,3-methylenedioxyberbine (**13a**, 60 mg, 22.5%) as pale yellowish crystals: mp 114–115 °C; NMR ($CDCl_3$) δ 1.52 (3 H, s, 8-CH_3), 1.72 (3 H, s, 8-CH_3), 3.83 (3 H, s, OCH_3), 3.87 (3 H, s, OCH_3), 5.83 (2, H, s, OCH_2O), 6.52 (1 H, s, ArH), 6.60 (1 H,

s, ArH), 7.17 (2 H, s, 2 ArH); IR ($CHCl_3$) 935 cm^{-1}; mass spectrum *m/e* 367, 352, 192, 176, 174.

Anal. Calcd for $C_{22}H_{25}NO_4$: C, 71.91; H, 6.86; N, 3.81. Found: C, 71.51; H, 6.77; N, 3.59.

The second fraction afforded the spirobenzylisoquinoline (**12a**, 25 mg, 9.4%) as a caramel: NMR ($CDCl_3$) δ 1.30 (3 H, d, J = 7 Hz, 8-CH_3), 2.33 (3 H, s, NCH_3), 3.80 (3 H, s, OCH_3), 3.86 (3 H, s, OCH_3), 5.75 (2 H, s, OCH_2O), 6.25 (1 H, s, ArH), 6.48 (1 H, s, ArH), 6.70 (1 H, d, J = 10 Hz, ArH), 6.88 (1 H, d, J = 10 Hz, ArH); IR ($CHCl_3$) 935 cm^{-1}; mass spectrum *m/e* 367, 352, 190, 188, 178, 163, which was converted into the hydrochloride. Recrystallization from methanol–ether afforded colorless crystals, mp 210–213 °C dec.

Anal. Calcd for $C_{22}H_{25}NO_4$·HCl: C, 65.42; H, 6.49; N, 3.47. Found: C, 65.59; H, 6.48; N, 3.38.

The third fraction gave 1-(2-ethyl-3,4-dimethoxybenzyl)-1,2,3,4-tetrahydro-2-methyl-6,7-methylenedioxyisoquinoline (**14a**, 40 mg, 15%) as a caramel: NMR ($CDCl_3$) δ 1.07 (3 H, t, J = 7 Hz, CH_2CH_3), 2.45 (3 H, s, NCH_3), 3.80 (6 H, s, 2 OCH_3), 5.76 (2 H, s, OCH_2O), 5.90 (1 H, s, ArH), 6.50 (1 H, s, ArH), 6.70 (1 H, s, ArH), 6.73 (1 H, s, ArH); IR ($CHCl_3$) 935 cm^{-1}, which was converted into the hydrochloride. Recrystallization from methanol–ether gave colorless crystals, mp 124–125 °C.

Anal. Calcd for $C_{22}H_{27}NO_4$·HCl·H_2O: C, 62.33; H, 6.90; N, 3.30. Found: C, 62.32; H, 7.17; N, 3.29.

Reaction of the Mixture of (±)-5,6,13,14α-Tetrahydro-9,10-dimethoxy-8α-methyl-2,3-methylenedioxyberbinium *trans*- and *cis*-Methiodides (10a and 11) with Sodium Bis(2-methoxyethoxy)aluminum Hydride. A solution of a mixture of **10a** and **11** (2.1 g, 4.24 mmol), which was obtained from the above mother liquor during the preparation of the *trans*-methiodide (**10a**), and 70% sodium bis(2-methoxyethoxy)aluminum hydride (12.2 g, 0.0424 mol) in dry dioxane (200 mL) was refluxed for 24 h under the same conditions as above and the workup of the reaction mixture left a brownish caramel, which was purified by silica gel column chromatography with benzene–methanol (99.5:0.5 v/v) as eluent. The first fraction afforded **13a** (187 mg, mp 114–115 °C), which was identical with the authentic sample prepared as above. The second fraction afforded **12a** (88 mg), which was identical with the authentic sample prepared as above. The third fraction gave **14a** (127 mg), which was also identical with the above authentic sample. Further elution with benzene–methanol (99:1 v/v) afforded **15** (315 mg) as a caramel: NMR ($CDCl_3$) δ 1.03 (3 H, d, J = 7 Hz, 8-CH_3), 2.33 (3 H, s, NCH_3), 3.70 (3, H, s, OCH_3), 3.73 (3 H, s, OCH_3) 6.46 (1 H, s, ArH), 6.49 (1 H, s, ArH), 6.73 (1 H, d, J = 10 Hz, ArH), 6.86 (1 H, d, J = 10 Hz, ArH); IR ($CHCl_3$) 935 cm^{-1}; mass spectrum *m/e* 367, 352, 190, 188, 178, 163, which was converted into the hydrochloride. Recrystallization from methanol–ether yielded colorless crystals, mp 223–225 °C dec.

Anal. Calcd for $C_{22}H_{25}NO_4$·HCl: C, 65.42; H, 6.49; N, 3.47. Found: C, 65.15; H, 6.56; N, 3.18.

Reaction of (±)-[*N*-C^2H_3]-5,6,13,14α-Tetrahydro-9,10-dimethoxy-8β-methyl-2,3-methylenedioxyberbinium *trans*-Methiodide (10b) with Sodium Bis(2-methoxyethoxy)aluminum Hydride. A mixture of **10b** (50 mg, 0.1 mmol) prepared according to the method in case of the methiodide (**10a**) and 70% sodium bis(2-methoxyethoxy)aluminum hydride (290 mg, 1.0 mmol) in dry dioxane (5 mL) was heated for 24 h under the same conditions as above. The same workup as above afforded a caramel, which was developed by preparative TLC on silica gel with methanol–chloroform (0.5:9.5 v/v) and then methanol–ethyl acetate–benzene (0.5:4:5.5 v/v). The part with R_f 0.8 gave **13b** (8.3 mg): NMR ($CDCl_3$) δ 1.52 (3 H, s, 8-CH_3), 3.83 (3 H, s, OCH_3), 3.87 (3 H, s, OCH_3), 5.83 (2 H, s, OCH_2O), 6.52 (1 H, s, ArH), 6.60 (1 H, s, ArH), 7.17 (2 H, s, 2 ArH). The part with R_f 0.65 yielded **14b** (3.2 mg): NMR ($CDCl_3$) δ 1.07 (3 H, t, J = 7 Hz, CH_2CH_3), 3.80 (6 H, s, 2 OCH_3), 5.76 (2 H, s, OCH_2O), 5.90 (1 H, s, ArH), 6.50 (1 H, s, ArH), 6.70 (1 H, s, ArH), 6.73 (1 H, s, ArH). The part with R_f 0.6 afforded **12b** (5.2 mg): NMR ($CDCl_3$) δ 1.30 (3 H, d, J = 7 Hz, 8-CH_3), 3.80 (3 H, s, OCH_3), 3.86 (3 H, s, OCH_3), 5.75 (2 H, s, OCH_2O), 6.25 (1 H, s, ArH), 6.48 (1 H, s, ArH), 6.70 (1 H, d, J = 10 Hz, ArH), 6.88 (1 H, d, J = 10 Hz, ArH).

Reaction of (±)-8β-Ethyl-2,3,10,11-tetramethoxy-14α*H*-berbinium *trans*-Methiodide (18) with Sodium Bis(2-methoxyethoxy)aluminum Hydride. A mixture of the methiodide **18** (100 mg, 0.19 mmol) and 70% sodium bis(2-methoxyethoxy)aluminum hydride (3 mL, 0.01 mol) in dry dioxane (15 mL) was refluxed for 24 h under the same conditions as above and worked up to give a gum (60.2 mg), which was chromatographed on silica gel by using benzene as an eluent, followed by benzene–methanol (99.8:0.2 v/v) and benzene–methanol (99.7:0.3 v/v). The eluate of the benzene–methanol (99.7:0.3 v/v) fraction was further purified by preparative TLC on silica gel developing with benzene–ethyl acetate–methanol (5:4:1 v/v).

A part with R_f 0.9 gave **17** (8.8 mg, 12%), 150–151 °C, whose spectral data were identical with those of the authentic sample. A part with R_f 0.55 gave the 8α-ethyl-8β-methylberbine (**22**, 11.5 mg, 15.2%), which was recrystallized from methanol to give yellowish needles: mp 165–167 °C; NMR ($CDCl_3$) δ 0.90 (3 H, t, J = 7 Hz, 8-CH_2CH_3), 1.52 (3 H, s, 8-CH_3), 3.85 (12 H, s, 4 OCH_3), 6.57, 6.63, 6.65, and 6.75 (each 1 H, each s, 4 ArH); mass spectrum *m/e* 397 (M^+), 382, 368, 206, 191.

Anal. Calcd for $C_{24}H_{31}NO_4$: N, 3.52. Found: N, 3.57.

A part with R_f 0.45 gave the spirobenzylisoquinoline **20** (23.5 mg, 31.0%) which was recrystallized from methanol to give colorless prisms: mp 121–122 °C; NMR ($CDCl_3$) δ 0.88 (3 H, t, J = 7 Hz, 8-CH_2CH_3), 1.50–1.99 (2 H, m, 8-CH_2CH_3), 2.22 (3 H, s, NCH_3), 3.50 (3 H, s, OCH_3), 3.80 (3 H, s, OCH_3), 3.87 (6 H, s, 2 OCH_3), 6.35, 6.45, 6.67, and 6.72 (each 1 H, each s, 4 ArH); mass spectrum *m/e* 397 (M^+), 382, 204, 192.

Anal. Calcd for $C_{24}H_{31}NO_4$: C, 72.51; H, 7.81; N, 3.52. Found: C, 72.42; H, 7.75; N, 3.46.

A part with R_f 0.18 gave the spiro isomer **21** (2 mg, 2.7%) as a syrup: NMR ($CDCl_3$) δ 0.90 (3 H, t, J = 6.2 Hz, 8-CH_2CH_3), 1.17–1.50 (2 H, m, 8-CH_2CH_3), 2.37 (3 H, s, NCH_3), 3.50 (3 H, s, OCH_3), 3.83 (9 H, s, 3 OCH_3), 6.37, 6.43, 6.70, and 6.75 (each 1 H, each s, 4 ArH).

Anal. Calcd for $C_{24}H_{31}NO_4$: 397.2253 (M^+). Found: 397.2234 (M^+).

Reaction of (±)-8β-Ethyl-2,3,10,11-tetramethoxy-14α*H*-berbinium *cis*-Methiodide (19). A mixture of the *cis*-methiodide **19** (785 mg, 1.5 mmol) and 70% sodium bis(2-methoxyethoxy)aluminum hydride (5 mL, 0.017 mol) in dry dioxane (35 mL) was refluxed for 24 h and worked up as above to give a gum, which was chromatographed on silica gel. Elution with benzene–methanol (99.7:0.3 v/v) afforded a gum, which was purified by a preparative TLC on silica gel with benzene–ethyl acetate–methanol (5:4:1 v/v) to give the 8β-ethyl-8α-methylberbine (**23**, 102.6 mg, 17.2%) as yellow prisms: mp 158–159 °C (from methanol); NMR ($CDCl_3$) δ 0.60 (3 H, t, J = 7 Hz, 8-CH_2CH_3), 1.37 (3 H, s, 8-CH_3), 3.87 (12 H, s, 4 OCH_3), 6.57, 6.61, 6.70, and 6.75 (each 1 H, each s, 4 ArH), mass spectrum *m/e* 397 (M^+), 382, 368, 206, 191.

Anal. Calcd for $C_{24}H_{31}NO_4$·0.25H_2O: C, 71.70; H, 7.89; N, 3.48. Found: C, 71.70; H, 7.80; N, 3.70.

Further elution with benzene–methanol (99.5:0.5 v/v) gave the 8α-ethyl-8β-methylberbine (**22**, 30.4 mg, 5.1%) as yellowish needles, mp 165–167 °C (from methanol), whose spectral data were identical with those of the authentic sample.

Further elution with benzene–methanol (99.4:0.6 v/v) gave a gum, which was further purified by a preparative TLC on silica gel with benzene–ethyl acetate–methanol (5:4:1 v/v). A part with R_f 0.45 gave the spirobenzylisoquinoline **20** (36.9 mg, 6.2%) as colorless prisms, mp 121–122 °C (from methanol), which was identical with the authentic sample.

A part with R_f 0.18 furnished the isomer **21** (120.9 mg, 20.3%) as a syrup, IR and NMR spectra of which were identical with those of the authentic sample.

Reaction of (*R*)-(+)-Canadine *trans*-Methiodide (39) with Sodium Bis(2-methoxyethoxy)aluminum Hydride. A mixture of (+)-canadine *trans*-methiodide (**39**, 400 mg, 0.83 mmol) and 70% sodium bis(2-methoxyethoxy)aluminum hydride (2.4 g, 8.3 mmol) in dry dioxane (40 mL) was refluxed for 24 h under a current of nitrogen and worked up as above to give a brownish caramel, which was purified by silica gel column chromatography. Elution with benzene–methanol (99.5:0.5 v/v) afforded a solid, recrystallization of which from ethanol yielded (+)-5,6,13,14β-tetrahydro-9,10-dimethoxy-8α-methyl-2,3-methylenedioxyberbine (**41**, 132 mg) as pale yellow crystals, mp 190–192 °C, $[\alpha]^{20}_D$ +208° (*c* 0.125, MeOH), whose spectral data were identical with those of the racemate (**9**).

Anal. Calcd for $C_{21}H_{23}NO_4$: C, 71.37; H, 6.56; N, 3.96. Found: C, 71.23; H, 6.51; N, 3.71.

Further elution with benzene–methanol (99:1 v/v) gave a solid, recrystallization of which from ethanol yielded (−)-9,10-dimethoxy-2,3-methylenedioxyochotensane (**40**, 98 mg) as colorless crystals: mp 104–105 °C (lit.[5] 104–105 °C); $[\alpha]^{18}_D$ −56° (lit.[5] $[\alpha]^{16}_D$ −60°); CD (MeOH) nm ($\Delta\varepsilon$) 294 (−1.80), 277 (+0.91), 210 (−44.27), 200 (+42.16).

Reaction of (*R*)-(+)-Canadine *cis*-Methiodide (42) with Sodium Bis(2-methoxyethoxy)aluminum Hydride. A mixture of **42** (160 mg, 0.33 mmol) and 70% sodium bis(2-methoxyethoxy)-aluminum hydride (952 mg, 3.3 mmol) in dry dioxane (5 mL) was heated for 24 h under the same conditions as above. The same workup as above gave a caramel, which was purified by silica gel column chromatography. Elution with benzene–methanol (99.5:0.5 v/v) afforded (+)-3-(2-ethyl-4,5-methylenedioxyphenyl)-1,2,3,4-tetrahy-

dro-7,8-dimethoxy-2-methylisoquinoline (**44**, 53 mg) as a caramel, whose spectral data were identical with those of the racemate. Further elution with benzene–methanol (99:1 v/v) gave a solid, which was recrystallized from ethanol to afford (+)-9,10-dimethoxy-2,3-methylenedioxyochotensane (**43**, 33 mg) as colorless crystals: mp 104–105 °C (lit.[5] 104–105 °C); $[\alpha]^{18}_D$ +54° (lit.[5] $[\alpha]^{16}_D$ +60°); CD (MeOH) nm ($\Delta\epsilon$) 294 (+1.70), 277 (−0.75), 210 (+44.12), 200 (−41.91).

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Registry No.—**1a**, 62860-05-3; **1b**, 62815-47-8; **2a**, 62815-48-9; **2b**, 62815-13-2; **3a**, 58116-07-7; **3b**, 62815-49-0; **4**, 62860-06-4; **8**, 62815-50-3; **9**, 60354-88-3; **10a**, 62815-51-4; **10b**, 62815-52-5; **11**, 62860-07-5; **12a**, 62815-53-6; **12a** HCl, 62815-54-7; **12b**, 62815-55-8; **13a**, 62815-56-9; **13b**, 62815-57-0; **14a**, 62815-58-1; **14a** HCl, 62815-59-2; **14b**, 62815-60-5; **15**, 62815-61-6; **15** HCl, 62815-62-7; **16**, 62815-64-9; **17**, 62815-65-0; **18**, 62860-08-6; **19**, 62815-33-2; **20**, 62815-34-3; **21**, 62815-35-4; **22**, 62815-36-5; **23**, 62815-37-6; **24**, 18028-11-0; **25**, 62815-38-7; **26**, 62815-39-8; **27**, 62815-40-1; **28**, 62815-41-2; **29** HCl, 60356-10-7; **30**, 62815-42-3; **31**, 62815-43-4; **32**, 62815-44-5; **39**, 62860-02-0; **40**, 56974-42-6; **41**, 62815-45-6; **42**, 62860-03-1; **43**, 56974-43-7; **44**, 62815-46-7; (±)-[13,13,14-$^2H_3$]xylopinine, 62860-04-2; propionic anhydride, 123-62-6; propionaldehyde, 123-38-6; (*R*)-(+)-canadine, 2086-96-6; sodium bis(2-methoxyethoxy)aluminum hydride, 21608-56-0.

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Heterogeneous Catalysis by Solid Superacids. 2.[1] Reduction of 2-Chloropropane and Its Reaction with Alkanes over Niobium Pentafluoride on Graphite

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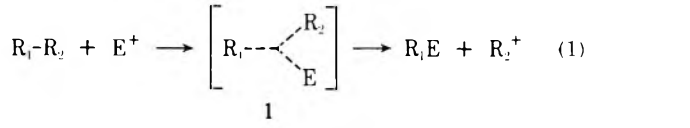
Niobium pentafluoride on graphite was found to be an effective catalyst for the reduction of 2-chloropropane and its reaction with alkanes. In the absence of alkanes, 2-chloropropane is reduced to propane. Reaction of 2-chloropropane with C_3–C_5 alkanes having secondary or tertiary carbon atoms occurs readily accompanied by reduction. The major reaction is Bartlett–Nenitzescu type hydrogen transfer between the generated isopropyl cation and the corresponding alkane. Alkylation products are also formed, but in lower yield. Pentane and 2-methylbutane give in addition substantial amounts of 2-methylpropane. Methane, ethane, and 2,2-dimethylpropane were found to be unreactive under the reaction conditions.

Electrophilic reactions at carbon–carbon and carbon–hydrogen single bonds by strong electrophiles have been well established in recent years.[3] Alkanes, being weak σ bases, are not easily attacked and relatively strong electrophiles are needed. Protolytic reactions of alkanes by superacids,[4–7] nitration by nitronium salts,[8] halogenation by "positive" halogens[9–11] (such as formed by the reaction of elementary halogen with silver salts), as well as alkylation by carbenium ions[12–14] were reported. The mechanism of these reactions involves front side attack of the electrophile on the corresponding σ bonds to form a two-electron three-center bonded carbonium ion (**1**), which then cleaves to give the substitution product and an ionic product, i.e., proton or carbenium ion (eq 1).



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The electrophilic reactions of alkanes were so far carried out primarily in solution, in low nucleophilicity media, and were catalyzed by superacid catalysts (usually based on SbF_5 or TaF_5). Prolonged reaction time and continuous contact with the catalyst can, however, cause extensive secondary reactions of the products. In contrast to electrophilic aromatic substitutions where products are generally stable (for example, nitrobenzenes, halobenzenes, or alkyl benzenes), this is not the case in electrophilic aliphatic substitution. For example, it is possible for R_1E (eq 1) to react further under the

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acidic reaction conditions. Tertiary nitro or halo compounds are extremely sensitive to acids, as are, to a somewhat lesser extent, secondary compounds. Branched alkanes are also prone to react under highly acidic conditions. Other possibilities are secondary reactions of R_2^+ (eq 1), like alkylation, fragmentation, or rearrangement.

The use of solid acid catalysts offers a convenient way to remove the products from further interaction with the catalyst. Conducting the reactions in a flow system enables controlling the contact time and separating the products easily without quenching the reaction mixtures.

Continuing our studies of solid superacid-catalyzed reactions we studied the reaction of 2-chloropropane (**2**) with alkanes in the gas phase over a catalyst comprised of niobium pentafluoride on graphite.

Experimental Section

Reactor. The reactions were carried out in a vertical glass tube reactor with a fixed bed catalyst. The catalyst was held in place by a glass wool plug and the reactants were passed through the catalyst bed. Gaseous reactants were introduced via flow controllers and liquids via syringe pumps. After initial mixing the reactants passed through a 70-cm glass tube heated to 70 °C to ensure complete evaporation and mixing. The catalyst was kept at 45 °C. Samples were taken at regular intervals with a gas syringe via a rubber septum and were analyzed by gas chromatography.

Experimental Procedure. Finely ground NbF_5 (10 g) (Ozark-Mahoning Co.) and 25 g of graphite (−20 + 65 mesh) were mixed thoroughly and heated in a slow stream of dry N_2 to 80 °C for 2 h. Intercalated NbF_5 was prepared by heating NbF_5 with graphite to 120 °C for 48 h under N_2 atmosphere. The catalyst thus prepared was charged into the reactor in N_2 atmosphere. The reactor was heated to 45 °C and the alkane introduced, replacing N_2, at the rate of 2 mmol/min. Samples were taken at time intervals and analyzed. Analysis showed only the presence of the unchanged alkane. 2-Chloropropane (**2**) was then added at the rate of 1.6 mmol/min to the feed. Under these conditions the average contact time of the feed with the catalyst was about 16 s. Fresh catalyst was used for each experiment in order to standardize conditions. In one experiment **2** was passed through the reactor at the rate of 1.6 mmol/min at 45 °C for 5 h. The used catalyst (12 g) was washed with ether to remove organic material and NbF_5,[15] leaving 7.8 g of graphite. The ether solution was washed with water and dried, and the ether evaporated. Oily polymer (1.1 g) was obtained. The material balance in NbF_5 was in good agreement with the initial composition of the catalyst. The weight of the polymer corresponds to 9% of the weight of **2** passed through the catalyst. ^1H NMR of the polymer shows a broad singlet at 0.9 ppm (~50% of the area), a broad triplet at 1.7 ppm (ca. 30%), and two small broad singlets at 2.1 and 2.6 ppm (15 and 5% of the area, respectively). Elementary analysis: C, 83.16; H, 11.01; Cl, 2.48; F, 0.07.

Analysis. Products were analyzed by gas chromatography on a squalane capillary column (150 ft × 0.01 in.) at 70 °C. This column separates well alkyl halides and C_5 and higher alkanes. C_1 to C_4 alkanes were separated on an alumina column (3 m × ⅛ in.) at 150 °C. Peak integrations were carried out with an Infotronics CRS-100 electronic integrator and the results were corrected for differences in the detector sensitivity.

Results and Discussion

The Catalyst. In the present study of the reaction of 2-chloropropane (**2**) with alkanes under heterogeneous gas-phase conditions, NbF_5 on graphite was used as catalyst. Niobium pentafluoride is known to be a Friedel–Crafts catalyst, but few details of its catalytic activity were given.[16] In recent years catalysts prepared from NbF_5 and strong protic acids, such as FSO_3H or CF_3SO_3H as well as HF, were found to be good catalysts in electrophilic reactions of alkanes[17] and aromatic compounds.[18]

The role of graphite in the catalyst is mostly that of a support. Solid, neat NbF_5 was also found to be an effective catalyst. For comparison we carried out the reaction between **2** and 2-methylbutane over NbF_5 on graphite, as well as over neat NbF_5. NbF_5 on graphite gave somewhat better yields and higher conversion. Adsorption of the reactants to graphite may seem to promote the reaction, but this effect is not very significant. The presence of graphite, however, reduces significantly the amount of polymer formed. In the absence of graphite, polymer formation is increased ca. ten times. Minimizing side reactions by the presence of graphite also affects the lifetime of the catalyst as the polymer blocks the active sites and reduces the activity. The dilution of NbF_5 by graphite, i.e., reduction of the concentration of the active sites, helps to decrease polymer formation.

Table I. Volatile Products of the Reaction of Neat 2 over NbF_5

Product composition, %	Onstream time, min 20	70	150	270
C_3H_8	39.0	25.0	8.5	1.7
i-C_4H_{10}	1.5	1.0	0.9	0.2
i-C_5H_{12}	0.2	0.2	0.1	Tr
i-PrCl	59.3	73.8	90.5	98.1

We have also prepared the intercalation compound of 20% NbF_5 in graphite. Lately, there is increased interest in the intercalation compounds of metal fluorides,[19] and their catalytic activity in Friedel–Crafts reaction was reported.[20] However, reactions over graphite intercalated NbF_5 showed low conversions and the reactivity of the catalyst was rather quickly reduced. In the graphite intercalated compound most of the NbF_5 is deposited between the lattice layers and thus is not readily accessible to the reactants. Only a small fraction of NbF_5 exposed at the surface edges is catalytically active, where the gaseous reactants can reach the catalyst. This may explain the lower activity of intercalated NbF_5, but a definite answer to this problem cannot yet be given.[21]

Reaction of Neat 2 in the Absence of Alkane. When neat **2** was passed over the catalyst copious evolution of HCl was observed. The mixture of gases was analyzed after different onstream times. The results are given in Table I. The major product is the corresponding parent alkane, i.e., propane, resulting from reduction of **2**. The yield of propane decreases with onstream time due to accumulation of polymer on the catalyst (vide infra). By simple graphic extrapolation the initial composition of products is 50% **2**, 48% propane, 2% 2-methylpropane, and 0.2% 2-methylbutane.

When **2** is passed over NbF_5 it is assumed to ionize via the equation

$$\underset{\mathbf{2}}{(CH_3)_2CHCl} + NbF_5 \rightarrow \underset{\mathbf{3}}{(CH_3)_2C^+H\ NbF_5Cl^-} \qquad (2)$$

to the isopropyl cation **3** or to form a highly polarized donor–acceptor complex (like the methyl fluoride–SbF_5 complex[12,22]), although with the reactive secondary system ionization seems probable. Several reaction paths are open to **3** to explain the results: chloride abstraction to regenerate **2** and NbF_5; proton elimination to form propene; and hydrogen abstraction to give propane.

Chloride abstraction producing **2** and NbF_5 cannot be distinguished from an incomplete reaction. The collapse of **3** to its starting materials, however, seems highly probable. It should be mentioned that abstraction of fluoride ion to give 2-fluoropropane and $NbClF_4$ is far less probable. Such a process is thermodynamically unfavorable. In addition 2-fluoropropane was not found as a product.

Proton elimination from **3** would form propene with HCl evolved and NbF_5 regenerated. Formally it is an E1 elimination reaction of **2**. Propene, however, has never been found in the gaseous products, not even in trace amounts. Being a much better nucleophile than alkanes, propene is readily attacked

by **3**, thus initiating a cationic polymerization process. The polymerized products are nonvolatile and stay in the reactor. Only viscous liquids are obtained under the reaction conditions, which do not favor high molecular weight products as the polymer chains are also cleaved by the acid catalyst. The amount of polymer formed in a typical experiment was 9% of **2** fed into the reactor. The strong methyl absorption at δ 0.9, in the ^{1}H NMR spectrum, indicates extensive branching of the polymer. Similar spectrum was obtained when butane was polymerized with SbF_5–FSO_3H.[23] Incorporation of Cl into the polymer, as found by elemental analysis, shows that chloride abstraction takes place in the termination step of the polymerization. On the other hand, the practical absence of fluorine incorporation indicates that there is neither chlorine–fluorine exchange nor quenching by fluoride ion to any significant degree.

Hydride abstraction by **3** with its reduction to propane has only two precedents. Formation of saturated hydrocarbons and HCl from 2-chloro-2-methylbutane and "anhydrous" $AlCl_3$ was first observed by Friedel and Crafts a century ago.[24] Such reactions were not further mentioned in the vast literature dealing with Friedel–Crafts chemistry. Only recently have Siskin and Schlosberg[25] reported that alkyl halides, including **2**, react with several strongly acidic media (HCl–$AlCl_3$, HBr–$AlBr_3$, HF–TaF_5), in the absence of added alkane, to give the parent alkane as a major product. This observation was not limited to secondary or tertiary halides because ethyl chloride and even methyl chloride were found to react to give the corresponding alkanes, i.e., ethane and methane in HF–TaF_5 solution.

The source of hydrogen required for the reduction of **2** to propane is not clear. The absence of any significant amount of protic acid in our system excludes the possibility of reduction by the catalyst. The source of the hydrogen must be a second molecule of **2**.[26] One possibility is that **3** hydride-abstracts from a second molecule of **2**.

$$\underset{\mathbf{3}}{(CH_3)_2C^+H} + \underset{\mathbf{2}}{(CH_3)_2CHCl} \rightarrow (CH_3)_2CH_2 + \underset{\mathbf{4}}{(CH_3)_2C^+Cl} \quad (3)$$

4 was found to be a stable carbocation under stable ion conditions[27] as were other α-halo carbenium ions.[28] **4** can subsequently proton-eliminate to give 2-chloropropene, which then can participate in the polymerization process. This may be another source for the chlorine incorporation into the polymer. Another possibility is hydride abstraction from propene by **2**, forming propane and allyl cation. The formation of diisopropylchloronium ion can also be involved

$$(CH_3)_2C^+H + ClCH(CH_3)_2 \rightleftharpoons [(CH_3)_2CH]_2Cl^+ \rightleftharpoons (CH_3)_2CHCl + HC^+(CH_3)_2 \quad (4)$$

but in the secondary system the latter is not expected to effect the reduction.

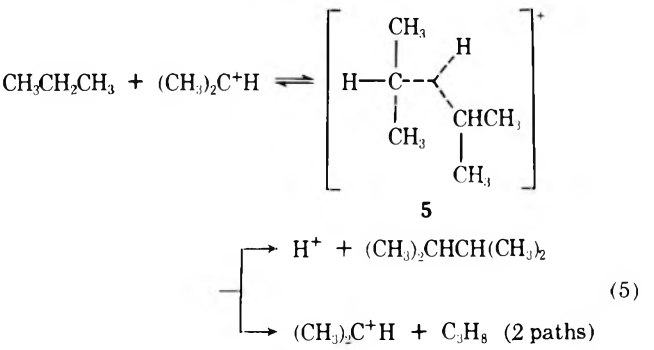
Attempted Reaction of 2 with Methane, Ethane, and 2,2-Dimethylpropane. **2** was reacted with three alkanes which contain only primary carbon–hydrogen bonds, i.e., methane, ethane, and 2,2-dimethylpropane. The ratio of **2** to the alkane was 1:1.25. In all cases the product hydrocarbon mixture obtained was strikingly similar. After 30 min onstream time the alkane composition was ~15% propane, ~1% 2-methylpropane, ~0.2% 2-methylbutane, and ~84% of the starting alkane. The yield of propane decreased with onstream time. For example, only 6.5% of propane was formed after 3 h. There is polymer formation in the reactor, which decreases the effectiveness of the catalyst.

Taking into account the independence of the product composition from the reactant alkane and the similarity to the products obtained from neat **2** (in all cases the hydrocarbon product composition is ~95% propane, ~4% 2-methylpropane, and ~1% 2-methylbutane) we are led to the conclusion that methane, butane, and 2,2-dimethylpropane do not react under the reaction conditions with **2** and we observe only the reduction of the latter.

Reaction of 2 with Propane. Reaction of **2** with propane gave, besides the starting materials, 0.5% of 2-methylpropane, 0.3% of 2-methylbutane, and 0.9% of 2,3-dimethylbutane. HCl was also evolved.

Nenitzescu and Dragan[29a] as well as Bartlett, Condon, and Schneider[29b] found that alkyl halides are reduced to the parent alkane when treated with isoalkane (containing tertiary hydrogen) in the presence of anhydrous aluminum halides. The carbenium ion formed abstracts hydrogen from the isoalkane to give the parent alkane and another carbenium ion. Further reaction of the newly formed ion then takes place. Such a hydrogen exchange is possible in our system too. But Bartlett–Nenitzescu hydrogen transfer between **3** formed from ionization of **2** and propane is a degenerate process. Hydrogen exchange was observed to occur between 3 and propane in SbF_5–SO_2ClF solution at −78 °C by NMR spectroscopy,[13] and the same process is expected to take place in the present system.

The reaction mechanism is shown in eq 5. The most convincing evidence for electrophilic attack on the secondary C–H bond of propane by **3** is the formation of the corresponding C_6 alkylation product, 2,3-dimethylbutane. Proton elimination from the carbonium ion intermediate **5** gives 2,3-dimethylbutane as product. Alternative cleavage of the three-center bond in **5** will re-form the starting materials according to the degenerate hydrogen transfer.



(5)

Reaction of 2 with Butanes. In the reaction of **2** with butanes the symmetry of pentacoordinated carbonium ion intermediate is removed and hydrogen exchange is no more a degenerate process. A higher degree of hydrogen exchange is expected in the case of 2-methylpropane due to its more active tertiary C–H bond. Typical product distributions of the reactions are given in Table II.

The amount of propane decreases with prolonged onstream time, but is fairly constant during the first 3 h. Again, polymer formation on the catalyst decreases its efficiency.

In the reaction of **2** with butane the composition of alkyl halides obtained were: 70% unreacted **2**, 23% of 2-chloro-2-methylpropane, and 7% of 2-chlorobutane. With 2-methylpropane 63% of **2** and 37% of 2-chloro-2-methylpropane were obtained. The relative yields of the alkylation products (C_6–C_8) are given in Table III. In both reactions the major reaction product is propane. This further strengthens the argument of a similar hydrogen transfer reaction with propane and **2** which, in this case, is degenerate and thus cannot be observed without labeling experiments. The 2-butyl cation which is formed in the hydrogen transfer of butane with **3** either gives 2-chlorobutane or rearranges to the *tert*-butyl cation and then gives 2-chloro-2-methylpropane. It must be noted that the amount of alkyl chlorides detected is always smaller than expected according to the stoichiometry of the interchange reactions. The most probable reason is that proton elimination from the intermediate alkyl cations (**3** and

Table II. Volatile Products of the Reaction of 2 with Butanes

	Reactant	
Alkane products	Butane	2-Methylpropane
Propane	28	38
Butane	70	
2-Methylpropane	1.5	60
C_6–C_8 alkanes	0.5	2

Table III. Relative Amounts of C_6–C_8 Alkanes Formed in Experiments Shown in Table II

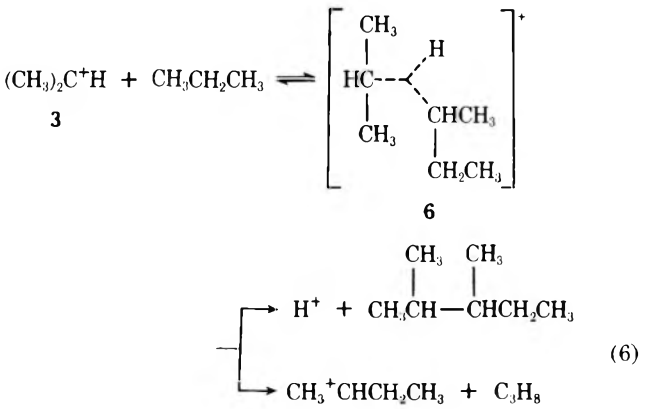
	Reactant	
Product	Butane	2-Methylpropane
2,3-Dimethylbutane	63	65
2,4-Dimethylpentane	18	14
2,2,3-Trimethylbutane	1.5	4
2-Methylhexane	7	7
2,3-Dimethylpentane	7	5
3-Methylhexane	1	5
Octanes	2.5	

2-butyl cation) gives alkenes which subsequently polymerize, competing with quenching by chloride anion. The relative amount of the butyl halides and **2** fits well the proportions of propane and butane. The ratio [propane]/[*n*-butane] is equal to the ratio ([*s*-BuCl] + [*t*-BuCl])/[*i*-PrCl] (in accordance with the assumption that the rate of proton elimination from both secondary cations is similar and that elimination from the more stable *tert*-butyl cation is less important).

The reaction of the alkanes is far from being complete. Only 28% of *n*-butane and 38% of 2-methylpropane reacted. The rather short contact time of the reactants with the catalyst in the flow system explains the relatively low yields, but at the same time side reactions are minimized.

Concerning alkylation products, some 2,3-dimethylbutane is always formed in the reactions. It indicates the reaction between **3** and propane formed in the reaction. Two isomeric octanes are formed when *n*-butane is the reactant formed via the alkylation of butane by the 2-butyl cation. Their absence in the reaction with isobutane hints to the relative lack of the reactivity of the *tert*-butyl cation toward alkanes.

Formation of heptanes, i.e., $C_3^+ + C_4$ alkylation products such as 2,3-dimethylpentane, from the reaction of *n*-butane is easily explained by proton elimination from the intermediate carbonium ion **6** (eq 6). In a similar way the formation



(6)

of 2,2,3-trimethylbutane from 2-methylpropane can be rationalized. But none of them is the major product. In order to account for the formation of the C_7 isomers one needs to consider additional reaction paths. Thus, 2-methylhexane can be obtained by attack of 1-butyl cation (formed from the 2-butyl cation by 1,2 H shift) on propane. 2,4-Dimethylpentane is formed by the attack of isobutyl cation (formed from the 2-butyl cation by 1,2 CH_3 shift) on propane. 3-Methylhexane is formed by the attack of the 1-propyl cation on *n*-butane.

Acid-catalyzed isomerization of the heptanes is a better explanation for the observed isomeric products than the direct independent alkylation processes. Indeed, the similarity of the C_7 fraction regardless which butane was used suggests ready interconversion of the isomeric heptanes. Once a C_7 alkane is formed it can ionize to a tertiary heptyl cation. This cation rapidly equilibrates with other tertiary heptyl cations and then hydrogen transfers to give the hydrocarbon. All heptanes present can ionize to give tertiary cations. 3-Ethylpentane was not detected in the products, but it was previously shown[30] that the related tertiary ion, viz. triethylcarbenium ion, is present in superacidic solution only at very low temperatures and rearranges readily to other, more stable, tertiary heptyl cations. All other isomeric heptanes absent from the products, i.e., *n*-heptane, 2,2-dimethylpentane, and 3,3-dimethylpentane, would be derived from energetically less favorable secondary or primary cations. The absence of the latter two alkanes from the products shows that the stability of the alkane itself is not a determining factor because these neutral alkanes have a low free energy of formation among the isomeric heptanes.[31]

Equilibration of heptyl cations in solution was observed both in FSO_3H–SbF_5[32] and in HF–SbF_5.[33] There is only a qualitative agreement between these ion compositions and our present results. As these were obtained in a heterogeneous system at a significantly higher temperature, such differences in composition are not unexpected.

The rate of rearrangement of heptyl cations is not yet known. Kinetic study of the rearrangement of tertiary hexyl cations in solution was reported.[33,34] The data show that the slower rearrangements (those involving a change in branching) have a rate constant of the order of 0.05 s^{-1} at 0 °C. From activation energies a half-life of ~0.1 s is estimated at 45 °C. Reactions which do not involve change in branching are appreciably faster. If similar rates of isomerization of heptanes are to be accepted under the present experimental conditions, there is sufficient time for equilibrium with the contact times of the present study.

Isomerization of *n*-heptane on several solid acid catalysts in the gas phase[35] showed the C_7 fraction to contain, apart from unrearranged starting material, the same products as observed in the present work. 2,2-Dimethylpentane, 3,3-dimethylpentane, and 3-ethylpentane were absent.

The reaction of **2** with butanes or that of butyl cations with propane in solution at −78 °C[13] showed that the heptane isomer distribution is dependent upon the starting materials. At the low reaction temperature there is relatively little isomerization of the intermediate cations. Upon hydrogen transfer still all isomeric heptanes were obtained, indicating significant amounts of 2,2-dimethylpentane, 3,3-dimethylpentane, and 3-ethylpentane.

Reaction of 2 with Pentanes. The products of the reaction of **2** with pentane and 2-methylbutane are given in Table IV. As already mentioned, 2,2-dimethylpropane does not react under these conditions.

As seen from the data 2-methylpropane is formed in substantial amounts. Once a C_8 carbonium ion is formed by the electrophilic attack of **3** on pentane it will readily rearrange and cleave to the *tert*-butyl cation and 2-methylpropane, both being very stable species.[31,36] This cleavage can be schematically shown by

$$C_3^+ + C_5 \rightarrow [C_8^+] \rightarrow [C'_8{}^+] \rightarrow (CH_3)_3C^+ + (CH_3)_3CH \quad (7)$$

The *tert*-butyl cation will then either proton eliminate and polymerize or be quenched by chloride to give 2-chloro-2-

Table IV. Reaction of 2 with Pentanes—Volatile Products

Products	Reactant	
	Pentane	2-Methylbutane
Propane	20	27
2-Methylpropane	4	30.5
2-Methylbutane	20	36
Pentane	49	
2,3-Dimethylbutane	2	2
3-Methylpentane		0.5
2-Chloropropane	3	2
2-Chloro-2-methylpropane	2	2

methylpropane. The amount of 2-methylpropane formed from pentane is smaller, probably because of incomplete reaction with **2** (pentane has no tertiary C–H bonds) or because of insufficient branching of the C_8 cation intermediate.

In order to substantiate this suggested reaction path we also reacted **2** and the highly branched 2,2,4-trimethylpentane in the presence of NbF_5 at room temperature, in the liquid phase (the reaction mixture is heterogeneous). Product analysis showed that additional isomeric octanes, all of them highly branched, form in small amounts. The main product is 2-methylpropane (from the fragmentation of the octyl cations according to eq 7).

Similar behavior is known in homogeneous superacid solution chemistry. Whereas C_7 cations are stable and do not cleave, but only rearrange, at −20 °C,[33] C_8 cations must be prepared at −100 °C and they begin to cleave to *tert*-butyl cations at −75 °C.[32] The great stabilities of the *tert*-butyl cation and 2-methylpropane make the cleavage energetically favorable.

Registry No.—**2**, 75-29-6; **3**, 62882-91-1; NbF_5, 7783-68-8; butane, 106-97-8; 2-methylpropane, 75-28-5; pentane, 109-66-0; 2-methylbutane, 78-78-4; methane, 74-82-8; ethane, 74-84-0; 2,2-dimethylpropane, 463-82-1; propane, 74-98-6.

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Action of Di-*tert*-butyl Peroxide or of γ-Radiations on 2,3-Dimethylbutane. Identification of the C_{12} Hydrocarbons

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The reaction between 2,3-dimethylbutane and di-*tert*-butyl peroxide might lead in principle to 21 saturated and unsaturated products. Capillary GLC reveals six major compounds which have been isolated by fractional preparative GLC and whose structure has been for the first time unambiguously determined by spectroscopy (^{1}H NMR, ^{13}C NMR, mass), independent synthesis, hydrogenation of reaction mixtures, and chromatographic retention data. These three last techniques permit also the plausible identification of ten other products present in lower concentrations and which were not separated from the reaction mixture. This study points also out that the dehydrodimerization of tertiary alkanes is not an interesting method for the synthesis of unsubstituted vicinal biquaternary hydrocarbons as erroneously suggested by Meshcheryakov and Erzyutova. It permits, however, a better understanding of the behavior of the intermediate alkyl and allyl radicals and emphasizes the particular physical properties of the vicinal biquaternary alkanes.

The dimerization of carbon-centered radicals has been much investigated. The dimerizing radicals are generally generated by the action of a peroxide on the corresponding alkane and the reaction is then called a dehydrodimerization:[2]

$$\text{peroxide} \xrightarrow[\text{light}]{\text{heat or}} 2Q\cdot \qquad (1)$$

$$Q\cdot + RH \rightarrow QH + R\cdot \qquad (2)$$

$$2R\cdot \rightarrow R\text{–}R \qquad (3)$$

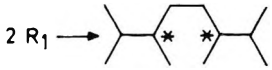
The R· radicals which lead to the formation of the R–R dimers are stabilized by substituents like phenyl, cyano, halogens, carbonyl, etc. A few studies deal with unsubstituted alkanes[2] but the nature of the reaction products is generally not determined. Meshcheryakov and Erzyutova, however, claim that the dehydrodimerization of 2-methylbutane, 2,2,4-trimethylpentane, and 3-ethylpentane leads in each case to the formation of the biquaternary dehydro dimer. However, in order to prove the structure of these compounds they mention only boiling points, refractive indexes, densities, and elemental analysis.[3]

We have reinvestigated the action of di-*tert*-butyl peroxide (DTBP) on 2-methylbutane and on 2,2,4-trimethylpentane. In both cases, the reaction mixture is quite complex as seen by capillary GLC.[4]

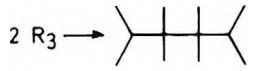
On the other hand, the γ-radiolysis of simple alkanes has been extensively studied. In these reactions different mechanisms are operative but in certain cases the radical one prevails to a large extent. Unfortunately, the exact nature of the reaction products is generally not determined.

In this paper we present the determination of the C_{12} products obtained by the action of di-*tert*-butyl peroxide (DTBP) or of γ-radiations on 2,3-dimethylbutane (2,3-DMB).

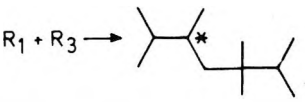
This compound gives primary (R_1) and tertiary (R_3) radicals. The former is statistically favored. The latter is, however, more stable ($R_{tert} > R_{sec} > R_{prim}$). For the coupling of these radicals three routes are possible:



(R1 R1) (4)



(R3 R3) (5)



(R1 R3) (6)

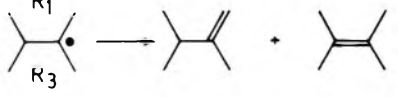
The R_1R_1 dimer has two asymmetric carbon atoms; therefore, the meso and racemic forms must be formed but may or may not be separated by GLC.[5]

Radicals are also able to disproportionate into alkane and alkene:

$$2R\cdot \rightarrow R(+H) + R(-H) \qquad (7)$$

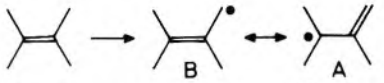
R_1 gives only the 1-butene, R_3 the 1- and 2-butenes:

(8)



(9)

These alkenes are more reactive than the corresponding alkanes and, although in lower concentrations, will therefore intervene in the reaction:



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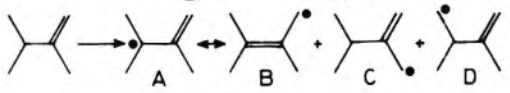


(11)

Radical D, being nonallylic, is less probable than radicals A ↔ B and C. The tendency to disproportionate (k_d) and to combine (k_c) is not the same for all radicals. For tertiary radicals $k_d \simeq 5k_c$, for secondary ones $k_d \simeq k_c$, and for primary ones $k_d \simeq \frac{1}{6}k_c$. For resonance-stabilized radicals k_d/k_c is very low.[2]

Thus from the A ↔ B, C, D, R_1, and R_3 radicals, 21 compounds are possible: three alkanes, eight monoalkenes, and ten nonconjugated dienes. Castello, Munari, and Grandi observed only three major peaks in the C_{12} range during γ-radiolysis of 2,3-DMB.[6-8] These authors attributed them to R_3R_3, R_1R_3, and R_1R_1, respectively, but did not give a precise description of their identification method.[9]

Other reactions may not in principle be rejected: for example, the combination of alkyl and alkoxyl radicals or the addition of radicals to an olefin. Such reactions may perhaps

Table I. Retention Times and GC Area Percentages for the C_{12} Hydrocarbons Obtained by Action of DTBP or of γ-Radiations on 2,3-DMB

Peak	Retention times, min[a]	GC area percentages: Peroxide reaction, UV (35 °C)	Peroxide reaction, 137 °C	γ-Radiolysis[20], Solid I[b]	γ-Radiolysis[20], Solid II[c]	γ-Radiolysis[20], Liquid[d]
2/3	31.9/32.2	2.3	11.6	4.1	1.7	8
4	32.9	32.8	17.1	15.3	6.6	8
5	33.9	1.8	1.2			
6	34.4	13.7	24.1	18.6	17.9	31
7	34.9	2.0	1.8	3.3	4.0	17
8/9	35.9/36.3	3.8	9.9	40.1	65.0	22
13	43.5	0.4	0.3	5.0	3.5	2
14	44.5	12.5	8.9	11.1	0.3	6
15	46.5	4.8	2.5			Tr
17	52.0	25.9	22.7	2.5	0.9	6

[a] For the GC analysis conditions, see Experimental Section. [b] Transparent glass. [c] Opaque solid after annealing. [d] At room temperature.

account for small quantities of products which elute before the C_{12} hydrocarbons. The yields of these products are, however, not important. This is not surprising since the disproportionation/combination ratio is much higher for alkyl/alkoxyl radical pairs than for alkyl/alkyl radical pairs.[10] On the other hand, alkoxyl radicals tend to abstract allylic hydrogen atoms much more than to add to double bonds.[11-13] At room temperature *tert*-butoxyl radicals are stable and give almost exclusively *tert*-butyl alcohol. At higher temperatures *tert*-butyl alcohol and acetone are obtained but the yields of the products eluting between them and the C_{12} hydrocarbons increase only slightly.[14] Actually, methyl radicals do not tend very much to add to crowded olefins. The "blocking effect" of methyl groups has been discussed by Szwarc.[16] Methyl radicals probably have more tendency to dimerize, to abstract hydrogen atoms, or eventually to combine with other radicals. The addition to olefins of more complex alkyl radicals has only scarcely been mentioned in the course of such reactions. Ipatieff has explained by such a mechanism the presence of 2-methyl-2,4-di-*p*-tolylpentane in the oxidation of *p*-cymene.[17]

Experimental Section

Analyses of the reaction mixtures were performed on a Varian 1440 chromatograph equipped with a glass capillary column (85 m × 0.5 mm) of silicone OV-1 and with a variable splitter adjusted to a 1:10 ratio. The flow of the nitrogen gas in the column was 3.8 mL/min. The temperatures of the column, the injector, and the detector were 92, 122, and 205 °C, respectively. Under these conditions the retention times of the C_{12} products range between 32 and 52 min (Table I). Under the same conditions the air peak appears after 9.5 min, *n*-decane elutes after 23.5 min, 2-methyldecane after 30.7 min (just after peak 1), *n*-undecane after 35.9 min (together with peak 8), and *n*-dodecane after 58.8 min. The separation of the products was achieved on a Varian 711 chromatograph equipped with aluminum columns (7 m × 0.375 in.) of silicone SE-30 (injector/detector 225 °C; column 140 °C; nitrogen 300 mL/min).

The ^{13}C NMR spectra were recorded on a Varian CFT-20 spectrometer, the ^{1}H NMR spectra on Varian XL-100 or EM-360 spectrometers. The mass spectra were taken on a Varian MAT 311 system.

The hydrogenation reactions were conducted at 70 °C in a 40-mL Pyrex vessel containing 200 μL of the olefin, 12 mL of cyclohexane, and 2 g of Raney nickel. The reactor was flushed by nitrogen and then by hydrogen. At the beginning of the reaction the hydrogen overpressure was 1 kg/cm^2. The reactor was vigorously shaken during the experiment which, for tetrasubstituted olefins, took about 20 h.

Boiling temperatures were automatically recorded on a Mettler FP 1 apparatus.

2,3-DMB (Koch-Light product) and DTBP (Fluka product) were irradiated by UV light (Q 300 original Hanau HP mercury lamp) in quartz tubes at 35 °C.[18] In other experiments the peroxide was thermally decomposed at 137 °C in Pyrex sealed tubes.[19] In both cases the reaction time was adjusted so that the major part of the peroxide (90–95%) was decomposed (approximately 32 and 16 h). The molar hydrocarbon/peroxide ratio was quite high (10:1) in order to avoid induced decomposition of the peroxide and also consecutive reactions leading to the formation of higher molecular weight material. After analysis of the C_{12} hydrocarbons the temperature of the GLC column was raised from 92 °C to 195 °C and maintained so for 1 h; only a limited amount of such material was found which was estimated to be 10–20% of the C_{12} fraction. Furthermore, chromatographic analysis of the reaction mixture at different times during the reaction showed that the relative percentages of the different peaks remain almost constant.

Results and Discussion

The chromatographic data (GLC retention times and area percentages) for the C_{12} compounds obtained during decomposition of DTBP in 2,3-DMB are given in Table I. In the γ-radiolysis of 2,3-DMB at 77 K,[20] the same products have been obtained except those corresponding to peaks **5** and **15**. In the liquid phase at room temperature only peak **5** is missing. In the peroxide reaction few compounds are found on the gas chromatograms between the light compounds (2,3-DMB, *tert*-butyl alcohol, acetone, etc., eluting just after the air peak) and the C_{12} fraction. This is, however, not the case in the γ-radiolysis, especially in the liquid phase at room temperature.[6,20]

After irradiation, the C_{12} compounds are separated from the light and heavy products by fractional distillation at 16 mmHg pressure (≃85 °C). The preparative chromatographic separation is quite poor on packed columns and for large amounts of products. Although compounds **4–9**, for example, reveal only one peak, samples collected at the beginning or at the end of the signal show slightly different compositions. It is therefore possible to obtain enriched fractions for the different products. By reinjecting these fractions ("fractional preparative GLC") the purity level may become high enough to permit their identification (Table II).

Mass Spectrometric Analysis. The mass spectra of the different samples do not yield much information about the structure of the compounds. Even at low excitation potentials, the molecular peak of such branched compounds is generally absent or very weak. Fraction C, however, reveals a weak peak at *m/e* 170, and fractions A, D, and E a weak peak at *m/e* 168. Therefore, it is likely that peaks **8/9** correspond to aliphatic dimers, probably R_1R_1, since this compound exists as a meso/racemic mixture and is more stable than the other two dimers. Furthermore, peaks **4**, **14**, and **15** must correspond to monoolefinic products. For alkanes, the major peaks are located at *m/e* 85, 71, 57, 43, and 29; for olefins, the peaks at *m/e* 83, 69, 55, 41, and 27 are appreciably increased. On this basis, compounds **6**, **8/9**, and **17** are alkanes and the olefinic nature of **4**, **14**, and **15** is confirmed. Sample E revealing also a peak

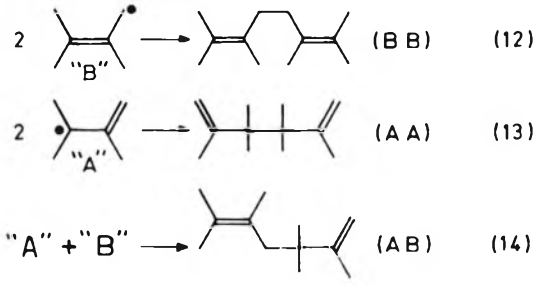
Table II. Compounds Isolated by Fractional Preparative GLC[a]

Sample[b]	Peak	Purity,[c] %	Major impurities[c]
A	4	73	1/2/3 (9%) 5/6/7 (17%)
B	6	46	4 (40%) 8/9 (14%)
C	8/9	49	4 (8%) 5/6/7 (42%)
D	14	83	11/12 (5%) 13 (4%) 15 (8%)
E	15	74	14 (13%) 16 (8%) 17 (5%)
F	17	95	

[a] Approximately 400 μL of each sample was obtained; for sample C, only 30 μL. [b] Other compounds were also isolated but at lower purity levels. [c] In each case, impurities correspond to major peaks of other samples.

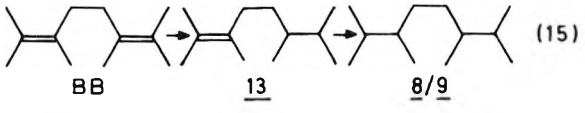
at *m/e* 166, compound **16**, is probably a diolefinic compound.

Independent Synthesis of Some C_{12} Hydrocarbons. The independent synthesis of all the 21 C_{12} compounds should be extremely long and tedious. Moreover, some classical methods like Wurtz synthesis give mixtures of products, the problem being thereby only displaced. Nevertheless, preparation of some of the 21 C_{12} compounds may greatly help in determining the structure of the others. For this purpose we have submitted 2,3-dimethyl-2-butene to the action of DTBP and UV light. The combination of the A and B "forms" of the allylic A ↔ B radical gives three products, AA, AB, and BB.



According to Cantrell,[21,22] essentially BB is formed, while Carless claims that BB and AB are obtained.[23] On packed columns (SE-30) only two peaks can indeed be seen. However, with an open tubular column of OV-1 at 110 °C, three products are detected[24] (Table III). They correspond to AB, AA, and BB, respectively, as evidenced by their ^1H NMR, ^{13}C NMR, and mass spectra.[25-27] It must be pointed out that chromatograms of the reaction of 2,3-DMB itself do not show important peaks corresponding to AA, AB, or BB.

The hydrogenation of BB leads to compound **13** and finally to a mixture of **8/9**. This confirms our assumption that peaks **8/9** correspond to the R_1R_1 dimers and allows also the identification of peak **13**.

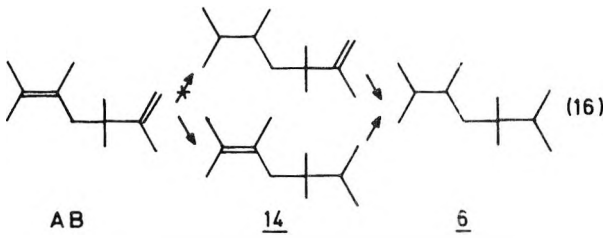


The hydrogenation of AB leads to **14** and finally to **6**. Thus peak **6** corresponds to R_1R_3 and compound **17**, the third saturated dimer, must be R_3R_3. Two monoolefins are possible starting from AB. However, tetrasubstituted olefins are very difficult to hydrogenate compared to disubstituted olefins and no doubt is therefore possible concerning the exact nature of **14**.

Table III. Retention Times and GC Area Percentages for the C_{12} Hydrocarbons Obtained by the Action of DTBP on 2,3-Dimethyl-2-butene and 2,3-Dimethyl-1-butene

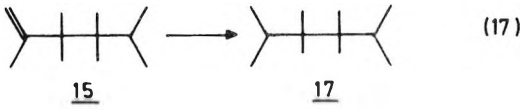
Peak	Retention times, min[a]	GC area percentages: 2,3-Dimethyl-2-butene	GC area percentages: 2,3-Dimethyl-1-butene
1	30.1		12.8
5	33.9		4.2
10′	38.5		0.7
12 + 12′	41.0[b]	34.0 + 14.0	26.1 + 10.7
12″	41.7		22.7
16	51.4[b]	52.0	22.8

[a] For the GC analysis conditions, see Experimental Section. [b] At 110 °C, compounds 12, 12′, and 16 elute at 24.7, 25.0, and 29.0 min, respectively.

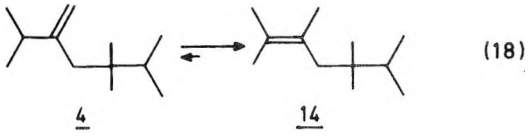


Hydrogenation of Reaction Mixtures. Hydrogenation of reaction mixtures obtained from the action of DTBP on 2,3-DMB itself confirms the preceding determinations and allows the identification of other peaks. Thus, the hydrogenation of a sample containing 68% **14** and 32% **15** gives a mixture containing 67% **6** and 33% **17**.

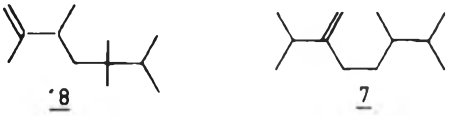
$$14 \rightarrow 6 \qquad (16')$$



With a mixture containing 57% **4**, 29% **6**, 6% **7** and 8% **8/9**, **4** is rapidly converted to **14** and then more slowly to **6**. The rapid reaction corresponds to an isomerization. Although the



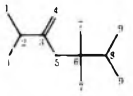
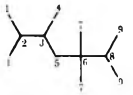
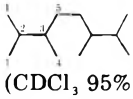
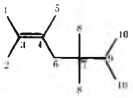
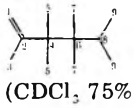
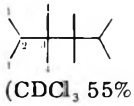
equilibrium is almost entirely displaced to the formation of **14**, the hydrogenation proceeds via the less substituted isomer **4** (and/or eventually its terminal isomer **18**). After complete hydrogenation, the mixture contains 84% **6** and 16% **8/9**. Therefore, compound **7** is a precursor of **8/9** and has most probably the structure CR_1.



^{13}C NMR Spectroscopy. For alkanes, chemical shifts may be predicted from structural parameters. The Grant and Paul equation[28] extended by Carman, Tarpley, and Goldstein[29] does not give the 4°(4°), 3°(4°), 4°(3°), . . ., parameters required for highly branched dimers. The 4°(2°), 2°(4°), and 3°(3°) parameters are furthermore based on a single observation. We have used the relation proposed by Lindeman and Adams:[30]

$$\delta_C(k) = B_S + \sum_{M=2}^{4} D_M A_{SM} + \gamma_S N_{k3} + \Delta_S N_{k4} \qquad (19)$$

Table IV. Calculated and Experimental ^{13}C Chemical Shifts and Experimental ^{1}H Chemical Shifts for the C_{12} Hydrocarbons

Registry no.	Hydrocarbon (solvent)	Carbon	^{13}C NMR: Obsd shift (multiplicity)	^{13}C NMR: Calcd shift	^{13}C NMR: $\Delta\delta$	^{1}H NMR: Obsd shift (multiplicity)
62816-29-9	 4 ($CDCl_3$ 50% v/v)	1	22.45 (q)	18.64–20.14	2.31	1.02 (d)
		2	34.86 (d)	32.53 ± ?		2.10 (m)
		3	154.49 (s)	154.20	0.29	
		4	109.66 (t)	109.51	0.15	4.68 (s); 4.89 (s)
		5	44.83 (t)	42.11	2.72	2.02 (s)
		6	36.52 (s)	34.85–36.35	0.17	
		7	24.31 (q)	23.79	0.52	0.82 (s)
		8	37.09 (d)	35.59	1.50	1.45 (m)
		9	17.68 (q)	16.15	1.53	0.86 (d)
52670-35-6	 6 ($CDCl_3$ 95% v/v)	1	18.09 (q) 20.29 (q)	19.14	−1.05 1.15	*d*
		2	32.23 (d?)	32.53	−0.30	*d*
		3	34.33 (?)	34.99	−0.66	*d*
		4	17.87 (q)	17.13	0.74	*d*
		5	44.15 (t)	42.71	1.44	*d*
		6	35.72 (s)	35.35	0.37	
		7	24.33 (q)	24.29	0.04	0.83 (s)
		8	36.71 (?)	36.09	0.62	*d*
		9	17.67 (q)	16.15	1.52	*d*
62816-30-2 62816-31-3	 8/9 ($CDCl_3$ 95% v/v)	1	18.09 (q) 20.29 (q)	19.14	−1.05 1.15	0.80 (d)
		2	32.23 (d?)	32.53	−0.30	1.45 (m)
		3	38.97 or 39.14 (d?)	39.13	−0.16 0.01	1.45 (m)
		4	15.51 (q)	16.15	−0.64	*d*
		5	32.02 (t?)	31.53	0.49	1.20 (m)
62816-32-4	 14 ($CDCl_3$ 50% v/v)	1	*a* (q)	19.14 ± ?		1.65 (s)
		2	*a* (q)	19.14 ± ?		1.65 (s)
		3	126.48 (s)[b]	128.02	−1.54	
		4	126.96 (s)[b]	128.49	−1.53	
		5	*a* (q)	17.13 ± ?		1.65 (s)
		6	43.37 (t)	42.11	1.26	2.04 (s)
		7	38.20 (s)	34.85–36.35	1.85	
		8	24.72 (q)	23.79	0.93	0.81 (s)
		9	38.50 (d)	35.59	2.91	1.55 (m)
		10	17.79 (q)	16.15	1.64	0.88 (d)
62816-33-5	 15 ($CDCl_3$ 75% v/v)	1	113.18 (t)	109.51	3.67	4.82 (s); 4.88 (s)
		2	152.82 (s)	154.20	1.38	
		3	23.93 (q?)	17.13 ± ?		1.83 (s)
		4	45.21 (s)	40.44 ± ?		
		5	25.39 (q)	17.81–19.31	6.08	1.08 (s)
		6	40.72 (s)	39.94–41.44	−0.72 0.78	
		7	21.39 (q)[c]	17.81	3.58	0.84 (s)
		8	31.65 (d)	31.45	0.20	?
		9	20.90 (q)[c]	17.68	3.22	0.86 (d)
52670-36-7	 17 ($CDCl_3$ 55% v/v)	1	21.09 (q)	17.13	3.96	0.91 (d)
		2	32.42 (d)	31.95	0.47	1.98 (m)
		3	41.50 (s)	40.44	1.06	
		4	21.87 (q)	18.31	3.56	0.83 (s)

[a] Peaks are observed at 22.08, 21.70, and 20.91 ppm. The exact attribution to each olefinic methyl is difficult. By comparison with *cis*- and *trans*-2-butenes and with other cis and trans 2-alkenes, it seems reasonable to attribute these three signals to carbons 1, 5, and 2, respectively. [b] The attribution is not certain and may be inverted. However, calculations give a slightly higher shift value for carbon 4. [c] The attributions for carbons 7 and 9 are questionable. [d] Compounds 6 and 8/9 being a mixture, exact attributions are not straightforward. For compound 6 a doublet (6 hydrogens) is observed at 0.84 ppm.

This more elaborated relation is also based on a larger number of observations.

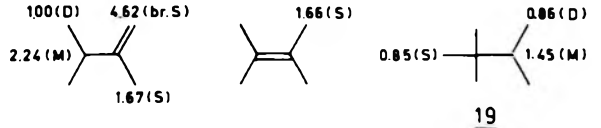
For olefinic carbons and for aliphatic carbons in unsaturated molecules, we have used the parameters and estimations proposed by Roberts.[31] Table IV compares calculated and observed shifts. The agreement is generally fairly good. It is, however, poorer for the most branched compounds 15 and 17. This proves that the relation 19 does not yet take into account all the possible structures and that additional parameters should be necessary in order to improve the precision of the predictions, for example, replacement of γ by A_{SM}-type parameters, as already suggested by Lindeman and Adams.[30] It seems also that the rules defined by Roberts for olefins were obtained from a too limited set of molecules and may not apply with great accuracy to very branched compounds.

^{1}H NMR Spectroscopy. The proton chemical shifts of the C_{12} compounds are given in the last column of Table IV. The identification of compound 4 (fraction A) is confirmed by comparison with 2,3-dimethyl-1-butene and 2,2,3-trimethylbutane (19). Compound 6 (fraction B) does not reveal the

Table V. Physical Properties of Some C_{12} Hydrocarbons

Hydrocarbon	Bp, °C	d^{20}_4	$n^{20}D$	IR ref	^{1}H NMR ref
R_1R_1 (8/9)	92 (20–22 mm)[33]	0.7593[a,33]	1.42527[a,33]		*b*
AB (12)	183.0		1.4653	23	23, 27
BR_3 (14)	193[c]		1.4365[c]		*b*
BB (16)	81–82 (13 mm)[35]	0.8081[35]	1.4623[35]	23	21, 23, 34
	87.5–88.5 (18 mm)[33]	0.7971[a,33]	1.45963[a,33]		
	81–83 (14 mm)[36]				
	202.7		1.4642		27
	38–40 (0.01 mm)[22]				
	100 (30 mm)[d,34]				
R_3R_3 (17)	208.5		1.4592		*b*

[a] At 25 °C. [b] See Table IV. [c] Purity 83% (see Table II). [d] Crude dimer.



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presence of olefinic protons (all signals below 2 ppm). No important differences (except for the olefinic protons) can be evidenced between the spectra of **4** and **6**. This confirms that they have the same carbon skeleton. Olefinic protons are also absent in compounds **8/9** (fraction C). Spectra of compounds **14** (fraction D) and **15** (fraction E) can be reconstructed from 2,2,3-trimethylbutane (**19**), 2,3-dimethyl-1-butene, and 2,3-dimethyl-2-butene. The spectrum of **17** (fraction F) must of course be the simplest one.

Physical Properties of the C_{12} Hydrocarbons. Of the 21 C_{12} hydrocarbons only one alkane, R_1R_1,[32,33] and two diolefins, AB[23] and BB,[21-23,33-36] have been mentioned in the literature. Table V collects the available information this work included. The values for R_3R_3 confirm the particular behavior of bi-quaternary compounds: they present much higher values for their refractive index and boiling point. The refractive index of most dodecanes lies in the range 1.4200–1.4300.[37] 2,4,4,5,5-Pentamethylheptane with two adjacent quaternary carbons has a value of 1.4402,[38] still significantly lower than that of R_3R_3 whose two vicinal quaternary carbons are flanked by tertiary ones! Quite branched dodecanes have generally boiling points below 200 °C. Once more, R_3R_3 is an interesting exception.

Probable Identification of the Other Peaks. It is probable that in the reaction medium much less 2,3-dimethyl-1-butene is formed than the corresponding 2-butene. Primary radicals R_1 show less tendency to disproportionate than tertiary ones and R_3 will probably give the more stable 2-butene. Therefore compounds containing the C and D radicals must be less abundant and their identification more difficult. The dehydrodimerization of 2,3-dimethyl-1-butene alone permits us, however, to make valuable suppositions concerning the nature of compounds not yet identified.

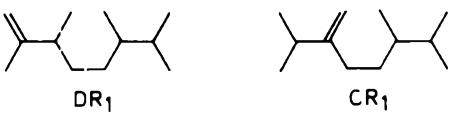
The action of peroxide and light on 2,3-dimethyl-1-butene leads in principle to the formation of ten diolefins from the A ↔ B, C, and D radicals. In practice seven peaks are observed by capillary GLC (Table III). Four peaks (**1**, **5**, **10′**, and **12″**) are not formed with the 2-butene. They must therefore contain the C (or, less probably, the D) radical. The two major peaks (**1** and **12″**) must of course correspond to AC and BC. From chromatographic data (to be discussed in the next paragraph), AC corresponds to peak **1** and BC to peak **12″**. Therefore, peak **5** should correspond to CC. Only compounds containing the less probable D radical (AD, BD, CD, and DD) have not yet been attributed. Peak **10′** is tentatively attributed to BD (rather than to AD because form B is more abundant than form A in the dehydro dimers). Compounds CD and DD must be negligible.

By adjusting the initial concentrations of 2,3-DMB and one of the 2,3-dimethylbutenes, one must favor the formation of monoolefinic C_{12} hydrocarbons. In fact, the reaction of 2,3-dimethyl-2-butene(1 part) and 2,3-DMB (4 parts) leads to the increased formation of the monoolefins BR_3 and AR_3 (peaks **14** and **15**). Under similar conditions we observed with 2,3-dimethyl-1-butene an increase of peaks **4** (CR_3), **14**, and **15**.

Except for peaks **2**, **3**, and **7**, all the peaks of Table I have been attributed. Since peaks **2** and **3** appear always in quite similar proportions, they may correspond to the threo and erythro isomers of DR_1. At 137 °C, the importance of these two peaks is enhanced (Table I). This should correspond to a larger proportion of attack on the primary sites with an increase of the reaction temperature.[39] Therefore, only peak **7** remains unattributed. It corresponds probably to CR_1 which has not yet been found.

Boiling Temperatures and Chromatographic Retention Times. Attributions made in the last paragraph are plausible suppositions concerning products which were not isolated from the reaction medium or synthesized by an independent reaction. These suppositions are also in agreement with chromatographic considerations.

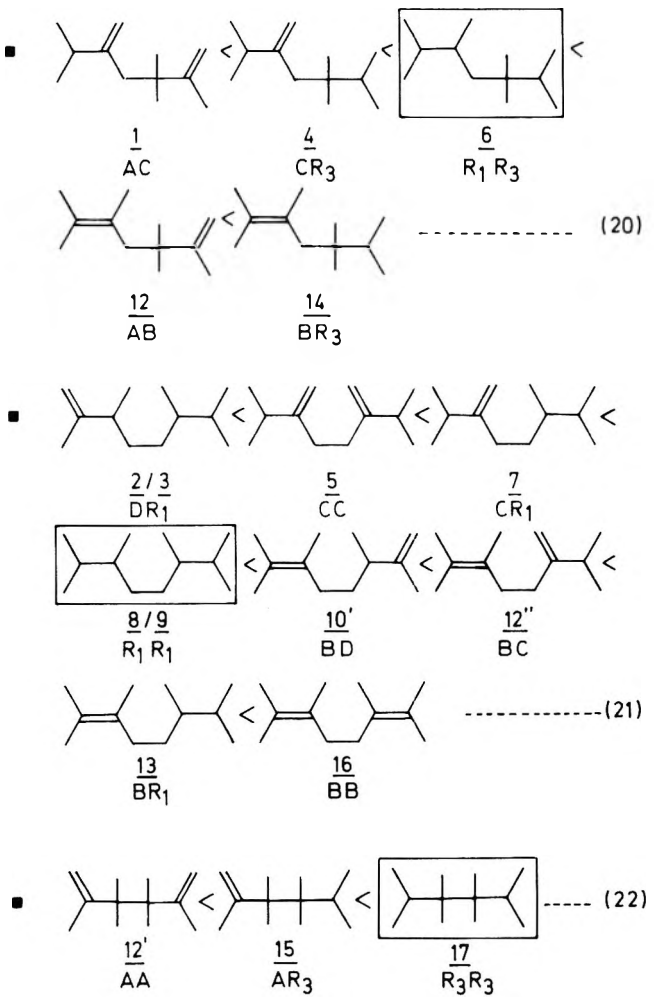
The presence of a tetrasubstituted double bond increases the boiling temperature of a hydrocarbon while the introduction of a 1,1-disubstituted double bond decreases it (2,3-DMB, 58.0 °C; 2,3-dimethyl-2-butene, 73.2 °C; 2,3-dimethyl-1-butene, 55.7 °C). The influence of an unsaturation must be less in the C_{12} than in the C_6 compounds. Moreover, different 1,1-disubstituted olefins exist, for example, CR_1 and



DR_1 CR_1

DR_1. With terminal olefins, the temperature lowering is larger. Although branching generally lowers boiling temperatures, an increase is, however, observed when two quaternary carbon atoms are vicinal. Alkanes, alkenes, and nonconjugated alkadienes, which are all of low polarity, elute on a nonpolar column like silicone OV-1, approximately according to their boiling temperature. From this point of view the observed retention time sequences 20 to 22 not only confirm the identifications made but are also in accordance with the attributions reported in the preceding paragraph.

Of all the possible C_{12} compounds, two monoolefins and three diolefins do not appear on the chromatograms. Similar considerations lead us to suppose that AD should be eluted before peak **1**, DD approximately at the same time, and CD not far after it. DR_3 and AR_1 should be eluted between peaks



1 and 4.[39] Table VI summarizes the C_{12} hydrocarbons formed by combination of the different radicals.

Importance of the Various Radicals. It is not possible from these reactions to determine exactly the relative reactivities of the tertiary and primary hydrogen atoms in 2,3-DMB. In fact, the A ↔ B, C, and D radicals may arise from R_1 as well as from R_3. If they originate only from R_1, Table I leads to a relative reactivity of 8.4. In the other borderline case (all radicals originating from R_3 only) a value of 40.2 is determined. In the chlorination of 2,3-DMB by *tert*-butyl hypochlorite, the relative reactivity tertiary/primary is near 40.[40-42] This value is due to *tert*-butoxyl radicals and not to chlorine atoms which are more reactive.[43] This leads us to conclude that the A ↔ B, C, and D radicals are generated more by R_3 than by R_1. In other words, tertiary radicals show a greater tendency to disproportionate than primary ones do.[2]

With allyl radicals, two resonance structures exist. For 2,3-dimethyl-2-butene, we observe 34% AB, 14% AA, and 52% BB. Thus in the dehydro dimers the B structure is present to an extent of 69% and the A structure to an extent of 31%. These values do not necessarily represent exactly the importance of the A and B structures in the allyl radical itself because steric hindrance to dimerization is not impossible for A. Nevertheless, the predominance of B structures has already been mentioned for the chloroallyl radical **20**[44]

$$\underset{\textbf{20B}}{ClCH{=}CHCH_2\cdot} \leftrightarrow \underset{\textbf{20A}}{ClCHCH{=}CH_2}$$

and for the methoxypentenyl radical **21**.[45]

$$\underset{\textbf{21B}}{CH_3OCH_2CH_2CH{=}CHCH_2\cdot} \leftrightarrow \underset{\textbf{21A}}{CH_3OCH_2CH_2CHCH{=}CH_2}$$

Table VI. C_{12} Hydrocarbons Formed by Combination of Indicated Radicals (Photochemical Reaction at 35 °C. Composition given in Percentage of GC Area. Peaks Numbers Are Given in Parentheses)

	R_3	R_1	C	B	A	D
D	*a*	2.3 (2/3)[a]		(10')		
A	4.8 (15)	*a*	Tr (1)	Tr (12)	Tr (12')	
B	12.5 (14)	0.4 (13)	Tr (12'')	Tr (16)		
C	32.8 (4)	2.0 (7)	1.8 (5)			
R_1	13.7 (6)	3.8 (8/9)				
R_3	25.9 (17)					

[a] See, however, note 39.

For 2,3-dimethyl-1-butene, two different allylic hydrogen atoms can be abstracted. Table III indicates that the extent of the different structures in the dehydro dimers is A, 30.3%; B, 47.7%; and C, 22.0%. Thus, for the A ↔ B resonating radical, the importance of the two structures (38 and 62%) is close to the results obtained with the 2-butene (31 and 69%). The primary allylic hydrogen atoms are only 1.2 less reactive than the tertiary ones. This may be explained by the high reactivity of allylic positions. Finally, radical D is almost absent at ordinary temperature but takes probably more importance in the thermal reaction.

In the γ-radiolysis of 2,3-DMB, the relative reactivities tertiary/primary are much lower: 0.7 and 10.0 for the two extreme cases (Table I). Although part of the products may be due to ionic reactions, the differences are large enough to conclude that the peroxide is much more selective than γ-radiations.

Registry No.—**19**, 464-06-2; BB, 18495-18-6; AA, 62816-34-6; AB, 53256-17-0; DTBP, 110-05-4; 2,3-DMB, 79-29-8; 2,3-dimethyl-2-butene, 563-79-1; 2,3-dimethyl-1-butene, 563-78-0.

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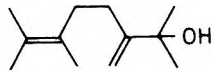
(25) During the preparative VPC, the two first peaks elute together but an important part of the second product disappears. This again is an indication of the AA structure, the most unstable of the three diolefins.
(26) On standing at room temperature for weeks in a closed Pyrex bottle, the diolefin BB gradually disappears although the liquid remains perfectly colorless. The capillary chromatograph reveals a new product eluting after *n*-dodecane. It is in fact the tertiary alcohol **22** as evidenced by ^{1}H NMR, ^{13}C NMR, IR, and mass spectrometry. Such a reaction is known to proceed rapidly in the presence of sensitizers like benzophenone.[46,47]



22

(27) Spectroscopic data follow. Compound BB (neat): ^{1}H NMR 1.63 (s); 2.05 (s); ^{13}C NMR 20.58, 20.02, and 18.65 (q), 33.61 (t), 123.73 and 128.02 (s). Compound AB (neat but slightly contaminated by AA): ^{1}H NMR 1.05, 1.65, 1.78, and 2.19 (s), 4.78 (m); ^{13}C NMR 20.00, 20.80, 21.57, and 27.53 (q), 45.30 and 109.56 (t), 40.81, 126.45, 126.84, and 153.11 (s). Compound AA (diluted in AB): ^{1}H NMR 1.08 and 1.81 (s), 4.89 (br s); ^{13}C NMR 151.92 (s), 44.25 (s?), 114.10 (t?), 24.71 (q), 23.45 (q?).
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Kinetics of the Interaction of Nitrosobenzenes with Substituted Benzaldehyde Phenylhydrazones

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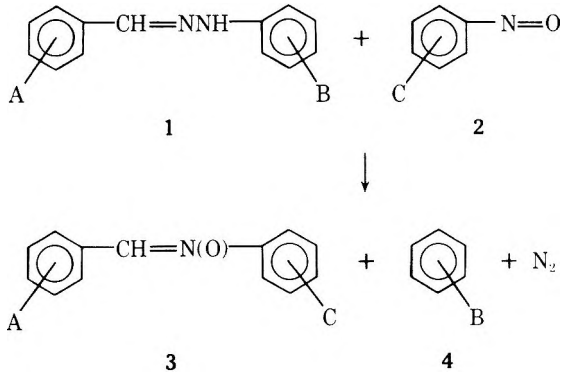
The reaction of benzaldehyde phenylhydrazone with nitrosobenzene follows second-order kinetics in either air or nitrogen at ambient temperature. Rates of reactions under nitrogen utilizing reactants substituted at meta and para positions of each of the three available aromatic rings have been correlated using the Hammett treatment. Reactions are facilitated by electron-donating substituents on benzaldehyde phenylhydrazones and by electron-withdrawing substituents on nitrosobenzenes. Oxygen exerts a more dramatic inhibition on reaction rates of substituted substrates than of parent compounds.

Benzaldehyde phenylhydrazone reacts with nitrosobenzene at ambient temperature to give nitrones, nitrogen, and benzene.[1] Phenylhydrazone derivatives of aromatic ketones and substituted benzaldehydes yield the corresponding nitrones, and product yields are sensitive to oxygen. The probable course of the reaction using reactants substituted at various aromatic rings may be summarized as shown in Scheme I.

Scheme I



Kinetics of this reaction have been studied to determine the order of the initial reaction of nitrosobenzenes with hydrazone substrates and to explore causes for oxygen sensitivity. The consequence of substitution (A, B, and C) at the aromatic rings has been investigated in order to elucidate the impact of electronic effects on the reaction.

Results and Discussion

General applicability of Scheme I is illustrated both by earlier synthetic work,[1] in which A- and B-ring substitution was investigated, and by formation of α-phenyl-*N*-*m*-chlorophenylnitrone (**3**, A = H, C = *m*-chloro) from reaction of *m*-chloronitrosobenzene with benzaldehyde phenylhydrazone (BPH). All three rings of reactants therefore could provide sites for substitution in this reaction system.

Initial kinetic investigations centered on the interaction of (unsubstituted) BPH with nitrosobenzene, and results indicated first-order rate dependency on both reactants. Plots of 1/(nitrosobenzene absorbance) vs. time for reactions in benzene, using equal initial concentrations of both reactants, were shown to be linear for at least three half-lives under *both* air and nitrogen atmospheres (average correlation coefficients of 0.9996 and 0.9995, respectively). It therefore was considered

Table I. Kinetics of Reactions of Phenylhydrazones with Nitrosobenzenes in Benzene at 24.2 ± 0.2 °C

Registry no.		Reaction[a]	1 A	1 B	2 C	k, M^{-1} s^{-1} First half-life	k, M^{-1} s^{-1} Overall
588-64-7	586-96-9	1-0	H	H	H	0.136	0.120
		1-1[b]	H	H	H	0.134	0.119
2829-27-8		2-0	p-NO_2	H	H	0.0738	0.0751
		2-1[c]	p-NO_2	H	H	0.0482	0.0448
7539-23-3		3-0	m-NO_2	H	H	0.108	0.111
		3-1[b]	m-NO_2	H	H	0.0871	0.0788
		3-2[d]	m-NO_2	H	H	0.0858	0.0819
351-24-6		4-0	m-F	H	H	0.0944	0.0948
34158-77-5		5-0	m-Cl	H	H	0.104	0.100
16917-42-3		6-0	p-Br	H	H	0.144	0.120
2829-26-7		7-0	p-Cl	H	H	0.149	0.145
2829-25-6		8-0	p-CH_3	H	H	0.171	0.155
352-06-7		9-0	p-F	H	H	0.180	0.176
622-73-1		10-0	p-OCH_3	H	H	0.229	0.218
2829-28-9		11-0	p-dma[e]	H	H	0.282	0.283
2989-41-5		12-0	H	m-Cl	H	0.0258	0.0242
2833-68-3		13-0	H	p-Cl	H	0.0750	0.0625
62698-28-6		14-0	H	m-CH_3	H	0.196	0.179
		14-1[b]	H	m-CH_3	H	0.180	0.154
352-07-8		15-0	H	p-F	H	0.224	0.248
		15-1[b]	H	p-F	H	0.204	0.191
1858-99-7		16-0	H	p-CH_3	H	0.330	0.452
		16-1[b]	H	p-CH_3	H	0.383	0.368
10407-20-2		17-0	H	p-OCH_3	H	1.18	1.38
		17-1[b]	H	p-OCH_3	H	0.438	0.246
	623-11-0	18-0	H	H	p-CH_3	0.0318	0.0253
	352-15-8	19-0	H	H	p-F	0.0612	0.0430
	620-26-8	20-0	H	H	m-CH_3	0.0985	0.0841
	26595-63-1	21-0	H	H	m-OCH_3	0.137	0.111
	932-98-9	22-0	H	H	p-Cl	0.409	0.329
	932-78-5	23-0	H	H	m-Cl	1.09	1.18
		23-1[b]	H	H	m-Cl	0.927	0.765
	7476-79-1	24-0	H	H	p-cbe[f]	3.61	4.92

[a] Unless otherwise indicated, under N_2. [b] Run in air. [c] From pseudo-first-order reaction. [d] Solvent pretreated with O_2. [e] Dimethylamino. [f] Carbethoxy.

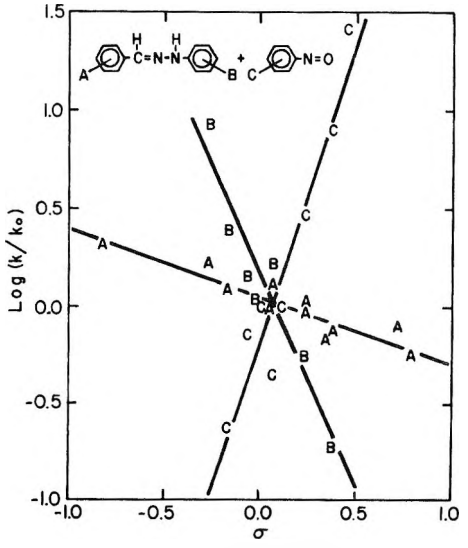


Figure 1. Log k/k_0 vs. Hammett σ for reactions in Table I of nitrosobenzenes with phenylhydrazones of benzaldehydes. For A points, B and C = H, etc.

that reaction rates derived from these plots might be used reliably as standards for a Hammett treatment.

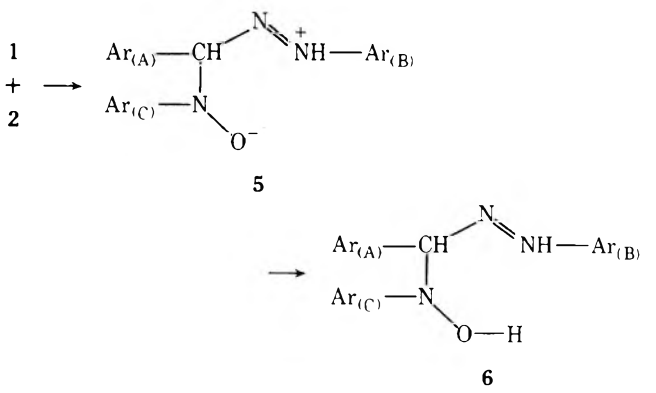
Three series of reactions were carried out employing reactants substituted at meta and para A-, B-, and C-ring positions indicated in Scheme I. Second-order rate constants for these reactions are shown in Table I. Excepting only reactions 16-0 and 17-0, linear second-order plots with correlation coefficients of at least 0.9999 were recorded for all reactions run with a nitrogen atmosphere. Reactions in air proved to be less consistent.

First half-life rate constants for reactions run under nitrogen were used to generate log k/k_0 vs. Hammett σ plots for the three reaction series, and these are shown in Figure 1. Results indicated that reactions are facilitated by meta and para electron-donating substituents at either ring of BPHs (A ring, $\rho = -0.3$; B ring, $\rho = -2.2$) and by electron-withdrawing substituents on nitrosobenzene (C ring, $\rho = +3.0$). Moreover, the relative magnitude of ρ values showed that the system was significantly more sensitive to substitution at either B- or C-ring sites than at A.

These results are consistent with a mechanism involving initial electrophilic attack by the nitrosobenzene upon the BPH benzylidine carbon, giving rise to intermediate **5** (Scheme II). Stability of this zwitterionic intermediate (and the transition state leading to it) could be greatly affected by either B- or C-ring substitution. A-ring substituents, which are insulated from centers of charge, would have relatively small influence, but electron-donating groups still would favor development of a positive charge on the adjacent, erstwhile hydrazone nitrogens. Hegarty and Scott noted parallel relative sensitivities for A- and B-ring substitution in the electrophilic attack of bromine on hydrazones ($\rho_A = -0.62$ and $\rho_B = -2.2$) and attributed their results to formation of an intermediate analogous to **5**.[2]

As reactions proceeded, it is possible that **5** was more or less rapidly converted to **6**, a species analogous to the ene product isolated by Knight from the reaction of nitrosobenzene with 2,3-dimethylbut-2-ene.[3] A similar ene-type product has been

Scheme II



isolated from the reaction of BPHs with alkoxycarbonylazo compounds.[4]

In experiments using ring-substituted hydrazone substrates, reaction rates proved to be more air sensitive than when unsubstituted BPH was used. This is most dramatically illustrated on comparison of reactions 17-0 and 17-1 with 1-0 and 1-1, but generally reactions in air of substituted BPHs not only were slower than in nitrogen initially, but rates also continued to diminish with time. These results were probably due in part to a competing reaction of BPH substrates with oxygen.[5] However, this factor does not explain why *m*-nitrobenzaldehyde phenylhydrazone, upon interaction with nitrosobenzene, was more sensitive to air than was BPH. (Contrast reactions 3-0, 3-1, and 3-2 with 1-0 and 1-1!). The *m*-nitro compound is reported to react more slowly with oxygen than BPH.[5a] Similarly, substrate oxidation does not explain why BPH should show greater sensitivity to air on reaction with *m*-chloronitrosobenzene (reactions 23-0 and 23-1) than with nitrosobenzene (reactions 1-0 and 1-1). Furthermore, experiments on a synthetic scale have shown that yields of the final product nitrone may be enhanced by an air atmosphere.[1]

These results may relate to pathways by which intermediates **5** and/or **6** ultimately were converted to nitrones and the other products in Scheme I. Mechanisms involving either ionic or radical intermediates may be operable;[6a] one possible pathway involves decomposition of intermediate **6** to give a nitrone and an aryl diazene, ArN_2H. The latter is known to yield, under certain circumstances, nitrogen and the corresponding aromatic compound.[6b]

Experimental Section

Melting points were determined on a Thomas-Hoover "Unimelt" apparatus and are uncorrected. Spectrophotometric grade benzene (Baker or Mallinckrodt) was used for kinetic studies. Benzaldehyde phenylhydrazones were prepared by standard methods from the corresponding aldehydes and phenylhydrazines or their hydrochlorides (Eastman, Aldrich, or Pierce), and melting points corresponded to literature values. Nitrosobenzene (Aldrich or Kings Labs) was recrystallized from ethanol, mp 66.5–67 °C (lit.[7] mp 64–67 °C). Substituted nitrosobenzenes were generally obtained using the procedure of Coleman and McCluskey:[7] *p*-nitrosotoluene, mp 46 °C (lit.[8] mp 48 °C); *p*-fluoronitrosobenzene, mp 39–40 °C (lit.[9] mp 39 °C); *m*-nitrosotoluene, mp 50–51.5 °C (lit.[10] mp 53 °C); *m*-methoxynitrosobenzene, mp 48 °C (lit.[11] mp 48 °C); *p*-chloronitrosobenzene, mp 89–91 °C (lit.[12] mp 90 °C); and *m*-chloronitrosobenzene, mp 71.5–72.5 °C (lit.[13] mp 72 °C). Ethyl *p*-nitrosobenzoate was synthesized in very moderate yield by a modified Caro's acid method,[13] mp 82 °C (lit.[12] mp 83 °C). Microanalysis was performed by Galbraith Laboratories.

Kinetic Procedure. All kinetic work was carried out using a Cary 15 ultraviolet–visible spectrophotometer with cell compartment thermostated by a Precision Scientific "lo-Temptrol" 154 bath set for 24.2 ± 0.2 °C. Concentration vs. absorbance plots for each of the nitrosobenzenes and *p*-nitrobenzaldehyde phenylhydrazone showed all but ethyl *p*-nitrosobenzoate to obey Beer's law in the concentration ranges under investigation.[14]

In experiments where oxygen was to be excluded, benzene was flushed with nitrogen for 0.5 h and stored for 0.5 h in the 24.2 °C bath before being used to make separate solutions of equal concentrations of a nitroso compound and a phenylhydrazone. The two solutions were added simultaneously to a flask flushed with nitrogen, and, after brief agitation, the reaction mixture was charged into a glass absorption cell. Reactant mixing, cell charging, and placement in the spectrophotometer usually required less than 1 min. Generally, reactions utilized a 5-cm cell and equal reactant concentrations of 0.00775 M. The more rapid reactions (no. 17, 23, and 24, Table I) in the B- and C-ring series used a 10-cm cell with equal reactant concentrations in the range of 0.004 M, and some of the slower reactions (no. 12, 13, 18, 19, 20, and 21, Table I) were carried out in a 1-cm cell at 0.0312–0.0390 M concentrations. Depletion of the nitroso compound absorption at 755 nm routinely was used to follow the progress of reactions through at least three half-lives; however, in reaction 24, the *p*-carbethoxynitrosobenzene absorption at 774 nm was monitored. Solution preparation and reagent mixing for reactions in the B-ring series were carried out in the dark due to the marked tendency toward light decomposition of certain of the phenylhydrazones.

In the pseudo-first-order reaction (reaction 2-1) of nitrosobenzene (0.0174 M) with *p*-nitrobenzaldehyde phenylhydrazone (1.74×10^{-5} M), the phenylhydrazone absorption of 410 nm was monitored. After a rapid initial decrease followed by a leveling out period, a slow *increase* in the absorbance was noted. A plot reflecting only *p*-nitrobenzaldehyde phenylhydrazone disappearance was obtained by (a) extrapolating a first-order appearance plot for the unknown product back to zero time, and (b) subtracting resulting absorbance values from the original plot to give a "difference" plot.[15]

α-Phenyl-*N*-*m*-chlorophenylnitrone.[16] A 0.196-g sample (1.0 mmol) of benzaldehyde phenylhydrazone was treated with 0.301 g (2.0 mmol) of *m*-chloronitrosobenzene in benzene under a nitrogen atmosphere using the nitrone synthesis procedure outlined in reference 1. Chromatography on silica gel using benzene and benzene–ethyl acetate yielded 0.121 g (0.52 mmol, a 52% yield) of crude product, mp 91 °C. Recrystallization from 50:50 ethanol/water and cyclohexane yielded an off-white solid, mp 96–96.5 °C. Prominent bands in the infrared spectrum were found at 1600, 1560, 1480, 1460, 1410, 1200, 1110, 1090, 840, 800, 770, 740, and 700 cm^{-1}.

Anal. Calcd for $C_{13}H_{10}ClNO$: C, 67.40; H, 4.35; N, 6.05. Found: C, 67.25; H, 4.34; N, 5.86.

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Registry No.—**3** (A = H; C = Cl), 32019-34-4.

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(15) We are indebted to Dr. G. C. Nieman for this data treatment.
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Desiccant Efficiency in Solvent Drying. A Reappraisal by Application of a Novel Method for Solvent Water Assay

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The chemical literature, very inconsistent on the subject of the drying of solvents, abounds with contradictory statements as to the efficiency of even the more common desiccants. The recent advent of a novel, highly sensitive method which utilizes a tritiated water tracer for the assay of solvent water content has enabled the first comprehensive study to be made of the efficiency of various desiccants which pertains unambiguously to solvents. Benzene, 1,4-dioxane, and acetonitrile, chosen as model solvents, were wetted with known amounts of tritiated water and treated with a spectrum of desiccants, and the residual water contents were then assayed. The results range from the expected to the highly surprising. Some anomalous results, obtained for benzene and acetonitrile with acidic and basic desiccants, respectively, are discussed in terms of isotopic exchange reactions.

The bench chemist is often confronted by the problem of the selection of desiccants for solvent drying, and although dry solvents are frequently required for use in both preparative situations and in physicochemical studies, there is a paucity of *real* information in the literature. Some authors[2] are content to dismiss drying with statements such as "Frequently a liquid can be freed from water by shaking with a drying agent such as anhydrous calcium chloride or phosphorus pentoxide". In the field of organic synthesis, the situation is little better; different reference texts are replete with bewildering contradictions. Thus, magnesium sulfate, described as either neutral[3a,b,f] or acidic,[3c,e] is alternately an excellent drying agent, rapid in its action,[3a,b,d,f] or is slow,[3h] removing only small amounts of water.[4] Aluminum oxide is recommended mainly for use in desiccators,[3f] or as being preferred by many workers for ultimate solvent or reagent drying.[3g] Calcium chloride is "fast",[3b,d,4] or alternately "not rapid" [3f] in its action, and in any case, the consensus appears to be that calcium sulfate is to be preferred as a faster[3a,b,f] and a more efficient[3a,f] desiccant, even though the only existing quantitative comparison for solvents[4] shows the complete reverse to be true. Metallic sodium, generally agreed upon[3b,d] as being efficient, but slow in its drying action, is ridiculed as a desiccant by Plesch,[3g] who states that "the widespread use of sodium as a drying agent by organic chemists is more a ritual than an effective process". Furthermore, there is no doubt that many literature prescriptions for desiccation rely, at least to some extent, on the "chemical intuition" of the author, inspired perhaps by the existence of ubiquitous indices of siccative efficiency.[3a,b,d,f,5] These are usually based on the results of detailed studies of the comparative drying efficiency of desiccants which have been made with regard to the dryness of *gases*,[3h,6] and direct extrapolation to the condensed phase often gives misleading if not totally erroneous information. For example, phosphorus pentoxide, long considered the ultimate drying standard,[6] is actually quite mediocre in certain situations (vide infra). In summary, no comprehensive study of solvent drying comparable to that made for gases appears to exist, and since the efficiency of a desiccant is dependent on the nature of the solvent, this is a serious omission.

Recently,[7] an extremely sensitive method using a tritiated water tracer for the determination of solvent water content has been developed, where essentially drying efficiency is determined by addition of a specified amount of tritium-labeled water to a rigorously dried solvent and subsequent determination of the decrease in activity of the solvent after treatment with various drying agents. With the limitation that, owing to the problem of isotopic exchange, the method is not applicable to protic solvents, it provides a rapid and extremely precise assay of solvent water content. This has prompted us to undertake a comprehensive study of the efficiency of drying of a number of desiccants for the solvents benzene, 1,4-dioxane, and acetonitrile, representative of a spectrum of others commonly used in the laboratory. Thus, while benzene is a model for a useful range of aromatic and hydrocarbon solvents, and dioxane exemplifies commonly used ethers and bisethers, acetonitrile probably parallels the solvent behavior of a number of other polar, and, on account of its very high dielectric constant, perhaps dipolar aprotic solvents. Although selection of drying agents was generally made on the basis of common usage, some more esoteric examples which have been recommended for use in particular situations were also examined. The results have enabled us not only to present a sensible evaluation of many time-honored solvent drying recipes, but also to advocate the use of novel agents in previously unfamiliar situations.

Results and Discussion

Drying of Benzene. Static Drying. Benzene, despite its carcinogenic properties, is a widely used solvent, which, because of its ease of purification and relative inertness in many chemical systems, has been adopted as a secondary standard. Benzene has a zero dipole moment and on account of its low polarity has little affinity for water, the maximum solubility of water in this solvent being 0.063% w/w at 25 °C. Consequently, benzene is a relatively easy solvent to dry. Drying has been accomplished in the literature[8] with the following desiccants: phosphorus pentoxide, metallic calcium, sodium wire, calcium hydride, and molecular sieves.

In this study benzene containing 100 ppm of water was dried with a selection of the more useful and efficient desiccants. The results, summarized in Table I, apply to 5% w/v desiccant loadings and to static drying conditions at ambient temperatures (25–29 °C). Treatment with molecular sieves, alumina, silica gel, calcium hydride, and lithium aluminum hydride gave *super-dry*[9] solvents within 1 day. Alumina in particular was found to be an excellent desiccant for benzene, reducing the solvent water content below 0.01 ppm over this period. These findings thus corroborate earlier conclusions[10] that alumina is a particularly effective drying agent for hydrocarbons, previously exemplified by α-methylstyrene and β-pinene. The *apparent* increase in water content after drying for 7 days is most likely due to exchange or equilibria processes which occur between trace amounts of adventitious moisture—released from the surface of the glass vessel or perhaps gaining entry via diffusion through the *clearfit* stopper seal—and labeled water adsorbed on the desiccant. In any case, it is probably unrealistic to attempt to maintain water contents of below 0.01 ppm outside of totally sealed systems.

Table I. Efficiency of Various Desiccants for Static Drying of Benzene[c]

Registry no.	Desiccant	Residual solvent water content, ppm 6 h	1 day	7 days
	4 Å molecular sieves	2	0.03	0.06
1344-28-1	Al_2O_3	0.6	0.006	0.2
	Silica gel	0.3	0.3	0.1
7789-78-8	CaH_2	0.2		0.03
16853-85-3	$LiAlH_4$	3	2 (0.03)[a]	0.7
7440-23-5	Na	1.5	2 (2)[a]	4 (4)[b]
1314-56-3	P_2O_5	7	12	>28[b]
10043-52-4	$CaCl_2$	12	0.1	
7757-82-6	Na_2SO_4	>28	>28	>28

[a] Scintillation solution purged with nitrogen and recounted. [b] Distilled sample. [c] Desiccant loading 5% w/v; initial water content 100 ppm (0.01% w/w).

Table II. Effect of Stirring on the Drying Efficiencies of Desiccants for Benzene[b]

Desiccant	Residual solvent water content, ppm 6 h Static	6 h Stirred	1 day Static	1 day Stirred
$CaCl_2$	12	0.8	0.1	1
$LiAlH_4$	3	0.7	1.6	0.3 (0.02)[a]

[a] Purged with nitrogen and reassayed. [b] Desiccant loading 5% w/v; initial water content 100 ppm (0.01% w/w).

Calcium and lithium aluminum hydrides are both effective desiccants. The values for the complex metal hydride are apparently high through contamination of the solvent with labeled hydrogen resulting from interaction of the hydride with the labeled water. This was confirmed by recounting the sample after purging with nitrogen whereupon the *apparent* water content was reduced dramatically from 2 to 0.03 ppm. Interestingly, purging had little or no effect on samples dried with calcium hydride and sodium, and this parallels a qualitative observation that lithium aluminum hydride, perhaps because of its finely divided form, appears to *bind* the hydrogen, viz., gas bubbles can still be released from the desiccant long after the solvent is essentially dry.

Sodium is observed to reduce the water content extensively within the first 6 h, but subsequently the *apparent* water content is seen to increase significantly. Since purging with nitrogen and distillation do not reduce the figure it may be speculated that sodium is actually able to metalate benzene, necessarily at an extremely low rate. Tritiation could then occur by reaction of organosodium intermediates with trace amounts of newly formed tritiated water, whose genesis would be identical with that proposed above.

Phosphorus pentoxide appears to be an ineffective drying agent. However, this conclusion must be tempered by the significant increase in *apparent* water content with time of drying. An increase of such magnitude can only reasonably be explained by the presence of exchange reactions. Indeed, phosphoric acid catalyzed exchange reactions have been used elsewhere[11] for the synthesis of tritiated aromatic compounds. The presence of exchange reactions thus unfortunately precludes any conclusion as to the efficiency of phosphorus pentoxide as a desiccant for benzene.

Calcium chloride is seen to be an effective drying agent, quite capable of giving *super-dry* benzene. In contrast, sodium sulfate is completely inept, and the samples obtained after drying were too active for direct counting, indicating little or no drying.

Effect of Stirring. The effect of stirring on rapidity of drying was investigated for calcium chloride and lithium aluminum hydride (Table II). In both cases stirring has an accelerating effect on drying. This is most likely due to breakdown of particle size which increases the effective desiccant surface rather than diffusion control of the drying process, since finely divided silica gel is a very rapid desiccant even under static drying conditions (Table I).

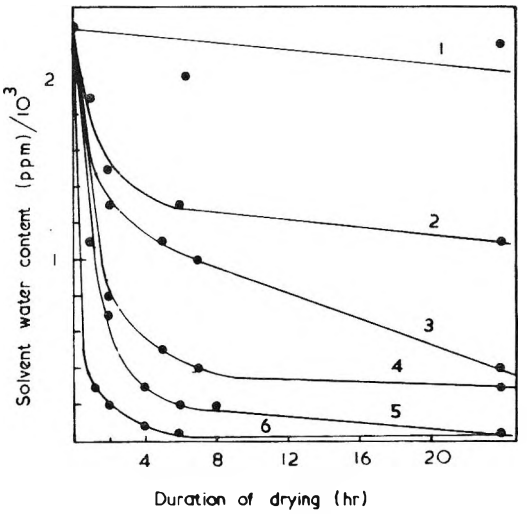

Figure 1. Drying of dioxane with various desiccants. Experimental conditions as for Table III. 1, $MgSO_4$; 2, KOH pellets; 3, P_2O_5; 4, $CaCl_2$; 5, 4 Å molecular sieves; 6, CaH_2.

Drying by Distillation. Fractionation of benzene with retention of the middle fraction, a time-honored process, has frequently been advocated as a method of drying. In this work it was found that the middle fraction, after discarding the first 20%, contained 15 ppm of water. This is significantly drier than the initial water content, but the drying pales in comparison with static drying by the majority of desiccants (Table I).

Drying of Dioxane. Static Drying. Dioxane, although not a very polar solvent (μ = 0.45), is completely miscible with water and is consequently far more difficult to dry than benzene. Drying is frequently tackled in at least two stages. Preliminary drying agents[8] include potassium hydroxide, calcium chloride, sodium hydroxide, and magnesium sulfate, whereas final drying[8] has been accomplished almost exclusively with sodium and occasionally with sodium–lead alloy.

In this study dioxane with an initial water content of 2300 ppm (0.23% w/w)[12] was dried with a selection of both preliminary and final drying agents. The initial rate of drying for a selection of desiccants is displayed in Figure 1. It is immediately apparent that magnesium sulfate is almost completely ineffective as a drying agent, whereas calcium hydride is both rapid and efficient. It is also interesting that, for the first 24 h at least, the speed of drying parallels desiccant efficiency. Remarkably, phosphorus pentoxide does not excel as a drying

Table III. Efficiency of Various Desiccants for Static Drying of Dioxane[c]

Registry no.	Desiccant	Residual solvent water content, ppm 6 h	1 day	7 days
	Na		20	6
	Na–K alloy	132 (22)[a]	22 (11)[a]	22 (6)[b]
	CaH_2	50	30	23
	4 Å molecular sieve	200	40	26
1310-58-3	KOH (ground)	204	150	14 (8)[b]
	$CaCl_2$	450	300	300
	P_2O_5	1050	400	60
	$LiAlH_4$	1200	900	1100 (340)[b]
	KOH (pellets)	1300	1100	200
	Silica gel	1300	1300	1200
	Al_2O_3		1700	1400
7778-18-9	$CaSO_4$		1600	1500
	Na_2SO_4		1900	1800
7487-88-9	$MgSO_4$		2200	2200

[a] After purging to remove H_2. [b] After distillation from desiccant. [c] Desiccant loading 5% w/v; initial water content 2300 ppm (0.23% w/w).

agent, being surpassed in both speed and efficiency by even calcium chloride.

Results for a wider range of desiccants and drying times are summarized in Table III. Sodium, sodium–potassium alloy (containing 80% by weight of potassium), calcium hydride, and molecular sieves are all seen to be very effective drying agents, although at these initial water loadings none of them dry dioxane to *super-dry* levels, which, however, could undoubtedly be achieved by repetitive drying. Sodium–potassium alloy, typically described as possessing a higher drying intensity than metallic sodium,[3h] has been advocated as a siccative in situations where extreme desiccation is required,[13] where its principal advantage over sodium, i.e., its liquid state at ambient temperatures, should expedite very efficient drying of solvents boiling below the melting point of the alkali metal. It is somewhat remarkable therefore that the alloy is not superior to sodium granules under static drying conditions. Powdering of KOH pellets is seen to have a dramatic effect on the rapidity *and* efficiency of drying, and supports a previous report[3c] that drying of diethyl ether and THF solely by treatment with powdered KOH gives material which is immediately suitable for the preparation of reactive organometallics. It is striking that powdered KOH, although slightly slower in action, actually surpasses calcium hydride and molecular sieves in ultimate efficiency.

$LiAlH_4$, though described as highly effective for drying ethers,[3h] actually appears strangely ineffective. The very high residual water contents cannot be explained in terms of labeled hydrogen contamination, and it is difficult to invoke any other interferences. A probable conclusion is that unlike CaH_2, $LiAlH_4$ is not effective under conditions of high initial water content, and this result must cast some doubt on its unqualified recommendation as a desiccant for THF.[14]

The almost complete ineffectiveness of alumina and silica gel for dioxane drying is a complete reversal of their behavior with benzene. This underscores the risks involved in extrapolating the results of gas drying to the liquid phase.

Magnesium and sodium sulfates are again[4] found to be slow and ineffective at these water concentrations. Sodium sulfate, in particular, has earlier[4] been shown to be an almost completely inept desiccant for ethers at *much higher* water concentration, viz., the water content of diethyl ether was reduced from 2.07% w/w to merely 1.83% w/w after a period of several weeks. The value of sodium sulfate, even as a preliminary drying agent, must therefore be questionable. In view of its unanimous recommendation, calcium sulfate also rates surprisingly poorly.

Effect of Stirring and Refluxing on Drying. Since solvents are frequently dried by refluxing over desiccants such as sodium and calcium hydride, the effect of refluxing was briefly investigated. It can be seen (Table IV) that while refluxing dioxane over CaH_2 results in moderate increases in efficiency and speed of drying, stirring is seen to be much more effective.

Table IV. Effect of Conditions on the Drying of Dioxane[a]

Desiccant	Drying time, h	Residual solvent water content, ppm Static	Refluxed	Stirred
CaH_2	2	200	110	
	6	50	29	
	24	30	14	4
	168	23		2
Na	24	20	5	
	48		3	

[a] Desiccant loading 5% w/v; initial water content 2300 ppm (0.23% w/w).

Table V. The Use of Visual Indicators in Dioxane Drying

Desiccant–indicator	Residual solvent water content after distillation, ppm
Sodium–benzophenone	20
BuLi[b]–triphenylmethane	22
BuLi–phenanthroline	17
Trityl fluoroborate[c]	650 (800)[a]

[a] As determined by the near IR method. Initial water content 2300 ppm (0.23% w/w). [b] Registry no., 109-72-8. [c] Registry no., 341-02-6.

Refluxing over sodium (Table IV) is seen to give an improvement in efficiency compared to static drying but prolonged refluxing is not particularly beneficial.[15] It is worthy of note that stirring over calcium hydride at ambient temperatures is as effective as refluxing over molten sodium.

Drying Agents with Visual Indication. Although desiccation prescriptions which include a visual indication of solvent dryness have become fairly common in recent years, no quantitative measure of their efficiency appears to have been made. These methods generally involve the in situ generation of small amounts of colored, highly moisture-sensitive intermediates, often by the action of the desiccant on an added "indicator", and the solvent presumed anhydrous when the indicator color persists. Table V, which displays a selection

Table VI. Efficiency of Various Desiccants for Static Drying of Acetonitrile

Registry no.	Desiccant	Residual solvent water content, ppm 1 day	7 days
	P_2O_5	9 (12)[a,b]	5
	3 Å molecular sieves	49	27
1303-86-2	B_2O_3	59[a]	
584-08-7	K_2CO_3	250	1300
	4 Å molecular sieves	450	500
	$CaCl_2$	1200	2200
	Silica gel	1300	1300
	Al_2O_3	1600	1700
	CaH_2	1900	1900[a] (1300)[a,c]
	KOH (powdered)	2200[a,b,d]	
	KOH (pellets)	2500	1300
	$CaSO_4$	2500	2200
	$Ph_3C^+{}^-BF_4$	2700[a] (2800)[a,c]	

[a] Distilled sample. [b] Colored residue. [c] By near IR method. [d] Strong amine smell in distillate. [e] Desiccant loading 5% w/v; initial water content 2800 ppm (0.28% w/w).

of those investigated for dioxane, reveals that although none of them give *super-dry* solvent (see, however, discussion below), the first three entries give comparable results to the best of those obtained for dioxane after static drying for 1 day (Table III). The intense blue sodium ketyl of benzophenone (entry 1), often used in the preparation of absolute diethyl ether,[16] where it presumably also serves to remove peroxides, gives similar results to butyllithium. The appearance of the red triphenylmethyl anion (entry 2) has been advocated as an indicator in the preparation of "anhydrous" THF.[17] We have found that if no special precautions, e.g., anaerobic conditions, are utilized, then the amount of butyllithium required to impart a persistent color to the solvent is excessively high, owing perhaps to consumption of the "indicator" by molecules other than water, e.g., oxygen. This shortcoming led to an experiment with 1,10-phenanthroline (entry 3), previously suggested as an indicator in the "alcohol method" of assaying BuLi.[18] The formation of the derived rust-red complex required only about half the butyllithium used in entry 2, and since the result was a slightly drier solvent, the use of this indicator is to be preferred. In the general context of the butyllithium experiments, it must also be pointed out that it is known that alkyllithiums react relatively slowly with THF,[19] to give, initially, 2-lithiotetrahydrofuran, which, if the analogous reaction were to occur with dioxane, may serve to label the ether, and hence raise the *apparent* water content, by reaction of metalated dioxane with tritiated water. While this reaction has not been reported for dioxane, and in any case would be expected to be extremely slow compared to reaction of the alkyllithium with water, some inflation of the *apparent* water content by this means cannot be altogether ruled out. Although trityl fluoroborate (entry 4) has not been previously used as a desiccant for ethers, it has been used to dry acetonitrile (vide infra), and this experiment was run to determine its efficiency in a different solvent type. Even though, at this solvent water concentration, the deep yellow color of the salt solution was not discharged, the recovered ether contained a surprisingly large amount of residual water, and this result was cross-checked by the near IR method. Compared to entries 1 to 3, trityl fluoroborate gives poor ultimate drying, which however, is still better than that obtainable with lithium aluminum hydride (Table III).

Drying of Acetonitrile. Static Drying. Acetonitrile, a polar aprotic solvent (μ = 3.44) of high solvating power and favorable physical properties, has been widely used as a solvent both in the study of chemical reactions and for physical measurements involving spectrophotometric and electrochemical techniques. However, because of its high affinity for water it is an outstandingly difficult solvent to completely dry. Drying is conventionally accomplished[8] by treatment with preliminary drying agents such as anhydrous sodium or potassium carbonate, anhydrous calcium chloride, silica gel, or 3 Å molecular sieves, and final drying with calcium hydride, phosphorus pentoxide, or more recently with trityl fluoroborate.[20]

The results of static drying with a range of desiccants are displayed in Table VI. In contradistinction to the other solvents investigated phosphorus pentoxide is seen to excel in its drying efficiency, but even so *super-dry* acetonitrile is not obtained. It is interesting to note that the residual water content is of similar order of magnitude to an earlier result which also utilized P_2O_5.[21] The only disadvantage to phosphorus pentoxide drying is the partial loss of solvent through polymerization, and possible contamination by desiccant residues.[22] Reasonably effective drying can also be achieved with 3 Å molecular sieves which reduce the water content to less than 30 ppm after 1 week. The relative inefficiency of 4 Å sieves emphasizes the need for careful selection of sieve pore size for effective drying. A hitherto little mentioned[3f] but useful desiccant is boric anhydride. Direct sampling proved impossible in this case since soluble desiccant residues interfered visually with the scintillant, but the sample distilled after 1 day stirring with the anhydride had a water content of 59 ppm. This reagent is advantageous compared to phosphorus pentoxide since it does not induce polymerization of the solvent nor does it appear to be significantly volatile. It also offers advantages in its ease of handling and disposal.

Silica gel and alumina are again, as with dioxane, largely ineffective. This may reflect their rather low capacity for effective drying at high water contents,[3g] but in any case makes them an unlikely choice for preliminary drying. Calcium sulfate, although generally strongly recommended for efficient drying, is seen to be the least effective of the examined desiccants, and is clearly surpassed by the underrated calcium chloride.[23]

The ineffectiveness of the previously excellent desiccants potassium hydroxide and calcium hydride seems anomalous. Careful examination of the results reveals that all the basic siccatives, potassium hydroxide, calcium hydride, and potassium carbonate, give apparently little drying. In addition the *apparent* water content in the presence of the weakly basic potassium carbonate increases very significantly from 251 to 1300 ppm over the course of 1 week. These observations appear indicative of a base-catalysed exchange reaction, viz.

$$CH_3CN + T_2O \overset{^-OH}{\rightleftharpoons} CH_2TCN + HOT$$

Such base-catalyzed exchange reactions of the α hydrogens

have been previously encountered with β-hydroxypropionitrile[24] but rather surprisingly it has been claimed[25] that acetonitrile itself does not exhibit similar behavior. In an attempt to confirm the presence of exchange reactions, the tracer experiment was cross-checked by the near IR method for the calcium hydride case. The near IR value of the water content is significantly lower, and this is suggestive of the presence of exchange reactions. Most unexpectedly, this determination also revealed that calcium hydride is largely ineffective for drying acetonitrile. This remarkable observation, together with the results for phosphorus pentoxide drying, undermines the intuitive assumption that the relative efficiencies of desiccants should, barring chemical incompatibility, be independent of solvent type.

The interference, by exchange reactions, unfortunately makes it impossible to draw many conclusions on the efficiency of the basic desiccants save that potassium carbonate is clearly a reasonable desiccant, at least for preliminary drying.

It is worthy of mention that drying with finely powdered potassium hydroxide gave rise to a colored residue and a significant amine content in the distilled fraction.[26]

Trityl Fluoroborate. The use of this stable, orange carbenium ion salt as a desiccant for acetonitrile would seem to be advantageous; it can be stored in a desiccator for extended periods without decomposition,[27] and is used as a siccative[20] simply by adding it in small batches to the wet nitrile until a strong yellow color persists, thus furnishing a visual indication of dryness. The results obtained by using this and the IR method are displayed in Table VI, and indicate that, at these water concentrations, the carbocation salt is a spectacularly ineffective desiccant. The reason for this impotence seems obscure, although acetonitrile, by virtue of its solvation ability, has a well-known moderating influence on the stability of carbenium ions,[28] and indeed, the drying of dioxane by trityl fluoroborate (vide supra) is significantly better than the present solvent. Whatever the true reason, it is clear that, as a desiccant for acetonitrile, the salt is completely worthless.

Merits of the Study. The present study should be of considerable heuristic value, particularly to the bench chemist in the provision of *directly* relevant data, and it is also worthwhile briefly emphasising again[7] that for reasons which include (1) contamination of the solvent by desiccant residues and possibly labeled hydrogen, (2) exchange reactions, and (3) the kinetic isotope effect, the *apparent* water contents, as reported above, will always represent the upper limits of the true content. Of course, this in no way detracts from the value of the work, and, to cite an example, merely means that it is entirely possible that alumina is able to dry benzene to below 6×10^{-3} ppm!

Experimental Section

Radioactive samples were assayed in a scintillation solution containing 0.4 g of 1,4-bis(5-phenyloxazol-2-yl)benzene (POPOP) and 4.0 g of 2,5-diphenyloxazole (PPO) per liter of toluene with a Beckman Model LS-100 liquid scintillation spectrometer. Determination of water content by the near IR method was performed using a Unicam SP700 spectrophotometer.[29] Tritium-labeled water was purchased from the Radiochemical Centre, Amersham, England, at an initial activity of 5 Ci/mL and was diluted with appropriate quantities of inactive water.

Desiccants. Lithium aluminum hydride and phosphorus pentoxide were used as supplied; calcium hydride (99.5%) and reagent grade potassium hydroxide were rapidly powdered immediately prior to use in a mortar and a mechanical blender, respectively. Chromatographic grades of neutral alumina (activity 1) and silica gel, as well as calcium, magnesium, and sodium sulfates, calcium chloride, potassium carbonate, and 3 and 4 Å molecular sieves were activated for 15 h at 300–320 °C before use. Since hydration occurs rapidly on cooling of these desiccants in moist air, cooling was carried out in a phosphorus pentoxide desiccator, and the samples then used immediately. Sodium metal, whose oxide crust had previously been removed by melting under xylene, was cut into 2-mm cubes under dry petroleum ether. Sodium–potassium alloy was prepared as detailed elsewhere[30a] from oxide-free metals. (It is worth noting that the fire hazard associated with destroying excess alloy is completely avoided if the disposal is carried out in two steps. Addition of a little dry ethyl acetate to the alloy in dioxane smoothly consumes potassium—presumably via an acyloin reaction. Unreacted sodium can then be destroyed conventionally using ethanol.) Trityl fluoroborate[27] and boric anhydride[3f] were respectively prepared from triphenylcarbinol and tetrafluoroboric acid, and by high-temperature (900 °C) dehydration of boric acid.

Solvents. Benzene. AR grade reagent was stirred for 24 h with finely ground calcium hydride, refluxed, carefully fractionated (bp 80.0 °C), and stored over 4 Å molecular sieves.

1,4-Dioxane. Commercial 1,4-dioxane was purified and dried according to a method cited by Fieser,[30b] whereby the glycol acetal impurity is removed by hydrolysis to acetaldehyde, which is itself voided by purging with nitrogen gas. Preliminary drying with potassium hydroxide pellets followed by fractionation (bp 101–101.5 °C) from sodium gave material which was stored in a dark bottle over 4 Å molecular sieves.

Acetonitrile. Following well-documented procedures,[8] reagent grade material, after being given a preliminary drying with potassium carbonate (24 h), was decanted on to phosphorus pentoxide and stirred at reflux for 2 h. Fractionation gave material of bp 81.5 °C, which was not stored, but used immediately.

Techniques. The procedure used for benzene serves as an example. A stock solution of benzene containing 100 ppm of labeled water was prepared by the addition of 18 μL of tritiated water, specific activity 40 mCi/mL, to 180 g of purified benzene; homogenization was accomplished by stirring overnight. Aliquots of the stock solution (15.0 ± 0.1 mL) were syringed directly onto 0.75 ± 0.03 g of activated desiccant contained in a 25-mL clear-fit round-bottom flask, which was then stoppered. Where appropriate samples were stirred magnetically. Samples (1.00 ± 0.02 mL) were taken at time intervals specified in the text—care was taken to avoid disturbing the desiccant—and syringed directly into the counting vials. Where possible, samples were distilled from the desiccant so as to provide a cross-check against contamination of the solvent by labeled desiccant residues. Samples were accumulated and assayed batchwise.

Similar procedures were used with dioxane and acetonitrile, except that higher water contents were examined and tritiated water of low specific activity (0.5 mCi/mL) was employed.

Registry No.—Benzene, 71-43-2; dioxane, 123-91-1; acetonitrile, 75-05-8.

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methylamine are dehydrated sufficiently that spin coupling of the adjacent N–H and C–H protons is observable in their NMR spectra: K. L. Henold, *Chem. Commun.*, 1340 (1970).
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Perhydrogenation of 2,8-Diaminopurine

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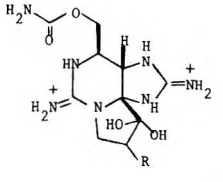
2,8-Diaminopurine (**7**) can be hydrogenated over PtO_2 in acidic medium to give 2-imino-4-guanidinomethyl-5-imidazolidinone (**11**) which can itself be further hydrogenated to 2-imino-4-guanidinomethylimidazolidine (**12**). The structures of **11** and **12** were proven by unambiguous synthesis. 2,8-Diamino-6-methylpurine (**37**) also can be hydrogenated in a similar manner to two analogous compounds, as isomeric mixtures, whose structures are inferred by comparison with **11** and **12**. A superior method has been developed for synthesizing the diaminopurines **7** and **37**, involving the condensation of the appropriate triaminopyrimidine with *N*-(methylmercaptochloromethyl)-*p*-toluenesulfonimide (**20**) followed by ring closure via the carbodiimide and detosylation with HF.

Saxitoxin is one of the most potent naturally occurring neurotoxins. It is the sole toxin produced by the marine dinoflagellate *Gonyaulax catenella*[1] and is a minor constituent of the toxins produced by *G. tamarensis*.[2] Ingestion of these dinoflagellates by several species of normally edible shellfish is frequently responsible for their toxicity to man. X-ray crystallographic analysis of two derivatives, the bis-*p*-bromobenzenesulfonate[3] and the ethyl hemiketal dihydrochloride,[4] have established structure **1** for crystalline saxitoxin hydrate, and ^{13}C NMR studies have also established this structure for the molecule in solution.[4] Recently[5] the major toxins of *G. tamarensis*, gonyautoxins II and III, also existing as the hydrates, were postulated to have the closely related structures **2** and **3**, respectively.



1, R=H
2, R=α-OH
3, R=β-OH

Saxitoxin and the gonyautoxins are unique among natural products in that their structures incorporate a tetrahydropurine moiety composed of two guanidine units fused together in an azaketal linkage which remains intact under ordinary conditions. We were therefore interested in preparing a simple model of the tetrahydropurine backbone of saxitoxin, devoid of the fused ketone bearing ring and the peripheral carbamate, for both chemical and biological investigations. We chose to study the catalytic hydrogenation of 2,8-diaminopurine (**7**), which conceivably could lead to 2,8-diiminotetrahydropurine (**10**) or its tautomers, the simplest possible tetrahydropurine model of saxitoxin. We now report the results of our study of the heterogeneous catalytic hydrogenation of 2,8-diaminopurines.

The literature relating to the catalytic reduction of purines is relatively meager. 1,6-Dihydropurine (**5**) has been prepared[6,7] from purine and 6-chloropurine (**4**), and in weak acid **5** was hydrolyzed to 4(5)-aminomethyl-5(4)-aminoimidazole (**6**). Similarly a tetrahydropurine is claimed[8] to result from catalytic reduction of 2,6,8-trichloropurine. More recently,[9] the catalytic reduction of 2,8-diaminopurine (**7**) is reported to yield a compound whose structure was assigned as 2-amino-5-guanidino-1,4,5,6-tetrahydro-6-oxopyrimidine (**8**). These authors also report the preparation of 2,8-diamino-4,5,6,9-tetrahydro-1,7,9-trimethylpurine by sodium borohydride reduction of 2,8-diamino-1,7,9-trimethylpurine, and claim to have electrolytically reduced **7** to **8** plus tetrahydropurine **10**, obtained as an inseparable mixture with another reduction product **9**.

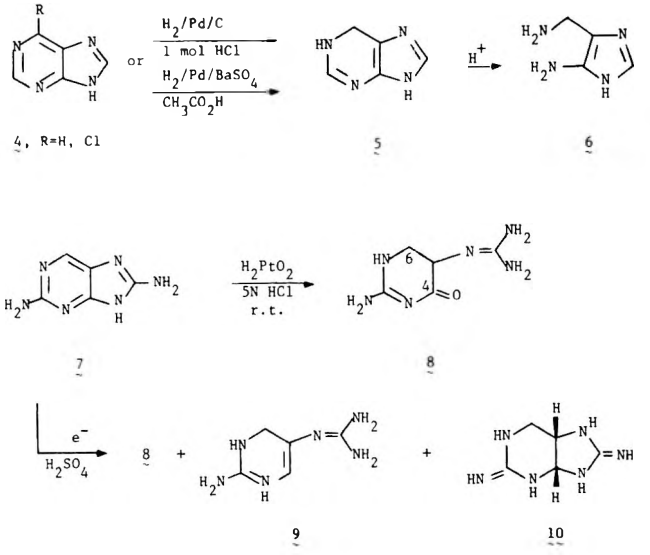
In contrast to that report, we have found that **7** is slowly hydrogenated with a PtO_2 catalyst in hydrochloric acid (pH 1.5) at room temperature and 20 psi pressure to give a single product, A, in quantitative yield. A could be further reduced under more drastic conditions (60 °C, 100 h) to give another product, B, also in quantitative yield. The ^1H NMR spectrum of A·2HCl consisted of a doublet (2 H, J = 5 Hz) and a triplet (1 H, J = 5 Hz); its ^{13}C NMR spectrum is tabulated in Table I.

These NMR data suggested that A was not a reduced purine with an intact bicyclic ring system but rather the five-membered monocyclic imidazolidinone **11**. The ^{13}C NMR absorption at δ 173 is clearly assigned to the amide carbonyl, and the simple doublet–triplet pattern of the ^1H NMR spectrum implies the freely rotating methylene group of **11**. The alternative six-membered ring structure **8** previously proposed[9] for the 2,8-diaminopurine reduction product should display

Table I. ^{13}C NMR Data[a] for 2,8-Diaminopurine (7) Reduction Products

C atom	A (11) δ	A (11) Mult[b]	A′[c] δ	C atom	B (12) δ	B (12) Mult[b]	B′[c] δ
2 or 8	158.3	(s)	158.6	2 or 8	159.4	(s)	159.4
			158.2				159.1
2 or 8	157.2	(s)	156.2	2 or 8	157.2	(s)	156.2
							152.3
4	58.8	(d)	63.0	4	54.0	(d)	58.7
			62.0				58.1
5	173.5	(s)	173.2	5 or 6	45.5	(t)	50.3
							50.1
6	40.8	(t)	48.4	5 or 6	43.9	(t)	45.3
			47.9				44.2
9			16.7	9			16.2
			14.8				15.6

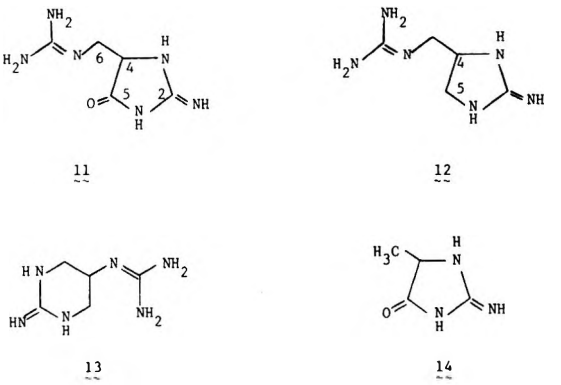
[a] Parts per million relative to dioxane (δ 66.5). [b] Assignments for 11 and 12 are based on proton off-resonance decoupled spectra and predicted chemical shifts. [c] Assignments for A′ and B′ are based on correlations with similar absorptions for 11 and 12.



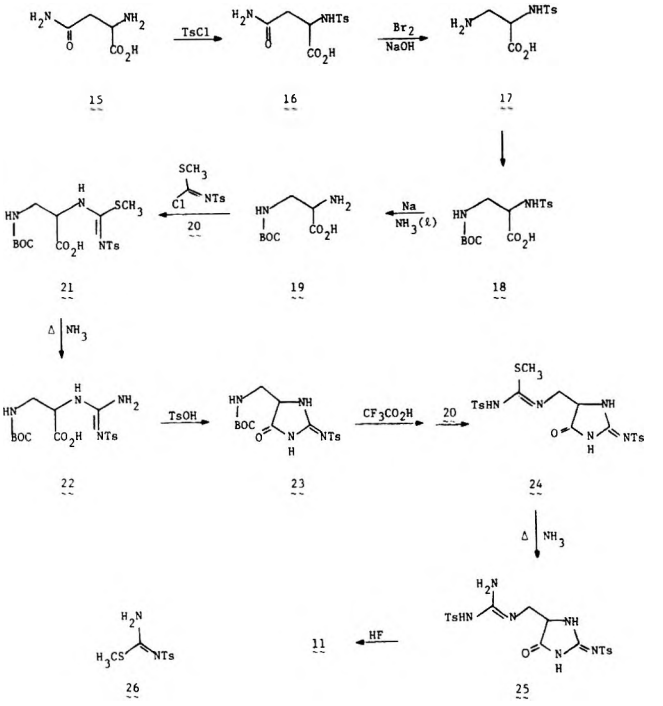
a much more complex ^1H NMR spectrum. One would expect the two C-6 protons in 8 to be nonequivalent and therefore to couple with each other and in a nonequivalent manner with the C-5 proton. A·2HCl has an ultraviolet absorption maximum in water at 223 nm (ε 7800), in a good agreement with the value of 223 nm (ε 9200) that we find under the same conditions for alacreatinine (14).[10] Elemental analysis of the sulfate salt of A is also consistent with structure 11.

The ^1H NMR of B·2HCl is considerably more complex than that of A, and its ^{13}C NMR absorptions are also tabulated in Table I. Replacement of the δ 173 absorption in A with a higher field absorption in B, all the other absorptions staying relatively constant, suggests that the carbonyl of 11 has merely been reduced to a methylene, and therefore the imidazolidine 12 was proposed as the structure for B. ^{13}C NMR off-resonance decoupling experiments (see Table I) show that there are two different kinds of methylene carbons in B, and thus rule out the alternative symmetrical six-membered ring structure 13. B·2HCl has no specific ultraviolet absorption above 210 nm, in agreement with the loss of the acylguanidine chromophore, and elemental analysis of the sulfate salt of B is also consistent with structure 12.

In order to conclusively establish the structures of A and B, unambiguous syntheses of 11 and 12 were undertaken. Asparagine (15) is ideally suited as a starting material for a two-stage guanylation synthesis of 11 since it contains two kinds of inherently different nitrogen functionality. N^{α}-*p*-Toluenesulfonylamino-N^{β}-*tert*-butyoxycarbonyl-L-α,β-diaminopropionic acid (L-18) has been prepared[11,12] from *p*-toluenesulfonyl-L-asparagine (L-16). The tosyl group of 18 was then removed with sodium in liquid ammonia and without isolation the intermediate N^{β}-*tert*-butyloxycarbonyl-L-α,β-diaminopropionic acid (L-19) was reacylated with benzyloxycarbonyl chloride.



Following the above literature procedures we were easily able to prepare DL-18 from DL-asparagine. For our purpose, the sodium and liquid ammonia removal of the tosyl group from DL-18 was immediately followed by acylation with *N*-(methylmercaptochloromethyl)-*p*-toluenesulfonimide (20)[13] to give the isothiourea 21 in 90% yield. This was then con-



verted to the guanidino acid **22** by treatment with liquid ammonia. We have found this two-step procedure superior to direct guanylation with *S*-methyl-*N*-*p*-toluenesulfonylisothiourea (**26**) which is usually a poor reaction and frequently fails completely; **20**, however, condenses readily at room temperature even with very hindered amines to give good yields of the corresponding isothioureas. Conversion to the guanidine with liquid ammonia is also usually quite efficient, and combined yields of 60% can be routinely realized.

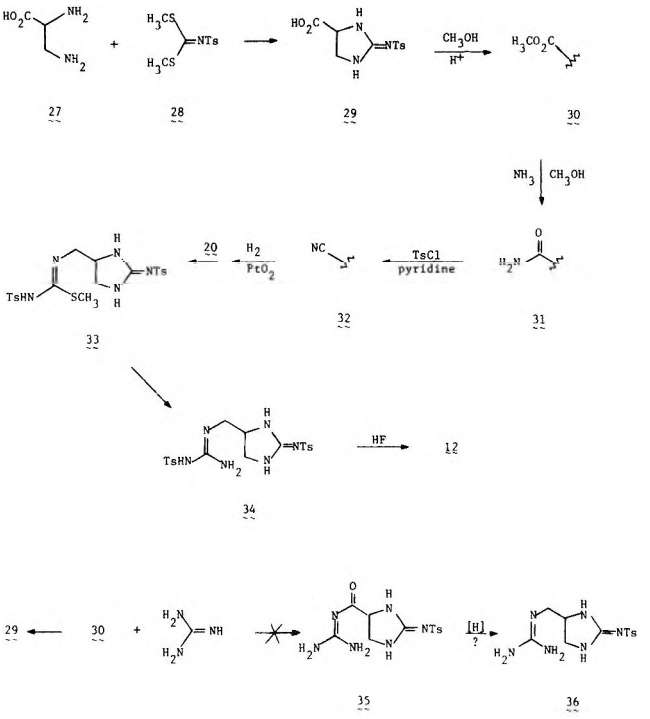
The guanidino acid **22** was not characterized or purified but was immediately cyclized with *p*-toluenesulfonic acid in refluxing THF to the imidazolidinone **23.** As might be expected from the presence of the acid-labile *t*-Boc group, the yield in this ring-closure step was only moderate (40–60%). The *t*-Boc group was removed with cold anhydrous trifluoroacetic acid and the intermediate reacylated with **20** to give the isothiourea **24** in 83% yield. Amination with liquid ammonia then gave the bistosylguanidine **25** in 61% yield. Treatment of **25** with anhydrous HF[14] followed by ion exchange chromatography gave the detosylated 2-imino-5-imidazolidinone **11** which was identical in all respects with compound A, obtained from the reduction of **7.**

The preparation of **12** was more straightforward since there is no potentially ambiguous cyclization involved. The imidazolidine ring was prepared in the first step by condensation of DL-diaminopropionic acid (**27**) with *S,S*-dimethyl *N*-*p*-toluenesulfonyliminodithiocarbonimidate (**28**)[14] to give **29** in 73% yield. The carboxy group of **29** was then converted into the tosylguanidino side chain of **34** by esterification to **30,** treatment of **30** with alcoholic ammonia to give amide **31,** and dehydration of **31** to nitrile **32** with *p*-toluenesulfonyl chloride in pyridine. Hydrogenation to the amine followed by immediate acylation with **20** gave the isothiourea **33,** and treatment with ammonia then gave the bistosylguanidine **34** which was detosylated with anhydrous HF to give the 2-iminoimidazolidine **12.** Individual product yields from **30** to **34** were from 73 to 92%. Imidazolidine **12,** so prepared, was found to be identical in all respects with compound B, obtained from the reduction of **7.**

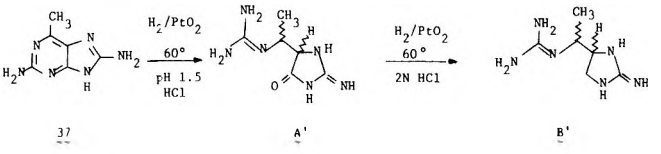
We had originally tried to save some steps in the reaction sequence leading to **12** by attempting to prepare acylguanidine **35** directly from ester **30** and guanidine (as the free base, prepared by passage of methanolic guanidine hydrochloride through an ion exchange column); hopefully **35** could then be reduced to **36.** However, only the acid **29** was recovered from the reaction, presumably resulting from hydrolysis by water contamination in the methanolic guanidine.

We have thus shown that the two products A and B, obtained from the catalytic hydrogenation of 2,8-diaminopurine (**7**), are respectively the 2-imino-5-imidazolidinone **11** and the 2-iminoimidazolidine **12.** We can now confidently make the ^{13}C NMR absorption assignments for both compounds as shown in Table I, and the doublet and triplet ^1H NMR pattern of **11** can be explained in terms of simple methylene–methine coupling. The appearance of a more complex ^1H NMR spectrum for **12** is due to the presence of the newly introduced ring methylene protons. The ^1H NMR spectrum of our A (**11**) appears to be identical with that reported[9] for product 8 resulting from the catalytic and electrolytic reduction of **7.** The dipicrate of our **11** had the same melting point and showed the same infrared absorption values as those reported for "8" dipicrate. Therefore we conclude that the previous structural assignment, based solely on an unlikely ^1H NMR interpretation, is incorrect, and should be revised to structure **11.**

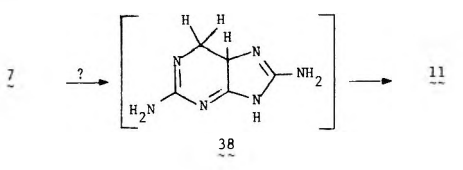
We also hydrogenated 2,8-diamino-6-methylpurine (**37**) under similar conditions and found that two reduction products, A′ and B′, were formed, analogous to A and B on the basis of spectral and chromatographic properties. A′ and B′ appear to be the epimeric mixture shown. The ^{13}C NMR



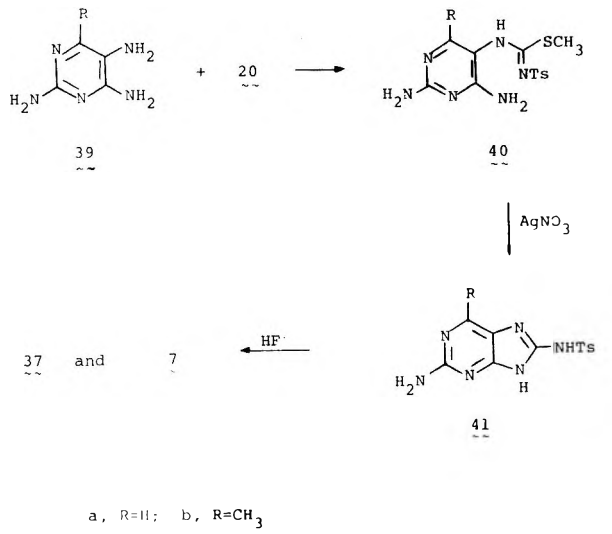
spectra (Table I) of A′ and B′ are very similar to those of A and B with the exception that most of the signals of the former group are doubled. The ^1H NMR spectra of A′ and B′ display distinct methyl doublets, but in a manner that suggested the presence of two different compounds, and the methyl signals are shifted in a manner consistent with the presence of two separate species on going from 60 to 100 to 220 Mz spectrometers.



The isolation of the 2-imino-5-imidazolidinone **11** was unexpected in view of the previous reports[6,7] of dihydropurine (**5**) formation from reduction of **4.** In a parallel fashion, one would expect that an initial dihydropurine resulting from **7,** because of the intact imidazole, would not easily cleave to **11.** To explain the behavior we observed, an initial "abnormal" 5,6-dihydropurine intermediate **38** might be involved, lacking the stable imidazole structure, which would then hydrolyze to give **11.** At this point, however, there is no experimental evidence to support an intermediate such as **38** since only **11** and **7** can be seen, by ^1H NMR, in partially completed reductions of **7.**



For the hydrogenation studies we required an efficient synthesis of purines **7** and **37,** which was found in a simple three-step process involving first the condensation of the corresponding triaminopyrimidines **39** with **20** to give good yield of the isothioureidopyrimidines **40,** with the position of acylation at N-5 assumed. These compounds were cyclized via a carbodiimide intermediate, generated by $AgSCH_3$ elimination,[15] to the 8-*p*-toluenesulfonylaminopurines **41.** Treatment with anhydrous HF as before gave the desired purines **7** and **37** in overall yields of 50 and 91%, respectively.



Experimental Section

Melting points were taken in open capillaries, unless otherwise specified, and are uncorrected. ^{1}H NMR spectra were determined at 60 MHz using Me_4Si as an internal standard (δ 0) unless otherwise noted and ^{13}C NMR spectra were determined at 25.14 MHz. Elemental analyses were performed by the Analytical Laboratory, Department of Chemistry, University of California, Berkeley. All evaporations were done in vacuo using a Berkeley rotary evaporator.

Hydrogenation of 2,8-Diaminopurine (7) to 2-Imino-4-guanidinomethyl-5-imidazolidinone (11). 2,8-Diaminopurine hydrochloride (**7**, 665 mg, 3.58 mmol) and 100 mg of PtO_2 in dilute HCl (55 mL, pH 1.5) were hydrogenated at 20 psi on a Parr shaker at room temperature for 46 h. The reaction mixture was filtered and the filtrate evaporated at 40 °C to give 840 mg of a residue that solidified into a crystalline mass on standing: ^{1}H NMR (220 MHz, D_2O, external Me_4Si) δ 4.8 (t, 1 H, J = 5 Hz), 3.9 (d, 2 H, J = 5 Hz); ^{13}C NMR (see Table I). A portion of the crude dihydrochloride was dissolved in water and passed through a Bio-Rad AG 21K anion exchange column (SO_4^{2-} form) to give the sulfate as fine needles (from water), mp 222–224 °C dec; UV (H_2O) λ_{max} 223 nm (ϵ 7800).

Anal. Calcd for $C_5H_{12}N_6O_5S\cdot\frac{1}{4}H_2O$: C, 22.0; H, 4.6; N, 30.8. Found (hygroscopic): C, 22.1; H, 5.0; N, 30.6.

The dipicrate, prepared from the dihydrochloride, had mp 220–221 °C dec (capillary), 227–228 °C dec (hot stage) after recrystallization from water: IR (KBr) ν_{max} 1778, 1704, 1672, 1636 cm^{-1} (lit.[9] values for a compound to which structure **8** was assigned: mp 227.5 °C; IR ν_{max} 1780, 1711, 1680, 1635 cm^{-1}).

2-Imino-4-guanidinomethylimidazolidine (12). **11** (200 mg, 0.82 mmol) as the dihydrochloride and 110 mg of PtO_2 were taken up in dilute HCl (55 mL, pH 1.5) and hydrogenated at 20 psi on a Parr shaker for 100 h at 60 °C. The reaction mixture was filtered and the filtrate evaporated to give 197 mg (97%) of a glassy residue: ^{1}H NMR (220 MHz, D_2O, external Me_4Si) δ 4.3 (m, 1 H), 3.8 (t, 1 H), 3.5 (d, 1 H), 3.4 (br s, 2 H); ^{13}C NMR (see Table I). A portion of the crude dihydrochloride was treated by the above ion exchange procedure to give the sulfate salt, mp 307–310 °C dec (from water).

Anal. Calcd for $C_5H_{14}N_6O_4S$: C, 23.6; H, 5.6; N, 33.1. Found: C, 23.6; H, 5.4; N, 33.3.

Hydrogenation of 2,8-Diamino-6-methylpurine (37) to Product A′. 2,8-Diamino-6-methylpurine (**37**, 636 mg, 3.17 mmol) and 100 mg of PtO_2 were hydrogenated in HCl (30 mL, pH 1.5) for 48 h at 60 °C and 35 psi on a Parr shaker. After filtration and evaporation of the solvent the glassy residue (720 mg) was applied to an ion exchange column (Bio-Rad AG-50 X8, 400 mesh; H^+ form; 50 mL bed volume) and eluted with 2 N HCl. Fractions of 15 mL were collected and analyzed by TLC (silica gel, phenol saturated with H_2O, visualized with Weber spray[16]). Fractions 80–110 gave 275 mg of product A′ (red Weber streak, R_f 0.1–0.3) and fractions 130–200 gave 212 mg (33%) of **37** (green Weber spot, R_f 0.5). A′ had ^{1}H NMR (D_2O, external Me_4Si) δ 4.8 (q at 60 MHz, t at 220 MHz, 1 H), 4.2 (m at 60 and 220 MHz, 1 H), 1.5 (d of d at 60 MHz, t at 220 MHz, 3 H); ^{13}C NMR (see Table I). A portion of the dihydrochloride was treated by the AG-21K ion exchange procedure to give the sulfate salt as fine needles (from water), mp 200–225 °C dec, UV (H_2O) λ_{max} 224 nm (ϵ 7400).

Anal. Calcd for $C_6H_{14}N_6O_5S\cdot H_2O$: C, 23.8; H, 6.0; N, 27.8. Found: C, 24.1; H, 6.0; N, 27.7.

Hydrogenation of 2,8-Diamino-6-methylpurine (37) to Product B′. **37** (654 mg, 3.46 mmol) and 110 mg of PtO_2 were hydrogenated in HCl (55 mL, pH 1.5) for 118 h at 60 °C and 20 psi on a Parr shaker. An additional 100 mg of catalyst was added after 46 h. After filtration and evaporation of the filtrate the glassy residue (540 mg) was chromatographed on the Bio-Rad AG-50 system used for product A′ above. On the basis of TLC and ^{1}H NMR, fractions containing 50 mg of A′ and fractions containing 228 mg of B′, as a glassy solid (purple Weber streak, R_f 0.1–0.3), were collected. B′ had ^{1}H NMR (60 MHz, D_2O, external Me_4Si) δ 4.7–3.6 (m, 4 H), 1.5 (t, 3 H); ^{1}H NMR (220 MHz, D_2O, external Me_4Si) δ 4.5 (m, 1 H), 4.2 (m, 2 H), 3.9 (m, 1 H), 1.5 (d of d, 3 H); ^{13}C NMR (see Table I). An unsuccessful attempt was made to secure a crystalline sulfate derivative by the above AG-21K ion exchange procedure.

***N*-*p*-Toluenesulfonyl-DL-asparagine (16).** The procedure[17] for the L isomer was used with 0.2 mol of DL-asparagine to give the white, crystalline product in 36% yield, mp 170–173 °C (lit.[17] mp 175 °C for L isomer).

***N*$^{\alpha}$-*p*-Toluenesulfonyl-DL-α,β-diaminopropionic Acid (17).** The procedure[18] for the L isomer was used on 0.07 mol of DL material to give the white, crystalline product in 49% yield, mp 230 °C dec (lit.[18] mp 225–226 °C for L isomer).

Anal. Calcd for $C_{10}H_{14}N_2O_4S$: C, 46.5; H, 5.5; N, 10.9. Found: C, 46.4; H, 5.4; N, 10.9.

***N*$^{\alpha}$-*p*-Toluenesulfonyl-*N*$^{\beta}$-*tert*-butyloxycarbonyl-DL-α,β-diaminopropionic Acid (18).** The method[11] for the L isomer was used on 7.75 mmol of DL material to give a white, crystalline product in 96% crude yield. Recrystallization from ethyl acetate gave a product in 84% yield, mp 124–128 °C (lit.[11] mp 127–128 °C for L isomer).

Anal. Calcd for $C_{15}H_{22}N_2O_6S$: C, 50.3; H, 6.2; N, 7.8. Found: C, 50.2; H, 6.2; N, 7.8.

***S*-Methyl-*N*-*p*-toluenesulfonyl-*N*′-(1-carboxyl-2-*tert*-butyloxycarbonylaminoethyl)isothiourea (21).** **16** (1.61 g, 4.5 mmol) was dissolved in liquid NH_3 (cooled in a dry ice–acetone bath) and treated with small pieces of sodium, while the reaction mixture was stirred vigorously, until the blue color persisted for 10 min. The blue color was discharged by addition of NH_4Cl and the white, powdery residue, obtained after removal of the NH_3, was dissolved in a solution of CH_3CN (22 mL) and water (40 mL). Triethylamine (1.35 mL, 9 mmol) and then **20**[13] (1.43 g, 5.4 mmol) were added. After stirring for 2.5 h at room temperature, most of the CH_3CN was evaporated and the remaining liquid was extracted twice with ether. The aqueous phase was cooled, acidified to pH 3.5 with cold, saturated citric acid, and extracted with two portions of ether. The combined ether extracts were dried over $MgSO_4$ and evaporated leaving 1.74 g (90%) of a clear, colorless residue: ^{1}H NMR ($CDCl_3$) δ 9.1 (br s, 2 H, NH), 7.5 (q, 5 H, ArH, NH), 4.5 (br s, 1 H, >CH), 3.6 (br s, 2 H, $>CH_2$), 2.4 (s, 6 H, SCH_3, $ArCH_3$), 1.4 [s, 9 H, $C(CH_3)_3$].

2-*p*-Toluenesulfonylimino-4-*tert*-butyloxycarbonylaminomethyl-5-imidazolidinone (23). **21** (1.74 g, 4.04 mmol) was heated in liquid NH_3 in a sealed tube at 40 °C for 3 h. The crude ammonium salt, obtained after evaporation, was dissolved in cold water, acidified to pH 1.3 with cold saturated citric acid, and extracted into CH_2Cl_2 which was dried over $MgSO_4$. Evaporation of the CH_2Cl_2 gave 1.53 g (95%) of crude guanidino acid **22** to which were added *p*-toluenesulfonic acid monohydrate (72 mg, 0.38 mmol) and 230 mL of THF. The reaction mixture was refluxed for 15 h through a small Soxhlet extractor filled with anhydrous $MgSO_4$. The THF was evaporated and the residue was chromatographed in a column packed with silica gel (160 g) eluting with 7% $CH_3OH/CHCl_3$. Pure **23** (565 mg, 39%) was thus obtained as a white solid: ^{1}H NMR ($CDCl_3$) δ 9.25 (br s, 1 H), 7.5 (t, 4 H, ArH), 5.1 (br m, 1 H), 4.2 (t, 1 H, >CH), 3.6 (d, 2 H, $>CH_2$), 2.4 (s, 3 H, $ArCH_3$), 1.4 [s, 9 H, $(CH_3)_3C$]; mp 196 °C dec from $CHCl_3$–petroleum ether (bp 30–60 °C).

Anal. Calcd for $C_{16}H_{22}N_4O_5S$: C, 50.2; H, 5.8; N, 14.6. Found: C, 49.8; H, 5.8; N, 14.4.

4-[(Methylmercapto-*N*-*p*-toluenesulfonylimino)methyl]-aminomethyl-2-*p*-toluenesulfonylimino-5-imidazolidinone (24). Cold trifluoroacetic acid (23 mL, freshly distilled) was added to **23** (407 mg, 10.6 mmol) and stirred at 0 °C for 1 h. The TFA was evaporated and the residue was dried briefly under high vacuum and then dissolved in a solution of water (10 mL) and CH_3CN (5 mL) and cooled in an ice bath. Triethylamine (1.0 mL, 10 mmol) and then, dropwise, a chilled solution of **20**[13] (282 mg, 1.06 mmol) in CH_3CN (5 mL) were added. The resulting solution was stirred overnight at 0 °C, most of the CH_3CN was evaporated at reduced pressure, an equal volume of water was added to the remaining solution, and the resulting oily product was extracted into CH_2Cl_2. The organic phase was dried over $MgSO_4$ and evaporated to give 618 mg of a solid which, after chromatography on silica gel (90 g, eluting with 4% MeOH/

$CHCl_3$), gave 449 mg (83%) of pure **24** as a white powder: ^1H NMR ($CDCl_3$) δ 7.4 (q, 8 H, ArH), 4.4 (br s, 1 H, >CH), 3.8 (br s, 2 H, $>CH_2$), 2.4 (d, 9 H, SCH_3, $ArCH_3$); mp 196–198 °C from $CHCl_3$.

Anal. Calcd for $C_{20}H_{23}N_5O_5S_3$: C, 47.1; H, 4.6; N, 1.37. Found: C, 46.8; H, 4.6; N, 13.6.

4-[(Amino-*N*-*p*-toluenesulfonylimino)methyl]aminomethyl-2-*p*-toluenesulfonylimino-5-imidazolidinone (25). 24 (449 mg, 0.88 mmol) was heated in a sealed tube with liquid NH_3 at 40 °C for 3 h. The crude product left after evaporation of the NH_3 was chromatographed on silica gel (104 g, eluting with 7% EtOH/$CHCl_3$) to give 250 mg (61%) of pure **25** as a white powder: ^1H NMR (acetone-d_6) δ 7.4 (q, 8 H, ArH), 4.4 (br s, 2 H, $>CH_2$), 2.4 (d, 9 H, SCH_3); mp 211–214 °C from aqueous ethanol.

Anal. Calcd for $C_{19}H_{22}N_6O_5S_2$: C, 47.7; H, 4.6; N, 17.6. Found: C, 47.5; H, 4.6; N, 17.4.

2-Imino-4-guanidinomethyl-5-imidazolidinone (11). 25 (200 mg, 0.418 mmol) was treated at room temperature with 12 mL of anhydrous HF[14] for 59 h. The HF was evaporated, the residue was removed from the reaction vessel with alternating portions of water and benzene, and the combined aqueous layers were further washed with two more portions of benzene and then filtered directly onto a column of Bio-Rad AG 50X8 50–100 mesh resin (25 mL bed volume, H^+ form). The column was washed with water until neutral and then with 230 mL of 3 N HCl. Since NMR analysis of the residue from the acidic eluate indicated that some tosyl-containing compound was still present, the crude product was further chromatographed on AG 50X8 resin (200–400 mesh, 30 mL bed volume, 2 N HCl eluate), monitoring elution by ultraviolet absorption. Evaporation of the appropriate column fractions gave 97 mg (95%) of **11**·2HCl whose NMR spectra (^1H and ^{13}C), TLC (silica gel, phenol saturated with H_2O, Weber spray) behavior, and sulfate salt were identical with those of the reduction product, A, of 2,8-diaminopurine (**7**).

4-Carboxy-2-*p*-toluenesulfonyliminoimidazolidine (29). DL-Diaminopropionic acid monohydrochloride (**27**, 2.80 g, 20 mmol) was dissolved in 40 mL of 1.0 N NaOH and 180 mL of ethanol and then *S,S*-dimethyl *N*-toluenesulfonyliminodithiocarbonimidate[19] (**28**, 5.50 g, 20 mmol) was added. The solution was held at reflux for 18 h and filtered, and most of the ethanol was evaporated. The resulting neutral aqueous solution was made alkaline with $NaHCO_3$ solution, extracted with 2 × 30 mL of $CHCl_3$, and adjusted to pH 1.3 with 4 N HCl. An oil that separated during acidification was just redissolved by addition of methanol. The resulting solution was extracted with 3 × 20 mL of $CHCl_3$, and the combined $CHCl_3$ extracts were then evaporated to give 3.33 g (59%) of a solid residue: ^1H NMR (Me_2SO-d_6) δ 7.9–7.1 (m, 6 H), 4.3 (q, 1 H), 3.9–3.5 (m, 2 H), 2.4 (s, 3 H). Cooling of the aqueous phase from the above extraction gave an additional 771 mg (14%) of product, mp 205–206 °C from water.

Anal. Calcd for $C_{11}H_{13}N_3O_4S$: C, 46.6; H, 4.6; N, 14.8. Found: C, 46.6; H, 4.7; N, 14.8.

4-Methoxycarbonyl-2-*p*-toluenesulfonyliminoimidazolidine (30). 29 (500 mg, 1.77 mmol) and concentrated H_2SO_4 (1 drop) were refluxed for 19 h in a mixture of methanol (4 mL) and 1,2-dichloroethane (4 mL). The solution was diluted with CH_2Cl_2 and washed with saturated $NaHCO_3$, the aqueous phase was extracted with CH_2Cl_2, and the combined organic extracts were dried over $MgSO_4$ and evaporated to give 530 mg (100%) of a solid that appeared pure by TLC (silica gel, 10% $CH_3OH/CHCl_3$). Recrystallization was effected by dissolving the solid in 10% $CH_3OH/CHCl_3$ and allowing the product to precipitate as a white powder: yield 368 mg (73%); mp 144–146 °C; ^1H NMR (Me_2SO-d_6) δ 7.9–7.1 (m, 6 H), 4.4 (q, 1 H), 3.9–3.5 (m) and 3.6 (s, 5 H), 2.5 (s, 3 H).

Anal. Calcd for $C_{12}H_{15}N_3O_4S$: C, 48.5; H, 5.1; N, 14.1. Found: C, 48.4; H, 5.1; N, 14.2.

4-Carbamoyl-2-*p*-toluenesulfonyliminoimidazolidine (31). 30 (1.0 g, 3.37 mmol) was added to a cold saturated solution of NH_3 in methanol. After reaching room temperature, the solution was stirred for 1 h and then evaporated to give 915 mg (97%) of a glassy solid: ^1H NMR (Me_2SO-d_6) δ 7.4 (m, 8 H, NH, ArH), 4.2 (t, 2 H, >CH), 3.5 (m, 2 H, $>CH_2$), 2.3 (s, 3 H, $ArCH_3$).

4-Cyano-2-*p*-toluenesulfonyliminoimidazolidine (32). 31 (1.79 g, 6.31 mmol) was dissolved in 9.5 mL of pyridine, *p*-toluenesulfonyl chloride was added, and the solution was heated at 50 °C for 23 h. The pyridine was evaporated, $CHCl_3$ was added and evaporated twice, and $CHCl_3$ and then water were added which gave rise to a white precipitate suspended in the $CHCl_3$ layer. This precipitate was collected and washed with cold $CHCl_3$ and water to give 1.19 g (71%) of **32**. An additional 119 mg (7%) was recovered from the $CHCl_3$ mother liquid after standing overnight, mp 210 °C from methanol.

Anal. Calcd for $C_{11}H_{12}N_4O_2S$: C, 49.79; H, 4.95; N, 21.12. Found: C, 49.97; H, 4.63; N, 21.08.

4-[(Methylmercapto-*N*-*p*-toluenesulfonylimino)methyl]aminomethyl-2-*p*-toluenesulfonyliminoimidazolidine (33). 32 (1.02 g, 3.85 mmol) and PtO_2 (400 mg) were suspended in glacial acetic acid (35 mL), and the mixture was hydrogenated on a Parr apparatus at 30 psi for 14 h. The catalyst was removed by filtration, and the filtrate was concentrated to a very small volume. Dilute HCl was added and evaporated twice, dilute HCl was again added, and the resulting cloudy solution was extracted three times with $CHCl_3$. The aqueous phase was evaporated to give 1.16 g (99%) of the amine as a solid: NMR (D_2O, external Me_4Si) δ 7.5 (q, 4 H, ArH), 4.6–3.2 (m, 5 H, >CH and $>CH_2$), 2.4 (s, 3 H, $ArCH_3$).

This solid and triethylamine (1.60 mL, 11.4 mmol) were dissolved in a solution of water (30 mL) and CH_3CN (30 mL). **20** (1.01 g, 3.81 mmol) was added, and the solution was stirred at room temperature for 7 h and then left overnight at 0 °C. The resulting white, powdery precipitate was washed with cold 50% CH_3CN–H_2O: yield 134 g (72%); pure by TLC (silica gel, 15% $CH_3OH/CHCl_3$); mp 183–185 °C from ethyl acetate.

Anal. Calcd for $C_{20}H_{25}N_5O_4S_3$: C, 48.5; H, 5.1; N, 14.1. Found: C, 48.3; H, 5.1; N, 14.2.

4-[(Amino-*N*-*p*-toluenesulfonylimino)methyl]aminomethyl-2-*p*-toluenesulfonyliminoimidazolidine (34). 33 (1.00 g, 2.02 mmol) was heated in liquid NH_3 at 40 °C in a sealed tube for 6 h. The residue, after evaporation of the NH_3, was chromatographed on 105 g of silica gel (7% $C_2H_5OH/CHCl_3$ eluate) to give 782 mg (83%) of pure **34**: mp 211–214 °C; ^1H NMR ($CDCl_3$) δ 7.7–6.5 (m, 13 H, NH, ArH), 4.1–3.0 (br m, 5 H, >CH and $>CH_2$), 2.4 (s, 6 H, $ArCH_3$).

Anal. Calcd for $C_{19}H_{24}N_6O_4S_2$: C, 49.1; H, 5.2; N, 18.1. Found: C, 48.8; H, 5.2; N, 17.7.

2-Imino-4-guanidinomethylimidazolidine (12). 34 (300 mg, 0.604 mmol) was treated as before with anhydrous HF. Ion exchange chromatography as before gave 140 mg (100%) of a glass whose ^1H and ^{13}C NMR spectra and TLC behavior were identical with those of the hydrochloride of compound B, obtained by hydrogenation. A crystalline sulfate salt was obtained, identical with the sulfate salt of compound B.

2,4-Diamino-5-[(methylmercapto-*N*-*p*-toluenesulfonylimino)methyl]aminopyrimidine (40a). 2,4,5-Triaminopyrimidine[20] (**39a**, 1.25 g, 10 mmol) was dissolved in a solution of water (15 mL) and CH_3CN (5 mL), triethylamine (2.8 mL, 20 mmol), and then, dropwise, a solution of **20** (2.64 g, 10 mmol) in CH_3CN (10 mL) were added. After stirring for 8 h at room temperature, the solvent was evaporated and the residue was washed with hot water and hot $CHCl_3$ to give 2.1 g (60%) of **40a** as a light brown powder: does not melt <300 °C; ^1H NMR (Me_2SO-d_6) δ 7.9–7.3 (m, 6 H, ArH, HetH, NH), 6.3 (br s, 4 H, NH), 2.4 (s, 3 H, $ArCH_3$), 2.3 (s, 3 H, SCH_3).

Anal. Calcd for $C_{13}H_{16}N_6O_2S_2$: C, 44.3; H, 4.6; N, 23.8. Found: C, 44.4; H, 4.6; N, 23.8.

2,4-Diamino-6-methyl-5-[(methylmercapto-*N*-*p*-toluenesulfonylimino)methyl]aminopyrimidine (40b). 20 (46.8 g, 0.178 mol) was dissolved in dry DMF (200 mL) and cooled in an ice bath. To this solution were then added dropwise triethylamine (24.8 mL, 0.178 mol) and a suspension of 0.18 mol of 6-methyl-2,4,5-triaminopyrimidine (**39b**)[21] in warm DMF (760 mL). The reaction mixture was warmed to room temperature and stirred for 3 days. The DMF was evaporated, and the residue was washed with water and then CH_2Cl_2 to give 62.8 g (96%) of **40b** as a pale brown powder: does not melt <300 °C; ^1H NMR (CF_3CO_2D) δ 7.5 (q, 4 H, ArH), 2.42 (m, 9 H, $ArCH_3$, SCH_3, $HetCH_3$).

Anal. Calcd for $C_{14}H_{18}N_6O_2S$: C, 45.9; H, 4.9; N, 22.9. Found: C, 46.2; H, 4.9; N, 22.7.

2-Amino-8-*p*-toluenesulfonylaminopurine (41a). To **40a** (8.26 g, 23.5 mmol) and triethylamine (4.90 mL, 35.3 mmol) dissolved in dry DMF (200 mL) was added dropwise a solution of $AgNO_3$ (4.00 g, 23.5 mmol) in DMF (15 mL). A yellow $AgSCH_3$ precipitate formed immediately, and stirring was continued at room temperature for 2 h and then at 75 °C for 5 h, after which time TLC (silica gel, 20% $C_2H_5OH/CHCl_3$) indicated the absence of starting material. The product appeared as a UV fluorescent spot at R_f 0.3. The mixture was filtered, the filtrate was evaporated, and the residue was dissolved in 10% NaOH. The $AgSCH_3$ precipitate was washed with 10% NaOH and the combined wash and residue solutions were carefully acidified to pH 2 with 4 N HCl, giving rise to **41a**: yield 6.0 g (84%); does not melt <300 °C; ^1H NMR (Me_2SO-d_6) δ 8.0–7.1 (m, 6 H, ArH, HetH, NH), 6.41 (br s, 2 H, NH), 2.3 (s, 3 H, $ArCH_3$).

2-Amino-6-methyl-8-*p*-toluenesulfonylaminopurine (41b). **40b** (46.0, 0.126 mol) and triethylamine (17.5 mL, 0.126 mol) in DMF (950 mL) were treated with $AgNO_3$ (21.4 g, 0.126 mol) in DMF (120 mL) as described above for 1 h at room temperature and 41 h at 75 °C. The isolation procedure followed that for **41a** above and gave 37.9 g

(95%) of **41b** as a white powder: ^{1}H NMR (Me_2SO-d_6) δ 7.5 (q, 4 H, ArH), 6.0 (br s, 2 H, NH), 2.3 (s, 6 H, $ArCH_3$, HetH); crystallized from DMF–95% ethanol, does not melt <300 °C.

Anal. Calcd for $C_{13}H_{14}N_6O_2S$: C, 49.0; H, 4.4; N, 26.4. Found: C, 48.9; H, 4.2; N, 26.0.

2,8-Diaminopurine Hydrochloride (7·HCl). 41a (3.04 g, 10 mmol) was treated with HF as before for 3 h. Ion exchange salt conversion on Bio-Rad AG-50 resin of the crude HF salt gave 1.9 g (100%) of **7**·HCl as a yellowish powder: ^{1}H NMR (D_2O, external Me_4Si) δ 8.3 (s); crystallized from aqueous ethanol, does not melt <360 °C.

Anal. Calcd for $C_5H_7N_6Cl$: C, 32.2; H, 3.8; N, 45.0. Found: C, 32.5; H, 3.8; N, 44.8.

2,8-Diamino-6-methylpurine Hydrochloride (37·HCl). 41b (15.0 g, 47.2 mmol) was treated with HF as before for 3 h. Ion exchange on Bio-Rad AG-50 resin gave 9.5 g (100%) of **37**·HCl: ^{1}H NMR (D_2O, external Me_4Si) δ 2.65 (s); crystallized from 95% ethanol–ether, does not melt <300 °C.

Anal. Calcd for $C_6H_9N_6Cl$: C, 35.9; H, 4.5; N, 41.9. Found (hygroscopic): C, 35.6; H, 5.0; N, 41.5.

Registry No.—**7** HCl, 62743-10-6; **8**, 60914-37-6; **11** 2HCl, 62743-11-7; **11** sulfate, 62743-13-9; **11** dipicrate, 62743-14-0; **12** 2HCl, 62743-15-1; **12** sulfate, 62743-17-3; **16**, 62743-18-4; **17**, 24571-53-7; **18**, 62778-08-9; **20**, 2973-83-3; **21**, 62743-19-5; **22**, 62743-20-8; **23**, 62743-21-9; **24**, 62743-22-0; **25**, 62743-23-1; **27** HCl, 54897-59-5; **28**, 2651-15-2; **29**, 62743-24-2; **30**, 62743-25-3; **31**, 62743-26-4; **32**, 62743-27-5; **32** 4-aminomethyl derivative, 62743-28-6; **33**, 62743-29-7; **34**, 62743-30-0; **37**, 60914-60-5; **37** HCl, 33704-87-9; **39a**, 3546-50-7; **39b**, 60914-71-8; **40a**, 62743-31-1; **40b**, 62743-32-2; **41a**, 62743-33-3; **41b**, 62778-09-0; A′ 2HCl epimer 1, 62743-34-4; A′ 2HCl epimer 2, 62743-35-5; A′ sulfate epimer 1, 62743-37-7; A′ sulfate epimer 2, 62743-39-9; B′ 2HCl epimer 1, 62743-40-2; B′ 2HCl epimer 2, 62743-41-3.

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Photochemistry of Phospholenes. 6. Photochemical Polar Addition of Alcohols Involving Participation by Trivalent Phosphorus[1]

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Irradiation of 1-phenyl-3-methyl-2-phospholene (**1**) in methanol–xylene solution afforded a mixture of the photoethers **2** and **3** (20%) and the exocyclic isomer **4** (50%). The addition was found to proceed completely regiospecifically. Thus, phenylphospholene **12** afforded 3-methoxyphospholane as a mixture of geometrical isomers upon similar irradiation. However, 2-methyl derivatives **19** were almost completely inert to photoaddition under similar conditions. Labeling studies with methanol-*O*-*d* showed that each of the products was formed in an ionic process involving photoprotonation at C-2. Deuterium was also found to be incorporated at the exo position of **4**, probably via a photochemical 1,3-phosphoryl shift. Investigation of the photoreactions of other phospholenes in alcohol revealed that the presence of trivalent phosphorus adjacent to the double bond is a necessity for the photoprotonation. The photoprotonation of **1** and **12** is therefore interpreted in terms of a reactive excited state displaying charge-transfer character resulting from the interaction of the double bond with the lone pair of electrons.

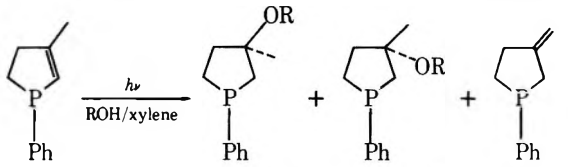
Simple cyclic isolated olefins, which have difficulty adopting a twisted configuration, undergo a variety of reactions from their excited state, including dimerization and various addition reactions. An example of the latter which has recently received considerable attention is the photosensitized polar addition of alcohols to six- and seven-membered olefins.[2,3] These reactions are believed to proceed through initial protonation of highly strained trans cycloalkenes or orthogonal triplet. In striking contrast, cyclopentene and other highly constrained cyclic olefins exhibit radical behavior on irradiation under similar conditions,[2,4] apparently due to the inability of these olefins to undergo cis → trans isomerization; the radical-type behavior exhibited in those cases probably originates from intermolecular reaction by the 3 (π, π^*) excited state itself. More recently, it has been shown[5] that the direct irradiation of the tri- and, particularly, tetrasubstituted cyclopentenes in hydroxylic media yielded unsaturated as well as saturated ethers. This photochemical behavior appears to involve the nucleophilic trapping of the π, R (3s) Rydberg excited state.

In the course of our studies[1,6] on the photochemistry of phospholenes, we have found[1b] that even five-membered cyclic olefins, in which double bonds are conjugated with trivalent phosphorus, gave the ethers and exocyclic isomer upon direct and/or sensitized irradiation in alcohols. While a large number of simple cyclic olefin systems have been examined as mentioned above, there is little known[7] concerning the role that α-heteroatoms may have on the photochemical polar

addition. Accordingly, we have studied this addition reaction in more detail to explore the exact nature of the reaction and now wish to present new data concerning the scope of the reaction.

Results and Discussion

Photoproducts. On irradiation in degassed methanol–xylene (1:10) solution, 1-phenyl-3-methyl-2-phospholene (**1**) underwent rapid disappearance. After ca. 70% of the starting material was consumed, the reaction mixture was separated by silica gel chromatography into three principal components under rigorously inert atmosphere. Isolation of the first component afforded a colorless liquid which was ultimately identified as an unresolved mixture of the starting olefin **1** and exo isomer **4**. The presence of two isomers was revealed by GC as well as NMR which displayed a broad singlet at δ 4.82 characteristic of exocyclic methylene protons in addition to



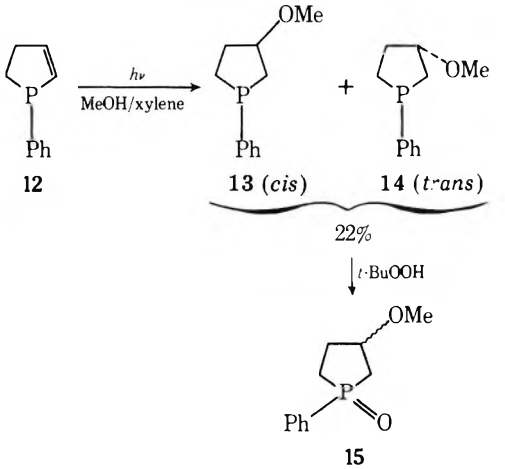
1a, R = Me **2** (*cis*) **3** (*trans*) **4**
b, R = Et
c, R = *i*-Pr
d, R = *t*-Bu

the vinyl proton doublet at δ 5.68 with large coupling (J_{PH} = 42 Hz) characteristic of starting olefin. Attempts to isolate **1** and **4** by several passes through the column were unsuccessful. The separation was easily achieved, however, by the chromatography after oxidation of the mixture with *tert*-butyl hydroperoxide to the corresponding phosphine oxides. The oxide of the exo isomer, indicating the methylene protons at δ 5.05, consumed 1 molar equiv of bromine rapidly to give an isomeric dibromide.

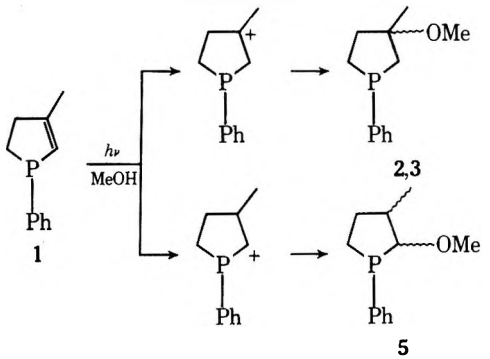
Isolation of the second chromatographic component afforded a colorless oil which was readily characterized as a methyl ether (**2a**) by the presence of a three-proton singlet at δ 3.02 in the NMR spectrum and by the appearance of a parent ion at *m/e* 208 in the mass spectrum. The third component was assigned the stereoisomeric structure **3a**, since it exhibited an NMR and mass spectrum similar to those of the ether **2a**, except for downfield shift of 0.13 ppm of methoxy protons. A priori, ionic addition of methanol to **1** might be expected to afford two sets of the ethers **2**, **3**, and **5**, as shown in Scheme I. However, since the photoethers exhibited no NMR bands attributable to either a proton adjacent to a methoxy group or secondary methyl protons, a structure such as **5** was clearly precluded.

Further proof for the correct assignment and isomeric relationship of **2a** and **3a** was easily provided by the chemical reaction of the ethers, as outlined in Scheme II and the Experimental Section. Thus, the 1-benzylphospholanium bromide of pure geometric isomers **6a** and **7a** were prepared and subjected to treatment with aqueous sodium hydroxide at room temperature. This resulted in the formation of the isomeric phospholane 1-oxides **8a** and **9a** with retention of configuration as previously observed[8] for other phospholane systems. The NMR spectra of the isomeric **8a** and **9a** were identical with those of the oxides **8a** and **9a** obtained by oxidation of **2** and **3** with *tert*-butyl hydroperoxide, a reaction also known[9] to occur with retention of configuration at phosphorus. The same reaction mixture of 2- and 3-phospholene oxide (**10** and **11**, respectively) was obtained from both isomers by base-induced elimination of methanol. The treatment of the benzyl bromide salts **6** and **7** with refluxing aqueous alkali resulted in the same reaction products. Apparently, 3-phospholene 1-oxide was formed by the base-induced isomerization[10] of **10** which should be the initial elimination product of **8** and **9**.

The regioselective introduction of the methoxy group at the C-3 position to the exclusion of other positional isomers was also observed in the irradiation in methanol of unsubstituted phospholene **12** which lacks the directive influence of the 3-CH_3 group. Thus, on irradiation in methanol–xylene solution, **12** was found to undergo relatively slow conversion to a mixture of two methyl ethers in 22% yield. The two photoethers were easily assigned the diastereomeric structures



Scheme I



Scheme II

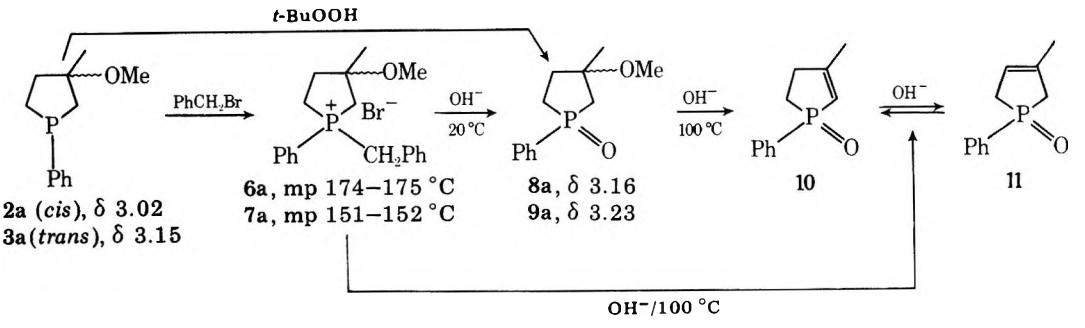


Table I. Irradiation[a] of 1-Phenyl-3-methyl-2-phospholene (1)

[MeOH], M	% convn[b]	% yield[b] 2 + 3	% yield[b] 4	4/(2 + 3)
0[c]	18		0	
0[d]	11		37	
0.15	23	8	43	5.4
0.75	26	14	66	4.7
1.5	31	20	54	2.7
1.5[e]	27	25	50	2.0
4.5	33	23	36	1.6
7.5	36	27	33	1.2
15	39	27	21	0.8
Neat	40	23	14	0.6

[a] Irradiations were carried out as described in the Experimental Section in a quartz tube of 5.0-mL capacity under nitrogen for 5 h using 5.0-mL xylene solutions containing 0.28 mmol of 1. [b] Determined by GC analysis of aliquots removed from the irradiation mixture. [c] Dry xylene was used. [d] Xylene saturated with water. [e] Contained 0.1 N NaOMe.

Table II. Irradiation[a] of 1 in Various Alcohols

Registry no.	Alcohol	% convn[b]	% yield[b] 2 + 3 (3/2)	% yield[b] 4	4/(2 + 3)
67-56-1	MeOH	31	20 (1.2)	54	2.7
64-17-5	EtOH	32	14 (1.1)	46	3.3
67-63-0	*i*-PrOH	28	13 (1.2)	42	3.2
75-65-0	*t*-BuOH	25	10 (1.3)	36	3.6

[a] Irradiations were carried out in a quartz tube of 5.0-mL capacity under nitrogen for 5 h using 0.15 M alcohol in xylene solution containing 0.28 mmol of 1. [b] Determined by GC analysis of aliquots removed from the irradiation mixture.

13 and **14**, predominantly **14**, based on the NMR and mass spectra. The assignment was further supported by direct comparison of the oxide of one of the ethers with a specimen of 1-phenyl-3-methoxyphospholane 1-oxide prepared independently by catalytic hydrogenation of corresponding 1-phenyl-3-methoxy-2-phospholene 1-oxide[11] (vide infra).

Stereochemical assignment of the photoethers was based on their NMR spectra. One isomer (i.e., **2a** or **13**) eluting faster than the other isomer from the column showed the methoxy protons resonating at higher field than those of the other isomer (i.e., **3a** or **14**). This chemical-shift difference is attributable to the orientation of the methoxy and phenyl groups. The conformation of the five-membered ring is usually discussed in terms of an envelope or twisted-envelope shape and these forms are flexible and undergo rapid pseudorotation. It has been shown[12a] that the parent phospholane ring is reasonably depicted in the same manner. Inspection of a model for the photoether in the twisted-envelope conformation reveals that the methoxy protons cis to the phenyl ring are located in a position such that they should resonate upfield due to the anisotropic effect of the phenyl substituent. The phenyl substituent should have little effect on the shifts of the methoxy protons trans to the substituent. Therefore, those methoxy protons shifted upfield in **2a** and **13** are assigned to those cis to the phenyl ring.[12b] The similar upfield shift of a methyl group by an analogous 1,3-anisotropic effect of a *cis*-phenyl group is noted[13] in the five-membered cyclic phosphites. The assignment was further supported by the finding that the 3-methyl signal of the oxide **8a** of the cis isomer showed a deshielding effect[14] by a P=O group to be operative on this group: the 3-CH_3 signal of **8a** is deshielded by 0.19 ppm relative to that of the oxide **9a** of the trans isomer. The same kind of deshielding effects of the ring alkyl substituents have been found[15] with five-membered ring phosphates.

The present stereochemical assignment to the phospholane system provided additional insight into the stereochemistry of catalytic hydrogenation. 3-Methoxy-1-phenylphospholane 1-oxide (**15**) obtained by hydrogenation of 3-methoxy-1-phenyl-2-phospholene 1-oxide in the presence of palladium-on-carbon catalyst, a reaction known[16] to occur completely stereospecifically, showed methoxy protons at 3.37 ppm, identical with the oxide **15** of the cis isomer of the photoether. Thus, it might be concluded that the reduction product arose from cis addition of hydrogen in the direction containing the P=O group across the double bond.

Additional insight into the present reaction was afforded by a series of irradiations conducted with **1** under a variety of conditions, as summarized in Tables I and II. Neither the isomerization nor the ether formation reaction was inhibited noticeably by the addition of sodium methoxide. Furthermore, dark control in the presence of a small amount of acid showed no formation of the products. These observations eliminate the possibility that acidic products, known[5a] to be generated in the photolysis of methanol, might induce the present reaction.

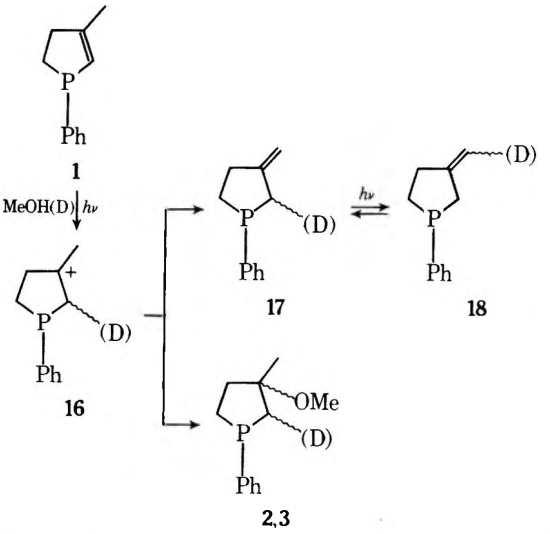
The ratio of exo isomer to the ether was significantly dependent on the concentration of methanol, favoring the ether formation with increasing concentration. This suggested the intervention of a common carbonium ion to both exo isomer and the ether. A priori, the exo isomer could be formed via intramolecular hydrogen shift. This was shown, however, not to be the case, since irradiation of **1** in dry xylene showed no formation of exo isomer, while similar irradiation in wet xylene resulted in a gradual built-up of exo isomer. Thus, initial protonation is shown to be a necessary step for the formation of both ether and exo isomer.

The substitution of other alcohols for methanol again afforded the ethers along with the isomerization product **4**, although the reaction was less efficient. This is in marked contrast, however, to the photochemical behavior of cyclohexene in alcohol, in which only isomerization was observed in the irradiation with *tert*-butyl alcohol even in the presence of acid. The marked enhancement in basicity of the excited state of **1** compared to that of cyclohexene apparently implies that species which undergo protonation in the present reaction should be essentially different in nature. The slight increase of the ratio of isomerization to ether formation in going from methanol to *tert*-butyl alcohol might be related to nucleophilicity and steric bulk of the alcohols.[16a]

Labeling Studies. From the foregoing experimental data it might be concluded that the 2-phospholene underdoes photochemical reaction in alcohols via an ionic process to yield exo isomer and ethers. In order to get more convincing support for the common carbonium ion mechanism as outlined in Scheme III, labeling studies were undertaken.

Irradiation of **1** in methanol-*O*-*d*–xylene solution again afforded the ethers and exo isomer. In the NMR spectrum of the resulting ether, the intensity of unresolved multiplet attributable to ring methylene at δ 1.45 ~ 2.40 was greatly reduced and the coupling patterns were significantly simplified as expected for the presence of deuteration at the ring carbon, although the exact position of deuteration was not clear because of its complexity. Likewise, analysis of the NMR spectrum of the recovered starting material clearly displayed the presence of some deuteration on the vinyl proton even in an irradiation interrupted at only partial conversion (10%), as has been observed[2,3] previously for other olefins which exhibit ionic photobehavior, and the gradual build-up of deuterium was observed as the reaction proceeded (Table III). Deuterium atom was also found to be incorporated at the ring carbon of the exo isomer. These observations suggest that both the ethers and exo isomer arise via an initial selective protonation

Scheme III



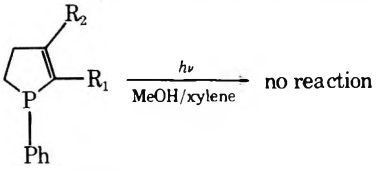
at C-2 of 1 to form common carbonium ion **16**, which in turn undergoes three competing reactions: (a) nucleophilic capture by solvent to afford the ethers, (b) elimination to exo cyclic olefin, and (c) deprotonation to regenerate the starting olefin **1**, as depicted in Scheme III.

Surprisingly, however, a marked attenuation of the doublet at δ 5.60 of exo isomer was noted, indicating substantial deuterium incorporation occurred at exo-methylene carbon. Control studies showed that the exo isomer is photolabile but does not afford any of the methyl ethers or endo olefin on irradiation in methanol: this precludes the possibility that the light-induced protonation on **4** is involved in this marked incorporation of deuterium at the exo position. The reversible 1,3-hydrogen shift was also precluded from the foregoing results. We tentatively propose a rapid reversible photochemical 1,3-phosphoryl shift

$$17 \overset{h\nu}{\rightleftarrows} 18$$

to explain the observed scrambling. The exact nature of this reaction is not clear at present and is the subject of continued study.

Methyl Substituent Effect. The unsubstituted phospholene **12** was shown to undergo photoprotonation to give 1-phenyl-3-methoxyphospholanes on irradiation in methanol. However, attempts to extend the reaction to 2-methyl derivatives **19** in order to learn the stereochemistry of the addition reaction lead to some surprising results. Thus, direct or pho-



19a, $R_1 = R_2 = Me$
b, $R_1 = Me$; $R_2 = H$

tosensitized irradiation of **19** in methanol under conditions in which the 3-methyl derivative **1** was completely converted to the mixture of the ethers and exo isomer resulted in almost total recovery of the starting olefins. In neither case was there any appreciable formation of exo isomer or an ionic- or radical-type addition product.

Photoreactions of Other Phospholenes in Alcohols. In contrast to the efficient photoprotonation of **1**, irradiation of 2-phospholene 1-oxide **10** in methanol leads to substantially different results. The only volatile product detected by GC was 3-methylphospholane 1-oxides **20**, as a 1:1 mixture of geometrical isomers, which was easily prepared by the reduction of the 3-phospholene 1-oxide **11**. No trace of the ethers **8** and **9** or exo isomer was detected even by GC. The yield of **20** increased in going from methanol to isopropyl alcohol, as indicated in Table IV, and acetone was detected in the irradiation with the latter solvent. The reduction was efficiently quenched by 1,3-pentadiene to yield linear Stern–Volmer plots with a slope of 14 M^{-1} (in isopropyl alcohol). The results suggest that the oxide **10** undergoes a similar radical type of reaction via excited triplet state, as has been observed[4] previously for cyclopentene. It has been reported[6c] that irradiation of 1-phenyl-3-methyl-3-phospholene in methanol was rapidly transformed into a complex mixture of products without any detectable formation of the ethers; the main reaction pathway was photochemical cleavage into isoprene and phenylphosphinidene, as has been observed[1a,6a] for the corresponding 3-phospholene oxides. These results strongly imply that the presence of trivalent phosphorus adjacent to the double bond is required for photoprotonation.

Table III. Deuterium Distribution[a] of the Oxides of 1 and 4

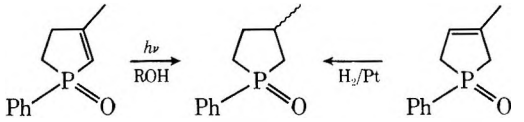
% convn	Oxide of 1 vinyl	Oxide of 4 Exo methylene	Oxide of 4 Ring methylenes
10	0.13 ± 0.01 D	0.47 ± 0.05 D	0.44 ± 0.06 D
21	0.20	0.52	0.53
44	0.44	0.64	0.86

[a] Calculated by relative NMR peak area to aromatic protons as standard.

Table IV. Irradiation[a] of 10 in Alcohols

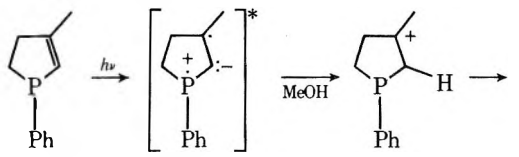
Alcohol	% convn[b]	21, % yield[b]
MeOH	18	2
EtOH	33	23
i-PrOH[c]	44	35
t-BuOH	17	0.7

[a] Irradiations were carried out in a quartz tube of 5.0-mL capacity under nitrogen for 3 h using a 5.0-mL alcohol solution of 0.25 mmol of **10**. [b] Determined by GC. [c] Acetone was detected by GC.



Reactive Excited State. It seems quite clear from foregoing data that photochemical reactions of 2-phospholenes in alcohol involve a common carbonium ion arising from photoprotonation at C-2 of the phospholene. There remains then the important question of what is the reactive intermediate which is undergoing protonation. The intervention of *trans*-olefin or orthogonal triplet state was clearly precluded because of a large distortion inherent in such a olefin. The radical type of reaction shown by 2-phospholene 1-oxide supports the assumption.

Weiner et al.[17] have observed the single major band above 220 nm in the UV spectra of vinylphosphine and assigned it to an electron-transfer type of transition, in which an electron is removed from the nonbonded orbital on trivalent phosphorus and transferred to the empty π^* orbital of the vinyl group. The necessity of the lone pair of electrons to the observed transition is demonstrated by the effective disappearance of any maximum above 200 nm in the spectrum of the vinylphosphine oxide. In accordance with their observation, 2-phospholenes **1** and **12** showed the strong single band at 256 nm in the UV spectra, whereas the corresponding



1 21

phosphine oxide showed weak absorption with vibrational fine structure, indicating the lack of interaction between phosphorus and the double bond.[18] Thus, the excited state of 2-phospholene should be polarized as in **21**, in which there is an increase of electron density on the α carbon atom relative to the ground state. Such charged character of 2p* clearly explains the following facts: (a) regiospecific protonation on C-2, (b) the enhanced basicity of the excited state of **1** compared to the photochemical behavior of cyclohexene, and (c) the necessity of trivalent phosphorus adjacent to the double bond.

Interestingly, the UV spectra of 2-methyl derivatives **19** show only weak absorption with unresolved vibrational fine structure similar to that of 2-phospholene oxide. This implies that the failure of these derivatives to undergo photoprotonation under irradiation in methanol is attributable to their inability to obtain an electron from the adjacent phosphorus and hence possess a polarized double bond in the lowest excited state. An electron-releasing α-methyl group might probably raise the energy of this reactive state to an upper level by destabilizing the negative charge on the α carbon.

Attempts to explore the multiplicity of the reactive excited state of phospholene were unsuccessful, since irradiation of **1** with quencher (1,3-pentadiene) or sensitizer (benzophenone) resulted in a complex mixture of the products including the ethers and exo isomer, probably arising from the possible reaction of **1** with quencher or sensitizer.[19]

The observation that complete absence of the ether or exo isomer in the acid-catalyzed reaction of **1** in methanol in the dark is in marked contrast to other simple olefins which undergo acid-catalyzed protonation in the absence of light. The major single band at 256 nm of **1** in methanol changed[20] gradually by the addition of diluted acid (HCl) in the dark to the weak band with vibrational fine structure similar to that of 2-phospholene 1-oxide, suggesting that protonation of the lone-pair electrons is probably occurring on phosphorus rather than on the double bond. There is, thus, a fine balance between the acidity of the solvent and basicity of phospholene in various states, with ground-state phospholene being protonated only by strong acid on phosphorus in the dark, while the excited-state phospholene is being protonated by weak acid like alcohol on the α carbon under irradiation.

Synthetically, the present photoreaction provides a method for selectively protonating a 2-phospholene system to afford the product which is not easily prepared in the dark reaction.

Experimental Section

General. All melting and boiling points were uncorrected. Infrared spectra were determined on a JASCO IR-G recording spectrometer. Proton magnetic resonance spectra were determined on a JEOL JNM-MH-100 NMR spectrometer: chemical shifts are reported in units of δ (part per million) downfield from Me_4Si. Mass spectra were obtained on a Hitachi RMS-4 spectrometer. Ultraviolet and fluorescence spectra were measured with a Shimadzu UV 250 recording spectrometer and a Hitachi MPF-2A spectrofluorometer, respectively. GC analyses were performed on a Yanagimoto instrument Model G-80 using a 2.0 m × 5.0 mm column packed with 10% SE-30 and 13% Apiezon L on 60–80 mesh Diasolid L. Woelm silica gel (activity III) was always used for column chromatography.

Materials. Phospholene 1-oxides were prepared by cycloaddition of dienes and phosphonous dihalides, followed by hydrolysis of the resulting adducts according to the general procedure of Quin.[10] 1-Phenyl-2-phospholenes were prepared by reduction[21] of diene–phenylphosphonous dichloride adducts with Mg and distilled prior to irradiations.

Irradiations. Unless otherwise indicated, all irradiations were conducted using a Halos 300-W high-pressure mercury lamp and a water-cooled quartz immersion well. A commercial mixture of *o*-, *m*-, and *p*-xylene was employed. The solution was purged with nitrogen 5–10 min before irradiation. Vigorous stirring during irradiation was effected by a magnetic stirring bar. The progress of photochemical reactions was monitored by GC analysis of aliquots removed periodically. For product identification the irradiation mixtures were concentrated on a rotary evaporator, and individual components were isolated by silica gel column chromatography and characterized either as described below or by comparison with authentic specimens. The irradiations outlined in Tables I, II, and IV were conducted in a sealed quartz tube of 5.0-mL capacity strapped to an immersion well. Control runs showed that no reaction occurred in the absence of light.

Irradiation of 1-Phenyl-3-methyl-2-phospholene (1). (A) In Methanol–Xylene. In a typical run, a 270-mL xylene solution containig 30 mL of methanol and 2.0 g of freshly distilled phospholene **1** was irradiated under nitrogen for 6 h. Isolation of the first major component (1.26 g) by column chromatography using petroleum ether (bp 40–60 °C) with an increasing amount of diethyl ether afforded a colorless liquid with strong phosphine odor, which was identified as an unresolved mixture of the starting olefin **1** and exo isomer by GC and NMR. Attempts to separate **1** and **4** by several passes through the column resulted in two poorly resolved pairs of isomers. The mixture was treated with a slight excess of *tert*-butyl hydroperoxide in xylene, followed by the column chromatography using ethyl ether as eluent. The first fraction (0.58 g, 42%) was identified as the oxide of exo isomer **4**: NMR ($CDCl_3$) 1.97–3.08 (m, 6 H, $-CH_2-$), 5.60 (d, J = 9.0 Hz, 2 H, $=CH_2$), and 7.30–7.95 (m, C_6H_5).

The dibromide, prepared in chloroform and recrystallized from benzene, had mp 136–137 °C. Anal. Calcd for $C_{11}H_{13}Br_2OP$: C, 37.53; H, 3.72. Found: C, 37.67; H, 3.54.

The second fraction (0.68 g) was identified as the oxide of **1** by comparison of its IR and NMR with those of an authentic sample.

Similar isolation of the second and third product components afforded *cis*- and *trans*-1-phenyl-3-methoxyphospholane (0.314 g, 19%), respectively. The NMR and mass spectra of each isomer are recorded in Table V. Benzyl bromide salts were prepared for each isomer in benzene and recrystallized from ethyl acetate. Analytical data and melting points for the salts are given in Table V.

(B) In Methanol-*O*-*d*–Xylene. A 280-mL xylene solution containing 10 mL of methanol-*O*-*d* (Merck and Co., Inc., 99.5 + atom % D) and 2.0 g of **1** was irradiated under nitrogen. Each of the components was isolated as described in part A. The oxides of recovered olefin **1** and exo isomer were found by NMR analysis to have the deuterium composition outlined in Table III. Control experiment showed that no deuterium exchange was observed in the separation step described above. The photoethers **2a** and **3a** exhibited the NMR spectra similar to those of materials obtained as described in part A, except for an attenuation of the bands at δ 1.45–2.40 to an integration corresponding to 1.0 ± 0.1 proton.

(C) In Other Alcohol–Xylene. A 270-mL xylene solution containing 30 mL of each alcohol and 2.0 g of **1** was irradiated and the irradiation mixtures were separated into individual components as described in part A. The NMR and mass spectra of each photoether are recorded in Table V together with melting points and analytical data for the benzyl bromide salts.

Irradiation of 1-Phenyl-2-phospholene (12). Irradiation of a 270-mL xylene solution containing 30 mL of methanol and 2.0 g of freshly distilled phospholene under nitrogen for 6 h followed by isolation of the product in the usual manner afforded the photoethers **13** and **14** in 10 and 12% yields, respectively.

The NMR and mass spectra of each isomer are given in Table V together with the melting points and analytical data of the benzyl bromide salts.

Irradiation of 1-Phenyl-3-methyl-2-phospholene 1-Oxide (10). Irradiation of the phospholene oxide **10** (2.1 g) in isopropyl alcohol (250 mL) under nitrogen for 7 h followed by isolation of the major product by column chromatography eluted with diethyl ether–methanol (9:1) afforded 1-phenyl-3-methylphospholane 1-oxide as a 1:1 mixture of geometrical isomers (655 mg, 39%), which was identical in all respects with an authentic specimen prepared[22] by catalytic hydrogenation of 1-phenyl-3-methyl-3-phospholene 1-oxide. GC analysis of the reaction mixture showed the presence of acetone.

For quenching experiments, the solutions of 50 mM **10** in 5.0 mL of isopropyl alcohol with or without piperylene were placed in closed quartz tubes. The tubes were irradiated simultaneously on a merry-go-round apparatus at room temperature for 3 h, and the amount of

Table V. 3-Alkoxyphospholanes and Their Benzyl Bromide Salts

Registry no.	Compd	^{1}H NMR[a], δ, ppm (J, Hz) C-CH_3	C-OR	-CH_2-	Mass (m/e)[b]	Benzyl bromide salt mp, °C	Formula	Carbon, % Calcd	Carbon, % Found	Hydrogen, % Calcd	Hydrogen, % Found
52561-64-5	**2a**	1.29[c]	3.02[c]	1.50–2.30[d]	208, 195, 178, 177, 176, 161, 138, 109, 108,	174–175	$C_{19}H_{24}BrOP$	60.17	59.66	6.38	6.40
52561-65-6	**3a**	1.29[c]	3.15[c]	1.45–2.40[d]	107, 91, 78, 77	151–155			59.79		6.39
62726-78-7	**2b**	1.16[c]	0.87(6.1)[e] 3.09(6.1)[f]	1.28–2.78[d]	222, 177, 178, 138, 123, 109,	167–171.5[g]	$C_{20}H_{26}BrOP$	61.08	60.91	6.66	6.65
62726-79-8	**3b**	1.08[c]	0.97(6.1)[e] 3.12(6.1)[f]	1.10–2.72[d]	108, 107, 91, 78, 77						
62726-80-1	**2c**	1.22[c]	1.09(6.9)[h] 3.42(6.9)[i]	1.15–2.70[d]	236, 209, 193, 178, 176, 138, 125, 124, 123,	172–177[g]	$C_{21}H_{28}BrOP$	61.92	60.14	6.93	7.02
62726-81-2	**3c**	1.21[c]	1.19(6.9)[h] 3.48(6.9)[i]	1.18–2.72[d]	109, 108, 107, 78, 77						
62726-82-3	**2d**	1.22[c]	1.09[c]	1.35–2.70[d]	250, 210, 178, 177, 176, 138, 131, 125, 124, 109, 108, 107,	181–188[g]	$C_{22}H_{30}BrOP$	62.71	62.93	7.18	7.08
62726-83-4	**3d**	1.21[c]	1.19[c]	1.34–2.50[d]	78, 77						
62726-84-5	**13**	*j*	3.17[c]	1.50–2.50[d]	194, 164, 163, 162, 109, 108,	78–79[g]	$C_{18}H_{22}BrOP$	59.19	58.54	6.07	6.10
62726-85-6	**14**	*j*	3.23[c]	1.50–2.40[d]	107, 78, 77						

[a] CD_3OD solution with internal standard. [b] m/e values reported include the parent ion and other significantly large peaks appearing above m/e 70. [c] Singlet. [d] Complex multiplet. [e] Triplet. [f] Quartet. [g] A mixture of cis and trans isomers. [h] Doublet. [i] Septet. [j] Complex multiplet at δ 3.80–4.15 attributable to CH-OMe.

consumed **10** was determined by GC. Five concentrations of piperylene in addition to blanks were used for the Stern–Volmer plot.

Base-Induced Reactions of Oxides and Benzyl Bromide Salts of 1-Phenyl-3-methyl-3-methoxyphospholanes. (A) Oxides 8 and 9. To pure **2a** (150 mg) in 5 mL of benzene at 5 °C was added 100 mg of *tert*-butyl hydroperoxide. The mixture was allowed to stand overnight and then concentrated, and the residue was chromatographed to yield **8a**: NMR ($CDCl_3$) 1.32 (d, J = 1.7 Hz, 3 H, C-Me), 1.52–2.73 (m, 6 H, $-CH_2-$), 3.23 (s, 3 H, OCH_3), and 7.23–8.07 (m, 5 H, C_6H_5).

Oxide **9a** was similarly prepared: NMR ($CDCl_3$) 1.41 (d, J = 1.3 Hz, 3 H, C-Me), 1.52–2.56 (m, 6 H, $-CH_2-$), 3.12 (s, 3 H, OCH_3), and 7.36–8.10 (m, 5 H, C_6H_5).

Two milliliters of 1.0 N NaOH was pipetted into a 5-mL flask containing 70 mg of either **8a** or **9a** and the resulting solution heated at reflux for 40 min. After cooling, the reaction mixture was neutralized, the aqueous layer was extracted with small portions of chloroform, and the extract was dried, concentrated, and chromatographed to yield **10** (48 mg, 80%) and **11** (10 mg, 16%).

(B) Benzyl Bromide Salts 6 and 7. Two milliliters of 1.0 N NaOH was added into a 5-mL flask containing 152 mg of either **6a** or **7a** and the resulting solution heated at reflux for 2 h. Toluene was detected by GC. Cooling and neutralization followed by chromatography afforded **10** (58 mg, 76%) and **11** (10 mg, 13%).

One milliliter of 1.0 N NaOH was added into a 5-mL flask containing 76.4 mg of **6a** and the resulting mixture was stirred vigorously at room temperature for 10 min. Isolation of the product in the above procedure gave 90% yield of the oxide, which displayed an NMR spectrum identical with that of **8a** obtained in part A.

Independent Preparation of 1-Phenyl-3-methoxyphospholane 1-Oxide. 1-Phenyl-3-methoxy-2-phospholene 1-oxide was prepared from chloroprene and phenylphosphonous dichloride followed by treatment with sodium methoxide in methanol, according to the literature[11] procedure for the P-methyl derivative, and recrystallized from PhH: mp 95–96 °C; IR ($CHCl_3$) ν 1588 (C=C), 1440 (P-Ph), 1188 (P=O), and 1108 cm^{-1} (COC); NMR ($CDCl_3$) 1.84–3.03 (m, 4 H, $-CH_2-$), 3.69 (s, 3 H, -OMe), 4.91 (d, J_{PH} = 16.0 Hz, 1 H, C=CH), and 7.25–7.91 (m, 5 H, $-C_6H_5$). Anal. Calcd for $C_{11}H_{13}O_2P$: C, 63.46; H, 6.29. Found: C, 63.25; H, 6.10.

To 1.35 g of 1-phenyl-3-methoxy-2-phospholene 1-oxide in 5 mL of absolute ethanol was added 0.5 g of 5% palladium-on-carbon, the mixture was hydrogenated for 6 h at 7 to ~8 kg/cm^2, the solution was filtered, and the solvent removed to give a yellow oil, which showed no vinyl proton but rather methoxy protons at δ 3.36, identical with that of the oxide obtained by oxidation of *cis*-1-phenyl-3-methoxyphospholane (**13**) with *tert*-butyl hydroperoxide.

Acknowledgments. We are grateful for partial support of this research by the Japan Ministry of Education and to Japan Synthetic Rubber Co. and Denki Kagaku Kogyo Co. for providing us with dienes.

Registry No.—**1**, 1445-83-6; **4**, 52561-63-4; **4** dibromide oxide, 52561-66-7; **4** oxide, 62726-86-7; **6a**, 62726-70-9; **6b**, 62726-71-0; **6c**, 62726-72-1; **6d**, 62726-73-2; **7a**, 62726-74-3; **7b**, 62726-75-4; **7c**, 62726-76-5; **7d**, 62726-77-6; **8a**, 62726-87-8; **9a**, 62726-88-9; **10**, 707-61-9; **12**, 28278-55-9; **13** benzyl bromide, 62726-68-5; **14** benzyl bromide, 62726-69-6; 1-phenyl-3-methoxy-2-phospholene 1-oxide, 62726-89-0.

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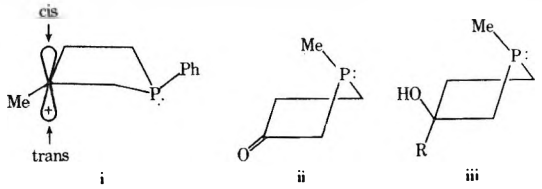

i ii iii

Photochemical Rearrangements of 4,7-Dimethyl-3-chromanone and Related Compounds[1]

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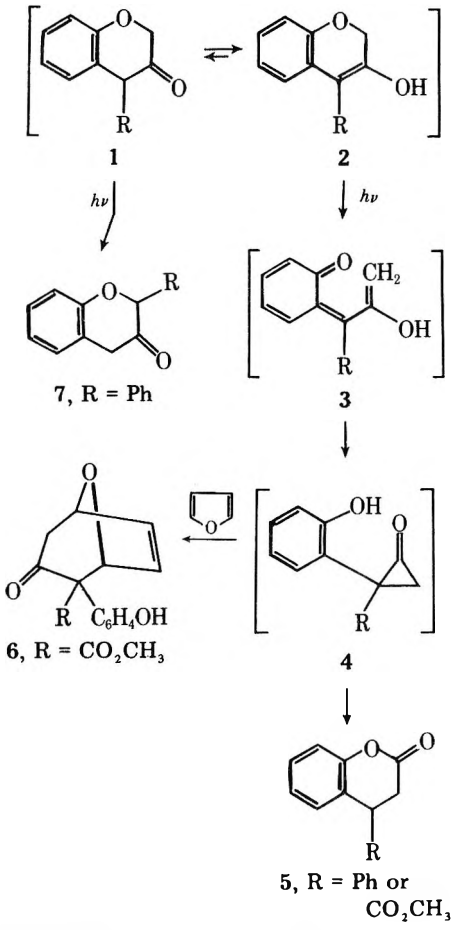
Photorearrangement reactions are described for 4,7-dimethyl-3-chromanone (**8**), 4,7-dimethyl-3-methoxychromene (**25**), and 1-phenyl-2-methoxy-3,4-dihydronaphthalene (**34**). Irradiation of **8** in basic methanol produces 2-hydroxy-3-methoxy-2,3,6-trimethyl-2,3-dihydrobenzofuran (**9**). The formation of **9** is readily explicable in terms of a photoinduced ring opening of the enol of **8** to give an o-quinoneallide intermediate (**17**) followed by 1,4-addition of methanol. Evidence for the proposed sequence was obtained by studying the photobehavior of the closely related 4,7-dimethyl-3-methoxychromene (**25**) system. Irradiation of **25** in methanol produced a mixture of 2,3-dimethoxy-3-(2-hydroxy-4-methylphenyl)-1-butene (**26**) and 2-methoxy-3-(2-hydroxy-4-methylphenyl)-1,3-butadiene (**27**). When the irradiation of **25** was carried out in benzene, a mixture of **27**, 2,6-dimethyl-2-methoxy-3-methylene-2,3-dihydrobenzofuran (**29**), and 1-methoxy-2-oxa-5,7-dimethylbenzobicyclo[3.1.0]hexene (**30**) was obtained. These products are most readily derived from an *o*-quinoneallide intermediate (**31**) formed by a photoinduced ring opening of the 3-chromene ring. The excited state behavior of the closely related 1-phenyl-2-methoxy-3,4-dihydronaphthalene (**34**) system was also studied and it was found to undergo a similar rearrangement.

In earlier reports from this laboratory,[2-4] evidence was presented which demonstrated that the enol content can be an overriding factor in determining the excited-state behavior of a carbonyl group. As part of our studies in this area, we investigated the photochemical rearrangement of several 4-substituted 3-chromanones (**1**) to 4-substituted dihydrocoumarins (**5**)[2,5] and found that the reaction involves the prior conversion of **1** into its enol tautomer **2**, which is subsequently converted to **5** on exposure to UV light in alcoholic solvents. When the irradiation was carried out in a nonpolar solvent, where the concentration of the enol form was negligible, photorearrangement from the keto tautomer occurred resulting in the formation of a rearranged 3-chromanone (i.e., **7**).[6] The unusual richness of the photochemistry of this system, which is a sensitive function of reaction conditions, including the choice of solvent, provides a useful probe for determination of reaction mechanism. The distribution of products and the ability to trap a cyclopropanone intermediate (i.e., **4**) with furan have permitted elucidation of the nature and sequence of intermediates involved in this photochemical system. We now wish to report that replacement of the 4-phenyl or carbomethoxy substituent with a methyl group markedly alters the outcome of the rearrangement. The present publication describes our findings with the 4,7-dimethyl-3-chromanone (**8**) system and delineates the significant role played by an *o*-quinoneallide intermediate in the overall photochemistry of this ring system.

Results and Discussion

4,7-Dimethyl-3-chromanone (**8**) was conveniently prepared by the series of reactions outlined in Scheme I. Its physical and spectroscopic properties are in excellent agreement with those previously reported by Still and Goldsmith.[7] The NMR spectrum of **8** in deuteriochloroform indicates that this system exists exclusively as the keto tautomer [60 MHz, τ 8.56 (d, 3 H, J = 7.0 Hz), 7.72 (s, 3 H), 6.52 (q, 1 H, J = 7.0 Hz), 5.67 (AB q, 2 H, J = 17.0 Hz), and 2.9–3.3 (m, 3 H)].

Irradiation of **8** in methanol resulted in a very slow and messy reaction; no characterizable products could be obtained. When a catalytic quantity of sodium methoxide was added to the solution, however, a very fast and clean reaction occurred upon irradiation. Under these conditions a high yield (75%) of 2-hydroxy-3-methoxy-2,3,6-trimethyl-2,3-dihydrobenzofuran (**9**) was obtained. The NMR spectrum of this compound showed that it consisted of a 79:21 equilibrium mixture of **9a** [(60 MHz, $CDCl_3$) τ 8.54 (s, 6 H), 7.68 (s, 3 H), 6.89 (s, 3 H), 4.85 (s, 1 H, exchanged with D_2O), and 2.8–3.5 (m, 3 H)] and 3-methoxy-3-(2-hydroxy-4-methylphenyl)-2-

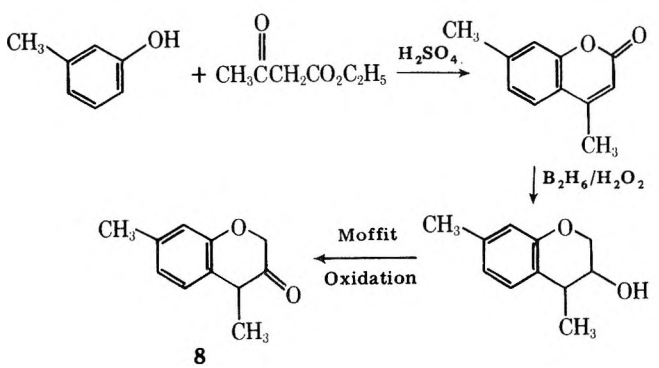


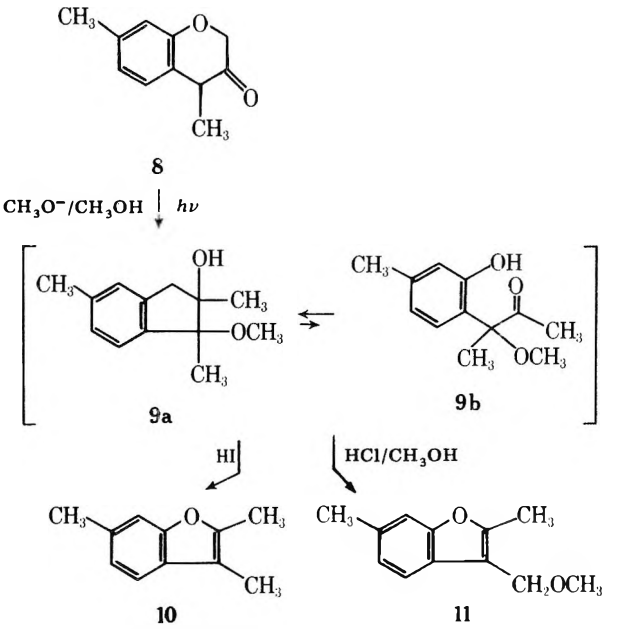
butanone (**9b**) [(60 MHz, $CDCl_3$) τ 8.31 (s, 3 H), 7.88 (s, 3 H), 7.72 (s, 3 H), 6.70 (s, 3 H), 2.8–3.5 (m, 3 H), and 1.94 (s, 1 H, exchanged with D_2O)]. Treatment of this equilibrium mixture with hydriodic acid resulted in the formation of 2,3,6-trimethylbenzofuran (**10**) in quantitative yield. Further evidence supporting the structure of the photoproduct was obtained by its ready conversion to 2,6-dimethyl-3-methoxybenzofuran (**11**) on treatment with acidic methanol.

A plausible mechanism for the formation of **11** from **9** is shown in Scheme II. Protonation of the ether oxygen will give carbonium ion **12** which subsequently loses a proton to produce allylic alcohol **13**, which, however, was not observed. Generation of the stable allylic cation **14** from **13** and reaction of this species with methanol readily rationalize the formation of **11**. As will be seen shortly, the closely related methyl ether derivative of alcohol **13** was also found to rapidly rearrange to **11** upon treatment with a trace of acid.

The formation of **9** from the irradiation of 3-chromanone **8** is readily explicable in terms of a photoinduced ring opening of enol **16** to give an *o*-quinoneallide intermediate **17** (see Scheme III). This transformation is analogous to the well-known ring openings of pyrans, chromenes, and other related

Scheme I

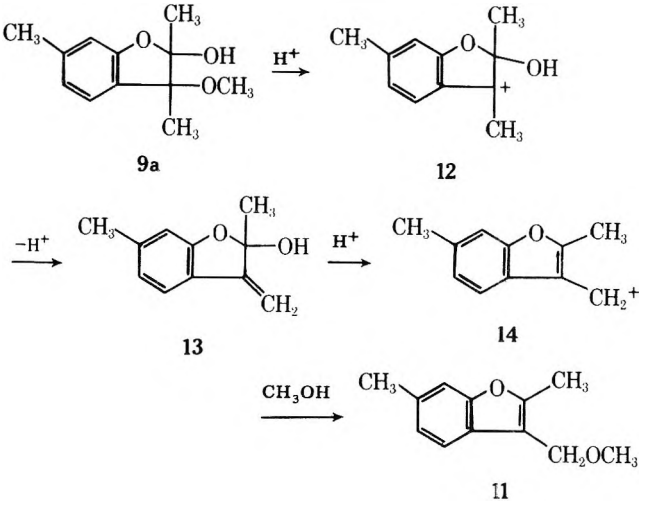




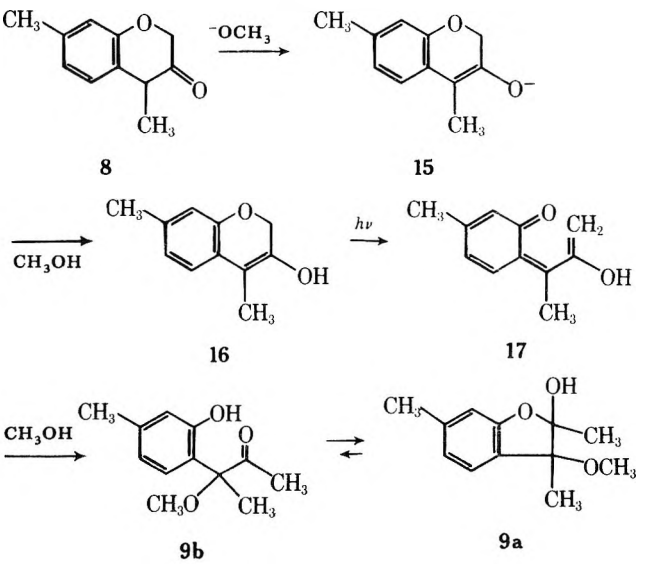
benzo-heterocyclic olefins.[8–15] Simple addition of methanol to *o*-quinoneallide **17** best rationalizes the formation of **9**.

Our present results are especially interesting in view of the fact that the irradiation of **8** does not afford any detectable quantities of a 4-substituted dihydrocoumarin (i.e., **5**, R = CH_3). As was pointed out in a previous report,[2] these hydroxyl

Scheme II

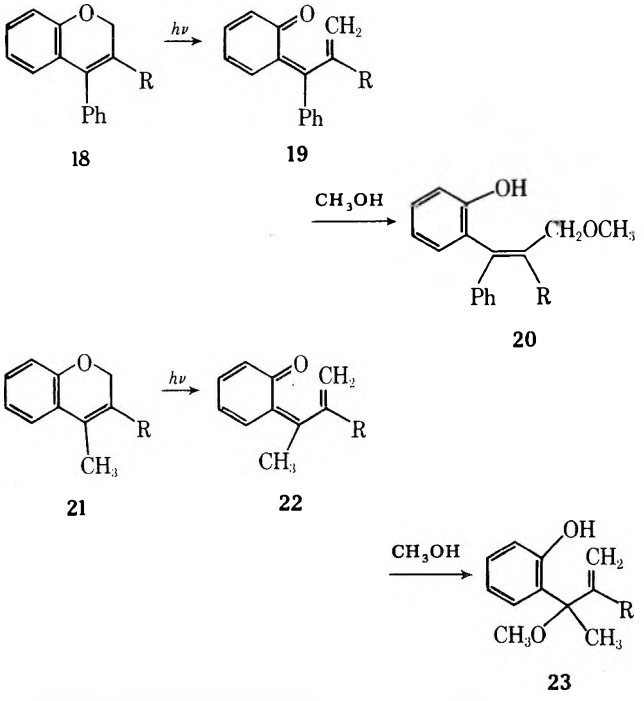


Scheme III



substituted o-quinoneallide intermediates (i.e., **3** or **17**) have the appropriate structural elements to undergo an internal Michael addition to give a phenolic cyclopropanone (**4**) which is ultimately converted to a 4-substituted dihydrocoumarin (**5**). This type of transformation does indeed occur in the phenyl and carbomethoxy series.[2] The o-quinoneallide intermediate (**17**) generated from the irradiation of **8**, however, prefers to undergo bimolecular addition of methanol across the C–C double bond. The diverse photobehavior of these substituted 3-chromanones may be related to the difference in reactivity of the o-quinoidal intermediates. Michael addition of methanol to the labile o-quinoneallide obtained from **8** would be expected to occur quite readily. This facile conjugate addition destroys the necessary chromophore for internal cyclization. Attack by methanol on the o-quinoidal intermediate containing a phenyl or carbomethoxy group on the β carbon is not as rapid, and consequently this species is long enough lived to undergo intramolecular cyclization to **5**. The reactivity difference is presumably related to the fact that both the phenyl and carbomethoxy groups can conjugate with the o-quinonemethide portion of the transient o-quinoneallide intermediate. This added conjugation provides a stabilizing effect and moderates the bimolecular addition of nucleophiles at the β position of the unsaturated ketone.

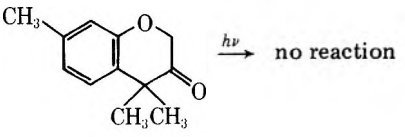
Evidence supporting the above hypothesis is available from some earlier studies dealing with the photochemical ring opening reactions of substituted chromenes.[8,16] These studies showed that the photolysis of 4-phenylchromenes (**18**) in methanol resulted in the exclusive formation of a 1,6-methanol adduct (**20**). In contrast, the irradiation of 4-methyl substituted chromenes (**21**) in methanol gave rise to a 1,4 adduct (**23**) as the exclusive photoproduct. The difference in the mode of attack of methanol on the o-quinoidal intermediate formed from these chromenes (i.e., **19** or **22**) can also be attributed to



18 19 20 21 22 23

a diminished propensity for bimolecular attack of methanol at the β position when a conjugating group is present on this carbon. The above data reinforce our contention that bimolecular conjugate addition of methanol is preferred over internal cyclization with o-quinoneallide **17**. This difference in reactivity is presumably the factor which is responsible for the variation in the structures of the photoproducts obtained from these 4-substituted 3-chromanones.

It is interesting to note that the irradiation of **8** in methanol is extremely complicated when the base was omitted. The effect of added base on the photochemistry of this system can best be rationalized in terms of the enol content present in solution. In pure methanol, insignificant amounts of the enol tautomer are present and consequently ring opening does not occur. The addition of sodium methoxide to a methanolic solution of **8** generates a sufficient quantity of the enol to allow the photochemical ring opening to proceed. Thus, the distribution of products obtained from the photolysis of the 3-chromanone system can be readily accounted for in terms of the small amount of enol (or enolate) present in tautomeric equilibrium with the keto form. Electronic excitation of the enol (or enolate) tautomer results in a photochemical ring opening to give an o-quinoneallide intermediate. The subsequent products obtained from the o-quinoneallide depend on the substituent groups present and the particular solvent employed. If the enol tautomer is unavailable, photochemical ring opening of the 3-chromanone system does not occur. For example, we note that 4,4,7-trimethyl-3-chromanone (**24**) fails to react even under lengthy photolytic conditions.



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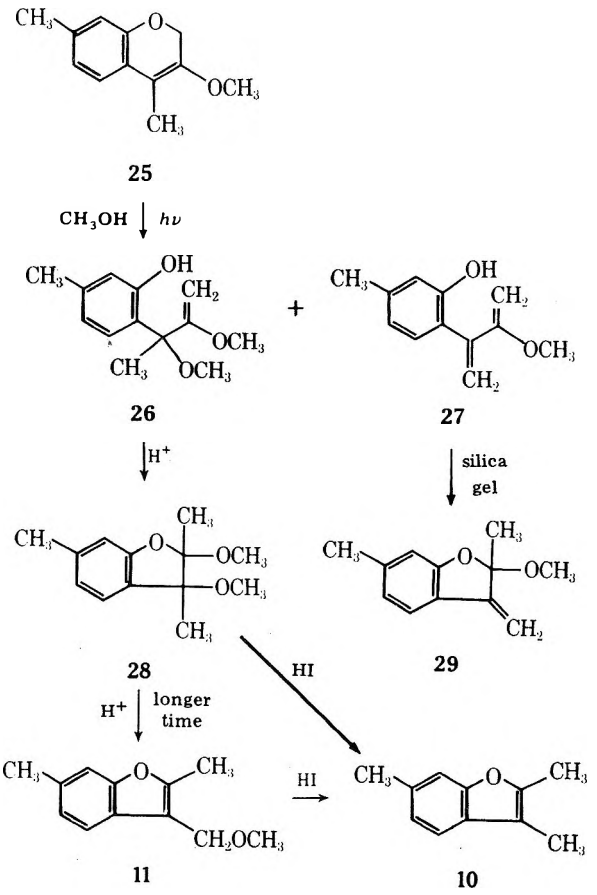
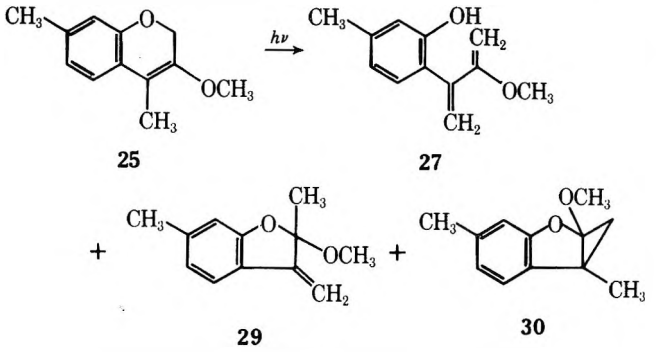
Since it was the 3-hydroxychromene tautomer of **8** which was suspected of giving rise to photoproduct **9**, we sought to permanently lock **8** into its enol form and examine the behavior of the resulting system. This was accomplished by synthesizing the corresponding enol ether **25** and studying its photochemical behavior. Irradiation of **25** in methanol produced a mixture of two compounds, **26** and **27**, in a 4:1 ratio. The structure of the major product (**26**) was established from its spectroscopic and chemical data (see Experimental Section). Chemical confirmation of structure **26** was obtained by

Scheme IV



treating it with acidic methanol and isolating 2,3,6-trimethyl-2,3-dimethoxy-2,3-dihydrobenzofuran (**28**) in quantitative yield. Prolonged treatment of **28** with acid produced benzofuran **11**. Both **11** and **28** gave 2,3,6-trimethylbenzofuran (**10**) when treated with hydriodic acid. The minor component (**27**) obtained from the photolysis of **25** rearranged on contact with silica gel to give 2,6-dimethyl-2-methoxy-3-methylene-2,3-dihydrobenzofuran (**29**). This material could be converted to **11** on treatment with a trace of acid. A summary of the results obtained is outlined in Scheme IV.

When the irradiation of enol ether **25** was carried out in benzene, the reaction followed a slightly different course. In this case a mixture of **27**, **29**, and 1-methoxy-2-oxa-5,7-dimethylbenzobicyclo[3.1.0]hexene (**30**) was isolated. The NMR spectrum of **30** showed doublets at τ 9.45 (1 H, J = 6.0 Hz) and

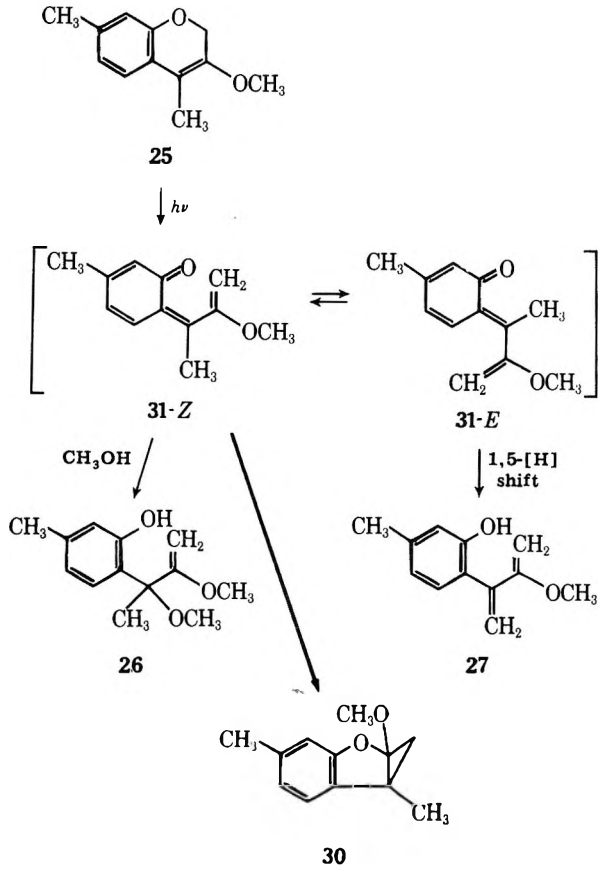


25 **27** **29** **30**

8.81 (1 H, J = 6.0 Hz) for the two cyclopropyl hydrogens and also contained three methyl singlets at τ 8.54, 7.72, and 6.48 in addition to the aromatic multiplet at τ 2.6–3.4.

We believe that all of the photochemical rearrangement products of **25** (i.e., **26**, **27**, **29**, and **30**) are derived from *o*-quinoneallide **31** as shown in Scheme V. The fate of **31** depends on the experimental conditions. The major product obtained in methanol corresponds to 1,4-addition of the solvent across the C–C double bond of **31**. The formation of **27**, on the other hand, involves a 1,5-sigmatropic hydrogen shift from the neighboring methyl group. In order for this transformation to proceed, the initially produced o-quinoneallide (**31**-*Z*) would have to undergo isomerization about the central double bond (i.e., formation of **31**-*E*) before it could be converted to **27**. This cis–trans isomerization could occur by a subsequent absorption of a photon of light. Alternatively, the photochemical ring opening of **25** could lead directly to an excited *o*-quinoneallide capable of subsequent geometrical isomerization to **31**-*E*. This latter possibility involves a direct conversion of an electronically excited state of the reactant (**25**) to an electronically excited state of the product (**31**-*Z*) followed by crossing to the ground state (**31**-*E*). Support for this viewpoint can be found in some work by Ullman and Huffman.[17,18] These authors found that the geometry of the photoenol produced in the photoenolization reaction of *o*-methylbenzophenone[19–21] is opposite that required for internal abstraction of a methyl hydrogen by the carbonyl group.[17] This observation was rationalized in terms of the formation of an excited enol which subsequently decayed to give a geometrically rearranged isomer. At this stage of our studies we do not have sufficient information to distinguish between the above two possibilities. Finally, the isolation of oxabenzobicyclohexene **30** from **25** in the benzene run is perfectly understandable since this solvent is incapable of undergoing conjugate addition to the *o*-quinoneallide intermediate and thus the system is sufficiently long enough lived to undergo cyclization by either thermal or photochemical means.[22]

Scheme V



25 **31**-*Z* **31**-*E* **26** **27** **30**

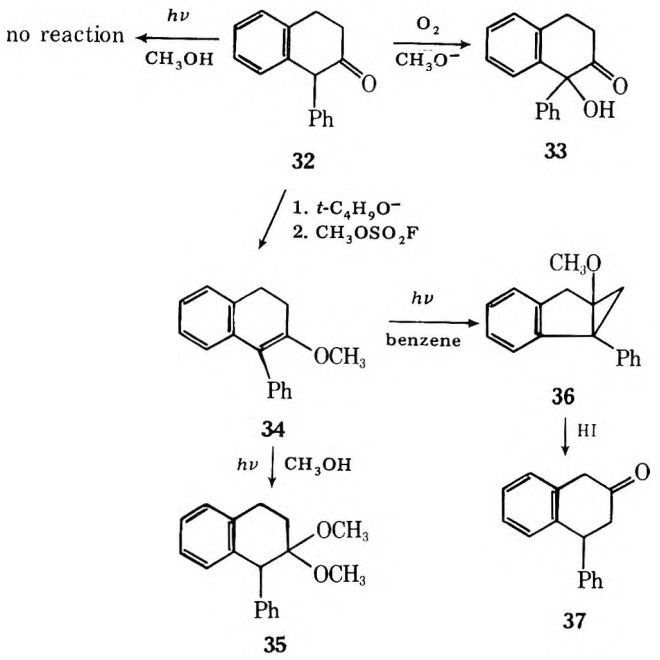
As part of our inquiries dealing with the photochemistry of carbonyl compounds through the enol form, we also decided to investigate the excited state behavior of the closely related 1-phenyl-2-tetralone (**32**) system. The procedure of Zaugg and co-workers[23] was followed for the preparation of this system. In contrast to the 4-phenyl-3-chromanone system,[2] this ketone was found to be inert toward a variety of photolytic conditions. When basic methanolic solutions were employed, the only reaction observed was the oxidation of **32** by trace amounts of oxygen present in solution. This oxidation, however, was subsequently shown to be a ground state reaction and can be attributed to the reaction of the enolate anion with ground state oxygen to give an α-hydroperoxy ketone which is subsequently reduced to **33**. Bordwell and others[24] have shown that related ketones undergo oxidative processes in the dark in the presence of base and oxygen via a similar path.

Although **32** was photochemically unreactive, the corresponding enol ether **34** did undergo smooth photochemistry. Irradiation of **34** in methanol produced 1-phenyl-2,2-dimethoxy-1,2,3,4-tetrahydronaphthalene (**35**) in high yield. A control experiment demonstrated that **34** was recovered unchanged from an acidic methanol solution which had been allowed to stand in the dark for 12 h. Thus, the formation of **35** involves a photochemical addition of methanol across the C–C double bond of starting material (Scheme VI). There have been several cases reported in the literature where olefins have been noted to undergo photoaddition with protic solvents.[25–29] It would appear, therefore, that **34** is another example of a system which undergoes a bona fide photochemical addition of methanol across the C–C double bond.

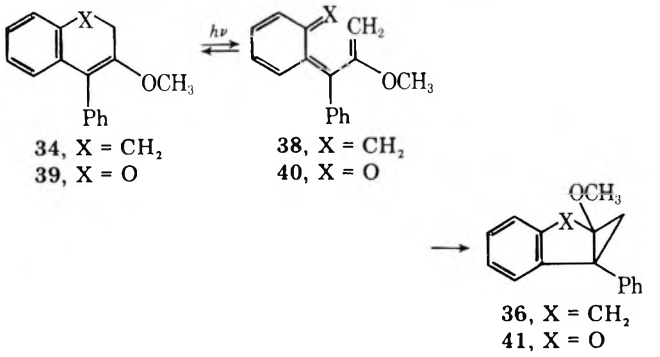
When the irradiation of **34** was carried out in benzene, the photoreaction followed an entirely different course. With this solvent system, a reaction analogous to that previously encountered with the 3-chromanone system occurred. Thus, the only product isolated upon direct irradiation of **34** in benzene was 1-methoxy-5-phenyl-3,4-benzobicyclo[3.1.0]-hexane (**36**). This material was readily converted to 4-phenyl-2-tetralone (**37**) on treatment with hydriodic acid.

The above results underscore the controlling effect of the oxygen atom on the photochemical behavior of these systems.

Scheme VI



Photolysis of **32** furnished none of the 2-tetralone (**37**) corresponding to dihydrocoumarin **5** but led instead to an overall oxidation (i.e., **33**). Similarly, irradiation of enol ether **34** does not produce a product derived from a ring-opened intermediate (i.e., **38**) when the irradiation is carried out in methanol. A possible explanation for the difference in the reactivity of this system relative to the chromene case (**39**) is that the initial ring-opened intermediate (**38**) derived from **34** may be converted back to starting material before it has a chance to react



further. This is probably related to the fact that **38** is incapable of undergoing a rapid thermal intramolecular Michael addition as was observed in the corresponding 3-chromanone system.[2] Bimolecular attack by methanol on **38** will also be a slow process. Thus the only path available to this system involves the addition of methanol to the excited state of **34** and formation of ketal **35**. In benzene, this competing mode of reaction cannot occur and the small amount of **38** present in steady state concentration eventually absorbs another photon of light and cyclizes to **36**. In support of this hypothesis, we note that the quantum yield for formation of **36** ($\Phi_{34\rightarrow 36}$ = 0.005) is much smaller than the value obtained in the 3-chromene system ($\Phi_{39\rightarrow 41}$ = 0.18).

In summary, the photolysis of 4-substituted 3-chromanones and their corresponding enol ether derivatives gives rise to a wide array of photoproducts. We have established plausible mechanisms for the observed rearrangements and have accounted for the role of solvent and substituent groups on the photobehavior of this ring system.

Experimental Section

All melting points are corrected and boiling points are uncorrected. Elemental analyses were performed by Scandinavian Microanalytical Laboratory, Herlev, Denmark. The infrared absorption spectra were determined on a Perkin-Elmer Infracord spectrophotometer, Model 137. The ultraviolet absorption spectra were measured with a Cary recording spectrophotometer, using 1-cm matched cells. The nuclear magnetic resonance spectra were determined at 100 MHz using a JEOL MH-100 spectrometer and at 60 MHz with a Varian T-60 spectrometer.

Preparation of 4,7-Dimethylchroman-3-one (8). 4,7-Dimethylcoumarin was prepared by a modification of the procedure described by Fries and Klostermann.[30] To a mixture containing 150 g of *m*-cresol and 130 g of ethyl acetoacetate at 0 °C was added 300 mL of concentrated sulfuric acid. After the addition was complete, the reaction mixture was allowed to warm to room temperature and stirred at 25 °C for 4 days. The deep red solution was poured onto ice and water was added until a white solid had formed. This material was collected and recrystallized from 95% ethanol to give 130 g (74%) of 4,7-dimethylcoumarin: mp 128–130 °C; IR (KBr) 5.82 μ; NMR ($CDCl_3$, 60 MHz) τ 7.41 (s, 6 H), 3.86 (s, 1 H), and 3.1–2.5 (m, 3 H).

A modification of the procedure described by Still and Goldsmith[7] was used to prepare 4,7-dimethylchroman-3-ol from 4,7-dimethylcoumarin. Diborane gas was generated by the dropwise addition of 50 g of boron trifluoride etherate to a solution of 11.5 g of sodium borohydride in 50 mL of diglyme. A nitrogen stream was used to transfer the diborane from the generating flask to the reaction vessel. The reaction vessel consisted of a gas drying tower with a fine frit, containing 30 g of 4,7-dimethylcoumarin in 300 mL of dry tetrahydrofuran. The entire system was thoroughly flushed with nitrogen and the reaction vessel was heated to 40 °C where it was maintained throughout the addition. When the gas flow was constant, the nitrogen stream was removed. The addition of diborane was complete after 3.5 h and the solution was transferred to a 1-L flask and allowed to stand at room temperature overnight. To this solution was added 160 mL of a 3 M sodium hydroxide solution followed by the cautious addition of 160 mL of a 30% hydrogen peroxide solution. The resulting mixture was stirred at room temperature for 6 h, acidified with a 10% hydrochloric acid solution, and extracted three times with ether. The ethereal extracts were washed with a 5% sodium hydroxide solution and water, and dried over magnesium sulfate. Concentration of the ether solution left a yellow oil which was distilled under reduced pressure to give 14 g (46%) of 4,7-dimethylchroman-3-ol: bp 128–132 °C (0.5 mm); mp 58–60 °C; IR (neat) 2.96 μ; NMR ($CDCl_3$, 60 MHz) τ 8.80 (d, 3 H, J = 7.0 Hz), 7.79 (s, 3 H), 7.26 (m, 1 H), 6.90 (s, 1 H, exchangeable with D_2O), 6.33 (m, 1 H), 6.03 (m, 2 H), and 3.4–2.9 (m, 3 H).

To an 8.0-g sample of 4,7-dimethylchroman-3-ol in 64 mL of anhydrous dimethyl sulfoxide was added 27.8 g of dicyclohexylcarbodiimide dissolved in 64 mL of anhydrous benzene. To this mixture was added 3.8 g of monophenyl phosphate in 10 mL of dry dimethyl sulfoxide. After the solution was stirred at room temperature for 2.5 h, 100 mL of ethyl acetate was added followed by the cautious addition of 100 mL of methanol containing 12.15 g of oxalic acid. The mixture was stirred for an additional 30 min and was then filtered. Benzene was added to the filtrate and the solution was washed several times with water, followed by a 5% sodium bicarbonate solution, dried over magnesium sulfate and concentrated under reduced pressure. The resulting oil was chromatographed on a silica gel column using a 20% ether–hexane mixture as the eluent. The oil obtained was distilled to give 6.4 g (81%) of 4,7-dimethylchroman-3-one (**8**): bp 65–67 °C (0.06 mm); IR (neat) 5.75, 6.12, 6.30, 6.65, 7.89, 9.48, and 12.26 μ; NMR ($CDCl_3$, 60 MHz) τ 8.56 (d, 3 H, J = 7.0 Hz), 7.72 (s, 3 H), 6.52 (q, 1 H, J = 7.0 Hz), 5.67 (AB q, 2 H, J_{AB} = 17 Hz), and 3.3–2.9 (m, 3 H); UV (methanol) 302 (shoulder) and 276 nm (ε 490 and 2100); *m/e* 176 (M^+), 161, 145, 133 (base), 105, 91, and 77.

Anal. Calcd for $C_{11}H_{12}O_2$: C, 74.97; H, 6.86. Found: C, 74.76; H, 6.92.

Irradiation of 4,7-Dimethyl-3-chromanone in Methanol Containing Sodium Methoxide. A solution containing 300 mg of 4,7-dimethyl-3-chromanone (**8**) in 190 mL of methanol was purged with argon for 1 h and then a catalytic amount of sodium hydride (99%) was added. The resulting solution was irradiated with a 550-W Hanovia lamp equipped with a Pyrex filter for 10 min. The photolysate was neutralized using 1 g of ammonium chloride and the solution was concentrated under reduced pressure. Ether was added and the ethereal solution was washed with water, dried over magnesium sulfate, and concentrated under reduced pressure. The oil obtained was purified by thick layer chromatography using a 10% acetone–hexane mixture as the eluent. The only band isolated contained 265 mg (75%) of an equilibrium mixture of 2-hydroxy-3-methoxy-2,3,6-trimethyldihydrobenzofuran (**9a**, 79%) and 3-methoxy-3-(2-hydroxy-4-methylphenyl)-2-butanone (**9b**, 21%). Major tautomer: IR (neat) 2.90 μ; NMR ($CDCl_3$, 60 MHz) τ 8.54 (s, 6 H), 7.68 (s, 3 H), 6.89 (s, 3 H), 4.85

(s, 1 H, exchangeable with D_2O), and 3.5–2.8 (m, 3 H); UV (methanol) 281 nm (ϵ 2500). Minor treatment: IR (neat) 5.81 μ; NMR ($CDCl_3$, 60 MHz) τ 8.31 (s, 3 H), 7.88 (s, 3 H), 7.72 (s, 3 H), 6.70 (s, 3 H), 3.5–2.8 (m, 3 H), and 1.94 (s, 1 H, exchangeable with D_2O).

Anal. Calcd for $C_{12}H_{16}O_3$: C, 69.21; H, 7.74. Found: C, 69.34; H, 7.82.

The structure of this tautomeric mixture was further verified by the chemical degradation studies outlined below. A 200-mg sample of 2-hydroxy-3-methoxy-2,3,6-trimethyldihydrobenzofuran (**9a**) was dissolved in 20 mL of methanol which contained 2 drops of concentrated hydrochloric acid. The resulting solution was stirred at room temperature for 4 h and was then concentrated under reduced pressure. Ether was added to the residue and the ethereal layer was washed with water, dried over magnesium sulfate, and concentrated under reduced pressure. The resulting oil was purified by thick layer chromatography using a 10% acetone–hexane solution as the eluent to give 172 mg (94%) of 2,6-dimethyl-3-methoxymethylbenzofuran (**11**) as a colorless oil: IR (neat) 3.43, 6.12, 6.70, 7.85, 9.15, and 12.30 μ; NMR ($CDCl_3$, 60 MHz) τ 7.63 (s, 6 H), 6.72 (s, 3 H), 5.56 (s, 2 H), and 3.3–2.6 (m, 3 H); UV (methanol) 288 and 282 nm (ϵ 2925 and 3000).

Anal. Calcd for $C_{12}H_{14}O_2$: C, 75.76; H, 7.42. Found: C, 75.73; H, 7.46.

A solution containing 500 mg of 2-hydroxy-3-methoxy-2,3,6-trimethyldihydrobenzofuran (**9a**) in 15 mL of acetic acid containing 2 mL of 57% hydriodic acid was stirred at room temperature for 20 min. The reaction mixture was diluted with water and extracted with ether. The ethereal layer was washed with a saturated sodium bicarbonate solution, a 10% sodium thiosulfate solution, and water, and then dried over magnesium sulfate. The oil obtained after the removal of the solvent under reduced pressure was purified by thick layer chromatography using a 10% acetone–hexane mixture as the eluent. The major component isolated contained 340 mg (89%) of 2,3,6-trimethylbenzofuran (**10**): IR (neat) 3.43, 6.10, 6.71, 7.85, 11.64, and 12.39 μ; NMR ($CDCl_3$, 60 MHz) τ 7.92 (s, 3 H), 7.69 (s, 3 H), 7.60 (s, 3 H), and 3.2–2.7 (m, 3 H); UV (methanol) 291 and 283 nm (ϵ 2565 and 2815).

Anal. Calcd for $C_{11}H_{12}O$: C, 82.46; H, 7.55. Found: C, 82.52; H, 7.49.

Preparation and Irradiation of 4,4,7-Trimethyl-3-chromanone (24). A solution containing 1.6 mL of diisopropylamine in 75 mL of freshly distilled tetrahydrofuran was cooled to 0 °C and treated with 4.2 mL of a 2.4 M solution of *n*-butyllithium. The resulting solution was stirred at 0 °C for 20 min and 1.76 g of 4,7-dimethyl-3-chromanone (**8**) in 20 mL of tetrahydrofuran was added. After this solution was stirred at 0 °C for 30 min, 5 mL of methyl iodide was added. The solution was allowed to warm to room temperature and stirred at 25 °C for 12 h. The reaction mixture was diluted with ether, washed with a 10% hydrochloric acid solution and water, dried over magnesium sulfate, and concentrated under reduced pressure. The residual oil obtained was distilled to give 1.2 g (63%) of 4,4,7-trimethyl-3-chromanone (**24**): bp 80 °C (0.06 mm); IR (neat) 5.78, 6.77, 7.96, 8.58, 9.47, and 12.28 μ; NMR ($CDCl_3$, 60 MHz) τ 8.58 (s, 6 H), 7.72 (s, 3 H), 5.58 (s, 2 H), and 3.4–2.8 (m, 3 H); UV (methanol) 278 nm (ϵ 2020); *m/e* 190 (M^+), 175, 161, 147 (base), 133, 119, 91, and 77.

Anal. Calcd for $C_{12}H_{14}O_2$: C, 75.76; H, 7.42. Found: C, 75.70; H, 7.28.

Irradiation of 4,4,7-trimethyl-3-chromanone (**24**) under a variety of conditions led to the slow decomposition of the starting material but failed to produce any characterizable products.

Preparation of 4,7-Dimethyl-3-methoxychromene (25). A solution containing 2.8 g of potassium *tert*-butoxide in 50 mL of hexamethylphosphoramide in a thoroughly dry 100-mL round-bottom flask under nitrogen was cooled to 0 °C. To this solution was added 1.76 g of 4,7-dimethyl-3-chromanone (**8**) in 5 mL of hexamethylphosphoramide. After the resulting solution was stirred at 0 °C for 5 min, 2 mL of methyl fluorosulfonate was added and the reaction mixture was stirred for an additional 5 min at 0 °C. Ether was added and the ethereal solution was washed with several portions of water, dried over magnesium sulfate, and concentrated under reduced pressure. The crude oil obtained was purified by liquid–liquid chromatography[31] followed by distillation at 80 °C (0.03 mm) to give 1.1 g (58%) of 4,7-dimethyl-3-methoxychromene (**25**): IR (neat) 3.42, 6.20, 6.30, 6.68, 8.19, 8.83, 9.52, and 12.38 μ; NMR ($CDCl_3$, 60 MHz) τ 8.12 (t, 3 H, J = 1.5 Hz), 7.78 (s, 3 H), 6.43 (s, 3 H), 5.34 (q, 2 H, J = 1.5 Hz), and 3.5–3.0 (m, 3 H); UV (methanol) 302 and 272 nm (ϵ 4150 and 4900); *m/e* 190 (M^+), 175, 161, 147, (base), 105, 91, and 77.

Anal. Calcd for $C_{12}H_{14}O_2$: C, 75.76; H, 7.42. Found: C, 75,81; H, 7.64.

Irradiation of 4,7-Dimethyl-3-methoxychromene in Methanol. A solution containing 200 mg of 4,7-dimethyl-3-methoxychromene (**25**) in 175 mL of methanol was irradiated with a 550-W Hanovia lamp equipped with a Pyrex filter for 1 h. Removal of the solvent under reduced pressure followed by purification of the residual oil by thick layer chromatography using a 10% acetone–hexane mixture as the eluent gave 185 mg (79%) of 2,3-dimethoxy-3-(4-methyl-2-hydroxyphenyl)-1-butene (**26**): IR (neat) 3.03, 3.43, 6.13, 6.34, 6.91, 8.75, 10.47, and 12.38 μ; NMR ($CDCl_3$, 60 MHz) τ 8.33 (s, 3 H), 7.78 (s, 3 H), 6.79 (s, 3 H), 6.52 (s, 3 H), 5.87 (d, 1 H, J = 3.0 Hz), 5.68 (d, 1 H, J = 3.0 Hz), 3.5–3.1 (m, 3 H), and 1.77 (s, 1 H, exchangeable with D_2O); UV (methanol) 281 (shoulder) and 276 nm (ϵ 2620 and 2690); *m/e* 222 (M^+), 207, 190, 175, 159 (base), 147, 133, 115, 105, 91, and 77. In addition to the signals described above, the crude photolysate contained peaks at 7.75 (s), 6.41 (s), 5.6–6.0 (m), 4.89 (m), 4.18 (m), 3.1–3.5 (m, 3 H), and 1.68 (s, 1 H, exchanged with D_2O) which were assigned to 2-methoxy-3-(2-hydroxy-4-methylphenyl)-1,3-butadiene (**27**). This material was unstable on silica gel giving rise to 2,6-dimethyl-2-methoxy-3-methylene-2,3-dihydrobenzofuran (**29**): IR (neat) 3.40, 6.15, 6.25, 6.67, 7.81, 8.86, 10.58, 11.65, and 12.31 μ; NMR ($CDCl_3$, 60 MHz) τ 8.42 (s, 3 H), 7.66 (s, 3 H), 6.87 (s, 3 H), 4.92 (s, 1 H), 4.44 (s, 1 H), and 3.4–2.6 (m, 3 H).

Anal. Calcd for $C_{12}H_{14}O_2$: C, 75.76; H, 7.42. Found: C, 75.92; H, 7.58.

The structure of **26** was further verified by treatment with acidic methanol. A solution containing 50 mg of 2,3-dimethoxy-3-(2-hydroxy-4-methylphenyl)-1-butene (**26**) in 15 mL of methanol containing 3 drops of concentrated hydrochloric acid was stirred at room temperature for 30 min. The solution was concentrated under reduced pressure and diluted with ether. The ethereal solution was washed with water, dried over magnesium sulfate, and concentrated under reduced pressure to give 45 mg (90%) of an oil which was identified as 2,3,6-trimethyl-2,3-dimethoxy-2,3-dihydrobenzofuran (**28**): IR (neat) 3.38, 6.14, 6.24, 6.67, 7.25, 8.89, 10.56, 11.49, 12.44, and 13.08 μ; NMR ($CDCl_3$, 60 MHz) τ 8.52 (s, 3 H), 8.42 (s, 3 H), 7.65 (s, 3 H), 7.02 (s, 3 H), 6.68 (s, 3 H), and 3.4–2.8 (m, 3 H); UV (methanol) 285 and 279 nm (ϵ 2570 and 2780); *m/e* 222 (M^+), 207, 190, 175, 159 (base), 133, 91, and 77.

Anal. Calcd for $C_{13}H_{18}O_3$: C, 70.24; H, 8.16. Found: C, 70.42; H, 8.25.

If the above reaction was repeated by extending the reaction time to 5 h, no detectable quantity of 2,3,6-trimethyl-2,3-dimethoxy-2,3-dihydrobenzofuran (**28**) was obtained. The only product isolated was identified as 2,6-dimethyl-3-methoxymethylbenzofuran (**11**).

The structure of **28** was further verified by treatment with hydriodic acid. A 45-mg sample of 2,3,6-trimethyl-2,3-dimethoxy-2,3-dihydrobenzofuran (**28**) was dissolved in a mixture containing 4 mL of glacial acetic acid and 1 mL of 57% hydriodic acid. After stirring the resulting solution at room temperature for 20 min, the reaction mixture was diluted with water and extracted with ether. The ethereal extracts were washed with a saturated sodium bicarbonate solution followed by a 10% sodium thiosulfate solution and water. The organic phase was dried over magnesium sulfate and concentrated under reduced pressure. The residual oil obtained was chromatographed on a thick layer plate using a 10% acetone–hexane mixture as the eluent to give 23 mg (71%) of 2,3,6-trimethylbenzofuran (**10**).

Irradiation of 3-Methoxy-4,7-dimethylchromene in Benzene. A solution containing 200 mg of 3-methoxy-4,7-dimethylchromene (**25**) in 175 mL of benzene was purged with argon and irradiated with a 550-W Hanovia lamp equipped with a Pyrex filter for 3 h. The solvent was removed under reduced pressure leaving an oil which was purified by thick layer chromatography using a 10% acetone–hexane mixture as the eluent. The major band isolated contained 100 mg of 2,6-dimethyl-2-methoxy-3-methylene-2,3-dihydrobenzofuran (**29**), while the minor band contained 35 mg of an oil whose structure was assigned as 1-methoxy-2-oxa-5,7-dimethylbenzobicyclo[3.1.0]hexene (**30**) on the basis of its NMR spectrum: NMR ($CDCl_3$, 60 MHz) τ 9.45 (d, 1 H, J = 6.0 Hz), 8.81 (d, 1 H, J = 6.0 Hz), 8.45 (s, 3 H), 7.72 (s, 3 H), 6.48 (s, 3 H), and 3.4–2.6 (m, 3 H). The NMR spectrum of the crude photolysate also contained peaks at 7.75 (s), 6.41 (s), 6.0–5.6 (m), 4.89 (m), and 4.18 ppm (m) which are assigned to 2-methoxy-3-(2-hydroxy-4-methylphenyl)-1,3-butadiene (**27**). If the NMR sample was allowed to stand at room temperature for 2 weeks or stirred with silica gel for 3 h, the peaks due to 2-methoxy-3-(2-hydroxy-4-methylphenyl)-1,3-butadiene (**27**) disappeared and those peaks assigned to 2,6-dimethyl-2-methoxy-3-methylene-2,3-dihydrobenzofuran (**29**) were enhanced. When a solution of **29** was treated with acidic methanol it rearranged to give 2,6-dimethyl-3-methoxymethylbenzofuran (**11**) in 90% yield.

Preparation of 1-Phenyl-2-tetralone (32). The procedure of Weiss[32] was followed for the preparation of 1-phenyl-3,4-dihydronaphthalene: bp 135–140 °C (2 mm); IR (neat) 3.44, 6.28, 6.72, 6.95, 12.08, 12.93, 13.53, and 14.31 μ; NMR ($CDCl_3$, 60 MHz) τ 7.90–7.00

(m, 4 H), 4.02 (t, 1 H, J = 4.0 Hz), and 3.1–2.6 (m, 9 H).

A solution containing 24 g of the above 1-phenyl-3,4-dihydronaphthalene in 200 mL of chloroform was cooled to −10 °C and 25.6 g of *m*-chloroperbenzoic acid (85%) in 485 mL of chloroform was added dropwise over a period of 3.5 h. The solution was stirred at −10 °C for an additional 2 h and was then washed with a 2 M sodium hydroxide solution followed by water. The organic layer was dried over sodium sulfate and concentrated under reduced pressure to give 19.5 g (76%) of 1-phenyl-1,3-epoxy-3,4-dihydronaphthalene: mp 94–97 °C; IR (KBr) 3.54, 6.23, 6.92, 7.66, 8.65, 10.45, 11.06, 12.35, 12.78, 13.17, and 14.22 μ; NMR ($CDCl_3$, 60 MHz) τ 8.5–6.4 (m, 5 H) and 3.2–2.4 (m, 9 H).

A 19.0-g sample of 1-phenyl-1,2-epoxy-3,4-dihydronaphthalene was refluxed with 200 mL of 30% sulfuric acid solution for 3.5 h. The reaction mixture was cooled and extracted with ether. The ethereal extracts were washed with a saturated sodium bicarbonate solution and water, dried over magnesium sulfate, and concentrated under reduced pressure. The residual oil obtained was distilled to give 14 g (74%) of 1-phenyl-2-tetralone (**32**): bp 110–112 °C (0.05 mm) [lit.[23] bp 141–142 °C (0.5 mm)]; IR (neat) 5.80, 6.25, 6.71, 6.91, 8.72, 13.40, and 14.31 μ; NMR ($CDCl_3$, 60 MHz) τ 7.64–7.33 (m, 2 H), 7.14–6.87 (m, 2 H), 5.34 (s, 1 H), and 3.26–2.64 (m, 9 H); UV (methanol) 290 (shoulder), 272, 266, and 259 nm (ε 570, 850, 910, and 900).

Anal. Calcd for $C_{16}H_{14}O$: C, 86.45; H, 6.35. Found: C, 86.32; H, 6.29.

Preparation of 1-Phenyl-2-methoxy-3,4-dihydronaphthalene (34). To a solution containing 2.8 g of potassium *tert*-butoxide in 50 mL of hexamethylphosphoramide at 0 °C was added 1.92 g of 1-phenyl-2-tetralone (**32**) in 5 mL of hexamethylphosphoramide. The resulting solution was stirred at 0 °C for 5 min and 2 mL of methyl fluorosulfonate was added. After this solution was stirred at 0 °C for 5 min, ether was added and the ethereal layer was removed, washed with water, dried over magnesium sulfate, and concentrated under reduced pressure. The solid obtained was recrystallized from 95% ethanol to give 1.2 g (59%) of 1-phenyl-2-methoxy-3,4-dihydronaphthalene (**34**): mp 81–82 °C; IR (KBr) 6.14, 6.76, 7.35, 7.99, 9.52, 13.12, 13.68, and 14.16 μ; NMR ($CDCl_3$, 60 MHz) τ 7.68–6.87 (m, 4 H), 6.53 (s, 3 H), and 3.45–2.52 (m, 9 H); UV (methanol) 276 nm (ε 10 800); *m/e* 236 (M^+, base), 221, 193, 178, 115, 91, and 77.

Anal. Calcd for $C_{17}H_{16}O$: C, 86.40; H, 6.83. Found: C, 86.26; H, 6.83.

Irradiation of 1-Phenyl-2-methoxy-3,4-dihydronaphthalene in Methanol. A solution containing 200 mg of 1-phenyl-2-methoxy-3,4-dihydronaphthalene (**34**) in 160 mL of methanol was irradiated with a 550-W Hanovia lamp equipped with a Pyrex filter sleeve for 3.5 h. The solvent was removed under reduced pressure and the residual oil was purified by thick layer chromatography using a 10% acetone–hexane mixture to give 160 mg (70%) of 1-phenyl-2,2-dimethoxy-1,2,3,4-tetrahydronaphthalene (**35**): IR (neat) 3.38, 6.24, 6.67, 6.88, 8.90, 9.04, 9.45, 11.15, 13.46, and 14.27 μ; NMR ($CDCl_3$, 100 MHz) τ 8.02 (t, 2 H, J = 8 Hz), 7.03 (t, 2 H, J = 8 Hz), 6.81 (s, 6 H), 5.64 (s, 1 H), and 3.2–2.6 (m, 9 H); UV (methanol) 272 and 263 nm (ε 440 and 650); *m/e* 236 (base), 221, 205, 191, 178, 105, 91, and 77.

Anal. Calcd for $C_{18}H_{20}O_2$: C, 80.56; H, 7.51. Found: C, 80.38; H, 7.46.

This same material was formed when the irradiation of **34** was carried out in the presence of 1 g of sodium bicarbonate in 150 mL of methanol. A control experiment showed that 1-phenyl-2-methoxy-3,4-dihydronaphthalene (**34**) was stable in the dark in the presence of methanol which contained formic acid.

The structure of **35** was further verified by hydrolysis to 1-phenyl-2-tetralone. A solution containing 100 mg of 1-phenyl-2,2-dimethoxy-1,2,3,4-tetrahydronaphthalene (**35**) in 25 mL of methanol was thoroughly deaerated with argon. To this solution was added 5 mL of a 10% hydrochloric acid solution and the resulting solution was stirred at room temperature for 2 h. The reaction mixture was diluted with ether, washed with water, dried over magnesium sulfate, and concentrated under reduced pressure to give 70 mg (84%) of 1-phenyl-2-tetralone (**32**).

Irradiation of 1-Phenyl-2-methoxy-3,4-dihydronaphthalene in Benzene. A solution containing 150 mg of 1-phenyl-2-methoxy-3,4-dihydronaphthalene (**34**) in 160 mL of benzene was irradiated using a 550-W Hanovia lamp equipped with a Pyrex filter sleeve for 20 h. The solvent was removed under reduced pressure and the residual oil was subjected to thick layer chromatography using a 10% acetone–hexane mixture as the eluent. The only band isolated contained 87 mg (58%) of 1-methoxy-5-phenyl-3,4-benzobicyclo-[3.1.0]hexene (**36**): IR (neat) 3.43, 6.27, 7.94, 8.71, 9.46, 10.97, 12.31, 13.12, and 14.30 μ; NMR ($CDCl_3$, 60 MHz) τ 9.19 (d, 1 H, J = 5.0 Hz), 7.98 (d, 1 H, J = 5.0 Hz), 6.73 (s, 3 H), 6.22 (s, 2 H), and 3.1–2.5 (m, 9 H); *m/e* 236 (M^+), 205 (base), 178, 159, 115, 91, and 77.

Anal. Calcd for $C_{17}H_{16}O$: C, 86.40; H, 6.83. Found: C, 86.34; H, 6.81.

The structure of the photoproduct was further verified by chemical degradation to 4-phenyl-2-tetralone. To a solution containing 80 mg of 1-methoxy-5-phenyl-3,4-benzobicyclo[3.1.0]hexene (**36**) in 3 mL of glacial acetic acid was added 0.5 mL of hydriodic acid (57%). The resulting solution was heated at reflux for 35 min. The reaction mixture was cooled, diluted with water, and extracted with ether. The ethereal layer was washed with a saturated sodium bicarbonate solution, a 10% sodium thiosulfate solution, and water. After drying over magnesium sulfate, the ethereal solution was concentrated under reduced pressure to give 37 mg (49%) of 4-phenyl-2-tetralone (**37**): IR (neat) 5.81, 6.22, 6.70, 6.90, 8.11, 13.32, and 14.31 μ; NMR ($CDCl_3$, 60 MHz) τ 7.20 (d, 2 H, J = 6 Hz), 6.46 (s, 2 H), 5.64 (t, 1 H, J = 6 Hz), and 3.2–2.6 (m, 9 H). This material was identical in every respect with an authentic sample prepared by the method of Fine and Stern.[33]

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Registry No.—**8**, 24454-30-6; **9a**, 62815-84-3; **9b**, 62815-85-4; **10**, 7137-22-6; **11**, 62815-86-5; **24**, 62815-87-6; **25**, 62815-88-7; **26**, 62815-89-8; **27**, 62815-90-1; **28**, 62815-91-2; **29**, 62815-92-3; **30**, 62815-93-4; **32**, 14578-75-7; **34**, 62815-94-5; **35**, 62815-95-6; **36**, 62815-96-7; **37**, 14195-35-8; *m*-cresol, 108-39-4; ethyl acetoacetate, 141-97-9; 4,7-dimethylcoumarin, 14002-90-5; 4,7-dimethylchroman-3-ol, 24454-21-5; 1-phenyl-3,4-dihydronaphthalene, 7469-40-1; 1-phenyl-1,3-epoxy-3,4-dihydronaphthalene, 62815-97-8.

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Aminocyclitols. 35. Synthesis of Deoxystreptamines[1]

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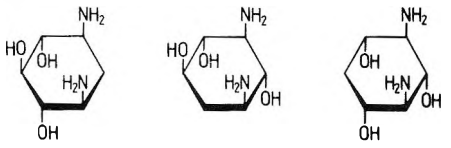
All three predicted positional isomers of deoxystreptamine have been synthesized. From the four disulfonates of cyclohexanepentols (**6**, **12a**, **14**, and **23a**) and the diepoxycyclohexanol (**24**), 2- (**1a**), 4- (**2a**), and 5-deoxystreptamine (**3a**) were obtained, together with the acetyl derivatives of four other diaminocyclohexanetriols (**9**, **15**, **28**, and **29**), by azidolysis or hydrazinolysis followed by catalytic reduction. Compounds **2a** and **3a** were also prepared starting from the suitably protected streptamine derivatives by deoxygenation via chlorination with sulfuryl chloride and successive hydrogenolysis. In addition, two triaminocyclohexanediols (**16** and **17**) were synthesized, which gave additional evidence on the structural elucidation of **15**.

In connection with the preceding paper,[2] synthesis of all the predicted deoxystreptamine isomers was carried out by azidolysis or hydrazinolysis and successive hydrogenation of dianhydro and disulfonate derivatives of cyclohexanepentols derived from *myo*-inositol, as well as by deoxygenation of the desired position of streptamine.



1a 2a 3a

2-Deoxystreptamine (**1a**), a common component of important aminocyclitol antibiotics,[3] has already been synthesized by several research groups.[4] (+)-4-Deoxystreptamine (**2a**) was first obtained from the antibiotic streptomycin in the course of the structural elucidation,[5] and, later, its optical antipode was synthesized from D-glucosamine.[6] On the other hand, synthesis of 5-deoxystreptamine (**3a**) has not been reported so far. The present synthetic procedure applied to labeled *myo*-inositol should lead to specifically labeled deoxystreptamines that are useful in studies on the biosynthesis of aminocyclitol antibiotics.

2-Deoxystreptamine (1a). On the basis of the previous results,[7] it was expected that hydrazinolysis of 1,5-di-*O*-tosyl-1,3,5/2,4-cyclohexanepentol, followed by hydrogenation, would give **1a** via the formation of the 1,3-hydrazino compound **7**. Therefore, the tri-*O*-acetyl derivative **6** was prepared by the following reaction sequence. Treatment of 4,5,6-tri-*O*-acetyl-1,3-di-*O*-tosyl-*myo*-inositol (**4**)[8] with sulfuryl chloride in pyridine gave tri-*O*-acetyl-5-chloro-5-deoxy-4,6-di-*O*-tosyl-*scyllo*-inositol (**5**) in 66% yield. Dechlorination of **5** was effected by treatment with tri-*n*-butyltin hydride in toluene in the presence of α,α'-azobis(isobutyronitrile),[9] and the corresponding deoxy compound **6** was obtained in 94% yield.[10]

Treatment of **6** with an excess of hydrazine in refluxing 2-methoxyethanol for 20 h, followed by catalytic hydrogenation with Raney nickel T-4[11] and conventional acetylation, gave a mixture of two penta-*N*,*O*-acetyl derivatives of diaminocyclohexanetriol that were resolved by chromatography on silica gel affording **1b** and **9** in 34 and 15% yields, respectively. Compound **1b** was identified with an authentic sample of tri-*O*-acetyl-(1,3/2,4,6)-4,6-diacetamido-1,2,3-cyclohexanetriol (penta-*N*,*O*-acetyl-2-deoxystreptamine)[12] by mixture melting point, IR, and ^{1}H NMR spectra. On the basis of ^{1}H NMR spectroscopy and the proposed reaction mechanism, **9** was assigned as tri-*O*-acetyl-(1,5/2,3,4)-2,4-diacetamido-1,3,5-cyclohexanetriol (penta-*N*,*O*-acetyl-5-deoxyepistreptamine). The ^{1}H NMR spectral data of the acetyl methyl protons listed in Table I[13] showed the presence of one axial acetoxy group and two magnetically equivalent equatorial acetoxy and two magnetically equivalent equatorial acetamido groups, indicating that **9** possessed the symmetrical structure. The signals due to ring methine protons were interpretable by a first-order method. Thus, 2-proton double triplets having 4.5-, 11-, and 11-Hz splittings at δ 4.96 were ascribed to H-1 and H-5, and a 1-proton triplet having 2.5-Hz splitting at δ 5.39 to H-3, establishing the 1,5/2*N*,3,4*N* stereochemistry. Formation of **1b** as the major product suggested that hydrazinolysis of **6** proceeded via initial cleavage of the acetate esters and intervention of an epoxide intermediate leading to the 1,3-hydrazino compounds such as **7** and **8**.

4-Deoxystreptamine (2a). This compound was first obtained by azidolysis of the dimesylate **12a** of cyclohexanepentol, followed by hydrogenation. Thus, readily available 3,4-*O*-cyclohexylidene-1,3,4/2,5-cyclohexanepentol (**10a**)[14] was converted into the corresponding trimesylate **10b** in the usual manner in 75% yield. Removal of the cyclohexylidene group of **10b** was accomplished by refluxing in 80% aqueous acetic acid for 20 min to give 1,2,5-tri-*O*-mesyl-1,3,4/2,5-cyclohexanepentol (**11**) in 73% yield. On the other hand, extension of the reaction time to 2.5 h resulted in partial displacement of the 5-mesyloxy function by an acetate ion giving the 1,2-dimesylate **12a** in 13% yield, along with **11** (53% yield). Compound **12a** was readily isolable as the triacetate **12b**[15] in 25% yield, after separation of **11** (52% yield) by crystallization.

Treatment of **12a** with an excess of sodium azide in refluxing 90% aqueous 2-methoxyethanol for 24 h gave a mixture of diazidocyclohexanetriols, which was not purified, but hydrogenated with Raney nickel followed by acetylation. The product thus obtained was separated by fractional crystallization to afford tri-*O*-acetyl-(1,3,5/2,4)-3,5-diacetamido-1,2,4-cyclohexanetriol (penta-*N*,*O*-acetyl-4-deoxystreptamine) (**2b**) and tri-*O*-acetyl-(1,4,5/2,3)-4,5-diacetamido-1,2,3-cyclohexanetriol (**15**) in 22 and 24% yields, respectively. Compound **2b** was shown to be identical with an optically active authentic sample[6] in all respects except optical activity. The assigned structure of **15** was confirmed on the basis of the following evidence. Compound **11** was treated under identical reaction conditions to give the known di-*O*-acetyl-(1,3/2,4,6)-2,4,6-triacetamido-1,3-cyclohexanediol (**16**)[16] and the hitherto unknown di-*O*-acetyltriacetamidocyclohexanediol (**17**) in 5 and 27% yields, and, when *N*,*N*-dimethylformamide was used instead as the reaction solvent, in 24 and 12% yields, respectively. The mechanism of azidolysis of **12a** might be considered as follows. The 1-mesyloxy group is initially replaced by an azide ion by an S_N2 mechanism, and then an intermediary epoxide formed on C-2 and C-3 is opened by an azide ion to give two azido compounds having 1,3*N*,5*N*/2,4 and 1,4*N*,5*N*/2,3 stereochemistries. A similar mechanism may be possible in the case of **11**, after replacement of the axially

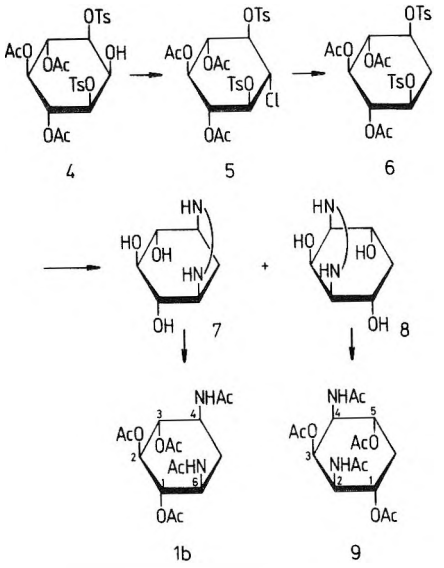


Figure 1. Synthesis of penta-*N,O*-acetyl-2-deoxystreptamine (**1b**) and -5-deoxyepistreptamine (**9**).

Table I. Chemical Shifts (δ) of Acetyl Methyl Protons of Penta-*N,O*-acetyldiaminocyclohexanetriols and -triaminocyclohexanediols in Dimethyl-d_6 Sulfoxide

Registry no.	Compd	Acetamido Ex	Acetamido Ax	Acetoxy Ex	Acetoxy Ax
62776-25-4	**2b**	1.73 1.75		1.88 1.93 1.97	
62708-18-3	**3b**	1.77[a]		1.92 1.98[a]	
62776-26-5	**9**	1.80[a]		2.04[a]	2.18
62776-27-6	**15**	1.78	1.94	1.94 2.02	2.10
62777-55-3	**16**	1.76 1.78[a]		1.92[a]	
62708-19-4	**17**	1.74 1.82	1.90	1.95	2.12
25850-50-4	**28**	1.78[a]		1.93[a]	2.13
62708-20-7	**29**	1.82	1.90	1.94 1.99	2.08

[a] Singlet for two methyl groups.

oriented 5-mesyloxy group by an azido group via an epoxide intermediate. The stereochemical assignments are supported by the ^{1}H NMR data which indicate that both **15** and **17** have one axial acetoxy group and one axial acetamido group in the favored conformations. Therefore, the stereochemistry of **17** is also assigned as 1,2/3*N*,4*N*,6*N*.

Alternatively, the selective synthesis of **2b** was developed by hydrazinolysis of the 2,5-dimesylate of 1,2,5/3,4-cyclohexanepentol. The dimesylate possessing the desired stereochemistry was available from **10b**. Thus, reaction of **10b** with sodium benzoate in *N,N*-dimethylformamide at 90 °C for 4 days resulted in preferential displacement of the 1-mesyloxy group by a benzoate group, affording 1-*O*-benzoyl-3,4-*O*-cyclohexylidene-2,5-di-*O*-mesyl-1,2,5/3,4-cyclohexanepentol (**13**) in 29% yield.[17] Treatment with aqueous acetic acid gave the corresponding de-*O*-cyclohexylidene derivative (**14**) in 84% yield. Hydrazinolysis of **14** in the usual manner, followed by hydrogenation and acetylation, gave **2b** as the sole crystalline product in 38% yield. This reaction seems to involve the selective formation of the 1,3-hydrazino compound **18**.

5-Deoxystreptamine (3a). Synthesis of the title compound was first attempted by hydrazinolysis of 1,5-di-*O*-tosyl-1,5/2,3,4-cyclohexanepentol derivative **23a**. Thus, chlorination

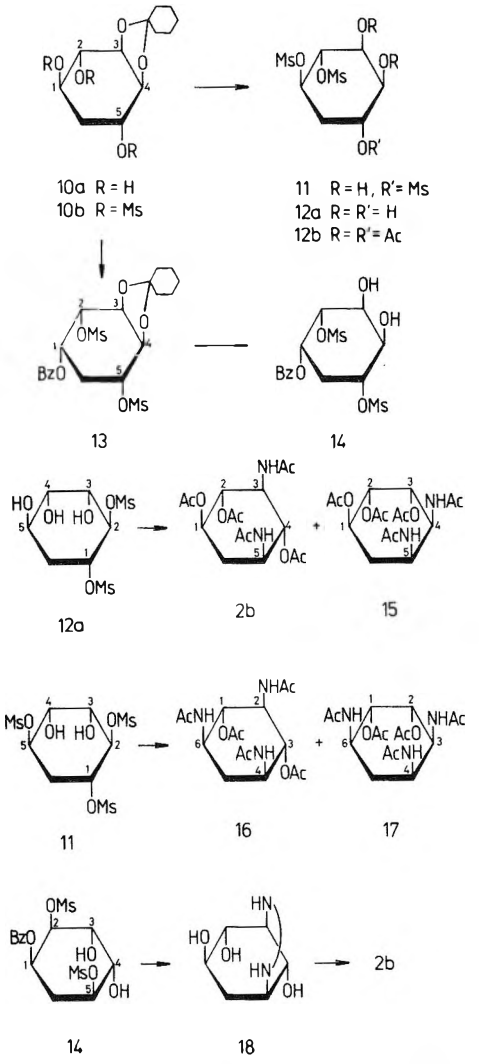


Figure 2. Synthesis of penta-*N,O*-acetyl-4-deoxystreptamine (**2b**) and the acetyl derivatives of diaminocyclohexanetriol (**15**) and two triaminocyclohexanediols (**16** and **17**).

of 1-*O*-benzoyl-2,3-*O*-cyclohexylidene-4,6-di-*O*-tosyl-*myo*-inositol (**19**)[18] with sulfuryl chloride in pyridine gave the chlorodeoxy compound **20**[18] in 91% yield, which was hydrogenated with tri-*n*-butyltin hydride, affording the corresponding deoxy compound **21** in 79% yield. De-*O*-cyclohexylidenation gave 2-*O*-benzoyl-1,5-di-*O*-tosyl-1,5/2,3,4-cyclohexanepentol (**23a**) in 48% yield. Alternatively, the di-*O*-acetyl derivative **23b** was obtained, in a yield of 94%, by dechlorination of 1,2-di-*O*-acetyl-3-*O*-benzoyl-5-chloro-5-deoxy-4,6-di-*O*-tosyl-*neo*-inositol (**22**)[18] in the usual way.

On hydrazinolysis followed by hydrogenation and acetylation, **23a** gave a complex mixture of tri-*O*-acetyldiacetamidocyclohexanetriols, from which **3b**, **28**, and **29** were isolated by chromatography on silica gel in 0.6, 42, and 8% yields, respectively. Under these conditions, substitution of the two tosyloxy groups was assumed to proceed via an epoxide intermediate, leading to the 1,3-hydrazino compounds **25** and **26** and the 1,4-hydrazino **27a** or the dihydrazino compound **27b**. Therefore, the three diaminocyclohexanetriols formed may possess 1,2,3/4*N*,6*N*, 1,3,5/2*N*,4*N*, and 1,3,4/2*N*,5*N* stereochemistries, and they can be differentiated from each other by comparing the spectral patterns of the signals due to acetyl methyl protons in the ^{1}H NMR spectra. The ^{1}H NMR data showed that both **3b** and **28** have symmetrical structures, and that the latter has one axial acetoxy group, whereas the ^{1}H NMR spectrum of **29** revealed five peaks due to acetyl methyl protons, indicating that **29** has an unsymmetrical structure. Furthermore, in the ^{1}H NMR spectrum

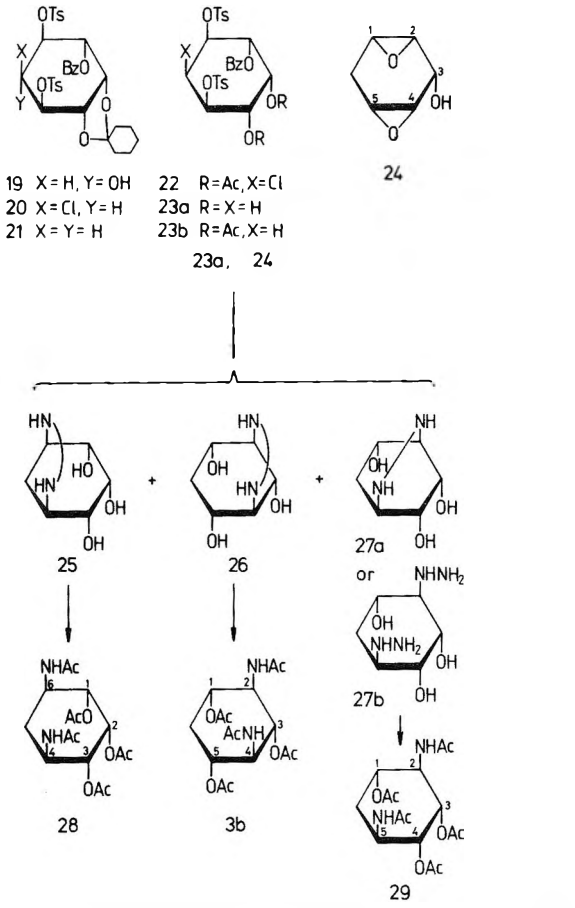


Figure 3. Synthesis of penta-*N,O*-acetyl-5-deoxystreptamine (**3b**) and the acetyl derivatives of two diaminocyclohexanetriols (**28** and **29**).

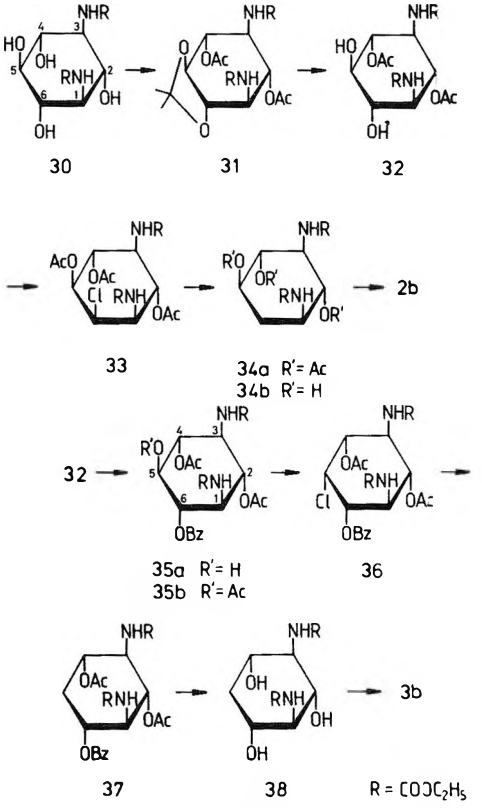


Figure 4. Deoxygenation of suitably protected streptamine derivatives.

of **28**, 2-proton double doublets having 2.5- and 11-Hz splittings at δ 4.91 are ascribed to H-1 and H-3, and a 1-proton narrow triplet at δ 5.69 ascribable to the equatorial methine proton was shown to be coupled with H-1 and H-3, being consistent with the proposed structure. Therefore, their structures were assigned as those formulated in Figure 3.

Under identical reaction conditions, **23b** was expected to give the same results as **23a** did. In order to avoid the complexity in the isolation of the reaction products, 1,2:4,5-dianhydro-1,2,3,4,5/0-cyclohexanepentol (**24**) derived by treating **23b** with methanolic sodium methoxide was subjected to the hydrazinolysis. After hydrogenation and acetylation, products were resolved by column chromatography giving **28** and **29** in 23 and 11% yields, respectively, along with a trace of **3b**.

Subsequently, for the purpose of obtaining **2a** as well as **3a** in large quantity, deoxygenation of the desired position of streptamine was studied using suitably protected derivatives. *N,N'*-Diethoxycarbonylstreptamine (**30**), obtainable by treating streptamine with ethyl chloroformate in basic solution, was allowed to react with 2,2-dimethoxypropane in *N,N*-dimethylformamide in the presence of *p*-toluenesulfonic acid, giving the *O*-isopropylidene derivative, which upon direct acetylation afforded di-*O*-acetyl-*N,N'*-diethoxycarbonyl-5,6-*O*-isopropylidenestreptamine (**31**) in 50% yield. Removal of the isopropylidene group gave 2,4-di-*O*-acetyl-*N,N'*-diethoxycarbonylstreptamine (**32**) in 81% yield.

Chlorination of **32** with sulfuryl chloride in pyridine proceeded selectively to give rise to a sole chlorodeoxy compound that was isolated as the triacetate **33** in 57% yield. The ^{1}H NMR spectrum of **33** revealed three peaks due to three acetoxy groups, indicating that **33** had the unsymmetrical structure, and that the chlorine atom was located on C-6. Hydrogenation of **33** with tri-*n*-butyltin hydride in the usual manner gave the tri-*O*-acetyl-*N,N'*-diethoxycarbonyl-4-deoxystreptamine (**34a**) in 82% yield, which was de-O-acylated with methanolic ammonia, affording the *N,N'*-diethoxycarbonyl derivative **34b** in 82% yield. The structure of **34b** was established by converting it into **2b** by hydrolysis with 6 M hydrochloric acid followed by acetylation.

Since the 6-hydroxyl group of **32** was found to be preferentially displaced by a chloride ion, protection of the 6 position was carried out by selective benzoylation, thus affording the 6-*O*-benzoyl derivative **35a** in 40% yield. The tri-*O*-acetyl derivative **35b** exhibited three peaks attributable to three acetoxy groups by ^{1}H NMR analysis, confirming the presence of the benzoyloxy group on C-6. Treatment of **35a** with sulfuryl chloride in pyridine gave a single chlorodeoxy compound **36** in 62% yield, which was subsequently dechlorinated with tri-*n*-butyltin hydride affording the corresponding deoxy compound **37** in 75% yield. De-O-acylation of **37** gave *N,N'*-diethoxycarbonyl-5-deoxystreptamine (**38**) in 73% yield, the structure of which was further established by converting it into **3b** in the usual manner.

Experimental Section[19]

1,2,3-Tri-*O*-acetyl-5-chloro-5-deoxy-4,6-di-*O*-tosyl-*scyllo*-inositol (5). To a stirred solution of 4,5,6-tri-*O*-acetyl-1,3-di-*O*-tosyl-*myo*-inositol (**4**)[8] (15 g) in dry pyridine (350 mL), sulfuryl chloride (7.9 mL, 4 equiv) was added dropwise at −10 to −20 °C for over 5 min. After having been stirred at −15 °C for 1 h, the solution was allowed to stand in a refrigerator overnight. The reaction mixture was evaporated to give a crystalline residue which was pulverized with ethanol and collected by filtration. The crude crystals were recrystallized from chloroform–ethanol to give 10.2 g (66%) of **5**: mp 222–224 °C; ^{1}H NMR ($CDCl_3$) δ 1.97 (s, 9, 3 OAc), 2.45 (s, 6, 2 tosyl CH_3).

Anal. Calcd for $C_{26}H_{29}ClO_{12}S_2$: C, 49.32; H, 4.62. Found: C, 49.32; H, 4.54.

Tri-*O*-acetyl-1,5-di-*O*-tosyl-1,3,5/2,4-cyclohexanepentol (6). To a solution of **5** (1 g) in dry toluene (60 mL) were added tri-*n*-butyltin hydride[20] (1 mL) and α,α'-azobis(isobutyronitrile) (10 mg), and the mixture was heated at 90 °C for 2 h under a nitrogen atmo-

sphere. The reaction mixture was evaporated to leave a crystalline residue, which was crystallized from chloroform–ethanol to give 0.89 g (94%) of **6**: mp 201–203 °C; ^{1}H NMR (Me_2SO-d_6) δ 1.70 (s, 6) and 1.90 (s, 3) (OAc), 2.48 (s, 6, 2 tosyl CH_3).

Anal. Calcd for $C_{26}H_{30}O_{12}S_2$: C, 52.17; H, 5.05; S, 10.71. Found: C, 52.39; H, 5.00; S, 10.47.

Tri-*O*-acetyl-(1,3/2,4,6)-4,6-diacetamido-1,2,3-cyclohexanetriol (Penta-*N,O*-acetyl-2-deoxystreptamine) (1b) and -(1,5/2,3,4)-2,4-diacetamido-1,3,5-cyclohexanetriol (Penta-*N,O*-acetyl-5-deoxyepistreptamine) (9). A mixture of **6** (2 g), anhydrous hydrazine (10 mL), and 2-methoxyethanol (20 mL) was heated under reflux for 20 h, and then evaporated to dryness. The residue was dissolved in water (20 mL) and treated with Amberlite IRA-400 (OH^-). The solution was then hydrogenated in a Parr shaker apparatus in the presence of Raney nickel T-4[11] under pressure (3.4 kg/cm^2) at room temperature overnight. The catalyst was removed by filtration and the filtrate was evaporated to dryness. The solid residue was treated with acetic anhydride (10 mL) and pyridine (10 mL) under stirring at room temperature for 2 days. The reaction mixture was evaporated to leave a partly crystalline residue that was chromatographed on silica gel (50 g) with chloroform–methanol (15:1, v/v). The fractions were combined according to the results of TLC in chloroform–methanol (10:1, v/v). The fractions (R_f 0.46) were evaporated and the residual crystals were recrystallized from ethanol to give 0.19 g (15%) of **9**: mp 246–247 °C; ^{1}H NMR (Me_2SO-d_6) δ 4.27 (br dt, 2, $J_{2,3} = J_{3,4} = 2.5$ Hz, $J_{1,2} = J_{4,5} = 11$ Hz, $J_{2,NH} = J_{4,NH} = 8.5$ Hz, H-2 and H-4), 4.96 (dt, 2, $J_{1,6ax} = J_{5,6ax} = 11$ Hz, $J_{1,6eq} = J_{5,6eq} = 4.5$ Hz, H-1 and H-5), 5.39 (t, 1, H-3), 8.12 (d, 2, 2 NHAc); other data, see Table I.

Anal. Calcd for $C_{16}H_{24}N_2O_8$: C, 51.60; H, 6.50; N, 7.52. Found: C, 51.32; H, 6.40; N, 7.37.

The fractions (R_f 0.40) were evaporated to give crystals that were recrystallized from ethanol affording 0.43 g (34%) of **1b**: mp 299–300 °C. This compound was identified with an authentic sample[12] by mixture melting point and by comparison of IR and ^{1}H NMR spectra.

3,4-*O*-Cyclohexylidene-1,2,5-tri-*O*-mesyl-1,3,4/2,5-cyclohexanepentol (10b). To a stirred solution of 3,4-*O*-cyclohexylidene-1,3,4/2,5-cyclohexanepentol (**10a**)[13] (1 g) in dry pyridine (20 mL) was added mesyl chloride (2 mL) under ice cooling, and the mixture was allowed to stand in a refrigerator for 2 days. The mixture was poured into ice water, and the resulting crystals were collected and recrystallized from chloroform to give 1.46 g (75%) of **10b**: mp 184.5–185.5 °C; ^{1}H NMR ($CDCl_3$) δ 3.14 (s, 3) and 3.22 (s, 6) (mesyl CH_3).

Anal. Calcd for $C_{15}H_{26}O_{11}S_3$: C, 37.65; H, 5.48; S, 20.10. Found: C, 37.58; H, 5.25; S, 19.89.

1,2,5-Tri-*O*-mesyl-1,3,4/2,5-cyclohexanepentol (11). A mixture of **10b** (2 g) and 80% aqueous acetic acid (40 mL) was refluxed for 20 min, and the reaction mixture was then evaporated to give a syrup that was crystallized from ethanol affording 1.2 g (73%) of **11**: mp 162–163 °C.

Anal. Calcd for $C_9H_{18}O_{11}S_3$: C, 27.15; H, 4.55; S, 24.14. Found: C, 27.61; H, 4.55; S, 23.84.

1,2-Di-*O*-mesyl-1,3,4/2,5-cyclohexanepentol (12a). (a) A mixture of **10b** (2 g) and 80% aqueous acetic acid (40 mL) refluxed for 3 h and then was evaporated to leave a syrup. Crystallization from chloroform–ethanol gave 0.9 g (53%) of **11**. The mother liquor was concentrated to a syrup that crystallized spontaneously to give 0.17 g (13%) of **12a**: mp 136–137 °C.

Anal. Calcd for $C_8H_{16}O_9S_2$: C, 29.99; H, 5.05; S, 20.01. Found: C, 29.90; H, 5.24; S, 19.73.

Compound **12a** (0.1 g) was treated with acetic anhydride (1 mL) in pyridine (1 mL) at room temperature overnight, and the mixture was poured into ice–water giving crystals. Recrystallization from chloroform–ethanol gave 0.1 g (71%) of the triacetate (**12b**): mp 193–195 °C; ^{1}H NMR ($CDCl_3$) δ 2.07 (s, 3) and 2.15 (s, 6) (OAc), 3.10 (s, 3) and 3.12 (s, 3) (mesyl CH_3).

Anal. Calcd for $C_{14}H_{22}O_{12}S_2$: C, 37.66; H, 4.97; S, 14.36. Found: C, 37.43; H, 5.23; S, 14.66.

(b) Compound **10b** (3.6 g) was treated with refluxing 80% aqueous acetic acid (70 mL) for 2.5 h. After **11** (1.6 g, 52%) had been isolated by crystallization from chloroform–ethanol, the mother liquor was concentrated and the residue was acetylated in the usual manner to give 0.84 g (24%) of **12b**: mp 189–192 °C.

1-*O*-Benzoyl-3,4-*O*-cyclohexylidene-2,5-di-*O*-mesyl-1,2,5/3,4-cyclohexanepentol (13). A mixture of **10b** (3.2 g) and sodium benzoate (5 g) in *N,N*-dimethylformamide (30 mL) was heated at 80–90 °C with stirring for 100 h. Insoluble material was removed by filtration and the filtrate was evaporated to dryness. The residue was extracted with hot 2-butanone (30 mL) and the extract was evaporated to leave a syrup that was chromatographed on silica gel (80 g) with benzene–2-butanone (15:1, v/v). The main fractions were combined and evaporated to give crystals that were recrystallized from ethanol giving 1 g (29%) of **13**: mp 157.5–159 °C; ^{1}H NMR ($CDCl_3$) δ 2.48 (t, 2, J = 6 Hz, H-6 and H-6′), 3.06 (s, 3) and 3.17 (s, 3) (mesyl CH_3), 4.54 (t, 1) and 4.71 (t, 1) (J = 5.5 Hz, H-3 and H-4), 5.02 (t, 1, H-5), 5.27 (dd, 1, $J_{1,2}$ = 3 Hz, H-2), 5.65 (dt, 1, H-1).

Anal. Calcd for $C_{21}H_{28}O_{10}S_2$: C, 49.99; H, 5.59; S, 12.71. Found: C, 49.70; H, 5.56; S, 12.35.

1-*O*-Benzoyl-2,5-di-*O*-mesyl-1,2,5/3,4-cyclohexanepentol (14). Compound **13** (0.4 g) was treated with refluxing 80% aqueous acetic acid (10 mL) for 1 h and then the reaction mixture was evaporated to dryness. The crystalline residue was recrystallized from ethanol to give 0.28 g (84%) of **14**: mp 194–195 °C.

Anal. Calcd for $C_{15}H_{20}O_{10}S_2$: C, 42.45; H, 4.75; S, 15.11. Found: C, 42.53; H, 4.73; S, 15.28.

Tri-*O*-acetyl-(1,3,5/2,4)-3,5-diacetamido-1,2,4-cyclohexanetriol (Penta-*N,O*-acetyl-4-deoxystreptamine) (2b) and -(1,4,5/2,3)-4,5-diacetamido-1,2,3-cyclohexanetriol (Penta-*N,O*-acetyl-3-deoxy-*allo*-inosadiamine-1,2) (15). (a) A mixture of **12a** (0.57 g), sodium azide (0.5 g), and 90% aqueous 2-methoxyethanol (20 mL) refluxed for 24 h and then was evaporated to dryness. The residual solid was treated with acetic anhydride (10 mL) and pyridine (15 mL) at room temperature overnight. Insoluble material was removed by filtration and the filtrate was evaporated to leave a syrup that was dissolved in chloroform and passed through a short alumina column. The chloroform solution was evaporated to give a syrup that was hydrogenated in ethanol solution (20 mL) as described above for the preparation of **1b** and **9**. The products were acetylated in the usual way to give a mixture of the penta-*N,O*-acetyldiaminocyclohexanetriols. Fractional crystallization from both ethanol–ether and ethanol–ethyl acetate gave 0.11 g (22%) of **2b**, mp 310–311 °C (dec), and 0.12 g (24%) of **15**, mp 246 °C: ^{1}H NMR data, see Table I.

Anal. Calcd for $C_{16}H_{24}N_2O_8$: C, 51.60; H, 6.50; N, 7.52. Hemihydrate: C, 50.39; H, 6.61; N, 7.34. Found for **2b**: C, 51.78; H, 6.48; N, 7.39, and for **15**: C, 50.91; H, 6.47; N, 7.26.

(b) A mixture of **14** (0.55 g), anhydrous hydrazine (2 mL), and 2-methoxyethanol (20 mL) was refluxed for 18 h, and then processed as described above for the preparation of **1b** and **9**. The crude products were fractionally crystallized from ethanol to give 0.18 g (38%) of **2b**, mp 290–293 °C dec. It was identical with the compound obtained above, and both were identified with an authentic optically active sample[6] by comparison of IR and ^{1}H NMR spectra in all respects except optical activity.

Di-*O*-acetyl-(1,3/2,4,6)-2,4,6-triacetamido-1,3-cyclohexanediol (Penta-*N,O*-acetyl-5-amino-2,5-dideoxystreptamine) (16) and -(1,2/3,4,6)-3,4,6-triacetamido-1,2-cyclohexanediol (Penta-*N,O*-acetyl-3-deoxy-*allo*-inosatriamine-1,2,4) (17). (a) A mixture of **11** (1 g), sodium azide (1 g), and 90% aqueous 2-methoxyethanol (50 mL) refluxed for 24 h and then was processed as described for the preparation of **2b** and **15**. The products were fractionally crystallized from ethanol–ethyl acetate to give 0.043 g (5%) of **16**, mp 310 °C dec (lit.[16] 355–357 °C dec), and 0.25 g (27%) of **17**, mp 252–253 °C: ^{1}H NMR (Me_2SO-d_6) for **16**, δ 4.89 (t, 2, $J_{1,2(2,3)} = J_{1,6(3,4)} = 10.5$ Hz, H-1 and H-3), 7.88 (d, 3, J = 8.5 Hz, three amido protons); for other data, see Table I.

Anal. Calcd for $C_{16}H_{25}N_3O_7$: C, 51.74; H, 6.79; N, 11.31. Hemihydrate: C, 50.52; H, 6.89; N, 11.05. Found for **16**: C, 51.94; H, 6.76; N, 11.43. Found for **17**: C, 51.20; H, 7.10; N, 10.69.

(b) A mixture of **11** (2 g), sodium azide (2 g), and 90% aqueous *N,N*-dimethylformamide (80 mL) was refluxed for 24 h. The reaction mixture was processed as described for the preparation of **2b** and **15**, and the products were fractionally crystallized from ethanol–ethyl acetate to give 0.46 g (24%) of **16** and 0.23 g (12%) of **17**.

1-*O*-Benzoyl-5-chloro-2,3-*O*-cyclohexylidene-5-deoxy-4,6-di-*O*-tosyl-*neo*-inositol (20). To a solution of 1-*O*-benzoyl-2,3-*O*-cyclohexylidene-4,6-di-*O*-tosyl-*myo*-inositol (**19**)[18] (3 g) in dry pyridine (90 mL), sulfuryl chloride (1.45 mL, 4 molar equiv) was added dropwise at −15 °C. After having been kept in a refrigerator overnight, the reaction mixture was evaporated and the residue was crystallized from chloroform–ethanol to give 2.8 g (91%) of **20**, mp 184–185 °C (lit.[18] 180–181 °C). This compound was identical with an authentic sample[18] in all respects.

2-*O*-Benzoyl-3,4-*O*-cyclohexylidene-1,5-di-*O*-tosyl-1,5/2,3,4-cyclohexanepentol (21). A mixture of **20** (0.5 g), tri-*n*-butyltin hydride (1 mL), and α,α′-azobis(isobutyronitrile) (10 mg) in dry toluene (25 mL) was heated at 90 °C under a nitrogen atmosphere for 2 h. The reaction mixture was evaporated to dryness and the crude product was crystallized from chloroform–ethanol to give 0.38 g (79%) of **21**: 174–177 °C; ^{1}H NMR ($CDCl_3$) δ 2.27 (s, 3) and 2.48 (s, 3) (tosyl CH_3), 5.12 (td, 1, $J_{1,6eq} = 4$ Hz, $J_{1,2} = J_{1,6ax} = 8$ Hz, H-1), 5.56 (dd, 1, $J_{2,3}$ =

3 Hz, H-3).

Anal. Calcd for $C_{33}H_{36}O_{10}S_2$: C, 60.35; H, 5.53; S, 9.76. Found: C, 59.93; H, 5.53; S, 10.00.

2-*O*-Benzoyl-1,5-di-*O*-tosyl-1,5/2,3,4-cyclohexanepentol (23a). A mixture of **21** (2.72 g) and 80% aqueous acetic acid (140 mL) refluxed for 3 h. The reaction mixture was evaporated to dryness and the residue was crystallized from methanol to give 1.13 g (48%) of **23a**: mp 156–157 °C.

Anal. Calcd for $C_{27}H_{28}O_{10}S_2$: C, 56.24; H, 4.89; S, 11.12. Found: C, 56.15; H, 5.11; S, 10.87.

2,3-Di-*O*-acetyl-4-*O*-benzoyl-1,5-di-*O*-tosyl-1,5/2,3,4-cyclohexanepentol (23b). 1,2-Di-*O*-acetyl-3-*O*-benzoyl-5-chloro-5-deoxy-4,6-di-*O*-tosyl-*neo*-inositol (**22**)[18] (1.5 g) was treated with tri-*n*-butyltin hydride in dry toluene as described above for **20**. The product was crystallized from chloroform–ethanol to give 1.3 g (94%) of **23b**: mp 158–161 °C; ^{1}H NMR ($CDCl_3$) δ 1.83 (s, 3) and 2.16 (s, 3) (OAc), 2.32 (s, 3) and 2.49 (s, 3) (tosyl CH_3). This compound was identical with the diacetate derived from **23a**.

Anal. Calcd for $C_{31}H_{32}O_{12}S_2$: C, 56.35; H, 4.88; S, 9.71. Found: C, 56.50; H, 5.03; S, 9.57.

1,2:4,5-Dianhydro-1,2,3,4,5/0-cyclohexanepentol (24). To a solution of **23b** (3 g) in chloroform (20 mL) and methanol (15 mL) was added 1 M methanolic sodium methoxide (14 mL, 3 molar equiv), and the mixture was allowed to stand at room temperature overnight. The mixture was evaporated to dryness and the residue was extracted with ethyl acetate (50 mL). The extract was evaporated and the product was recrystallized from ethanol–ether to give 0.41 g (70%) of **24**: mp 121–122 °C; ^{1}H NMR ($CDCl_3$) δ 2.11 (m, 1, H-6), 2.76 (br d, 1, J_{gem} = 17 Hz, H-6′), 3.02 (m, 1, OH), 3.37 (m, 4, H-1, -2, -4, and -5), 4.38 (br d, 1, $J_{3,OH}$ = 11 Hz, H-3).

Anal. Calcd for $C_6H_8O_3$: C, 56.24; H, 6.29. Found: C, 56.06; H, 6.22.

Tri-*O*-acetyl-(1,3,5/2,4)-2,4-diacetamido-1,3,5-cyclohexanetriol (Penta-*N,O*-acetyl-5-deoxystreptamine) (3b), -(1,2,3/4,6)-4,6-diacetamido-1,2,3-cyclohexanetriol (Penta-*N,O*-acetyl-2-deoxy-*neo*-inosadiamine-1,3) (28), and -(1,3,4/2,5)-2,5-diacetamido-1,3,4-cyclohexanetriol (Penta-*N,O*-acetyl-2-deoxy-*chiro*-inosadiamine-1,4) (29). (a) A mixture of **23a** (2.6 g), hydrazine hydrate (3.3 mL), and 2-methoxyethanol (30 mL) refluxed for 4.5 h and then was evaporated to dryness. After treatment with Amberlite IRA-400 (OH^-) in an aqueous solution (30 mL), the residual product was hydrogenated as described for the preparation of **1b** and **9**. The reduction product was treated with acetic anhydride (20 mL) and pyridine (20 mL) at room temperature under stirring for 2 days, and the resulting precipitates were collected by filtration to give 0.7 g (42%) of **28** as homogeneous crystals. Recrystallization from methanol gave a pure sample: mp 293–294 °C (lit.[16] 250–255 °C dec); for ^{1}H NMR data, see Table I.

Anal. Calcd for $C_{16}H_{24}N_2O_8$: C, 51.60; H, 6.50; N, 7.52. Found: C, 51.71; H, 6.52; N, 7.55.

The reaction mixture obtained by filtration of **28** was evaporated to dryness and the residual syrup was chromatographed on silica gel (30 g) with chloroform–methanol (20:1, v/v). The main fractions were further fractionally crystallized from ethanol–ether to give 10 mg (0.6%) of **3b**, mp 305–306 °C dec, and 0.14 g (8.4%) of **29**, mp 219–220 °C: ^{1}H NMR (Me_2SO-d_6) for **3b** δ 4.05 (q, 2, $J_{1,2(4,5)} = J_{2,3(3,4)}$ = 10.5 Hz, $J_{2(4),NH}$ = 9 Hz, H-2 and H-4), 4.83 (m, 2, H-1 and H-5), 7.80 (d, 2, two amido protons); for other data, see Table I.

Anal. Calcd for $C_{16}H_{24}N_2O_8$: C, 51.60; H, 6.50; N, 7.52. Found for **3b**: C, 51.34; H, 6.49; N, 7.39. Found for **29**: C, 51.39; H, 6.52; N, 7.34.

(b) A mixture of **24** (0.36 g), anhydrous hydrazine (2 mL), and 2-methoxyethanol (20 mL) refluxed for 4.5 h. At this time, TLC indicated the formation of two new components [R_f 0.18 and 0.29 in 1-butanol–ethanol–water–28% aqueous ammonia (8:10:7:5, v/v)]. The reaction mixture was evaporated to dryness and the residual product was hydrogenated in water (20 mL) in the presence of Raney nickel catalyst in the usual manner. The reduction product was treated with acetic anhydride (20 mL) and pyridine (20 mL) at room temperature with stirring for 3 days. The resulting precipitates were collected by filtration and recrystallized from methanol to give 0.31 g (23%) of **28**: mp 293–294 °C. The filtrate was concentrated to a syrup which was crystallized from ethyl acetate to give an additional crop of **28** (0.02 g, total yield 25%). The remaining syrup was chromatographed on silica gel (10 g) with chloroform–methanol (10:1, v/v). The main fractions were evaporated and the product was crystallized from isopropyl alcohol–petroleum ether to give 0.12 g (11%) of **29**: mp 219–220 °C. The presence of a trace of **3b** was observed by TLC, but further separation was not attempted.

***N,N′*-Diethoxycarbonylstreptamine (30).** A solution of streptamine sulfate[21] (1.24 g) in water (150 mL) was treated with Amberlite IRA-400 (OH^-) (30 mL) and then evaporated to give the free base as a white powder. It was treated with ethyl chloroformate (1.7 mL) in water (30 mL) under vigorous agitation, the pH of the reaction mixture being adjusted to 7–8 by addition of 1 M aqueous sodium hydroxide. After standing overnight, the mixture was evaporated to dryness and the residue was extracted with hot dioxane (3 × 30 mL). The extracts were evaporated to give a white powder that was crystallized from methanol to give 0.59 g (44%) of **30**: mp 244–246 °C.

Anal. Calcd for $C_{13}H_{22}N_2O_6$: C, 44.72; H, 6.88; N, 8.69. Found: C, 44.74; H, 6.73; N, 8.52.

2,4-Di-*O*-acetyl-*N,N′*-diethoxycarbonyl-5,6-*O*-isopropylidenestreptamine (31). A mixture of **30** (2 g), 2,2-dimethoxypropane (12 mL), and *N,N*-dimethylformamide (48 mL) was heated in the presence of *p*-toluenesulfonic acid (0.15 g) at 80 °C for 4 h. After cooling, the reaction mixture was treated with Amberlite IRA-400 (OH^-), and then evaporated to give the crude *O*-isopropylidene derivative (1.25 g). Without further purification, it was treated with acetic anhydride (10 mL) in pyridine (20 ml) at room temperature overnight. The mixture was poured into ice–water, and the resulting crystals were collected and recrystallized from ethanol to give 1.4 g (50%) of **31**: mp 240–242 °C; ^{1}H NMR ($CDCl_3$) δ 1.24 (t, 6, J = 8 Hz, two ethoxycarbonyl CH_3), 1.45 (s, 3) and 1.48 (s, 3) (isopropylidene CH_3), 2.08 (s, 3) and 2.12 (s, 3) (OAc), 4.15 (q, 4, two ethoxycarbonyl CH_2).

Anal. Calcd for $C_{19}H_{30}N_2O_{10}$: C, 51.12; H, 6.77; N, 6.27. Found: C, 50.86; H, 6.66; N, 6.20.

2,4-Di-*O*-acetyl-*N,N′*-diethoxycarbonylstreptamine (32). A mixture of **31** (1.4 g) and 50% aqueous acetic acid (100 mL) was heated at 70 °C for 2 h. The reaction mixture was evaporated to dryness and the residue was crystallized from ethanol–ethyl acetate to give 1 g (81%) of **32**: mp 180–181 °C; ^{1}H NMR (Me_2SO-d_6) δ 1.13 (t, 3) and 1.15 (t, 3) (J = 7 Hz, ethoxycarbonyl CH_3), 1.88 (s, 3) and 1.97 (s, 3) (OAc), 4.00 (q, 4, two ethoxycarbonyl CH_2).

Anal. Calcd for $C_{16}H_{26}N_2O_{10}$: C, 47.29; H, 6.45; N, 6.89. Found: C, 47.06; H, 6.33; N, 6.90.

Tri-*O*-acetyl-(1,2,3,5/4,6)-2-chloro-3,5-diethoxycarbonylamino-1,4,6-cyclohexanetriol (33). To a stirred solution of **32** (1.5 g) in dry pyridine (50 mL), sulfuryl chloride (1.8 mL, 6 molar equiv) was added dropwise at −18 °C, and the reaction mixture was then allowed to stand in a refrigerator for 6 h. The mixture was poured into ice-cooled saturated aqueous sodium hydrogen carbonate and extracted with chloroform (3 × 30 mL). The extracts were washed with water, dried over anhydrous sodium sulfate, and evaporated to give a syrupy product. It was treated with acetic anhydride (10 mL) in pyridine (20 mL) at room temperature overnight. The reaction mixture was evaporated and the residual syrup was taken up in chloroform. After passage through a short alumina column, the solution was evaporated and crystallized from chloroform–ethanol to give 1 g (57%) of **33**: mp 180–182 °C; ^{1}H NMR ($CDCl_3$) δ 1.22 (t, 3) and 1.25 (t, 3) (J = 7 Hz, ethoxycarbonyl CH_3), 2.05 (s, 3), 2.07 (s, 3), and 2.10 (s, 3) (OAc), 4.13 (q, 2) and 4.17 (q, 2) (ethoxycarbonyl CH_2).

Anal. Calcd for $C_{18}H_{24}ClN_2O_{10}$: C, 46.61; H, 5.22; N, 6.04; Cl, 7.64. Found: C, 46.43; H, 5.48; N, 5.76; Cl, 7.92.

Tri-*O*-acetyl-(1,3,5/2,4)-3,5-diethoxycarbonylamino-1,3,5-cyclohexanetriol (Tri-*O*-acetyl-*N,N′*-diethoxycarbonyl-4-deoxystreptamine) (34a). A solution of **33** (0.3 g) in dry toluene (20 mL) was treated with tri-*n*-butyltin hydride (0.5 mL) in the presence of α,α'-azobis(isobutyronitrile) at 90 °C under a nitrogen atmosphere for 2 h. The reaction mixture was evaporated and the residue was recrystallized from chloroform–ether to give 0.23 g (82%) of **34a**: mp 214–215 °C; ^{1}H NMR ($CDCl_3$) δ 1.23 (t, 6, J = 7 Hz, two ethoxycarbonyl CH_3), 2.03 (s, 3), 2.05 (s, 3), and 2.09 (s, 3) (OAc), 4.14 (q, 4, two ethoxycarbonyl CH_2).

Anal. Calcd for $C_{18}H_{25}N_2O_{10}$: C, 50.35; H, 5.87; N, 6.52. Found: C, 50.06; H, 6.24; N, 6.61.

(1,3,5/2,4)-3,5-Diethoxycarbonylamino-1,3,5-cyclohexanetriol (*N,N′*-Diethoxycarbonyl-4-deoxystreptamine) (34b). Compound **34a** (0.47 g) was treated with methanolic ammonia (30 mL) at room temperature overnight. The mixture was evaporated to dryness and the product was crystallized from ethanol–ethyl acetate to give 0.3 g (88%) of **34b**: mp 178–180 °C.

Anal. Calcd for $C_{12}H_{22}N_2O_7$: C, 47.05; H, 7.24; N, 9.14. Found: C, 46.34; H, 6.90; N, 8.90.

Compound **34b** (0.27 g) was heated in refluxing 6 M hydrochloric acid (20 mL) overnight. The mixture was evaporated to give a crude dihydrochloride which was treated with Amberlite IRA-400 (OH^-) in an aqueous solution. The solution was evaporated and the crude free base obtained was directly treated with acetic anhydride and pyridine in the usual manner. The product was crystallized from methanol to give 0.14 g (42%) of **2b**: mp 310–311 °C dec. This compound was found to be identical with **2b** obtained before.

2,4-Di-*O*-acetyl-6-*O*-benzoyl-*N,N'*-diethoxycarbonylstreptamine (35a). To a solution of **32** (3 g) in dry pyridine (120 mL) was added benzoyl chloride (1.3 mL, 3 molar equiv) at −10 °C in two portions in 1-day intervals, and then the reaction mixture was kept in a refrigerator for 2 days. At this time, TLC in benzene–ethanol (7:1, v/v) showed that **32** was almost consumed and two new components (R_f 0.49 and 0.63) formed. The reaction mixture was poured into ice–water and the resulting crystals (1.2 g), consisting of two components, were collected by filtration. The filtrate (300 mL) was evaporated to give a partly crystalline residue. It was dissolved in chloroform (50 mL) and the solution was washed with aqueous sodium hydrogen carbonate and water, dried over anhydrous sodium sulfate, and evaporated to give crystals. Recrystallization from ethyl acetate–methanol gave 1.28 g (40%) of **35a** as homogeneous crystals: mp 176–180 °C. Further crystallization of the crystals from chloroform–ether raised its melting point to 184–185 °C; ^{1}H NMR ($CDCl_3$) δ 0.93 (t, 3) and 1.15 (t, 3) (J = 7 Hz, ethoxycarbonyl CH_3), 1.91 (s, 3) and 1.98 (s, 3) (OAc), 3.86 (q, 2) and 4.03 (q, 2) (ethoxycarbonyl CH_2).

Anal. Calcd for $C_{23}H_{30}N_2O_{11}$: C, 54.11; H, 5.92; N, 5.49. Found: C, 54.02; H, 5.88; N, 5.46.

Treatment of **35a** (0.05 g) with acetic anhydride (3 mL) and pyridine (3 mL) at room temperature overnight. The product was crystallized from chloroform–ether to give 0.045 g (83%) of the triacetate (**35b**): mp 218–220 °C; ^{1}H NMR ($CDCl_3$) δ 1.02 (t, 3) and 1.23 (t, 3) (J = 7 Hz, ethoxycarbonyl CH_3), 1.91 (s, 3), 2.07 (s, 3), and 2.12 (s, 3) (OAc), 3.98 (q, 2) and 4.04 (q, 2) (ethoxycarbonyl CH_2).

Anal. Calcd for $C_{25}H_{32}N_2O_{12}$: C, 54,34; H, 5.84; N, 5.07. Found: C, 54.07; H, 5.81; N, 4.94.

1,5-Di-*O*-acetyl-3-*O*-benzoyl-(1,2,3,5/4,6)-4,6-diethoxycarbonylamino-2-chloro-1,3,5-cyclohexanetriol (36). To a solution of **35a** (1 g) in dry pyridine (30 mL) was added sulfuryl chloride (0.65 mL, 4 molar equiv) at −16 °C and the mixture was kept in a refrigerator for 7 h. The reaction mixture was processed as described for **33**. The crude syrupy product was chromatographed on silica gel with ethyl acetate–petroleum ether, giving a crystalline product. Recrystallization from ether gave 0.64 g (62%) of **36**: mp 192–193 °C; ^{1}H NMR ($CDCl_3$) δ 1.20 (t, 3) and 1.23 (t, 3) (J = 7 Hz, ethoxycarbonyl CH_3), 2.10 (s, 3) and 2.12 (s, 3) (OAc), 4.02 (q, 2) and 4.03 (q, 2) (ethoxycarbonyl CH_2), 4.58 (ddd, 2, J = 9, 10, and 10 Hz, H-4 and H-6), 5.00 (dd, 1, $J_{1,2}$ = 3 Hz, H-1).

Anal. Calcd for $C_{23}H_{29}ClN_2O_{10}$: C, 52.23; H, 5.53; N, 5.30; Cl, 6.70. Found: C, 52.28; H, 5.59; N, 5.23; Cl, 6.84.

1,3-Di-*O*-acetyl-5-*O*-benzoyl-(1,3,5/2,4)-2,4-diethoxycarbonylamino-1,3,5-cyclohexanetriol (37). A mixture of **36** (0.41 g), tri-*n*-butyltin hydride (0.5 mL), dry toluene (20 mL), and a catalytic amount of α,α'-azobis(isobutyronitrile) was heated at 90 °C under a nitrogen atmosphere for 2 h. The mixture was evaporated to give a crystalline residue that was recrystallized from chloroform–ethanol to give 0.29 g (75%) of **37**: mp 221–222 °C; ^{1}H NMR ($CDCl_3$) δ 1.07 (t, 3) and 1.23 (t, 3) (J = 7 Hz, ethoxycarbonyl CH_3), 2.07 (s, 3) and 2.12 (s, 3) (OAc), 4.02 (q, 2) and 4.13 (q, 2) (ethoxycarbonyl CH_2).

Anal. Calcd for $C_{23}H_{30}N_2O_{10}$: C, 55.86; H, 6.12; N, 5.66. Found: C, 55.67; H, 6.04; N, 5.76.

(1,3,5/2,4)-2,4-Diethoxycarbonylamino-1,3,5-cyclohexanetriol (*N,N'*-Diethoxycarbonyl-5-deoxystreptamine) (38). Compound **37** (0.22 g) was treated with methanolic ammonia (10 mL) at room temperature for 2 days. The reaction mixture was evaporated to give a syrup that was crystallized from ethyl acetate giving 0.1 g (73%) of **38**: mp 187–188 °C.

Anal. Calcd for $C_{12}H_{22}N_2O_7$: C, 47.05; H, 7.24; N, 9.14. Found: C, 46.65; H, 7.00; N, 8.88.

Compound **38** (0.08 g) was hydrolyzed with refluxing 6 M hydrochloric acid (15 mL), followed by acetylation, as described for the preparation of **2b** from **34b**. The product was crystallized from ethanol to give 0.06 g (61%) of **3b**: mp 305–306 °C (dec). This compound was identical with the sample obtained before.

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Registry No.—**1a**, 2037-48-1; **1b**, 6216-31-5; **2a**, 62708-21-8; **3a**, 62708-22-9; **4**, 34405-77-1; **5**, 62708-23-0; **6**, 62708-24-1; **10a**, 38836-67-8; **10b**, 62742-93-2; **11**, 62742-94-3; **12a**, 62708-25-2; **12b**, 62776-28-7; **13**, 62742-95-4; **14**, 62708-26-3; **19**, 39726-11-9; **20**, 62776-29-8; **21**, 62708-27-4; **22**, 62777-56-4; **23a**, 62708-28-5; **23b**, 62708-29-6; **24**, 62776-30-1; **30**, 62708-30-9; **31**, 62742-96-5; **32**, 62708-31-0; **33**, 62708-32-1; **34a**, 62708-33-2; **34b**, 627-08-34-3; **35a**, 62708-35-4; **35b**, 62708-36-5; **36**, 62708-37-6; **37**, 62708-38-7; **38**, 62708-39-8; sulfuryl chloride, 7791-25-5; mesyl chloride, 124-63-0; sodium benzoate, 532-32-1; sodium azide, 26628-22-8; streptamine sulfate, 62776-31-2; benzoyl chloride, 98-88-4.

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Reaction of Dimethyl 3-Ketoglutarate with 1,2-Dicarbonyl Compounds. 8.[1] Selective Base-Catalyzed Decarbomethoxylation of Tetramethyl 3,7-Dioxo-*cis*-bicyclo[3.3.0]octane-2,4,6,8-tetracarboxylate. Preparation of 2,6-Dicarbomethoxy-*cis*-bicyclo[3.3.0]octane-3,7-dione

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Tetramethyl 3,7-dioxo-*cis*-bicyclo[3.3.0]octane-2,4,6,8-tetracarboxylate (1), very easily available from dimethyl 3-ketoglutarate and glyoxal, readily loses two of its carbomethoxyls on mild warming with 10 mol of NaOMe in Me_2SO/MeOH, giving exclusively the 2,6-diester 3 in >90% yield. The corresponding triester 2, presumably an intermediate, can be isolated in low yield when a smaller excess of base is taken. Energetic treatment of 3 with NaOMe in Me_2SO/MeOH produces a very small amount of the monoester 4. Acid-catalyzed hydrolysis and decarboxylation of 3 yield the known *cis*-bicyclo[3.3.0]octane-3,7-dione; the stereochemistry of the parent ring system has thus remained unchanged during the treatment with base. Diazomethane converts 1 and 3 into the enolic dimethyl ethers, 8 and 7; 8 does not lose carbomethoxyl under the conditions where its parent 1 does so readily.

The removal of carbomethoxy groups from β-keto esters is a reaction which has been given considerable attention in recent years;[2] its utility in synthetic work is obvious. In the papers quoted,[2] this reaction was generally applied to monoesters, yielding the parent ketone. We now wish to describe a reaction where some, but not all, of the carbomethoxy groups were cleaved off specifically from tetramethyl 3,7-dioxo-*cis*-bicyclo[3.3.0]octane-2,4,6,8-tetracarboxylate (1). This compound is prepared extremely readily from dimethyl β-ketoglutarate and glyoxal at room temperature in aqueous medium at slightly acidic[3a] or alkaline[3b] reaction.

We have observed that 1, on being warmed with excess sodium methoxide in Me_2SO containing 10 mol % methanol,[4] can be made to lose one, two, or three of its carbomethoxyls, producing the tri-, di-, and monocarbomethoxy derivatives of *cis*-bicyclo[3.3.0]octane-3,7-dione (compounds 2, 3, and 4, respectively). Of these reactions, the one yielding the dicarbomethoxy compound (shown below to be the 2,6 isomer 3) is very strongly favored, so that this substance, a potentially useful synthetic intermediate, becomes very readily accessible. In contrast, the tricarbomethoxy derivative 2 was obtained only when a smaller excess of NaOMe was used, and even then the yields were very low; presumably, it is very rapidly converted further into 3. Finally, the monocarbomethoxy compound 4 can be prepared from 3 by prolonged heating with NaOMe in Me_2SO–MeOH, but even under these drastic conditions only very minute amounts of the compound were produced, most of the 3 surviving unchanged.

Warming the β-keto ester 1, prepared by the method of ref 3b, with 10 mol of NaOMe at 55 °C in Me_2SO–MeOH for 15 h yielded better than 90% of dimethyl 2,7-dioxobicyclo[3.3.0]-octanedicarboxylate,[5] mp 110 °C (from ethanol), mol wt 254 (mass spectrometry). This ester could have structure 3, 5, or 6. Of these, 5 is eliminated by the fact that the ^{13}C NMR spectrum does not contain any signal from an isolated cyclopentanone carbonyl, and by the very ready formation of the dienol ether 7,[5] mp 178 °C (from chloroform–petroleum ether), on treatment with diazomethane in ether, i.e., under conditions where the carbonyl of a β-keto ester, but not that of a simple ketone, would be expected to react. Under the same conditions 1, shown[6] by NMR spectrometry to be present virtually completely as the enol 1a, readily gave the dimethyl ether 8, mp 135 °C (from chloroform–petroleum ether).

Of the two remaining structures, 3 was shown to be the correct one by the ^1H and ^{13}C NMR spectra of the compound itself and its ether 7. In particular, the single-frequency off-resonance decoupled ^{13}C NMR spectrum of 7 showed only *one* doublet for the bridgehead carbons 1 and 5; in the ether derived from 6, the marked structural differences in the environment of these carbons (one of them being bisallylic) would undoubtedly give rise to very different signals.

Treatment of 1 under otherwise identical conditions with only 3 mol of NaOMe produced small amounts of 3 and of the tricarbomethoxy compound 2,[5] mp 78 °C (from ethanol). Ester 4[7] was obtained in minute (1%) yield upon treatment of 3 in the same mixed solvent with 10 mol of NaOMe at 70–80 °C for 36 h, mp 84 °C (from ethanol).

The identification of 2 and 4 rests upon their formation from 1 and 3, respectively, their mass-spectrometric molecular weights, and their spectroscopic characteristics. Since 1 is known[8] to be derived from *cis*-bicyclo[3.3.0]octane, compounds 2, 3, and 4 should likewise belong to the cis series. The inherently improbable possibility of inversion at one of the two backbone carbons during the base-catalyzed decarbomethoxylations was eliminated by acid-catalyzed hydrolysis and decarboxylation[3a] of 3, which gave *cis*-bicyclo[3.3.0]octane-3,7-dione (9) identical with authentic material.

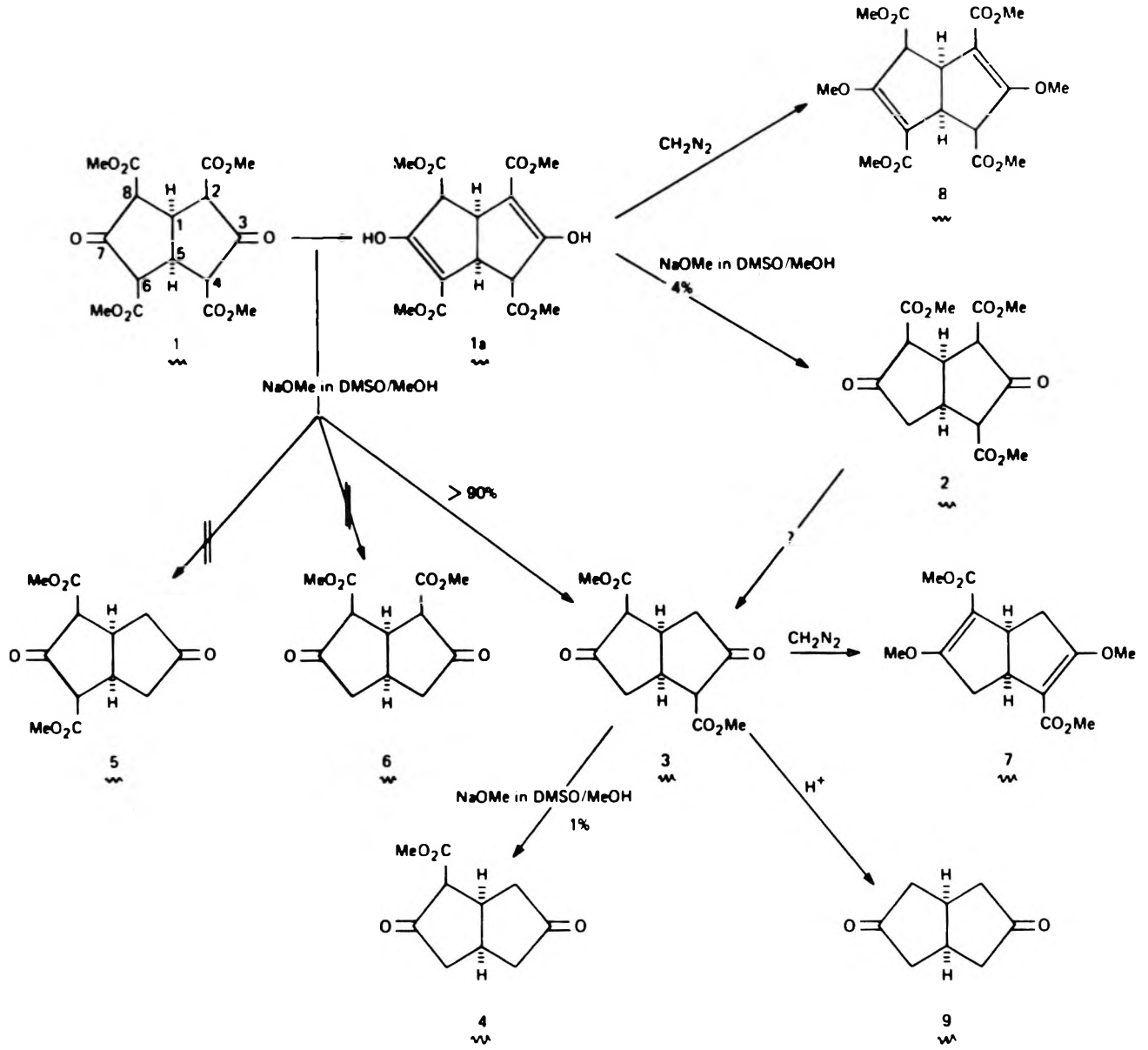
The removal of one, two, or three carbomethoxy groups to give 2, 3, and 4 proceeds undoubtedly through loss of dimethyl carbonate in a reversal of the well-known base-catalyzed carbomethoxylation[9] of $-CO-CH_2-$ by this reagent. Cases of reversal of this reaction have been observed.[10] The failure of the enol ether 8 to undergo analogous decarbomethoxylation supports this view.

Evidently, the removal of CO_2Me occurs very readily as long as the number of carbomethoxy groups exceeds that of ketonic carbonyls; as soon as a 1:1 relationship is reached in 3, further removal becomes much more difficult. These facts, and the formation of 3 to the exclusion of its isomers 5 and 6, can be explained by the mechanism shown in Scheme II.

Experimental Section

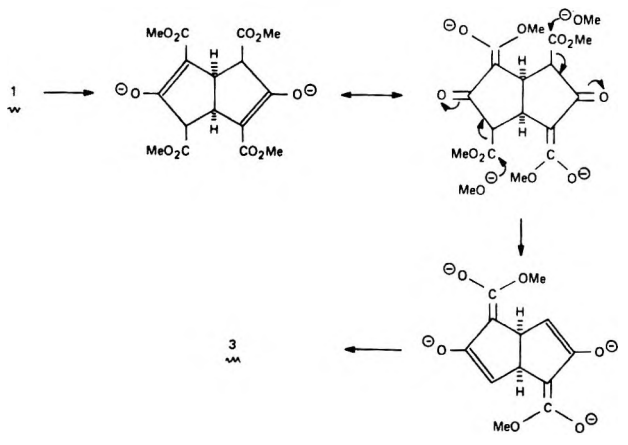
General Methods. Infrared spectra were obtained using a Perkin-Elmer Model 257 grating spectrophotometer. Nuclear magnetic resonance spectra were recorded on either a Varian HR-220 or a Varian A-60 instrument. Mass spectra were obtained on Finnigan

Scheme I



1015D GC/MS or Hitachi Perkin-Elmer RMU-GE mass spectrometers. The ^{13}C NMR spectra were obtained at 15.04 MHz using the JEOL FX-60. Typically, accumulation of 1000 free-induction decays from 300 pulses provided a spectrum from a ~0.3 M solution. Data were accumulated for 1 s with a pulse-repetition rate of 1.2 s; an 8K Fourier transform provided resolution of approximately 1 Hz. Thin-layer chromatography (TLC) was carried out using 250-μm layers of silica gel GF obtained from Analtech, Inc., Newark, Del.; for preparative TLC, 20 × 20 cm glass plates coated with 1000-μm layers of silica gel GF (obtained from Analtech) were used with hexane/acetone (7:3) containing 1% formic acid as solvent system.

Scheme II



Decarbomethoxylation of β-Keto Ester 1. (A) To Dimethyl 3,7-Dioxobicyclo[3.3.0]octane 2,6-dicarboxylate of mixture A (**3**). β-keto ester **1**[3b] (3.7 g, 10 mmol) and sodium methoxide (5.4 g, 100 mmol) in 150 mL of Me_2SO containing 10 mol % methanol was stirred at 55 °C in an oil bath for 15 h. The ether extract of the acidified (10% aqueous HCl) reaction mixture was washed with brine solution, dried over anhydrous sodium sulfate, and evaporated in vacuo. The residue (2.45 g), which was mainly ester **3** by TLC, was recrystallized from ethanol: fine needles; mp 110 °C; yield 2.3 g (90%); ν ($CHCl_3$) 1755, 1730, 1660, 1630 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.90 (6 H), 3.50 (2 H), 2.5–2.9 (4 H), 10.5 (2 H); ^{13}C NMR ($CDCl_3$) 38.5 (C-4, 8), 38.9 (C-1, 5), 51.2 (CO_2CH_3), 103.0 (C-2, 6), 165.6, 169.7 (C-3, 7 and CO_2CH_3); M^+ *m/e* 254. Anal. Calcd for $C_{12}H_{14}O_6$: C, 56.69; H, 5.55. Found: C, 56.41; H, 5.50.

(B) To Trimethyl 3,7-Dioxobicyclo[3.3.0]octane-2,4,6-tricarboxylate **2**. A mixture of β-keto ester **1** (1.5 g, 4.05 mmol) and sodium methoxide (0.656 g, 12.15 mmol) in 60 mL of Me_2SO containing 10 mol % of methanol was stirred at 55 °C for 15 h. The reaction mixture was worked up as in expt A. The residue showed three spots on TLC (r_f 0.181, 0.280, 0.360). The three compounds were separated by preparative TLC. The major component was identified as unreacted starting material, the other two were characterized as ester **3** and **2**. Ester **2** was crystallized from ethanol: yield ~4% (0.05 g); mp 78 °C; ν ($CHCl_3$) 1755, 1670, 1630 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.81 (9 H), 3.6–3.7 (3 H), 2.5–2.9 (2 H), 10.4 (2 H); M^+ *m/e* 312. Anal. Calcd for $C_{14}H_{16}O_8$: C, 53.84; H, 5.16; Found: C, 53.57, H, 5.11.

Enol Ether 7 of 3. Ester **3** (0.5 g, 1.96 mmol) was added to an ice-

cold ethereal solution containing diazomethane (0.250 g, 5.9 mmol), and was left overnight in the refrigerator. On evaporation of solvent the enol ether 7 was obtained in almost quantitative yield: mp 178 °C (from chloroform/petroleum ether); ν ($CHCl_3$) 1675, 1640, 1275–1200, 1075–1020 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.84 (s, 6 H), 3.75 (s, 6 H), 3.5 (2 H), 2.6–2.9 (4 H); ^{13}C NMR ($CDCl_3$) 37.9 (t, single-frequency off-resonance decoupling, C-4, 8), 39.8 (d, C-1, 5), 50.8 (q, CO_2CH_3), 57.7 (q, CH_3O-C-3.7), 106.1 (s, C-2, 6), 165.6 (s), 169.7 (s), (C-3, 7 and CO_2CH_3).

Partial Decarbomethoxylation of β-Keto Ester 3 to the Monoester 4. A mixture of β-keto ester 3 (1 g, 3.9 mmol) and sodium methoxide (2.12 g, 39 mmol) in 60 mL of Me_2SO containing 10 mol % methanol was stirred at 70–80 °C for 36 h. The reaction mixture was worked up as before; the residue showed two spots on TLC; both components were isolated by preparative TLC. The major compound was found to be unreacted starting material. The other component, isolated in about 1% yield (0.007 g), mp 84 °C (from ethanol), was identified as ester 4: ν ($CHCl_3$) 1755, 1730, 1660, 1630 cm^{-1}; ^1H NMR ($CDCl_4$) δ 3.8 (3 H), 3.5 (2 H), 2.09–3.01 (6 H); M^+ *m/e* 196.

Decarbomethoxylation of Ester 3 to the Diketone 9. The ester 3 (0.5 g, 1.96 mmol) was refluxed with 6 N HCl (10 mL) for 3.5 h. The reaction mixture was cooled, and ice-cold water was added. Extraction with methylene chloride, washing with brine solution, drying (Na_2SO_4), and evaporation gave a residue which was crystallized from methanol, mp 84–85 °C. The compound was found identical with the authentic sample of 9 by mixture melting point, co-TLC, superimposable infrared, NMR, and mass spectra.

Enol Ether 8 of β-Keto Ester 1. Ester 1 (0.5 g, 1.35 mmol) was added to an ice-cold ethereal solution containing diazomethane (0.250 g, 5.9 mmol); the solution was left overnight in the refrigerator. On usual workup the enol ether 8 was obtained; it was crystallized from chloroform/petroleum ether in 90% yield (0.48 g): mp 135 °C; ν ($CHCl_3$) 1740, 1685, 1630 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.86 (6 H), 3.57 (6 H), 3.50 (6 H), 3.90 (2 H), 3.60 (2 H); ^{13}C NMR 49.0 (d, C-1, 5), 51.4 (q, C-2, 6 CO_2CH_3), 52.8 (q, C-4, 8, CO_2CH_3), 58.9 (d, C-4, 8), 59.0 (q, C-3, 7 OCH_3), 108.5 (s, C-2, 6), 164.5, 165.5 (s, C-3, 7/C-2, 6 CO_2CH_3), 171.9 (s, C-4, 8 CO_2CH_3); M^+ *m/e* 398. Anal. Calcd for $C_{18}H_{22}O_{10}$: C, 54.27; H, 5.57. Found: C, 54.46; H, 5.53.

Acknowledgments. We are indebted to Dr. Lin Tsai for valuable discussions, and to Mr. William R. Landis and Noel F. Whittaker for mass spectra.

Registry No.—1, 58648-36-5; 2, 62708-46-7; 3, 62708-47-8; 4, 62708-48-9; 7, 62708-49-0; 8, 62708-50-3; 9, 51716-63-3; dimethyl β-ketoglutarate, 1830-54-2; glyoxal, 107-22-2.

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Pentacyclic Steroids. Synthesis of 4,6β-Ethanoestradiol, 4,6β-Ethanoestrone, and 17α-Ethynyl-4,6β-ethanoestradiol

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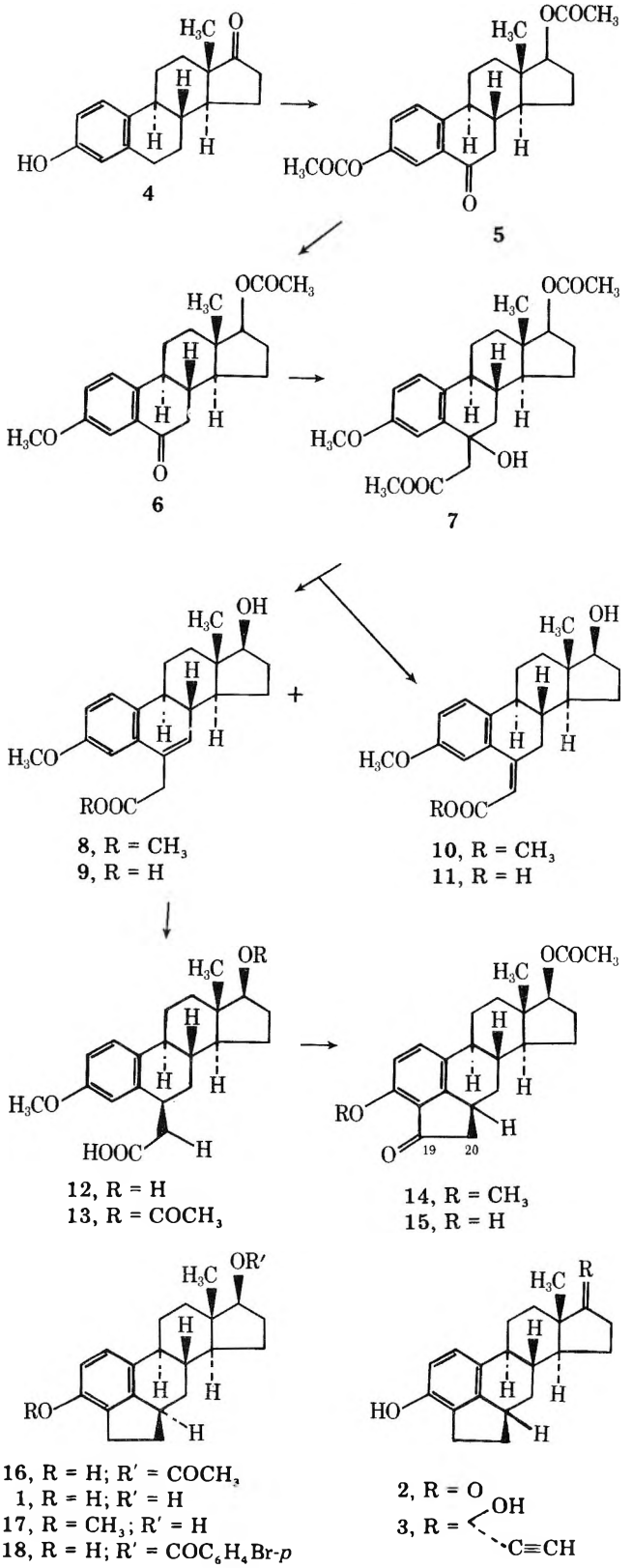
Synthesis of a new series of pentacyclic steroids, 4,6β-ethanoestradiol (1), 4,6β-ethanoestrone (2), and 17α-ethynyl-4,6β-ethanoestradiol (3), is described. Estrone is converted into the key intermediate 17β-acetoxy-3-methoxy-1,3,5(10)-estratriene-6β-acetic acid (13) in 11 steps. Friedel–Crafts cyclization of the acid chloride of 13 with aluminum chloride provides compounds 14 and 15. Further structural modifications lead to 1, 2, and 3. The absolute configuration of the *p*-bromobenzoate derivative of 1 has been confirmed by x-ray crystallography. Fusion of the ethano bridge at positions C-4 and C-6 from the β face leads to a unique class of steroids in which the B ring assumes a highly distorted conformation.

Substitution of the steroidal skeleton at C-6 has led to a number of important oral contraceptives.[1,2] Examples include dimethisterone, Provera (17α-acetoxy-6α-methylpregn-4-ene-3,20-dione), and megesterol acetate. Activity of such compounds has been explained on the assumption that the presence of alkyl substitution at C-6 prevents metabolic hydroxylation at this position. The syntheses of steroidal compounds with an ethano bridge across C-4 and C-6 are of special interest, since significant changes in the stereochemistry of steroidal skeleton can be effected with such substitutions. Studies with Dreiding models show that fusion of an ethano bridge at positions C-4 and C-6, from the β face, in the estrone molecule leads to a unique class of steroids in which the B ring assumes a highly distorted conformation. Little is known in the literature[3] about the formation and biological activities of steroids containing such a distorted B ring. We report here the synthesis of three such compounds, 4,6β-ethanoestradiol (1), 4,6β-ethanoestrone (2), and 17α-ethynyl-4,6β-ethanoestradiol (3). Further modifications could lead to a new class of steroids, whose biological profile remains to be examined.

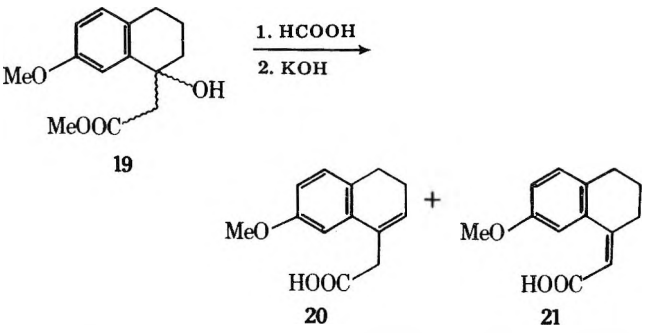
The starting material was estrone (4), which was converted into 5 in three steps (Scheme I).[4] Hydrolysis, methylation, and acetylation[5] led to compound 6. Reformatsky reaction upon 6 provided 7, which on dehydration with formic acid gave a mixture of the esters 8 and 10. Hydrolysis of this product with potassium hydroxide led to the unsaturated acids 9 and 11. NMR spectra of the esters 8 and 10 (δ 5.98, endo olefinic H,

Scheme I



and 6.36, exo olefinic H, ratio 85:15) and of the acids **9** (δ 6.0 ppm, olefinic H) and **11** indicated that the endo isomers **8** and **9** were the major products in these reactions. This was also confirmed from studies[6] on the conversion of the model compound **19** into a mixture of **20** and **21**. Once again, the endo acid **20** was the predominant product (NMR δ 6.07, endo olefinic H, and 6.33, exo olefinic H, ratio 90:10).

Without separation, the mixture of **9** and **11** was hydrogenated, using 10% Pd/C as the catalyst. The product was primarily (>95% by NMR) the desired 6α-H acid **12**. The stereochemistry of **12** was assigned on the basis of its mode of formation (hydrogenation from α face) and from well-established precedence in literature.[7-9] Previously, it has been shown that hydrogenation of 6-dehydro-6-methylestrone leads to 6β-methylestrone.[9]



Attempts to cyclize compound **12** with anhydrous HF led to a complex mixture. Compound **12** was acetylated to **13**, cyclization of which with HF was also unsuccessful. Treatment of the acid chloride of **13** with 2–2.5 mol of anhydrous $AlCl_3$, however, yielded the desired ketone **14** in excellent yield. When more than 3 mol of anhydrous $AlCl_3$ was used, the product was the demethylated compound **15**.

It was interesting to note that in thin layer chromatography (silica gel, C_6H_6–CH_3OH, 85:15) the phenolic ketone **15** had a higher R_f value than the methoxy ketone **14**. This could be due to the hydrogen bonding between the five-member ketone and the hydroxyl group at position 3. Also, the cyclization of **13** into **15** was very facile and gave a remarkably high yield (86%). Clemmensen reduction and subsequent base hydrolysis proceeded smoothly to give the 4,6β-ethanoestradiol (**1**). Methylation of **1** led to **17** whereas oxidation with CrO_3 yielded estrone analogue **2**. The latter, upon treatment with lithium acetylide–ethylenediamine complex, provided 17α-ethynyl-4,6β-ethanoestradiol (**3**). The stereochemistry at C-17 in **3** was assigned on the basis of literature precedence.[10,11]

In order to define unambiguously the configuration at C(6) in 4,6β-ethanoestradiol (**1**), and to determine the conformation of the distorted B ring and its influence on the overall conformation of the molecule, the structure of 17p-bromobenzoate derivative **18** was examined by x-ray crystallography.[12] Single crystals of **18** were grown by evaporation of a cyclohexane–benzene solution. The crystal data follow: a = 13.417 (2), b = 23.404 (2), c = 7.333 (1) Å, space group $P2_12_12_1$. The structure was solved by conventional heavy-atom techniques and refined by full matrix least squares with hydrogen atoms placed at their geometrically expected positions and included in the structure-factor calculations for the final refinement. The final reliability index (R) was 9.9% for the 1361 observable spectra.

The α configuration of the hydrogen substituent at C-6 was unambiguously defined as illustrated in Figure 1. The B ring conformation in **18** was found to be highly distorted. From a

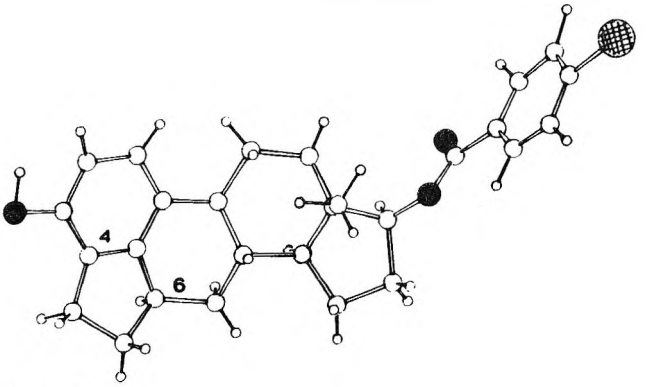


Figure 1.

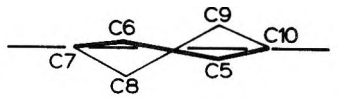


Figure 2.

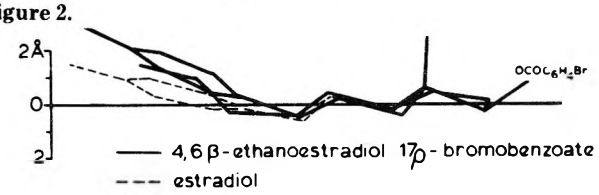


Figure 3.

projection along a line joining the midpoints of the C(5)–C(6) and C(8)–C(9) bonds (Figures 2), it is clear that atoms C(5) and C(6) are displaced from the horizontal plane far less than are atoms C(8) and C(9). If atoms C(7), C(6), C(5), and C(10) were coplanar, the ring would have a half-chair conformation. If, on the other hand, the C(5) and C(6) atoms were displaced to the same degree that the C(8) and C(9) atoms are, the ring would have a twist conformation.[13] There is no example in the literature of a steroid with a B ring so distorted. Its presence in the steroid results in a greatly enhanced bowing of the molecule toward the β face, as is illustrated in Figure 3, where the structure is superimposed upon that of estradiol.[14]

The results on the biological activities of **1**, **2**, and **3** will be published elsewhere.

Experimental Section

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were obtained on a Perkin-Elmer infrared spectrophotometer 700. Mass spectra were obtained on a Hitachi Perkin-Elmer RMU 6L and a CEC 110 mass spectrometer. Proton nuclear magnetic resonance spectra (NMR) were recorded on a Varian T-60 spectrometer, using tetramethylsilane as the internal standard. Thin layer chromatography (TLC) was performed on precoated TLC plates (silica gel 60 F254, EM reagents). Microanalyses were carried out by Spang Microanalytical Laboratories, Ann Arbor, Mich.

17β-Acetoxy-3-methoxy-6-oxo-1,3,5(10)-estratriene (6). Following the procedure described in the literature,[4,5] estrone (**4**) was converted into 3,17β-diacetoxy-6-oxo-1,3,5(10) estratriene (**5**): mp 173–175 °C (lit.[4,5] mp 173.5–175 °C); IR 1765 (phenolic acetate >C=O), 1730 cm^{-1} (alcoholic acetate >C=O); NMR ($CDCl_3$) δ 0.83 (3 H, CCH_3), 2.05 [3 H, $OC(=O)CH_3$ at 17], and 2.28 [3 H, $OC(=O)CH_3$ at 3].

The 6-oxoacetate **5** (2 g) was hydrolyzed by methanolic potassium hydroxide solution to afford 1.5 g (97%) of 3,17β-dihydroxy-6-oxo-1,3,5(10)estratriene: mp 280 °C (lit.[4] mp 280–282 °C); IR 3525 (alcoholic OH), 3225 (phenolic OH), and 1670 cm^{-1} (six-member conjugated >C=O).

Following the procedure described by Kundu,[5] 0.75 g of 3,17β-dihydroxy-6-oxo-1,3,5(10)estratriene was converted to 0.73 g (91%) of 17β-hydroxy-3-methoxy-6-oxo-1,3,5(10)-estratriene: mp 80–82 °C (solidified and remelted at 130–132 °C) (lit.[5] mp 82–84 °C, solidified and remelted at 130–132 °C); IR 3470 (17β-OH), 1675 cm^{-1} (six-member conjugated >C=O); NMR ($CDCl_3$) δ 0.78 (3 H, CCH_3) and 3.83 (3 H, OCH_3).

Following literature procedure,[5] 17β-hydroxy-3-methoxy-6-oxo-1,3,5(10)-estratriene (1.3 g) was converted to 1.45 g (99%) of **6**: mp 167–169 °C (lit.[5] mp 168–169 °C); IR 1730 (acetate >C=O), 1680 cm^{-1} (six-member conjugated >C=O); NMR ($CDCl_3$) δ 0.83 (3 H, CCH_3), 2.05 [3 H, $OC(=O)CH_3$], and 3.83 (3 H, OCH_3).

17β-Acetoxy-6ζ-hydroxy-3-methoxy-1,3,5(10)-estratriene-6ζ-acetic Acid Methyl Ester (7). From 1.37 g of 3-methoxy-6-oxoestradiol 17β-acetate (**6**), 1.6 g of zinc, and 1.3 g of methyl bromoacetate in 40 ml of ether–benzene (1:1), there was obtained 1.6 g (96%) of the hydroxy ester **7**: IR 3520 (OH), 1740 (ester >C=O), and 1730 cm^{-1} (acetate >C=O); NMR ($CDCl_3$) δ 0.85 (3 H, CCH_3), 2.05 [3 H, $OC(=O)CH_3$], 3.75 [3 H, $-C(=O)OCH_3$], 3.8 (3 H, OCH_3), 6.8 and 7.2 (3 H, ArH).

17β-Hydroxy-3-methoxy-1,3,5(10),6-estratetraene-6-acetic Acid (9) and Compound 11. A solution of the hydroxy ester **7** (1.6 g, 3.9 mmol) and 97% formic acid (4 mL) was heated under reflux for 50 min. The reaction mixture was evaporated under reduced pressure to afford the unsaturated esters (**8** and **10**) as an oil (1.5 g, 98%), which showed a single spot on TLC: IR 1735 (ester >C=O) and 1725 cm^{-1} (acetate >C=O); NMR ($CDCl_3$) δ 0.85 (3 H, CCH_3), 2.07 [3 H, $OC(=O)CH_3$], 3.45 [2 H, $CH_2C(=O)OCH_3$], 3.7 [3 H, $OC(=O)CH_3$], 3.85 (3 H, OCH_3), 5.98 (endocyclic olefinic H), and 6.36 (exocyclic olefinic H) (ratio endo:exo 85:15), 6.8 and 7.16 (3 H, ArH). The acetate was hydrolyzed by stirring at room temperature for 48 h with a solution of potassium hydroxide (1 g) in methanol (18 mL) and water (2 mL). The crude acid (mixture of **9** and **11**) was crystallized from a mixture of ether, methylene chloride, and petroleum ether (bp 30–60 °C) to furnish the unsaturated acid **9** (1.10 g, 80%): mp 128–130 °C dec; IR 3440 (OH) and 1710 cm^{-1} (acid >C=O); NMR (CD_3OD) δ 0.75 (3 H, CCH_3), 3.8 (3 H, OCH_3), 6.0 (1 H, olefinic), 6.8 and 7.1 (3 H, ArH); MS *m/e* 342 (M^+, 68%), 298 (99%), 282 (67%), 171 (77%). Anal. Calcd for $C_{21}H_{26}O_4$: C, 73.64; H, 7.65. Found: C, 73.52; H, 7.58.

17β-Hydroxy-3-methoxy-1,3,5(10)-estratriene-6β-acetic Acid (12). A solution of **9** and **11** (0.4 g, 1.2 mmol) in ethyl acetate (8 mL) and methanol (2 mL) was hydrogenated with 10% Pd/C (0.06 g) at room temperature. The calculated amount of hydrogen was absorbed during 2 h. The reaction mixture was filtered and the solvent was evaporated to afford 0.395 g (98%) of the crystalline reduced acid **12**. Recrystallization from a mixture of chloroform and petroleum ether afforded needles: mp 186 °C; IR 3450 (OH) and 1715 cm^{-1} (acid >C=O); NMR (CD_3OD) δ 0.8 (3 H, CCH_3), 3.75 (3 H, OCH_3), 6.7 and 7.2 (3 H, ArH); MS *m/e* 344 (M^+, 100%), 326 (3%), 298 (9%), 284 (29%), 258 (32%), 171 (31%). Anal. Calcd for $C_{21}H_{28}O_4$: C, 73.22; H, 8.19. Found: C, 73.18; H, 8.15.

17β-Acetoxy-3-methoxy-1,3,5(10)-estratriene-6β-acetic Acid (13). A solution of the acid **12** (0.316 g) in pyridine (1.5 mL) and acetic anhydride (1 mL) was kept at room temperature for 24 h. It was then decomposed with water and was made acidic with hydrochloric acid. The product was extracted with ether to afford 0.35 g (99%) of the acetate **13**. Recrystallization from chloroform–ether–methanol gave analytical sample: mp 185–186 °C; IR 1730 (acetate >C=O) and 1715 cm^{-1} (acid >C=O); NMR ($CDCl_3$) δ 0.85 (3 H, CH_3), 2.1 [3 H, $OC(=O)CH_3$], 3.8 (3 H, OCH_3), 6.8 and 7.3 (3 H, ArH). Anal. Calcd for $C_{23}H_{30}O_5$: C, 71.47; H, 7.82. Found: C, 71.28; H, 7.93.

17β-Acetoxy-3-methoxy-19-oxo-4,6β-ethano-1,3,5(10)-estratriene (14) and 17β-Acetoxy-19-oxo-4,6β-ethano-1,3,5(10)-estratrien-3-ol (15). A solution of the acid **13** (1.2 g, 3.2 mmol), thionyl chloride (2 mL), and pyridine (8 drops) in methylene chloride (20 mL) was stirred at room temperature for 3 h. The solvent was removed by distillation at reduced pressure, and the last traces of thionyl chloride were eliminated by codistillation three times with 20-mL portions of methylene chloride. A solution of the acid chloride in methylene chloride (20 mL) was added dropwise over a period of 10 min to a stirred and cooled (ice bath) suspension of anhydrous aluminum chloride (1.8 g, 14.2 mmol) in methylene chloride (40 mL). After stirring for 3 h in the cold, the reaction mixture was kept at room temperature for 16 h. After treatment with ice–water (40 mL) and concentrated hydrochloric acid (2 mL), the mixture was extracted with ether (3 × 50 mL). The organic layer was separated and washed with water, 5% Na_2CO_3 solution, and finally with water. Evaporation of the solvent afforded 1.1 g of a crude product. TLC showed that the mixture was mainly the phenolic ketone **15**, contaminated with a small amount of methoxy ketone **14**. Chromatography on silica gel (33 g) with ethyl acetate–benzene (5:95) as eluate separated 0.95 g (86%) of the phenolic ketone **15**. This was recrystallized from methylene chloride–petroleum ether to furnish **15**: mp 208–209 °C; IR 3310 (OH), 1730 (acetate >C=O), and 1690 cm^{-1} (five-member conjugated and hydrogen-bonded >C=O); NMR ($CDCl_3$) δ 0.78 (3 H, CCH_3), 2.05 [3 H, $OC(=O)CH_3$], 6.7 and 7.25 (2 H, ArH), 7.0 (1 H, phenolic OH); MS *m/e* 354 (M^+, 99.9%). Anal. Calcd for $C_{22}H_{26}O_4$: C, 74.55; H, 7.39. Found: C, 74.30; H, 7.30.

In another experiment, with a smaller proportion of $AlCl_3$, the acid **13** (0.3 g, 0.8 mmol) was converted to its acid chloride as above. The crude acid chloride in methylene chloride (6 mL) was added to a solution of anhydrous aluminum chloride (0.27 g, 2 mmol) in methylene chloride (8 mL). The reaction mixture was stirred for 3 h at 5 °C and 14 h at 25 °C. Workup and recrystallization from methylene chloride–petroleum ether (bp 30–60 °C) furnished compound **14** (0.24 g, 84%): mp 249 °C; IR 1730 (acetate >C=O), 1710 cm^{-1} (five-member conjugated >C=O); NMR ($CDCl_3$) δ 0.80 (3 H, CCH_3), 2.06 [3 H, $OC(=O)CH_3$], 3.97 (3 H, $-OCH_3$), 6.80 and 7.4 (2 H, ArH); MS *m/e* 368 (M^+). Anal. Calcd for $C_{23}H_{28}O_4$: C, 74.97; H, 7.66. Found: C, 74.70; H, 7.54.

4,6β-Ethanoestradiol (1). A mixture of mossy zinc (6 g) and 5% $HgCl_2$ solution (12 mL) was kept at room temperature for 1 h with occasional shaking and the aqueous layer was then decanted. The amalgamated Zn was covered with concentrated HCl (30 mL) and H_2O (20 mL), and the ketone **15** (0.8 g) and toluene (7 mL) were added. The mixture was heated under reflux for 2.5 h, cooled, and

worked up to give 0.69 g of a crude mixture of **16** and **1**. This was hydrolyzed by refluxing for 2 h with a solution of 0.5 g of KOH in CH_3OH (10 mL). Methanol was removed and the residue was diluted with H_2O. The clear alkaline solution was acidified and worked up to furnish 0.575 g of the crude diol **1**. It was crystallized from ether–petroleum ether to afford 0.51 g (76%) of **1**: mp 206–207 °C; IR 3350 cm^{-1} (broad OH); NMR ($CDCl_3$) δ 0.74 (3 H, CCH_3), 6.65 and 7.02 (2 H, ArH); MS *m/e* 298 (M^+, 99%). Anal. Calcd for $C_{20}H_{26}O_2$: C, 80.50; H, 8.78. Found: C, 80.50; H, 8.76.

A bis-*p*-bromobenzoate was obtained by treatment of **1** with *p*-bromobenzoyl chloride and pyridine at room temperature. Selective hydrolysis[12] of the phenolic ester with sodium carbonate solution at room temperature provided compound **18**, mp 258–260 °C. Anal. Calcd for $C_{27}H_{29}O_3Br$: C, 67.4; H, 6.1; Br, 16.6. Found: C, 67.14; H, 6.08; Br, Br, 16.61.

4,6β-Ethanoestradiol 3-Methyl Ether (17). To a solution of **1** (0.075 g) in methanol (2 mL) and 1 N KOH (5 mL), dimethyl sulfate (0.7 mL) was added dropwise. The mixture was stirred for 4 h at room temperature and left overnight. The separated solid was collected by filtration and dried to yield 0.0555 g (69.4%) of the methylated product **17**. Recrystallization from methanol–chloroform–ether yielded a semisolid: NMR ($CDCl_3$) δ 0.70 (3 H, CCH_3), 3.84 (3 H, OCH_3), 6.83 and 7.05 (2 H, ArH); MS *m/e* 312 (M^+). Anal. Calcd for $C_{21}H_{28}O_2 \cdot 2CH_3OH$: C, 73.37; H, 9.64. Found: C, 73.46; H, 9.34.

4,6β-Ethanoestrone (2). Jones reagent[15] (0.15 mL) was added to a solution of 4,6β-ethanoestradiol **1** (0.08 g) in acetone (20 mL) cooled to 5 °C and the mixture was stirred for 10 min. The reaction mixture was diluted with water and extracted with ether to afford the ketone **2** (0.06 g, 75%) which on recrystallization from ether–petroleum ether gave needles: mp 220–222 °C; IR 3370 (phenolic OH), 1730 cm^{-1} (five-member C=O); MS *m/e* 296 (M^+). Anal. Calcd for $C_{20}H_{24}O_2 \cdot \frac{1}{2}H_2O$: C, 78.65; H, 7.89. Found: C, 78.47; H. 7.60.

17α-Ethynyl-4,6β-ethanoestradiol (3). Acetylene gas was bubbled into a solution of compound **2** (0.175 g) in dimethyl sulfoxide (6 mL) under N_2 for 10 min. Lithium acetylide–ethylenediamine complex[10,11] (0.3 g) was then added and the acetylene was continued for another 3 h. After the reaction mixture had stood overnight at room temperature, it was decomposed with a saturated solution of ammonium chloride. The reaction mixture was extracted with ethyl acetate. The solid left after removal of the solvent was purified by preparative thin layer chromatography (silica gel, $CH_3OH/CHCl_3$, 20:80) to give 0.13 g (68.4%) of **3**. Recrystallization from a mixture of chloroform, ether, and petroleum ether afforded a material: mp 162–164 °C; IR 3400 and 3325 cm^{-1}; NMR ($CDCl_3$) δ 0.80 (3 H, CH_3), 2.63 (1 H, $-C{\equiv}CH$), 6.7 and 6.88 (2 H, ArH); MS *m/e* 322 (M^+). Anal. Calcd for $C_{22}H_{26}O_2$: C, 81.95; H, 8.13. Found: C, 81.74; H, 8.12.

Acknowledgment. The authors would like to express their sincere thanks to Professor J. C. Sheehan and Drs. R. K. Razdan, H. C. Dalzell, and H. G. Pars for valuable suggestions throughout the period of this research. This work was supported by a contract from NICHD, NIH, Bethesda, Md. (NO1-HD-3-2733). The x-ray work was supported in part by Grant CA 10906, awarded by the National Cancer Institute, DHEW. We gratefully acknowledge the help of Dr. C. W. Weeks during x-ray crystallographic studies and Dr. C. Costello of The Massachusetts Institute of Technology for recording the mass spectra. Our thanks are also due to Schering AG., Berlin; Syntex S. A., Palo Alto, Calif.; and G. D. Searle, Chicago, Ill., for generous supplies of estrone.

Registry No.—**1**, 62842-06-2; **1** bis-*p*-bromobenzoate, 62842-07-3; **2**, 62842-08-4; **3**, 62842-09-5; **5**, 3434-45-5; **6**, 20823-31-8; **7**, 62842-10-8; **8**, 62842-11-9; **9**, 62842-12-0; **10**, 62842-13-1; **11**, 62842-14-2; **12**, 62842-15-3; **13**, 62842-16-4; **13** acid chloride, 62842-17-5; **14**, 62842-18-6; **15**, 62842-19-7; **16**, 62842-20-0; **17**, 62842-21-1; **18**, 62230-95-9; 3,17β-dihydroxy-6-oxo-1,3,5(10)estratriene, 571-92-6; 17β-hydroxy-3-methoxy-6-oxo-1,3,5(10)-estratriene, 50731-96-9.

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Notes

A Convenient Synthesis of (Chloromethyl)thio Aromatics and (Chloromethyl)thio Heteroaromatics

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Received January 24, 1977

(Chloromethyl)thio aromatics, and methods for their preparation, have been previously described in the literature. German Patent 845 511 describes the preparation of (chloromethyl)thio aromatics by treating 1 mol of aromatic thiol with at least 1 mol of formaldehyde in the presence of hydrogen chloride:

$$ArSH + CH_2{=}O \xrightarrow[HCl]{} ArSCH_2Cl \quad (1)$$

Dolman et al.[1] described the reaction of 1 mol of an aromatic thiol with 1 mol of formaldehyde in the presence of a catalytic amount of sodium methoxide to give the corresponding (hydroxymethyl)thio aromatic which was subsequently treated with 1.1 mol of thionyl chloride to afford the corresponding (chloromethyl)thio aromatic:

$$ArSH + CH_2{=}O \xrightarrow[NaOCH_3]{} ArSCH_2OH \xrightarrow{SOCl_2} ArSCH_2Cl \quad (2)$$

Senning and Lawesson[2] described the preparation of 1-[(chloromethyl)thio]-2,3,4,5,6-pentachlorobenzene by the chlorination of 1-(methylthio)-2,3,4,5,6-pentachlorobenzene with chlorine in refluxing carbon tetrachloride.

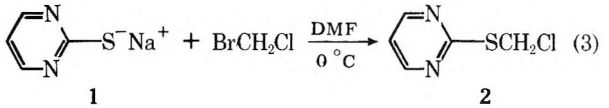
More recently, several examples of the preparation of (chloromethyl)thio heteroaromatics from the corresponding thiol and bromochloromethane have been described. In 1967, Pashkurov and Reznik[3] reported that the reaction of the so-

Table I. (Chloromethyl)thio Aromatics and (Chloromethyl)thio Heteroaromatics

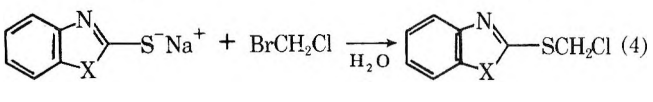
Thiol[h]	Product[i]	Yield, %[a]	Mp or bp (mm), °C	Mol of thiol	Mol of BrCH$_2$Cl	Mol of BTEAB	Temp, °C	Reaction time, h
Benzenethiol	1-[(Chloromethyl)thio]benzene	57	83 (1.5)	0.50	11.53	0.0036	16–50	2.5
4-(1,1-Dimethylethyl)benzenethiol	1-[(Chloromethyl)thio]-4-(1,1-dimethylethyl)benzene	60	100–106 (3.0)	0.10	4.61	0.00055	*b*	*b*
2,4,6-Tribromobenzenethiol	1-[(Chloromethyl)thio]-2,4,6-tribromobenzene	91[f]	71–72	0.025	2.31	0.001	*b*	*b*
2,3,5,6-Tetrafluorobenzenethiol	1-[(Chloromethyl)thio]-2,3,5,6-tetrafluorobenzene	84	65–66 (1.0)	0.055	3.85	0.001	25–38	1.25[c]
2,3,5,6-Tetrachlorobenzenethiol	1-[(Chloromethyl)thio]-2,3,5,6-tetrachlorobenzene	82	81–82	0.025	3.07	0.001	25–55	1.5
N,*N*-Diethyl-2-mercapto-3,4,5-trichlorobenzenesulfonamide	2-[(Chloromethyl)thio]-*N*,*N*-diethyl-3,4,5-trichlorobenzenesulfonamide	83	82–83	0.025	2.31	0.0015	26–30	2.33[d]
2,3,4,5,6-Pentachlorobenzenethiol	1-[(Chloromethyl)thio]-2,3,4,5,6-pentachlorobenzene	46	121–122	0.025	2.31	0.0015	26–31	2.25[d]
2,4′,6-Trichloro-4-mercaptobiphenyl	4-[(Chloromethyl)thio]-2,4′,6-trichlorobiphenyl	95	100–101	0.01	1.5	0.00055	25–27	1.25[e]
2-Mercaptoquinoline	2-[(Chloromethyl)thio]quinoline	43	51–53	0.33	7.69	0.0018	22–56	2.0
2-Mercaptobenzoxazole	2-[(Chloromethyl)thio]benzoxazole	80	53–54	0.05	3.07	0.00077	25–50	1.5
2-Mercaptobenzothiazole	2-[(Chloromethyl)thio]benzothiazole	58	43–44	0.50	15.38	0.0029	25–60	2.0
5-Chloro-2-mercaptobenzothiazole	5-Chloro-2-[(chloromethyl)thio]benzothiazole	97[g]	86–87	0.05	4.61	0.00099	30–50	3.0
6-Ethoxy-2-mercaptobenzothiazole	2-[(Chloromethyl)thio]-6-ethoxybenzothiazole	93	112–113	0.50	15.38	0.0037	*b*	*b*
2-Mercaptopyrimidine	2-[(Chloromethyl)thio]pyrimidine	58	46	0.20	3.07	0.0018	24–58	2.0

[a] Isolated yield employing 85% potassium hydroxide unless otherwise specified. [b] See Experimental Section. [c] Subsequently heated at 60 °C for 1.5 h. [d] Subsequently heated at reflux for 0.5 h. [e] Subsequently heated at 45 °C for 1.5 h. [f] A 78% yield was obtained when lithium hydroxide monohydrate was used. [g] Sodium hydroxide was used. [h] Registry no. are respectively 108-98-5, 2396-68-1, 24207-66-7, 769-40-4, 4707-16-8, 62669-51-6, 133-49-3, 62601-11-0, 2637-37-8, 2382-96-9, 149-30-4, 5331-91-9, 120-53-6, 1450-85-7. [i] Registry no. are respectively 7205-91-6, 62601-12-1, 62601-13-2, 62601-14-3, 62601-15-4, 62601-16-5, 62601-17-6, 62601-18-7, 62601-19-8, 37118-31-3, 28908-00-1, 62601-20-1, 62601-21-2, 19834-93-6.

dium salt of 2-pyrimidinethiol (1) with bromochloromethane at 0 °C in dry dimethylformamide gave 2-[(chloromethyl)thio]pyrimidine (2) in 35% yield (eq 3). In 1972, Pera and Raths[4] reported the preparation of 2-[(chloromethyl)thio]benzoxazoles, 2-[(chloromethyl)thio]benzothiazoles, and 2-[(chloromethyl)thio]benzimidazoles by the reaction of the sodium salt of the corresponding thiol with bromochloromethane in an aqueous system in the presence of a nonionic surfactant (eq 4).



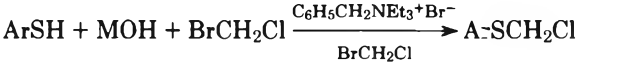
1 2 (3)



(4)

X = NH, O, S

We have developed an improved procedure in which (chloromethyl)thio aromatics and (chloromethyl)thio heteroaromatics were prepared by the reaction of the corresponding thiol with 1 equiv of an alkali metal hydroxide (lithium, sodium, or potassium hydroxide) in bromochloromethane (using bromochloromethane as both reactant and solvent) in the presence of a catalytic amount (0.5–10 mol %) of benzyltriethylammonium bromide (BTEAB) (eq 5).[5] The procedure involved no aqueous phase, and was very simple to operate. A slurry of the finely powdered alkali metal hydroxide in bromochloromethane was prepared; the thiol was then added followed by the benzyltriethylammonium bromide. A mild exotherm was observed immediately upon adding the catalyst, and the reaction mixture was generally allowed to stir until it returned to room temperature)in some instances a 0.5-h reflux period was employed). The reaction mixture was then filtered to remove the alkali metal bromide which had precipitated. The filtrate was then dried, and the excess bromochloromethane removed in vacuo leaving the (chloromethyl)thio compound which was purified by recrystallization or distillation (several representative preparations are given in the Experimental Section). A variety of aromatic and heteroaromatic thiols have been employed in this reaction, and the results are summarized in Table I.



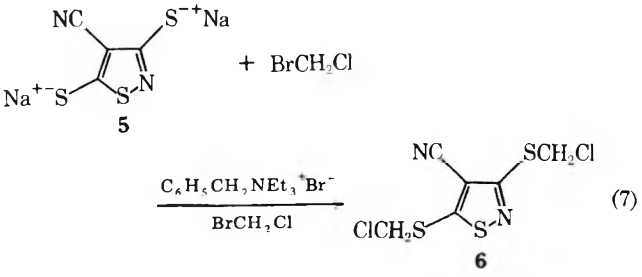
+ H_2O + MBr (5)

Ar = aromatic or heteroaromatic

M = Li, Na, or K

The reaction can also be carried out with a preformed alkali metal salt of an aromatic thiol. Thus, the dipotassium salt of 2,5-dimercapto-1,3,4-thiadiazole (3) afforded 2,5-bis[(chloromethyl)thio]-1,3,4-thiadiazole (4, eq 6) in 71% yield, and the

3 4 (6)



5 6 (7)

disodium salt of 4-cyano-3,5-(dimercapto)isothiazole (**5**) gave 4-cyano-3,5-bis[(chloromethyl)thio]isothiazole (**6**) in 60% yield (eq 7).

Experimental Section[6]

1-[(Chloromethyl)thio]-4-(1,1-dimethylethyl)benzene. To a slurry of 6.50 g (0.10 mol) of finely powdered 85% potassium hydroxide in 300 mL of bromochloromethane were added 12.5 g (0.10 mol) of 4-(1,1-dimethylethyl)benzenethiol. To this mixture, 0.125 g (0.00055 mol) of benzyltriethylammonium bromide was added, and the reaction mixture was stirred at 25–30 °C for 0.5 h. The reaction mixture was amber in color, and a pale yellow solid had precipitated. The reaction mixture was filtered, and the bromochloromethane removed in vacuo leaving a light amber oil. The oil was dissolved in 100 mL of ether, and the resulting solution filtered through anhydrous magnesium sulfate. The ether was removed in vacuo from the filtrate leaving 16.5 g of nearly colorless oil. The oil was distilled under reduced pressure to give 12.30 g (60% yield) of the title compound as a colorless liquid, bp 100–106 °C (3 mm).

1-[(Chloromethyl)thio]-2,4,6-tribromobenzene. To a slurry of 1.63 g (0.025 mol) of finely powdered 85% potassium hydroxide in 150 mL of bromochloromethane was added 8.70 g (0.025 mol) of 2,4,6-tribromobenzenethiol. To this mixture, 0.30 g of benzyltriethylammonium bromide was added, and the temperature rose from 26 to 28 °C in several minutes. The reaction mixture was stirred for 2 h and then filtered to remove the sodium bromide which separated. The bromochloromethane was removed in vacuo from the filtrate leaving a light, red-brown oil. The oil was treated with 75 mL of ether dissolving most of the material and leaving a small amount of red-brown oil. The ether solution was dried over anhydrous magnesium sulfate and filtered. The ether was diluted with an equivalent amount of hexane, and the resulting solution concentrated in vacuo to give 4.20 g of the title compound, mp 71–72 °C. Further concentration gave an additional 4.80 g, mp 71–72 °C (total yield 91%).

2-[(Chloromethyl)thio]-6-ethoxybenzothiazole. To a well-stirred slurry of 105.7 g (0.50 mol) of 6-ethoxy-2-mercaptobenzothiazole in 1 L of bromochloromethane were added 32.5 g (0.50 mol) of finely powdered 85% potassium hydroxide and 1.0 g of benzyltriethylammonium bromide. The temperature of the reaction mixture slowly rose from 23 to 38 °C over a period of 1.75 h. The stirring was continued for an additional 1 h, during which the temperature slowly fell to 32 °C. The precipitated potassium bromide was filtered off, and the organic filtrate washed with 500 mL of water. The organic layer was dried over anhydrous calcium chloride, and the bromochloromethane removed in vacuo leaving a damp powder. The powder was slurried with anhydrous diethyl ether to give an insoluble white powder which was filtered and dried to give 102 g of the title compound, mp 112–113 °C. A 24-g second crop was obtained from the ether filtrate (total yield 93%). A sample of this material was recrystallized from chloroform to give white plates, mp 112–113 °C.

2,5-Bis[(chloromethyl)thio]-1,3,4-thiadiazole (4). A slurry of 100 g (0.44 mol) of the dipotassium salt of 2,5-dimercapto-1,3,4-thiadiazole (**3**) in 850 mL of bromochloromethane containing 2 g of benzyltriethylammonium bromide was stirred for 6 h at 35–55 °C. The potassium bromide formed was filtered off and dissolved in water leaving 0.5 g of polymeric material. Acidification of the aqueous filtrate precipitated 2,5-dimercapto-1,3,4-thiadiazole equivalent to 17 g of the starting salt indicating 83% conversion. The bromochloromethane was removed in vacuo from the organic filtrate leaving a thick liquid which was extracted with 1 L of anhydrous ether. The ether was removed in vacuo leaving 71.0 g (78% yield) of the title compound as a white solid, mp 60–61 °C. Recrystallization from ether gave crystals with mp 64–65 °C.

Anal. Calcd for $C_4H_4Cl_2N_2S_3$: C, 19.40; H, 1.63; Cl, 28.70; N, 11.34; S, 39.90. Found: C, 19.90; H, 1.72; Cl, 28.50; N, 11.63; S, 39.20.

3,5-Bis[(chloromethyl)thio]-4-cyanoisothiazole (6). In a 500-mL flask equipped with a reflux condenser, a mechanical stirrer, and a thermometer were placed 10.90 g (0.05 mol) of the disodium salt of 4-cyano-3,5-dimercaptoisothiazole (**5**) and 300 mL of bromochloromethane. To this slurry, 0.44 g of benzyltriethylammonium bromide was added, and the reaction mixture was heated at 24–55 °C for 5 h. The reaction mixture was filtered to remove the sodium bromide produced, and the bromochloromethane was removed in vacuo from the filtrate leaving a tan solid. The solid was extracted with hot ether, and the ether solution was concentrated in vacuo to give 6.00 g of the title compound as a light yellow powder, mp 92–93 °C. Further concentration gave an additional 2.10 g, mp 88–89 °C (total yield, 60%).

Anal. Calcd for $C_6H_4Cl_2N_2S_3$: C, 26.57; H, 1.48; N, 10.33; S, 35.47. Found: C, 26.80; H, 1.73; N, 10.46; S, 36.18.

Registry No.—**3** 2K, 4628-94-8; **4**, 62601-22-3; **5** 2Na, 2076-67-7; **6**, 62653-99-0; bromochloromethane, 74-97-5.

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(6) All melting points and boiling points are uncorrected. All new compounds gave satisfactory elemental analyses and displayed infrared and NMR spectra which were in agreement with the assigned structures.

Electronic Effects in Multicenter Rearrangements of Compounds with Nitrogen–Nitrogen Bonds

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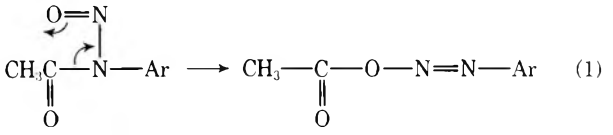
Huisgen and co-workers[1] and Hey and co-workers[2] have shown that the rates of rearrangements of *N*-nitroso amides **1** (eq 1) are but slightly influenced by either electron-withdrawing or electron-donating substituents.



(1)

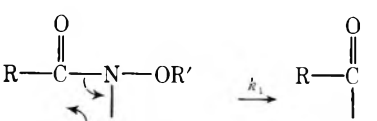
1 **2**

A plot of rate data reported by these authors against Hammett σ^+ [4] constants shows some scattering of points but the best straight line has a slope of zero. Likewise we have measured the rates of rearrangement of *N*-nitroso-*N*-cyclohexylbenzamides, and found little effect from placing either electron-donating or electron-withdrawing substituents on the aromatic ring. These data have been interpreted as being consistent with a multicenter process[1,2] rather than an ionic process. In a multicenter process involving simultaneous bond breaking and bond formation, the influence of electron-donating and electron-withdrawing substituents would be conflicting.

We wanted to see if electronic effects on the decomposition of **3** by a multicenter process would likewise be confusing.

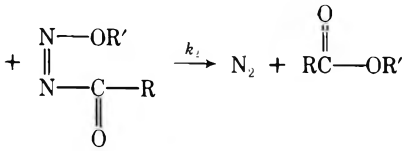
Previous work[3] has shown that the spontaneous reaction of **3a** in refluxing methanol or benzyl alcohol at room temperature occurred by a concerted process, while reaction in refluxing benzyl alcohol or with added acid occurred with the generation of a free acylium ion.

Scheme I



3

3a, R = CH_3; R′ = NC_3H_7
b, R = XC_6H_4; R′ = $C_6H_5CH_2$
c, R = CH_3; R′ = $XC_6H_4CH_2$



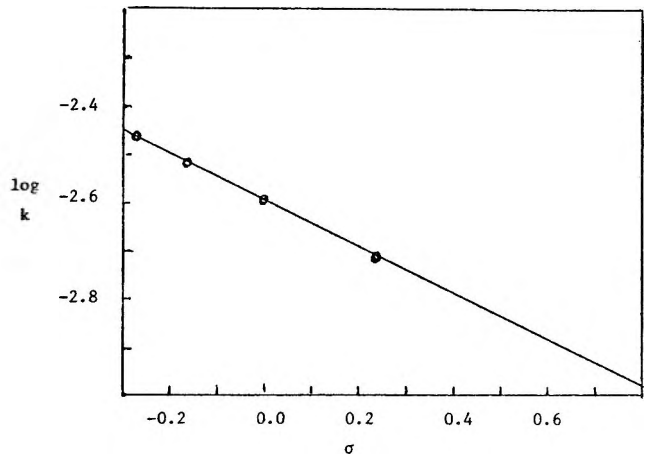


Figure 1. Log k vs. σ for N,N'-di-p-X-benzoyl-N,N'-dibenzyloxyhydrazines in chloroform at 30.1 ± 0.1 °C, $p = -0.47$.

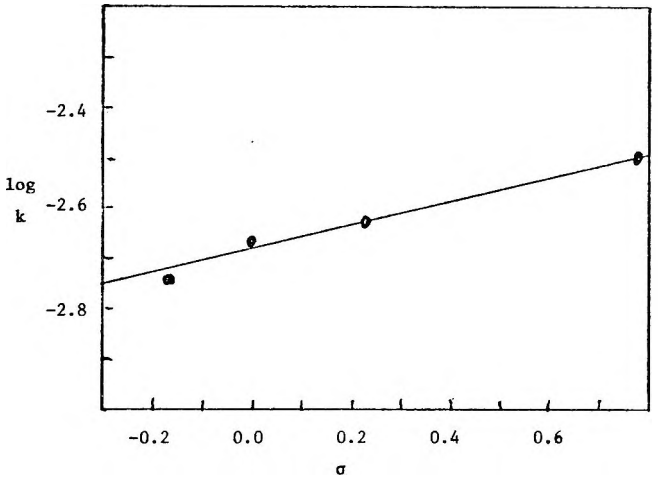


Figure 2. Log k vs. σ for N,N'-diacetyl-N,N'-di-p-X-benzyloxyhydrazines in chloroform at 59.4 ± 0.3 °C, $p = 0.22$.

Electron-donating substituents on R in **3b** with electron-withdrawing substituents on R′ in **3c** were found to accelerate the rates of reaction. Plots of log k vs. σ (Figures 1 and 2) for the two series of compounds **3b** and **3c** showed straight lines and ρ values of −0.47 and +0.22 were calculated, respectively. These indicate the expected stabilization of incipient alkoxide anions and acylium ions of the transition state.

Experimental Section

Melting points were determined using a Thomas-Hoover Uni-melt capillary apparatus and are corrected. Visible absorption spectra were measured with a Perkin-Elmer Model 202 ultraviolet-visible spectrophotometer or a Beckman DU spectrophotometer. Molecular weights were determined with a Hitachi Perkin-Elmer molecular weight apparatus, Model 115.

Preparation of Amides. Amides were prepared by the method of White.[4] Previously unknown amides included N-cyclohexyl-m-chlorobenzamide, mp 121 °C, N-cyclohexyl-m-methylbenzamide, mp 121 °C, and N-cyclohexyl-m-nitrobenzamide, mp 146 °C.[5]

***N*-Nitroso-*N*-cyclohexyl-Substituted Benzamides.** The procedure described by Huisgen and Kraus[16] was used to prepare the nitroso amides. Solutions of these nitroso amides in carbon tetrachloride were prepared and held in a constant temperature bath at 25.0 ± 0.01 °C. Samples were withdrawn and changes in the absorption at 430 nm were recorded. From these data the rates shown in Table I were calculated. Similarly rates of decomposition of N-nitroso-N-cyclohexyl-substituted benzamides in acetic acid were measured and the results are in Table II.

Rate of Decomposition of *N,N'*-Diacyl-*N,N'*-dialkoxyhydrazines. These unstable compounds were prepared by lead tetraacetate oxidation of N-acyl-O-alkylhydroxylamines as described before.[3] Solutions of initial concentration in the range 5×10^{-2} to 5×10^{-3} m in chloroform were accurately prepared and kept in a constant temperature bath. Aliquots were withdrawn at 2-h intervals, and the molecular weights were measured using a Hitachi Perkin-Elmer molecular weight apparatus, Model 115. First-order rate constants were determined from the slope of the plot of $M_\infty - M_t$ against time.

Table I. Rate Constants for Decomposition of *N*-Nitroso-*N*-cyclohexyl-Substituted Benzamides in Carbon Tetrachloride

Substituent	Constant, s^{-1}	Substituent	Constant, s^{-1}
p-OCH_3	3.0×10^{-4}	m-CH_3	3.0×10^{-4}
m-Cl	3.5×10^{-4}	H	4.0×10^{-4}

Table II. Rate Constants for Decomposition of *N*-Nitroso-*N*-cyclohexyl-Substituted Benzamides in Acetic Acid

Registry no.	Substituent	Constant, s^{-1}
62250-57-1	m-CH_3	2.0×10^{-3}
62250-58-2	p-Nitro	5.36×10^{-4}
62250-59-3	m-Chloro	1.24×10^{-3}
62250-60-6	m-Nitro	9.39×10^{-4}
62250-61-7	p-Methoxy	1.39×10^{-3}
62250-62-8	None	1.73×10^{-3}

Registry No.—**3b** (X = p-CH_3), 62250-50-4; **3b** (X = H), 38636-07-6; **3b** (X = p-Cl), 62250-51-5; **3b** (X = p-OCH_3), 62250-52-6; **3c** (X = p-OCH_3), 53821-07-1; **3c** (X = H), 62250-53-7; **3c** (X = p-Cl), 62250-54-8; **3c** (X = p-NO_2), 62250-55-9; N-cyclohexyl-m-chlorobenzamide, 62250-56-0; N-cyclohexyl-m-methylbenzamide, 53205-66-6; N-cyclohexyl-m-nitrobenzamide, 2702-32-1.

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(5) Satisfactory microanalyses (0.3% absolute) were obtained on all new compounds.

Synthetic Methods and Reactions. 35.[1] Regioselective Oxidation of Alkyl (Cycloalkyl) Methyl Ethers to Carbonyl Compounds with Nitronium Tetrafluoroborate

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In our previous work we have shown that nitrosonium salts oxidize benzylic alcohols and the trimethylsilyl and tributylstannyl derivatives of secondary alcohols to carbonyl compounds,[2] and cleave benzylic esters[3] with ease. We now wish to report a related study on the reaction of alkyl (cycloalkyl) methyl ethers with nitronium tetrafluoroborate leading to a facile, regioselective oxidative cleavage.

Contrary to the nitrosonium ion, nitronium ion generally does not act as a hydride acceptor. However, it is a better electrophile toward π, n, and σ donors, as illustrated by, for example, aromatic nitration,[4] nitrate ester formation,[5] and

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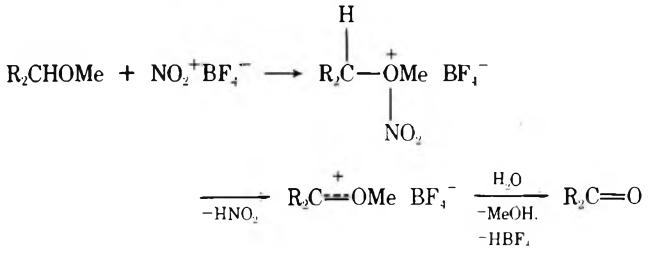
Table I. Oxidative Cleavage of Methyl Ethers ROMe with NO_2BF_4

R	Registry no.	Product	Registry no.	Yield, %
Benzyl	538-86-3	Benzaldehyde	100-52-7	89
p-Methylbenzyl	3395-88-8	*p*-Tolualdehyde	104-87-0	85
o-Methylbenzyl	15018-12-9	*o*-Tolualdehyde	529-20-4	82
p-Nitrobenzyl	1515-83-9	*p*-Nitrobenzaldehyde	555-16-8	93
2-Octyl	1541-09-9	2-Octanone	111-13-7	63
Cycloheptyl	42604-04-6	Cycloheptanone	502-42-1	57
Cyclohexyl	931-56-6	Methyl 5-oximinocaproate	62344-93-8	60
Cyclopentyl	5614-37-9	Methyl 4-oximinovalerate	62842-23-3	53

the nitration (nitrolysis) of alkanes,[6] respectively. Thus alkyl ethers are expected to react smoothly with nitronium salts to form oxonium ion intermediates which should decompose via nitrous acid elimination. The direction of proton loss is dictated by the stability of the incipient cation; therefore, in most methyl ethers the methoxycarbenium ions would ensue, and the net reaction (with hydrolytic workup) is then a formal demethanation.

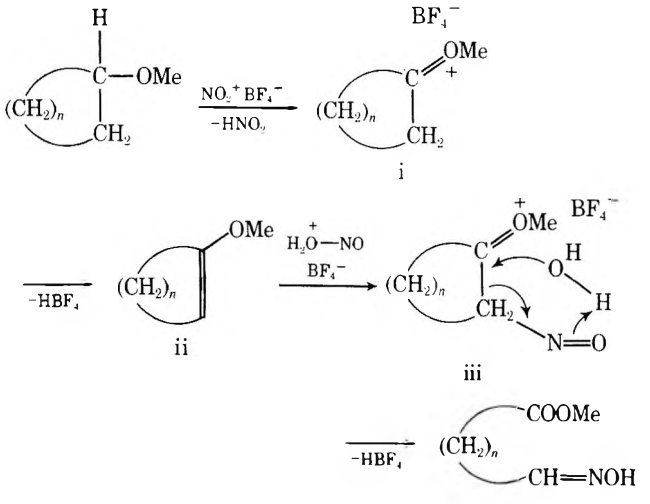


Results summarized in Table I clearly show the generality of methyl ether oxidation. Interestingly, under the experimental conditions methyl ethers of cyclohexanol and cyclopentanol suffer ring fission which is readily accommodated by Scheme I.

It should be noted that cyclohexanone undergoes ring cleavage[7] on reaction with nitrosyl chloride in alcoholic solvents. A similar mechanism involving enol ether formation and nitrosation steps has been formulated. In our cases the enol ethers and the nitrosating agent are only inferred as intermediates. The different behaviors of the cycloalkyl ethers (e.g., cyclohexyl vs. cycloheptyl) can be correlated with the enolizabilities of the corresponding ketones. Thus tautomerization of the methoxycarbenium ions (i) to enol ethers (ii) by elimination of HBF_4 is more favorable when the ring size is either five or six membered.

Methods for oxidative cleavage of *simple* primary alkyl ethers are scarce. One addition is our recently reported process utilizing uranium(VI) fluoride.[8] Most of the existing procedures are concerned with fission of tertiary ethers[9] using trityl salts and silyl and stannyl derivatives of alcohols with various reagents.[2,10] The present method is complementary to others and suggests the feasibility of cleaving enol ethers with nitrosonium salts.

Scheme I



Experimental Section

Oxidative Cleavage of Methyl Ethers with Nitronium Tetrafluoroborate. To a suspension of nitronium tetrafluoroborate[11] (0.565 g, 5 mmol) in dry dichloromethane (5 mL) was added dropwise a solution of a methyl ether (5 mmol) in the same solvent (5 mL) with ice cooling and magnetic stirring. After the vigorous reaction subsided, the ice bath was removed and stirring was continued for 1 h at room temperature. The reaction mixture was quenched with water and extracted with dichloromethane (3 × 20 mL), and the dried ($MgSO_4$) extracts were rotary evaporated to give the product which was microdistilled or recrystallized, and identified by comparison with an authentic sample.

Acknowledgment. Support of our work by the National Institutes of Health is gratefully acknowledged.

Registry No.—Nitronium tetrafluoroborate, 13826-86-3.

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Analysis of Reactivity of Alkenylidenecyclopropanes with Electrophilic Reagents

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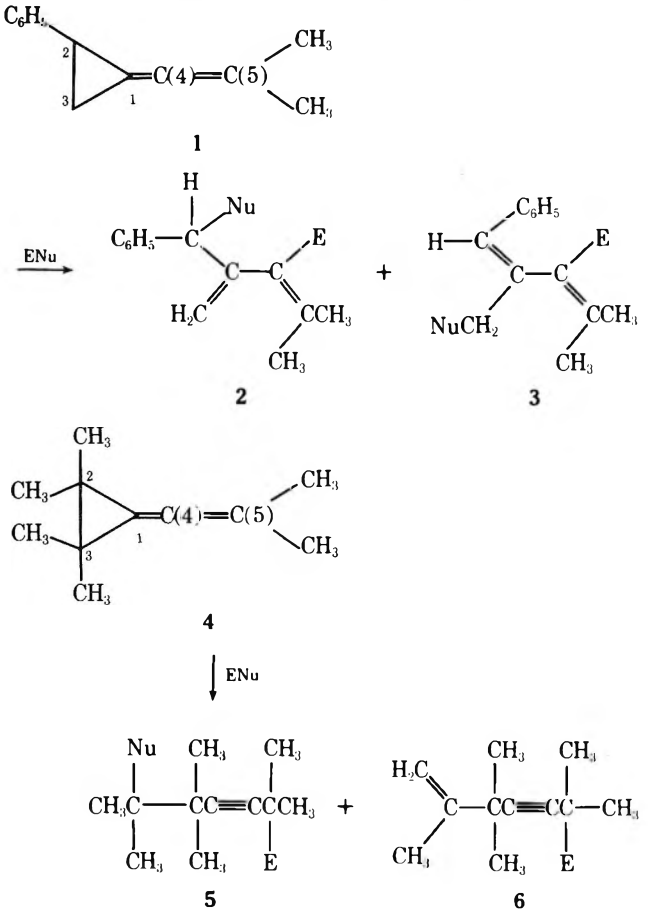
In previous studies on the reactions of differently ring-substituted alkenylidenecyclopropanes with electrophilic reagents, differences in both mode of reaction and reactivity were noted.[1,2] Notably, the phenyl-substituted compound **1** reacted with chlorosulfonyl isocyanide (CSI),[1] acetic acid in the presence of *p*-toluenesulfonic acid (*p*-TS),[2] mercuric acetate,[2] and benzenesulfenyl chloride[2] exclusively at the p orbital on central allene carbon C(4) of the C(1)–C(4) double

bond to produce ring-opened products of general structure **2** and **3**. In contrast, the tetramethyl compound **4** reacted with the same reagents exclusively at the terminal allene carbon C(5) (of the C(4)–C(5) double bond) to produce products having the general structure **5** and **6** (or the cyclic lactam in



the case of CSI).[2] The present note describes the results of a qualitative kinetic study of the reaction of alkenylidenecyclopropanes with an electrophilic reagent, and a molecular orbital rationale for the dramatic differences in mode of reaction and reactivity.

Results

Preliminary kinetic studies of **1** and **4** with a variety of electrophilic reagents indicated that a single reagent could not be found which would allow a convenient and accurate measurement of the rates of reactions of the two extremes of the reactivity scale. Reaction with trichloroacetic acid (TCA) in carbon tetrachloride solution proved to be the most acceptable system for rate measurements.[3] The structures of the reaction products formed under the kinetic conditions were determined by comparison of chemical shifts with the products formed in the *p*-TS-catalyzed addition of acetic acid.[2] In several cases, however, isolation of all of the initially formed products was precluded by the presence of facile acid-catalyzed isomerizations (for example **7** → **8**) and apparent further addition reactions of TCA to the initial products. The products characterized in this manner are illustrated in Scheme I.

An attempt was made to determine the kinetic order of the reaction of TCA with **1**. Although third-order kinetic plots (first-order in **1**, second-order in TCA) were reasonably linear, the resulting specific rate constants were not constant with change in TCA concentration, the k_3's increasing with increasing TCA concentration. A plot of ln k_3 vs. TCA concentration gave a slope of approximately 1.8, indicating a kinetic order in TCA of approximately 4. Instead of trying to measure accurate specific rate constants, a standard set of reaction conditions was adopted and half-lives of the reactions were measured for comparison purposes. The half-lives thus measured are tabulated in Table I.

Table I. Relative Reactivities of Alkenylidenecyclopropane with Trichloroacetic Acid in Chloroform at 30 °C

Compd	Registry no.	$t_{1/2}$, min	% attack at C(5)
1	4544-23-4	30	0
13a	33530-27-7	22	0
13b	33530-26-6	19	0
10	40922-91-6	16	0
15a	37817-46-2	0.25	>95[a]
15b	37817-36-0	≤0.1	>95[a]
4	13303-30-5	<0.1	>90[a]

[a] Peaks corresponding to the products indicated in Scheme I were evident in the NMR spectra up to ~50% reaction, whereupon peaks arising from isomerization and apparent further addition of TCA became evident. The indicated minimum percentages are based on analysis of the spectra early in the course of the reactions.

Table II. Orbital Energies and Charges for 22, 23, and 4 from CNDO/2 Calculations

Compd	E_{HOMO}, eV	$E_{2nd\ OMO}$	Total charge C(5)	Total charge C(4)
4	−10.0259	−12.1638	−0.0059	−0.0073
22[a]	−10.1592	−11.8211	+0.0133	−0.0037
23	−10.2653	−11.8320	+0.0171	−0.0060

[a] Registry no.: **22**, 59055-15-1.

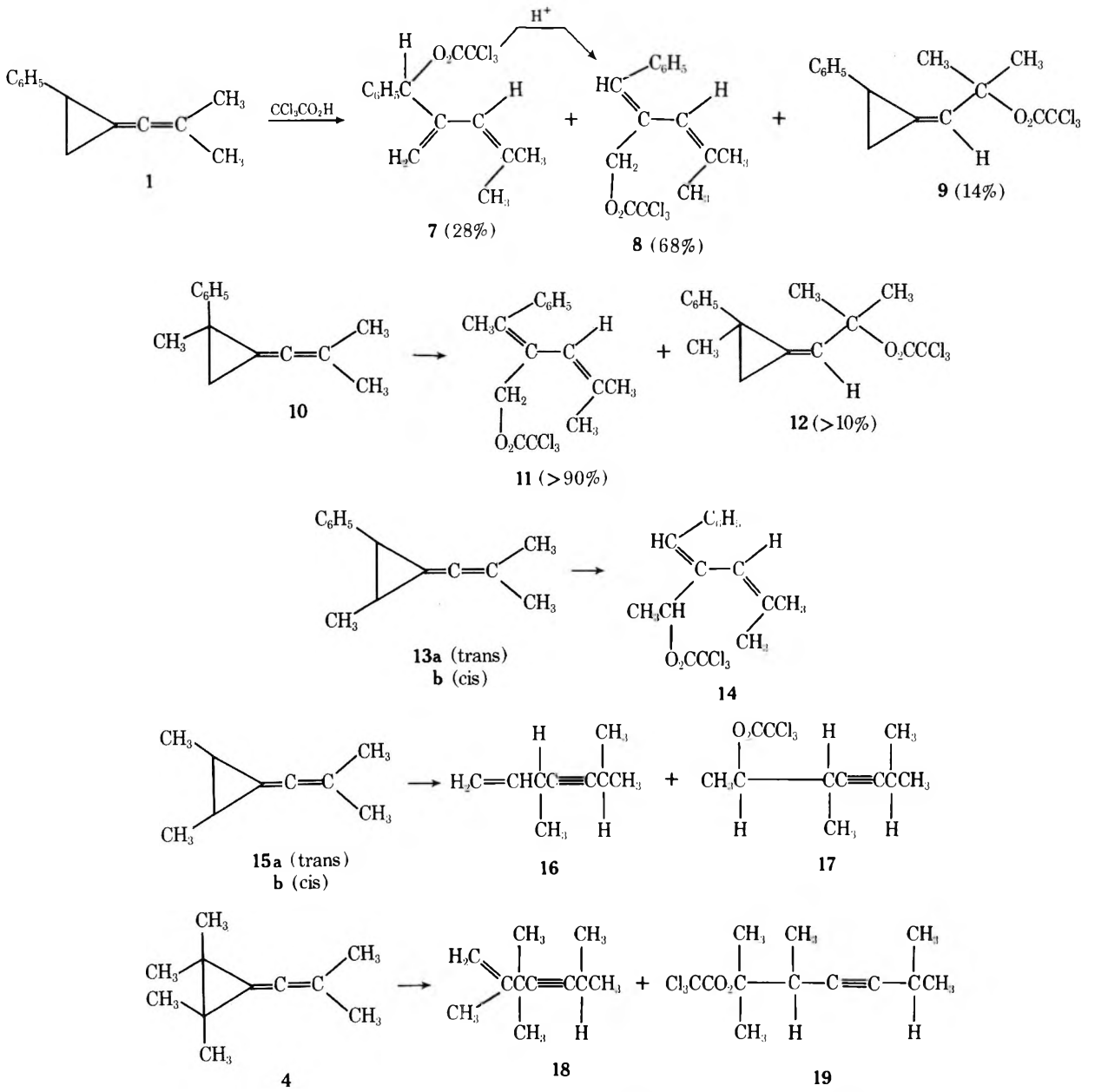
Discussion

Inspection of the structural data presented in Scheme I shows that the phenyl-substituted substrates **1** and **10** undergo attack by proton predominantly on the p orbital on C(4) of the C(1)–C(4) double bond, while **13a** and **13b** react exclusively in this manner. Adducts **9** and **12** are formed by addition across the C(4)–C(5) double bond, a process not previously observed in electrophilic additions to these systems. The formation of **9** and **12** is attributed to a possible concerted electrophilic addition component due to the less polar solvent used in these reactions, as indicated by the more complex reaction kinetics. Integration of the product distribution data with the relative reactivity data shows a difference in reactivity toward electrophilic attack at C(4) vs. C(5) in the phenyl- and tetramethylalkenylidenecyclopropanes of *>10 000!*

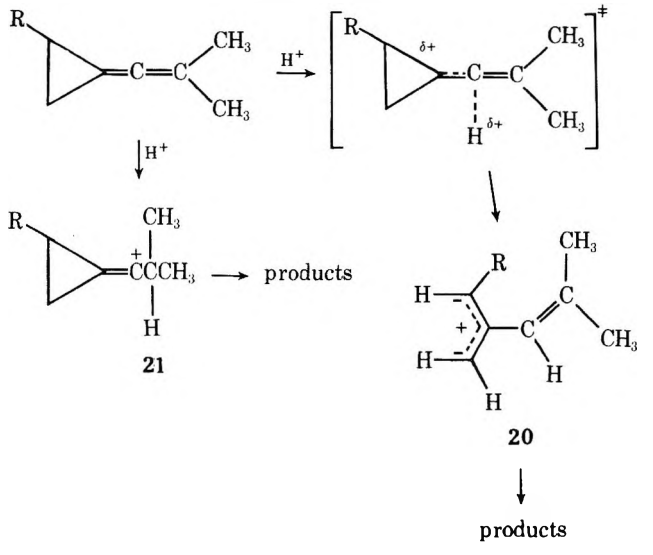
This large difference in reactivity cannot be attributed solely to the stability of intermediates (or transition states) formed in the two different modes of reaction. Electrophilic attack at C(4) of the C(1)–C(4) double bond results in the formation of a cyclopropyl cation which opens to the allyl cation intermediate **20**.[5] The greater stabilization afforded the allyl cation portion of **20** by the phenyl relative to a methyl group cannot be a factor until very late in the ring-opening process. Thus, on this basis one would not expect functions attached to the ring to have a great effect on the reactivity of electrophilic attack at C(4) of the C(1)–C(4) π bond.

Electrophilic attack at C(5) results in the formation of cation **21**, which derives extensive stabilization by interaction of the vacant p orbital on C(4) with the Walsh orbitals[6] of the ring.[1,2,7] Alkyl groups attached to the three-membered ring interact moderately strongly with Walsh orbitals of the ring,[8] whereas an aryl group does not.[9] On this basis alkyl-substi-

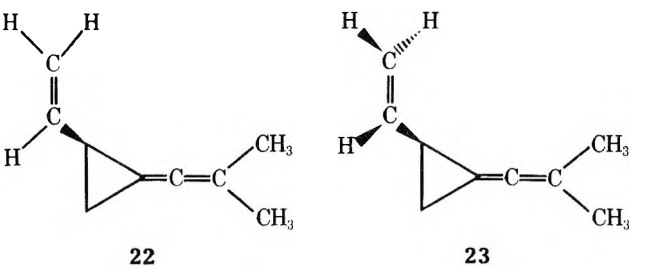
Scheme I



tuted alkenylidenecyclopropanes should be more reactive toward electrophilic attack at C(5) than aryl derivatives. This does not, however, explain the difference in position of electrophilic attack between the alkyl- and aryl-substituted systems.



Insight into the reasons for the difference is gained from the results of CNDO/2 MO calculations for the planar and perpendicular conformations of 2-vinylisobutenylidenecyclopropane (22 and 23) (as abbreviated models of the corresponding phenyl derivatives[10]) and the 2,2,3,3-tetramethyl compound 4. In all three molecules the HOMO is that derived by mixing of the C(4)–C(5) π bond with the Walsh orbitals of the three-membered ring,[8] while the second highest occupied MO is that of the C(1)–C(4) π bond. According to the principles of second-order perturbation MO theory,[11] electrophilic



attack on the tetramethyl compound **4** is favored both by orbital energy (i.e., the energy of the HOMO) and electrostatic interactions. In contrast, electrophilic attack on the phenyl-substituted derivatives involves attack on the lower energy second OMO[12] resulting in a slower reaction, the position of attack being governed by electrostatic interactions. In these cases the electrostatic interaction energy term dominates the attractive bonding interaction energy terms, whose magnitude is inversely proportional to the orbital energy.

Experimental Section

General Conditions for Reactions of Alkenylidenecyclopropanes with Trichloroacetic Acid. To a solution of 0.25 mequiv of the alkenylidenecyclopropane in 0.50 mL of carbon tetrachloride in an NMR tube was added 0.25 mequiv of trichloroacetic acid (TCA) in 0.10 mL of carbon tetrachloride. The solution was rapidly mixed and immediately placed in the NMR probe. The NMR spectrum was periodically integrated over a region containing only characteristic peaks of the starting alkenylidenecyclopropane (~5 s elapsed time from mixing to recording of first integral scan). The percent unreacted alkenylidenecyclopropane was plotted vs. time and $t_{1/2}$ taken as the time corresponding to 50% reaction. In all cases, the reactions proceeded to >95%.

Reaction of 1 with TCA. The final NMR spectrum at >95% reaction showed the presence of adducts **8** and **9**, which were separated by high-pressure liquid chromatographic techniques on a 2 ft × ⅜ in. Corasil column using hexane as eluent.

8: NMR ($CDCl_3$, ^1H FT spectrum on pure fraction isolated by HPLC, integral from CW spectrum of mixture of **8** and **9**) δ 1.77 (overlapping d's, J's = 2.2 and 1.6 Hz, 6 H), 4.95 (s, 2 H), 5.79 (br s, 1 H), 6.62 (br s, 1 H), 7.30 (m, 5 H); MS calcd for $C_{15}H_{15}{}^{35}Cl_3O_2$ 332.0137, obsd 332.0137.

9: NMR ($CDCl_3$) δ 1.38 (dd, J's = 10.6, 6.1 Hz, 1 H), 1.44 (s, 6 H), 1.75 (dd, J's = 8.1, 6.1 Hz), 2.56 (dd, J's = 10.6, 8.1 Hz, 1 H), 5.32 (br s, 1 H), 7.25 (br s, 5 H); MS calcd for $C_{15}H_{15}{}^{35}Cl_3O_2$ 332.0137, obsd 332.0144.

NMR spectra recorded early during the reaction indicated the presence of **7** (br s; at δ 5.11 and 5.46) which on longer reaction times is converted to **8**.[2] Integration of NMR spectra taken after low conversions indicate that **7**, **8**, and **9** are initially formed in a 2:4:1 ratio.

Reaction of 10 with TCA. NMR spectra recorded after short reaction times clearly showed the presence of **11** and **12** (>9:1 ratio), and possibly very small quantities of the isomer of **11** (corresponding to **7** formed from **1**). NMR spectra recorded later in the reaction showed the presence of other components (unidentified) and decreasing quantities of **11** and **12**. Attempts to isolate pure samples of **11** and **12** were not successful. **11**: NMR ($CDCl_3$, from a mixture of **11** and **12**) δ 1.70 (br s, 3 H), 1.83 (overlapping d's, $J \approx 1.2$ and 2.1 Hz, 6 H), 4.74 (s, 2 H), 5.75 (br s, 1 H), 7.30 (m, 5 H). **12**: NMR δ 1.52 (s, 3 H), 1.63 (s, 6 H), 5.11 (br s, 1 H), 7.3 (m, 5 H). The ring methylene hydrogens of **11** and **12** appear as poorly resolved multiplets partially obscured by the methyl resonances of **11** and **12**.

Reaction of 13a and 13b with TCA. The NMR spectrum of the product derived from both **13a** and **13b** showed the presence of a single adduct, **14**: NMR ($CDCl_3$) δ 1.34 (d, J = 1.8 Hz, 3 H), 1.53 (d, J = 6.7 Hz, 3 H), 1.77 (d, J = 1.3 Hz, 3 H), 5.57 (q, J = 6.7 Hz, 1 H), 5.83 (m, 1 H), 6.65 (m, 1 H), 7.3 (br s, 5 H); MS calcd for $C_{16}H_{17}{}^{35}Cl_3O_2$ 346.0294, obsd 346.0288.

Reaction of 15a and 15b with TCA. The reaction of **15a** and **15b** with TCA produced a mixture whose NMR spectrum was very complex and could not be interpreted. No resonance in the δ 5.8 region ($-CH{=}C(CH_3)_2$) could be detected. Although the initial reaction was complete in ~1 min, the NMR spectrum of the product mixture continued to change. After 5 min a substantial portion of the initially formed product had disappeared.

Reaction of 4 with TCA. The reaction of **4** with TCA immediately produced a mixture of **18** and **19** in an approximate 1:1 ratio. Product **18** was identified by comparison of ^1H chemical shifts previously observed.[2] Product **19** was identified by comparison of the ^1H chemical shifts with the corresponding acetate previously characterized,[2] all chemical shifts corresponding to ±0.01 ppm. In addition to **18** and **19** a minor product appears to have been formed, as evidenced by the appearance of two methyl singlets in the NMR. This adduct could not be isolated and it is not known whether this adduct is a primary or secondary product.

Registry No.—**7**, 62861-82-9; **8**, 62861-83-0; **9**, 62861-84-1; **11**, 62861-85-2; **12**, 62861-86-3; **14**, 62861-87-4; trichloroacetic acid, 76-03-9.

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(3) Although CSI and benzenesulfenyl chloride offered certain advantages in such a kinetic study, it was highly desirable to use an electrophilic reagent which did not add via a possible concerted process[1] or via an onium ion intermediate.[2]
(4) Calculated on the basis of 95% situselectivity (assumed limits of NMR detectability of product formation) in the aryl- and alkyl-substituted cases. An assumed 99% situselectivity would yield a reactivity difference of >300 000.
(5) The formation of ring-retained products from **1** and **10** differs from earlier observations in which only ring-opened products were formed.[1,2] The formation of ring-retained products probably occurs via concerted addition pathways which are competitive with cation intermediate pathways in the less polar solvent carbon tetrachloride.
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(11) See A. Devaquet and L. Salem, *J. Am. Chem. Soc.*, **91**, 3793 (1969).
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High Pressure Assisted Synthesis. Evidence for Nucleophilic Displacement on 2,2,2-Trifluoro-1-phenylethyl Tosylate

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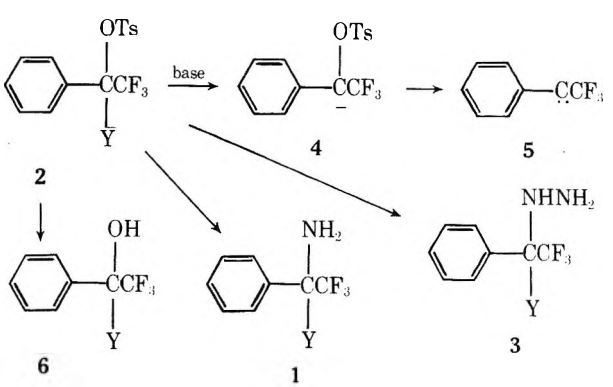
While searching for a practical synthesis of 2,2,2-trifluoro-1-phenylethylamine[1] (**1h**), we contemplated the report[2] that 2,2,2-trifluoro-1-phenylethyl tosylate (**2h**) reacts with hydrazine to afford the alkylated hydrazine **3h**. Trifluoromethyl groups severely impede S_N1 or S_N2 reactions when α to the reaction site.[3a-b] However, the hydrazinolysis reaction might conceivably proceed via attack upon hydrazine by the electrophilic carbene **5**, formed from α elimination of tosylate ion from carbanion **4**.



d, Y = D
h, Y = H

Comparative reactions show that tosylate **2h** is essentially inert to ammonia under conditions which cause complete hydrazinolysis.[4] However, at 6 kbar pressure the tosylate reacts smoothly with ammonia in dry THF (saturated at 0 °C, 1 atm) within 4 h at 130 °C to afford amine **1h** as the major product (>95%) with <2% of alcohol **6h** also formed. Alcohol **6h** may arise either from traces of water present or from attack by ammonia at sulfur. High pressure facilitates reactions developing charge separation in the transition state by enhancing solvent of the charged species (i.e., "electrostriction").[5]

To determine whether chiral amine results from chiral tosylate and to provide additional mechanistic information, chiral deuterated tosylate **2d** was similarly treated and found to afford racemic nondeuterated amine **1h.** Shorter reaction times allowed recovery of residual tosylate, which was found to have lost essentially all of its deuterium, as judged from ^{19}F NMR.[6] Addition of water to the reaction reduces the rate of the exchange reaction relative to that of the ammonolysis reaction.[7] For example, heating (*R*)-(−)-deuteriotosylate **2d,** $[\alpha]^{25}_D$ −54.5° (c 3.9, $CHCl_3$), prepared from enantiomerically pure deuterated (*R*)-(−)-carbinol, with ammonia dissolved in 90:10 THF–H_2O at 130 °C and 6 kbar pressure for 4 h converts 54% of the tosylate into a 61:39 mixture of nondeuterated–deuterated amine **1** and 5.8% into a 62:38 mixture of nondeuterated–deuterated alcohol **6.** The residual tosylate (40.2%) contains but 4% of the original deuterium. The isolated amine has $[\alpha]^{25}_D$ +9.2° (*c* 12.0, ethanol), 38% of the value reported for enantiomerically pure *S* amine **1h.**[1] Examination of the 90-MHz NMR spectrum of the isotopic mixture of amines **1h–d** using (*R*)-(−)-2,2,2-trifluoro-1-(9-anthryl)ethanol[8] as a chiral solvating agent shows the protonated amine **1h** to be racemic. Therefore, deuterated amine **1d** must be essentially enantiomerically pure and configurationally inverted with respect to its tosylate precursor. Isolated alcohol **6** has $[\alpha]^{25}_D$ +12.9° (neat), 31% of the magnitude of the value reported[9] for the *S*-(+) enantiomer, $[\alpha]^{25}_D$ 41.2° (neat). Examination of the ^1H and ^{19}F NMR spectra of this alcohol in the presence of (*R*)-(+)-1-(1-naphthyl)ethylamine shows[10] the protonated alcohol to be racemic and the deuterated alcohol to be of high enantiomeric purity.[11] The recovered tosylate exhibits $[\alpha]^{25}_D$ − 1.61° (*c* 3.9, $CHCl_3$), which corresponds to 2.9% of its original value. It should be noted that the preparation of tosylate **2d** from alcohol **6d** proceeds *without* loss of deuterium. Thus, **2d** is of the same enantiomeric purity as its alcohol precursor. This alcohol, resolved via the large scale chromatographic separation of its diastereomeric (*R*)-(+)-1-(1-naphthyl)ethylamine carbamates,[12,13] showed no resonances attributable to the second enantiomer when its spectrum was determined in (*R*)-(+)-1-(1-naphthyl)ethylamine.[10] Thus, alcohol **6d** was enantiomerically pure within experimental limits. Control experiments show amine **1d** and alcohol **6d** to be configurationally stable under the ammonolysis conditions.

On the basis of the preceding results, it can be stated that, within the accuracy of the NMR measurements and the assumption that the deuterated and nondeuterated amines have essentially the same specific rotation, the major portion of amine **1** has arisen by ammonia displacement of tosylate ion with inversion of configuration. Owing to the accompaniment of the relatively fast tosylate exchange–racemization reaction, the question as to whether any of amine **1** has resulted from a carbene process is still moot. However, we have detected (^{19}F NMR) no product which might arise from reaction of carbene with solvent. Moreover, while the first step in the formation of carbene **5** is likely to be enhanced by increased pressure, since charge is formed, the overall process for carbene formation should be disfavored at high pressure. Presumably, the transition state for the fragmentation of anion **4** would involve an increase in volume and a loss of electrostriction owing to the greater electron delocalization in tosylate ion than in anion **4.** Finally, it is also evident that the presence of water gives rise to alcohol **6** by a process similar to that involved in ammonolysis, but possibly mitigated to a small extent by displacement at sulfur.

Experimental Section

Melting points were taken on a Buchi apparatus and are uncorrected. Infrared spectra were obtained with a Beckman IR-12 or a Perkin-Elmer 237B spectrophotometer. Proton and fluorine NMR spectra were obtained with Varian Associates A-60A, EM-390, HA-100, or HR-220 instruments. Mass spectra were determined using a Varian MAT CH-5 spectrometer. Microanalyses were performed by Nemeth and his colleagues.

All compounds in this study have been previously reported in the nondeuterated forms. The deuterated compounds were prepared as follows.

2,2,2,-Trifluoro-1-deuterio-1-phenylethanol (6d). Sodium borodeuteride[15] was added portionwise to a solution of 2,2,2-trifluoroacetophenone (5.9 mmol, 1.03 g) in dry methanol (25 mL) until such addition no longer produced an exothermic reaction. After the reaction mixture cooled to room temperature, it was diluted with 25 mL of water, washed with 30 mL of 3 M HCl, and extracted with two 50-mL portions of methylene chloride. The combined extracts were dried over anhydrous magnesium sulfate and concentrated, and the crude alcohol distilled [bp 92 °C (15 mm)] to afford **6d** in 96% yield: NMR ($CDCl_3$) δ 3.68 (br s, OH), 7.42 (br s, C_6H_5); IR (neat) 3450 (OH), 1250, 1150, 1050, 1000 (CF_3) cm^{-1}; mass spectrum (70 eV) *m/e* (rel intensity) 177 (40, M^+).

Anal. Calcd for $C_8H_6DF_3O$: C, 54.24; H, 3.41. Found: C, 54.19; H, 3.29.

Resolution of (*R*)-(−)-2,2,2-Trifluoro-1-deuterio-1-phenylethanol (6d). Deuterated carbinol **6d** was converted to the diastereomeric (*R*)-(+)-1-(1-naphthyl)ethylamine carbamates, which were chromatographically separated as previously described.[12,13] The appropriate diastereomerically pure carbamate was converted with refluxing sodium ethoxide–ethanol into enantiomerically pure (*R*)-(−)-deuteriocarbinol **6d,** $[\alpha]^{25}_D$ −41.09° (neat) with no apparent deuterium loss (NMR).

(*R*)-(−)-2,2,2-Trifluoro-1-deuterio-1-phenylethyl tosylate (2d) was prepared from deuteriocarbinol **6d** in 90% yield by a previously described procedure.[2] Again, no loss of deuterium was evidenced by NMR: mp 113–114 °C; NMR ($CDCl_3$) δ 2.36 (br s, C_6H_4-*p*-CH_3), 7.18–7.80 (m, C_6H_5, C_6H_4); mass spectrum (70 eV) *m/e* (rel intensity) 331 (27, M^+); $[\alpha]^{25}_D$ −54.5° (c 3.9, $CHCl_3$).

Anal. Calcd for $C_{15}H_{12}DF_3O_3S$: C, 54.38; H, 3.65. Found: C, 54.26; H, 3.59.

2,2,2-Trifluoro-1-deuterio-1-phenylethylamine (1d). High-pressure ammonolysis of 500-mg portions of tosylate **2d** was conducted for 4 h at 103 °C and 6 kbar in 1-oz screw-cap polyethylene bottles in a conventional high-pressure apparatus previously described.[14] Ammonical THF solutions were prepared by addition of 10% (volume) water to dry THF saturated at 0 °C with ammonia. Amine **1d** was isolated using an extractive workup and is a colorless liquid: bp 88 °C (22 mm); NMR ($CDCl_3$) δ 1.84 (br s, NH), 7.23–7.41 (m, C_6H_5); IR (neat) 3400 (NH), 3000, 1595, 1500, 1460, 1255, 1170, 1120 cm^{-1}; mass spectrum (70 eV) *m/e* (rel intensity) 176 (14, M^+), 137 (5), 108 (65), 107 (100).

Anal. Calcd for $C_8H_7DF_3N$: C, 54.55; H, 4.01; N, 7.95. Found: C, 54.41; H, 3.96; N, 7.91.

Acknowledgment. This work was partially supported by grants from the National Science Foundation and the National Institutes of Health.

Registry No.—**1d,** 62929-95-7; (*R*)-(−)-**2d,** 62929-96-8; **6d,** 62929-97-9; (*R*)-(−)-**6d,** 62961-05-1; 2,2,2-trifluoroacetophenone, 434-45-7.

References and Notes

(1) W. H. Pirkle and J. R. Hauske, *J. Org. Chem.*, **42,** 1839 (1977).
(2) W. E. Pereira, Jr., M. Solomon, and B. Halpern, *Aust. J. Chem.*, **24,** 1103 (1971).
(3) (a) J. Hine and R. G. Ghirardelli, *J. Org. Chem.*, **21,** 1550 (1956); (b) J. Hine and W. H. Brader, *J. Am. Chem. Soc.*, **75,** 3964 (1953).
(4) The reported[2] procedure for preparing **3** involves heating the tosylate and hydrazine hydrate to reflux for 12 h. In our hands, this *heterogeneous* reaction affords substantial quantities of a material tentatively identified as the bis-alkylated hydrazine. Use of a cosolvent to render the mixture *ho-*

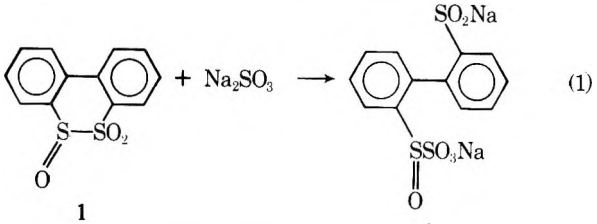
mogeneous prevents formation of the bis product. For example, overnight heating of a solution of 33 g of tosylate and 32 g of anhydrous hydrazine in 150 mL of triethylene glycol in a 110 °C bath affords complete conversion of tosylate to hydrazine **3** (^{19}F NMR). Under these conditions, deuterated tosylate **2d** affords hydrazine, retaining 89% of the deuterium.
(5) W. J. Le Nobel, *Prog. Phys. Org. Chem.*, **5**, 207 (1967).
(6) For compounds **1**, **2**, **3**, and **6**, the isotopic shift at 84.6 MHz causes the slightly broadened singlet of the deuterated species to coincide with the upfield line of the doublet arising from the protonated species.
(7) Both water and *dry* ethanol have this effect, presumably as a consequence of solvation-altered basicity and nucleophilicity.
(8) W. H. Pirkle, D. L. Sikkenga, and M. S. Pavlin, *J. Org. Chem.*, **42**, 384 (1977).
(9) H. M. Peters, D. M. Fiegl, and H. S. Mosher, *J. Org. Chem.*, **33**, 4245 (1968).
(10) W. H. Pirkle and S. D. Beare, *J. Am. Chem. Soc.*, **89**, 5485 (1967).
(11) The simultaneous determination of two nonidentical enantiomeric purities for compounds differing only by isotopic substitution illustrates the power of chiral solvating agents for NMR determination of enantiomeric purity and absolute configuration.
(12) (a) W. H. Pirkle and J. R. Hauske, *J. Org. Chem.*, **42**, 1839 (1977); (b) W. H. Pirkle and M. S. Hoekstra, *ibid.*, **39**, 3904 (1974).
(13) W. H. Pirkle and R. W. Anderson, *J. Org. Chem.*, **39**, 3901 (1974).
(14) R. A. Grieger and C. A. Eckert, *J. Am. Chem. Soc.*, **92**, 7149 (1970).
(15) Sodium borodeuteride was purchased from Ventron Corp. and was used without further purification.

Communications

Synthesis and Properties of a Bunte Salt *S*-Oxide[1]

Summary: Reaction of sulfite ion with dibenzo[c,*e*]-1,2-dithiin 1,1,2-trioxide leads to the formation of a compound having a Bunte salt *S*-oxide functional group, $-S(O)SO_3^-$, the first example of a compound with such a functionality; in acid solution the Bunte salt *S*-oxide undergoes a striking and extremely rapid decomposition to the cyclic thiolsulfonate, dibenzo[c,*e*]-1,2-dithiin 1,1-dioxide.

Sir: As part of a general study of the reactions of nucleophiles with oxidized derivatives of dibenzo[c,*e*]-1,2-dithiin we have examined the reaction of sulfite ion with dibenzo[c,*e*]-1,2-dithiin 1,1,2-trioxide[2] (**1**) and have been able to isolate as the exclusive reaction product the salt having structure **2** (eq 1).

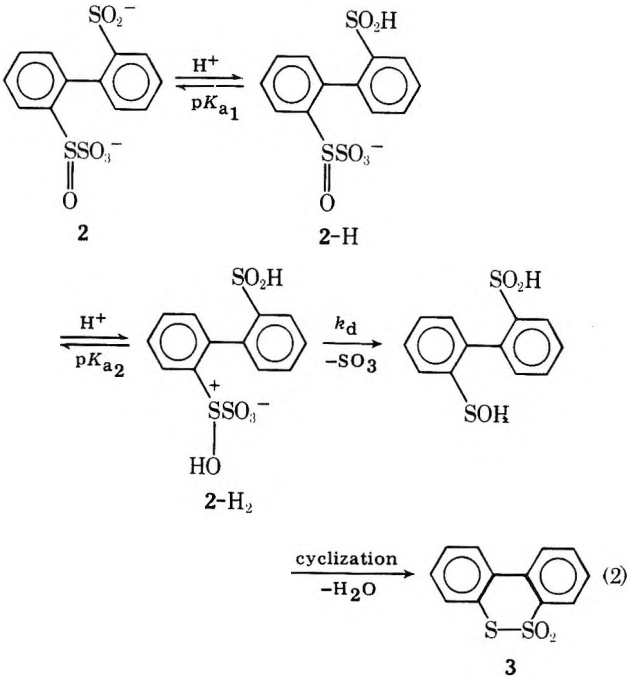


1 2 (1)

Salt **2** contains a Bunte salt *S*-oxide functional group, $-S(O)SO_3^-$, and is the first reported example of a compound containing this functionality. It exhibits some striking and interesting chemical behavior in acid solution.

Bunte salt *S*-oxide **2** was prepared by rapidly adding a 0.05 M solution of **1** in anhydrous dioxane to an equal volume of 0.05 M aqueous sodium sulfite at room temperature. Kinetic studies had shown that the reaction of **1** with sulfite is extremely rapid, $k_2 = 3 \times 10^5$ M^{-1} s^{-1}, and is characterized in the ultraviolet by the disappearance of the absorption maximum at 310 nm characteristic of **1** and the appearance of a new maximum at 280 nm (ϵ 6400) due to **2**. As soon as the addition of **1** to the sulfite solution was complete, the solution was frozen and the solvent was removed by lyophilization to give **2** as a white, powdery solid.[3] The infrared spectrum of **2** (KBr) showed a strong band at 1220 cm^{-1} ($-SO_3^-$) and a series of strong absorptions in the 950–1050-cm^{-1} region (>S=O, $-SO_2^-$, $-SO_3^-$) consistent with structure **2**, but not with any possible isomeric structure.

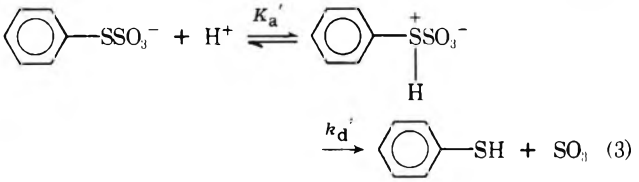
The stability of **2** in solution and the nature of its decomposition products vary dramatically with the pH of the solution. At 25 °C in 60% dioxane containing 0.01 M $HClO_4$ **2** (10^{-4} M) disappears *extremely rapidly* ($k_1 = 1.2$ s^{-1}) and yields the cyclic thiolsulfonate **3**[4] as the exclusive organic product. In contrast, in a 1:1 acetate/acetic acid buffer **2** disappears much more slowly ($k_1 = 2.2 \times 10^{-4}$ s^{-1}, rate independent of total buffer concentration) and yields *none* of the cyclic thiolsulfonate [the major organic product under these conditions is diphenyl 2,2′-disulfinate[2] (**4**)[5]]. Study of the rate and products of the disappearance of **2** in trifluoroacetate, dichloroacetate, and chloroacetate buffers in 60% dioxane indicates that the facile decomposition of **2** to give thiolsulfonate **3** is acid catalyzed and takes place by the mechanism shown in eq 2. The



(2)

key steps in this mechanism are the reversible protonation of the sulfinyl group of the Bunte salt *S*-oxide (K_{a_2}) and the loss of sulfur trioxide from the sulfinyl-protonated form (k_d).

Ordinary Bunte salts undergo acid-catalyzed decomposition by an analogous mechanism[6] (eq 3), but at a rate which is



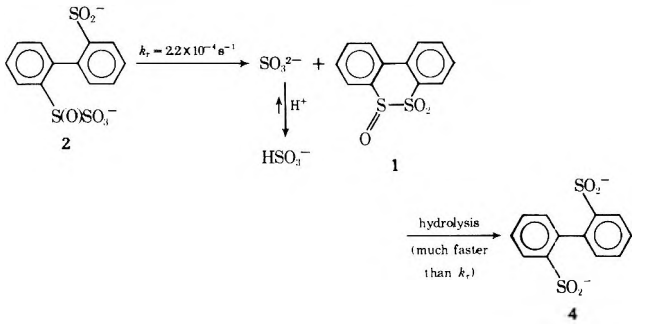
(3)

about 3×10^8 *slower* under the same conditions (k_1 for acid-catalyzed decomposition of $PhSSO_3^-$ in 60% dioxane containing 0.01 M $HClO_4$ at 25 °C is calculated[6] to be only 4×10^{-9} s^{-1}). The Bunte salt *S*-oxide is thus *over* 10^8 *less stable* in acid solution than a similar Bunte salt. One important contributor to this phenomenal difference in stability is almost certainly the much greater basicity of the sulfinyl function in the *S*-oxide as compared to the sulfide sulfur in the Bunte salt, i.e., K_{a2} in eq 2 $\ll K_a'$ in eq 3. Sulfinyl groups are known to be much more basic than analogously substituted sulfide groups.[7]

Given the interesting chemical behavior and high reactivity shown by **2**, we are now searching for a synthetic route that will permit the preparation of a simple Bunte salt *S*-oxide containing no other functional group than the $-S(O)SO_3^-$ function.

References and Notes

(1) This research supported by the Robert A. Welch Foundation (Grant D-650).
(2) M. M. Chau and J. L. Kice, *J. Org. Chem.*, in press.
(3) Upon being heated in a melting point tube a sample of **2** begins to undergo slow thermal decomposition at slightly above 40 °C. This thermal decomposition of the solid, which is rapid at 70 °C, appears to lead to the formation of significant amounts of sulfur trioxide. The other products of the decomposition have not been identified, but do not melt below 300 °C.
(4) H. J. Barber and S. Smiles, *J. Chem. Soc.*, 1141 (1928).
(5) Formation of disulfinate **4** from **2** in the acetate buffer occurs by rate-determining slow reversion of **2** to **1** plus sulfite, followed by rapid hydrolysis of **1** to **4**. In the acetate buffer sulfite is protonated to HSO_3^- as soon as it is formed, preventing the reverse reaction of **1** with sulfite.



(6) J. L. Kice, J. M. Anderson, and N. E. Pawloski, *J. Am. Chem. Soc.*, **88**, 5245 (1966).
(7) Dimethyl sulfoxide[8a] is slightly over 10^5 stronger base than dimethyl sulfide.[8b]
(8) (a) D. Landini, G. Modena, G. Scorrano, and F. Taddei, *J. Am. Chem. Soc.*, **91**, 6703 (1969); (b) P. Bonvicini, A. Levi, V. Lucchini, and G. Scorrano, *J. Chem. Soc., Perkin Trans. 2*, 2267 (1972).

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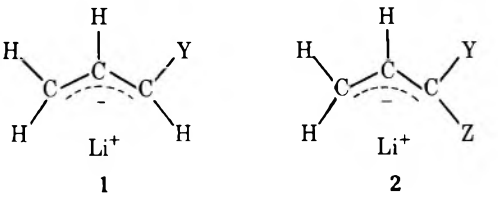
A General Route to Terminally Substituted Allylic Derivatives of Silicon and Tin. Preparation of Allylic Lithium Reagents

Summary: Wittig reactions of the appropriate β-trimethylstannyl- and β-trimethylsilylethyltriphenylphosphonium salt-derived ylides ($Ph_3P{=}CHCH_2SnMe_3$, $Ph_3P{=}CHCH_2SiMe_3$, $Ph_3P{=}C(Me)CH_2SiMe_3$ in the examples presented) with aldehydes and ketones provide a useful, general route to allylic compounds of silicon and tin.

Sir: We have reported recently concerning the synthesis and the unusual regioselectivity of *gem*-dichloroallyllithium in carbonyl addition reactions.[1] The results of this study prompted further interest in unsymmetrically substituted allyllithium reagents of general types **1** and **2**. Three major



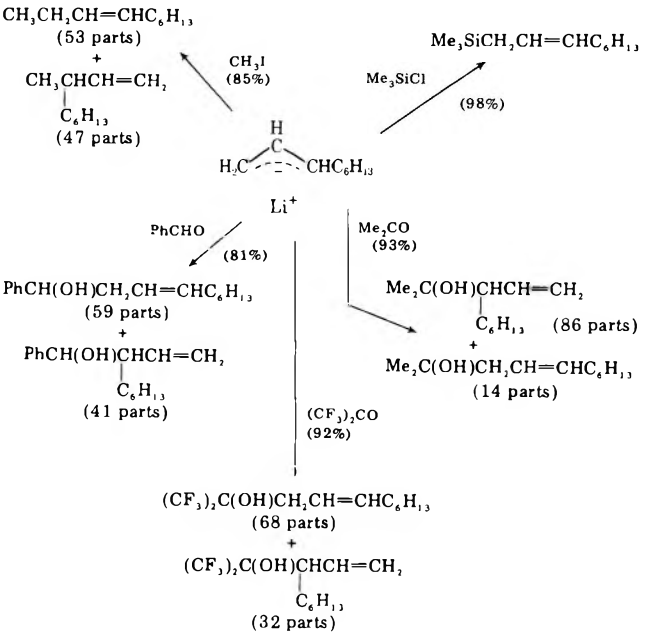
routes are available for the synthesis of allylic lithium reagents: direct lithiation of olefins,[2] allyl ether cleavage with metallic lithium,[3] and transmetalation reactions of allylic derivatives of heavy metals, principally of tin and lead.[1,4]

We describe here a new, general route to allylic derivatives of tin of types **3** and **4**. These are useful starting materials

$Me_3SnCH_2CH{=}CHR$ (**3**) $\quad$ $Me_3SnCH_2CH{=}CRR'$ (**4**)

for allylic lithium reagents of types **1** and **2**, where Y and Z = alkyl and aryl. Our new allyltin synthesis has added impor-

Scheme I. Reactions of *n*-Hexylallyllithium



Scheme II. Reactions of 1,1-Cyclopentamethyleneallyllithium

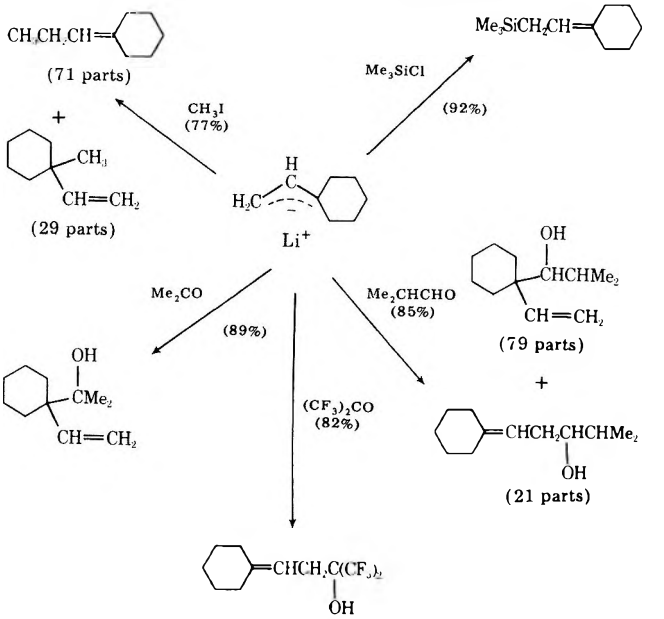
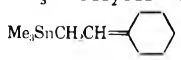
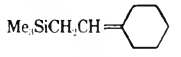
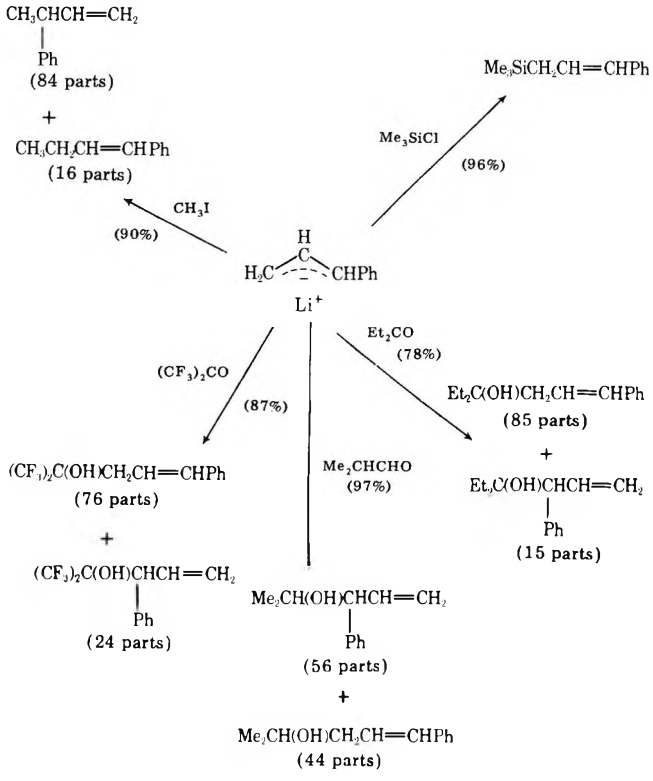


Table I. Preparation of Allylic Silicon and Tin Compounds[a]

Ylide reagent	Carbonyl reactant	Allylic product (% yield)	Trans/cis ratio
$Ph_3P{=}CHCH_2SnMe_3$	n-$C_6H_{13}CH{=}O$	$Me_3SnCH_2CH{=}CHC_6H_{13}$-$n$ (98)	70/30
		 (79)	
	$C_6H_5CH{=}O$	$Me_3SnCH_2CH{=}CHC_6H_5$ (70)	95/5
$Ph_3P{=}CHCH_2SiMe_3$	n-$C_6H_{13}CH{=}O$	$Me_3SiCH_2CH{=}CHC_6H_{13}$-$n$ (71)	75/25
		 (85)	
	$C_6H_5CH{=}O$	$Me_3SiCH_2CH{=}CHC_6H_5$ (63)	64/36
	$(C_2H_5)_2C{=}O$	$Me_3SiCH_2CH{=}C(C_2H_5)_2$ (38)[b]	
	$(CF_3)_2C{=}O$	$Me_3SiCH_2CH{=}C(CF_3)_2$ (43)	
$Ph_3P{=}C(CH_3)CH_2SiMe_3$	$C_2H_5CH{=}O$	$Me_3SiCH_2C(CH_3){=}CHC_2H_5$ (74)	55/45[c]
	$C_6H_5CH{=}O$	$Me_3SiCH_2C(CH_3){=}CHC_6H_5$ (72)	50/50
		(deprotonation regenerated the starting phosphonium salt)	

[a] Reactions were carried out in THF medium. The reactants were mixed at room temperature and the reaction mixture was stirred and heated at reflux under nitrogen for 12–15 h. Trap-to-trap distillation at 0.05–0.1 mm into a receiver cooled to −78 °C gave a solution of the product, which was analyzed by GLC. In larger preparative-scale reactions the product was isolated by vacuum distillation. [b] The procedure in *a* gave only a yield of 27%. In this reaction the THF solvent was replaced by toluene and the reaction mixture then was heated at reflux for 40 h. [c] Stereochemistry was not assigned.

Scheme III. Reactions of Phenylallyllithium



tance in view of the newly developed utility of the allyltin compounds themselves in organic and organometallic synthesis.[5] Furthermore, this general procedure can be extended to the synthesis of allylsilicon compounds analogous to **3** and **4**, and, although this has not yet been examined, also of allyl compounds of germanium and lead. This is of interest, since allylsilanes also have found useful applications in organic synthesis in recent years.[6]

The general concept involved in our allylmetallics synthesis is based on an allyltin preparation of Hannon and Traylor.[7] These workers used the reaction of trimethyltinlithium with vinyltriphenylphosphonium bromide to prepare the ylide $Ph_3P{=}CHCH_2SnMe_3$, which could be used in a Wittig reaction with cyclohexanone.[8] In our hands, however, this procedure gave only moderate yields of the expected allyltin compound, $Me_3SnCH_2CH{=}C_6H_{10}$-c (44%, Wittig reaction at −93 °C; 48%, at room temperature), based on the 1:1 Me_3SnLi/$[Ph_3PCH{=}CH_2]Br$ stoichiometry used, and, moreover, a considerable portion (~50%) of the trimethyltinlithium was converted to hexamethylditin during the course of the reaction.

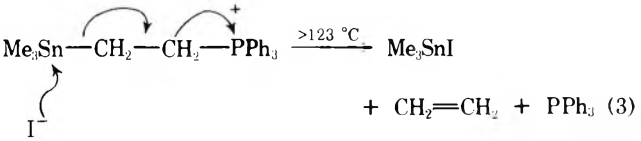
Our new procedure uses the same Wittig reagent, but involves a different preparation, as shown in eq 1 and 2.

$$Ph_3P{=}CH_2 + Me_3MCH_2I \rightarrow [Ph_3PCH_2CH_2MMe_3]I \quad (1)$$
$$(M = Sn, Si)$$

$$[Ph_3PCH_2CH_2MMe_3]I + RLi \rightarrow Ph_3P{=}CHCH_2MMe_3 + RH + LiI \quad (2)$$
$$(R = (Me_2CH)_2N \text{ when } M = Sn;\ R = CH_3 \text{ when } M = Si)$$

The phosphonium halides, $[Ph_3PCH_2CH_2SnMe_3]I$ and $[Ph_3PCH_2CH_2SiMe_3]I$, were isolated in better than 85% yield and were fully characterized. That this procedure is extendable to the synthesis of $[Ph_3PCH(R)CH_2MMe_3]I$ salts was demonstrated by the preparation of $[Ph_3PCH(Me)CH_2SiMe_3]I$ by reaction of $Ph_3P{=}CHCH_3$ with Me_3SiCH_2I. This procedure is simple and easily carried out. The preparation of the required phosphorus ylides presents no special difficulties, and the iodomethyl compounds are fairly easily prepared; Me_3SiCH_2I by the action of sodium iodide in anhydrous medium on the readily available Me_3SiCH_2Cl,[9] and Me_3SnCH_2I by the reaction of ICH_2ZnI with trimethyltin chloride.[10] The ethereal phosphorus ylide solution is added slowly to the cooled (ice bath) ether solution of the iodomethyl compound (nitrogen atmosphere). The reaction mixture is stirred at room temperature for 12–15 h and then the phosphonium halide which was precipitated is filtered. In the case of the $Ph_3P{=}CH_2/Me_3SnCH_2I$ reaction, the phosphonium salt product was obtained admixed with 10–15% of $[Ph_3PMe]I$. Although this impurity may be removed by fractional crystallization, such processing is rather wasteful. Since the impurity in subsequent Wittig reactions gives olefinic products which are much more volatile (and hence easily separated) than the allyltin products, it is our usual practice to use the crude $[Ph_3PCH_2CH_2SnMe_3]I$ after its purity has been assessed by NMR spectroscopy.

The β-trimethylstannylethylphosphonium iodide undergoes thermal decomposition at its melting point, evolving ethylene in a β-elimination reaction (eq 3), but the silicon

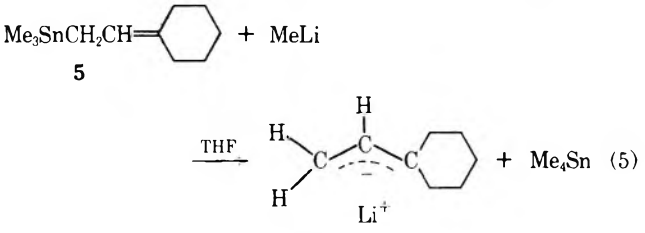


analogue is stable well above its melting point of 163–164.5 °C.

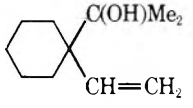
The β-stannyl- and β-silyl-substituted phosphonium halides may be deprotonated to the respective ylides, both of which form deep red-orange solutions in diethyl ether and in tetrahydrofuran. Methyllithium serves well as the base in the case of $[Ph_3PCH_2CH_2SiMe_3]I$ and $[Ph_3PCH(CH_3)CH_2SiMe_3]I$, but for the deprotonation of $[Ph_3PCH_2CH_2SnMe_3]I$, lithium amides, R_2NLi (R = Me_2CH or Me_3Si), must be used, since organolithium reagents do not react regiospecifically, attacking in part at tin as well as at the protons α to phosphorus. The ylides formed, $Ph_3P{=}CHCH_2SnMe_3$, $Ph_3P{=}CHCH_2SiMe_3$, and $Ph_3P{=}C(Me)CH_2SiMe_3$, react readily with aldehydes and, in general, somewhat less well with ketones, to give the expected allylstannanes and allylsilanes (eq 4; Table I).

$$Ph_3P{=}CHCH_2MMe_3 + RR'C{=}O \xrightarrow{THF} Me_3MCH_2CH{=}CRR' + Ph_3PO \quad (4)$$

The three allylic tin compounds in Table I undergo ready conversion to the respective allylic lithium reagents, e.g., eq 5. In a typical reaction, **5** (3.74 mmol) in 200 mL of dry THF



at 0 °C, under nitrogen, was treated with 4.1 mmol of methyllithium in diethyl ether. The resulting yellow solution was stirred for 30 min at 0 °C and then 20 mmol of acetone was added. After the reaction mixture had been stirred at room temperature for 30 min, hydrolytic workup was followed by GLC analysis of the organic phase to establish the presence of **6** in 89% yield. The results of these experiments are illus-



6

trated in Schemes I–III. The product yields are uniformly excellent. A discussion of the observed regioselectivities in the reactions of these ambident reagents will be deferred until this study has been completed.

It is obvious that this new route to allylic compounds of silicon and tin should be quite general in its scope of applicability. By appropriate variation of the phosphorus ylide and the carbonyl substrate in these reactions, allylic derivatives of silicon and tin of type $Me_3MCH_2C(R){=}CR'R''$, where R, R′, and R″ should be capable of wide variation, should be accessible. The allyltins thus prepared would provide starting materials for many new allylic lithium reagents. In many cases the direct lithiation procedure, the reaction of RLi/Lewis base or RLi/Me_3COK with an appropriate unsaturated hydrocarbon, would provide the simplest route to the desired allylic lithium reagent.[2] However, the additives which usually are required to effect such metalations may not always be compatible with other functionality in the carbonyl reactant or may interfere in other ways. Also, there will be instances when the appropriate unsaturated hydrocarbon is not available. Thus the versatility of our new procedure and its ease of application may prove very useful in organic and organometallic synthesis.

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Conjugate Addition–Elimination in the Reaction of *B*-1-Alkynyl-9-borabicyclo[3.3.1]nonanes with 4-Methoxy-3-buten-2-one and Related Derivatives. A Convenient New Route to Conjugated Enynones

Summary: *B*-1-Alkynyl-9-borabicyclo[3.3.1]nonanes (*B*-1-alkynyl-9-BBN), easily and quantitatively prepared by the reaction of boron trifluoride diethyl etherate with the corresponding lithium methyl alkynyldialkylborinate,[1] undergo a remarkably facile reaction with the readily available 4-methoxy-3-buten-2-one and related derivatives in hexane at room temperature to provide, in excellent yield, conjugated enynones.

Sir: Recently we described the conjugate addition of *B*-1-alkynyl-9-borabicyclo[3.3.1]nonanes to a variety of α,β-unsaturated ketones, which provided a valuable synthesis of γ,δ-alkynyl ketones.[2] House has suggested that reduction potentials may be used to determine the suitability of substrates toward conjugate addition of organocuprates and perhaps other organometallic reagents.[3] Hooz and Layton, in their work on dialkylalkenyl alanes and dialkylalkynyl alanes, point out that the yields of conjugate addition product appear to correlate well with the reduction potentials of the substrates utilized.[4]

Table I. Conversion of Alkynes into 4-Alkynyl-3-buten-2-ones by the Reaction of the Corresponding *B*-1-Alkynyl-9-BBN Derivatives with 4-Methoxy-3-buten-2-one[a]

Alkyne	Product[b]	Isolated yield, %	Bp, °C (mmHg)	n^{20}D	Mol wt[c] Calcd	Found
1-Hexyne	*trans*-3-Decen-5-yn-2-one	85	86–88 (3.5)	1.5060	150.104	150.102
1-Decyne	*trans*-3-Tetradecen-5-yn-2-one	81	86 (0.001)	1.4922	206.167	206.164
Phenylethyne	*trans*-6-Phenyl-3-hexen-5-yn-2-one	88[d]	45–46[e]		170.073	170.074
3,3-Dimethyl-1-butyne	*trans*-7,7-Dimethyl-3-octen-5-yn-2-one	98[d]	71–72 (3)	1.4898	150.104	150.107
Cyclohexylethyne	*trans*-6-Cyclohexyl-3-hexen-5-yn-2-one	72	54 (0.015)	1.5294	176.120	176.118
5-Chloro-1-pentyne	*trans*-9-Chloro-3-nonen-5-yn-2-one	74	59 (0.015)	1.5296	170.050	170.048
2-Methyl-1-buten-3-yne	*trans*-7-Methyl-3,7-octadien-5-yn-2-one	90[d]	33 (0.016)	1.5488	134.073	134.074

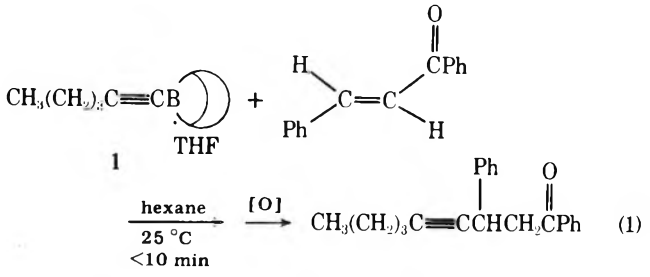
[a] A 20% excess of 4-methoxy-3-buten-2-one was employed in all reactions. [b] Satisfactory IR and ^{1}H NMR were obtained for all compounds. [c] Exact mass was measured on a CEC-21-110 mass spectrometer. [d] Crude yield, >97% pure by GLC analysis. ^{1}H NMR and IR appear identical before and after purification. [e] Melting point.

Table II. Synthesis of Conjugated Enynones by the Addition–Elimination Reaction of *B*-1-*tert*-Butylethynyl-9-BBN with β-Alkoxy α,β-Unsaturated Ketones

Alkoxy enone[a]	Product(s)[b]	Reaction time	% GC yield
(*E*)-4-Methoxy-3-buten-2-one (**5**)	(*E*)-7,7-Dimethyl-3-octen-5-yn-2-one	1 h	100
(*E*)-4,4-Dimethyl-1-methoxy-1-penten-3-one (**6**)	(*E*)-2,2,8,8-Tetramethyl-4-nonen-6-yn-3-one	1 h	100
(*E*)-3-Methoxy-1-phenyl-2-propen-1-one (**7**)	(*E*)-6,6-Dimethyl-1-phenyl-2-hepten-4-yn-1-one	1 h	65
(*E*)-1-Methoxy-2-methyl-1-penten-3-one (**8**)	(*E*)-4,8,8-Trimethyl-4-nonen-6-yn-3-one	4 h	94
4-Methoxy-3-penten-2-one (**9**) (84:16 mixture of *Z*:*E*)[c]	4,7,7-Trimethyl-3-octen-5-yn-2-one (2.1:1 mixture of *E*:*Z*)[c]	2 days	29
(*E*)-4-Methoxy-3-penten-2-one (**10**)[d]	4,7,7-Trimethyl-3-octen-5-yn-2-one (2.7:1 mixture of *E*:*Z*)[c]	2 days	17
3-Ethoxy-2-cyclohexen-1-one (**11**)	3-[3,3-Dimethyl-1-butynyl]-2-cyclohexen-1-one	5 days	0

[a] A 20% excess of alkoxy enone was employed in all reactions. [b] Satisfactory IR, ^{1}H NMR, and exact mass was obtained for all products. [c] Measured by ^{1}H NMR. [d] It is interesting to note that the reaction of this methoxy enone with *B*-1-hexynyl-9-BBN provided a 70% isolated yield of 3-decen-5-yn-2-one after 5 days.

In our studies on the conjugate addition of alkynylboranes, we noted that the addition of *B*-1-hexynyl-9-BBN–THF complex (**1**) to benzalacetophenone was rapid and quantitative, as expected from the increased reduction potential (eq 1).

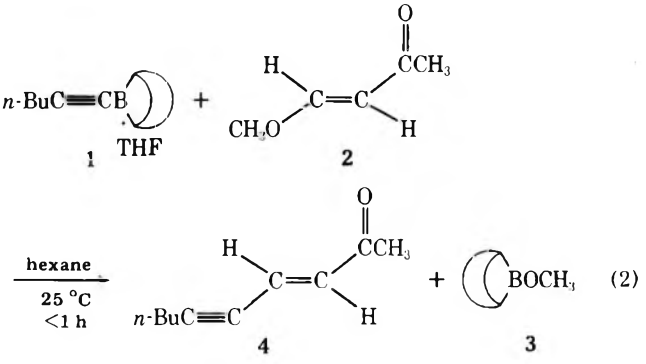


(1)

On the other hand, a β-methoxy substituent lowers the reduction potential, presumably making the substrate less susceptible to conjugate addition. Surprisingly, the reaction of **1** with 4-methoxy-3-buten-2-one (**2**) proved to be exceedingly rapid, complete in <1 h at 25 °C. Moreover, the conjugate addition was accompanied by the facile elimination of *B*-methoxy-9-BBN (**3**), providing the corresponding *trans*-4-alkynyl-3-buten-2-one (**4**) in nearly quantitative yield (eq 2). This appeared to be an exceptionally promising synthesis of conjugated enynones. Consequently, we undertook to explore this discovery.

Only two routes to 4-alkynyl-3-buten-2-ones have been described.[5,6] Both methods require preparation of several intermediates and provide only moderate yields of product. Neither has been demonstrated to be general for a variety of alkynes.

In view of these limitations, we undertook to explore the generality of the new procedure, utilizing a representative variety of *B*-1-alkynyl-9-BBN compounds. Indeed, this study



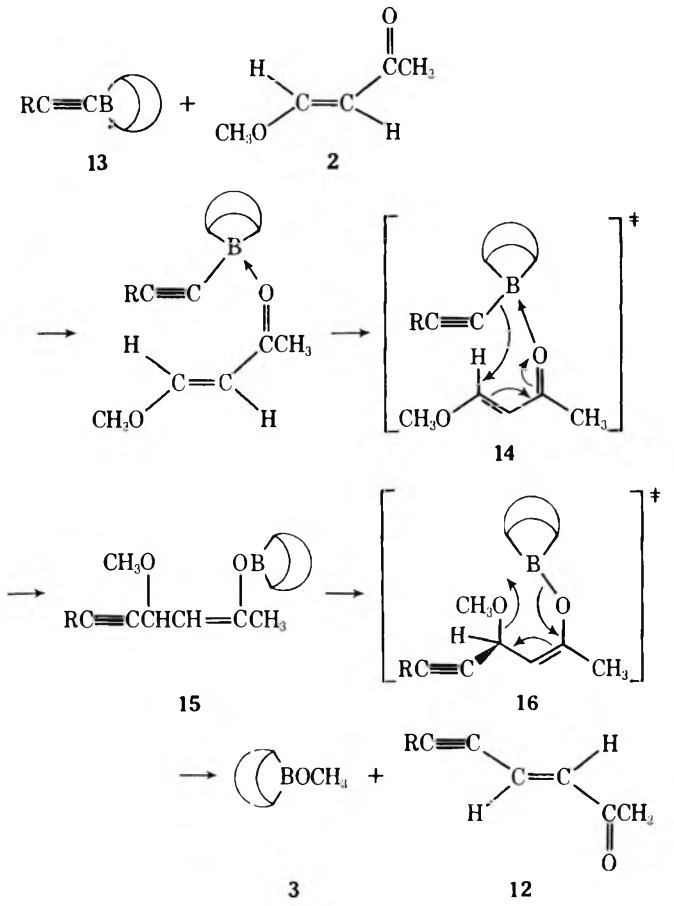
(2)

revealed that this synthesis proceeds with remarkable ease with a wide variety of alkynylboranes (Table I).

We utilized *B*-1-*tert*-butylethynyl-9-BBN in a brief exploration of this reaction with other β-methoxy α,β-unsaturated ketones. Ketones capable of assuming a cisoid conformation (**5**–**10**) reacted satisfactorily to give products in the indicated yields. On the other hand, that derivative not capable of assuming such a cisoid conformation (**11**) gave no indication of reaction in the desired manner (Table II).

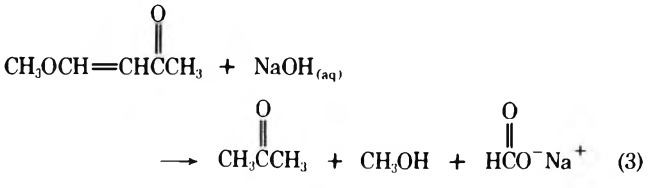
Proton NMR experiments confirm that the 4-alkynyl-3-buten-2-one (**12**) and *B*-methoxy-9-BBN (**3**) are produced spontaneously in the reaction mixture and are not a result of the workup conditions. These results are consistent with a process that involves an initial coordination of the carbonyl group at the ketone **2** with the boron atom of the 9-BBN derivative **13**, followed by the formation of a cyclic transition state, **14**, giving the intermediate **15**, which rapidly eliminates *B*-methoxy-9-BBN (**3**) through another cyclic transition state **16**, yielding the desired product **12** (Scheme I). In all but one case, the reaction is stereospecific, producing only the *E* isomers, as indicated by GLC analysis, ^{13}C NMR, ^{1}H NMR (J_{vinyl}

Scheme I



= 16 Hz), and IR (960–965 cm^{-1}) spectra.

The simple work-up procedure for this reaction provides highly pure products (≥97%) without the need for further purification of the crude material. The small excess of 4-methoxy-3-buten-2-one utilized in the reaction is conveniently hydrolyzed under the basic workup conditions to by-products which are water soluble and/or highly volatile and therefore can be readily removed from the desired products (eq 3).[7]



(3)

Likewise, the *B*-methoxy-9-BBN by-product is converted by the standard peroxide oxidation[8] into water-soluble *cis*-1,5-cyclooctanediol and boric acid, providing clean products after simple extraction of the reaction mixture.

The following procedure for the preparation of *trans*-7,7-dimethyl-3-octen-5-yn-2-one is representative. To 7.44 g (27.1 mmol) of 3,3-dimethyl-*B*-1-butynyl-9-BBN–THF complex,[1] in an oven-dried nitrogen-flushed 100-mL flask equipped with a magnetic stirring bar, a septum inlet, and a gas inlet tube with stopcock, was added 40 mL of dry hexane. To the solution was added 3.26 g (32.6 mmol) of 4-methoxy-3-buten-2-one[9] and the reaction mixture was stirred for 1 h at 25 °C to ensure complete reaction. Oxidation was accomplished by the rapid addition of 12 mL of 3 M NaOH, followed by dropwise addition of 12 mL of 30% H_2O_2 (*Caution:* exothermic!). After stirring at 25 °C for 2 h, the reaction mixture was poured into a separatory funnel and the layers were separated. The aqueous layer was washed with pentane (three 15-mL portions) and the combined organic extracts were washed with a 1:1 H_2O–THF solution (three 30-mL portions). The organic phase was dried over anhydrous $MgSO_4$ and filtered, and the volatiles were removed in vacuo to provide 3.99 g (98%) of *trans*-7,7-dimethyl-3-octen-5-yn-2-one, 97% pure by GLC analysis: $n^{20}D$ 1.4898; IR (neat) 2230, 1670, 1595, 960 cm^{-1}; ^1H NMR (CCl_4, Me_4Si) δ 1.23 (s, 9 H), 2.18 (s, 3 H), 6.22 (d, 1 H, J = 16 Hz), 6.58 (d, 1 H, J = 16 Hz). Distillation, bp 71–72 °C (3 mmHg), provided analytically pure material.

It is evident that this procedure makes it practical to synthesize highly functionalized, stereospecific products in high yields that should be useful in organic synthesis. Furthermore, this development makes available an exciting new reaction of organoboranes, and research is underway to examine its full potential.

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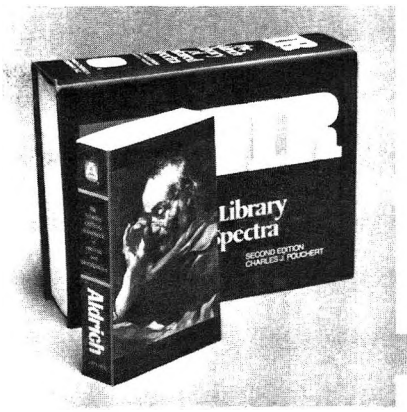

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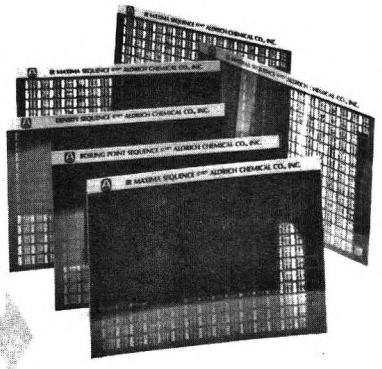

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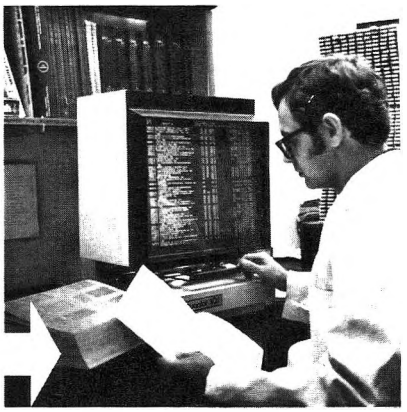

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