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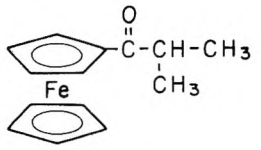

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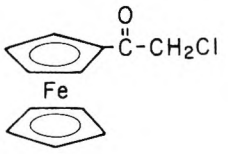

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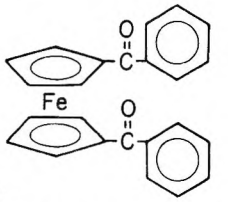

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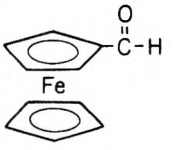

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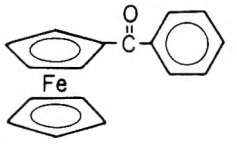

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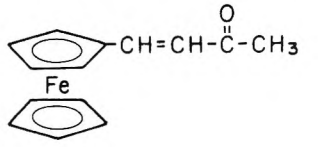

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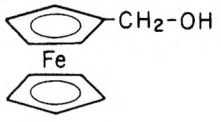

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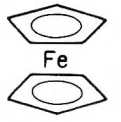

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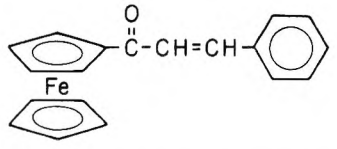

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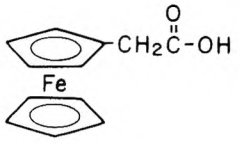

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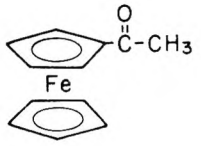

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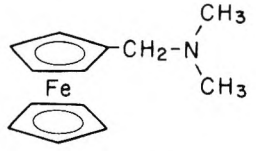

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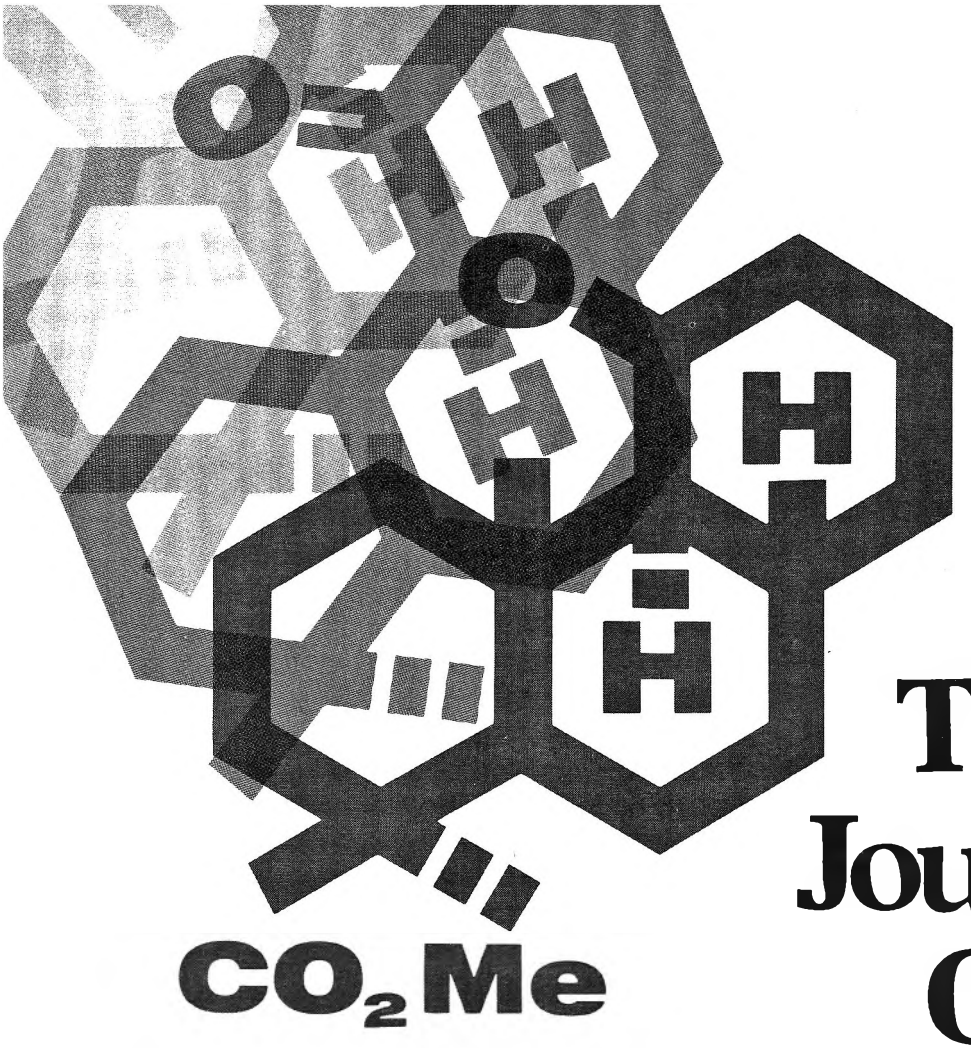

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JULY 11, 1975

2-Thiazolines in Organic Synthesis. A Synthesis of Mono-, Di-, and Trialkylacetaldehydes

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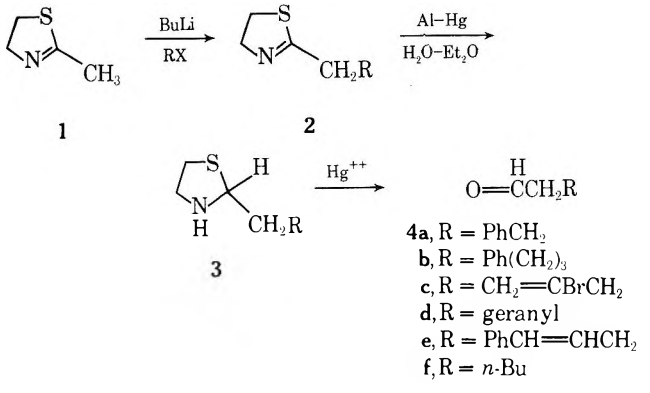
Department of Chemistry, Colorado State University, Fort Collins, Colorado 80523

Received February 18, 1975

Metalation of 2-methyl-2-thiazoline (1) using *n*-butyllithium at low temperature furnishes a nucleophilic thiazoline anion which may be alkylated to *n*-(alkylmethyl)thiazolines (2). This process may be repeated to produce dialkylated (5 and 9) and trialkylated thiazolines 14. Reduction of the C=N link was readily accomplished using aluminum amalgam in wet ether affording the thiazolidines 3, 6, and 15, respectively. Release of the aldehydes 4, 7, 10, and 16 was then performed in aqueous acetonitrile containing mercuric chloride. Deuteration of C-1 of the aldehydes was also demonstrated by carrying out the aluminum amalgam reduction using ether moistened with deuterium oxide.

The use of heterocycles as precursors in the synthesis of functionalized aliphatic compounds has recently been discussed.[1] Several years ago we described in preliminary form[2] a synthesis of aldehydes from 2-methyl-2-thiazoline (7), a simple commercially available heterocycle. We wish to describe here more extensive studies which demonstrate the intrinsic value of this technique for preparing a variety of substituted acetaldehyde derivatives and their C-1 deuterated analogs. A major feature of this process rests in the fact that the immediate precursor to the elaborated acetaldehyde is the thiazolidine 3, which releases the product under neutral conditions. This circumvents the acidic conditions necessary to accomplish this same task in the Wittig[3] and oxazine[4] routes to aldehydes and thus avoids a variety of undesirable side reactions usually encountered with acid-sensitive aldehydes or their acid-sensitive substituents.

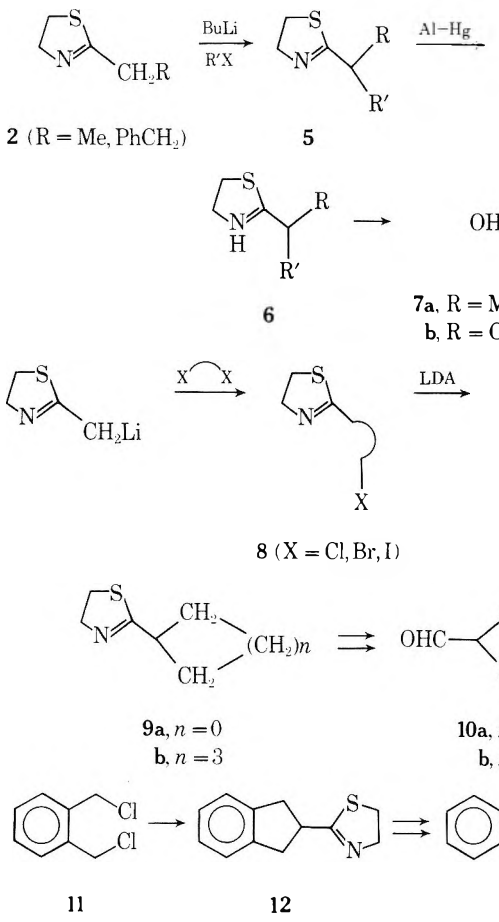
In the preparation of monoalkylated acetaldehydes, the scheme involves the metalation of 1 with *n*-butyllithium in THF at −78°. The resulting lithio salt was then treated with 1.0 equiv of various alkyl iodides or benzyl or allylic chlorides, furnishing the elaborated thiazolines 2 in 80–95% yield. A small amount (1–2%) of dialkylated material could be detected by GLC. The use of alkyl bromides gave somewhat lower yields (55–65%) whereas alkyl chlorides resulted in negligible alkylation (0–10%). The next step involved reduction of 2 to the thiazolidine 3 and this was readily accomplished using aluminum amalgam in moist ether, adapted from the procedure described by Cooper[5] for penicillins. For small-scale runs (<1 g), aluminum foil was utilized to make the amalgam, whereas it was more convenient to employ granular aluminum for larger scale reactions. In order to assess the feasibility of using other reducing agents it was found that sodium borohydride gave reasonable (45–53%) yields of thiazolidine but only under strict pH control (4–6) and the hydrochloride of 2 had to be initially prepared prior to reduction.[6a] Most other conditions involving sodium borohydride led to mixtures of thiazolidine and overreduced open-chain compounds unless *N*-alkyl quaternary salts were used.[6b] Reductions of 2 using aluminum amalgam consistently gave 90–97% yields of thiazolidines 3 and this was undoubtedly the method of choice. Cleavage to the aldehydes was performed using a slight excess of mercuric chloride in 80% aqueous acetonitrile at room temperature for 1–2 hr. Thus, the scheme led to monoalkyl acetaldehydes in 30–70% overall yield. The yields varied somewhat with the particular aldehyde prepared, being partly dependent upon the purity and stability of certain halides in the first step. For example, geranyl chloride was rather unstable and gave the corresponding thiazoline **2d** in only 48% yield. Furthermore, the intermediates 2 and 3 were purified (TLC, distillation, or column) in some cases which resulted in loss of material. Alkylation of the lithio thiazoline was also accomplished with 2-iodopropane and 2-iodohexane, giving 2 (R = *i*-Pr) and 2 (R = 2-hexyl) in 78 and 50% yield, respectively. Although these products were not brought forward to the corresponding aldehydes, the results indicate that secondary halides are also useful electrophiles in this process.



1 2 3

4a, R = $PhCH_2$
b, R = $Ph(CH_2)_3$
c, R = CH_2=$CBrCH_2$
d, R = geranyl
e, R = PhCH=$CHCH_2$
f, R = *n*-Bu

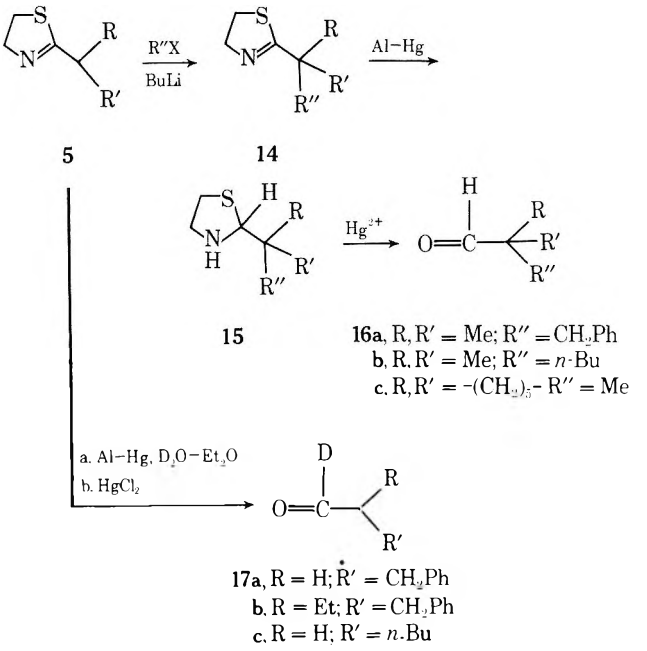
The scheme was further studied with respect to prepar-



ing dialkylacetaldehydes. Thus 2-ethyl and 2-phenethyl thiazolines (**2**) were subjected to low-temperature metalation with butyllithium and treated with benzyl chloride and ethyl iodide, respectively. This furnished **5** (R = Me; R′ = $PhCH_2$) and **5** (R = $PhCH_2$; R′ = Et) in good yield. In order to obtain aldehydic products completely free from monoalkyl derivatives, it was necessary to purify **5** prior to reduction and cleavage. This was accomplished merely by distillation which provided the dialkylated thiazolines **5** in high purity (>98% via GLC). Reduction of the latter using aluminum amalgam gave the thiazolidines **6** (90–94%), which were cleaved by mercuric chloride as mentioned earlier, affording 2-methyl-3-phenylpropionaldehyde (**7a**, 95%) and 2-ethyl-3-phenylpropionaldehyde (**7b**, 88%).

α,ω-Dihalides could be sequentially alkylated by first forming the haloalkyl thiazolines **8**, which were then metalated (with or without prior purification) to the cycloalkyl thiazolines **9**. In this manner, the 2-(cyclopropyl) **9a** and 2-(cyclohexyl) **9b** were prepared in 61 and 60% yields, respectively. Reduction and cleavage led to cyclopropane- and cyclohexanecarboxaldehydes (**10a** and **10b**). The synthesis of 2-indancarboxaldehyde (**13**) was also accomplished starting from o-xylenyl dichloride (**11**). The cyclic thiazoline **12**, however, was formed in lower yield (30%) owing to competing side reactions during the cyclization step. The acidity of the chlorobenzyl protons was assumed to be competing with proton removal from the α position of the thiazoline side chain. Furthermore, if **8** contained a bromo or iodo atom, the cyclization was best carried out using lithium diisopropylamide (LDA) to avoid halogen–metal interchange when butyllithium was employed. To form the cyclopropyl thiazoline, 1-chloro-2-bromoethane was used, since 1,2-dibromoethane undergoes rapid elimination to ethylene.[4]

Trialkylated acetaldehydes **16** were also prepared by metalation of dialkylthiazolines **5**. It was found that although butyllithium performed satisfactorily as the base, LDA



gave cleaner products and somewhat higher yields of alkylation (90–95%) to the trialkylated thiazolines **14**. Once again, in order to eliminate troublesome side products such as the dialkylated starting materials **5**, the trialkylated thiazolines were distilled prior to reduction. The purification could be made convenient by appropriate choice of alkyl group introduction. For example, if 2-ethylthiazoline (**5**, R = Me; R′ = H) is alkylated sequentially with 1,5-dibromopentane giving the 1-methyl-1-cyclohexylthiazoline **14** [R = Me; R′ and R″ = $-(CH_2)_5-$], distillative separation is simple. On the other hand, if this trisubstituted thiazoline is prepared from 2-(cyclohexyl)thiazoline [**5**, R = R′ = $-(CH_2)_5-$] and methyl iodide, the separation becomes more difficult owing to the closeness of the boiling points of the starting and final products. Reduction of **14** in the usual fashion gave the corresponding trisubstituted thiazolidines **15**, which were cleaved without purification to the trialkylacetaldehydes in good yield.

Finally, several representative examples of C-1 deuterated aldehydes were prepared. Thus, by reduction of dialkyl thiazolines **5** in ether saturated with deuterium oxide, the aluminum amalgam furnished the appropriate thiazolidines, which were readily cleaved with mercuric chloride in aqueous acetonitrile to produce the deuterated aldehydes **17a–c**. The deuterium content was determined by mass and NMR spectra and found to be 94 ± 3%. This technique compares favorably with the deuterated aldehydes prepared from the dihydro-1,3-oxazine route[4] while utilizing deuterium oxide rather than the more expensive sodium borodeuteride.

In summary, the 2-thiazoline **1** provides a useful template on which to construct mono-, di-, or trialkylacetaldehydes. This overcomes the limitation in the oxazine–aldehyde synthesis wherein no dialkylation or trialkylation could be performed owing to the competing reactions observed for secondary or tertiary oxazine carbanions.[4] In the following article the use of the mild neutral cleavage to release the aldehyde from the thiazolidine allows the preparation of protected β-hydroxy aldehydes and products derived therefrom.

Experimental Section[7]

Monoalkylation of 2-Methyl-2-thiazoline to 2. A dry 250-ml flask fitted with rubber septums, three-way stopcock, and magnetic stirrer was evacuated and flushed with nitrogen. A 0.8 *M* solution (10.0 g/90 ml) of 2-methyl-2-thiazoline (Aldrich) in THF was

syringed into the flask and cooled to −78° with Dry Ice–acetone. After 15 min, a hexane solution of *n*-butyllithium (1.05 equiv) was added over a 20-min period via a syringe. A precipitate formed within 15 min after the complete addition of the lithium reagent. The mixture was stirred for 1.5 hr at −78°, the alkyl halide (1.03–1.05 equiv) in 20 ml of THF was added dropwise via a syringe (5–10 min), and the clear resulting solution was stirred for an additional 1 hr at −78°. The mixture was slowly allowed to come to room temperature (2–3 hr) or allowed to stir overnight, prior to quenching in 150 ml of ice–water. The aqueous mixture was adjusted to pH 2–3 with dilute hydrochloric acid. The organic layer (hexane–THF) was separated and the aqueous layer was extracted with 100 ml of *n*-pentane. The organic extracts were discarded. The aqueous solution was neutralized with 20% potassium hydroxide (pH 10), saturated with salt, and extracted with ether. Concentration of the dried ethereal extracts (K_2CO_3) gave the crude alkylated thiazolines **2** in 90–95% yield (88–92% purity by GLC, UCW-98). Further purification was accomplished by distillation.

2-(2-Phenethyl)-2-thiazoline (2a) was prepared from benzyl chloride: bp 127–130° (2.4 Torr); 86% yield; ir (film) 1625, 1610, 1503, 1460, 760, 710 cm^{-1}; NMR (CCl_4) δ 2.6–3.3 (m, 6), 4.1 (t, 2), 7.3 (br s, 5).

Anal. Calcd for $C_{11}H_{13}NS$: C, 69.09; H, 6.85; N, 7.32. Found: C, 68.92; H, 6.92; N, 7.59.

2-(4-Phenylbutyl)-2-thiazoline (2b) was prepared from 3-phenylpropyl iodide: bp 153–156° (2.4 Torr); 74% yield; ir (film) 1625, 1608, 1500, 1200, 987, 755, 710 cm^{-1}; NMR (CCl_4) δ 1.6 (m, 4), 2.2–2.8 (m, 4), 3.02 (t, 2), 4.05 (t, 2), 7.18 (m, 5).

Anal. Calcd for $C_{13}H_{17}NS$: C, 71.18; H, 7.81; N, 6.39. Found: C, 70.99; H, 7.80; N, 6.44.

2-(3-Bromo-3-butenyl)-2-thiazoline (2c) was prepared from 2,3-dibromopropene: bp 80–82° (0.45 Torr); 68% yield; ir (film) 2940, 2855, 1630, 1435, 1425, 1200, 1092, 1033, 975, 912, 887 cm^{-1}; NMR ($CDCl_3$) δ 2.8 (br s, 4), 3.3 (t, 2), 4.25 (t, 2), 5.45 (d, 1), 5.65 (d, 1).

Anal. Calcd for $C_7H_{10}NSBr$: C, 38.19; H, 4.58; N, 6.36. Found: C, 37.95; H, 9.76; N, 6.25.

2-(Geranylmethyl)-2-thiazoline (2d) was prepared from geranyl chloride, which in turn was prepared from geraniol according to Collington and Meyers.[8] The geranyl chloride used here was ~80% pure and contained ~20% mesylate from the homoallylic alcohol present in geraniol. Bulb-to-bulb distillation of crude **2d** gave 50% yield: ir (film) 1628, 1605, 1592, 1493, 1452, 1379, 994, 981, 745, 700 cm^{-1}; NMR ($CDCl_3$) δ 1.6 (m, 9), 2.02 (m, 4), 2.5 (m, 4), 3.3 (t, 2), 4.2 (t, 2), 5.2 (m, 2).

Anal. Calcd for $C_{14}H_{23}NS$: C, 70.83; H, 9.76; N, 5.90. Found: C, 71.03; H, 9.71; N, 5.85.

***trans*-2-(4-Phenyl-3-butenyl)-2-thiazoline (2e)** was prepared from cinnamyl chloride (crude) used in 20% excess in the alkylation. Bulb-to-bulb distillation gave **2e:** 55% yield; ir (film) 1626, 1596, 1575, 1492, 962, 740, 690 cm^{-1}; NMR ($CDCl_3$) δ 2.6 (m, 4), 3.2 (m, 4), 4.2 (t, 2), 5.9–6.6 (m, 2), 7.1–7.5 (m, 5).

Anal. Calcd for $C_{13}H_{15}NS$: C, 71.84; H, 6.96; N, 6.45. Found: 71.21; H, 7.10; N, 6.40.

2-(*n*-Pentyl)-2-thiazoline (2f) was prepared from *n*-butyl iodide: 88% yield after bulb-to-bulb distillations; ir (film) 1627, 1460, 995, 915 cm^{-1}; NMR ($CDCl_3$) δ 0.9 (t, 3), 1.0–2.1 (m, 6), 2.55 (t, 2), 3.3 (t, 2), 4.2 (t, 2).

Anal. Calcd for $C_8H_{15}NS$: C, 61.09; H, 9.61; N, 8.91. Found: C, 60.89; H, 9.80; N, 9.13.

n-Butyl bromide gave **2f** in 66% yield; *n*-butyl chloride gave no product.

2-(2-Methylpropyl)-2-thiazoline (2, R = *i*-Pr) was prepared from **1** and isopropyl iodide: bp 70–73° (10 Torr); 78% yield; ir (film) 1625, 1462, 1383, 1366, 1150, 984 cm^{-1}; NMR ($CDCl_3$) δ 1.95 (d, 6), 1.84–2.4 (heptet, 1), 2.4 (d, 2), 3.2 (t, 2), 4.2 (t, 2).

Anal. Calcd for $C_7H_{13}NS$: C, 58.69; H, 9.15. Found: C, 58.55; H, 9.78.

Isopropyl bromide gave only ~10% alkylation product.

2-(Dialkyl)-2-thiazolines. 2-(1-benzylethyl)-2-thiazoline (5, R = Me; R′ = CH_2Ph). A solution of 2-ethyl-2-thiazoline (**2**, R = Me, 4.00 g, 34.8 mmol) in 40 ml of dry THF was placed in the previously described apparatus and cooled to −78°. *n*-Butyllithium (22 ml, 35.0 mmol) was added dropwise over 10 min and the suspension was stirred at −78° for 1.5 hr, after which 6.2 g (4.3 ml) of benzyl bromide was added. Stirring was continued for 30 min, and the solution was allowed to warm to ambient and poured into 40 ml of ice–water. The pH was adjusted to 2–3 and the organic layer was separated and discarded. The aqueous layer was extracted with pentane and the latter layer was also discarded. The aqueous solution was neutralized (10% KOH) to pH 10 and then extracted with ether. The ethereal solution was dried (K_2CO_3) and concentrated, leaving 6.01 g of crude product. Distillation, bp 97–99° (0.25 Torr), gave 4.95 g (70%) of **5** (R = Me; R′ = CH_2Ph): ir (film) 1624, 1495, 1450, 970, 920 cm^{-1}; NMR ($CDCl_3$) δ 1.2 (d, 3), 2.6–3.3 (m, 5), 4.2 (t, 2), 7.2 (m, 5); mass spectrum *m/e* 205 (M^+).

2-(1-Benzylpropyl)-2-thiazoline (5, R = CH_2Ph; R′ = Et) was prepared from 12.1 g of 2-phenethyl-2-thiazoline (**2**, R = CH_2Ph) and 17.1 g of ethyl iodide in a manner identical with above. The ethereal residue gave 12.7 g of crude product which was distilled, bp 137–140 (2.2 Torr), to give 11.1 g (79%) of pure product: ir (film) 1627, 1500, 1410, 990, 755, 710 cm^{-1}; NMR ($CDCl_3$) δ 0.88 (t, 3), 1.3–1.8 (m, 2), 2.8–3.2 (m, 5), 4.1 (t, 2), 7.2 (m, 5).

Anal. Calcd for $C_{13}H_{17}NS$: C, 71.18; H, 7.81; N, 6.39. Found: C, 70.89; H, 7.81; N, 6.56.

2-(Cyclopropyl)-2-thiazoline (9a, *n* = 0). In the usual apparatus 8.12 g (80.4 mmol) of 2-methyl-2-thiazoline was dissolved in 105 ml of dry THF and cooled to −78°. *n*-Butyllithium (51.1 ml, 82.4 mmol) was added dropwise over a 20-min period and the suspension was stirred at −78° for 1.5 hr. A solution of 1-bromo-2-chloroethane (11.5 g, 80.5 mmol) in 20 ml of THF was added over 5 min and the solution was stirred for 1.5 hr. A second portion of *n*-butyllithium (51.5 ml) was then added over a 20-min period and the solution again was allowed to stir for 40 min at −78°. After this period the mixture was slowly warmed to ambient and stirring was continued overnight. The reaction mixture was quenched in ice–water, and the work-up proceeded as described for **2** or **5**. Distillation of the ethereal residue gave 6.5 g (62%) of pure cyclopropylthiazoline: bp 51–54° (0.5 Torr); ir (film) 1622, 1380, 1228, 1205, 1183 cm^{-1}; NMR ($CDCl_3$) δ 0.9 (d, 4), 1.85 (q, 1), 3.25 (t, 2), 4.2 (t, 2).

Anal. Calcd for C_6H_9NS: C, 56.65; H, 7.13; N, 11.01. Found: C, 56.50, H, 7.25; N, 10.84.

2-(Cyclohexyl)-2-thiazoline (9b, *n* = 3). The lithio salt of 2-methyl-2-thiazoline was prepared as described above, and quickly transferred (via syringe) to a flask containing 3 equiv of 1,5-dibromopentane in 50 ml of THF, previously cooled to −78°. After stirring for 1.5 hr, the mixture was warmed to −30° and kept at this temperature for an additional 1 hr, after which it was quenched in ice–water. The solution was acidified to pH 2 with 6 *N* hydrochloric acid, and then the organic layer was separated and discarded. The aqueous acidic solution was extracted once with pentane and the latter was also discarded. The aqueous solution was made alkaline with 10% sodium hydroxide and the organic material was removed by ether extraction. The ethereal solution was dried (K_2CO_3) and concentrated at or below room temperature. The residue, 2-(6-bromohexyl)-2-thiazoline, was dried further by dissolving it in 20 ml of THF and adding Linde molecular sieves, 4A. The drying agent was removed by filtration (after 2 hr) and the 0.1 *M* THF solution containing the bromoalkylthiazoline was introduced into a reaction flask, cooled to −78°, and treated with 1.1 equiv of lithium diisopropylamide (prepared just prior to use from *n*-butyllithium and diisopropylamine, THF, 0°). The reaction was stirred for 5 hr at −78° and then allowed to warm to 0–5°, quenched in 25–35 ml of ice water, and worked up as in **2** or **5**. Bulb-to-bulb distillation of the ethereal residue gave 0.91 g (62%) of 2-(cyclohexyl)-2-thiazoline: ir (film) 1625, 1450, 990 cm^{-1}; NMR ($CDCl_3$) δ 4.2 (t, 2), 3.2 (t, 2), 2.8–0.7 (m, 11); mass spectrum *m/e* 169 (M^+), 114 (base).

The formation of **9b** (*n* = 3) was also accomplished by sequential addition of *n*-butyllithium and lithium diisopropylamide (1.0 equiv), each of which eliminated the need to isolate the intermediate bromoalkylthiazoline. If *n*-butyllithium was used in the cyclization step in place of LDA, various yields (10–30%) of 2-(*n*-hexyl)-2-thiazoline were formed arising from halogen–metal interchange. A small amount of 1,6-(dithiazolinyl)hexane was also detected in these reactions.

2-(2-Indanyl)-2-thiazoline (12) was prepared from α,α'-dichloro-o-xylene (10.7 g, 62 mmol) and 2-methyl-2-thiazoline (1.1 g, 11 mmol) according to the above detailed procedure for **9b:** yield 25% of an oil, 0.53 g from bulb-to-bulb distillation; mass spectrum *m/e* 203 (M^+), 115, 116; ir (film) 1630 cm^{-1}; NMR ($CDCl_3$) δ 3.0–3.7 (overlapping multiplet, triplet, 7), 4.2 (t, 2), 7.2 (m, 4).

2-(Trialkyl)-2-thiazoline (14). General Procedure. The dialkylmethylthiazolines **5** (2–11 mmol) were dissolved in sufficient dry THF to make the solutions 0.7–0.8 *M*. The solution was cooled in the previously described apparatus to −78° and *n*-butyllithium (1.1 equiv)[9] was added dropwise over 5–10 min. The reaction mixture was stirred at −78° for 2–3 hr and the alkyl halide (1.1 equiv) in THF was added over 10–20 min. Stirring was continued for 2–3 hr and the clear solution was allowed to warm to room temperature

and poured into 100 ml of ice–water, and 20–30 ml of ether was then added. The two-phase solution was made acidic with 6 *M* hydrochloric acid and the aqueous layers were combined. The aqueous solution was rendered alkaline by addition of 20% sodium hydroxide, saturated with sodium chloride, and then extracted with four 25-ml portions of ether. The dried (K_2CO_3) ethereal extracts were concentrated and the residues were distilled in the Kugelrohr apparatus. Specific data for trialkylthiazolines follow.

2-(1,1-Dimethylphenethyl)-2-thiazoline (14, R, R′ = Me; R″ = CH_2Ph) was prepared from 0.57 g (4.4 mmol) of 2-(isopropyl)-2-thiazoline and benzyl chloride: yield 0.58 g (65%); ir (film) 1620, 1495, 1458, 1454, 1385, 1365, 1030, 989, 744, 700 cm^{-1}; NMR ($CDCl_3$) δ 1.2 (s, 6), 2.9 (s, 2), 3.2 (t, 2), 4.2 (t, 2), 7.2 (m, 5).

Anal. Calcd for $C_{13}H_{17}NS$: C, 71.18; H, 7.81. Found: C, 70.91; H, 7.78.

2-(1,1-Dimethyl-*n*-pentyl)-2-thiazoline (14, R, R′ = Me; R″ = *n*-Bu). Using lithium diisopropylamide as the base, 0.88 g (6.8 mmol) of 2-(isopropyl)-2-thiazoline and *n*-butyl iodide (1.05 equiv) gave 1.06 g (84%) of product: ir (film) 1621, 1470, 1460, 1386, 1365, 1035, 990, 925 cm^{-1}; NMR ($CDCl_3$) δ 0.92 (t, 3), 1.2 (s, 6), 1.1–1.8 (m, 6), 3.2 (t, 2), 4.2 (t, 2).

Anal. Calcd for $C_{10}H_{19}NS$: C, 64.81; N, 10.32. Found: C, 64.54; H, 10.22.

2-(1-Methylcyclohexyl)-2-thiazoline [14, R, R′ = $-(CH_2)_5-$; R″ = Me] was prepared from 2-ethyl-2-thiazoline (**2**, R = Me, 1.32 g, 11.5 mmol) and 1,5-dibromopentane (13.4 g) according to the cyclization procedure for **9**: yield 1.19 g (57%); mass spectrum *m/e* 183 (M^+), 128, 40 (base).

Anal. Calcd for $C_{10}H_{17}NS$: C, 65.52; H, 9.35. Found: C, 64.82; H, 9.17.

Aluminum Amalgam Reduction of 2-Thiazolines. General Procedure. Aluminum foil (1.0–1.3 g, 10–12 g-atoms excess) was roughed with sandpaper, cut into 0.5-in. squares, and weighed in the reaction flask. The aluminum was etched with 5% potassium hydroxide solution until vigorous evolution of hydrogen occurred. The basic solution was removed by decantation and the aluminum was rinsed once with water and covered with 0.5% mercuric chloride solution for 1.5–2.0 min. The mercuric chloride solution was poured off, the aluminum was washed with water, and the mercuric chloride solution was reintroduced for 1.5–2.0 min. Once again the mercuric chloride solution was decanted away, and water was added to rinse the aluminum, followed by successive rinsing with absolute ethanol and ether. A solution of the 2-thiazoline to be reduced (1.0–2.0 g in 75 ml of ether previously shaken with water) was added to the freshly prepared amalgam and the mixture was heated to reflux for 1–2 hr. The progress of the reduction was followed by examining aliquots on TLC plates. The reductions were usually complete in less than 1 hr of reflux. Alternatively, the reductions were carried out at room temperature and were usually complete in 4 hr. Isolation of the thiazolidines was accomplished by filtering the reaction mixture to remove the hydroxides and drying the ethereal solution (K_2CO_3) prior to concentration. The residue (usually amounted to 90–95% material of 90–95% purity) was determined by ir (loss of C=N band at 1620–1630 cm^{-1}) and NMR (exchangeable proton when D_2O was added; position varied with concentration but found mainly between 1.0 and 2.0 ppm). No further purification of the thiazolidines **3, 6,** and **15** was performed prior to cleavage to aldehydes. It was found convenient to use granular aluminum (8–20 mesh) on larger scale reductions and this was performed as follows. Granular aluminum (7.5–8.5 g) was used for reduction of 4–5 g of thiazoline and the amalgam was prepared in the same manner as the foil by successive treatment of KOH, $HgCl_2$, water, etc. As before, the amalgam prepared was used immediately for reduction of the thiazolines.

Cleavage of Thiazolidines 3, 6, and 15. General Procedure. A solution of thiazolidines (3.8–4.2 g) in the minimum amount of acetonitrile was added dropwise to 7.5–8.3 g of mercuric chloride in 30 ml of acetonitrile–water (4:1) over a 15-min period. A precipitate formed immediately and the mixture was stirred at room temperature for 2 hr. Water (25 ml) was added and the mixture was filtered. The filtrate was extracted with pentane or pentane–ether (1:1) and the organic extract was dried over sodium or potassium carbonate. Concentration of the solution gave the crude aldehydes, which were 90–95% pure (via GLC and NMR). The following aldehydes were all obtained using this procedure and the yields of cleavage are given.

3-Phenylpropionaldehyde: 64.5%; 2,4-DNP, mp 152–153° (lit.[4] mp 153–154°)

5-Phenylvaleraldehyde: 71.1%; *p*-nitrophenylhydrazone, mp 81–83° (lit.[10] mp 82–84°)

4-Bromo-4-pentenal (4c): 57%; oil; ir (film) 2818, 2730, 1726, 1687, 1630 cm^{-1}; NMR ($CDCl_3$) δ 2.8 (br s, 4), 5.5 (d, 1), 5.7 (d, 1), 9.8 (t, 1) (purity >95% via NMR); mass spectrum *m/e* 163 (M^+).

Anal. Calcd for C_5H_7BrO: C, 36.31; H, 4.29. Found: C, 36.77; H, 4.31.

Geranylacetaldehyde (4d): 74.4% crude, 61% after bulb-to-bulb distillation; ir (film) 2710, 1728, 1675, 1450, 1384, 1375, 1110, 1055, 830 cm^{-1}; NMR ($CDCl_3$) δ 1.62 (m, 9), 2.02 (m, 4), 2.42 (m, 4), 5.15 (m, 2), 9.7 (t, 1); mass spectrum *m/e* 180 (M^+), 137, 69 (base); 4-phenylsemicarbazone, mp 57–59° (lit.[11] mp 58°).

***trans*-5-Phenyl-4-pentenal (4e):** 54% oil; ir (film) 3030, 2830, 2725, 1725, 1653, 1600, 1580, 965, 745, 692 cm^{-1}; NMR ($CDCl_3$) δ 2.45 (br s, 4), 5.8–6.5 (m, 2), 7.25 (m, 5), 9.67 (t, 1); mass spectrum *m/e* 160 (M^+), 132, 131, 129, 117, 116, 115, 104 (base), 91; semicarbazone, mp 132–133°.

Anal. Calcd for $C_{11}H_{12}O$: C, 82.46; H, 7.55. Found: C, 82.05, H, 7.37.

***n*-Hexaldehyde (4f):** 88%; 2,4-DNP mp 104–105° (lit.[12] mp 104°).

2-Methyl-3-phenylpropionaldehyde (7a): 83%; bp 44–45° (0.2 Torr), identical with authentic sample.[4]

2-Benzylbutyraldehyde (7b): 79%; 2,4-DNP mp 112–113.5° (lit.[13] mp 114–115°)

Cyclopropanecarboxaldehyde (10a): 64%; 2,4-DNP mp 182–183° (lit.[4] mp 184–185°). $CaCO_3$ (0.3 g) was added to the mercuric chloride in aqueous acetonitrile to neutralize slight traces of acid formed during the cleavage. The aldehyde and acetonitrile codistilled, making purification difficult. Yield was determined by GLC and NMR spectrum.

Cyclohexanecarboxyaldehyde (10b): 66%; unstable and partially decomposes upon distillation; bp 80–82° (25 mm), semicarbazone mp 172–174° (lit.[12] mp 173).

2-Indancarboxaldehyde (13): 84.7%; purified by column chromatography (silica gel, 9:1 hexane–benzene), oil, purity 95%; mass spectrum *m/e* 146 (M^+), 116, 115, 89, 92, 91; ir (film) 3050, 2920, 2820, 2710, 1725, 740 cm^{-1}; NMR ($CDCl_3$) δ 2.8 (m, 1), 3.2 (s, 4), 7.2 (br s, 4), 9.7 (d, 1).

2,2-Dimethyl-3-phenylpropionaldehyde (16a): 83.3%; 2,4-DNP mp 151–152° (lit.[14] mp 154–155°).

2,2-Dimethylhexanal (16b): 80.8%; semicarbazone mp 130–131° (lit.[15] mp 134–135°).

1-Methylcyclohexanecarboxaldehyde (16c): 71.4%; 2,4-DNP mp 152–153° (lit.[16] mp 154–155°). The product was air sensitive and decomposed slightly during molecular distillation at atmospheric pressure.

Formation of C-1 Deuterated Aldehydes 17a–c. Reduction of 2-thiazolines was performed in the following manner. The procedure for preparing the aluminum amalgam given above was followed exactly through the second treatment with 0.5% mercuric chloride. The amalgam was then washed once with distilled water, twice with absolute ethanol, three times with reagent-grade acetone, and three times with anhydrous THF. The thiazoline was dissolved in ether saturated with D_2O (98.5%) (anhydrous ether was employed) and added to the freshly prepared amalgam in an oven-dried flask containing a drying tube. The reaction mixture was stirred for 1–1.5 hr, filtered, and worked up in the manner used for protioaldehydes. Cleavage to the deuterioaldehydes was also performed in the usual manner. Distillation gave the following.

3-Phenylpropionaldehyde-d_1 (17a), 91 ± 2% deuterium (NMR and *m/e*).

2-Ethyl-3-phenylprionaldehyde-d_1 (17b), 94 ± 3% deuterium (NMR).

***n*-Hexanal-d_1 (17c),** 90 ± 3% deuterium (NMR).

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Registry No.—**1,** 2346-00-1; **2a,** 25478-36-8; **2b,** 55089-11-7; **2c,** 55089-12-8; **2d,** 55089-13-9; **2e,** 55089-14-0; **2f,** 21226-52-8; **2** (R = *i*-Pr), 26851-79-6; **2** (R = Me), 16982-46-0; **3a,** 55089-15-1; **3b,** 55089-16-2; **3c,** 55781-93-6; **3d,** 55089-18-4; **3e,** 55089-19-5; **3f,** 41204-65-3; **4a,** 104-53-0; **4b,** 36884-28-3; **4c,** 36884-29-4; **4d,** 55089-20-8; **4e,** 36884-75-0; **4e** semicarbazone, 55089-21-9; **4f,** 66-25-1; **5** (R = Me; R′ = CH_2Ph), 55089-22-0; **5** (R = CH_2Ph; R′ = Et), 37873-55-5; **5** (R, R′ = Me), 45533-49-1; **6a,** 55089-23-1; **6b,** 55089-24-2; **7a,** 5445-77-2; **7b,** 24569-60-6; **9a,** 55089-25-3; **9b,** 55089-26-4; **10a,** 1489-69-6; **10b,** 2043-61-1; **11,** 612-12-4; **12,**

55089-27-5; **13**, 37414-44-1; **14a**, 55089-28-6; **14b**, 55089-29-7; **14c**, 55089-30-0; **15a**, 55089-31-1; **15b**, 55089-32-2; **15c**, 55089-33-3; **16a**, 1009-62-7; **16b**, 996-12-3; **16c**, 6140-64-3; benzyl chloride, 100-44-7; 3-phenylpropyl iodide, 4119-41-9; 2,3-dibromopropene, 513-31-5; geranyl chloride, 5389-87-7; cinnamyl chloride, 2687-12-9; *n*-butyl iodide, 542-69-8; *n*-butyl bromide, 109-65-9; isopropyl iodide, 75-30-9; benzyl bromide, 100-39-0; ethyl iodide, 75-03-6; 1-bromo-2-chloroethane, 107-04-0; 1,5-dibromopentane, 111-24-0; 2-(6-bromohexyl)-2-thiazoline, 55089-34-4.

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2-Thiazolines in Organic Synthesis. Formation of β-Hydroxy Aldehydes with Protected Hydroxy Groups. A Synthesis of Homoallylic Alcohols

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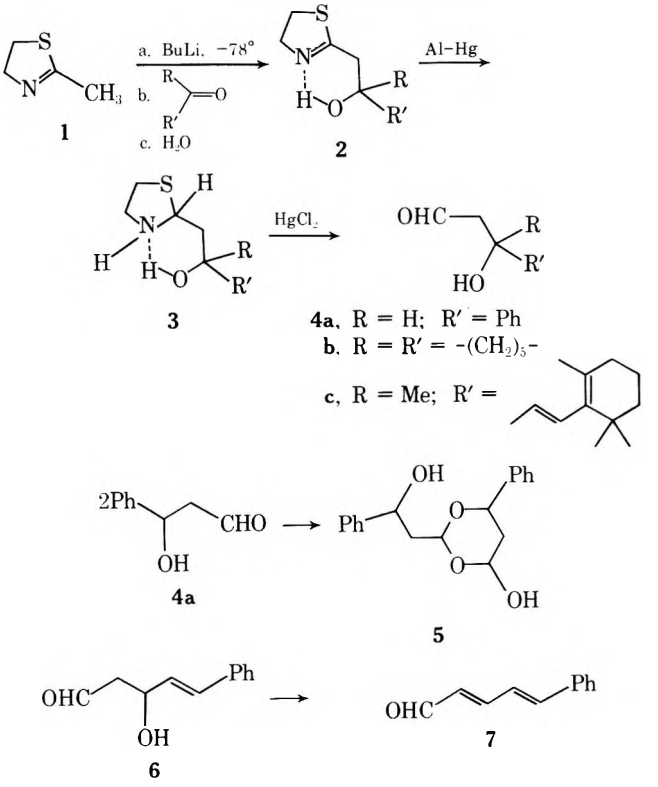
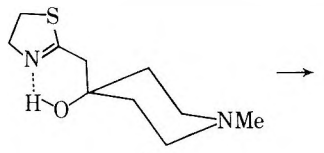
The addition of lithiothiazoline to carbonyl compounds provides an adduct which may be transformed into β-hydroxy aldehydes. The latter are rather labile compounds and may be stabilized by temporarily masking the β-hydroxy group to avoid retro-aldol condensation. The use of chloromethyl methyl ether to trap the thiazoline–carbonyl adduct **12** proved to be synthetically useful with respect to the preparation of β-oxy aldehydes. This masking group was stable to all the conditions necessary to construct β-hydroxy aldehydes. Wittig olefin condensations were employed to convert the β-hydroxy aldehydes to homoallylic alcohols, after release of the hydroxy protecting group.

In the previous article[1] we described the preparation of mono-, di-, and trialkylated acetaldehydes by sequential metalation–alkylation of 2-methyl-2-thiazoline (**1**). We wish to further exemplify the utility of **1** with respect to forming β-hydroxy aldehydes, **4**, the elusive primary adducts of aldol condensations,[2] and derivatives containing a temporarily masked hydroxy function **13**. The latter are useful precursors to homoallylic alcohols **16** by the usual Wittig condensations.

Metalation of **1** with *n*-butyllithium (THF, −78°) followed by addition of an aldehyde or ketone gave, after hydrolytic work-up, the hydroxy thiazoline in 80–95% yield. Attempts to purify **2**, when they were oils, by distillation resulted in thermal reversal to the original carbonyl component and **1**. Alternatively, attempts to pass the hydroxy thiazolines through silica gel columns resulted in considerable reversal to starting materials. However, this was not a major deterrent, since the crude hydroxy thiazolines were of sufficient purity (88–94% via NMR and TLC) to proceed further. Reduction to the thiazolidine derivative **3** was accomplished in 80–90% yield using aluminum amalgam in moist ether as previously described.[1] In some instances, the pure thiazolidine was isolated and completely characterized (Experimental Section), whereas in most cases the crude material (85–95% purity via NMR and TLC) was treated directly with mercuric chloride in aqueous acetonitrile. The β-hydroxy aldehydes **4** released in this mild fashion were obtained in good yield and the crude material was of 90–95% purity. Herein lies the major feature of this technique. The neutral conditions employed for the cleavage of **3** allow for the isolation of the usually labile β-hydroxy aldehydes. However, the extreme lability of these substances was consistently observed when more complex structures were involved. For example, 3-phenyl-3-hydroxypropional-



dehyde (**4a**) was isolated as its condensed dimer **5**, which when treated with 2,4-dinitrophenylhydrazine gave the 2,4-DNP of cinnamaldehyde. Reaction of the lithio salt of **1** with cinnamaldehyde gave good yields of the expected adduct **2** (R = H; R′ = CHC=CHPh) as well as the corresponding thiazolidine **3**. However, upon mercuric chloride cleavage of the latter, a mixture (~2.5:1) of the hydroxy aldehyde **6** and the diene aldehyde **7** was obtained. Thus, even this mild cleavage step caused dehydration. The use of buffers during the mercuric chloride step failed to change this result. The ease of dehydration to the dienal was demonstrated further when the mixture of **6** and **7** was passed through an alumina column providing pure **7**. When β-ionone was alkylated with the lithio salt of **1**, good yields of the adduct **2** were also obtained. The reduction to **3** and the cleavage to the β-hydroxy aldehyde **4c** also proceeded without event. However, the latter (90–95% purity) upon attempts at dehydration to the unsaturated aldehyde in a manner similar to that used for **7**, gave only retro-aldol products (β-ionone recovered quantitatively). The generality of the thiazoline alkylation and reduction was further demonstrated by use of 1-methyl-4-piperidone, which furnished **8** and **9**, respectively. Cleavage with mercuric chloride, however, gave only 1-methyl-4-piperidone and none of the hydroxy aldehyde **10** was isolated. These results suggested that a hydroxyl protecting group would be necessary to avoid the retro-aldol process.



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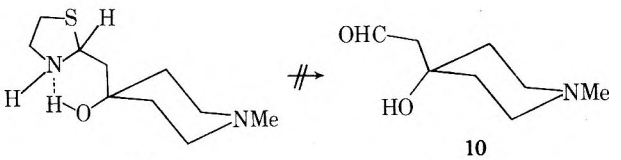
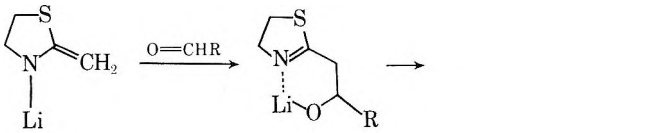
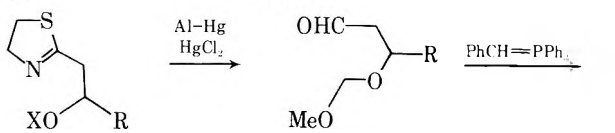


9 **10**

We, therefore, investigated the feasibility of introducing a hydroxyl protecting group during the sequence which would withstand all the conditions encountered along the route to the aldehyde. The most obvious point in which to introduce a masking group appears in the acylation of **11** to the lithio adduct **12**. Without isolation, **12** could be treated with an appropriate electrophile, furnishing **13**. When acetyl chloride was introduced to the solution of **12**, a poor (10–20%) yield of **13b** was obtained, the major product being elimination. Use of trimethylsilyl chloride gave **13a** in 70–75% yield, but subsequent treatment with mercuric chloride to free the protected aldehyde resulted in loss of the trimethylsilyl group. The mercuric ion was found to be responsible for the aqueous instability of the *O*-trimethylsilyl group and therefore this route was abandoned. On the other hand, introduction of a slight excess of chloromethyl methyl ether to the solution of **12** gave the methoxymethyl ethers **13c** in 63–72% distilled yield. The crude thiazoline product **13c** was always contaminated with 5–10% of the hydroxy thiazoline **13** (X = H) and attempts to use a larger excess of chloromethyl methyl ether resulted in poor yields of **13c**. It was shown that excess chloromethyl methyl ether slowly forms a highly colored, unstable quaternary salt with the thiazoline in THF solution. Reduction of **13c** using aluminum amalgam in moist ether proceeded in 80–88% yield to furnish the corresponding thiazolidines, which were then cleaved, using mercuric chloride, to the β-methoxymethyleneoxy aldehydes **14**. The protecting group survived the two previous steps without incident and the pure aldehydes were isolated in 42–53% yield.

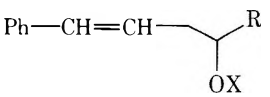


11 **12**



13a, X = Me_3Si
b, X = $COCH_3$
c, X = CH_2OMe

14a, R = Pr
b, R = *n*-Hex
c, R = cyclopentyl



15, X = CH_2OMe
16, X = H

Several additional experiments were performed using ketones in place of aldehydes. The in situ methoxymethylation proceeded in 40–50% yield (as estimated by NMR spectra), which presumably was a result of increased steric interaction. Further experimentation will be needed before tertiary alkoxides can be adequately protected.

In order to demonstrate that these β-alkoxy aldehydes were suitable for further synthetic transformations, we elected to carry out typical Wittig couplings with benzyltriphenylphosphoranes. The couplings proceeded smoothly (71–84% yields) giving rise to the olefinic acetals **15** as mixtures of cis and trans isomers with the latter predominating by 2–4:1 (GLC). Geometrically pure materials could be collected from the GLC instrument although this was only done in one case.

Hydrolysis to the homoallylic alcohols **16** was accomplished in 95–98% yield by treatment with dilute hydrochloric acid in aqueous tetrahydrofuran. The reaction proceeded with no discernible dehydration to the corresponding dienes nor with any change in the cis:trans ratio present in the olefinic acetals.

In summary, this and the previous article demonstrate rather convincingly that a route to alkylated acetaldehydes and their β-hydroxy derivatives is indeed feasible and that homoallylic alcohols can be prepared with a wide variety of structural features whose architecture is compatible with the schemes described. This method should take its place among other routes to homoallylic alcohols which involve (a) addition of allylic metallics to carbonyl compounds, (b) reaction of formaldehyde with olefins,[3] (c) allylic ether rearrangements,[4] and (d) ring cleavage of THF derivatives.[5,6]

Experimental Section[7]

Condensation of Carbonyl Compounds with 2-Methyl-2-thiazoline (1). General Procedure. The lithio salt of 2-methyl-2-thiazoline was prepared as described previously.[1] A solution of 1.05 equiv of the carbonyl compound in 20 ml of dry THF was added at −78° over 5–10 min, resulting in the disappearance of the suspension of the lithiothiazoline. The mixture was allowed (2–3 hr) to warm to room temperature and then poured into 150 ml of ice–water, acidified to pH 2–3 with 6 *N* hydrochloric acid, and extracted with pentane–ether (1:1). The latter extracts containing only unreacted carbonyl compounds were discarded and the aqueous layer was rendered alkaline by slow addition of 20% sodium hydroxide. The resulting oil was removed by extraction with ether (three times) and the combined ether extracts were dried (K_2CO_3)

and concentrated to give 85–97% of crude hydroxy thiazoline **2**. Purification procedures varied for each compound; however, the purity (85–95%) of the crude material was sufficient to proceed further. Distillation of **2** could not be performed for purification since reversal to starting materials occurred for all compounds above 120–140°. The following were prepared according to this method.

2-(2-Hydroxy-2-phenethyl)-2-thiazoline (2, R = H; R′ = Ph) was obtained from 3.39 g (33 mmol) of **1**, 21.0 ml (34 mmol) of *n*-butyllithium in hexane, and 4.20 g (38 mmol) of benzaldehyde. The yield of product was 5.91 g (87%) of a viscous yellow oil: ir (neat) 3300, 1625 cm^{-1}; NMR ($CDCl_3$) δ 7.3 (s, 5), 2.6–2.8 (d, 2), 3.0–3.3 (t, 2), 4.0–4.3 (t, 2), 3.7 (br s, 1, exchangeable with D_2O), 4.8–5.2 (t, 1). The product was 93 ± 2% pure as determined by the NMR spectrum. Attempts to assess purity by GLC led to varying amounts of starting materials which depended on the temperature of both the injection port and column.

2-(1-Hydroxycyclohexylmethyl)-2-thiazoline [2, R, R′ = $-(CH_2)_5-$] was prepared on the same scale as the previous product, giving 94% crude material (95% purity) which was recrystallized from hexane: mp 92–94°; ir (KBr) 3600–3000, 1615, 1170, 1018 cm^{-1}; NMR ($CDCl_3$) δ 1.2–2.0 (m, 10), 2.6 (t, 2), 3.3 (t, 2), 4.4 (m, 3, one proton exchanges with D_2O leaving this signal as a triplet).

Anal. Calcd for $C_{10}H_{17}NOS$: C, 60.26; H, 8.60; N, 7.03; S, 16.08. Found: C, 60.50; H, 8.43; N, 6.96; S, 16.30.

2-[(2-Hydroxy-4-phenyl)-*trans*-3-butenyl]-2-thiazoline (2, R = H; R′ = CH=CHPh) was obtained from 10 g of **1** and 10.35 g of cinnamaldehyde in 95% crude yield (18.8 g). Recrystallization from benzene–hexane (1:1) gave pure material: mp 81–83°; ir (KBr) 3600–3000, 1625, 740, 700 cm^{-1}; NMR ($CDCl_3$) δ 2.7 (broad d, 2, long-range coupling through the C=N to C-4), 3.2 (t, m, 2), 4.2 (t, 2), 4.4–4.9 (m, 2, one proton exchanges with D_2O), 6.2 (d of d, J = 5, 16 Hz, 1), 6.7 (d, 1), 7.3 (m, 5); *m/e* 233 (M^+).

Anal. Calcd for $C_{13}H_{15}NSO$: C, 66.92; H, 6.48; N, 6.00; S, 13.74. Found: C, 66.84; H, 6.44; N, 5.84; S, 13.98.

β-Ionone Adduct 2 (R = Me; R′ = β-ididonyl) was prepared from 3.7 g of **1** and 7.13 g of β-ionone to give 10.9 g (97%) of crude product (~95% purity) as an oil: TLC (ether) gave one major spot (R_f 0.48) and several minor spots; ir (film) 3600–3610, 1623 cm^{-1}; NMR ($CDCl_3$) δ 0.95 (s, 6), 1.37 (s, 3), 1.63 (s, 3), 1.4–2.3 (m, 6), 2.7 (t, 2), 3.2 (t, 2), 4.2 (t, 2), 5.1 (m, 1, exchangeable with D_2O), 5.5 (d, J = 16 Hz, 1), 6.2 (d, J = 16 Hz, 1).

2-(4-Hydroxy-1-methylpiperdinylmethyl)-2-thiazoline (8) was prepared from 1.87 g (18 mmol) of **1** and 1.92 g (17 mmol) of 1-methyl-4-piperidone, giving 3.25 g (90%) of **8**: mp 88–89.5° (hexane); ir (KBr) 3600–3100, 1615 cm^{-1}; NMR ($CDCl_3$) δ 1.5 (m, 4), 2.3 (s, 1), 2.3–2.8 (m, 7), 3.2 (t, 2), 4.3 (m, 3, one proton exchangeable with D_2O leaving a triplet of two protons).

Anal. Calcd for $C_{10}H_{18}N_2OS$: C, 56.01; H, 8.46; N, 13.08. Found: C, 56.14; H, 8.61; N, 12.84.

Reduction to 2-(2-Hydroxy-2-alkylethyl)-2-thiazolidines (3). General Procedure. The aluminum amalgam was prepared as previously described[1] from either aluminum foil or granular aluminum (8–20 mesh) and the reductions were carried out in ether which had been previously saturated with water (or deuterium oxide). The thiazolines **2** or **8** dissolved (0.05–0.1 *M*) in moist ether were treated with the freshly prepared amalgam (10–12 g-atoms excess) and the mixture was heated to reflux gently for 2 hr. The solids were removed by filtration and washed with small portions of ether. The combined ethereal solutions were dried (K_2CO_3) and concentrated to leave the crude thiazolidines. Purification was only performed on crystalline products although the spectral data indicated that all reduced materials were at least 90% pure and could be carried on to produce the aldehydes.

2-(2-Hydroxy-2-phenethyl)-1,3-thiazolidine (3, R = H; R′ = Ph) was obtained in 86% yield: mp 81–82.5; ir (KBr) 3250, the peaks at 1630 (C=N) and 2350 cm^{-1} (SH) were absent, indicating complete reduction and no ring cleavage to mercapto amines; NMR ($CDCl_3$) δ 4.4–5.1 (m, 2), 2.7–3.6 (m, 6, two protons were exchangeable with D_2O), 1.8–2.3 (m, 2).

Anal. Calcd for $C_{11}H_{15}NOS$: C, 63.14; H, 7.23; N, 6.69. Found: C, 63.09; H, 7.15; N, 6.50.

2-(1-Hydroxycyclohexylmethyl)-1,3-thiazolidine [3, R, R′ = $-(CH_2)_5-$] was prepared in 97% yield: mp 81–82° (from silica gel chromatography); ir (KBr) 3200, 1445, 1200, 973, 945, 920, 905 cm^{-1}; NMR ($CDCl_3$) δ 1.1–2.1 (m, 10), 2.4–3.6 (m, 2, exchanges with D_2O), 3.0 (m, 2), 3.3 (m, 2), 4.8 (d of d, 1); MS *m/e* 201 (M^+), 183, 158, 155, 154, 103, 99, 88 (base).

2-[(2-Hydroxy-4-phenyl)-*trans*-3-butenyl]-1,3-thiazolidine (3, R = H; R′ = CH=CHPh) was prepared in 94% crude yield: mp 79–81° [benzene–hexane (1:1)]; ir (KBr) 3240, 3140, 1595, 1490 cm^{-1}; NMR ($CDCl_3$) δ 1.7–2.2 (m, 2), 2.6–3.5 (m, 6, two protons exchange with D_2O), 4.6 (m, 2), 6.1 (d of d, J = 4, 16 Hz, 1), 6.6 (d of d, J = 2, 16 Hz, 1), 7.2 (m, 5); *m/e* 235 (M^+).

β-Ionyl-1,3-thiazolidine (3, R = Me; R′ = β-ididonyl) gave 82.4% of crude product (>90% purity) which was recrystallized from hexane: mp 90–91°; ir (KBr) 3600–3100, 1460–1430, 1370, 1360, 1215, 1145 cm^{-1}; NMR ($CDCl_3$) δ 1.0 (s, 6), 1.25 (s, 3), 1.7 (s, 3), 1.3–2.2 (m, 8), 2.5–3.5 (m, 4, two protons exchange with D_2O), 4.8 (t, 2), 5.5 (d, J = 16 Hz, 1), 6.3 (d, J = 16 Hz, 1); MS *m/e* 295 (M^+), 281, 262, 237, 193, 192, 177 (base), 143, 88.

2-(4-Hydroxy-1-methylpiperdinylmethyl)-1,3-thiazolidine (9) was obtained in 83% yield as a viscous oil: ir (film) 3600–3000 cm^{-1}; NMR ($CDCl_3$) δ 1.4–2.0 (m), 2.25 (s, 3), 2.2–3.5 (m), 4.9 (t, 1); *m/e* 216 (M^+). Cleavage to the corresponding aldehyde **4** [R, R′ = $-(CH_2)_4NMe$] proceeded only to return 1-methyl-4-pyridone and no aldehydic product could be isolated.

Cleavage to β-Hydroxy Aldehydes 4. General Procedure. The thiazolidine (1.5 g) was dissolved in 3 ml of acetonitrile and slowly added to a solution of mercuric chloride (2.5 g) in 30 ml of 80% acetonitrile–water which resulted in a suspension. The mixture was stirred for 1.5 hr and then diluted with 25 ml of water and filtered. The filtrate was extracted several times with ether–pentane (1:1) and the organic layer was dried (K_2CO_3 or $MgSO_4$) prior to concentration. The crude aldehydes were generally 90+% pure. The following were prepared in this manner.

3-Phenyl-3-hydroxypropionaldehyde dimer (5) was obtained in 75% yield as a viscous oil: ir (neat) 3400 cm^{-1}, no C=O absorption; NMR ($CDCl_3$) δ 7.0–7.4 (m, 10), 4.1–4.8 (m, 4), 1.0–2.7 (m, 6). Treatment of the dimer with 2,4-dinitrophenylhydrazine solution gave the 2,4-DNP derivative of cinnamaldehyde, mp 251–252° (lit.[8] mp 252°).

2-(1-Hydroxycyclohexyl)acetaldehyde [4b, R, R′ = $-(CH_2)_5-$] was prepared in 94% yield: mp 92–94° (hexane); ir (KBr) 3440, 2740, 1720 cm^{-1}; NMR ($CDCl_3$) δ 1.6 (br s, 10), 2.6 (d, J = 1.5 Hz, 2), 3.5 (br s, 1, exchangeable with D_2O), 10.0 (t, J = 1.5 Hz, 1). On standing at room temperature for several hours, the product slowly dehydrates to the α,β- and β,γ-unsaturated aldehyde as seen by vinyl absorptions appearing in the 5–6-ppm region. The hydroxy aldehyde is stable for long periods of time when stored in the freezer (−20°). A 2,4-DNP derivative gave mp 194–195° and when admixed with an authentic sample of the 2,4-DNP of cyclohexylidineacetaldehyde[9] produced no melting point depression.

Aldol of β-ionone and acetaldehyde 4c (R = Me; R′ = β-ididonyl) was obtained in 64% yield (>90% purity) from the mercuric chloride cleavage as a viscous oil: ir (film) 3430, 2730, 1721, 1655 cm^{-1}; NMR ($CDCl_3$) δ 1.0 (s, 6), 1.4 (s, 3), 1.63 (s, 3), 1.0–2.4 (m, 6), 2.65 (d, J = 2 Hz, 2), 3.4 (br s, 1, exchangeable with D_2O), 5.5 (d, J = 16 Hz, 1), 6.2 (br d, 1), 10.0 (t, J = 2 Hz, 1). Attempts to dehydrate **4c** to the unsaturated aldehyde by passing through neutral alumina (activity 1) gave only β-ionone by a retro-aldol reaction.

5-Phenyl-2,4-pentadienal (7). Mercuric chloride cleavage of the corresponding thiazolidine **3** gave, after work-up, a mixture of the β-hydroxy aldehyde **6** and the dienal **7**. Passage through acid-washed alumina (hexane–ether) furnished **7**, mp 37–39° (lit.[9] mp 37–39°).

2-(2-Cyclopentyl-2-methoxymethyloxyethyl)-2-thiazoline (13c, R = Cyclopentyl). A solution of 2-methyl-2-thiazoline (**1**, 9.76 g, 96.6 mmol) in 95 ml of dry THF was cooled to −78°. *n*-Butyllithium (44.5 ml, 97.8 mmol) in hexane was added dropwise over 35–40 min. The resulting suspension was stirred for 30 min after *n*-butyllithium addition and 11.1 ml (106 mmol) of cyclopentanecarboxaldehyde was added over 30 min at −78°. The clear solution was stirred for 30 min and then allowed to warm to ambient temperature (2–3 hr). Chloromethyl methyl ether (7.5 ml, 2–3% excess) was added and the solution was stirred overnight, after which it was poured into 100 ml of ice–water. The pH of the aqueous mixture was adjusted to 2–3 with 6 *N* hydrochloric acid while kept at 0–5° and extracted with 100 ml of hexane. The organic layer was discarded and the aqueous layer was neutralized to pH 10 using 20% sodium hydroxide, saturated with sodium chloride, and extracted with 4 × 100 ml of ether. The dried extracts (K_2CO_3) were concentrated, giving 21.9 g of an oil which was distilled (bulb-to-bulb) furnishing 16.6 g (72%) of **13c**: ir (film) 1625, 1450, 1210, 1145 cm^{-1}; NMR ($CDCl_3$) δ 4.75 (AB quartet, $-OCH_2O$), 4.2 (t, 2), 3.8 (q, −CHO), 3.4 (s, 3), 3.2 (t, 2), 2.8 (d, 2), 1.1–2.2 (m, 9); *m/e* 243 (M^+).

2-(2-Methoxymethyloxyoctyl)-2-thiazoline (13c, R = *n*-Hexyl). Under the same reaction conditions, 9.48 g of **1**, 43.5 ml of

n-butyllithium, 13.8 ml (1.1 equiv) of *n*-heptaldehyde, 7.25 ml (1.03 equiv) of chloromethyl methyl ether, and 95 ml of THF were used. Bulb-to-bulb distillation gave 15.3 g (64%) of product: ir (film) 1625, 1150, 1095, 1035 cm^{-1}; NMR ($CDCl_3$) δ 0.8–1.8 (m, 13), 2.8 (d, 2), 3.3 (t, 2), 3.4 (s, 3), 4.0 (q, 1), 4.3 (t, 2), 4.75 (s, 2).

Anal. Calcd for $C_{13}H_{25}NO_2S$: C, 60.19; H, 9.71. Found: C, 60.26; H, 9.87.

2-(2-Methoxymethyloxypentyl)-2-thiazoline (13c, R = *n*-Propyl). Under the same reaction conditions, 5.2 g of **1**, 24.0 ml of *n*-butyllithium, 4.95 ml of butyraldehyde, 3.95 ml of chloromethyl methyl ether, and 65 ml of THF were used. Purification of the crude reaction product on 15 g of silica gel (hexane–benzene) gave 7.05 g (72%) of pure product: ir (film) 1622, 1150, 1095, 1035, 910, 673 cm^{-1}; NMR ($CDCl_3$) δ 0.9 (m, 3), 1.2–1.8 (m, 4), 2.75 (d of d, J = 7, 2 Hz, 2), 3.3 (t of d, J = 7, 2 Hz, 2), 3.4 (s, 3), 4.0 (p, 1), 4.2 (t, 2), 4.7 (s, 2).

2-(2-Methoxymethyloxyphenethyl)-2-thiazoline (13c, R = Ph). Under the same reaction conditions, 1.81 g of **1**, 8.4 ml of *n*-butyllithium, 2.0 ml of benzaldehyde, 1.36 ml of chloromethyl methyl ether, and 35 ml of THF were used. Bulb-to-bulb distillation furnished 3.42 g (75%) of product: ir (film) 1620, 1145, 1095, 1060, 1020 cm^{-1}; NMR ($CDCl_3$) δ 2.9 (d, 2), 3.2 (t, 2), 3.3 (s, 3), 4.2 (t, 2), 4.5 (s, 2), 5.0 (d of d, 1), 7.3 (m, 5).

Reduction of 13c to Thiazolidines. General. The previously described preparation of aluminum amalgam was employed. A tenfold excess of aluminum foil was used. Approximately 100 ml of moist ether was used for each 2.0–2.5 g of thiazoline **13c**. This solution was added to the amalgam immediately after its preparation and the mixture was stirred vigorously. Spontaneous reflux usually occurred; however, if it did not, heat was applied to the flask to bring about gentle reflux. Progress of the reduction was followed by TLC and the complete absence of starting material was noted after 2–4 hr. Isolation of the thiazolidines was identical with that described for **3**. No attempts were made to purify the products, although cursory examination by NMR and ir spectroscopy indicated that the products were 85–95% pure, with crude yields of 87–94%.

3-(Methoxymethyloxy)alkylacetaldehydes (14). General Procedure. The crude thiazolidines from above were dissolved in 30–40 ml of acetonitrile–water (4:1). Solid sodium bicarbonate (100–200 mg to neutralize any hydrochloric acid that might form) was added followed by 2.5–3.0 g of mercuric chloride. The immediately formed precipitate, which often became pasty and required mechanical separation, was stirred or manually agitated for 1–2 hr. Saturated brine was added (30–40 ml) and the solids were removed by suction filtration. Extraction and washing of the aqueous solution and the solids, respectively, with *n*-hexane gave a combined *n*-hexane extract which was washed once with cold 2 *N* hydrochloric acid followed by 5% aqueous bicarbonate. Drying (K_2CO_3) and concentration gave the protected aldehydes **14** listed below.

3-(Methoxymethyloxy)hexaldehyde (14a) was obtained in 55% distilled yield: bp 78–80° (20 Torr); ir (film) 2710, 1720 cm^{-1}; NMR ($CDCl_3$) δ 0.9–1.8 (m, 7), 2.6 (d of d, 2), 3.4 (s, 3), 4.1 (p, 1), 4.7 (s, 2), 9.8 (t, 1); m/e 160 (M^+).

Anal. Calcd for $C_8H_{16}O_3$: C, 59.98; H, 10.07. Found: C, 59.76; H, 10.07.

3-(Methoxymethyloxy)nonaldehyde (14b) was obtained in 61% distilled yield: bp 73–74° (0.30 Torr); ir (film) 2710, 1723, 1640, 1370, 1205, 1150, 1100, 1031, 915 cm^{-1}; NMR ($CDCl_3$) δ 0.9 (t, 3), 1.0–1.8 (m, 10), 2.6 (d of d, J = 7, 2 Hz, 2), 3.4 (s, 3), 4.1 (p, 1), 4.7 (s, 2), 9.8 (t, J = 2 Hz, 1).

Anal. Calcd for $C_{11}H_{22}O_3$: C, 65.31; H, 10.96. Found: C, 65.15; H, 10.80.

3-Cyclopentyl-3-(methoxymethyloxy)propionaldehyde (14c) was obtained in 59% distilled yield: bp 74–75 (0.35 Torr); ir (film) 2710, 1723, 1450, 1210, 1155, 1095, 1031, 915, 753 cm^{-1}; NMR ($CDCl_3$) δ 1.0–2.4 (m, 9), 2.6 (d of d, J = 7, 2 Hz, 2), 3.4 (s, 3), 4.0 (p, 1), 4.7 (s, 2), 9.8 (t, J = 2 Hz, 1).

Anal. Calcd for $C_{10}H_{18}O_3$: C, 64.49; H, 9.74. Found: C, 64.22; H, 9.83.

1-Alkyl-1-(methoxymethyloxy)-4-phenyl-3-butene (15, R = *n*-Propyl, *n*-Hexyl, Cyclopentyl). A suspension of benzyltriphenylphosphonium chloride (1.5 g) in 10 ml of dry THF was treated with an equivalent quantity of *n*-butyllithium at 0°. The reddish-brown solution was stirred for 45 min and 1.0 equiv of the aldehyde **14a** or **14c** in 1–2 ml of THF was added. The color of the phosphorane disappeared and the solution was stirred for 8 hr at room temperature. The reaction mixture was poured into 10–12 ml of water and acidified (pH 4) and the mixture was extracted with 4 × 25 ml of ether. The dried (K_2CO_3) extracts were concentrated and the residue was passed through 10–15 g of Florosil using hexane–benzene (1:1). The olefins were examined by GLC. The yields of **15** (R = *n*-propyl), **15** (R = cyclopentyl), and **15** (R = *n*-hexyl) were 78, 71, and 84%, respectively.

1-*n*-Propyl-1-(methoxymethyloxy)-4-phenyl-3-butene (15, R = *n*-propyl) was composed of 82% trans and 18% cis isomers. Collected from GLC (FFAP) was pure trans isomer: NMR ($CDCl_3$) δ 0.9 (m, 3), 1.5 (m, 4), 2.4 (t, J = 7 Hz, 2), 3.4 (s, 3), 3.6 (m, 1), 4.7 (s, 2), 6.1 (d of d, J = 6, 16 Hz, 1), 6.5 (d, J = 16 Hz. 1), 7.3 (m, 5).

Anal. Calcd for $C_{15}H_{22}O_2$: C, 76.88; H, 9.46. Found: C, 76.69; H, 9.22.

1-*n*-Hexyl-1-(methoxymethyloxy)-4-phenyl-3-butene (15, R = *n*-hexyl) was composed of 76% trans and 24% cis isomers. No separations were attempted. The NMR spectrum was quite similar to that of **15** (R = *n*-propyl) at chemical shifts downfield from 2 ppm.

1-Cyclopentyl-1-(methoxymethyloxy)-4-phenyl-3-butene (15, R = cyclopentyl) was isolated from Florosil (hexane–benzene) as a 63:37 mixture of trans:cis isomers. The NMR spectrum was indicative of the mixture and showed considerable similarities downfield from 2 ppm to **15** (R = *n*-propyl).

1-Alkyl-1-hydroxy-4-phenyl-3-butenes (16). The olefinic acetals **15** (0.5–0.6 g) were dissolved in a solution comprised of THF (0.23 ml), water (2 ml), and 6 *M* hydrochloric acid (5 ml) and heated at 50–55° for 6–8 hr. The reaction mixture was poured into an equal volume of saturated sodium chloride solution and the mixture was extracted with ether (3 × 10 ml). The dried ethereal extracts (K_2CO_3) were concentrated to give the homoallylic alcohols **16**. GLC analysis indicated that the ratio of the cis to trans isomers were unchanged.

1-(*n*-Hexyl)-1-hydroxy-4-phenyl-3-butene (16, R = *n*-hexyl) was recovered in 94% yield, cis:trans (25:75): ir (film) 3400, 3030, 3060, 3080, 1599, 1493, 1040, 963, 930, 740, 690 cm^{-1}; NMR ($CDCl_3$) δ 0.8–1.0 (m, 3), 1.2–1.8 (m, 10), 1.9 (s, 1, exchangeable with D_2O), 2.4 (d of d, m, 2), 3.7 (m, 1), 6.1 (d, J = 16, 0.76 Hz), 6.5 (d, J = 16, 0.76 Hz), 7.3 (m, 5); m/e 232 (M^+, weak).

Anal. Calcd for $C_{16}H_{24}O$: C, 82.70; H, 10.41. Found: C, 82.58; H, 10.27.

1-Cyclopentyl-1-hydroxy-4-phenyl-3-butene (16, R = cyclopentyl) was recovered in 95% yield, cis:trans (37:63): ir (film) 3400, 3020, 3060, 3080, 1595, 1490, 1445, 1030, 965, 740, 690 cm^{-1}; NMR ($CDCl_3$) δ 0.8–2.2 (m, 9), 2.1 (s, 1, exchangeable with D_2O), 2.4 (m, 2), 3.5 (m, 1), 5.6–6.7 (m, 2, cis and trans vinyl H), 7.3 (m, 5); m/e 216 (M^+, weak).

Anal. Calcd for $C_{15}H_{20}O$: C, 83.29; H, 9.32. Found: C, 82.99; H, 9.22.

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Registry No.—**1**, 2346-00-1; **2a**, 55089-92-4; **2b**, 55089-93-5; **2c**, 55089-94-6; **2** (R = H; R′ = CH=CHPh), 55089-95-7; **3a**, 55089-96-8; **3b**, 55089-97-9; **3c**, 55089-98-0; **3** (R = H; R′ = CH=CHPh), 55089-99-1; **4a**, 39850-43-6; **4b**, 39850-40-3; **4c**, 55090-00-1; **5**, 38754-96-0; **7**, 13466-40-5; **8**, 55090-01-2; **9**, 55090-02-3; **13c** (R = cyclopentyl), 55090-03-4; **13c** (R = *n*-hexyl), 55090-04-5; **13c** (R = *n*-propyl), 55090-05-6; **13c** (R = Ph), 55090-06-7; **14a**, 55090-07-8; **14b**, 55090-08-9; **14c**, 55090-09-0; *cis*-**15a**, 55090-10-3; *trans*-**15a**, 55090-11-4; *cis*-**15b**, 55090-12-5; *trans*-**15b**, 55090-13-6; *cis*-**15c**, 55090-14-7; *trans*-**15c**, 55090-15-8; *cis*-**16b**, 54985-33-0; *trans*-**16b**, 54985-37-4; *cis*-**16c**, 55090-16-9; *trans*-**16c**, 55090-17-0; benzaldehyde, 100-52-7; cyclohexanecarboxaldehyde, 2043-61-0; cinnamaldehyde, 104-55-2; β-ionone, 14901-07-6; 1-methyl-4-piperidone, 1445-73-4; acetaldehyde, 75-07-0; cyclopentanecarboxaldehyde, 872-53-7; chloromethyl methyl ether, 107-30-2; *n*-heptaldehyde, 111-71-7; butyraldehyde, 123-72-8.

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A Novel General Synthesis of 2-Substituted 1,2-Benzisothiazolin-3-ones. Cyclization of N-Substituted 2-Methoxycarbonylbenzenesulfenamides

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Reaction of methyl 2-mercaptobenzoate (**2**) or dimethyl 2,2′-dithiodibenzoate (**3**) with bromine, chlorine, or sulfuryl chloride gave 2-methoxycarbonylbenzenesulfenyl halides (**4**), which were not isolated. Halides **4** reacted with primary aliphatic, aromatic, and heterocyclic amines to yield N-substituted 2-methoxycarbonylbenzenesulfenamides **5**. The latter underwent catalytic cyclization by strong bases, providing 2-substituted 1,2-benzisothiazolin-3-ones (**6**) in good to excellent overall yields. Evidence supports a general base catalyzed mechanism initiated by the abstraction of a proton from the sulfenamide nitrogen, and followed by intramolecular attack on the ester carbonyl group and expulsion of methoxide ion. This route is simple and presented as a new general method for the synthesis of 2-substituted 1,2-benzisothiazolin-3-ones.

The first preparation of 1,2-benzisothiazolin-3-one was reported[1] by McKibben and McClelland in 1923. A few years later the synthesis of 2-substituted 1,2-benzisothiazolin-3-ones (**6**) was achieved.[2] The chemistry of **6** was reviewed[3] in 1947. Since that time, it has been discovered that structure **6** possesses high antibacterial and antifungal activity,[4,5] which have also been reviewed recently.[6] A few years ago, the first commercial product (**6**, R = H) useful for the preservation of aqueous media containing organic matter was introduced.[7] It seems quite possible that other members of the benzisothiazolinone series will be introduced for similar commercial applications.

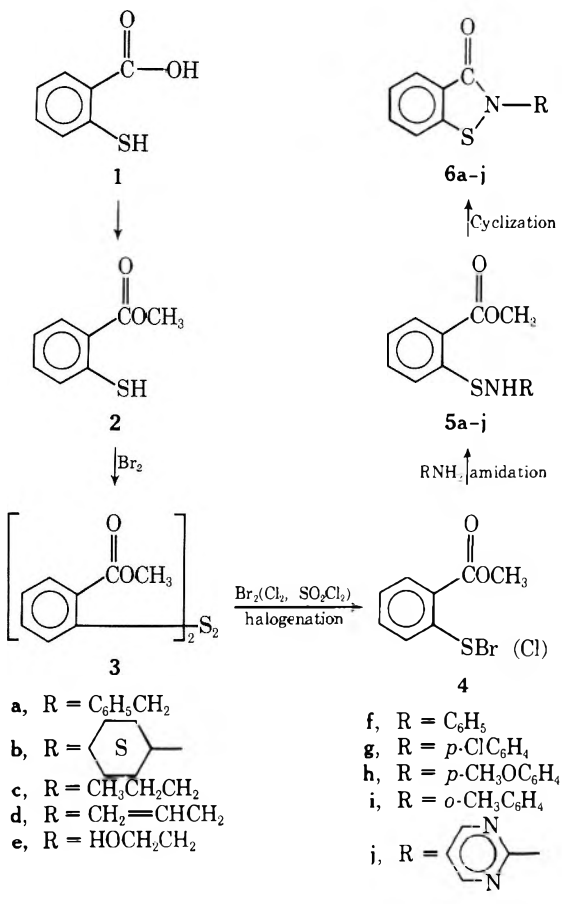
Benzisothiazolinones are prepared according to two well-established routes,[8] both of which use 2,2′-dithiodibenzoic acid as starting material. The acid is firstly[9] treated with thionyl chloride to give 2,2′-dithiodibenzoyl chloride, which is converted into the desired diamide, treated with bromine, and cyclized in boiling glacial acetic acid. Alternatively, halogenation of the acid chloride can precede amidation and cyclization. In this report, a third general synthesis utilizing methyl 2-mercaptobenzoate for starting material is presented.

Results and Discussion

Our continued interest in the chemistry of benzisothiazolinones led to a search for a different synthetic route, possibly circumventing the key intermediate 2,2′-dithiodibenzoyl chloride. For this purpose methyl 2-mercaptobenzoate (**2**), obtained directly by the Sandmeyer reaction on methyl anthranilate, was chosen as the starting material. It was thought that **2**, or its oxidation product **3**, could be easily converted into sulfenamides **5**, which might subsequently undergo cyclization to **6** (Scheme I).

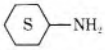
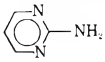
In this work, methyl 2-mercaptobenzoate (**2**) was prepared from commercially available **1** by passing dry hydrogen chloride through a solution of **1** in methanol.[10] Oxidation of **2** by the theoretical amount of bromine gave solid **3**, which was also used extensively as starting material. In fact, oxidation of **2** to **3** by bromine was found to be a more convenient laboratory preparation as compared to the known preparation of **3** by esterification[11] of 2,2′-dithiodibenzoic acid or methanolysis[12] of its acid chloride. Furthermore, the isolation of **3** in high yield confirmed existing evidence[13] that nearly all of the thiol is converted into disulfide before the latter is cleaved into sulfenyl halide by halogenating agents. Attempts to prepare **6a** from **2** by treating **4** with an equimolar amount of benzylamine in pyridine gave **7**.

Scheme I



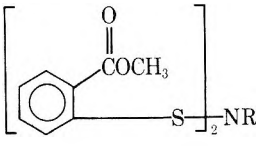
The fact that **7** (mp 131–132°) was not disulfide **3** (mp 131–133°) was shown conclusively by elemental analysis, mixture melting point, and the appearance of the methylene signal (singlet at 4.62 ppm) in the NMR spectrum. When an excess of benzylamine or triethylamine was used instead of pyridine, amidation of **4** to **5a** proceeded

Table I
2-Methoxycarbonylbenzenesulfenamides (2, 3 → 4 → 5)

Reactants			Final Product[a]			
Compd brominated	Amine	HBr Binder[b]	Compd	Mp, °C	Recrystn solvent[c]	Yield, %
2	$C_6H_5CH_2NH_2$	Et_3N	5a	61–62.5	B	80
3		Et_3N	5b	*d, e*		95[h]
3	$CH_3CH_2CH_2NH_2$	A	5c	*d, f*		95[h]
2	$CH_2{=}CHCH_2NH_2$	A	5d	*g*		90[h]
2	$HOCH_2CH_2NH_2$	Et_3N	5e	*g*		95[h]
3	$C_6H_5NH_2$	A	5f	154–155.5	B	85
3	p-$ClC_6H_4NH_2$	A	5g	152–153	C	82
3	p-$CH_3OC_6H_4NH_2$	A	5h	106–107	C	79
3	o-$CH_3C_6H_4NH_2$	Et_3N	5i	113–114	C	85
3		Et_3N	5j	157–158	B	88

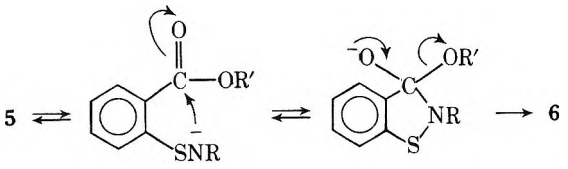
[a] All sulfenamides are new compounds. Acceptable microanalyses (±0.3% for C, H, N, S) for all 5 except 5d and 5e were obtained. [b] A = excess of RNH_2. [c] B = MeOH; C = CH_2Cl_2–MeOH: crude product was dissolved in CH_2Cl_2, clarified, concentrated, diluted with MeOH, concentrated to a small volume, and cooled. [d] Thick liquids, decomposing near 200° (0.1 mm). Purified by column chromatography only. [e] $n^{25}D$ 1.5833. [f] $n^{25}D$ 1.5764. [g] Compound was not purified. [h] Crude yield.

smoothly. Pure **5a** was thus isolated in 60% yield although conversions better than 90% (**2** → **3** → **4** → **5a**) were indicated (TLC).



7, R = $CH_2C_6H_5$
8, R = H

A few attempts to effect cyclization in nonpolar solvents were unsuccessful. Crude **5a**, for example, remained virtually unchanged (TLC) in carbon tetrachloride at reflux for several hours. On the other hand, heating under reflux in 2-propanol for 7 hr did give **6a** in 20% yield. It was then discovered that complete cyclization occurred when crude **5a** was heated on a steam bath for 4–6 hr or allowed to stand at room temperature over 4 weeks, but a melt of pure **5a** was partially (50%) converted into **6a** even after 20 hr at 95°. The difference in reactivity between crude and pure **5a** was finally traced to a small amount of residual benzylamine present in the former. The catalytic effect of bases was subsequently demonstrated by the high-yield cyclization of pure **5a** in methanol in the presence of sodium methoxide. Experiments with a few common bases such as sodium alkoxides, potassium or sodium hydroxide, and tetramethylammonium hydroxide in lower alcohols proved that strong bases are essential in effecting fast and complete cyclization. The rate of cyclization increased with increasing base strength and concentration, both of which are compatible with a general base catalyzed mechanism initiated by the abstraction of a proton from the sulfenamide nitrogen. This proton abstraction is also indicative of the weakly acidic but not basic[14] nature of sulfenamides. The remarkable drop in basicity of nitrogen bonded to bivalent sulfur may be explained in terms of a $(p\text{–}d)_\pi$ overlap resulting in a significantly reduced negative charge on nitrogen.



In order to expand the scope of this reaction, a number of new sulfenamides (**5a–j**) were prepared[15] in good yields by employing primary aliphatic, aromatic, and heterocyclic amines. Bromine, sulfuryl chloride, and chlorine were used as halogenating agents, but yields of **5** or **6** decreased in the same order, the best yields being obtained with bromine. Sulfenamides **5a** and **5f–j** were easily purifiable and stable solids. On the other hand, attempted purification of liquids **5b** and **5c** by distillation at reduced pressure (0.05–0.1 mm) caused decomposition and cyclization. Analytical samples were, therefore, prepared by column chromatography without subsequent distillation. No attempts to purify **5d** and **5e** were made. They were employed in the crude form for the preparation of the corresponding **6** by cyclization. These experiments have been summarized in Table I. All **5** exhibited ir and NMR spectra consistent with their assigned structures. The ν(NH) and ν(C=O) vibrations appeared as sharp peaks at 3300–3400 and 1700–1710 cm^{-1}, respectively. In $CDCl_3$, the NMR signals showed the ester methyl group at 3.85–3.92 ppm and the nitrogen proton at 2.54–2.85, 4.94–5.14, and 8.19 ppm, when R in **5** was an aliphatic, aromatic, and 2-pyrimidyl group, respectively. Moreover, all NH assignments were secured by deuterium exchange determinations.

The cyclization step proceeded smoothly in every case in lower aliphatic alcohols and in the presence of strong bases, to give the corresponding benzisothiazolinones[16] in good to excellent yields. These products were identified by mixture melting point, ir, and NMR spectra against authentic samples prepared according to published methods. Table II represents a summary of the cyclization reactions.

A cursory investigation of the effect of strong acids on **5a** showed that methanolic sulfuric acid ruptures the sulfur–nitrogen bond depending on the acid concentration to yield **7** or **3**. A similar behavior of sulfenamides toward hydrochloric or acetic acid has been reported.[18] In contrast, p-toluenesulfonic acid did promote cyclization. For example, heating **5a** at 90° for 22 hr gave **6a** in 50% yield (TLC); the same conditions in the presence of 10 mol % of p-toluenesulfonic acid resulted in 85% cyclization (TLC), from which **6a** was isolated in 65% yield. In 2-propanol at reflux for 52 hr a 1 mol % acid caused a threefold acceleration of the cyclization, from 20% to 60%. The mechanism for an acid-catalyzed cyclization may be initiated by proton attachment on one of the ester oxygens, but since the sulfenamide ni-

Table II
Preparation of 1,2-Benzisothiazolin-3-ones (5 → 6)

Compd 5	Solvent	Catalyst	Product 6	Recrystn solvent[a]	Mp[b] (bp), °C	Lit. mp (bp), °C	Ref	Yield, %
5a	MeOH	NaOMe	6a	A	86–89	89	17	92
5b	EtOH	NaOMe	6b	B	86–88	87–88	5b	82
5c	MeOH	KOH	6c		(126–128)[c] (0.2 mm)	(170–172) (0.8 mm)	5b	72[d]
5d	MeOH	KOH	6d	B	49–50.5[c,e]			56[d,e]
5e	MeOH	Triton B	6e	C	112–114[c]	104–106	5b	72[d]
5f	Me_2CHOH	$NaOCHMe_2$	6f	D	142–143.5	143–144	20	82
5g	MeOH	NaOMe	6g	D	129–130	130–131	8	93
5h	EtOH	NaOMe	6h	D	147–149	148–149	5b	85
5i	MeOH	NaOMe	6i	E	122–123	124	5b	87[d]
5j	EtOH	NaOMe	6j	D	237–238	236	5b	70[d]

[a] A, 2-propanol; B, ether–hexane; C, acetone; D, ethanol; E, methylene chloride–methanol. [b] After a single crystallization. [c] Satisfactory microanalysis for C, H, N, S, (±0.3%) was obtained. [d] Overall yield (2 → 3 → 4 → 5 → 6). [e] Product was purified by distillation under reduced pressure before final crystallization.

trogen is a poor nucleophile the catalytic effect of acids is small, which is in accord with our experiments.

An extremely slow cyclization of pure liquid sulfenamides **5b** and **5c** at room temperature over prolonged periods of time, and the sluggish cyclization of **5a** in 2-propanol, have already been mentioned. An additional example of cyclization in the absence of catalysts was provided with the preparation of **6c** from **5c** above 130° under reduced pressure. In that **5c** suffered concurrent decomposition, the 42% yield of **6c** isolated was significant. The mechanistic path here could involve protonation of the ester group by the sulfenamide hydrogen (autocatalysis). Again, the low nucleophilicity of the sulfenamide nitrogen precludes fast rates of cyclization, or requires such high temperatures that side reactions become significant.

Finally, basic cyclization is the method of choice. The reaction mechanism should operate with any ortho ester groups capable of acyl–oxygen cleavage, and substitution at any of the four positions of the sulfenamide phenyl ring may not be expected to alter cyclization rates significantly. Isolation of intermediates **4** and **5** is not necessary and overall yields (**2** → **3** → **4** → **5** → **6**) are good to excellent. On the other hand, a few attempts to prepare **5** (R = H) by treating **4** with ammonia failed, since disulfenamide **8** was obtained instead in good yield. A similar behavior for ammonia has been reported.[18]

Experimental Section[19]

Dimethyl 2,2′-Dithiodibenzoate (3). A solution of bromine (80 g, 0.5 mol) in carbon tetrachloride (350 ml) was added dropwise with stirring and cooling to a solution of methyl 2-mercaptobenzoate (**2**, 168.2 g, 1 mol) in carbon tetrachloride (150 ml) over a period of 40 min. The reaction took place with the evolution of hydrogen bromide. After the addition had been completed, the reaction mixture was stirred at room temperature for 1 hr, and the precipitated product was filtered off and dried to give 140.5 g (84%) of very pure **3**: mp 131.5–133° (lit.[12] mp 131–133°); NMR ($CDCl_3$) δ 3.85 (s, 6, OCH_3), 7–7.3 (m, 4, aromatic H), 7.74 (d, 2, aromatic H), 8.01 (d, 2, aromatic H); ir ($CHCl_3$) 1710 cm^{-1} (C=O).

***N,N*-Bis(2-methoxycarbonylphenylthio)benzylamine (7).** Dry chlorine was bubbled through a stirred solution of methyl 2-mercaptobenzoate (5 g, 0.03 mol) in carbon tetrachloride (25 ml) at 15–20° until detected at the outlet with potassium iodide–starch paper. Dry nitrogen was then bubbled through to remove excess of chlorine and the red solution obtained was added dropwise with stirring to benzylamine (3.2 g, 0.03 mol) in pyridine (25 ml) at 25–30° over a period of 20 min. After the addition had been completed, the mixture was heated at 75–80° for 30 min and added warm with stirring to 3 *N* HCl (125 ml) and ice. The solvent layer was separated, dried ($MgSO_4$), and evaporated to dryness in vacuo, yielding an oil. Addition of ether (10 ml) followed by hexane (2 ml) caused the crystallization of almost pure product (mp 129–130.5°, 2.8 g, 42.5%), which was recrystallized once from acetone–hexane: mp 131–132°; NMR ($CDCl_3$) δ 3.85 (s, 6, OCH_3), 4.63 (s, 2, CH_2N), 7–7.6 (m, 12, aromatic H), 7.97 (d, 2, aromatic H); ir (Nujol) 1708 cm^{-1} (C=O).

Anal. Calcd for $C_{23}H_{21}NO_4S_2$: C, 62.85; H, 4.82; N, 3.19; S, 14.59. Found: C, 62.94; H, 4.84; N, 3.27; S, 14.94.

Mixture melting point with diester **3** (mp 131.5–133°) was depressed. In a larger scale experiment crude **7** was obtained in 59% yield.

General Laboratory Procedure for the Preparation of Sulfenamides 5. A solution of bromine (16 g, 0.1 mol) in carbon tetrachloride (100 ml) was added dropwise at ambient temperature to a stirred suspension of dimethyl 2,2′-dithiodibenzoate (**3**, 16.7 g, 0.1 mol) in the same solvent (100 ml) over a period of 30 min. After the addition had been completed, the red solution of bromide **4** obtained was stirred for 30 min and added dropwise with stirring to a solution of the desired primary amine (0.41 mol) or to a stoichiometric amount of the amine (0.2 mol) and triethylamine (0.21 mol) in carbon tetrachloride (200 ml) at 25–30° in 30 min. The reaction mixture was stirred at room temperature for 1 hr or refluxed briefly and the precipitated hydrobromide was filtered off. Depending on solubility, product **5** may partially precipitate along with the amine hydrobromide. The latter was removed by dissolving in water, in which **5** is insoluble. The filtrate of carbon tetrachloride was concentrated to a small volume and cooled or evaporated to dryness in vacuo to give another crop of crude **5**, which can be purified or used as such in the subsequent cyclization step. All compounds had ir bands at 3300–3400 (ν_{NH}) and 1700–1710 cm^{-1} ($\nu_{C=O}$); δ ($CDCl_3$) 3.85–3.90 (s, 2). A specific example of such a preparation is as follows.

***N*-(*o*-Tolyl)-2-methoxycarbonylbenzenesulfenamide (5i).** A solution of bromine (80 g, 0.5 mol) in carbon tetrachloride (100 ml) was added dropwise with stirring to disulfide **3** (167.2 g, 0.5 mol) in carbon tetrachloride (400 ml) over a period of 30 min. The red solution of sulfenyl bromide **4** obtained was stirred at ambient temperature for 30 min and added to a stirred solution of o-toluidine (113 g, 1.05 mol) and triethylamine (106 g, 1.05 mol) in carbon tetrachloride (1000 ml) at 20–25° within 90 min. The reaction mixture was stirred at room temperature for 1 hr, heated under reflux for 1 hr, cooled, and filtered from a solid. The solid was stirred in water (1000 ml) to dissolve triethylamine hydrobromide, leaving a small amount of crude product (**5i**, mp 111–112°, 6.9 g, 2.5%). The filtrate was concentrated to about one-half volume, cooled, and filtered to give 225 g (82.5%) of nearly pure **5i** (mp 112–113.5°). The analytical sample was obtained by recrystallization from CH_2Cl_2–MeOH: mp 113–114°; NMR ($CDCl_3$) δ 2.26 (s, 3, CCH_3), 3.90 (s, 3, OCH_3), 4.98 (s, 1, NH), 6.6–8 (m, 8, aromatic H); ir (CS_2) 3380 (NH), 1703 cm^{-1} (C=O).

Anal. Calcd for $C_{15}H_{15}NO_2S$: C, 65.90; H, 5.53; N, 5.12; S, 11.72. Found: C, 65.79; H, 5.45; N, 5.03; S, 11.83.

General Method for the Preparation of 2-Substituted 1,2-Benzisothiazolin-3-ones (6). A concentrated solution of sulfenamide **5** in methanol containing 1–10 mol % of NaOMe, KOH, or

NaOH was refluxed until cyclization was completed (10 min–3 hr) as shown by TLC. Silica gel plates and mixtures of benzene–chloroform or chloroform–methanol of suitable polarity were used. When solid, the crude product was obtained by concentrating and cooling, or by bringing the reaction mixture to dryness. Liquids **6** were isolated by evaporation of the reaction mixture to dryness and distillation at reduced pressure. The catalyst used can be neutralized by an equivalent amount of hydrochloric acid before working up the reaction mixture or extracted with water. Following are two examples of the cyclization method.

2-Cyclohexyl-1,2-benzisothiazolin-3-one (6b). An ethanolic solution of sodium hydroxide (80 mg, 2 mmol, in 2 ml of ethanol) was added to a stirred solution of crude **5b** (5.3 g, 20 mmol) in ethanol (25 ml). A mild exothermic reaction raised the temperature to 40°. The reaction mixture was stirred at ambient temperature for 1 hr and evaporated to dryness under reduced pressure to yield an oil residue. This residue was dissolved in chloroform, washed with water, and evaporated to dryness, giving crude **6b** as an oil which solidified upon standing. The product (mp 83–86°) was purified by crystallization from ether–hexane, mp 86–88° (lit.[5b] mp 87–88°), yield 82%.

2-Phenyl-1,2-benzisothiazolin-3-one (6f). Sulfenamide **5f** (2.6 g, 10 mmol) in 2-propanol (8 ml) containing 0.1 mmol of sodium isopropoxide (obtained by addition of the calculated amount of sodium hydride) was heated under reflux for 2 hr. Upon cooling **6f** (2.3 g, mp 135–139°) crystallized out, and was filtered off and purified by recrystallization from ethanol and then acetone, mp 142–143.5° (lit. mp[20] 143–144°).

2-Propyl-1,2-benzisothiazolin-3-one (6c) by Heating Neat 5c at Reduced Pressure. A sample of crude **5c** (4 g) was heated at 0.1 mm by means of an oil bath in a flask connected for distillation. Near 130° an increase in pressure to 1 mm was recorded indicating thermal decomposition. Heating was continued until the temperature of the liquid bath increased to 230°. Nearly pure **6c** was distilled over. Redistillation gave pure **6c**: bp 126–128° (0.05 mm); yield 1.4 g (42%); NMR (CCl_4) δ 0.98 (t, 3, CH_2CH_3), 1.78 (sextet, 2, CH_2CH_3), 3.83 (t, 2, NCH_2), 7.2–7.6 (m, 3, aromatic H), 8.01 (d, 1, aromatic H); ir spectrum was identical with that of an authentic sample.

Anal. Calcd for $C_{10}H_{11}NOS$: C, 62.14; H, 5.74; N, 7.25; S, 16.59. Found: C, 62.02; H, 5.79; N, 7.09; S, 16.45.

***N*-2-Methoxycarbonylphenylthio-2-methoxycarbonylbenzenesulfenamide (8).** To a suspension of dimethyl 2,2′-dithiodibenzoate (3, 6.7 g, 0.02 mol) in carbon tetrachloride (60 ml), bromine (3.2 g, 0.02 mol) was added dropwise with stirring. The red solution obtained was added dropwise to a stirred solution of ammonium hydroxide (6.7 g, ~0.1 mol) in dioxane (100 ml), and the precipitated crude product was filtered off. The filtrate was diluted with water, yielding a second crop. The two crops were combined (5.3 g, 75%), washed with water, and recrystallized from methanol to give pure **8**: mp 200–202.5° dec; yield 5.3 g (75%); ir ($CHCl_3$) 3350 (NH), 1700 cm^{-1} (C=O).

Anal. Calcd for $C_{16}H_{15}NO_4S_2$: C, 55.00; H, 4.33; N, 4.01; S, 18.35. Found: C, 54.76; H, 4.25; N, 3.99; S, 18.35.

Action of Sulfuric Acid on *N*-Benzyl-2-methoxycarbonylbenzenesulfenamide (5a). A. Isolation of *N,N*-Bis(2-methoxycarbonylphenylthio)benzylamine (7). Concentrated sulfuric acid (0.14 ml, 0.0025 mol) was added to a suspension of **5a** (2.7 g, 0.01 mol) in methanol (20 ml), and the mixture was heated under reflux for 1 hr and cooled. The precipitated crude product was filtered off, dissolved in chloroform (100 ml), extracted with water (3 × 50 ml), and dried ($MgSO_4$). Evaporation of the solvent gave almost pure **7**, which was purified by one crystallization from methanol and identified by mixture melting point and ir and NMR spectra, mp 130–132°, yield 1.2 g (54%).

B. Isolation of Bis(2-methoxycarbonylphenyl) Disulfide (3). To a suspension of **5a** (2.7 g, 0.01 mol) in methanol (10 ml) was added concentrated sulfuric acid (0.28 ml, 0.005 mol), and the mixture was heated under reflux for 10 min. Upon cooling pure **3** (mp 129–130°, 1.1 g, 66%) crystallized out and was identified by mixture melting point with an authentic sample and ir and NMR spectra.

Registry No.—**1**, 147-93-3; **2**, 4892-02-8; **3**, 5459-63-2; **4**, 55255-07-7; **5a**, 34757-96-5; **5b**, 34757-97-6; **5c**, 34757-98-7; **5d**, 55255-08-8; **5e**, 55255-09-9; **5f**, 34757-99-8; **5g**, 55255-10-2; **5h**, 55255-11-3; **5i**, 55255-12-4; **5j**, 34758-00-4; **6a**, 2514-36-5; **6b**, 2527-02-8; **6c**, 4299-05-2; **6d**, 35159-81-0; **6e**, 4299-09-6; **6f**, 2527-03-9; **6g**, 2620-91-9; **6h**, 2514-33-2; **6i**, 4299-23-4; **6j**, 4337-41-1; **7**, 55255-13-5; **8**, 55255-14-6; $C_6H_5CH_2NH_2$, 100-46-9; cyclohexylamine, 108-91-8; $CH_3CH_2CH_2NH_2$, 107-10-8; $CH_2{=}CHCH_2NH_2$, 107-11-9; $C_6H_5NH_2$, 62-53-3; *p*-$ClC_6H_4NH_2$, 106-47-8; *p*-$CH_3OC_6H_4NH_2$, 104-94-9; *o*-$CH_3C_6H_4NH_2$, 95-53-4; 2-aminopyrimidine, 109-12-6; $HOCH_2CH_2NH_2$, 141-43-5; sulfuric acid, 7664-93-9.

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Synthesis of B/C-*cis*- and -*trans*-6-Hydroxy-12-methyl-1,3,4,9,10,10a-hexahydro-2*H*-10,4a-methanoiminoethanophenanthrene

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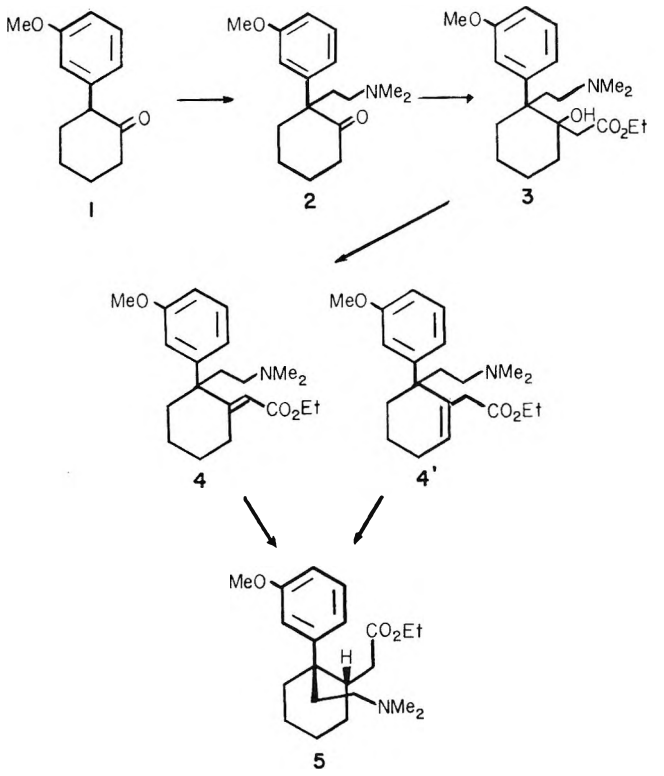
Ring-D-enlarged morphinans and isomorphinans (**13** and **21**) have been synthesized. A five-step sequence [from 2-(*m*-methoxyphenyl)cyclohexanone (**1**)] gave B/C-*cis*-4a(2-dimethylaminoethyl)-6-methoxy-1,2,3,4,4a,10a-hexahydro-10*H*-9-phenanthrone (**6**); the B/C-trans isomer (**17**) resulted in six steps from the α-tetralone, **14**. Compounds **6** and **17** were converted to their *N*-methyl analogs, followed by the Mannich reaction to afford the B/C-*cis*- and -*trans*-9-keto D-ring homomorphinans, **10** and **19**, from which **13** and **21**, respectively, were obtained.

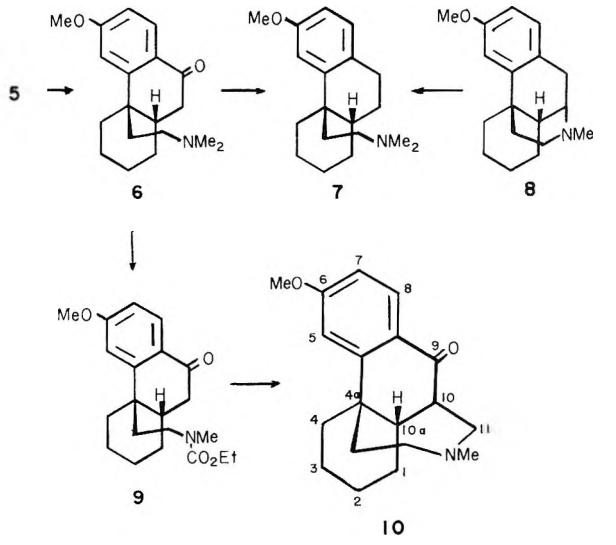
Recently, intramolecular Mannich reaction of 4-(2-methylaminoethyl)-3,4-dihydronaphthalen-1(2*H*)-one derivatives was shown to give seven-membered, nitrogen heterocycles,[2a] some of which exhibit considerable analgesic activity.[2b] This reaction has now been used to prepare the heterocyclic compounds **13b** and **21b**, ring-D-enlarged morphinans having an extra methylene group between the nitrogen and the bridgehead carbon.

2-(2-Dimethylaminoethyl)-2-(*m*-methoxyphenyl)cyclohexanone (**2**)[3] prepared by the condensation of 2-(*m*-methoxyphenyl)cyclohexanone (**1**) and *N*,*N*-dimethylaminoethyl chloride was alkylated with $LiCH_2CO_2Et$ to give compound **3**. Dehydration of **3** afforded a mixture of two olefinic compounds, **4** and **4'** (4.5:1), which were separated by fractional recrystallization of their hydrochlorides.

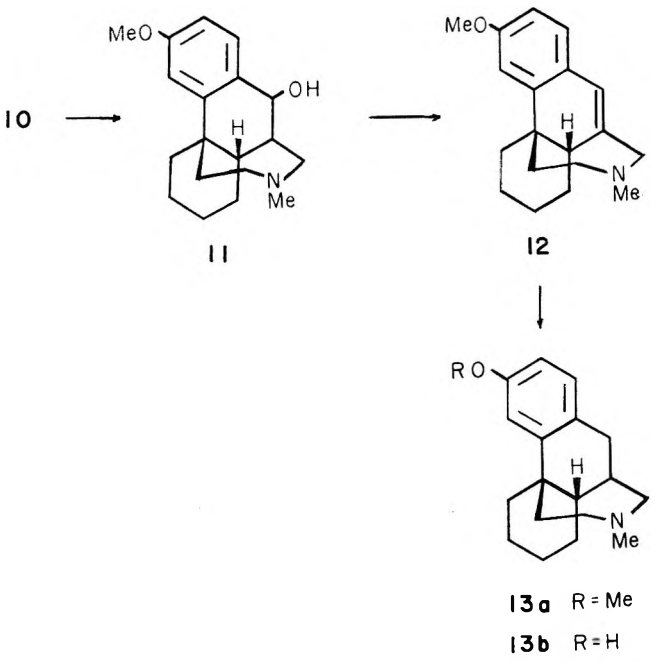


Hydrogenation of **4** over Pt in methanol and in ethanol–HCl and **4'** over Pt in methanol gave the same product, **5**. The configuration of **5** was established by its cyclization to **6** and as follows. If the conformation of the aminoethyl group of **4** and **4'** in methanol is axial, and the aromatic group is equatorially oriented, then the catalytic hydrogenation of **4** and **4'** should be influenced by an anchoring effect of the amino group, giving the cis isomer. Under strongly acidic conditions, the aminoethyl group would exist equatorially, preferentially, owing to solvation around the ammonium cation. Consequently, hydrogen should attack from the less hindered side to again give the cis isomer. Indeed, subsequent reactions indicated the validity of these rationalizations.

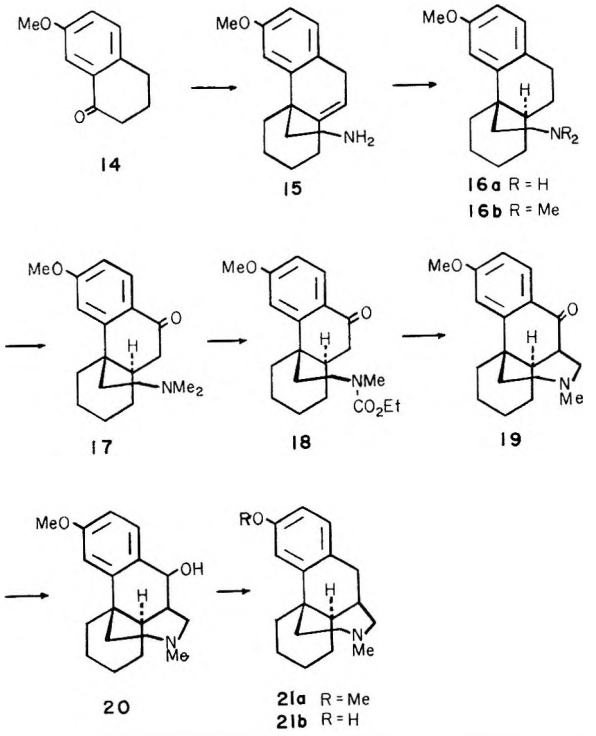
Compound **5** was hydrolyzed with $Ba(OH)_2$, followed by cyclization with PPA to give a phenanthrenone derivative, **6**. The B/C-cis ring junction of **6** was confirmed by the fact that the Wolff–Kishner reduction product **7**, from **6**, was identical with the B/C-cis product obtained from (±)-3-methoxy-*N*-methylmorphinan (**8**) by Hofmann elimination and hydrogenation.[4]



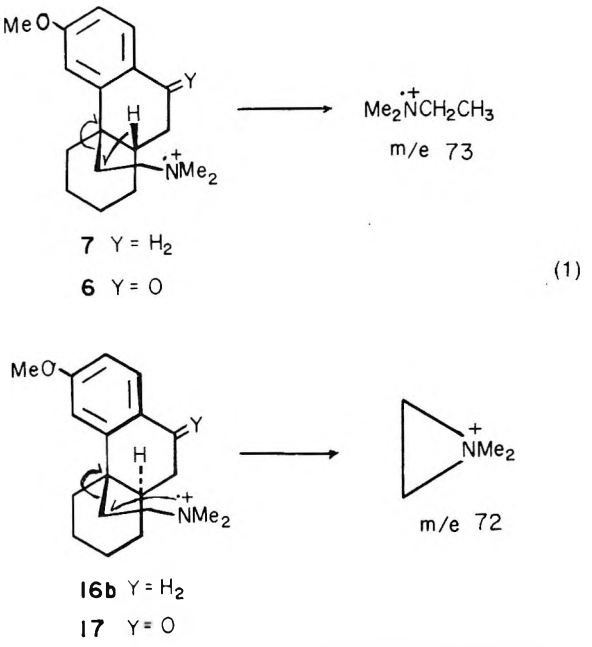
Reaction of **6** with $ClCO_2Et$ in refluxing benzene afforded carbamate **9**. Subsequent hydrolysis and a Mannich reaction with formaldehyde gave the desired B/C-cis homomorphinan, **10**. Reduction of **10** with $LiAlH_4$ gave the hydroxy compound **11**. On treating with HCl in methanol, compound **11** was easily converted to olefinic compound **12**. Structural assignment of **12** was made by spectral measurements. It showed no OH absorption band in the ir. The uv spectrum gave λ_{max} (EtOH) 216 nm (log ε 4.71) and 287 (4.24). The NMR spectrum indicated an olefinic proton singlet at 6.13 ppm. The mass spectrum showed the molecular ion at *m/e* 283. Although structure **12** is obviously in violation of Bredt's rule, these data, examination of Dreiding models, and conversion of **12** (hydrogenation over Pd/C, followed by hydrolysis with refluxing 48% HBr) to the desired B/C-cis homomorphinan, **13b**, leave little doubt about its correctness.



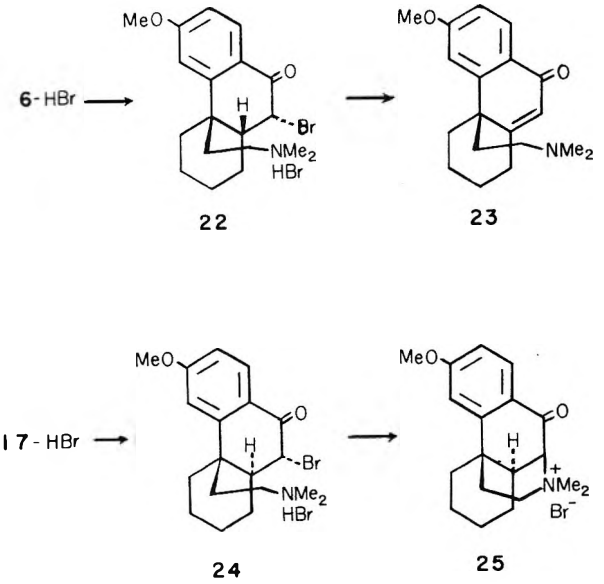
The B/C-trans isomers, **19, 20, 21a,** and **21b,** were synthesized by the following route. Compound **15** was prepared from 7-methoxy-3,4-dihydronaphthalen-1(2*H*)-one (**14**).[5] It was hydrogenated (Pt) in AcOH–$HClO_4$, followed by N-methylation with HCO_2H–CH_2O to give compound **16b.** Oxidation of **16b** with $Na_2Cr_2O_7$ in aqueous H_2SO_4 afforded oxo compound **17.** The carbonyl absorption band at 1675 cm^{-1}, a doublet at 7.98 ppm (J = 9.0 Hz, aromatic proton at the peri position to the carbonyl group), and an m/e 301 for the molecular ion provided the principal basis for the structural assignment of **17.**



The trans geometry for **16b** and **17** was suggested by the following facts. The intensity of the peak m/e 72 in **16b** and **17** is greater than that of m/e 73, while the m/e peak at 73 in **7** and **6** is more intense than that of m/e 72. These differences are similar to the observations made in the *trans*- and *cis*-morphinan series,[6] and are due to the fact that the hydrogen at C-10a in **16b** and **17** is unable to participate in the formation of an m/e 73 fragment (eq 1). Since the



NMR spectrum of **17** suggested, but did not prove, its trans configuration, owing to overlap of the C-10 methylene proton signals with other proton signals, compound **17** was transformed to the α-bromo keto derivative **24.** The NMR spectrum of **24** exhibited a doublet for C-10 proton at 5.28 ppm (J = 12.0 Hz) [the corresponding B/C-cis isomer **22** showed a doublet for the C-10 proton at 6.07 ppm (J = 4.5 Hz)]. The large coupling constant in compound **24** indicates a trans-diaxial arrangement of the C-10 and C-10a protons in **24.** Treatment of the bromo compound **24** with $NaHCO_3$ produced the B/C-trans morphinan derivatives **25,** while the cis α-bromo isomer **22** gave an olefinic compound **23.** These results are similar to those in the *cis*- and



trans-4-(2-dimethylaminoethyl)-3-methyl-3,4-dihydronaphthalen-1(2*H*)-one series,[7] and support a cis arrangement of C-10 bromine and C-10a proton in **24** and a trans arrangement of C-10 bromine and C-10a proton in **22.**

Reaction of **17** with $ClCO_2Et$ in refluxing benzene gave carbamate **18.** Hydrolysis, and the subsequent Mannich reaction of **18,** afforded the B/C-trans homomorphinan derivative **19.** The carbonyl group in **19** was reduced with $LiAlH_4$ to give an alcoholic compound, **20.** Treatment of **20** with HCl gave a mixture of several compounds, unlike the cis isomer, which could not be separated by chromatogra-

phy. Hydrogenolysis of the hydroxyl group in **20** over Pd/C gave compound **21a**, which was transformed to the desired **21b** by refluxing with hydrobromic acid.

Compound **13b** appears to be as active as morphine in preliminary animal tests.

Experimental Section

Melting points (Hershberg) are corrected. Infrared data were obtained on a Perkin-Elmer 257, ultraviolet spectra from a Beckman DBG spectrometer, mass spectra from an Hitachi RMU-6E double-focusing spectrometer at 70 eV, and CI mass spectra from a Finnigan 1015D spectrometer. NMR spectra, at 100 MHz, were obtained on a Varian HA-100 or 60 MHz on a Varian A-60 (Me_4Si at δ 0.00 ppm as internal standard).

1-Carbethoxymethylene-2-(*m*-methoxyphenyl)-2-(2-dimethyaminoethyl)cyclohexane (4) and Ethyl 6-(*m*-Methoxyphenyl)-6-(2-dimethylaminoethyl)-1-cyclohexaneacetate (4'). BuLi (1 *M*) in hexane (65 ml) was added to a stirred solution of $(Me_3Si)_2NH$ (9.9 g) in ether (50 ml) over 15 min under N_2 and with ice cooling. After gentle refluxing (30 min) and stirring at room temperature (1.5 hr), the solution was evaporated in vacuo. The resultant mass was dissolved in dry THF (100 ml) and cooled in a Dry Ice–acetone bath (−80°). To this cooled solution was added a solution of AcOEt (5.0 g) in dry ether (20 ml) during 25 min. After stirring at this temperature for 30 min, a solution of **2**[3] (14.0 g) in ether (100 ml) was added during 40 min (under N_2) with stirring; stirring was continued for 3 hr. After addition of H_2O (20 ml), the cold bath was removed. The mixture (at room temperature) was poured into H_2O (100 ml). The dried ($MgSO_4$) organic layer gave 18.0 g of **3** as a yellow oil, which was used without purification: ir (neat) 3500 (OH), 2770, 2820 (NMe_2), 1715 cm^{-1} (CO_2Et); NMR ($CDCl_3$) δ 1.19 (t, J = 7.0 Hz, 3, OCH_2CH_3), 2.16 (s, 6, NMe_2), 3.83 (s, 3, OMe), 4.06 (q, J = 7.0 Hz, 2, OCH_2CH_3), 3.93 (broad s, 1, OH, removed by D_2O), 6.70–7.35 (m, 4, aromatic).

Ester **3** (17.5 g), *p*-TsOH·H_2O (28 g), C_6H_6 (300 ml), and PhMe (700 ml) were refluxed (H_2O separator) for 1 week, made alkaline with 20% NaOH, washed with H_2O, dried ($MgSO_4$), and evaporated to give 12.7 g of a yellow oil, which was converted to the HCl salt and fractionally recrystallized from EtOH–Me_2CO to give 4.5 g of **4** HCl, mp 196–199°, 1.05 g of **4'** HCl, mp 167–168.5°, and 2.9 g of a mixture of **4**·HCl and **4'**·HCl.

4 HCl: Anal. Calcd for $C_{21}H_{31}NO_3$·HCl: C, 66.04; H, 8.45; N, 3.67. Found: C, 65.80; H, 8.72; N, 3.55.

The free base showed ν_{max} (film) 2770, 2820 (NMe_2), 1717 (CO_2Et), 1640 cm^{-1} (C=C); NMR ($CDCl_3$) δ 1.31 (t, J = 7.0 Hz, 3, OCH_2CH_3), 2.13 (s, 6, NMe_2), 3.81 (s, 3, OMe), 4.24 (q, J = 7.0 Hz, 2, OCH_2CH_3), 5.99 (s, 1, C=C**H**CO_2Et), 6.65–7.35 (m, 4, aromatic).

4' HCl: Anal. Calcd for $C_{21}H_{31}NO_3$·HCl: C, 66.04; H, 8.45; N, 3.67, Found: C, 65.63; H, 8.52; N, 3.42.

The free base showed ν_{max} (film) 2760, 2810 (NMe_2), 1735 cm^{-1} (CO_2Et); NMR ($CDCl_3$) δ 1.22 (t, J = 7.0 Hz, 3, OCH_2CH_3), 2.30 (s, 6, NMe_2), 3.83 (s, 3, OMe), 2.85 (broad, one peak, =C-CH_2CO_2Et), 4.11 (q, J = 7.0 Hz, 2, OCH_2CH_3), 6.01 (broad, one peak, 1, -CH=C<), 6.67–7.33 (m, 4, aromatic).

Ethyl 2-(2-Dimethylaminoethyl)-2-(*m*-methoxyphenyl)cyclohexane-1-acetate (5). A. Hydrogenation of **4** (0.9 g) over PtO_2 (0.1 g) in MeOH (25 ml) for 19 hr gave 0.9 g of **5** as a colorless oil: ir (neat) 2760, 2810 (NMe_2), 1730 cm^{-1} (CO_2Et); NMR ($CDCl_3$) δ 1.15 (t, J = 7.0 Hz, 3, OCH_2CH_3), 2.12 (s, 6, NMe_2), 3.82 (s, 3, OMe), 4.02 (q, J = 7.0 Hz, 2, OCH_2CH_3), 6.60–7.30 (m, 4, aromatic).

B. Hydrogenation of **4'** (0.6 g) over PtO_2 (1.0 g) in MeOH (30 ml) for 4.5 days gave 0.6 g of a colorless oil identical with **5** obtained from **4** (ir, GLC).

C. Hydrogenation of **4** (1.5 g) (in 12 *M* HCl, 10 ml) over PtO_2 (0.3 g) in EtOH (25 ml) followed by removal of solvent gave a product which was dissolved in H_2O, basified with 20% NaOH, extracted with ether, and dried ($MgSO_4$). Removal of solvent gave 1.0 of colorless oil which was identical with the product obtained in A and B (ir, GLC).

B/C-*cis*-4a-(2-Dimethylaminoethyl)-6-methoxy-1,2,3,4,4a,10a-hexahydro-10*H*-9-phenanthrone (6) Hydrochloride. Ester **5** (0.87 g), $Ba(OH)_2$·$8H_2O$ (8.0 g), and H_2O (50 ml) were refluxed for 18 hr, cooled, neutralized with dilute H_2SO_4, and filtered (Celite). The filtrate was evaporated to dryness. The residue (0.8 g) and PPA (25 g) were heated at 110–130° for 0.5 hr and at 150–160° for 0.5 hr, cooled, treated with ice–H_2O, basified with KOH, and extracted with $CHCl_3$. Drying (K_2CO_3) and evaporation of solvent gave 0.66 g of a yellow oil. It was converted to HCl salt which, recrystallized from Me_2CO, gave 0.5 g of **6** HCl, mp 229.5–232°.

Anal. Calcd for $C_{19}H_{27}NO_2$·HCl: C, 67.54; H, 8.35; N, 4.15. Found: C, 67.33; H, 8.11; N, 4.07.

The free base was molecularly distilled (bath temperature 180–200°, 0.2 mm): ir (neat) 2760, 2810 (NMe_2), 1675 cm^{-1} (C=O); NMR ($CDCl_3$) δ 2.12 (s, 6, NMe_2), 3.82 (s, 3, OMe), 6.74 (d, $J_{5,7}$ = 3.0 Hz, 1, C-5 H), 6.78 (q, $J_{5,7}$ = 3.0, $J_{7,8}$ = 9.0 Hz, 1, C-7 H), 8.01 (d, $J_{7,8}$ = 9.0 Hz, 1, C-8 H); mass spectrum *m/e* 301 (M^+), 230 (M^+ − $Me_2NCH{=}CH_2$), 229 (M^+ − $Me_2NCH_2CH_2$·), 228 (M^+ − Me_2NEt), 73 ($EtN^{\cdot+}Me_2$), 72 (c-$C_2H_4N^+Me_2$), 58 ($CH_2{=}C\text{-}NMe_2{\cdot}^+$); *m/e* 73 > *m/e* 72.

B/C-*cis*-4a-(2-Dimethylaminoethyl)-6-methoxy-1,2,3,4,4a,9,10,10a-octahydrophenanthrene (7). The hydrochloride of **6** (54 mg), KOH (0.1 g), 95% NH_2NH_2 (0.1 ml), and triethylene glycol (1 ml) were kept at 160–170° for 18 hr, then at 200° for 1 hr. The cooled mixture was treated with H_2O and ether. Evaporation of the dried (K_2CO_3) ethereal layer gave 44.2 mg of crude **7**, which was distilled in vacuo to give a pure sample of **7**, colorless oil of bp 160–180° (0.05 mm) (bath temperature). The distillate was identical with the sample prepared from (±)-3-methoxy-*N*-methylmorphinan (**8**) by Hofmann elimination and hydrogenation[4] [ir, GLC, TLC (silica gel, 8:2 $CHCl_3$–MeOH)]: NMR ($CDCl_3$) δ 2.15 (s, 6, NMe_2), 2.72 (br t, 2, C-9 H,), 3.74 (s, 3, OMe), 6.64 (q, $J_{7,8}$ = 8.0, $J_{7,5}$ = 2.5 Hz, 1, C-7 H), 6.77 (d, $J_{5,7}$ = 2.5 Hz, 1, C-5 H), 6.96 (d, $J_{7,8}$ = 8.0 Hz, 1, C-8 H); mass spectrum *m/e* 287 (M^+), 216 (M^+ − $Me_2NCH{=}CH_2$), 73 ($Me_2N{\cdot}^+Et$), 72 (c-$C_2H_4N^+Me_2$), 58 ($Me_2N^+{=}CH_2$), 45 ($Me_2N{\cdot}^+H$); *m/e* 73 > *m/e* 72.

Picrate: mp 158–160° (from MeOH) (lit. [4]mp 158–159°).

Anal. Calcd for $C_{25}H_{32}N_4O_8$: C, 58.13; H, 6.25; N, 10.85. Found: C, 58.37; H, 6.18; N, 10.61.

B/C-*cis*-6-Methoxy-12-methyl-1,3,4,10a-tetrahydro-2*H*-10,4a-methanoiminoethano-10*H*-9-phenanthrone (10). $ClCO_2Et$ (360 mg) was rapidly added to a refluxing solution of **6** (664 mg) in benzene (25 ml). The mixture was refluxed for 2.5 hr. The cooled mixture was washed with 10% HCl and H_2O and dried ($MgSO_4$). Evaporation of the benzene gave 752 mg of carbamate **9**: ir (neat) 1675 (C=O), 1695 cm^{-1} (>NCO_2Et); NMR ($CDCl_3$) δ 1.20 (t, J = 7.0 Hz, 3, OCH_2CH_3), 2.77 (s, 3, NMe), 3.88 (s, 3, OMe), 4.07 (q, J = 7.0 Hz, 2, OCH_2CH_3), 6.81 (d, $J_{5,7}$ = 2.2 Hz, 1, C-5 H), 6.84 (q, $J_{7,5}$ = 2.2, $J_{7,8}$ = 9.6 Hz, 1, C-7 H), 8.10 (d, $J_{8,7}$ = 9.5 Hz, 1, C-8 H).

Carbamate **9** (730 mg), 12 *M* HCl (50 ml), and AcOH (25 ml) were refluxed for 24 hr. After evaporation of AcOH and HCl, the light-brown syrup was dissolved in MeOH (10 ml) and Formalin (35–40%, 1.5 ml). The mixture was kept at 55–60° for 44 hr. After evaporation to dryness, the residue was dissolved in H_2O, basified with 20% NaOH, extracted with ether, and dried ($MgSO_4$). The residue from the ethereal solution was chromatographed on a silica gel column (20 g). Elution with $CHCl_3$–MeOH (99:1) gave 319 mg of pure **10**: mp 92–95.5°; ir (Nujol) 2750, 2800 (NMe), 1665 cm^{-1} (C=O); NMR ($CDCl_3$) δ 2.30 (s, 3, NMe), 3.88 (s, 3, OMe), 2.80–3.38 (AB part of ABX, J_{AB} = 12.0, J_{AX} = 7.0, J_{BX} = 3.0 Hz, 2, C-11 H), 6.76 (d, $J_{5,7}$ = 3.0 Hz, 1, C-5 H), 6.81 (q, $J_{7,8}$ = 9.0, $J_{7,5}$ = 3.0 Hz, 1, C-7 H), 8.04 (d, $J_{8,7}$ = 9.0 Hz, 1, C-8 H); mass spectrum *m/e* 299 (M^+), 284 (M^+ − Me), 230 (M^+ − C_4H_7N), 71 [$MeN^{\cdot+}{=}CH_2)CH_2CH_2$·], 70 [$MeN^+(=CH_2)CH{=}CH_2$]. Picrate: mp 221–223° (from Me_2CO).

Anal. Calcd for $C_{25}H_{28}N_4O_9$: C, 56.80; H, 5.34; N, 10.60. Found: C, 56.90; H, 5.15; N, 10.39.

B/C-*cis*-6-Methoxy-12-methyl-1,3,4,9,10,10a-hexahydro-2*H*-10,4a-methanoiminoethano-9-phenanthrol (11). A mixture of $LiAlH_4$ (0.5 g) and **10** (0.9 g) in Et_2O (70 ml) was refluxed for 2 hr. When cooled, the mixture was treated with H_2O and sodium tartrate solution. The aqueous layer was extracted with $CHCl_3$. The ethereal layer and the $CHCl_3$ extract were combined, washed with H_2O, dried (K_2CO_3), and evaporated to give 0.85 g of compound **11** as a colorless syrup: ir (neat) 3400 cm^{-1} (OH); NMR ($CDCl_3$) δ 2.14 (s, 3, NMe), 2.74–3.06 (AB part of ABX, J_{AB} = 14.0, J_{AX} = 5.5, J_{BX} = 3.0 Hz, 2, C-11 H_2), 3.74 (s, 3, OMe), 4.42 (broad s, removed by D_2O, 1, OH), 4.48 (d, J = 8.0 Hz, C-9 H), 6.67 (d, $J_{5,7}$ = 3.0 Hz, 1, C-5 H), 6.77 (q, $J_{7,5}$ = 3.0, $J_{7,8}$ = 8.0 Hz, 1, C-7 H), 7.73 (d, $J_{8,7}$ = 8.0 Hz, 1, C-8 H); CI mass spectrum *m/e* 302 (M^+ for 301).

B/C-*cis*-6-Methoxy-12-methyl-1,3,4,10a-tetrahydro-2*H*-10,4a-methanoiminoethanophenanthrene (12). A solution of **11** (426 mg) in ether was treated with dry HCl gas to give a colorless, crystalline precipitate, which was recrystallized from MeOH–Me_2CO to give 350 mg of **12** HCl, mp 142.5–144.5°.

Anal. Calcd for $C_{19}H_{25}NO$·HCl·MeOH: C, 68.26; H, 8.59; N, 3.98. Found: C, 68.03; H, 8.62; N, 3.98.

Free base: uv λ_{max} (EtOH) 216 nm (log ϵ 4.71), 287 (4.24); NMR ($CDCl_3$) δ 2.32 (s, 3, NMe), 2.86–3.57 (AB quartet, J = 10.0 Hz, 2, C-11 H_2), 3.78 (s, 3, OMe), 6.13 (s, 1, C-9 H), 6.67 (q, $J_{7,8}$ = 8.0, $J_{7,5}$ = 3.0 Hz, 1, C-7 H), 6.80 (d, $J_{5,7}$ = 3.0 Hz, 1, C-5 H), 7.10 (d, $J_{8,7}$ = 8.0 Hz, 1, C-8 H); mass spectrum m/e 283 (M^+).

B/C-*cis*-6-Methoxy- (13a) and B/C-*cis*-6-Hydroxy-12-methyl-1,3,4,9,10,10a-hexahydro-2*H*-10,4a-methanoiminoethanophenanthrene (13b). Hydrogenation of **12** (400 mg) over 10% Pd/C (0.3 g) in MeOH (20 ml) and 10% HCl (10 ml) for 6 hr gave a colorless residue which was dissolved in H_2O, made alkaline with 20% NaOH, and extracted with ether. The residue (375 mg) of the dried (K_2CO_3) ethereal solution was distilled (bath temperature 170–180°, 0.05 mm) to give 370 mg of **13a** as a colorless oil: NMR ($CDCl_3$) δ 2.22 (s, 3, NMe), 2.32–2.98 (AB part of ABX, J_{AB} = 13.0, J_{AX} = 5.0, J_{BX} = 5.0 Hz, 2, C-11 H_2), 2.47–3.13 (AB part of ABX, J_{AB} = 16.0, J_{AX} = 8.0, J_{BX} = 2.5 Hz, 2, C-9 H_2), 3.76 (s, 3, OMe), 6.67 (q, $J_{7,8}$ = 8.0, $J_{7,5}$ = 2.5 Hz, 1, C-7 H), 6.79 (d, $J_{5,7}$ = 2.5 Hz, 1, C-5 H), 6.99 (d, $J_{8,7}$ = 8.0 Hz, 1, C-8 H); mass spectrum m/e 285 (M^+), 214 ($M^+ - C_4H_9N$), 213 ($M^+ - C_4H_{10}N$), 212 ($M^+ - C_4H_{11}N$), 73 ($Me_2N{\cdot}^+Et$), 72 [$MeN^+(=CH_2)Et$], 71 ($Me_2N{\cdot}^+CH{=}CH_2$), 70 [$MeN^+(=CH_2)CH{=}CH_2$].

Anal. Calcd for $C_{19}H_{27}NO$: C, 79.95; H, 9.54; N, 4.91. Found: C, 80.01; H, 9.62; N, 4.86.

Methoxy compound **13a** (106 mg) and 48% HBr (3 ml) were refluxed for 30 min. Evaporation and recrystallization from MeOH–Me_2CO gave 102 mg of **13b** HBr, mp 240–242°.

Anal. Calcd for $C_{18}H_{25}NO{\cdot}HBr{\cdot}\frac{1}{3}H_2O$: C, 60.33; H, 7.50; N, 3.91. Found: C, 60.40; H, 7.13; N, 3.97.

Ir (Nujol) 3200 (OH), 2640 cm^{-1} ($^+$NH); NMR (CD_3OD) δ 2.86 (s, 3, $^+$NMe), 6.66 (q, $J_{7,8}$ = 8.0, $J_{7,5}$ = 2.5 Hz, 1, C-7 H), 6.74 (d, $J_{5,7}$ = 2.5 Hz, 1, C-5 H), 7.02 (d, $J_{8,7}$ = 8.0 Hz, 1, C-8 H); CI mass spectrum m/e 272 (M^+ for 271).

B/C-*trans*-4a-(2-Dimethylaminoethyl)-6-methoxy-1,2,3,4,4a,9,10,10a-octahydrophenanthrene (16b). Hydrogenation of **15**[5] (2.0 g) over PtO_2 (0.3 g) in 60% $HClO_4$ (1.0 ml) and AcOH (50 ml) for 6 hr gave a residual solid which was dissolved in H_2O, made alkaline with 20% NaOH, extracted with ether, and dried (K_2CO_3). Evaporation of the ether gave 1.9 g of **16a**. Primary amine **16a** (1.9 g), HCO_2H (10 ml), and Formalin (35–40%, 10 ml) were heated on a steam bath for 1.5 hr. After evaporation to dryness, the residue was dissolved in H_2O, basified with 20% NaOH, extracted with $CHCl_3$, and dried (K_2CO_3). Evaporation of the $CHCl_3$ gave 2.0 g of crude **16b**, which was distilled in vacuo to give 1.8 g of pure **16b**: bp 175–185° (0.05 mm) (bath temperature); ir (neat) 2760, 2810 cm^{-1} (NMe_2); NMR ($CDCl_3$) δ 2.08 (s, 6, NMe_2), 2.80 (br t, 2, C-9 H), 3.73 (s, 3, OMe), 6.64 (q, $J_{7,8}$ = 8.0, $J_{7,5}$ = 2.0 Hz, 1, C-7 H), 6.71 (d, $J_{5,7}$ = 2.0 Hz, 1, C-5 H), 6.96 (d, $J_{8,7}$ = 8.0 Hz, 1, C-8 H); mass spectrum m/e 287 (M^+), 216 ($M^+ - Me_2N{-}CH{=}CH_2$), 73 ($Me_2N{\cdot}^+Et$), 72 (Me_2N^+-c-C_2H_4), 58 ($Me_2N{-}^+{=}CH_2$); m/e 73 $\ll$ m/e 72 (see eq 1).

Oxalate: mp 205–208° (from MeOH–Me_2CO).

Anal. Calcd for $C_{21}H_{31}NO_5$: C, 66.82; H, 8.28; N, 3.71. Found: C, 66.55; H, 8.36; N, 3.63.

B/C-*trans*-4a-(2-Dimethylaminoethyl)-6-methoxy-1,2,3,4,4a,10a-hexahydro-10*H*-9-phenanthrone (17). To a stirred mixture of **16b** (750 mg) and $Na_2Cr_2O_7$ (1.0 g) in 1 *N* H_2SO_4 (30 ml) was added 10 *N* H_2SO_4 (60 ml) at room temperature during 2 hr. After stirring for 17 hr, the mixture was cooled (ice bath), basified with 12 *M* NH_4OH, extracted with ether, and dried (K_2CO_3). Evaporation of the ether gave 600 mg of crude **17**, which was purified by recrystallization of its hydrochloride from MeOH–Me_2CO, mp 233–235°.

Anal. Calcd for $C_{19}H_{27}NO_2$·HCl·MeOH: C, 64.94; H, 8.72; N, 3.79. Found: C, 64.67; H, 8.61; N, 3.71.

The free base: ir (neat) 2760, 2810 (NMe_2), 1675 cm^{-1} (C=O); NMR ($CDCl_3$) δ 2.05 (s, 6, NMe_2), 3.82 (s, 3, OMe), 6.77 (q, $J_{7,8}$ = 9.0, $J_{7,5}$ = 2.5 Hz, 1, C-7 H), 6.74 (d, $J_{5,7}$ = 2.5 Hz, 1, C-5 H), 7.98 (d, $J_{8,7}$ = 9.0 Hz, 1, C-8 H); mass spectrum m/e 301 (M^+), 230 ($M^+ - Me_2NCH{=}CH_2$), 73 ($Me_2N{\cdot}^+Et$), 72 (c-$C_2H_4N^+Me_2$), 58 ($Me_2N^+{=}CH_2$), 45 ($Me_2N{\cdot}^+H$) (m/e 73 < m/e 72).

B/C-*trans*-6-Methoxy-12-methyl-1,3,4,10a-tetrahydro-2*H*-10,4a-methanoiminoethano-10*H*-9-phenanthrone (19). To a refluxing solution of **17** (720 mg) in C_6H_6 (50 ml) was added a solution of $ClCO_2Et$ (400 mg) in C_6H_6 (10 ml) during 7 min. After refluxing for 2 hr, the mixture was cooled, washed with 10% HCl, dried ($MeSO_4$), and evaporated to give 827 mg of **18**: ir (neat) 1680 (C=O), 1700 cm^{-1} (NCO_2Et); NMR ($CDCl_3$) δ 1.76 (t, J = 7.0 Hz, 3, OCH_2CH_3), 2.65 (s, 3, NMe), 3.86 (s, 3, OMe) 4.04 (q, J = 7.0 Hz, 2, OCH_2CH_3), 6.77 (d, $J_{5,7}$ = 2.5 Hz, 1, C-5 H), 6.82 (q, $J_{7,8}$ = 8.5, $J_{7,5}$ = 2.5 Hz, 1, C-7 H), 8.04 (d, $J_{8,7}$ = 8.5 Hz, 1, C-8 H).

Carbamate **18** (1.47 g), 12 *M* HCl (70 ml), and AcOH (30 ml) were refluxed for 24 hr. The mixture was evaporated, dissolved in MeOH (20 ml) and Formalin (2.0 ml), and kept at 60–70° for 3.5 days. After evaporation to dryness, the residue was dissolved in H_2O, basified with 20% NaOH, extracted with ether, and dried ($MgSO_4$). The residue (1.08 g) of the ethereal solution was chromatographed on a silica gel (20 g) column. Elution with $CHCl_3$–MeOH (99:1) gave 0.9 g of **19** as an almost colorless oil: ir (neat) 2760, 2805 (NMe), 1670 cm^{-1} (C=O); NMR ($CDCl_3$) δ 2.22 (s, 3, NMe), 2.83–3.29 (AB part of ABX, J_{AB} = 12.5, J_{AX} = 6.0, J_{BX} = 2.5 Hz, 2, C-11 H), 3.84 (s, 3, OMe), 6.81 (q, $J_{7,8}$ = 9.5, $J_{7,5}$ = 2.0 Hz, 1, C-7 H), 6.83 (d, $J_{5,7}$ = 2.0 Hz, 1, C-5 H), 8.03 (d, $J_{8,7}$ = 9.5 Hz, 1, C-8 H).

Picrate: mp 228–230° (from MeOH).

Anal. Calcd for $C_{25}H_{28}N_4O_9$: C, 56.80; H, 5.34; N, 10.60. Found: C, 56.92; H, 5.45; N, 10.66.

B/C-*trans*-6-Methoxy- (21a) and B/C-*trans*-6-Hydroxy-12-methyl-1,3,4,9,10,10a-hexahydro-2*H*-10,4a-methanoiminoethanophenanthrene (21b). A mixture of **19** (592 mg) and $LiAlH_4$ (0.3 g) in ether (50 ml) was refluxed for 2 hr. After cooling, the mixture was treated with H_2O and sodium tartrate solution. The aqueous layer was extracted with $CHCl_3$. The ethereal layer and the extract were combined, washed with H_2O, and dried (K_2CO_3). Evaporation of the solvent gave 608 mg of **20** as a slightly yellow syrup: ir (neat) 3430 (OH), 2770, 2810 cm^{-1} (NMe); NMR ($CDCl_3$) δ 2.14 (s, 3, NMe), 2.59–3.02 (six lines, AB part of ABX, J_{AB} = 14.0, J_{AX} = 6.5, J_{BX} = 0 Hz, 2, C-11 H_2), 3.78 (s, 3, OMe), 4.89 (d, J = 7.5 Hz, 1, C-9 H), 6.75 (d, $J_{5,7}$ = 2.5 Hz, 1, C-5 H), 6.78 (q, $J_{7,8}$ = 9.0, $J_{7,5}$ = 2.5 Hz, 1, C-7 H), 7.53 (d, $J_{8,7}$ = 9.0 Hz, C-8 H).

Hydrogenation of **20** (500 mg) in 10% HCl (6 ml) and MeOH (20 ml) over 10% Pd/C (0.3 g) for 5.5 hr gave, after removal of the catalyst and solvent, a residue which was dissolved in H_2O, made alkaline with 20% NaOH, extracted with ether, and dried (K_2CO_3). Evaporation of the solvent gave 421 mg of **21a** as a colorless oil, distilled at 155–170° (bath temperature, 0.01 mm): NMR ($CDCl_3$) δ 2.38 (s, 3, NMe), 3.76 (s, 3, OMe), 6.70 (q, $J_{7,8}$ = 8.5, $J_{7,5}$ = 2.5 Hz, 1, C-7 H), 6.78 (d, $J_{5,7}$ = 2.5 Hz, 1, C-5 H), 7.00 (d, $J_{8,7}$ = 8.5 Hz, 1, C-8 H).

Picrate: mp 186–189° (from MeOH).

Anal. Calcd for $C_{25}H_{30}N_4O_8$: C, 58.36; H, 5.88; N, 10.89. Found: C, 58.04; H, 6.02; N, 10.99.

A mixture of **21a** (157 mg) and 48% HBr (3.5 ml) was refluxed for 30 min. Evaporation and recrystallization from MeOH gave 161 mg of **21b** HBr as colorless crystals: mp 287–289°; ir (Nujol) 3390 (OH), 2650 cm^{-1} ($^+$NH); NMR (CD_3OD) δ 2.81 (s, 3, $^+$NMe), 6.65 (q, $J_{7,8}$ = 8.0, $J_{7,5}$ = 2.5 Hz, 1, C-7 H), 6.72 (d, $J_{5,7}$ = 2.5 Hz, 1, C-5 H), 6.99 (d, $J_{8,7}$ = 8.0 Hz, 1, C-8 H); CI mass spectrum m/e 272 (M^+ for 271).

Anal. Calcd for $C_{18}H_{25}NO$·HBr: C, 61.36; H, 7.44; N, 3.98. Found: C, 61.08; H, 7.69; N, 3.90.

B/C-*cis*-10-Bromo-4a-(2-dimethylaminoethyl)-6-methoxy-1,2,3,4,4a,10a-hexahydro-10*H*-9-phenanthrone Hydrobromide (22). Ketone **6** was converted to the hydrobromide (mp 227–230° from MeOH–Me_2CO). This hydrobromide (191 mg) in refluxing AcOH (1 ml) was treated with Br_2 (108 mg) in AcOH (1.2 ml) during 5 min. The solution was refluxed for 10 min and ether was added to precipitate a crystalline mass. After refrigeration, the bromo derivative separated and was recrystallized from MeOH–Me_2CO to give 175 mg of pure **22**, colorless plates: mp 192–194°; ir (Nujol) 2350–2710 ($^+$NH), 1690 cm^{-1} (C=O); NMR (DMSO-d_6) δ 3.33 (s, 6, $>N^+Me_2$), 3.86 (s, 3, OMe), 6.07 (d, J = 4.5 Hz, 1, C-10 H), 6.89 (d, $J_{5,7}$ = 2.5 Hz, 1, C-5 H), 7.03 (q, $J_{7,8}$ = 9.0, $J_{7,5}$ = 2.5 Hz, 1, C-7 H), 7.98 (d, $J_{8,7}$ = 9.0 Hz, 1, C-8 H).

Anal. Calcd for $C_{19}H_{26}BrNO_2$·HBr: C, 49.49; H, 5.90; N, 3.04. Found: C, 49.24; H, 6.13; N, 2.95.

4a-(2-Dimethylaminoethyl)-6-methoxy-2,3,4,4a-tetrahydro-1*H*-9-phenanthrone (23). To **22** (64.3 mg) in H_2O (25 ml) was added $NaHCO_3$ (100 mg). Extraction with ether, drying ($MgSO_4$), and evaporation of the ether gave 49.3 mg of an oil which soon solidified. The solid product was recrystallized from Me_2CO to give **23** HBr as colorless, fine needles: mp 230–233°; ir (Nujol) 2390 (broad, $^+$NH), 1660 cm^{-1} (C=O); NMR (CD_3OD) δ 2.70 (s, 6, $>^+NMe_2$), 3.90 (s, 3, OMe), 6.38 (s, 1, C-10 H), 7.05 (q, $J_{7,8}$ = 9.0, $J_{7,5}$ = 2.5 Hz, 1, C-7 H), 7.23 (d, $J_{5,7}$ = 2.5 Hz, 1, C-5 H), 8.09 (d, $J_{8,7}$ = 9.0 Hz, 1, C-8 H).

Anal. Calcd for $C_{19}H_{25}NO_2$·HBr: C, 60.00; H, 6.89; N, 3.68. Found: C, 59.91; H, 6.80; N, 3.72.

B/C-*trans*-10-Bromo-4a-(2-dimethylaminoethyl)-6-methoxy-1,2,3,4,4a,10a-hexahydro-10*H*-9-phenanthrone Hydrobromide (24). Ketone **17** was converted to the hydrobromide (mp 236–238° from MeOH–Me_2CO). As described in the bromination of **6** HBr, the hydrobromide (152 mg) and Br_2 (77 mg) yielded, after addition of ether to the reaction mixture and cooling, 145 mg of **24**: mp 188–190°; ir (Nujol) 2400–2700 (N^+H), 1680 cm^{-1} (C=O); NMR (DMSO-d_6) δ 3.33 (s, 6, $>N^+Me_2$), 3.88 (s, 3, OMe), 5.28 (d, J = 12.0 Hz, 1, C-10 H), 6.87 (d, $J_{5,7}$ = 2.5 Hz, 1, C-5 H), 7.03 (q, $J_{7,5}$ = 2.5, $J_{7,8}$ = 8.5 Hz, 1, C-7 H), 7.92 (d, $J_{8,7}$ = 8.5 Hz, 1, C-8 H).

Anal. Calcd for $C_{19}H_{26}BrNO_2$·HBr: C, 49.48; H, 5.90; N, 3.04. Found: C, 49.77; H, 5.80; N, 2.95.

3-Methoxy-10-oxo-*N*-methylisomorphinan Methobromide (25). The bromo ketone hydrobromide **24** (58 mg) was converted to the free base (40 mg). It solidified on standing. Recrystallization from MeOH–Me_2CO gave **25** as colorless prisms: mp 234–235°; ir (Nujol) 1675 cm^{-1} (C=O); NMR (CD_3OD) δ 3.04 (s, 3, N^+Me), 3.48 (s, 3, N^+Me), 3.90 (s, 3, OMe), 3.95 (d, J = 6.0 Hz, 1, C-9 H), 6.98–7.10 (m, 2, C-2 and C-4 H), 8.02 (d, J = 9.0 Hz, 1, C-1 H).

Anal. Calcd for $C_{19}H_{26}BrNO_2$: C, 60.00; H, 6.81; N, 3.68. Found: C, 60.01; H, 6.99; N, 3.61.

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Registry No.—**2**, 53661-21-5; **3**, 55156-34-8; **4**, 55156-35-9; **4** HCl, 55156-36-0; **4′**, 55156-37-1; **4′** HCl, 55156-38-2; **5**, 55156-39-3; **6**, 55156-40-6; **6** HCl, 55156-41-7; **6** HBr, 55156-42-8; **7**, 55156-43-9; **7** picrate, 55156-44-0; **9**, 55156-45-1; **10**, 55156-46-2; **10** picrate, 55177-18-9; **11**, 55156-47-3; **12**, 55156-48-4; **12** HCl, 55177-19-0; **13a**, 55156-49-5; **13b** HBr, 55156-50-8; **15**, 50282-12-7; **16b**, 55156-51-9; **16b** oxalate, 55156-52-0; **17**, 55156-53-1; **17** HCl, 55156-54-2; **17** HBr, 55156-55-3; **18**, 55156-56-4; **19**, 55177-20-3; **19** picrate, 55220-80-9; **20**, 55156-47-3; **21a**, 55177-21-4; **21a** picrate, 55220-81-0; **21b** HBr, 55177-22-5; **22**, 55156-57-5; **23** HBr, 55156-58-6; **24**, 55156-59-7; **24** HBr, 55156-60-0; **25**, 55177-47-4.

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Aromatic Nucleophilic Substitution Reactions of Ambident Nucleophiles. II.[1a] Reactions of Nitrite Ion with Nitrohalobenzenes

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Nitrophenols are the eventual products of the aromatic nucleophilic substitution reactions of the ambident nitrite ion with suitably substituted nitrobenzenes. This is the case no matter whether the nitrogen or the oxygen of the nitrite ion is the original site for bonding to aromatic carbon. However, the intermediacy of di- or trinitroaromatics, i.e., the first products of N-attack, has been demonstrated by labeling the substituted nitrobenzenes with deuterium, or with a methyl group, or by using $^{15}NO_2^-$ as the nucleophile. N-Attack is faster than O-attack when Cl, Br, or I is displaced from the nitrohalobenzenes by nitrite ion but O-attack is faster when fluorine is displaced. Reactions are about 10^5 faster in dipolar aprotic solvents than in methanol and the rate of O-attack is enhanced more than N-attack on transfer from methanol to dipolar aprotic solvents. The principles discussed here enable one to optimize the conditions for a maximum yield of the initial product of N-attack and for a minimum yield of nitrophenols. If the substrate has a substituent ortho to the site of nucleophilic attack, the proportion of nitrophenol to dinitrobenzene is very high throughout the reaction.

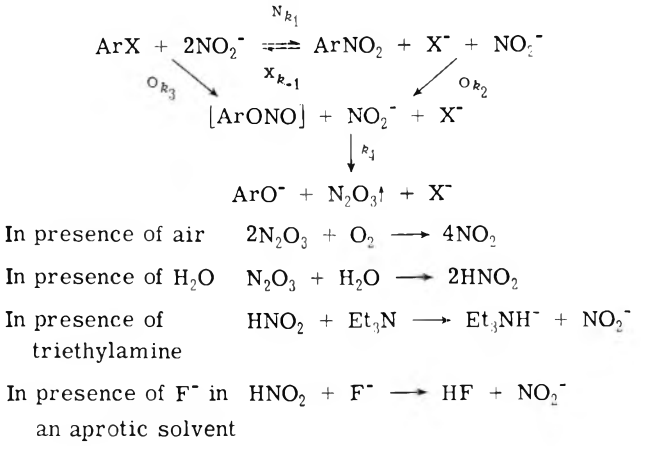
Aromatic nucleophilic substitution (SNAr) reactions of aryl halides (ArX) with nitrite ion have the potential for preparing nitroaromatic compounds in which the nitro group is in a specifically predetermined position. This position might be inaccessible by electrophilic nitration procedures.[1c] However, SNAr reactions of nitrite ion with many aryl halides give phenols rather than nitroaromatics as the major or only product. This paper investigates such reactions in an attempt to optimize conditions for a maximum yield of nitroaromatics.

The SNAr reactions of nitrite ion have been studied in methanol, DMF, DMSO, and HMPT. This choice of solvents allows a wide range of substrate (ArX) reactivity to be covered, including ArX as the weakly activated ortho and para nitrohalobenzenes, as well as the 2,4-dinitrohalobenzenes.

Nucleophilic substitution by nitrite ion at a *saturated* carbon atom gives both nitro compounds (RNO_2) and nitrite esters RONO.[2,3] Kornblum has noted that bonding by oxygen to saturated carbon (O-attack) is pronounced when the transition state has a well-developed positive charge on the carbon atom (loose SN2 or SN1 reactions) and bonding by nitrogen to carbon (N-attack) is pronounced in tight SN2 transition states where the carbon is softer and carries little if any positive charge.[2] Pearson's hard and soft acids and bases principle is relevant;[4] the harder oxygen atom of NO_2^- prefers to bond to hard positively charged carbon in the loose transition state, the softer nitrogen of NO_2^- prefers to bond to softer carbon in the tighter transition state.

The situation for nucleophilic substitution of ArX by nitrite ion at an *aromatic* (sp^2) carbon atom requires different considerations. Aromatic nitrite esters ArONO are very unstable under SNAr conditions. The nitro group in $ArNO_2$ is an extremely labile leaving group in the presence of nucleophiles. Thus SNAr reactions of nitrite ion are often complicated by reactions in which the entering nitrite ion is displaced from the initial product by the leaving group, by other nucleophiles, or by another nitrite ion. The pathways for the reactions of nitrite ion with aromatics are set out in Scheme I. They are similar to those proposed by Rosen-

Scheme I



blatt, Dennis, and Goodin[5] from work with 2,4-dinitrohalobenzenes in aqueous acetonitrile.

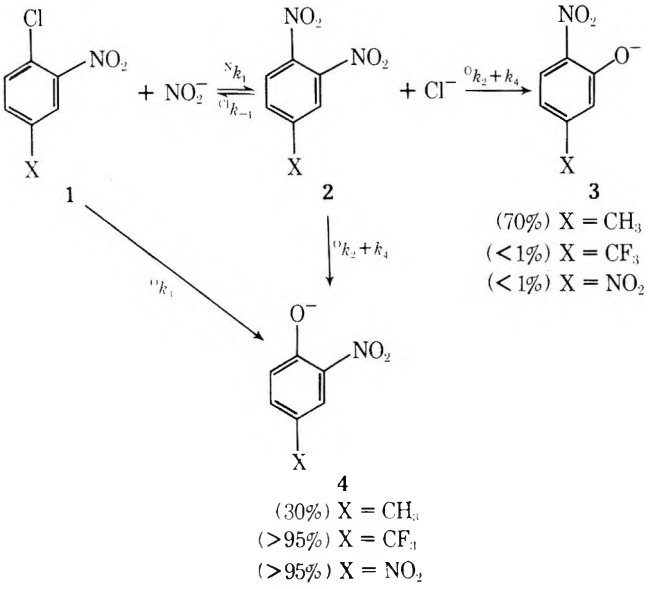
As shown in Scheme I and by this work, nitrite ion produces phenoxides from ArX in three ways: (1) by consecutive O-attack of $ArNO_2$ following N-attack of ArX, i.e., ${}^{N}k_1$, ${}^{O}k_2$, k_4; (2) by direct O-attack of ArX, i.e., ${}^{O}k_3$, k_4; (3) by reversal of N-attack followed by O-attack of ArX, i.e., ${}^{N}k_1$, ${}^{X}k_{-1}$, ${}^{O}k_3$, k_4.

It is useful to identify the pathways shown in Scheme I and to measure the values of the various rate constants. This is because we are interested in the effects of different leaving groups X, of different substituents in Ar, and in the effects of solvents on the nucleophilicities of NO_2^-. We are also interested in the leaving group tendencies of NO_2 from $ArNO_2$ in reactions ${}^{O}k_2$ and ${}^{X}k_{-1}$. Evidence which adds strong support for Scheme I follows.

Results and Discussion

Kinetics and Stoichiometry. The kinetics of the reaction of 1-chloro-2,4-dinitrobenzene (Ar″Cl) with sodium nitrite in DMSO at 25° and in methanol at 45° show that the rate of production of 2,4-dinitrophenoxide is first order in nitrite ion and in Ar″Cl. However, 2 mol of nitrite ion were consumed per mole of 2,4-dinitrophenoxide produced as required by Scheme I. In methanol, no 2,4-dinitroanisole was detected (i.e., <1%), which excludes methanolysis of a 1,2,4-trinitrobenzene intermediate and, by analogy, excludes hydrolysis as a pathway to Ar″OH in DMSO–water mixtures. 1,2,4-Trinitrobenzene (Ar″NO_2) reacted much faster than Ar″Cl with NO_2^- (${}^{O}k_2 > {}^{N}k_1$ or ${}^{O}k_3$) to give a quantitative yield of 2,4-dinitrophenoxide in both methanol and DMSO. Only 1 mol of nitrite was consumed per mole of 2,4-dinitrophenoxide produced (Scheme I). In dry DMSO a brown gas was evolved from the reaction of nitrite ion with Ar″Cl. Scheme I caters for some further reactions of the N_2O_3 produced by reaction of ArONO with nitrite ion. In wetted DMSO, no gas was evolved, but the solution increased in acidity owing to the formation of nitrous acid as the reaction proceeded. The stoichiometry of Scheme I in moist DMSO was 2 mol of nitrite per mole of Ar″Cl for its complete conversion to phenoxide. However, this stoichiometry in moist DMSO was reduced to less than 1 mol of nitrite per mole of Ar″Cl by adding the base triethylamine. The reaction of 1-fluoro-2,4-dinitrobenzene (Ar″F) with nitrite ion in slightly moist DMSO, unlike the same reaction of Ar″Cl, had a stoichiometry of less than 1 mol of nitrite per mole of Ar″F. One explanation for the difference between Ar″Cl and Ar″F is that HNO_2, formed by the reaction of N_2O_3 with water, is not a nucleophile under the reaction conditions, but in the presence of strongly basic triethylamine or fluoride ion in moist DMSO, nitrite ion is regenerated from the weak nitrous acid and is available for further reaction with Ar″X. However, chloride ion, unlike fluoride, is too weak a base in moist DMSO to regenerate nitrite ion from weak nitrous acid. These observations are consistent with Scheme I.

Scheme II



Like Russell,[6] we detected no radicals (ESR) and believe that the decomposition of the very unstable nitrite esters (k_4 in Scheme I) is a heterolytic reaction involving nucleophilic attack by NO_2^- on the nitrogen of ArONO to displace ArO^- and form N_2O_3.

N-Attack vs. O-Attack. As noted, phenols could be formed by the consecutive reactions ${}^{N}k_1$, ${}^{O}k_2$ then k_4, by the concurrent reaction ${}^{O}k_3$ then k_4, or by reversal of reaction ${}^{N}k_1$ (i.e., ${}^{X}k_{-1}$) then ${}^{O}k_3$ and k_4 in Scheme I. The following evidence suggests that all three pathways are used in different situations.

As shown in Table IV, during the reaction of NO_2^- with 2,4-dinitrochlorobenzene (Ar″Cl) in DMSO, the rate of production of 2,4-dinitrophenoxide ion (Ar″O^-) lagged behind the rate of chloride ion production, i.e., [Ar″O^-]/[Cl^-] was 0.85 during the first half-life of chloride ion production. Thus a small steady-state concentration of an organic product, other than Ar″O^-, presumably 1,2,4-trinitrobenzene (Ar″NO_2), must be present in the early stages of reaction. At the completion of reaction, the concentration of Ar″O^- equaled that of chloride ion, so that the assumed 1,2,4-trinitrobenzene is a true intermediate in the formation of 2,4-dinitrophenoxide, as shown in Scheme I. As noted, a separate experiment showed that Ar″NO_2 rapidly gave Ar″O^- with NO_2^- in DMSO.

Scheme II records and explains the products of some reaction of 4-chloro-3-nitro substituted aromatics with nitrite ion in DMSO. A very weakly deactivating methyl group is used to detect the intermediacy of 3,4-dinitrotoluene (**2**, X = CH_3). As shown in Scheme II (X = CH_3), the product was a mixture of 3-hydroxy-4-nitrotoluene with rather less 4-hydroxy-3-nitrotoluene. Thus, 3,4-dinitrotoluene, which is the product of reaction ${}^{N}k_1$ in Scheme II (X = CH_3), is an intermediate and N-attack ${}^{N}k_1$ is faster than O-attack ${}^{O}k_3$. If ${}^{O}k_3$ were the sole route to phenoxides, then the reaction would give only **4** (X = CH_3), as was obtained when **1** (X = CH_3) was hydroxydechlorinated with sodium hydroxide in 75% DMSO–water. Further confirmation was obtained when 3,4-dinitrotoluene was treated with sodium nitrite in DMSO. This very rapidly produced a similar distribution of **3** (X = CH_3) and **4** (X = CH_3) as in the

Table I
Isotopic Analysis of Some SNAr Reactions of $Na^{15}NO_2$[a] in HMPT at 100°

Substrate[b]	Product	M:M + 1	$^{N}k_1/^{O}k_3$[c]
p-Ar'NO_2	*p*-Ar'OH	100:20	2
o-Ar'NO_2	*o*-Ar'OH	100:16	3/2
p-Ar'F	*p*-Ar'OH	100:26	4

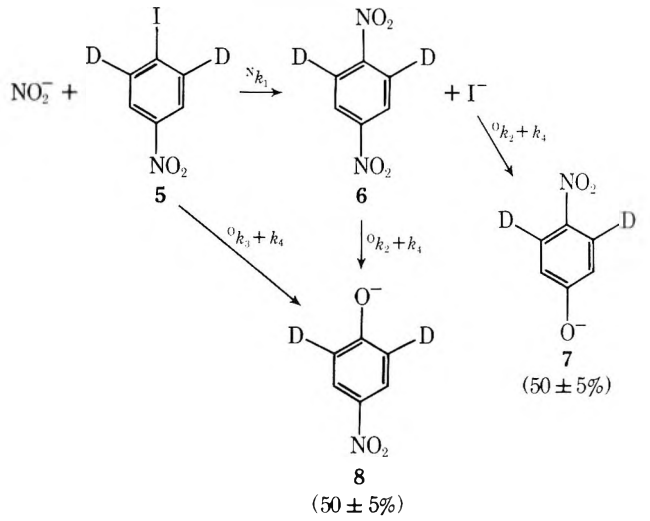
[a] $Na^{15}NO_2$ contained 33% ^{15}N and was present in at least 40-fold excess. [b] *p*-Ar' is 4-$NO_2C_6H_4$ and *o*-Ar' is 2-$NO_2C_6N_4$. [c] Calculated as described in the text.

reaction of NO_2^- with 4-chloro-3-nitrotoluene. The preponderence of phenoxide **3** over **4** (X = CH_3) from reaction of **2** (X = CH_3) is a result of the small deactivating electron-donating effect of methyl when para to a SNAr reaction center; thus the 3-nitro group is displaced more readily than 4-nitro. Similar differences in lability of the two nitro groups have been observed in reaction of **2** (X = CH_3) with other nucleophiles.[7]

As shown in Scheme II and Table I, when X is CF_3 or NO_2 rather than CH_3, the sole product is **4**, i.e., the presence of strongly SNAr activating CF_3 and NO_2 groups (X) leads to only one product, 4-OH-3-$NO_2C_6H_3X$. With these compounds, there is thus no way of telling whether the pathway is via the intermediate **2** and $^{N}k_1$ or directly from **1** and $^{O}k_3$, because both **1** and **2** give the same product.

The results of some deuterium-labeling experiments are explained and presented in Scheme III. Compound **5** was

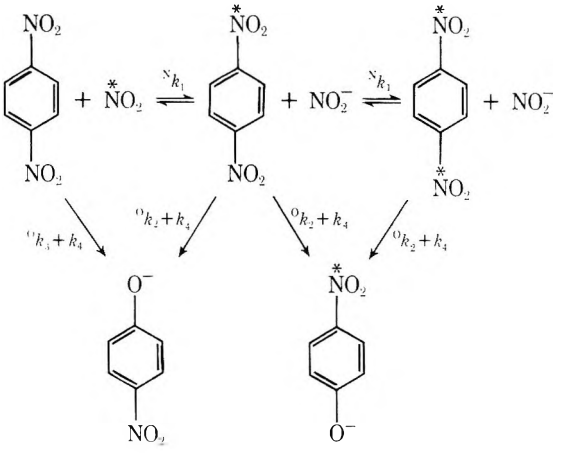
Scheme III



prepared with >95% isotopic purity. Its NMR spectrum showed only a singlet at 7.96 ppm. After reaction of **5** with $NaNO_2$ in DMSO, the phenolic products were isolated and in acetone showed two singlets of approximately similar intensity at 7.68 and 6.53 ppm. This is as expected for an equimolar mixture of compounds **7** and **8**. There can be little direct O-attack by NO_2^- on **5**, because reaction $^{O}k_3 + k_4$ of compound **5** in Scheme III would give only phenol **8** and no **7**; the intermediate **6**, however, gives roughly equal amounts of **7** and **8** as found for reaction of **5** with nitrite ion.

The results of some experiments with ^{15}N-labeled sodium nitrite are in Table I and are explained by Scheme IV. *p*-Dinitrobenzene was treated with excess $NaNO_2$ (assaying 33% ^{15}N) in hexamethylphosphoramide at 100°. The product was 4-nitrophenol and this was analyzed for ^{14}N, ^{15}N proportions by mass spectrometry. The corrected

Scheme IV



M:M + 1 ratio was 100:20. Sole O-attack ($^{O}k_3 + k_4$ in Scheme IV) would give M:M + 1 as 100:0, sole N-attack ($^{N}k_1$) would give 100:50, and equal proportions of N- to O-attack would give 100:12.5 in the 4-nitrophenol. The observed M:M + 1 of 100:20 means that N-attack of 4-dinitrobenzene by nitrite ion in HMPT is twice as fast as O-attack. Other $^{N}k_1$:$^{O}k_3$ ratios in Table I were calculated by similar reasoning.

A detailed kinetic analysis of the rate of ^{15}N incorporation into the phenolic product and of the rate of phenoxide production for reaction of nitrite ion in DMSO at 100° with various substrates was then carried out. Analysis was by mass spectrometry. For reaction with *p*-dinitrobenzene, the rate constant for ^{15}N incorporation was 6.4×10^{-4} M^{-1} sec^{-1}, that for phenoxide production was 2.7×10^{-4} M^{-1} sec^{-1}. Table I shows values of $^{N}k_1$:$^{O}k_3$, i.e., relative rates of initial N-attack and O-attack, by nitrite ion on various substrates. The results in Table I confirm that direct O-attack ($^{O}k_3$ in Scheme I) is usually slower than direct N-attack ($^{N}k_1$). However, some direct O-attack is usually observed; i.e., both the concurrent as well as the consecutive route to phenols are utilized in the SNAr reactions of nitrite ion.

Reactions of Mononitro-Substituted Benzenes. The concentrations of aryl substrate and nitro intermediate from reaction of mononitro-substituted benzenes with nitrite ion in DMSO were analyzed by GLC and concentrations of phenoxide were estimated spectrophotometrically at various stages of reaction. Results are in Table II, together with rate constants for these reactions. A comparison of the proportion of phenoxide product, Ar'O^-, to nitro compound, Ar'NO_2, over the first 10% of reaction gives, as shown in Table II, the ratio of N-attack to O-attack ($^{N}k_1$:$^{O}k_3$). This is because in Scheme I a negligible amount of phenoxide (Ar'O^-) is produced from the aryl substrate (Ar'X) via aryl nitro compound (Ar'NO_2), i.e., via $^{N}k_1$, $^{O}k_2$, k_4 during the first 10% of reaction. As we show later, the rates $^{N}k_1$[Ar'X] are $\gg$ $^{O}k_2$[Ar'NO_2] up to 10% reaction, when [Ar'NO_2] is small. Thus phenoxide produced in the first 10% reaction is almost entirely from direct O-attack on Ar'X (i.e., by $^{O}k_3$ in Scheme I).

The maximum possible yield of nitro intermediate from the consecutive reactions $^{N}k_1$, $^{O}k_2$, k_4 and the stage of consumption of Ar'X at which [Ar'NO_2] is a maximum are topics of interest and are shown in Table II. The greatest yield of Ar'NO_2 occurs in the absence of bulky substituents ortho to the reaction center, i.e., from the 4-nitro-substituted benzenes. As shown in Table II, the ratio $^{N}k_1$:$^{O}k_3$ for N- and O-attack on *o*-Ar'X increases according to the leaving group in the series of X = F < NO_2 ≈ Cl < I. There is a similar tendency for attack on *p*-Ar'X, but there is more

Table II
Reaction of Ortho- and Para-Mononitro-Substituted Benzenes Ar′X with $NaNO_2$ in DMSO at 100°

Substrate[a] Ar′X	Registry no.	$10^4 k$, l. mol^{-1} sec^{-1}	$N_{k_1}:O_{k_3}$[b,h]	$100[ArNO_2]/[ArX]_0$[g]	$100([Ar'X]_0 - [Ar'X])/[Ar'X]_0$ max[i]
o-Ar′F	1493-27-2	4.2[d]	1:3	4	30
o-Ar′NO_2	528-29-0	46[d]	3:2[e]		
o-Ar′Cl	88-73-3	4.5[c,d]	3:2	5	25
o-Ar′I	609-73-4	~9[d]	7:1	15	30
p-Ar′F	350-46-9	16.2[f]	4:1	40	70
p-Ar′NO_2	100-25-4	2.7[d]	2:1[e]		
p-Ar′Cl	100-00-5	2.7[c]	2:1	25	50
p-Ar′I	636-98-6	~6[d]	8:1	25	60

[a] o-Ar′ is 2-$NO_2C_6H_4$; *p*-Ar′ is 4-$NO_2C_6H_4$. [b] The error in GLC analysis is estimated at ±10% and $[Ar'X]_t$, $[Ar'NO_2]_t$, and $[Ar'NO_2]_{max}$ were measured by GLC. [c] This is the rate constant for production of Cl^-. [d] This is the rate constant for production of $Ar'O^-$ measured spectrophotometrically. [e] From mass spectral analyses as discussed for data in Table I. [f] This is the rate constant for consumption of NO_2^-. [g] This represents the maximum percent yield of $Ar'NO_2$ which can ever be obtained under these reaction conditions. As reaction proceeds the concentration of $Ar'NO_2$ decreases (see text). [h] I.e., $[Ar'NO_2]_t:[Ar'O^-]_t$ (see text) where t is a time in the first 10% of consumption of Ar′X at which the concentrations of $Ar'O^-$ and $Ar'NO_2$ were determined. [i] This represents the percentage of consumption of Ar′X at which the yield of $Ar'NO_2$ is a maximum from these consecutive reactions.

N-attack on *p*-nitrofluorobenzene than on 4-nitrochlorobenzene.

While considering reactivity patterns, it is noteworthy in Table II that fluorine is displaced more slowly than iodine from the ortho nitrohalobenzenes and only slightly more rapidly than iodine from the para nitrohalobenzenes by nitrite ion in DMSO. In SNAr reactions with many nucleophiles (e.g., OMe^- in MeOH[8], N_3^- in DMF[9]), fluorine is displaced very much more rapidly than iodine from Ar′Hal. These reactivity differences have important mechanistic implications, which will be discussed in a later paper.

Reactions of 2,4-Dinitrohalobenzenes. The reactions of the 2,4-dinitrohalobenzenes with nitrite ion and other nucleophiles were studied in a variety of solvents. The reactions were measured under pseudo-first-order conditions, with excess (10^{-2} *M*) of nucleophile, and the rate of production of 2,4-dinitrophenoxide ion, as measured spectrophotometrically at 360 nm, is recorded as a second-order rate constant in Table III.

Table III
Rates of Production of 2,4-Dinitrophenoxide Ion from 1-X,2,4-Dinitrobenzene (Ar″X)[e] in Various Solvents at 25°

Nucleophile	X in Ar″X[g]	DMSO	DMF	HMPT	MeOH[f]
NO_2^-	NO_2	8	96		3.8×10^{-3}
NO_2^-	F	0.14	0.24	11	10.8×10^{-3}
NO_2^-	Cl	1.05	7.5	1150	0.19×10^{-3} [b]
NO_2^-	SCN	~1.5	9.2		3×10^{-3} [c]
NO_2^-	I	0.27[a]	1.4	132	0.11×10^{-3}
F^-	NO_2	16			
Cl^-	NO_2	0.05			
I^-	NO_2	~0.001[d]			

[a] E_a = 16.3 kcal/mol, $\Delta S^\ddagger$ = −8 eu. [b] E_a = 17.9 kcal/mol, $\Delta S^\ddagger$ = −25 eu. [c] Reference 12. [d] Reaction is subject to interference from the production of iodine. [e] Rates are recorded as second-order rate constants (M^{-1} sec^{-1}) for production of 2,4-dinitrophenoxide ion. [f] At 45°. [g] Registry no. are, respectively, 121-14-2, 70-34-8, 97-00-7, 1594-56-5, 709-49-9.

The kinetic expressions for the reaction steps of Scheme I in terms of the rate of production of $Ar''O^-$ are shown in Scheme V.[10] Some account must be taken of the relative basicity of halide and nitrite ions toward carbon. In methanol as solvent, the reverse reaction $^Xk_{-1}$ is not significant, because in methanol nitrite ion is a much stronger base toward aromatic carbon than the halide ions. However, in dipolar aprotic solvents, chloride and fluoride ions are stronger bases than NO_2^- toward aromatic carbon. Thus tetramethylammonium chloride, bromide, and fluoride readily produced 2,4-dinitrophenoxide when treated with 1,2,4-trinitrobenzene ($Ar''NO_2$) in DMSO, presumably by the reactions $^Xk_{-1}$, $^Ok_3$ and $^Ok_2$, then k_4. However, there is no phenoxide produced by halide ions in methanol as solvent.

Scheme V
Kinetics Expressions for the Reaction of NO_2^- with 2,4-Dinitrohalobenzenes (cf. Scheme I) in Terms of the Rate of Production of 2,4-Dinitrophenoxide Ion

$$\underset{[A_2]}{Ar''Hal} + \underset{[A_1]}{NO_2^-} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \underset{[A_3]}{Ar''NO_2} + \underset{[A_5]}{Hal^-}$$

$$\underset{[A_1]}{NO_2^-} + \underset{[A_3]}{Ar''NO_2} \xrightarrow{k_2} \underset{[A_4]}{Ar''O^-} + N_2O_3$$

Case 1 Assume $[A_2]$ is the initial reactant, $\frac{d[A_3]}{dt} = 0$

then $\frac{d[Ar''O^-]}{dt} = \frac{k_2k_1[A_1][A_1][A_2]}{k_{-1}[A_5] + k_2[A_1]}$

(a) if $k_2[A_1] >> k_{-1}[A_5]$, $\frac{d[Ar''O^-]}{dt} = k_1[A_1][A_2]$

(b) if $k_{-1}[A_5] >> k_2[A_1]$, $\frac{d[Ar''O^-]}{dt} = Kk_2[A_1]$

where K = equilibrium constant = k_1/k_{-1}

Case 2 Assume $[A_3]$ is the initial reactant, $\frac{d[A_1]}{dt} = 0$

then $\frac{d[Ar''O^-]}{dt} = \frac{k_{-1}k_2[A_3][A_3][A_5]}{k_1[A_2] + k_2[A_3]}$

if $k_2[A_3] >> k_1[A_2]$ $\frac{d[Ar''O^-]}{dt} = k_{-1}[A_3][A_5]$

From Table III it can be seen that the rate of production of $Ar''O^-$ from Ar″F is *faster* than the rate of production of $Ar''O^-$ from $Ar''NO_2$ by nitrite ion in methanol. Thus the consecutive sequence $^Nk_1$, $^Ok_2$ then k_4 of Scheme I for production of $Ar''O^-$ via N-attack and the intermediate $Ar''NO_2$ must play a minor role in the overall production of $Ar''O^-$ from Ar″F. The observed rate in Table III must be largely for direct O-attack on Ar″F, i.e., via route $^Ok_3$ of Scheme I and $^Ok_3$ is greater than $^Ok_2$. A GLC analysis of the products of reaction of Ar″F with nitrite ion in metha-

Table IV
Product Analyses of the Reaction of Ar″Cl and Ar″SCN with Nitrite Ion in DMSO

% reaction of Ar″SCN[a]	8	15	20	24	30
	[Ar″O⁻]/[SCN⁻]				
Observed	0.21	0.30	0.45	0.52	0.62
Calculated[b]	0.18	0.28	0.44	0.50	0.56
% reaction of Ar″Cl[c]	19	26	30	43	
	[Ar″O⁻]/[Cl⁻]				
Observed	0.86	0.78	0.90	0.89	
Calculated[b]	0.46	0.59	0.62	0.76	
Calculated[d]	0.81	0.86	0.87	0.91	
Calculated[e]	0.72	0.79	0.81	0.87	

[a] At 0.4° Ar″SCN = 0.025 *M*, NO_2^- = 0.025 *N*, $^Ok_2$ = 4.5 M^{-1} sec^{-1}, $^Nk_1$ = 0.91 M^{-1} sec^{-1}. [b] Assuming $^Ok_3$ negligible relative to $^Nk_1$. [c] At −19° Ar″Cl = 0.014 *M*, NO_2^- = 0.041 *M*, $^Ok_2$ = 0.52 M^{-1} sec^{-1}, $^Nk_1$ = 0.082 M^{-1} sec^{-1}. [d] Computed for a $^Nk_1$:$^Ok_3$ rate ratio of 1:2. [e] Computed for a $^Nk_1$:$^Ok_3$ ratio of 1:1.

nol during the early stages of reaction confirmed this interpretation. No more than 1% of Ar″NO_2 (as a percentage of products) could be detected at any stage of reaction. If a consecutive $^Nk_1$, $^Ok_2$ sequence was significant with $^Nk_1 \geq {}^Ok_2$, then at least 30% Ar″NO_2 would be detected under the reaction conditions. In contrast, a GLC analysis of the reaction of NO_2^- with Ar″Cl in methanol detected a maximum of 5 ± 1% Ar″NO_2. A maximum of 4.2% of Ar″NO_2 was expected by calculation from the concentrations of Ar″Cl and NO_2^-, the overall rate for production of Ar″O^- and from $^Ok_2$ (Table III). Such a calculation assumes that $^Ok_3$ is negligible for reaction of Ar″Cl with NO_2^- and the correspondence between observed and calculated maximum concentration of Ar″NO_2 confirms that in contrast to the reaction with Ar″F, $^Ok_3$ is negligible for reaction of NO_2^- with Ar″Cl.

Thus for reaction of Ar″F with NO_2^- in methanol, direct O-attack on Ar″F by step $^Ok_3$ is favored by at least 10:1 over direct N-attack by step $^Nk_1$. The corresponding reactions of Ar″Cl in methanol proceed mainly by N-attack via $^Nk_1$. The reasons for the change in the mode of attack by nitrite ion with change of leaving group will be discussed in a later paper. Similar rate relationships and conclusions were reached by Rosenblatt, Dennis, and Goodin[5] using aqueous acetonitrile as a solvent; however, it should be noted their rate constants have been calculated by a different method from us. Rosenblatt and Dennis now agree[11] that the rate constants for O-attack by NO_2^- in aqueous acetonitrile at 25° on Ar″Cl and Ar″Br are 2.5 × 10^{-5} and 2.2 × 10^{-5} M^{-1} min^{-1}, respectively. The N:O ratio ($^Nk_1$:$^Ok_3$) of nitrite attack on Ar″Cl in aqueous acetonitrile is therefore about 70:1 and not 18,000:1 as implied from their stated rate constants. The rates of production of Ar″O^- in DMSO as solvent (Table III) introduce new considerations. The rate of production of 2,4-dinitrophenoxide from 1,2,4-trinitrobenzene by halide ions in DMSO (Table III) follows the kinetic expression[10] corresponding to case 2 in Scheme V where $k_2[A_3] \gg k_1[A_2]$.

Table III shows that the displacement of nitrite ion by halide, $^Xk_{-1}$ of Scheme I, is not kinetically significant for reaction of nitrite ion with Ar″Cl or Ar″I in DMSO (X = Cl^- or I^-). For reaction of Ar″F with nitrite ion in DMSO, displacement of nitrite ion by the strongly nucleophilic fluoride ion in DMSO ($^Fk_{-1}$) must be considered when evaluating the kinetics of Ar″O^- production. The step $^Fk_{-1}$ would be kinetically significant if the consecutive route to Ar″O^- involving N-attack ($^Nk_1$, $^Ok_2$ then k_4, Scheme I) were being utilized. However, two observations suggest that $^Fk_{-1}$ and hence $^Nk_1$ is not kinetically significant in the production of Ar″O^- from the reaction of Ar″F with NO_2^- in DMSO and that preequilibrium does not occur.

(1) Thorium nitrate, which completely suppresses the normally fast reaction of KF with Ar″NO_2 ($^Fk_{-1}$) in DMSO, has no effect on the rate of Ar″O^- production from Ar″F and NO_2^- in DMSO.

(2) For a range of nitrite ion concentrations, the overall rate of Ar″O^- production from Ar″F with NO_2^- in DMSO follows a simple second-order rate law. There was no rate acceleration during the initial stages of the reaction to indicate any significant formation of Ar″NO_2. If $^Fk_{-1}$ were kinetically significant, then from case I, Scheme V, we would expect a more complex rate law to be followed for nitrite ion concentrations where $^Fk_{-1}[F^-] \approx k_2[NO_2^-]$).

These observations confirm that in DMSO, just as in methanol, $^Ok_3$ is much faster than $^Nk_1$ for reaction of Ar″F with NO_2^-.

The extent of O-attack ($^Ok_3$) to N-attack ($^Nk_1$) in the $^Nk_1$ reaction of nitrite ion with Ar″SCN[12] and Ar″Cl in DMSO was readily determined by comparing the rate of thiocyanate or chloride ion production with the rate of phenoxide ion production (Table IV). From the rate constants for the consecutive reactions, assuming complete N-attack ($^Nk_1$ and $^Ok_2$ then k_4) and no $^Ok_3$, the concentrations of Ar″O^- and Cl^- or SCN^- can be computed at any part in the reaction. Deviations of the observed concentrations from the concentrations computed on the above assumption thus reflect the extent of competitive O-attack, $^Ok_3$. In Table IV, the computed and observed amounts of Ar″O^-, Cl^-, or SCN^- are compared.

It can be seen in Table IV that Ar″Cl gives a much higher [Ar″O^-]:[Cl^-] ratio than the [Ar″O^-]:[SCN^-] ratio from Ar″SCN at any stage of reaction. The calculated values show that >5% of Ar″SCN and about 60% of Ar″Cl ($^Nk_1$:$^Ok_3$ ≈ 1:1.5) reacts via direct O-attack, $^Ok_3$, of the nitrite ion in DMSO. Ar″SCN thus reacts unusually slowly in step $^Ok_3$ relative to Ar″Cl and Ar″F. This may be due to a preference for a "soft" nucleophilic attack by the soft nitrogen "end" of NO_2^- when attacking Ar″SCN.

The substantial proportion of direct O-attack by nitrite ion on Ar″Cl in DMSO ($^Ok_3/{}^Nk_1 \approx 1.5$) contrasts to the much smaller proportion of direct O-attack on this substrate in methanol and aqueous acetonitrile ($^Ok_3$:$^Nk_1 \approx$ 0.014) but correlates with that found for *o*-nitrochlorobenzene in DMSO (Table II). Apparently there is a significant solvent effect, whereby protic solvents "deactivate" the oxygen more than the nitrogen of NO_2^-.

To summarize, the nitrite ion attacks 2,4-dinitrohalobenzenes both via N- and O-attack in methanol and in DMSO or DMF. However, there is a significant solvent effect favoring O-attack in the dipolar aprotic solvents and the proportions of N- to O-attack depend on the leaving group.

Experimental Section

Melting points were determined using a Kofler micro hot stage and were uncorrected. NMR spectra were recorded on a Varian Associates A-60 spectrometer. Carbon tetrachloride was the solvent. All chemical shifts are quoted on the τ scale relative to an internal standard, tetramethylsilane. The percentage of ^{15}N in nitrogenous samples was determined by mass spectroscopy using an Associated Electronic Industries Model MS3 spectrometer by courtesy of Dr. C. A. Parker, Department of Soil Science, Institute of Agriculture, University of Western Australia. Isotopic measurements on the phenolic products were made using a MS9 spectrophotometer. Uv and visible spectroscopic measurements were made using a Gilford Model 240 spectrophotometer.

The 4-nitrohalobenzenes, the 2,4-dinitrohalobenzenes, *o*- and *p*-dinitrobenzene, 2-nitrochlorobenzene, 4-chloro-3-nitrobenzotrifluoromethane, and 4-chloro-3-nitrotoluene were commercial

products and were purified by recrystallization or fractional distillation. Melting points correspond to within 1° of literature values,[13] and, where applicable, analysis of the group displaced by excess base in 80% DMSO–methanol at 100° was quantitative.

1,2,4-Trinitrobenzene was donated by Dr. D. E. Giles.

2-Fluoronitrobenzene, bp 90–95° (9 mm) [lit.[13] bp 86–87° (11 mm)], was prepared by halide exchange of 2-chloronitrobenzene with potassium fluoride in DMSO.[14] A Beilstein flame test confirmed the absence of chlorine in the product.

3,4-Dinitrotoluene, mp 61° (ethanol) (lit.[13] mp 61°), was prepared by stepwise oxidation of 4-amino-3-nitrotoluene using Caro's acid and hot fuming nitric acid. 4-Amino-3-nitrotoluene was obtained by nitration of *p*-methylacetanilide followed by hydrolysis.

4-Hydroxy-3-nitrotoluene, mp 30–33° (ethanol–water) (lit.[13] mp 36.5°), was prepared by the hydroxydechlorination of 4-chloro-3-nitrotoluene at 100° in 70% DMSO–water.

[2,4,6-$^2H_3$]-Iodobenzene. [N,N,N,2,4,6-$^2H_6$]-aniline hydrochloride was prepared by heating aniline hydrochloride with deuterium oxide for 24 hr at 100°, removing the water, and repeating the procedure twice.[15] The NMR spectrum consisted of one peak (τ 2.60) (2 H, referred to internal standard of methylene chloride). Diazotization and decomposition of the diazonium salt with potassium iodide gave [2,4,6-$^2H_3$]-iodobenzene. The NMR spectrum consisted of one peak (τ 3.00) (2 H).

[4,6-$^2H_2$]-2-Nitro- and [2,6-$^2H_2$]-4-nitroiodobenzene[16] were prepared as a mixture from the nitration of [2,4,6-$^2H_3$]-iodobenzene with a solution of potassium nitrate (10 g) in [$^2H_2$]-sulfuric acid at 25° for 24 hr. Fractional crystallization (pentane) of the product gave [2,6-$^2H_2$]-4-nitroiodobenzene, mp 171–172° (lit.[13] $^1H_4$ mp 172°). The NMR spectrum consisted of one peak (τ 2.04) (2 H). Steam distillation of the product mixture gave [4,6-$^2H_2$]-2-nitroiodobenzene, mp 53–54° (lit.[13] $^1H_4$ mp 54°). The NMR spectrum consisted of two broad doublets [τ 2.64, 3.10 (2 H) with J_{meta} = 5 Hz].

Analytical grade sodium nitrite was dried by heating to 120° for 2 hr and stored in a desiccator. Spectrophotometric analysis[17] showed this material to be 99.5% sodium nitrite.

Nitrous anhydride was prepared by the oxidation of arsenious oxide with dilute nitric acid[18] (sp gr 1.3). Condensation of the equimolar gaseous mixture of nitric oxide and nitrogen dioxide in a Dry Ice–acetone trap gave liquid nitrous anhydride (N_2O_3).

General Reaction Conditions. Sodium nitrite (3.5 g, 0.05 mol) was added to a stirred solution of the aromatic compound (0.02 mol) in DMSO (50 ml). The mixture was allowed to react, diluted with water (200 ml), and extracted with ether to get neutral products. The aqueous layer was acidified (1 *M* HCl) and extracted with ether. The ether extract was dried (Na_2SO_4) and evaporated to dryness to get acidic products.

For reactions yielding 2-nitrophenol and 4-nitrophenol, excess 2-chloroaniline was added to prevent further nitrosation of the phenol. Spectroscopic measurements of rate data were carried out directly in a 1-cm cell using a Gilford Model 240 spectrophotometer. Measurement was at the absorption maximum of the phenoxide ion. At least a 20-fold excess of NO_2^- was used with aromatic substrates at 10^{-4}–10^{-5} *M* to give pseudo-first-order rate constants.

GC Analysis. o-and *p*-nitrofluoro-, nitrochloro-, and dinitrobenzene were separated on a 6 ft × 0.25 in. packed column coated with APL in the temperature range 140–180°. 4-Nitroiodobenzene and *p*-dinitrobenzene were separated on a 6 ft × 0.25 in. packed column coated with Carbowax 20M at a temperature of 190°. Peak areas were measured by planimetry. The extent of reaction was determined from the reaction time and decrease in the area of the substrate peak.

Registry No.—3,4-Dinitrotoluene, 610-39-9; 4-amino-3-nitrotoluene, 89-62-3; 4-hydroxy-3-nitrotoluene, 119-33-5; 4-chloro-3-nitrotoluene, 89-60-1; [2,4,6-$^2H_3$]-iodobenzene, 13122-40-2; [N,N,N,2,4,6-$^2H_6$]-aniline hydrochloride, 55223-35-3; [4,6-$^2H_2$]-2-nitroiodobenzene, 55223-36-4; [2,6-$^2H_2$]-4-nitroiodobenzene, 55223-37-5.

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Reaction of 2-Carboalkoxymethylenecyclopropanes with Phenyl Azide[1a]

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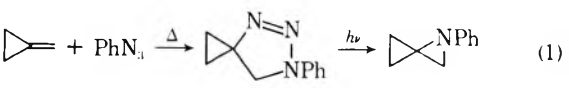
The reaction of phenyl azide with several 2-carboalkoxymethylenecyclopropanes has been examined. 2,3-Dicarbomethoxymethylenecyclopropane (**1a**) gives 1-phenyl-4-(1,2-dicarbomethoxyethyl)-1,2,3-triazole (**2a**). Similarly, esters **1b** and **1c** yield triazoles **2b** and **2c**, respectively. The ^{13}C spectra of triazoles **2a–c** are given. The formation of these triazoles is rationalized in terms of a rearrangement of an intermediate triazoline adduct.

We have recently reported on the synthesis of the novel 1-azaspiropentane structure.[2,3] This highly strained heterocyclic system was formed by photochemical expulsion of molecular nitrogen from the appropriate triazoline precursor, which was itself obtained from the thermal cycloaddition of phenyl azide to the corresponding methylenecyclopropane (see eq 1). In the present paper we relate our unsuccessful attempts to apply this synthetic scheme to methylenecyclopropanes bearing alkoxycarbonyl substituents on the cyclopropyl ring. In this instance, 1,2,3-triazoles isomeric with the desired triazolines are produced in the initial reaction of the synthetic sequence.



(1)

Table I
^{13}C Spectra of Triazoles[a]

Compd	Tr-4	Tr-5	*N*-Ph	*o*-Ph	*m*-Ph	*p*-Ph
3	134.0	121.7	136.6	120.2	129.4	128.4
2a	144.6	120.3	136.8	120.3	129.6	128.6
2b	146.9	119.4	137.0	120.2	129.5	128.4

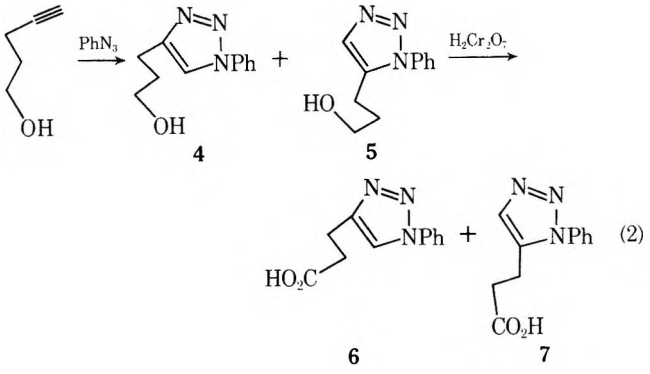
[a] Chemical shifts in parts per million relative to Me_4Si internal standard.

The reaction of phenyl azide with 2,3-dicarbomethoxymethylenecyclopropane (**1a**) led to a white, crystalline solid subsequently identified as 1-phenyl-4-(1,2-dicarbomethoxyethyl)-1,2,3-triazole (**2a**). This material shows an ABX pattern in the aliphatic hydrogen region of its NMR spectrum with coupling constants J_{AX} = 6, J_{BX} = 8, and J_{AB} = 17 Hz, in addition to a one-proton singlet at δ 7.98. In a similar fashion, 2-carbethoxymethylenecyclopropane (**1b**) gave 1-phenyl-4-(2-carbethoxyethyl)-1,2,3-triazole (**2b**). The NMR spectrum of **2b** shows a sharp singlet at δ 7.75 for the triazole ring proton as well as a pair of triplets for the aliphatic side chain. Ir and NMR spectral data were also obtained for the incompletely characterized 1-phenyl-4-(2-carbethoxypropyl)-1,2,3-triazole (**2c**) produced from the addition of phenyl azide to 2-carbethoxy-2-methylmethylenecyclopropane (**1c**). The methyl group of **2c** appears as a doublet at δ 1.24 in the NMR spectrum and the triazole ring proton gives a sharp singlet at δ 7.74. (Compound **1c** was obtained in a mixture with its isomer, 1-carbethoxyethylidenecyclopropane, by photochemical decomposition of the pyrazoline resulting from addition of diazomethane to ethyl 2-methyl-2,3-butadienoate.)

The uv spectra of **2a** and **2b** evidence intense maxima at 251 and 248 nm, respectively. Under the same conditions, 1-phenyl-1,2,3-triazole (**3**) exhibits a 245-nm band arising from conjugation of the phenyl and triazole rings. The observed bathochromic shift of the absorption bands for **2a** and **2b** supports assignment as 4-substituted 1-phenyl-1,2,3-triazoles. Substitution at the 5 position of the triazole ring would be expected to disrupt interaction between the two aromatic rings shifting the maximum to shorter wavelength.[4]

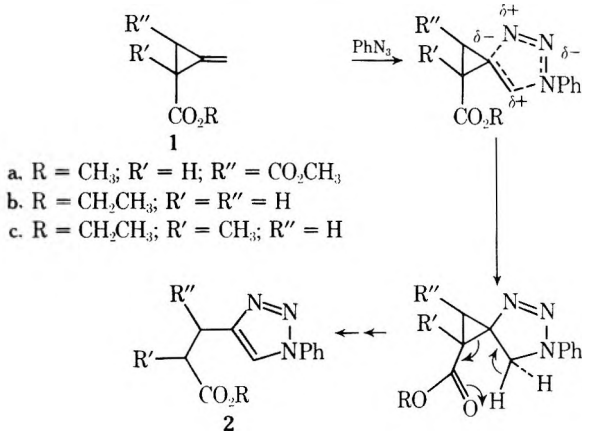
The structural assignments of **2a** and **2b** were confirmed by ^{13}C NMR. Table I gives the chemical shifts of the triazole and phenyl ring carbons for **3, 2a,** and **2b.** Substitution at the 4 position of **3** gives rise to a ca. 10-ppm downfield shift at that carbon along with a slight upfield shift of C-5 of the triazole. The ortho carbons of the phenyl ring prove to be an important indicator for the triazole ring-substitution pattern. The presence of a substituent on C-4 of the triazole ring leaves the ortho carbons of the phenyl relatively unaffected, whereas substitution at C-5 moves these carbons downfield to ca. 124.5 ppm. In this case, the triazole C-4 carbon moves upfield slightly as well.[5] The ^{13}C spectra of **2a** and **2b** given in Table I behave as expected for 4-substituted 1-phenyl-1,2,3-triazoles, supporting the structural assignments given.

Finally, an authentic sample of the free acid derived from **2b** was obtained by an independent synthetic route. Phenyl azide reacted with 4-pentyn-1-ol to yield a 2:1 mixture of 4- and 5-(3-hydroxypropyl)-1,2,3-triazole (**4** and **5**). Each of the NMR signals of the major isomer appears at lower field than the corresponding one of the minor isomer.[6] The triazole ring protons are particularly characteristic of this situation, appearing at δ 7.76 and 7.53 for **4** and **5,** respectively. Chromic acid oxidation of the mixture of alcohols gave a mixture of carboxylic acids **6** and **7.** The NMR signals for the two isomers bore the same relationship as for the alcohols, with the triazole ring protons appearing at δ 7.78 and 7.58 for **6** and **7,** respectively. The major isomer of this mixture was isolated and shown to be identical in all respects with a sample obtained from hydrolysis of **2b.**



The formation of triazoles **2a, 2b,** and **2c** is rationalized by the addition of phenyl azide to the methylenecyclopropane substrate as shown in Scheme I. The substituent-bearing nitrogen of phenyl azide ordinarily bonds to the olefinic carbon best able to bear a positive charge.[7] In this case, the cyclopropyl ring apparently directs the addition of phenyl azide onto the *exo*-methylene carbon in the fashion indicated, because of the interaction of the cyclopropyl ring with the double bond. A similar orientational preference has been proposed for the triazolines arising from reaction of phenyl azide with methylenecyclopropane and its phenyl-substituted analogs.[2] The intermediate triazolines from **1a, 1b,** and **1c** are all unstable under the reaction conditions and undergo rearrangement[8] to the aromatic triazole isomers. This hydrogen transfer probably occurs with the assistance of the proximal ester carbonyl as shown below.

Scheme I



Experimental Section

General. NMR spectra were recorded for $CDCl_3$ solutions on a Varian HR-220 spectrometer. Ir spectra were obtained on neat samples or $CHCl_3$ solutions using a Perkin-Elmer 137 Infracord. Carbon-13 spectra were obtained on $CHCl_3$ solutions using a Varian XL-100-15 NMR spectrometer operating in Fourier-transform mode; chemical shifts are given in parts per million relative to internal Me_4Si. Mass spectra (70 eV) were obtained on Varian MAT CH-7 and AEI MS-9 spectrometers. Gas chromatography (GLC) was performed on an Aerograph A-700 preparative instrument. Analyses were run by Midwest Microlab, Inc. Anhydrous $MgSO_4$ was routinely used as a drying agent.

Reaction of Phenyl Azide with 1a. A mixture of 2 g of **1a** and 10 ml of phenyl azide was heated on a steam bath for 12 hr. The reaction mixture was cooled and hexane was added to dissolve remaining phenyl azide. The supernatant layer was decanted and the

resulting brown solid was recrystallized from acetone–cyclohexane to yield 3.1 g (91%) of **2a**. A pure sample of **2a** was obtained by recrystallization from ethyl acetate: mp 114–115°; ir 5.68, 8.0, and 9.6 μ; uv (ethanol) λ_{max} 251 nm (log ε 3.22); NMR (ABX pattern for three protons) δ_A 3.06, δ_B 3.21, δ_X 4.39 (J_{AB} = 17, J_{AX} = 6, J_{BX} = 8 Hz), 3.69 (s, 3), 3.74 (s, 3), 7.5 (m, 3), 7.71 (d, 2, J = 6 Hz), and 7.98 (s, 1); ^{13}C NMR δ 35.7, 39.1, 51.9, 52.6, 120.3, 128.6, 129.6, 136.8, 144.6, 171.5, and 171.7; mass spectrum *m/e* (rel intensity) 289 (7), 258 (15), 247 (10), 203 (13), 202 (100), 201 (27), 188 (20), 170 (17), 160 (13), 143 (18), 142 (20), 104 (17), 77 (87), 59 (17), and 51 (35).

Anal. Calcd for $C_{14}H_{15}N_3O_4$: C, 58.13; H, 5.23; N, 14.53. Found: C, 57.7; H, 5.1; N, 14.5.

Reaction of 1b with Phenyl Azide. A mixture of 770 mg of **1b**[9] and 2.75 g of phenyl azide was heated on a steam bath under nitrogen for 24 hr. The reaction was cooled and pentane was added to dissolve the remaining phenyl azide. The supernatant layer was decanted and the resulting crystalline material was dissolved in ethyl acetate. Precipitation with pentane gave 730 mg (50%) of tan crystals. Recrystallization from ethyl acetate–pentane gave pure **2b**: mp 61.5–63°; ir 5.81, 9.7, 13.2, and 14.8 μ; uv (ethanol) λ_{max} 248 nm (log ε 3.46); NMR δ 1.18 (t, 3, J = 7 Hz), 2.74 (t, 2, J = 7.5 Hz), 3.02 (t, 2, J = 7.5 Hz), 4.08 (q, 2, J = 7 Hz), 7.3–7.7 (m, 5) and 7.75 (s, 1); ^{13}C NMR δ 14.2, 21.0, 33.6, 60.5, 119.4, 120.2, 128.4, 129.5, 137.0, 146.9, and 172.5; mass spectrum *m/e* (rel intensity) 245 (1), 217 (3), 200 (18), 188 (13), 144 (10), 131 (10), 130 (100), 104 (10), 77 (62), and 51 (16).

Anal. Calcd for $C_{13}H_{15}N_3O_2$: C, 63.66; H, 6.16; N, 17.13. Found: C, 63.4; H, 6.2; N, 17.2.

Hydrolysis of 2b. A 218-mg sample of **2b** was refluxed for 4 hr in 10 ml of methanol with one KOH pellet. The solvent was removed and the residue was dissolved in ether, washed with water, and dried. The ether was removed to yield 50 mg (26%) of 1-phenyl-4-(2-carboxyethyl)-1,2,3-triazole (**6**), mp 125–126°.

2-Carbethoxy-2-methylmethylenecyclopropane (1c). Ethyl 2-methyl-2,3-butadienoate[10] (2.9 g, 23 mmol) in 60 ml of ether was combined with 42 ml of a 0.58 *M* solution of diazomethane in ether (23 mmol) and the foil-wrapped flask was stored at 0° for 48 hr.[11] The colorless solution was concentrated and the resulting oily pyrazoline was dissolved in enough benzene to make a 2% solution. Photolysis for 5 hr in a Rayonet photochemical reactor with 3130-Å bulbs gave 2.5 g (78%) of a 55:45 mixture of two products which were separated by GLC. Compound **1c** showed ir 5.83 (br), 7.82, 8.79, 9.73, and 11.2 μ; NMR (CCl_4) δ 1.20 (t of m, 4, J = 7.5 Hz), 1.33 (s, 3), 1.89 (d of t, 1, J = 9, 2 Hz), 4.01 (q, 2, J = 7.5 Hz), 5.33 (t of m, 1, J = 2 Hz), and 5.39 (t of m, 1, J = 2 Hz); NMR (benzene-d_6) δ 0.89 (t, 3, J = 7 Hz), 1.00 (d of t, 1, J = 8.5, 2.5 Hz), 1.35 (s, 3), 2.00 (d of t, 1, J = 8.5, 2.5 Hz), 3.88 (q, 2, J = 7 Hz), 5.73 (t of m, 1, J = 2.5 Hz), and 5.77 (t of m, 1, J = 3 Hz); mass spectrum *m/e* (rel intensity) 140 (0.1), 125 (1), 112 (100), 97 (12), 95 (16), 69 (17), 67 (25), 43 (18), 41 (27), and 39 (24).

Anal. Calcd for $C_8H_{12}O_2$: C, 68.55; H, 8.63. Found: C, 68.7; H, 8.5.

1-Carbethoxyethylidenecyclopropane showed ir 5.87, 7.78, 8.89, and 11.6 μ; NMR (CCl_4) δ 1.09 (t of m, 2, J = 7 Hz), 1.27 (t, 3, J = 7 Hz), 1.37 (t of m, 2, J = 7 Hz), 1.96 (m, 3) and 4.10 (q, 2, J = 7 Hz); NMR (benzene-d_6) δ 0.71 (t of q, 2, J = 8.5, 1.5 Hz), 1.01 (t, 3, J = 7 Hz), 1.21 (t of q, 2, J = 9, 2 Hz), 2.06 (m, 3) and 4.07 (q, 2, J = 7 Hz); mass spectrum *m/e* (rel intensity) 140 (1), 112 (100), 111 (20), 97 (18), 95 (24), 83 (18), 69 (31), 67 (38), 43 (38), 41 (41), and 39 (40).

Anal. Calcd for $C_8H_{12}O_2$: C, 68.55; H, 8.63. Found: C, 68.5; H, 8.6.

Reaction of 1c with Phenyl Azide. A mixture of 103 mg (0.7 mmol) of **1c** and 265 mg (2.2 mmol) of phenyl azide was heated on a steam bath under nitrogen for 22 hr. The reaction mixture was cooled and pentane was added to dissolve remaining phenyl azide. The supernatant layer was decanted and NMR and ir examination of the residue showed only **2c**: ir 5.79, 6.86, 8.2, 8.6, and 9.6 μ; NMR δ 1.20 (t, 3, J = 7 Hz), 1.24 (d, 3, J = 7 Hz), 2.91 (m, 2), 3.14 (m, 1), 4.08 (q, 2, J = 7 Hz), 7.3–7.7 (m, 5), and 7.74 (s, 1).

1-Phenyl-1,2,3-triazole (3). Compound **3** synthesized by the method of El Khadem[12] showed uv (EtOH) λ_{max} 245 nm (log ε 4.02); NMR (60 MHz) δ 7.3–7.8 (m, 5), 7.81 (d, 1, J = 1 Hz), and 8.12 (d, 1, J = 1 Hz); NMR (220 MHz) δ 7.35–7.55 (m, 3), 7.68–7.78 (m, 2), 7.83 (s, 1), and 8.00 (s, 1); ^{13}C NMR δ 120.2, 121.7, 128.4, 129.4, 134.0, and 136.6; mass spectrum *m/e* (rel intensity) 145 (15), 117 (24), 90 (5), 77 (100), and 51 (43).

1-Phenyl-4-(2-carboxyethyl)-1,2,3-triazole (6). Phenyl azide (2.3 g, 16.5 mmol) was stirred with 800 mg (9.5 mmol) of 4-pentyn-1-ol at 100° for 15 hr. The resulting mixture was cooled and hexane was added to dissolve remaining phenyl azide. The supernatant layer was decanted, leaving 1.82 g (94%) of a dark oil. NMR examination showed a 67:33 mixture of **4** and **5**. Compound **4** showed NMR δ 1.94 (p, 2, J = 7 Hz), 2.84 (t, 2, J = 7 Hz), 3.68 (t, 2, J = 7 Hz), 4.99 (s, 1), 7.25–7.65 (m, 5), and 7.76 (s, 1). Compound **5** showed NMR δ 1.81 (p, 2, J = 7 Hz), 2.72 (t, 2, J = 7 Hz), 3.59 (t, 2, J = 7 Hz), 4.99 (s, 1), 7.25–7.50 (m, 5), and 7.53 (s, 1).

A 2.38-g (1.06 mmol) sample of the crude mixture of **4** and **5** was dissolved in 50 ml of acetone and cooled to 0° and 6 ml of 8 *N* chromic acid was added over 15 min. After stirring for an additional 15 min, the layers were separated and the aqueous layer was extracted several times with ether. The extract was washed with saturated NaCl and dried. Solvent removal gave 1.26 g (46%) of tan crystals. NMR examination showed a 67:33 mixture of 4- and 5-(2-carboxyethyl)-1-phenyl-1,2,3-triazole (**6** and **7**). Compound **6** showed NMR δ 2.63 (t, 2, J = 7 Hz), 2.96 (t, 2, J = 7 Hz), 7.25–7.50 (m, 5), and 7.58 (s, 1).

Pure **6** crystallized from a benzene solution of the mixture: mp 125–126° (no melting point depression was observed on mixing with material obtained from hydrolysis of **2b**); ir 3.0 (br), 5.85, 9.5, 13.1, and 14.5 μ; NMR δ 2.81 (t, 2, J = 7 Hz), 3.08 (t, 2, J = 7 Hz), 7.3–7.5 (m, 3), 7.64 (d, 2, J = 9 Hz), and 7.78 (s, 1); mass spectrum *m/e* (rel intensity) 143 (1), 131 (2), 130 (61), 77 (54), and 51 (18).

Treatment of **6** with ethereal diazomethane gave 1-phenyl-4-(2-carbomethoxyethyl)-1,2,3-triazole, mp 95–98°. A 100-mg sample of the methyl ester was stirred and refluxed for 24 hr in 5 ml of ethanol and 10 drops of concentrated H_2SO_4. The reaction mixture was diluted with water and extracted with chloroform. The organic layer was washed with water and dried and the solvent was removed to give 105 mg (100%) of **2b**, mp 62–63°, which was spectroscopically identical with material obtained from the reaction of **1b** with phenyl azide.

Acknowledgment. We thank Dr. Anibal C. Rojas for obtaining the ^{13}C NMR spectra.

Registry No.—**1a**, 55281-54-4; **1b**, 18941-94-1; **1c**, 55281-55-5; **2a**, 55281-56-6; **2b**, 55281-57-7; **2c**, 55281-58-8; **3**, 1453-81-2; **4**, 4600-03-7; **5**, 55281-59-9; **6**, 55281-60-2; **7**, 55281-61-3; phenyl azide, 622-37-7; ethyl 2-methyl-2,3-butadienoate, 5717-41-9; 1-carbethoxyethylidenecyclopropane, 55281-62-4; 4-pentyn-1-ol, 5390-04-5; 1-phenyl-4-(2-carbomethoxyethyl)-1,2,3-triazole, 55281-63-5.

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Reaction of *N*-Isopropylallenimine with Organic Azides[1]

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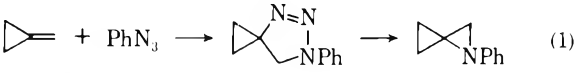
The reaction of *N*-isopropylallenimine (1) with several organic azides has been examined. Phenyl azide gives a mixture of triazole 3 and amidine 7. *p*-Toluenesulfonyl azide reacts with 1 to give only amidine 11; likewise *tert*-butyl and ethyl azidoformate give 12 and 13, respectively. Reaction of 12 with dry HCl gives *N*-isopropyl-β-lactamimide (14). The formation of the amidines and triazole 3 is rationalized in terms of triazoline intermediates.

We have recently reported on the highly strained 1-azaspiropentane structure.[2,3] This novel heterocyclic system was obtained by photochemical decomposition of triazoline precursors derived from thermal cycloaddition of phenyl azide to methylenecyclopropanes (see eq 1). We now report on our attempts to extend this synthetic sequence to allenimine 1 in hopes of effecting conversion to a 1,4-diazaspiropentane (2).



(1)

N-Isopropylallenimine (1) reacts slowly with phenyl azide to yield 1-phenyl-5-(*N*-isopropylaminomethyl)-1,2,3-triazole (3) as the major product. The NMR of 3 shows, among other features, a sharp singlet for the aliphatic methylene group and a one-proton singlet at δ 7.66 for the triazole ring proton. The uv spectrum of 3 displays a maximum at 228 nm, supporting assignment as a 5-substituted 1-phenyl-1,2,3-triazole. Substitution at the 4 position of the triazole ring is known to shift the uv maximum of the parent 1-phenyl-1,2,3-triazole (4) (248 nm) to longer wavelength, whereas substitution at the 5 position causes a shift to shorter wavelength.[4] ^{13}C NMR confirms the 5-substituted 1-phenyl-1,2,3-triazole structure for 3; the chemical shifts of the triazole and phenyl carbons of 3 and 4 are listed in Table I. The C-5 carbon of the triazole ring in 3 is shifted downfield 14.5 ppm relative to 4, indicating substitution at that position, whereas the C-4 carbon experiences only a slight upfield shift. An important indicator of substitution at the 5 position of 3 is the ca. 4.5-ppm downfield shift of the phenyl ortho carbons relative to 4. This is an effect seen in 5-substituted triazoles,[5] presumably resulting from steric interaction between the substituents.

Table I
^{13}C Spectra of Triazoles[a]

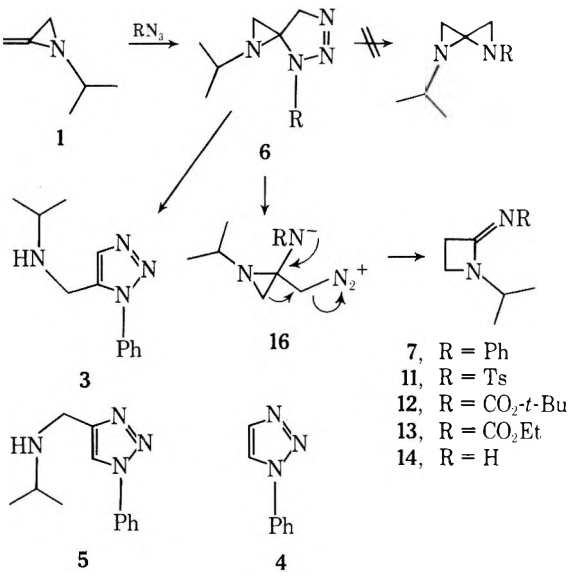
Compd	C-4	C-5	*N*-Ph	*o*-Ph	*m*-Ph	*p*-Ph
3	133.3	136.3	136.6	124.7	129.3	129.3
4	134.0	121.7	136.6	120.2	129.4	128.4

[a] Chemical shifts in parts per million relative to internal Me_4Si.

An authentic sample of 3 was obtained by independent synthesis. Phenyl azide reacts with *N*-isopropylpropargylamine to yield a 60:40 mixture of 4- and 5-(*N*-isopropylaminomethyl)-1-phenyl-1,2,3-triazole (5 and 3). Each of the NMR signals of the major isomer appears at lower field than the corresponding one of the minor isomer. The triazole ring protons are particularly characteristic of this, appearing at δ 7.85 for 5 and δ 7.66 for 3. A sample of pure 3 was obtained by column chromatography and shown to be identical with the product obtained from the reaction of 1 with phenyl azide.

The formation of 3 is rationalized by the addition of phenyl azide to 1 to give triazoline 6 as shown in Scheme I.

Scheme I

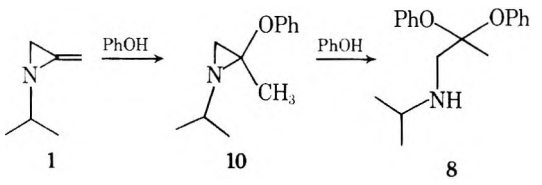


Azides ordinarily react with double bonds so that the substituted nitrogen atom of the azide bonds with the olefinic carbon best able to bear a positive charge;[7] this is the exclusive mode of addition for enamines.[8] The triazoline thus formed is unstable to the reaction conditions and isomerizes to the aromatic triazole 3 with the concomitant relief of strain inherent in the three-membered ring.

A second product isolated from the reaction of 1 with phenyl azide was identified as *N*-isopropyl-*N'*-phenyl-β-lactamimide (7), the first example of this small-ring heterocyclic system. Amidine 7 is a pale yellow oil, surprisingly stable to a variety of reaction conditions, e.g., acid, base, pyrolysis, photolysis, and chemical reduction. The ir spectrum of 7 shows a characteristic 6.0-μ imine band, while the pertinent features of the NMR spectrum consist of a pair of two-proton triplets in the aliphatic region. The mass spectrum of 7 shows a prominent peak at *m/e* 117 corresponding to the ketenimine fragment arising from retro-cycloaddition of the four-membered ring. This places the phenyl substituent on the imine nitrogen, fixing the assigned structure.

Yields of triazole 3 and amidine 7 from the reaction of 1 with phenyl azide varied erratically, and, in some cases, a third product was formed in the reaction. This latter product was isolated and identified as 1-*N*-isopropylamino-2-propanone diphenyl ketal (8) on the basis of its spectral properties and its reaction with ethereal HCl to yield phenol and the hydrochloride salt of 1-*N*-isopropylamino-2-propanone (9).

An authentic sample of 8 was rapidly and smoothly obtained from the reaction of 1 with excess phenol at 25°. This reaction probably proceeds by Markovnikov addition of phenol to the exocyclic double bond of 1 to yield 10,



1 10 8

which subsequently adds a second phenol in the expected manner to give **8**. The origin of **8** in the reaction of **1** with phenyl azide was baffling until it was ascertained that phenol was present as an impurity in the phenyl azide. (In a subsequent experiment, purified phenyl azide reacted with **1** to yield a 65:35 mixture of **3** and **7**; no **8** was observed.)

Reaction of **1** with *p*-toluenesulfonyl azide yielded amidine **11** as the only product. *N*-Isopropyl-*N'*-*p*-toluenesulfonyl-β-lactamimide (**11**) is a pale yellow solid possessing a characteristic 6.11-μ imine band in the ir. Basic hydrolysis of **11** yields *p*-toluenesulfonamide and *N*-isopropyl-β-aminoproprionic acid (isolated and identified as the ethyl ester.[9])

In a similar fashion, **1** reacted with *tert*-butyl and ethyl azidoformate to give the corresponding lactamimides **12** and **13**. The ester function of **12** is readily cleaved in ethereal HCl to yield the parent *N*-isopropyl-β-lactamimide (**14**). Amidine **14** shows significant bands at 3.1, 5.97, and 12.3 μ in the ir spectrum. The NMR includes a pair of triplets in the aliphatic region and a broad singlet at δ 4.07 attributed to the imine hydrogen. The mass spectrum of **14** displays a peak at *m/e* 84 (and the appropriate metastable) corresponding to the carbodiimide fragment from retrocycloaddition of the four-membered ring.

The ^{13}C chemical shifts for the ring carbons of amidines **7**, **11**, **13**, and **14** are listed in Table II, along with *N*-isopropyl-β-lactam (**15**) for comparison. Each of the three ring carbons of amidine **14** shows a higher field resonance than the corresponding carbon of lactam **15**. This can be rationalized in terms of higher electronic charge on the carbons in the amidine owing to the smaller polarization of the C=N bond relative to the C=O function. There are also significant differences among the ring-carbon resonances of the substituted amidines, but again the chemical shifts increase with the electron-withdrawing ability of the imide substituents.

Table II
^{13}C Spectra of Amidines[a]

Compd	C_2	C_3	C_4
7	158.8	29.3	39.2
11	167.3	32.1	42.3
13	162.1	32.0	41.6
14	165.4	31.0	37.9
15	166.4	35.3	43.3

[a] Chemical shifts in parts per million relative to internal Me_4Si.

The formation of the amidine products can be rationalized readily by the pathway shown in Scheme I. Triazoline **6** can open to betaine **16**, which, upon extrusion of molecular nitrogen and rearrangement, leads to the corresponding amidine. The presence of strong electron-withdrawing functions on the azides favors formation of betaine **16** and the ultimate predominance of amidine products.[10]

Experimental Section

General. NMR spectra were recorded for $CDCl_3$ solutions on a Varian HR-220 spectrometer. Ir spectra were obtained on neat samples or $CHCl_3$ solutions using a Perkin-Elmer 137 Infracord. Carbon-13 spectra were obtained on $CHCl_3$ solutions with a Varian XL-100-15 NMR spectrometer operating in the Fourier-transform mode; chemical shifts are given in parts per million relative to internal Me_4Si. Mass spectra (70 eV) were obtained on Varian MAT CH-7 and AEI MS-9 spectrometers. Gas chromatography (GLC) was performed on an Aerograph A-700 preparative instrument. Analyses were run by Midwest Microlab, Inc. Anhydrous $MgSO_4$ was routinely used as a drying agent.

Reaction of 1 with Phenyl Azide. A mixture of 1 g of **1**[11] and 2.5 g of phenyl azide was heated at 90° for 4 days under a nitrogen atmosphere. NMR examination of the crude reaction mixture showed a 16:37:32:15 mixture of **1**, **3**, **7**, and **8**. Separation of the products was accomplished by column chromatography on silica gel. Ketal **8** showed bp 115° (0.1 mm); ir 6.26, 6.71, 7.24, 8.2, 9.2, 11.2, 13.3, and 14.4 μ; NMR δ 0.86 (br s, 1), 0.92 (d, 6, *J* = 7 Hz), 1.76 (s, 3), 2.55 (septet, 1, *J* = 7 Hz), 2.84 (s, 2), 6.94 (t, 2, *J* = 6 Hz), and 7.12 (m, 8); ^{13}C NMR δ 22.9, 48.8, 52.8, 58.1, 106.6, 121.1, 123.1, 129.1, and 150.9; mass spectrum *m/e* (rel intensity) 285 (0.01), 213 (40), 192 (100), 176 (27), 134 (15), 133 (13), 105 (11), 99 (69), 94 (63), 84 (44), 83 (20), 82 (10), 77 (33), 72 (57), 65 (16), 56 (35), 43 (76), and 30 (37).

Anal. Calcd for $C_{18}H_{23}NO_2$: C, 75.76; H, 8.12; N, 4.91. Found: C, 76.0; H, 8.1; N, 5.1.

Amidine **7** showed bp 130° (0.1 mm); ir 6.0, 7.2, 8.0, 8.32, 11.2, 12.8, and 14.7 μ; NMR δ 1.16 (d, 6, *J* = 7 Hz), 2.76 (t, 2, *J* = 4 Hz), 3.31 (t, 2, *J* = 4 Hz), 3.90 (septet, 1, *J* = 7 Hz), 3.63 (d, 2, *J* = 6 Hz), 6.74 (t, 1, *J* = 6 Hz), and 7.02 (t, 2, *J* = 6 Hz); ^{13}C NMR δ 19.7, 29.3, 39.2, 43.7, 121.9, 122.2, 128.6, 149.0, and 158.8; mass spectrum *m/e* (rel intensity) 188 (27), 118 (83), 117 (25), 97 (14), 91 (10), 77 (33), 56 (20), and 51 (15).

Anal. Calcd for $C_{12}H_{16}N_2$: C, 76.56; H, 8.57; N, 14.87. Found: C, 76.2; H, 8.2; N, 15.0.

Distillation of crude **3** at 130° (0.1 mm) gave a pure sample: mp 46–47.5°; ir 3.05, 6.9, 8.55, 10.3, 13.2, and 14.5 μ; uv (ethanol) λ_{max} 227 nm (log ε 4.12); NMR δ 0.99 (d, 6, *J* = 7 Hz), 1.89 (br s, 1), 2.77 (septet, 1, *J* = 7 Hz), 3.80 (s, 2), 7.45 (m, 3), 7.55 (m, 2), and 7.66 (s, 1); ^{13}C NMR δ 22.7, 39.9, 48.2, 124.7, 129.3, 133.3, 136.3, and 136.6; mass spectrum *m/e* (rel intensity) 217 (2), 216 (0.3), 201 (2), 173 (19), 130 (44), 118 (19), 117 (37), 96 (48), 77 (58), 72 (100), and 51 (25).

Anal. Calcd for $C_{12}H_{16}N_4$: C, 66.64; H, 7.46; N, 25.90. Found: C, 66.4; H, 7.5; N, 26.1.

Similar reactions were run on a number of occasions. In general, triazole **3** was the major constituent (50% or greater) of the product mixture with either **7** or **8** as a second component in an erratic manner depending upon the source and age of the reactants, among other variables.

A mixture of 2.5 g of phenyl azide (purified by base extraction and redistillation) and 1 g of **1** was stirred at 90° for 5 days under a nitrogen atmosphere. NMR examination of the crude material showed a 9:59:32 ratio of **1**, **3** and **7**.

1-Phenyl-5-(*N*-isopropylaminomethyl)-1,2,3-triazole (3). A mixture of 1.5 g of *N*-isopropylpropargylamine and 1.8 g of phenyl azide in 25 ml of toluene was heated on a steam bath for 28 hr. The toluene was removed by distillation and the residue was washed with pentane. NMR examination of the oily precipitate showed a 60:40 mixture of 4- and 5-(*N*-isopropylaminomethyl)-1-phenyl-1,2,3-triazole (**5** and **3**). Compound **5** showed NMR δ 1.11 (d, 6, *J* = 7 Hz), 2.88 (septet, 1, *J* = 8 Hz), 3.93 (s, 2), 7.25–7.60 (m, 5), and 7.85 (s, 1). A pure sample of **3** was obtained by column chromatography on silica gel. Triazole **3** obtained by this method was spectroscopically identical with the material from the reaction of **1** with phenyl azide.

Attempted Reaction of 7. A. A 71-mg sample of **7** was stirred with 0.5 ml of 10% HCl in 1 ml of THF for 17 hr at 70°. The mixture was poured into water, adjusted to pH 10 with 10% NaOH, and extracted with ether. The ether layer was washed with water, dried, and concentrated. Ir examination of the residue showed only **7**.

B. A 30-μl sample of **7** was refluxed for 2 hr in 250 μl of methanol with 10 mg of NaOH. The reaction mixture was diluted with water and extracted with ether. After drying and solvent removal, NMR examination showed only **7**.

C. A 33-mg sample of **7** was vacuum transferred (0.01 mm) through a 15 × 1 cm quartz tube packed with quartz chips at 500°. The transferred material was trapped in methanol cooled to −78°. Solvent removal gave 32 mg of unchanged **7**.

D. A 100-mg sample of **7** in 10 ml of benzene was irradiated for 6 hr through quartz with a 450-W high-pressure mercury lamp. After solvent removal, ir and TLC examination showed only **7**.

E. A 61-mg sample of **7** (0.3 mmol) was stirred and refluxed for 2 hr in 2 ml of dry THF with 10 mg (0.3 mmol) of $LiAlH_4$. The reac-

tion mixture was hydrolyzed with water and extracted with ether. After drying and solvent removal, ir showed only **7**.

Reaction of 8 with HCl. A 112-mg sample of **8** was dissolved in 2 ml of ether and 5 ml of ethereal HCl was added. Solvent removal and recrystallization from acetone gave 25 mg of **9** as white needles: mp 179–180°; ir 5.75 μ; NMR δ 1.19 (d, 6, J = 7 Hz), 2.27 (s, 3), 3.45 (septet, 1, J = 7 Hz), and 3.95 (s, 2); mass spectrum m/e (rel intensity) 115 (2), 100 (4), 72 (65), 57 (6), 43 (16), and 30 (100).

The mother liquors from the recrystallization were concentrated to yield 55 mg of phenol.

1-*N*-Isopropylamino-2-propanonone Diphenyl Ketal (8). Crystalline phenol (3 g) was combined with 1 g of **1** and the resulting solution was stirred for 10 min at 25° with cooling in a water bath (exothermic reaction). NMR examination of the crude mixture showed only **8** and phenol. A pure sample of **8** was obtained by column chromatography on silica gel and shown to be spectroscopically identical with **8** from the reaction of **1** with phenyl azide.

Reaction of 1 with *p*-Toluenesulfonyl Azide. A 0.5-g sample of **1** was combined with 1 g of *p*-toluenesulfonyl azide and heated slowly to 45°, at which point gas evolution commenced. After stirring at 45° for 3.5 hr, the dark red mixture was cooled and allowed to stand overnight. The resulting crystalline material (1.35 g) was washed with hexane. Pure **11** was obtained as light yellow plates by column chromatography on neutral alumina: mp 92.5–93.5°; ir 6.11, 8.70, 9.15, and 11.1 μ; NMR δ 1.11 (d, 6, J = 7 Hz), 2.35 (s, 3), 3.18 (t, 2, J = 3 Hz), 3.51 (t, 2, J = 3 Hz), 3.93 (septet, 1, J = 7 Hz), 7.20 (d, 2, J = 8 Hz), and 7.70 (d, 2, J = 8 Hz); ^{13}C NMR δ 19.6, 21.4, 32.1, 42.3, 45.0, 126.2, 129.1, 140.2, 142.1, and 167.3; mass spectrum m/e (rel intensity) 266 (9), 251 (6), 155 (64), 111 (20), 91 (100), 83 (5), and 65 (20).

Anal. Calcd for $C_{13}H_{18}N_2O_2S$: C, 58.60; H, 6.82; N, 10.52. Found: C, 58.4; H, 6.7; N, 10.5.

Hydrolysis of 11. A 132-mg (0.5 mmol) sample of **11** was heated at 60° for 12 hr with 2 ml of 10% NaOH. The reaction mixture was cooled, diluted with water, and acidified with 10% HCl. The water layer was extracted with ether and the ether extract was dried and concentrated to give 54 mg of *p*-toluenesulfonamide. The water layer was concentrated to dryness on a rotary evaporator. The residual solids were dissolved in 2 ml of anhydrous ethanol containing 1 drop of concentrated H_2SO_4 and heated at 60° for 24 hr. The reaction mixture was cooled, diluted with 10% $NaHCO_3$ solution, and extracted with ether. The ether was washed with saturated NaCl solution and dried. Solvent removal gave 44 mg of a 50:50 mixture of *p*-toluenesulfonamide (76 mg total, 90%) and ethyl *N*-isopropyl-3-aminoproprionate (22 mg, 28%) which was spectroscopically identical with authentic material.[9]

Reaction of 1 with Ethyl Azidoformate. A mixture of 5.0 g of allenimine **1** and 5.75 g of ethyl azidoformate was stirred at 75° for 36 hr, at which time the ir spectrum showed little remaining azide. The resulting red-brown product was distilled under vacuum to give 5.6 g (60%) of pure **13**: bp 99–102° (1 mm); ir 5.96, 6.15, 6.93, 7.93, 8.05, 8.34, 9.17, and 9.53 μ; NMR δ 1.16 (d, 6, J = 6.5 Hz), 1.27 (t, 3, J = 7 Hz), 3.23 (t, 2, J = 3.5 Hz), 3.56 (t, 2, J = 3.5 Hz), 4.08 (q, 2, J = 7 Hz), and 4.12 (septet, 1, J = 6.5 Hz); ^{13}C NMR δ 13.8, 19.0, 32.0, 41.6, 43.6, 60.0, 162.1, and 171.0; mass spectrum m/e (rel intensity) 184 (54), 169 (10), 156 (10), 142 (4), 139 (92), 113 (4), 112 (12), 97 (100), 84 (11), 83 (11), 71 (13), 70 (32), 69 (62), 68 (13), 56 (71), and 43 (75).

Anal. Calcd for $C_9H_{16}N_2O_2$: C, 58.65; H, 8.76; N, 15.21. Found: C, 58.4; H, 8.7; N, 15.5.

Reaction of 1 with *tert*-Butyl Azidoformate. A mixture of **1** (2.00 g) and *tert*-butyl azidoformate (2.88 g) was stirred for 24 hr at 85°. Ir examination showed only **12** and a trace of the starting azide. Pure **12** obtained by sublimation at 90° (2 mm) showed mp 68.5–70°; ir 5.95, 6.12, 8.0, 8.23, 8.62, 9.4, and 9.8 μ; NMR δ 1.09 (d, 6, J = 6.5 Hz), 1.47 (s, 9), 3.23 (t, 2, J = 4 Hz), 3.53 (t, 2, J = 4 Hz), and 4.16 (septet, 1, J = 6.5 Hz); mass spectrum m/e (rel intensity) 212 (2), 157 (4), 156 (6), 139 (11), 97 (10), 59 (50), 57 (100), and 41 (43).

Anal. Calcd for $C_{11}H_{20}N_2O_2$: C, 62.21; H, 9.50; N, 13.20. Found: C, 62.3; H, 9.7; N, 13.4.

Hydrolysis of 12. An 835-mg sample of crude **12** was stirred with ether saturated with HCl at 50° for 20 hr. The yellow supernatant ether layer was decanted and the oily red residue (522 mg) was taken up in water and carefully neutralized to pH 7 with 10% NaOH. The water layer was extracted with $CHCl_3$; the $CHCl_3$ was dried and concentrated to give 90 mg of a red tar, ir 5.85 μ. The water layer was then adjusted to pH 10 and reextracted with $CHCl_3$. The solvent was dried and removed to yield 200 mg (85%) of **14**: ir 3.1, 5.97, 8.0, and 13.3 μ; NMR δ 1.12 (d, 6, J = 6.5 Hz), 2.71 (t, 2, J = 4.5 Hz), 3.30 (t, 2, J = 4.5 Hz), 3.78 (septet, 1, J = 6.5 Hz), and 4.07 (br s, 1); ^{13}C NMR 19.6, 31.0, 37.9, 43.4, and 165.4; mass spectrum m/e (rel intensity) 112 (55), 97 (54), 85 (48), 84 (18), 83 (84), 70 (23), 69 (75), 56 (100), 54 (19), 43 (81), 42 (44), and 41 (55).

Exact mass. Calcd for $C_6H_{12}N_2$: 112.1001. Found: 112.098.

Registry No.—**1**, 55268-35-4; **3**, 55268-36-5; **5**, 55268-37-6; **7**, 55268-38-7; **8**, 55268-39-8; **9**, 55268-40-1; **11**, 55268-41-2; **12**, 55268-42-3; **13**, 55268-43-4; **14**, 55268-44-5; phenyl azide, 622-37-7; *N*-isopropylpropargylamine, 6943-48-2; hydrochloric acid, 7647-01-0; *p*-tolunesulfonyl azide, 941-55-9; ethyl azidoformate, 817-87-8; *tert*-butyl azidoformate, 1070-19-5.

References and Notes

(1) Support of this work by a grant from the National Science Foundation is gratefully acknowledged.
(2) J. K. Crandall and W. W. Conover, *J. Org. Chem.*, **39**, 63 (1974).
(3) D. H. Aue, R. B. Lorens, and G. S. Helwig, *Tetrahedron Lett.*, 4795 (1973).
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Deprotonation of Ternary Iminium Salts[1]

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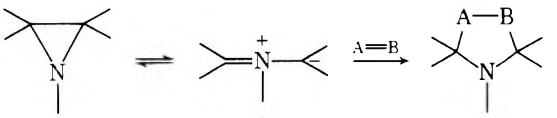
A series of aldiminium and ketiminium salts were prepared by alkylation of imines with methyl fluorosulfonate. Deprotonation of these salts was envisioned as an alternative route to azomethine ylides and thus as a new aziridine synthesis. Proton abstraction from these salts was attempted with a wide variety of bases. Of these, sodium bis(trimethylsilyl)amide proved to give the most favorable ratio of deprotonation to dealkylation in the conversion of *N*-(benzhydrylidene)methyl-*tert*-butylaminium fluorosulfonate to 1-*tert*-butyl-2,2-diphenylaziridine. Related aldiminium salts yielded products (1,2-diaminostilbenes and aminomethylaziridines) which were apparently derived from initial loss of the aldiminium vinyl proton. The mechanisms and implications of these reactions are discussed as well as the chemistry of some of the products.

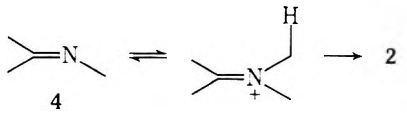
The thermal and photochemical ring openings of aziridines (**1**) have been studied extensively and the product azomethine ylides (**2**) have been employed in heterocyclic syntheses by taking advantage of the 1,3-dipolarophilic character of **2**.[2,3] Although reversion of **2** to **1** has been noted previously, this reversion has never been taken advantage of as a synthetic route to aziridines. Our interest in



1 **2**

the synthesis of functionally substituted and/or sterically crowded aziridines has prompted us to investigate the potential utility of azomethine ylide ring closures.

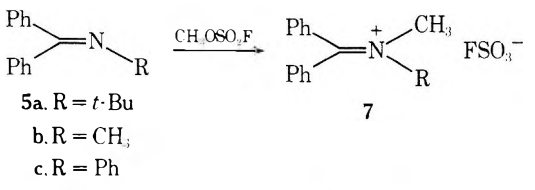
Our proposed approach to these ylides involved the deprotonation of iminium salts (**3**). These salts should in turn be available from the alkylation of the corresponding imines (**4**). The major anticipated problem with this approach



4 **3**

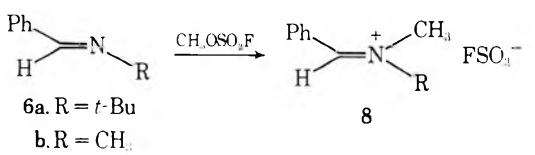
was the possible ease with which dealkylation of **3** could compete with the desired deprotonation. In this paper we would like to report the initial exploratory experiments by which we probed the potential utility of this synthetic approach.

Synthesis of Aldiminium and Ketiminium Salts. A series of ketimines (**5**) and aldimines (**6**) were prepared by standard procedures and alkylated with methyl fluorosulfonate and (in one case) methyl triflate. These alkylating agents were selected because of their reactivity and because the product anions would be relatively nonnucleophilic and thereby not contribute to competing dealkylation. The resultant salts were relatively stable and in one case (**7a**) could be purified sufficiently for analysis. The other salts, particularly the aldiminium salts (**8**), were less stable and hygroscopic.



5a. R = *t*-Bu
b. R = CH_3
c. R = Ph

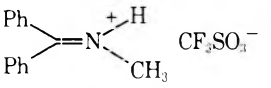
7



6a. R = *t*-Bu
b. R = CH_3

8

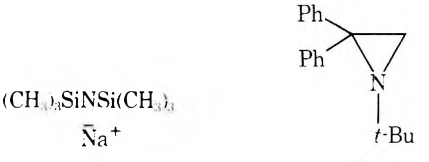
Although insoluble in most organic solvents, the salts were soluble in acetone, dimethyl sulfoxide, and liquid sulfur dioxide. The latter solvent was particularly useful for obtaining the NMR spectra which confirmed the assigned structures. The triflate analog of **7a** decomposed at its melting point (128°) with the liberation of a gas, presumably isobutene. A crystalline residue was assigned structure **9** on the basis of its NMR spectrum, which showed a de-



9

shielded methyl singlet (δ 3.47) and the conspicuous absence of a *tert*-butyl peak.

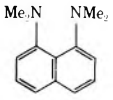
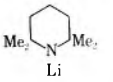
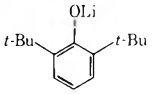
Deprotonation of the Ketiminium Salts. Our initial studies were directed toward deprotonation of iminium salt **7a**. A wide variety of previously and currently fashionable bases were tried and the results of these attempts are summarized in Table I. All deprotonations were carried out in an atmosphere of dry nitrogen at the indicated temperature. The reactions, following appropriate work-up, were analyzed by NMR spectroscopy. Most of the bases produced the desired aziridine. In most cases, however, the dealkylation product **5a** was present in relatively large amounts. Only in the case of sodium bis(trimethylsilyl)amide (**10**) was the high (nearly quantitative) conversion to the desired aziridine (**11**) achieved.



10 **11**

Aziridine **11** was identified by its NMR spectrum and elemental analysis. The former showed the characteristic aziridine methylene two-proton singlet at δ 2.16 in addition to the ten aryl protons and nine *tert*-butyl hydrogens. This aziridine is relatively unstable toward a variety of reagents and conditions. For example, passage of **11** through a column of Florisil afforded a mixture of 1-*tert*-butylamino-2,2-diphenylethylene and diphenylacetaldehyde (Scheme I). The latter presumably is a hydrolysis product of the enamine and can be reconverted to the enamine with *tert*-butylamine. This apparent acid-catalyzed ring opening of

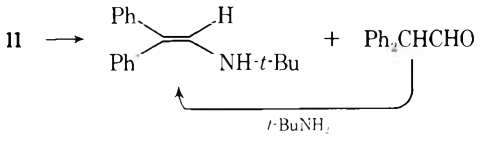
Table I
Aziridine:Imine (11:5a) Distribution Obtained from the Reaction of [Ph_2C=N(Me)*t*-Bu](OSO$_2$F) (7a) with Various Base–Solvent Combinations

Base	Ref	Solvent(s)	T_0[a]	11:5a[b]
n-BuLi		Ether–hexane	25	0[c]
	4	Ether	−78	*f*
	5	Ether–hexane	25	~0.7
		Ether–hexane	−78	1[d]
$NaCH_2S(O)Me$	6	DMSO[e]	25	2
KO-*t*-Bu	7	HMPA[e]	0	0.4
		Ether	−78	13
$KOCEt_3$	8	Xylene	25	13
$NaN(SiMe_3)_2$	9	SO_2	−78	0
(10)		DMSO[e]	25	11
		Ether	25	16
		Benzene	25	18
		Hexane	25	22

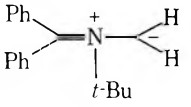
[a] Initial reaction temperature, °C. [b] Mole percent by NMR spectral assay. [c] Little, if any, 11 detected. [d] Recovered 70% of the iminium salt. [e] Homogeneous mixture. [f] No reaction.

11 has ample precedent and is apparently facilitated by the ability of the two phenyl groups to stabilize positive charge.[10]

Scheme I



Although all successful reactions were accompanied by a transient deep red color, attempts to trap intermediate 12 were unsuccessful. Norbornene, for example, failed to divert 12 from its ring closure to 11. Other dipolarophiles

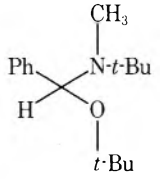


12

were either unreactive or consumed by the strongly basic conditions. Failure to trap the intermediate 1,3-dipole does not, of course, rule out its intermediacy.[11] The possible low steady-state concentration of 12 and the steric interference to cycloaddition posed by the two terminal phenyl groups could be expected to make trapping of the intermediates noncompetitive with ring closure.

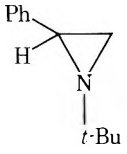
Attempted deprotonation of the other iminium salts (**7b** and **7c**) were less successful. Reaction between these salts and **10** did occur (as evidenced by the formation of FSO_3Na and formation of organic solvent soluble material). The NMR spectral analyses of the reaction mixtures in some cases showed peaks in the area expected for the products. In addition, however, sizable amounts of dealkylated imines and other products were also noted, even when the optimal conditions developed for **7a** were employed. Because of the poor yields, the apparent lability of these aziridines, and the similar physical properties of imine and aziridine, the aziridines were not separated from the reaction mixture. The reasons for the depressed aziridine yields from the iminium salts **7b** and **7c** are not clear. Presumably, the bulk of the *tert*-butyl group (either by direct effect on the reactive site or indirect effect via imposing conformations on the phenyl groups) is especially favorable toward deprotonation as opposed to dealkylations.

Deprotonation Studies of the Aldiminium Salts. Products from the attempted deprotonation of the aldiminium salts **8a** and **8b** were dependent on the nature of the base. Potassium *tert*-butoxide in ether resulted in addition to the iminium bond of **8a** to yield *tert*-butyl ether **13** in



13

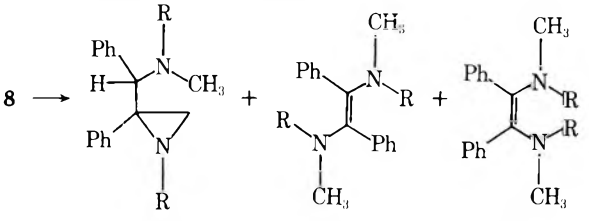
addition to dealkylation product and benzaldehyde. Comparison of the NMR spectrum of the crude reaction mixture with the spectrum of authentic[13] aziridine **14** revealed that **14** was not a component of the reaction mixture.



14

Treatment of the aldiminium salts **8a** and **8b** with **10** in benzene produced the unexpected results indicated in

Table II
Deprotonation of Aldiminium Salts



15 16 17

a, R = *t*-Bu	88[a,b]	11[a]	0[a]
b, R = CH_3	50[a]	25[a]	25[a]

[a] Product percentage. [b] Two diastereoisomers in ca. 5:1 ratio.

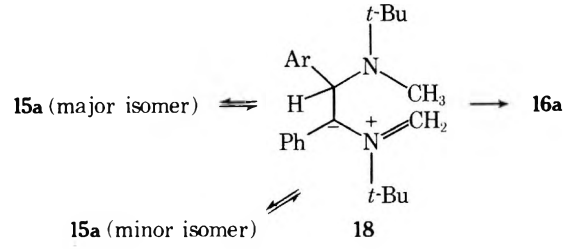
Table II. Neither salt yielded any isolable or spectrally detectable amounts of the desired aziridine **14.** Careful chromatography of the reaction mixture from **8a** yielded three isomers (as indicated by mass spectral and elementary analyses). Two of these were obviously closely related in structure and are assigned to the two diastereoisomers of **15a.** Each of the two diastereoisomers showed two *tert*-butyl groups, one methyl group, and ten aromatic protons in their NMR spectra. Both isomers showed a pair of doublets with chemical shifts and coupling constants in agreement with the assigned aziridine methylene group. In addition, both isomers showed a single unsplit methine proton. Neither isomer showed NH or imine peaks in their infrared spectra.[14]

The corresponding aziridines (**15b**) from **8b** could be detected spectrally but were too unstable to withstand chromotographic separation. Two other components were isolated and shown to be identical with the mixture of *E*- and *Z* diaminostilbenes **16b** and **17b** which had previously been prepared in a condensation reaction by Scheeren and van Helvoort.[15]

We assigned structure **17b** to the isomer with the more shielded methyl groups based on the assumption that two cis phenyl groups could not be coplanar with the double bond and in the resultant nonplanar conformation would effectively shield the methyl groups. The more deshielded methyl groups would thus correspond to the structure **16b** where the methyl groups could lie in the plane of the π system. In agreement with these assignments, **8a** produces only one (presumably less sterically crowded) isomer, **16a**. The chemical shift of the methyl group in this isomer corresponds closely to those assigned to **16b**.

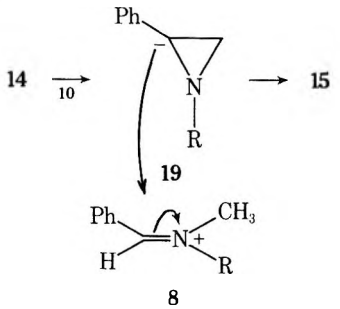
Further support for these assigned structures was found in the thermal chemistry of the two isomers of **15a**. Upon heating at 250°, both pure isomers produced mixtures which consisted of **16a** along with lesser amounts of the two diastereoisomers of **15a**. This process can be envisioned as an electrocyclic ring opening of aziridine **15a** to give 1,3-dipolar intermediate **18**. This intermediate can easily return to a mixture of the two isomers of **15a** or undergo 1,4-suprafacial hydrogen shift to **16a** (Scheme II).

Scheme II



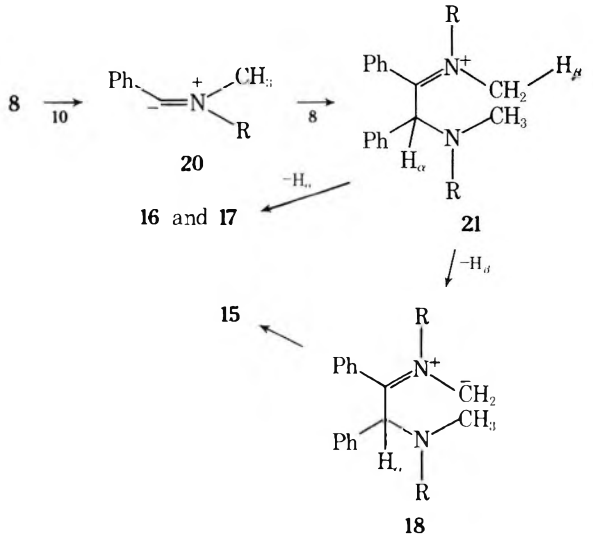
Several routes may be envisioned to explain the formation of **15–17**. It is, of course, possible that the desired aziridine **14** was produced in the reaction, deprotonated, and the resultant anion **19** attacked **8a** thereby yielding **15** (Scheme III). In order to test this hypothesis the reaction

Scheme III



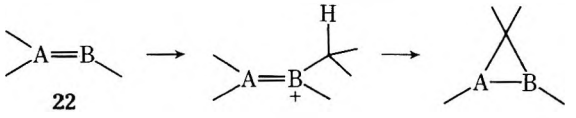
of **8a** with **10** was carried out in the presence of added authentic **14**. Upon completion of the reaction products **15–17** were again detected along with unchanged **14**. We conclude from this result (and the previously described product distributions) that aziridine **14** was neither produced nor consumed during this reaction. A second alternative is that depicted in Scheme IV. According to this alternative, the strong base removes a vinyl proton from **8** to produce intermediate **20**. The acidity of this vinyl hydrogen adjacent to a positively charged nitrogen is not surprising.[16] Attack of **20** on another molecule of **8a** would yield intermediate **21**. This intermediate has two acidic protons, H_α and H_β. Loss of H_β would yield 1,3-dipole **18**, which could, as previously mentioned, undergo ring closure to yield **15**. Loss of H_α would yield **16** and **17** directly. Although H_α is presumably the more acidic proton, it is also a sterically hindered proton. In agreement with the role of steric factors in the deprotonation of **21**, it is interesting to note that **21b** loses approximately equal amounts of H_α and H_β whereas **21a** prefers H_β to H_α by a factor of approximately 8:1. Alternatively, **16** and **17** could arise via 1,4-suprafacial shift indirectly via **18**.[17]

Scheme IV



Conclusions

The techniques for alkylation of imines and subsequent deprotonation described herein do not yet appear to constitute a general route to aziridines. Further work is needed (and in progress) to delineate the source of the limitations and hopefully to expand the reaction's scope. Application of this approach to related heterounsaturated systems (general formula **22**) also appears possible and a promising



route to a variety of heterocycles. Finally, the synthetic applications and chemistry of **20** and related ylides warrant additional investigation.

Registry No.—**5a,** 27126-13-2; **5b,** 13280-16-5; **5c,** 574-45-8; **6a,** 6852-58-0; **6b,** 622-29-7; **7a,** 55103-11-2; **7b,** 55103-12-3; **7c,** 55103-14-5; **8a,** 55103-16-7; **8b,** 55103-17-8; **9,** 55103-18-9; **10,** 1070-89-9; **11,** 55103-19-0; **13,** 55103-20-3; **14,** 18366-49-9; **15a** isomer 1, 55103-22-5; **15a** isomer 2, 55103-23-6; **15b,** 55103-21-4; **16a,** 55103-24-7; **16b,** 55103-25-8; **17b,** 55103-26-9; methyl fluorosulfonate, 421-20-5; *N*-(benzhydrylidene)methyl-*tert*-butylaminium triflate, 55103-27-0; 1-*tert*-butylamino-2,2-diphenylethylene, 55103-28-1; diphenylacetaldehyde, 947-91-1; *tert*-butylamine, 75-64-9; *N*-methyl-*N*-*tert*-butylbenzamide, 49690-12-2; *tert*-butylamine hydrochloride, 10017-37-5; benzoyl chloride, 98-88-4; hexamethyldisilazane, 999-97-3.

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EXPERIMENTAL SECTION

Melting points were determined with a Thomas-Hoover Unimelt capillary melting point apparatus and are uncorrected. Infrared spectra were recorded with a Perkin-Elmer Model 137 spectrometer. Nuclear magnetic resonance (nmr) spectra were recorded on a 60 MHz Varian Associates A-60A high-resolution spectrometer at a sweep width of 500 Hz. Chemical shifts (δ) are reported in parts per million downfield from internal tetramethylsilane standard. Low-resolution mass spectra were measured on either an Hitachi Perkin-Elmer RMU-6E spectrometer or an AEI-MS-30 double-beam instrument. Microanalyses were performed by Atlantic Microlab, Inc., Atlanta, Georgia.

Except as noted, the syntheses, isolations and reactions of moisture-sensitive compounds were effected in a Labconco (Kansas City, Missouri) fiberglass drybox purged with dry nitrogen and equipped with an aspirator for suction filtration.

Ketimines 5a[19], 5b[19] and 5c[20] were prepared by the method of Moretti and Torre.[19] Aldimines 6a[21] and 6b[22] were formed from the corresponding amine and benzaldehyde. Molecular seives (4A) were used to remove water during the reaction.

General Procedure for the Preparation of the Ketiminium Salts. A 500-ml round-bottomed flask was equipped with a magnetic stirrer, placed in a drybox, and charged with the appropriate ketimine (5, 0.05-0.08 mol) and dry solvent. The flask was immersed in a Dry Ice-acetone bath and treated with approximately two equivalents of the appropriate alkylating agent. The cold bath was removed, and the system was stirred overnight at ambient temperature. The ketiminium salts thus prepared were collected by suction filtration in the drybox, washed with ether, dried, and weighed.

N-(Benzhydrylidene)methyl-tert-butylaminium Fluorosulfonate (7a). The general alkylation procedure was carried out with a mixture of N-(benzhydrylidene)tert-butylamine (5a, 11.87 g, 50.0 mmol), methyl fluorosulfonate (10.6 g, 7.5 ml, 93 mmole), and anhydrous ether (75 ml). The crude N-(benzhydrylidene)methyl-tert-butylaminium fluorosulfonate (7a, 16.95 g, 97%) melted with decomposition at 125°. Three recrystallizations from absolute ethanol produced the analytical sample of 7a: mp 128-128.5° dec; ir (Nujol) ν1590, 1290, 1180, 1080 cm^{-1}; nmr (SO_2) δ1.58 (singlet, 9H, tert-butyl), 3.78 (singlet, 3H, NCH_3), 7.2-7.8 (multiplet, 10H, aromatic); mass spectrum (15eV) m/e 41, 56 (base), 118, 194, 195; (70eV) m/e 77, 118 (base), 194, 195 (P^+ 351 unobsd).

Anal. Calcd for $C_{18}H_{22}FNO_3S$: C, 61.51; H, 6.31; N, 3.99. Found: C, 61.40; H, 6.39; N, 4.02.

N-(Benzhydrylidene)methyl-tert-butylaminium Triflate. This compound was prepared by a modification of the general alkylation procedure. Into a 25-ml round-bottomed flask equipped with a magnetic stirrer was placed N-(benzhydrylidene)tert-butylamine (5a, 2.85 g, 12 mmol) and dry chloroform (10 ml). The solution was stirred in an atmosphere of nitrogen, cooled to 0°, and treated with methyl triflate (1.97 g, 2.00 ml, 12 mmol). The opaque mixture was stirred at room temperature for 4.5 hours, and then concentrated in vacuo. Trituration of the residue with anhydrous ether produced a solid, which was collected by filtration, washed with ether, and dried. The crude N-(benzhydrylidene)-methyl-tert-butylaminium triflate was isolated in quantitative yield. It melted with decomposition at 113°. Two recrystallizations from ethanol-ether afforded the analytical sample: mp 114-115.5° dec; nmr (DMSO-d_6) δ1.48 (singlet, 9H, tert-butyl), 3.68 (singlet, 3H, NCH_3), 7.58 (ca. singlet, ca. 10H, aromatic).

Anal. Calcd for $C_{19}H_{22}F_3NO_3S$: C, 56.84; H, 5.52; N, 3.49. Found: C, 56.75; H, 5.60; N, 3.48.

N-(Benzhydrylidene)dimethylaminium Fluorosulfonate (7b). The general alkylation procedure was carried out with a mixture of N-(benzhydrylidene)methylamine (5b, 15.6 g, 80 mmol), methyl fluorosulfonate (17.0 g, 12.0 ml, 150 mmol), and ether (200 ml). Additional ether (150 ml) was added after the mixture had warmed to ambient temperature, to facilitate stirring. The usual work-up afforded N-(benzhydrylidene)dimethylaminium fluorosulfonate (7b, 24.6 g, 100%) as a white powder, which melted at 131-142°. Nmr (SO_2) δ3.86 (singlet, 6H, CH_3), 7.6-7.9 (multiplet, 10H, aromatic).

N-(Benzhydrylidene)methylanilinium Fluorosulfonate (7c). The general alkylation procedure was applied to the synthesis of salt 7c, starting with N-(benzhydrylidene)aniline (5c, 12.87 g, 50.0 mmol), methyl fluorosulfonate (10.6 g, 7.5 ml, 93 mmol), and ether (125 ml). Ketimine 5c was found to be relatively insoluble in ether at -78°, but the alkylation proceeded in the usual fashion. The crude N-(benzhydrylidene)methylanilinium fluorosulfonate (7c, 17.79 g, 96%) was obtained as a pale yellow powder: mp 215.5-220°; nmr (SO_2) δ4.22 (singlet, 3H, CH_3), 7.33 (ca. singlet, 5H, aromatic), 7.51 (ca. singlet, 5H, aromatic), 7.73 (singlet, 5H, aromatic).

Pyrolysis of N-(Benzhydrylidene)methyl-tert-butylaminium Triflate. N-(Benzhydrylidene)methyliminium Triflate (9). N-(Benzhydrylidene)-methyl-tert-butylaminium triflate (2.01 g, 5.0 mmol) was placed in a 2x20-cm Pyrex pyrolysis tube equipped for quantitating gas evolution. The tube was evacuated, filled with dry nitrogen, and heated with an oil bath at about 130°, until the volume of collected gas (98 ml, ca. 90% of the theoretical amount of isobutene) remained constant. Upon cooling, the melt solidified. The pyrolysis tube was cracked open and the crude N-(benzhydrylidene)methyliminium triflate (9) was recovered in quantitative yield: mp 108-110°; nmr (DMSO-d_6) δ3.47 (singlet, ca. 3H, CH_3), 7.70 (ca. singlet, ca. 10H, aromatic).

General Procedure for the Preparation of the Aldiminium Salts (8). All operations were performed in a drybox. Into an oven-dried flask equipped with a magnetic stirrer was placed a solution of the appropriate aldimine (6) in anhydrous ether. The flask was immersed in a Dry Ice-acetone bath, and to it was added (with stirring) methyl fluorosulfonate (1.8 equivalents). The cold bath was removed, and the mixture was allowed to stir overnight at ambient temperature. The aldiminium salt was then collected by filtration, washed with ether, dried, weighed, and stored in the drybox.

N-(Benzylidene)methyl-tert-butylaminium Fluorosulfonate (8a). The general alkylation procedure was followed with N-(benzylidene)-tert-butylamine (6a, 32.3 g, 0.200 mol), methyl fluorosulfonate (42.4 g, 30 ml, 0.37 mol), and ether (200 ml), in a 500-ml round-bottomed flask. The thick, white precipitate that resulted was allowed to warm to ambient temperature, and diluted with ether (100 ml) to facilitate stirring. The usual work-up afforded crude N-(benzylidene)methyl-tert-butylaminium fluorosulfonate (8a, 54.7 g, 99%) as a white powder which melted at ca. 154-173°. Nmr (SO_2): δ1.73 (singlet, 9H, tert-butyl), 3.83 (doublet, J=ca. 1.0 Hz, 3H, NCH_3), 7.6-8.1 (multiplet, 5H, aromatic), 9.03 (broad pseudosinglet, 1H, N=CH).

N-(Benzylidene)dimethylaminium Fluorosulfonate (8b). Aldiminium salt 8b was prepared in an inert atmosphere, but not in a drybox as per the general procedure. An oven-dried 500-ml three-necked round-bottomed flask was equipped with a gas inlet, drying tube, and magnetic stirrer. The flask was charged with N-(benzylidene)-methylamine (8b, 11.9 g, 0.100 mol) and anhydrous ether (100 ml), cooled with an ice bath, and purged with dry nitrogen. At 0°, methyl fluorosulfonate (21 g, 15 ml, 0.18 mol) was added, and the immediate, white precipitate was treated with additional ether (100 ml) to facilitate stirring. The thick mixture was stirred at 0° for one hour and then transferred to a drybox, where it was filtered, washed with ether, and dried. The crude N-(benzylidene)dimethylaminium fluorosulfonate (8b) was isolated as a white powder (22.3 g, 96%) which melted at 80-88.5° (sealed capillary). Nmr (SO_2) showed δ3.88 (doublet, J=ca. 1.3 Hz, 3H, CH_3), 3.98 (doublet, J=ca. 1.0 Hz, 3H, CH_3), 7.6-8.1 (multiplet, 5H, aromatic), 8.9-9.0 (multiplet, 1H, N=CH).

Sodium Bis(trimethylsilyl)amide (10). Sodium bis(trimethylsilyl)-amide (10) was prepared by slight modification of the method of Krüger and Niederprüm.[9] A 500-ml round-bottomed flask was placed in a drybox and charged with sodium amide (MC/B, Practical Grade, 19.51 g, 0.500 mol), hexamethyldisilazane (PCR, Inc., 80.7 g, 104 ml, 0.500 mol), molecular sieves (4A, ca. 10 g), and dry benzene (250 ml). The flask was stoppered and removed from the drybox. The black mixture was refluxed for four days, returned to the drybox, and filtered (hot) through Celite. The clear, colorless filtrate was evaporated to dryness in vacuo, first with a trapped water aspirator and then with a vacuum pump (ca. 0.03 mm). Precautions were taken to exclude moisture from the pure white powder. The sodium bis(trimethylsilyl)amide (10) was both weighed (81.02 g, 88%) and stored in the drybox.

Preparation and Titration of a Solution of Sodium Bis(trimethylsilyl)amide (10) in Benzene. A mixture of sodium bis(trimethylsilyl)-amide (10, 22.01 g, 0.120 mol) and molecular sieves (4A, ca. 5 g) was stirred in dry benzene (300 ml) in a drybox until all of the base had dissolved. The molecular sieves and any insoluble impurities were separated from the solution by filtration through Celite in the drybox. The filtrate was diluted with more benzene (100 ml) and the solution was stored in the drybox in an amber bottle.

The solution of 10 in benzene was assayed by carefully measuring three aliquots into 10-ml volumetric flasks, removing the flasks from the drybox, and quantitatively transferring their contents to three 100-ml round-bottomed flasks. Benzene was used to facilitate the transfer. The diluted aliquots were decomposed with distilled water (ca. 10 ml), and the resulting mixture was concentrated to dryness at reduced pressure. The residual sodium hydroxide was treated with distilled water (ca. 10 ml) and methyl red indicator (0.1% w/v in ethanol, 2 drops). In a typical assay, neutralization of the three samples required 25.9, 26.2, and 26.1 ml of standard 0.1000 M hydrochloric acid, indicating that the concentration of sodium bis(trimethylsilyl)amide in the benzene solution was 0.26 molar.

Treatment of 7a with Sodium Bis(trimethylsilyl)amide (10) in Hexane at 25° C. Purification of 1-tert-Butyl-2,2-diphenylaziridine (11). A mixture of N-(benzhydrylidene)methyl-tert-butylaminium fluorosulfonate (7a, 0.53 g, 1.5 mmol) and sodium bis(trimethylsilyl)amide (10, 0.29 g, 1.6 mmol) was stirred magnetically in a 25-ml round-bottomed flask, in a drybox. Hexane (10 ml) was added, and the mixture was stirred at ambient temperature for one hour. It was then removed from the drybox and filtered. The filtrate was concentrated in vacuo, and the residue was weighed (0.32 g) and then assayed by careful integration of its nmr spectrum. The relative distribution of 1-tert-butyl-2,2-diphenylaziridine (11), N-(benzhydrylidene)tert-butylamine (5a), and benzophenone was 215:1.0:1.3.[23]

The crude product from the reaction of 7a with NaN(SiMe$_3$)$_2$ in hexane was dissolved in carbon tetrachloride (10 ml) and applied to a 2.5x16-cm column of Fisher Adsorption Alumina (80-200 mesh), which was packed in 20-40° petroleum ether. The column was eluted with 150 ml of carbon tetrachloride, at which point a 25-ml fraction was collected. Concentration of the fraction in vacuo produced a clear, colorless oil which crystallized on standing. The solid (mp 50-52°) was dissolved in ether, and the ethereal solution was treated with anhydrous magnesium sulfate and activated charcoal, filtered, and evaporated in vacuo. The dried (40°/0.20 mm) analytical sample of 1-tert-butyl-2,2-diphenylaziridine (11) melted at 50-52.5° and analyzed as follows: nmr (CCl_4) δ0.88 (singlet, 9H, tert-butyl), 2.16 (singlet, 2H, methylene), 7.0-7.5 (multiplet, 10H, aromatic); mass spectrum (70eV) m/e 194, 195 (base), 236, 251 (P^+).

Anal. Calcd for $C_{18}H_{21}N$: C, 86.01; H, 8.42; N, 5.57. Found: C, 86.01; H, 8.44; N, 5.53.

Authentic 1-tert-Butylamino-2,2-diphenylethylene. Into a 250-ml round-bottomed flask equipped with a reflux condenser and heating mantle was placed diphenylacetaldehyde (19.6 g, 17.8 ml, 0.100 mol), tert-butylamine (14.6 g, 20 ml, 0.20 mol), molecular sieves (4A, ca. 10 g), and benzene (100 ml). The mixture was refluxed for two hours, and the resulting dark amber solution was cooled, treated with activated charcoal and anhydrous magnesium sulfate, and filtered through Celite. Concentration of the yellow filtrate in vacuo produced an oil, which was submitted to bulb-to-bulb distillation with a rotary evaporator (0.10 mm) and a Bunsen burner. The viscous, yellow distillate of 1-tert-butylamino-2,2-diphenylethylene (20.0 g, 80%) solidified on standing. It was recrystallized four times from absolute methanol to furnish the analytical sample of 31 as white crystals: mp 77-83°; nmr (CCl_4) δ1.18 (singlet, 9H, tert-butyl), 3.66 (broad doublet, J=13 Hz, 1H, NH, exchanges with D_2O), 6.54 (broad doublet, J=13 Hz, 1H, vinyl, collapses to a singlet with D_2O), 7.00 (ca. singlet, 5H, aromatic), 7.22 (ca. singlet, 5H, aromatic).

Anal. Calcd for $C_{18}H_{21}N$: C, 86.01; H, 8.42; N, 5.57. Found: C, 85.88; H, 8.45; N, 5.61.

Treatment of 1-tert-Butyl-2,2-diphenylaziridine (11) with Florisil. 1-tert-Butylamino-2,2-diphenylethylene. A solution of crude 1-tert-butyl-2,2-diphenylaziridine (11, 0.50 g) in a mixed solvent of 20-40° petroleum ether and benzene (1:1, 10 ml) was applied to a 1.5x25-cm column of Florisil (Fisher, 100-200 mesh), packed in the same mixed solvent. The column was also eluted with the mixed solvent. The first 10-ml fraction that was eluted after the forerun was shown by nmr spectral comparison with authentic material to contain only 1-tert-butylamino-2,2-diphenylethylene (0.04 g). The concentrated, second 10-ml fraction consisted of a mixture (0.10 g) of enamine and diphenylacetaldehyde.

Attempting Trapping of the Ylide 12 with Norbornene. A 10-ml round-bottomed flask was placed in a drybox and charged with a mixture of N-(benzhydrylidene)methyl-tert-butylaminium fluorosulfonate (7a, 0.35 g, 1.0 mmol) and norbornene (0.94 g, 10 mmol). The mixture was stirred magnetically, and to it was added a solution of 0.26 M sodium bis(trimethylsilyl)amide (10) in benzene (5.5 ml, 1.4 mmol). The resulting slurry was stirred for one hour, and then filtered. Nmr spectral assay of the filtrate showed it to contain only the usual reaction product, 1-tert-butyl-2,2-diphenylaziridine (11), and unreacted norbornene.

Treatment of N-(Benzhydrylidene)dimethylaminium Fluorosulfonate (7b) with the Silylamide Base (10). A 300-ml round-bottomed flask was placed in a drybox and charged with N-(benzhydrylidene) dimethylaminium fluorosulfonate (7b, 9.28 g, 30 mmol). A solution of sodium bis(trimethylsilyl)amide (5.87 g, 32 mmol) in benzene (200 ml) was filtered onto the stirring salt. An immediate purple color developed, but it changed to brown during the 60-minute reaction time. Upon removal of the mixture from the drybox and exposure to the air, the mixture turned yellow. Filtration produced a clear, yellow solution, which darkened upon evaporation in vacuo at 35°. The residue was an amorphous, tan foam (6.26 g) whose nmr spectrum showed only broad, unidentified resonances.

Treatment of N-(Benzhydrylidene)methylanilinium Fluorosulfonate (7c) with the Silylamide Base (10). A 500-ml round-bottomed flask equipped with a magnetic stirrer was placed in a drybox and charged with N-(benzhydrylidene)methylanilinium fluorosulfonate (7c, 11.14 g, 30.0 mmol) and sodium bis(trimethylsilyl)-amide (5.87 g, 32.0 mmol). To the stirring solids was added dry benzene (250 ml). An immediate, persistent, deep red color developed. The mixture was stirred for one hour, removed from the drybox, and filtered. The filtrate was evaporated in vacuo (35°), and the dark red residue was treated with pentane at -78°. Evaporation of the pentane-soluble decantate produced a clear, dark amber syrup (6.46 g), whose nmr spectrum (CCl_4) showed a species with a prominent singlet at δ2.77. In addition, smaller amounts of N-(benzhydrylidene)aniline (5c), benzophenone, and N-methylaniline were indicated. Only the latter was recovered (in toto, ca. 5% by weight of the crude mixture) by extraction of the mixture with 1% aqueous perchloric acid, followed by basification (5% aqueous sodium bicarbonate) and extraction into carbon tetrachloride. The species which resonated at δ2.77 was not recovered by silica gel chromatography (Silica Gel G, E. Merck AG, 20-40° petroleum ether eluent). It could not be purified by distillation (0.15 mm) or by alumina column chromatography (e.g., 10% and 20% deactivated, benzene and 20-40° petroleum ether eluents).

Authentic N-Methyl-N-tert-butylbenzamide. A 25-ml round-bottomed flask equipped with a magnetic stirrer was charged with methyl-tert-butylamine hydrochloride[24] (1.24 g, 0.010 mol). The solid was stirred and cooled with an ice bath, and to it was added benzoyl chloride (Eastman, 1.57 g, 1.3 ml, 0.011 mol) and 10% aqueous sodium hydroxide (8 ml, 0.020 mol). After stirring for five minutes, the mixture was extracted with carbon tetrachloride. The organic extract was washed with water and saturated sodium chloride, dried with anhydrous magnesium sulfate, and concentrated in vacuo. The off-white residue (3.35 g) was freed of unreacted benzoyl chloride by washing with cold pentane. The crude N-methyl-N-tert-butylbenzamide (0.98 g, 51%) melted at 60-65°. Two recrystallizations from hot pentane afforded the analytical sample: mp 80-82°; ir (KBr) ν1625 cm^{-1}; nmr (CCl_4) δ1.42 (singlet, 9H, tert-butyl), 2.75 (singlet, 3H, NCH_3), 7.1-7.4 (multiplet, 5H, aromatic); mass spectrum (70eV) m/e 77, 105 (base), 106, 176, 191 (P^+).

Anal. Calcd for $C_{12}H_{17}NO$: C, 75.35; H, 8.96; N, 7.32. Found: C, 75.48; H, 9.00; N, 7.23.

Authentic 1-tert-Butyl-2-phenylaziridine (14). 1-tert-Butyl-2-phenylaziridine (14) was prepared according to the procedure of Moyer.[13] The compound exhibited the following nmr spectrum in carbon tetrachloride: δ0.96 (singlet, 9H, tert-butyl), 1.44 (d of doublets, 1H, H_{cis}), 1.73 (d of doublets, 1H, H_{trans}), 2.46 (d of doublets, 1H, benzyl), 7.0-7.3 (multiplet, 5H, aromatic).

Treatment of N-(Benzylidene)methyl-tert-butylaminium Fluorosulfonate (8a) with Potassium tert-Butoxide. Isolation and Purification of Aminoether 13. N-(Benzylidene)methyl-tert-butylaminium fluorosulfonate (8a, 13.77 g, 50 mmol) was placed in a 500-ml round-bottomed flask in a drybox. The flask was immersed in a Dry Ice-acetone bath, and to salt 8a was added, with magnetic stirring, potassium tert-butoxide (5.83 g, 52 mmol) and anhydrous ether (300 ml). The cold bath was removed, and the pale yellow slurry was stirred for one hour. The mixture was then filtered through Celite, and the filtrate was removed from the drybox and evaporated in vacuo. The residue thus obtained was a clear, viscous, yellow oil (5.73 g) whose nmr spectrum indicated (vide infra) a product distribution of aminoether (8b):aldimine (6a): PhCHO:dimers (15a and 16a)::80:12:5:3 mol-%.

The crude mixture was distilled at reduced pressure (0.05 mm) and the fraction which boiled at 123-125° (0.98 g) was redistilled. The second distillation afforded the analytical sample of aminoether 8a: bp 73°/0.01 mm; nmr (CCl_4) δ1.15 (singlet, 9H, tert-butyl), 1.23 (singlet, 9H, tert-butyl), 2.21 (singlet, 3H, NCH_3), 5.65 (singlet, 1H, benzyl), 7.0-7.6 (multiplet, 5H, aromatic); mass spectrum (70eV) m/e 59 (base), 72, 77, 105, 106 (P^+ 249 unobsd).

Anal. Calcd for $C_{16}H_{27}NO$: C, 77.05; H, 10.91; N, 5.62. Found: C, 77.02; H, 10.95; N, 5.64.

Decomposition of Aminoether 13 with Deuterium Oxide. Deuterium oxide (MSD of Canada, Ltd., min 99.7 atom-% D, one drop) was added

to aminoether 13 in carbon tetrachloride. There was no spectral evidence for reaction within IS minutes of the addition. However, it was shown by integralinq the singlets at δ5.58 (13, benzyl) and 9.95 (PhCHO) that about half of the aminoether had decomposed after four hours. Complete decomposition of 13 was accomplished overnight. The reaction products, which were produced in equimolar quantities, were benzaldehyde, tcrt-butyl deuteroxide (t-BuOD), and the deuterated amine ON(Me)t-Bu. These products were identified by spiking the mixture with authentic samples, and noting their equivalence in th.. nmr spectrum.

Decomposition of Aminoether 13 with Aqueous Base. A mixture of aminoether 13 (1.00 g, 4.0 mlnol) and 10% aqueous sodium hydroxide (24 ml, 4 mmol) was stirred magnetically in a 1.5x15-cm test tube. Benzoyl chloride (0.62 'I, 0.51 ml, 4.4 mmol) was added, and the turbid, white mixture was stirred for five minutes. The system was extracted with carbon tetraChloride, and the organic e"tract WIS washed with saturated sodium Chloride, dried with molecular sieves (4A), and evaporated in vacuo. The crude N-methyl-N-tert-butylbenzamide (0.12 g, 42%) was recrystallized from hot pentane, and the purified amide was found to melt at 79-81°. Its mixture meltinq point with an "uthentic sample was not depressed.

Treatment of N-(Benzylidene)methyl-tert-butylaminiUlll Fluorosulfonate (8a) with Sodium Bis(trimethylsilyl)amide (10). Isolation and Purification of Diaminostilbene 16a and the Major and Minor AminolIIethylaziridine Isomers (15a). A lOCO-ml round-bottomed flask was placed in a drybox and charged with sodium bis(trimethylsilyl)amide (10, 22.01 g, 120 mlnol) and dry benzene (460 ml). The system was stirred magnetically until solution was effected, at which time N-(benzylide"e)methyl-tert-butylami"ium fluorosulfonate (8a, 16.52 'I' 60.0 mmol) was added. An immediate, intense yellow color was produced, but it lightened appreciably within five minutes after the addition of 8a. The slurry was stirred for one hour, removed from the drybox, and filtered. The filtrate was evaporated at reduced pressure, and the residue was treated with hexane, activllted charcoal, and anhydrous magnesium sulfate. The mixture was filtered, and the filtrate was concentrated in vacuo. The runr spectrum (benzene-d_6) of the resulting dark oil (1).77'1) indicated (vide infra) the presence of the diaminostilbenc 16a and the major and minor isomers of the aminomethylaziridine 15, in the approximate ratio of 1.0: 6.7:1.1. Also present were smaller amounts of N-(benzylidene)-tert-butylamine (6a) and several unidentified silylated species (1-6 Hz downfield from TMS).

A filtered solution of the crude product mixture (12.88 g) in benzene (100 ml) was chromatographed on a 2.5x65-cm column of silica gel (Baker, 60-200 mesh) packed in 10_60° petroleum ether. The column was eluted initially with benzene. The first six 10-ml fractions were cocnbined and concentrated in vacuo to produce the crude diaminostilbene (16a) as a yellow powder. Recrystallization of the material from 95% ethanol, followed by sublimation (95-100°/0.025 mm), afforded the analytical sample of α,α'-bis(methyl-tert-butylamino)stilbene, 16a: mp 109.5-114.5°; nmr (CCl_4) δ0.91 (singlet, 18H, tert-butyl), 2.35 (singlet, 6H, NCH)}, 7.0-7.5 (multipl.et, 10H, aromatic); mass spectrum (70eV) m/e 41 (base), 69, 149 (p+ ISI unobsd).

Anal. Calcd for $C_{24}H_{34}N_2$: C, 82.2); H, 9.78: N, 7.99. C, 81.96: H, 9.86; N, 8.01.

An additional 40-ml fraction was eluted from the column, and was shown by tlc analysis (ben'Zene eluent) to contain a mixture of the di1lminostilbene 16a (R_f 0.7) and the major aminomethylaziridine isomer (R_f 0.0-0.4). The next 100-ml fraction was evaporated in vacuo to afford the crude, major isomer of 15a (4.01 g) as a pale yellow powder. The material was purified by rec:rystallization from 95% eth"nol, and SUblimed (95°/0.025 mm). The off-white sample of major-15a melted at 117_119°, and analyzed as follows: nmr (CCl_4) δ0.71 (singlet, 9H, tert-butyl), 0.89 (sinqlet, 9H, tert-butyl), 1.74 and 1.98 (doublets, J=1.4 Hz, 2H, methylene), 2.33 (singlet, ll!, NCH)), 4.48 (singlet, Ill, benzyl), 7.0-7.5 (multiplet, 10H, aromatic); mass spectrum (70eV) m/e 41, 42, 120, 176 (base), ISI (weak P J.

Anal. Calcd for $C_{24}H_{34}N_2$: C, 82.23; H, 9.78; N, 7.99. Found: C, 82.13; Il, 9.79: N, 8.06.

A final 150 m.l of benzene was eluted, and the column was flushed with methanol. The first lO-ml fraction of methanol was discarded. The next 250-ml fraction was evaporated in vacuo, and the residue was dissolved in carbon tetrachloride. The solution was washed with saturated sodium chloride, dried with anhydrous magnesium sulfate, and concentrated in vacuo. The crude minor aminomethylaziridine isomer was obtained as a viscous, amber oil (0.91 'I), which was crystallized at low temperature. The analytical sample of minor-15a, after recrystallization from 95% ethanol and sublimation (ca. 76°/0.025 mm), melted at 17.5-79°; nmr (CCl_4) 60.77 (singlet, 91l, tert-butyl), 0.8) (singlet, 9H, tert-butyl), 1.13 and 1.68 (doublets, J=1.4 Hz, 2H, methylene), 2.78 (singlet, lH, NCH_3), 4.13 (singlet, IH, benzyl), 7.0-7.5 (multiplet, lOll, aromatic); mass spectrum p OeV) m/e 57, 72, 119, 206 (base),)51 (weak p^+).

Anal. Calcd for $C_{24}H_{34}N_2$: C, 82.23: ll, 9.78; N, 7.99. Found, C, 82.10; ll, 9.82; N, 8.00.

pyrolyses of the Major and Minor Isomers of Aminomethylaziridine 15a A 1.7x90-mm melting point capillary tube was filled to a depth of about 15 mm with the major isomer of aminomethylaziridine 15a. The capillary tube was scaled, and then heated in a Thomas-Hoover Unimelt capillary meltinq point apparatus (ca. 10 deq/min). The sample was observed to melt at 114.5_117°; the melt qradually became yellow (ca. 200°1, and turned orange upon continued he3ting. When the oil bath had reached 250°, the capillary was withdrawn, cleaned with carbon tetrachloride, and cracked open. The section of the capillary which contained the orange melt waS inserted into an nmr sample tube, and carbon tetrachloride (ca. 0.5 I'll) and the tetramethylsilane standard were added. The nmr sample tube was capped and shaken to leach the melt from the broken capillary. The nmr spectrum of the reSUlting solution indicated that the predominant pyrolysis product of major-15a was the diaminostilbene 16a, in additio" to lesser amounts of the starting material and the minor isomer (8.6:1). These spoctral assignments were supported by tlcassay.

The pyrolysis was repeated with the minor isomer of aminomethylaziridine 15a. This compound melted at 77_80°, but showed the same color changes as d.id major-15a. The nmr spectrum of the melt also indicated that diaminostilbene 16 was the predominant pyrolysis product. Compound 16 was accompanied by smaller amounts of the starting isomer (minor-15a) and the major isomer (1:1.5).

Attempted Trapping with Norbornene. A 25-ml round-bottomed flask was placed in a drybox and charged with N-(benzylidene}methyl-tert-butylaminium fluorosulfonate (7a, 0.41 q, loS mmol), norbornene (lo41 q, 15 mmol) and dry benzene (5 I'll). was stirred magnetically, and to it was added a 0.26 M solution of sodium bis(tri..m,ethylsilyl)amide (10) in benzene (11.5 I'll, 1.0 mmol). The system was stirred at ambient temperature for one hour, removed from the drybox, and filtered through Celite. The filtrate was concentrated in vacuo (thereby removing any unreacted norbornene), and the resulting amber semisolid (0.45 g) was shown by runr spectral assay to contain only the usual re"ction products (vide supra).

Stability of l-tert-Butyl-2-phenylaziridine (14) to the DeprOtonation Conditions. l-tert-Butyl-2-phenylaziridine (14, ca. 75 mg) was diSSolved in benzene-d_6 (ca. 1 ml) in an runr sample tube. Sodium bis(trimethylsilyl)amide (10, ca. 100 mg) was then added. The mixture was shaken mechanically for one hour, "nd then treated with deuterium oxide (3 drops). The sample tube was shaken again and centrifu'led. The nmr spectrum of the organic layer indicated that nO deuterium exchange had taken place.

In a related experiment, a mixture of l-tert-butyl-2-phenylaziridine (14, 0.26 g, 1.5 mlnol) and a 0.26 M solution of sodium bis(trimethylsilyl)amide (10) in benzene (5.8 mI, 1.5 mmol) was stirred magnetically in a 10-ml round-bottomed flask, in a drybox. "fter one hour, N-(benzylidene)methyl-tert-butylaminium fluorosulfonate (8a, 0.41 'l, 1.5 mmol) was added. The slurry was stirred for an additional 60 minutes, removed from the drybox, and filtered. The filtrate was concentrated in vacuo to produc:e a clellr, dark amber liquid (0.57 'I), whose nmr spectrum indicated only the usual mixture of products (vide supra) and the intact I-tert-butyl-2-phenylaziridine (14).

Stability of the Major Isomer of Aminomethylaziridine 15a to Sodium Bi.s(trimethylsilyl)amide (10). ,\ 25-ml round-bottomed flask was placed in a drybox and charged with the 1Il"jor isomer of 15a (0.21 '1,0.60 mmol), sodium bis(trimethylsilyl)amide (10, 0.44 g, 2.4 mmol), and dry benzene (10 ml} The SOlution was stirred magnetically for one hour, removed from the drybox, and washed with water. The benzene layer was treated with activated charcoal and anhydrous magnesium sulfate, filtered, and concentrated in vacuo. The resulting pale yellow powder was shown by nmr spectroscopy to be the recovered aminomethylaziridine, major-15a (0.19 g,

Authentic 0.Il'-Bis(dimethylamino)stilbene Isomers (16b and 17bl. The mixture of E- and Z-isomers of compound (1Gb and 17b) was prepared from α-(dimethylamino)phenylacetonitrile[25] by a published procedure.15 The crude product mixture was shown by nmr spectroScopy to contain approximately equal amounts of the two isomers. Although the isomers were not separated, the mixture was purified by double distillation (l09-110°/0.025 mm) and two column chromatographies (fisher Alumina, Basic, Brockman Activity I, benzene eluentl. nmr (CCl_4), entgegen (16b) δ2.28 (singlet, 12H, Cll)), 7.18 (ca. 'singlet, lOll, aromatic); zusammen (17b) δ2.67 (singlet, 1211, CH_3), 6.88 (ca. singlet, 10H, aromatic).

Treatment of N-(Benzylideneldimethylaminium Fluorosulfonate (8b) with the Silylamide Base (10). A 200-ml round-bottomed flask was pl"ced in a drybox and charged with N-(benzylidene)dimethylaminium fluorosulfonate (8b, 3.50 g, 0.015 mol) and sodium bis(trimethylsilyl)amide (10, 5.50 g, 0.010 mol). To the stirring mixture was added dry benzene (1:5 ml) A brilliant orange color developed immediately, but it faded to y"llow within one minute after the rapid addition of benzene. The mixture was stirred at ambient temperature for one hour, removed from the drybox, and filtered through eelite. Concentration of the filtrate in vacuo produced a dark semisolid (4.43 'I) whose nmr spectrum (CCl_4) indicated the presence of the "minomethylaziridine 15b [δ2.02 and 2.13 (dOUblets, methyle"e), 2.20 (amino-CH)'S), 4.45 (singlet, benzyl)1, and about an equal amount of the diaminostilbene isomers 16b and 17b (ca. 1:1). In addition, there were many other unidentified reson"nceS present in the spectrum.

In a typical separation attempt, the crude product mixture was dissolved in benzene (15 ml) and applied to a 2x20-cm column of basic alumina (Fisher, Brockman Activity I, 80-200 mesh) packed in 30-60° petroleum ether. The first lorang",) 20-ml fraction of eluate was shown by runr spectroscopy to contain the mixture of the α,α'-bis{dirnethylamino)stilbene isomers (16b and 17b, 0.35 gl. The supposed aminolllethyl1lziridines 15b were not eluted from the column, even after flushing with methanol.

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(1) We wish to thank the National Science Foundation (Grant GP-17642) for partial support of this research.

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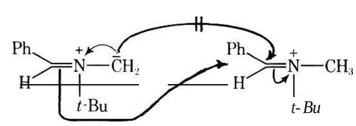

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Decomposition Reactions of Hydroxyalkylphosphorus Compounds. II. Reaction of Benzylbis(α-hydroxybenzyl)phosphine Oxide with Benzaldehyde Imines[1a]

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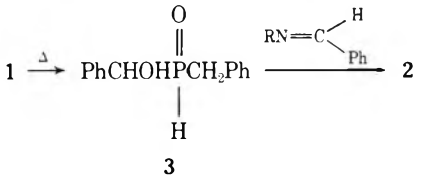
The reaction of benzylbis(α-hydroxybenzyl)phosphine oxide (1) with benzaldehyde imines produced the amino alcohols, $RNHCHPhP(=O)(CH_2Ph)CHOHPh$. If 2 mol of the imine are used then the diamine, $(RNHCHPh)_2P(=O)CH_2Ph$, resulted. For all of the benzaldehyde imines (RN=CHPh), even when R = *tert*-butyl, the reaction with 1 proceeded smoothly indicating that there was no steric hindrance. During decomposition, 1 must have lost benzaldehyde to form the secondary phosphine oxide $[PhCHOHP(=O)(H)CH_2Ph]$ since 1 itself could not react with the imines to form the amino alcohols. The role of the imine was confirmed when the *p*-tolualdehyde imine of benzylamine ($PhCH_2N=CHC_6H_4$-*p*-CH_3) was treated with 1. Only the amino alcohol having the *p*-tolyl group was obtained. The decomposition, which appeared to be temperature dependent, required reflux conditions in benzene. The ambient temperature experiments gave a quantitative recovery of 1.

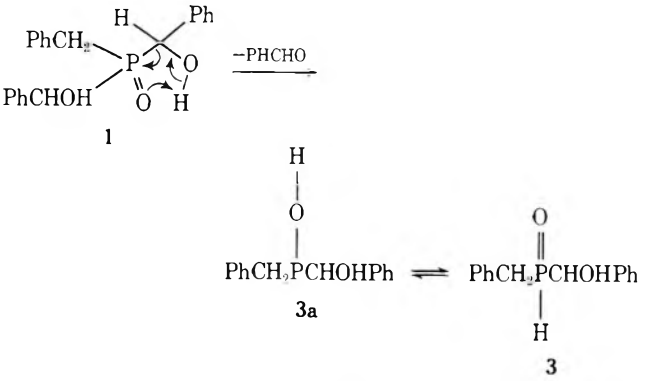
We have shown[2] that benzylbis(α-hydroxybenzyl)phosphine oxide (1) reacted with primary amines to form phosphorus amino alcohols [$RNHCHPhP(=O)(CH_2Ph)CHOHPh$, 2]. In a mechanism proposed for this reaction, 1 loses benzaldehyde to form a secondary phosphine oxide 3 which adds to the imine (formed from the free benzaldehyde and the amine) to produce 2. If this mechanism is operative, then 1, on decomposition through loss of benzaldehyde, should react with imines[3-6] to produce the amino alcohols.



Results and Discussion

Oxide 1 was treated with *N*-benzylidenebenzylamine (4) under several sets of conditions. Reaction occurred when the two were heated in refluxing benzene for 4 hr with or without catalysis by *p*-toluenesulfonic acid. The yield of 2 (R = benzyl) was higher without acid catalysis. In similar experiments at room temperature for extended times, recovery of 1 was quantitative. Subsequent reactions were conducted by heating equimolar amounts of 1 and the imine in benzene at reflux for 4 hr.

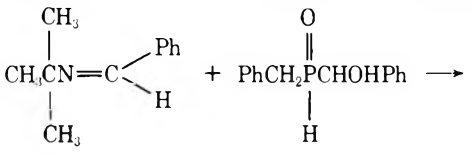
It is highly improbable that 1 combines with the imine, since tertiary phosphine oxides are notoriously poor phosphorus nucleophiles[7] and reaction, if it occurred, would involve oxygen attack on the carbon which would not yield the amino alcohol. These results indicate that decomposition, through loss of benzaldehyde, to form the secondary phosphine oxide 3 and subsequent addition of 3 to the imine is the operative mechanism. Possibly the imine base catalyzes the loss of benzaldehyde. However, imines are invariably weaker bases than the corresponding amines by as much as 5 pK units.[8] Base catalysis by the imine is unnecessary. Miller et al.[9] and Abramov et al.[10] demonstrated that α-hydroxyalkylphosphine oxides decompose on heating in the absence of acid or base to yield the carbonyl compound. Abramov[10] proposed a cyclic transition state for the decomposition of 1-hydroxyalkyl-1-phosphonate esters which is a reasonable pathway for decomposition of 1 to 3. While spectroscopic evidence shows that the phosphoryl structure, $R_2P(O)H$, is highly preferred for compounds of the type R_2POH, kinetic studies have shown that extremely low concentrations of the trivalent form, R_2POH, are present in the nucleophilic reactions of these types of compounds.[11] Thus while 3 and similar compounds will be referred to as "secondary phosphine oxides", it is postulated that, under neutral or acidic conditions, the reactive species is the trivalent phosphorus hydroxyl tautomer, R_2POH.



The imines of aromatic aldehydes are generally considered quite stable, being susceptible to hydrolysis only by aqueous mineral acids.[12] Thus it is highly improbable that decomposition of the imine to release the free amine is occurring under the conditions of reaction. Proof of this is afforded by the reaction of 1 with *N*-benzylidenemethylamine (5) in refluxing benzene. The reaction produced the amino alcohol (2, R = CH_3) in 73% yield with no evidence of evolution of methylamine. (The reaction of methylamine with 1 under refluxing benzene will not give the appropriate amino alcohol because of the low boiling point of the amine.) Prior preparation of the imine permits extension of the amino alcohol synthesis to low-boiling and gaseous amines. The reaction sequence was also successfully applied to cyclopropylamine.

We found[2] that reaction of 1 with primary amines did not yield any of the amino alcohol when the carbon adjacent to the nitrogen was tertiary. It was of interest to determine if steric inhibition existed in the reaction of 1 with imines possessing similar substitution. The imine of *tert*-butylamine and benzaldehyde [*N*-benzylidene-1,1-dimethylethylamine (6)] was prepared with some difficulty as water was not evolved until a catalytic amount of *p*-toluenesulfonic acid was added. Even then the formation of the imine was slow, taking 2–3 hr to reach completion. The reaction of 1 with 6 proceeded readily and 76% of the amino

alcohol 7 was obtained. These results indicated no steric inhibition of attack by the secondary phosphine oxide on 6.



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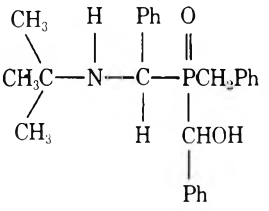

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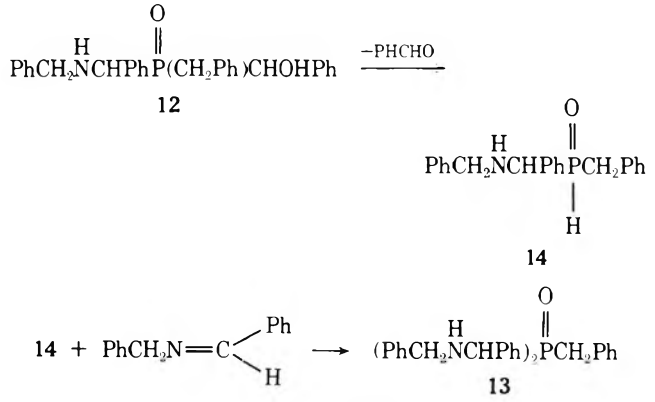
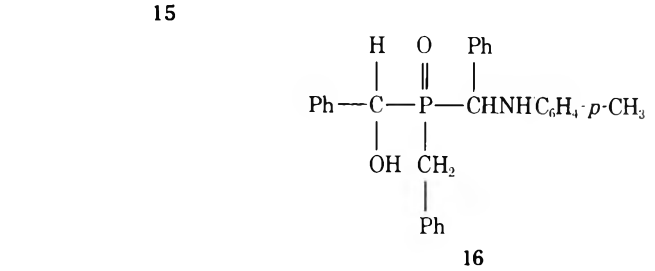
In the preparation of all the other imines used in this reaction sequence (see Table I) water evolution was rapid and complete in 2–15 min, with considerable heat evolution. Recovery of 1 from the reactions with *tert*-butyl- and *tert*-octylamine, as reported earlier,[2] was evidently due to steric difficulties in the formation of the imine. This difficulty was unexpected from reports in the literature.[5,13] Table I summarizes results from the reaction of 1 with several imines. Yields of product generally were higher from reactions of 1 with the imines than with the amine.[2] However, in both of the benzylamine examples, 12 and 13, yields were lower.

Oxide 1 reacted with 2 mol of *N*-benzylidenebenzylamine (4) to form the diamine 13. In this process 1 mol of benzaldehyde was lost from the amino alcohol 12 to form the secondary phosphine oxide 14, which adds to a second mole of the imine to form the diamine 13.



12 14 13

The role of the imine in the reaction was confirmed by the reaction of 1 with the *p*-tolualdehyde imine of benzylamine, 15. The only product isolated from this reaction was the amino alcohol 16, which has the *p*-tolyl group on the carbon α to phosphorus. The reaction of 1 with imines is



15 16

another demonstration[2,14] of decomposition of α-hydroxyalkylphosphine oxides through loss of the carbonyl function.

Table I
Products from the Reaction of 1 with Benzaldehyde Imines

R	Crude yield, %[a]	Recrystallizing solvent	Compd	Mp, °C
CH_3	73	Methanol–acetone–ethyl acetate	8	159–161
C_3H_5	49	Methanol–ether	9	172–173
$(CH_3)_3$	63	Methanol–ethyl acetate–acetone	7	160–161
$CH_3CH_2CH_2CH_2$	46	Acetone	10	146–148
Ph	75	Methanol–water	11	168–169
$PhCH_2$	61	Acetone	12	151–152
$PhCH_2$	43[b]	Methanol–water	13	145–147

[a] Based on the amino alcohol. [b] Based on the diamine since 2 mol of the imine were used.

Experimental Section

Reagent grade chemicals and solvents were used without further purification. Other chemicals and solvents were purified as stated. Benzene was dried for 24 hr or more over Linde molecular sieve 4A before use.

The ir spectra were taken on a Perkin-Elmer 137 with NaCl optics. Solid samples were run as KBr pellets using about 1% of the sample. The NMR spectra were taken on a Varian A-60A or Jeolco MH-60-II. Elemental analyses were performed by Enviro Analytical Laboratory, Knoxville, Tenn., and Galbraith Laboratories, Inc., Knoxville, Tenn. All melting points are uncorrected.

Benzylbis(σ-hydroxybenzyl)phosphine oxide (1) was prepared as described in the previous publication.[2]

Imine Preparation. All imines were prepared in essentially the same manner which consisted of mixing the neat liquid amine (where possible) and benzaldehyde together with rapid magnetic stirring. Heat evolution and water evolution were complete in a matter of minutes; the imine was taken up in CH_2Cl_2 or ether and the organic layer was separated and dried over Na_2SO_4. The solvent was removed in vacuo and the oily residue was vacuum distilled.

***N*-Benzylidenebenzylamine (4).** A mixture of 21.2 g (0.2 mol) of benzaldehyde and 21.43 g (0.2 mol) of benzylamine after reaction and work-up afforded 34.74 g (92% yield) of a colorless liquid, 4, bp 124° (0.5 mm), $n^{20}D$ 1.6014 (lit.[15] bp 116–117° (0.1 mm), $n^{20}D$ 1.6017). The ir spectrum of 4 showed a strong C=N absorption at 6.05 μ.

Benzyl(α-benzylaminobenzyl)(α'-hydroxybenzyl)phosphine Oxide (12). Treatment of 1 with 4 was carried out under five sets of conditions: (1) 3.33 mmol of each were stirred together in 30 ml of ethanol at room temperature for 24 hr; (2) same as 1 except one or two crystals of TsOH were added; (3) same as 1 except 30 ml of benzene was used; (4) 3.33 mmol of each were stirred together at 80° in 150 ml of refluxing benzene for 4 hr; and (5) 3.33 mmol of 1 was heated in 150 ml of refluxing benzene for 2 hr with a crystal of TsOH, then 3.33 mmol of 4 was added and reflux was resumed for 2 hr. Methods 1, 2, and 3 led to 100% recovery of starting material. Method 4 yielded 61% of 12 and 5 gave 20% of 12. Method 4 was used for the rest of the reactions of 1 with imines. Recrystallization of the product twice from acetone yielded white platelets, mp 151–152°. The infrared spectrum was identical with that of the higher melting amino alcohol already identified.[2]

***N*-Benzylidenemethylamine (5).** A mixture of 0.1 mol of methylamine (50.75 g of a 5.7% solution in benzene) and 0.1 mol of benzaldehyde afforded after reaction and work-up 9.39 g (80% yield) of a colorless, white liquid, 5: bp 40° (1.5 mm), $n^{20}D$ 1.5524 (lit.[16] $n^{20}D$ 1.5519). The ir spectrum of 5 showed the C=N absorption at 6.05 μ.

Benzyl(α-hydroxybenzyl)(α'-methylaminobenzyl)phosphine Oxide (8). A mixture of 3.52 g (10 mmol) of 1, 1.19 g (10 mmol) of 5, and 300 ml of dry benzene was refluxed for 4.5 hr. The benzene was removed in vacuo, the oily residue was dissolved in 200 ml of ether, and the solution was cooled in the freezer. The precipitate, which formed slowly, was collected over the next 3 months for a 73% yield. Recrystallization from methanol–acetone,

then methanol-acetone–ethyl acetate, yielded the analytical sample, **8**: mp 159–161°; ir (KBr) 2.95 (NH), 3.05, 3.13, and 3.24 (hydrogen bonded OH), 8.7 and 8.92 μ (P=O); an interpretable NMR spectrum of **8** could not be obtained owing to its poor solubility in the normal NMR solvents.

Anal. Calcd for $C_{22}H_{24}NO_2P$: C, 72.31; H, 6.62; N, 3.83; P, 8.48. Found: C, 72.40; H, 6.68; N, 3.72; P, 8.68.

***N*-Benzylidenecyclopropylamine (18).** A mixture of 70 mmol (4.0 g) of cyclopropylamine and 70 mmol (7.43 g) of benzaldehyde after reaction and work-up gave 6.86 g (68% yield) of a pale yellow liquid, **18**, bp 52–55° (1.5 mm), $n^{25}D$ 1.5728 (lit.[17] $n^{25}D$ 1.5728). The ir spectrum of **18** shows the C=N absorption at 6.09 μ.

Benzyl(α-cyclopropylaminobenzyl)(α′-hydroxybenzyl)-phosphine Oxide (9). A mixture of 3.52 g (10 mmol) of **1**, 1.45 g (10 mmol) of **18**, and 300 ml of dry benzene was refluxed for 4.5 hr. The benzene was removed in vacuo and the oily residue was dissolved in 300 ml of ether. No solid had formed after several days; so the oil was triturated with a mixture of ether–petroleum ether on the steam bath until most of the solvent had been removed and some solid had formed. Ether (150 ml) was added and the mixture was returned to the freezer. The solid which precipitated (1.94 g, 49% yield) had mp 160–162°. Recrystallization from methanol–ether afforded the analytical sample, **9**: mp 172–173°; ir (KBr) 3.0 (NH), 3.22 (hydrogen-bonded OH), 8.72 and 8.88 μ (P=O); an interpretable NMR spectrum could not be obtained owing to the low solubility of **9** in normal NMR solvents. The ir spectrum of **9** was identical with that of the same derivative (**12**) previously prepared in a different manner.[2] However, the melting point and carbon analysis of **12** were consistently low so the elemental analysis of **9** is reported.

Anal. Calcd for $C_{24}H_{26}NO_2P$: C, 73.64; H, 6.70; N, 3.58; P, 7.91. Found: C, 73.51; H, 6.82; N, 3.65; P, 7.82.

***N*-Benzylidene-1,1-dimethylethylamine (6).** Imine **6** was prepared in a slightly different manner than were the other primary amines. Benzaldehyde (10.6 g, 0.1 mol) was mixed vigorously with *tert*-butylamine (7.3 g, 0.1 mol) at room temperature for 30 min with no evolution of water or heat. A crystal of TsOH added to the mixture caused the solution to warm and water evolution was noticeable within 30 min. After reaction has proceeded for 3 hr, ether was added and the organic layer was extracted once with 5% Na_2CO_3. The ether layer was dried over Na_2SO_4, the solvent was removed in vacuo, and the oily residue was vacuum distilled to yield 12.19 g (76% yield) of a clear liquid, **6**, bp 48–50° (1.5 mm), $n^{20}D$ 1.5210 (lit.[18] $n^{20}D$ 1.5211). The ir spectrum of **6** showed the C=N absorption at 6.08 μ.

Benzyl(α-1,1-dimethylethylaminobenzyl)(α′-hydroxybenzyl)phosphine Oxide (7). A mixture of 3.52 g (10 mmol) of **1**, 1.61 g (10 mmol) of **6**, and 300 ml of benzene was refluxed for 4 hr. The benzene was removed in vacuo and the oily residue was dissolved in 300 ml of ether. Within 2 weeks, 2.54 g (63% yield) of white solid was collected, mp 146–151°. Two recrystallizations from methanol–ethyl acetate–acetone yielded the analytical sample, **7**: mp 160–161°; ir (KBr) 2.97 (NH), 3.15 (hydrogen-bonded OH), 3.32 (aliphatic CH), 8.71 μ (P=O); NMR ($CDCl_3$) δ 0.98 (s, 9 H, $(CH_3)_3C$), 2.85 (m, 2 H, PCH_2), 4.34–4.62 (m, 1 H, PCHN), 5.21 (d, J = 3 Hz, 0.6 H, PCHO), 5.57 (d, J = 11 Hz, 0.4 H, PCHO), 6.67–7.67 (m, 15 H, aromatics). The NMR spectrum showed **7** to be an isomeric mixture.

Anal. Calcd for $C_{25}H_{30}NO_2P$: C, 73.69; H, 7.42; N, 3.44; P, 7.60. Found: C, 73.70; H, 7.33; N, 3.37; P, 7.75.

***N*-Benzylidenebutylamine (19).** A mixture of 0.1 mol (7.31 g) of *n*-butylamine and 0.1 mol (10.6 g) of benzaldehyde gave after reaction and work-up 13.29 g (83% yield) of a clear liquid, **19**, bp 67°, (0.6 mm), $n^{20}D$ 1.5249 (lit.[16] $n^{20}D$ 1.5252). The ir spectrum of **19** showed the C=N absorption at 6.05 μ.

Benzyl(α-butylaminobenzyl)(α′-hydroxybenzyl)phosphine Oxide (10). A mixture of 3.52 g (10 mmol) of **1**, 1.61 g (10 mmol) of **19**, and 300 ml of benzene was refluxed for 4 hr. The benzene was removed in vacuo, the oily residue was taken up in ether, and the flask was put in the freezer. After several days no solid had formed; so the ether was removed with the addition of petroleum ether. Solid slowly began to precipitate and 1.88 g (46% yield) was collected which had mp 120–145°. Recrystallization from acetone gave the analytical sample, **10**: mp 146–148°; ir (KBr) 3.0 (shoulder, NH), 3.06, 3.15, and 3.22 (hydrogen-bonded OH), 3.35 (aliphatic CH), 8.68 μ (P=O); NMR ($CDCl_3$) δ 0.6–1.7 [m, 7 H, $CH_3(CH_2)_2$], 3.95 (d, J = 17.5 Hz, 0.5 H, PCHN), 4.06 (d, J = 7.5 Hz, 0.5 H, PCHN), 5.0 (d, J = 11 Hz, 0.5 H, PCHO), 5.13, (d, J = 8 Hz, 0.5 H, PCHO), 6.67–7.67 (m, 15 H, aromatics); the assignments were made on the D_2O-exchanged spectrum. In the earlier publication only one pure isomer was obtained.[2] The NMR spectrum showed **10** to be an equal mixture of two isomers; thus the elemental analysis is reported.

Anal. Calcd for $C_{25}H_{30}NO_2P$: C, 73.69; H, 7.42; N, 3.44; P, 7.60. Found: C, 73.46; H, 7.28; N, 3.26; P, 7.83.

Benzalaniline (17). Imine **17** was prepared by the method of Bigelow and Eatough[19] using 0.1 mol (10.6 g) of benzaldehyde and 0.1 mol (9.3 g) of aniline. The solid which formed was collected (17.07 g, 94% yield) and had mp 48–50°. One recrystallization of the light-yellow solid afforded pure **17**, mp 50–51° (lit.[20] mp 51°). The ir of **17** showed a strong C=N absorption at 6.08 μ.

Benzyl(α-anilinobenzyl)(α′-hydroxybenzyl)phosphine Oxide (11). A mixture of 3.52 g (10 mmol) of **1**, 1.81 g (10 mmol) of **17**, and 300 ml of benzene was refluxed for 4.5 hr. The benzene was removed in vacuo and the oily residue was dissolved in 200 ml of ether. Over a period of 4 weeks 3.18 g (75%) of white solid was collected. Two recrystallizations from methanol–water afforded the analytical sample, **11**: mp 168–169°; ir (KBr) 2.95 (NH), 3.15 and 3.25 (hydrogen-bonded OH), 6.25 and 6.67 (intense C=C), 8.7 and 8.9 μ (P=O); NMR (DMSO-d_6) δ 2.7–3.6 (m, 2 H, PCH_2), 4.6–5.5 (m, 2 H, PCHN and PCHO), 6.1–7.8 (m, 20 H, aromatics); the assignments were made after D_2O exchange. The ir of **11** prepared by the imine reaction was identical with that of the amino alcohol obtained in the amine reaction.[2]

Benzylbis(α-benzylaminobenzyl)phosphine Oxide (13). A mixture of 1.76 g (5 mmol) of **1**, 1.95 g (10 mmol) of **4**, and 200 ml of benzene was refluxed for 21 hr. The benzene was removed in vacuo and the resultant yellow oil was dissolved in 200 ml of ether. Within 2 weeks, 1.13 g (43% yield) of white solid was collected. Recrystallization twice from methanol–water afforded the analytical sample, **13**: mp 145–147°; ir (KBr) 3.02 (NH), 3.25 (aromatic CH), 3.49 (aliphatic CH), 8.59 and 8.67 μ (P=O); NMR ($CDCl_3$) δ 2.5–4.5 (m, 10 H, PCH_2, NCH_2, NH, PCHN), 6.9–7.6 (m, 25 H, aromatics), two protons were lost from the 2.5–4.5 region on D_2O exchange. There are significant differences between **13** and the same product formed in the primary amine reaction. The complexity of the NMR spectrum of **13** indicated an isomeric mixture while the NMR spectrum of the same compound, prepared by the primary amine reaction, afforded the meso isomer.[2]

Anal. Calcd for $C_{35}H_{35}N_2OP$: C, 79.22; H, 6.65; N, 5.28; P, 5.84. Found: C, 78.85; H, 6.67; N, 5.13; P, 6.08.

***N*-(*p*-Methylbenzylidene)benzylamine (15).** A mixture of 21.43 g (0.2 mol) of benzylamine and 23.6 g (0.2 mol) of *p*-tolualdehyde after reaction and work-up afforded 32.9 g of pale yellow liquid (79.5% yield) which hardened to a white solid on cooling, **15**, mp 27° (lit.[21] mp 27°). The ir spectrum of **15** shows the C=N absorption at 6.04 μ.

Benzyl(α-hydroxybenzyl)(α′-*p*-methylbenzylaminobenzyl)phosphine Oxide (16). A mixture of 3.52 g (10 mmol) of **1**, 2.07 g (10 mmol) of **15**, and 300 ml of benzene was refluxed for 4.5 hr. The benzene was removed in vacuo and the oily residue was dissolved in 300 ml of ether. The ether was allowed to evaporate slowly at ambient temperature. The solid which was collected (1.57 g, 35% yield) was recrystallized twice from acetone to afford long white needles as the analytical sample, **16**: mp 151–152; ir (KBr) 2.97 (NH), 3.22 (hydrogen-bonded OH), 8.7 and 8.88 μ (P=O); NMR ($CDCl_3$) δ 2.43 (broad s, 3 H, CH_3Ph), 2.6–4.4 (m, 5 H, PCH_2, NCH_2, PCHN), 4.9–5.5 (m, 1 H, PCHO), 6.9–7.6 (m, 19 H, aromatics). These assignments were made on the D_2O-exchanged spectrum since the NH and OH protons were spread along the base line and interferred with accurate integration. The methine proton on the carbon bonded to both phosphorus and oxygen appeared as two distinct, though broadened, doublets indicating an isomeric mixture in a 60:40 ratio. The isomeric mixture is also evidenced by the broadened singlet for the tolyl methyl group.

Anal. Calcd for $C_{29}H_{30}NO_2P$: C, 76.49; H, 6.64; N, 3.08; P, 6.80. Found: C, 76.46; H, 6.40; N, 3.14; P, 6.82.

Registry No.—**1**, 36871-68-8; **4**, 780-25-6; **5**, 622-29-7; **6**, 6852-58-0; **7**, 55133-75-0; **8**, 55133-76-1; **9**, 54617-90-2; **10**, 54617-86-6; **11**, 54617-97-9; **12**, 54617-83-3; **13**, 55176-53-9; **15**, 24431-15-0; **16**, 55133-77-2; **17**, 538-51-2; **18**, 3187-77-7; **19**, 1077-18-5; benzaldehyde, 100-52-7; benzylamine, 100-46-9; methylamine, 74-89-5; cyclopropylamine, 765-30-0; *tert*-butylamine, 75-64-9; *n*-butylamine, 109-73-9; *p*-tolualdehyde, 104-87-0.

References and Notes

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Decomposition Reactions of Hydroxyalkylphosphorus Compounds. III. Reaction of Benzylbis(α-hydroxybenzyl)phosphine Oxide with Benzaldehyde and *p*-Tolualdehyde[1a]

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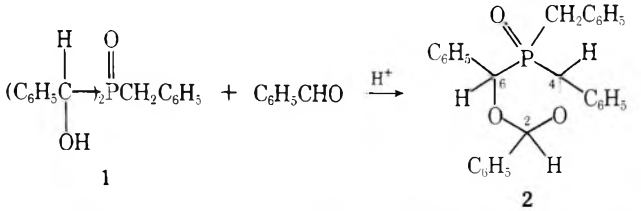
The reaction of benzylbis(α-hydroxybenzyl)phosphine oxide (**1**), a *dl*-diol, with benzaldehyde yielded both *dl* (**2a**) and meso (**2s**) cyclic acetals (5-benzyl-2,4,6-triphenyl-1,3,5-dioxaphosphorinane 5-oxides). The interconversion of **2a** and **2s** was found to occur with the equilibrium constant expressed as $K_{dl} = 3.8 \pm 0.4$. The mechanisms proposed for both of these reactions involve P–C bond cleavage between the oxygen-substituted carbon and phosphorus. The reaction of **1** with *p*-tolualdehyde afforded, as the only isolable product (15% yield), a meso cyclic acetal (**13**) which had *two* *p*-tolyl groups adjacent to phosphorus (5-benzyl-4,6-di-*p*-tolyl-2-phenyl-1,3,5-dioxaphosphorinane 5-oxide). The production of **13** required P–C bond cleavage twice and the loss of 2 mol of benzaldehyde from **1**.

Buckler has shown that the reaction of benzylbis(α-hydroxybenzyl)phosphine oxide (**1**) with benzaldehyde affords the cyclic acetal **2** as a mixture of isomers.[2] The isomers, when separated, had markedly different ir and NMR spectra and were identified from NMR spectra and symmetry considerations as one meso and one *dl* form.[3] Since the starting diol **1** was the *dl* form,[3] we studied the mechanism by which meso acetal was produced from *dl* diol.

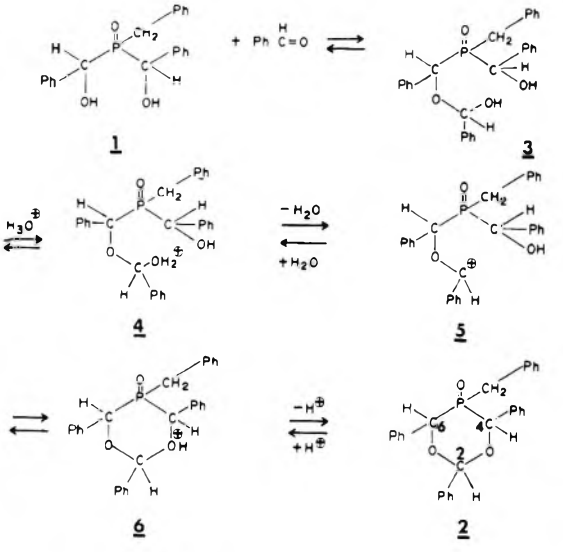


1 **2**

Results and Discussion

The expected mechanism for the formation of **2** is shown in Scheme I. Diol **1** plus benzaldehyde forms the intermediate hemiacetal **3**. It does not matter which carbon is involved, since in this step the absolute configuration at the carbon will be unchanged. This hemiacetal can be protonated at either of the two remaining hydroxyl groups. Elimination of water to form the carbonium ion and closure to the cyclic acetal **2** occurs readily. However, since the starting material **1** is the *dl* isomer and closure leads predominantly to the *dl* cyclic isomer, it follows that carbonium ion formation occurs predominantly at the carbon adjacent to the ether oxygen (**5**). This is as expected for carbonium ion stability, since the oxygen has free electron pairs capable of resonance stabilization of the carbonium ion while the phosphoryl group would destabilize the carbonium ion.

Scheme I
Mechanism for the Formation of the Cyclic Acetal 2

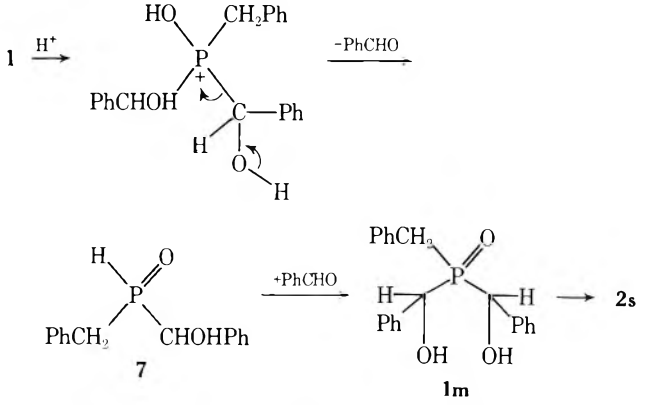


1 **3** **4** **5** **6** **2**

Therefore, the absolute configuration of the carbons adjacent to the phosphorus is not affected and the *dl* isomer is obtained.

The production of the meso isomer could occur by carbonium ion formation adjacent to the phosphorus. This would allow change of configuration at C-4 (or C-6) and produce the meso isomer. However, the large differences in relative carbonium ion stability (between C-2 and C-4 or C-6) make this possibility remote.

Another possibility, which seems more reasonable and for which there is precedent,[4] is the protonation of the phosphoryl oxygen with subsequent loss of benzaldehyde to form the secondary phosphine oxide, **7**. This could add to benzaldehyde[5] to form the meso diol **1m** (actually there are two meso forms of **1**[3]). The meso diol, on reaction with another mole of benzaldehyde, would form the meso acetal **2s**.



Decomposition of **1** through loss of benzaldehyde has already been demonstrated in a different type of reaction.[6,7]

Isomeric Stability. Only two isomers were obtained from the reaction, and since Eliel[8] has shown that the formation of 1,3-dioxanes yields thermodynamically controlled products, these isomers were probably the most thermodynamically stable of all the possible isomers. It is conceivable, therefore, that the meso acetal (**2s**) was formed from the *dl* acetal (**2a**) under the conditions of the reaction.

Each of the isomers was heated under reflux in benzene with a catalytic amount of *p*-toluenesulfonic acid. Aliquots were taken at prescribed intervals, the solid was recovered, and the NMR spectrum was obtained in $CDCl_3$. In this manner, it was possible to integrate directly the signals due to each isomer present. Within the limits of NMR detectability, only two isomers were observed as evidenced by the singlet at δ 6.25 for the *dl* form and the doublet at δ 6.02 for the meso form.[3] Since the other peaks of these two forms overlapped, only the signals for the protons at C-2 could be accurately integrated. The results of the equilibration of each isomer are shown in Table I.

The NMR study demonstrated that equilibrium is reached after 24–31 hr of heating in benzene under reflux with catalytic amounts of *p*-toluenesulfonic acid. An average of all the percentages, at equilibrium for both examples, yielded a value of 79.2% *dl* and 20.8% meso. The equilibrium constant for the interconversion can then be given by

$$K_{dl} = \frac{dl}{\text{meso}} = \frac{79.2}{20.8} = 3.8 \pm 0.4$$

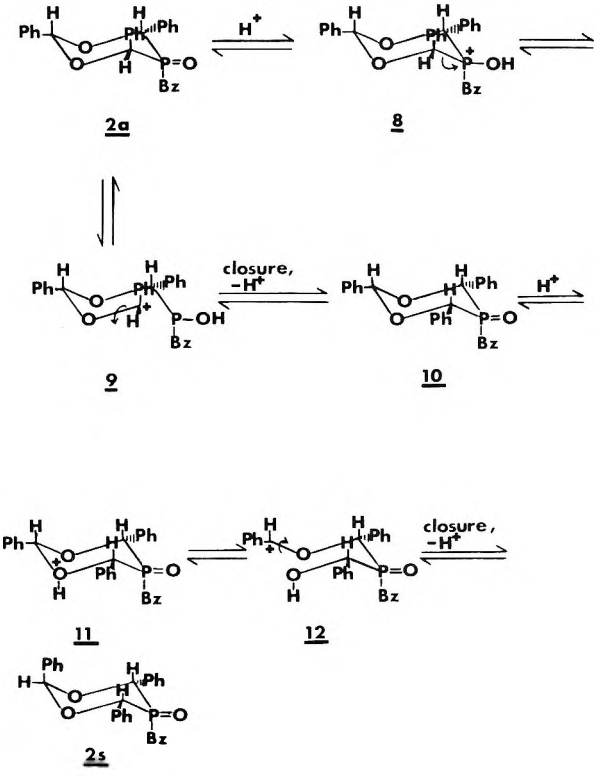
The error involved is expected to be within 10%.[9] Scheme II shows the probable mechanism for the interconversion of **2a** and **2s**.

The most basic oxygen in **2a**, the phosphoryl oxygen, is protonated to form **8**, which then ring opens with P–C bond cleavage to form the carbonium ion at C-4 (or C-6), **9**. The benzyl carbonium ion is further stabilized through delocalization of the charge by the oxygen lone pairs. The carbonium ion, being planar, can close in either of two ways, to reform **2a** or to form **10**, after the loss of a proton. The formation of **2s** from **10** occurs in the reverse of the acetal formation by bond cleavage at C-2. The phosphorus in **9** is shown in the trivalent form, which is the reactive species under acidic conditions.[6,7]

Table I
Isomeric Stability of Cyclic Acetal Isomers 2a and 2s

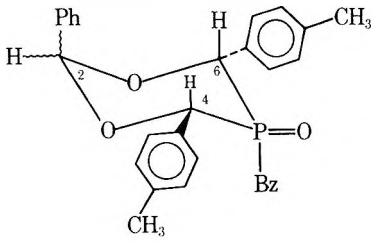
Hr of heating	Integration of singlet	Integration of doublet	% *dl*
	dl Isomer **2a**		
0	10.0		100
24	7.0	1.5	82
48	5.5	1.5	79
96	23.0	7.0	77
120	16.0	5.0	76
144	12.5	3.0	81
	Meso Isomer **2s**		
0		6.5	0
11	11.5	6.5	64
15	12.0	6.0	67
31	18.5	4.0	82
55	10.5	3.0	78

Scheme II
Equilibrium between 2a and 2s



Exchange Reactions. Oxide **1** was treated with *p*-tolualdehyde in an attempt to produce the cyclic acetal (or acetals) with the *p*-tolyl group at C-2. Another possible product from this reaction would be the exchange product wherein *p*-tolyl groups have replaced the phenyl groups in **1**. The procedure used was that described by Buckler[2] for the production of **2** from the reaction of **1** and benzaldehyde. The first solid isolated (15% yield) was an acetal

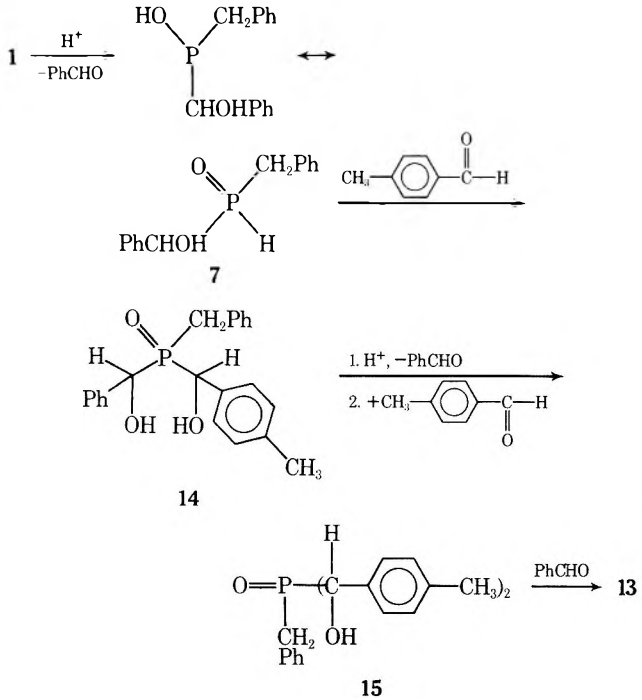
which contained *two* *p*-tolyl groups. The NMR spectrum of the product, **13**, exhibits a singlet for the tolyl methyl protons, a doublet (J = 15 Hz) for the benzyl methylene protons, and a doublet (J = 14 Hz) for the ring methine protons (at C_4 and C_6). The equivalence of the tolyl methyl groups can occur only if the *p*-tolyl groups are both adjacent to phosphorus, unless there is accidental chemical shift equivalence. However, as discussed earlier,[3] the simplicity of the NMR spectrum is diagnostic for the meso form and this requires both *p*-tolyl groups to be adjacent to phosphorus as any combination of *p*-tolyl and phenyl groups at C-4 and C-6 would yield a *dl* form. Nothing definitive can be said about the proton at C-2 as the signal is a broadened singlet which may indicate a small coupling to phosphorus. Using the reasoning developed earlier[3] for **2s**, the structure of **13** can be represented as below, where the configuration at C-2 is not designated.



13

The next solid collected (10% yield) was primarily a mixture of the *dl* diol and *dl* acetal as evidenced by its NMR spectrum, which showed exchangeable protons and at least two signals for the tolyl methyl groups. Eventually 11% of starting **1** was recovered while the rest of the reaction mixture remained as a viscous oil.

While **13** is not the major product of this reaction, its formation must arise from the loss of benzaldehyde from **1**. The loss of benzaldehyde leads to the formation of the secondary phosphine oxide **7**, which then reacts with *p*-tolualdehyde to form the mixed diol **14**. The mixed diol can lose benzaldehyde and react with *p*-tolualdehyde to form the diol **15**. The meso form of **15** would react with benzaldehyde to form **13**. It is not surprising that most of the reaction mixture could not be resolved, as the *dl* forms of **14** and the meso and *dl* forms of **15** can react with either benzaldehyde or *p*-tolualdehyde to form many different cyclic acetals.



In an attempted exchange reaction, **2a** was heated at 80° (refluxing benzene) with an equimolar quantity of *p*-tolualdehyde in the presence of a catalytic amount of *p*-toluenesulfonic acid. Fractional crystallization of the solid product yielded 75% of unchanged starting material while the filtrates afforded 13% of a solid which was identified as a mixture of acetals having an average of one *p*-tolyl group per acetal. These results further demonstrate the lability of these cyclic acetals, since they will exchange one aldehyde group for another.

Mechanistic Implications. The production of the *dl* and meso acetals (**2a** and **2s**, respectively) from the *dl* diol (**1**) revealed that some mechanism other than the classical acetal-forming mechanism (Scheme I) was involved. The interconversion of the acetals indicated one way in which **2s** was formed. The exchange of *p*-tolualdehyde for part of the benzaldehyde in **2a** showed that aldehyde exchange processes do occur. The isolation of the meso acetal **13** from the treatment of **1** with *p*-tolualdehyde demonstrated that benzaldehyde is being lost from **1**. Based on these results, we concluded that the meso acetal **2s** could be formed from the *dl* diol **1** through the intermediate formation of the secondary phosphine oxide **7**, which adds to free benzaldehyde to form the meso diol **1m**. Closure through the classical acetal mechanism affords the meso acetal **2s**. Previous observations[6,7] suggest that the loss of benzaldehyde from **1** might be thermally induced rather than acid catalyzed.

Experimental Section

Reagent grade chemicals and solvents were used without further purification. Other chemicals and solvents were purified as stated. Benzene was dried for 24 hr or more over Linde molecular sieve 4A[10] before use.

The ir spectra were taken on a Perkin-Elmer 137[10] with NaCl optics. Solid samples were run as KBr pellets using about 1% of the sample. The NMR spectra were taken on a Varian A-60A[10] or Jeolco MH-60-II.[10] Elemental analyses were performed by Enviro Analytical Laboratory, Knoxville, Tenn., and Galbraith Laboratories, Inc., Knoxville, Tenn. All melting points are uncorrected.

Benzylbis(α-hydroxybenzyl)phosphine Oxide (1). The preparation of **1** was carried out exactly as described by Buckler.[2] The physical properties of **1** are reported in the earlier publication.[3]

5-Benzyl-2,4,6-triphenyl-1,3,5-dioxaphosphorinane 5-Oxide (2). The preparation of **2** was carried out in a manner similar to Buckler's procedure.[2] The meso (**2s**) and *dl* (**2a**) isomers were separated and identified according to the reported procedure.[3]

Interconversion of 2a and 2s. For this study, 0.5 g of the appropriate isomer (either **2a** or **2s**) was heated to reflux in 100 ml of dry benzene with one or two crystals of *p*-toluenesulfonic acid (TsOH). Aliquots (20 ml) were taken at predetermined intervals, the benzene was removed in vacuo, and the solid present was collected by washing with anhydrous ethyl ether onto a filter. The NMR spectrum of the solid in $CDCl_3$ was obtained and the signals of the protons at C-2 due to each isomer were carefully integrated. The results of these experiments are shown in Table I.

Reaction of 1 with *p*-Tolualdehyde. A solution of 7 ml of *p*-tolualdehyde, 27 ml of dry benzene, a crystal of TsOH, and 3.52 g (0.01 mol) of **1** was heated under reflux for 20 hr. Only 0.08 ml of water had collected (theoretical 0.18 ml) but reflux was stopped and the benzene was removed in vacuo. The oily residue was dissolved in 40 ml of ether and put aside. The white solid which formed was collected in two fractions, the first (0.72 g) melting at 185–196° and the second (0.45 g) at 142–170°. Recrystallization of these solids from 2-propanol–dioxane yielded, as the only pure product, the meso acetal 5-benzyl-4,6-di-*p*-tolyl-2-phenyl-1,3,5-dioxaphosphorinane 5-oxide (0.7 g, 15% yield). A second recrystallization from methanol–dioxane afforded the analytical sample **13**: mp 218–220°; ir (KBr) 3.27 (aromatic CH), 3.40 and 3.47 (aliphatic CH), 6.6, 6.7, and 6.9 (aromatic C=C), 8.4 and 8.48 μ (P=O); NMR ($CDCl_3$) δ 2.3 (s, 6 H, CH_3), 3.14 (d, J = 15 Hz, 2 H, PCH_2), 5.35 (d, J = 14 Hz, 2 H, PCHO), 5.96 (s, 1 H, OCHO), 6.75–7.75 (m, 18 H, aromatics).

Anal. Calcd for $C_{30}H_{29}O_3P$: C, 76.94; H, 6.20; P, 6.62. Found: C, 76.91; H, 6.31; P, 6.65.

The filtrates from these recrystallizations were evaporated to dryness and the recovered solid was shown to be a mixture of *dl* diols and *dl* acetals by NMR. There were clearly exchangeable protons and at least two different aromatic methyl groups in the NMR spectrum of the solid. Also 11% of the starting 1 was recovered and identified by its ir and NMR spectra.

Reaction of 2a with *p*-Tolualdehyde. An exchange reaction was attempted wherein **2a** (0.88 g, 2 mmol) was heated with an equimolar amount of *p*-tolualdehyde (0.24 g, 2 mmol) in refluxing benzene with one or two crystals of TsOH for 24 hr. After the reaction mixture was cooled for 1 hr, the solid present was collected (0.45 g), washed with ether, and identified as unchanged **2a** by its NMR spectrum (51% recovery). The filtrate was dried in vacuo and the solid which formed was collected by washing with ether (0.26 g, 29.5% yield based on one *p*-tolualdehyde group per acetal). The second solid was shown to contain 30% of the *p*-tolualdehyde moiety by its NMR spectrum. A third crop of solid (0.07 g, 8% yield) was shown to contain about 60% of the *p*-tolualdehyde moiety. These percentages of *p*-tolualdehyde are expressed in terms of one of the benzaldehyde groups being replaced by *p*-tolualdehyde and were arrived at by taking the integration of the aromatic protons signal and dividing by 19 (the number of aromatic protons if there are three phenyl groups and one *p*-tolyl group). The integration of the aromatic methyl region was divided by 3 and the ratio of the integration per hydrogen in the methyl region to that value in the aromatic region was used as the measure of incorporation of the *p*-tolualdehyde group in the acetal. Recrystallization of the latter two solids removed most of **2a** as crystalline compound (0.18 g of 0.30 g). The filtrates were allowed to evaporate to dryness at room temperature and the solid was collected by washing with ether. This solid (0.11 g) contained 75% of one *p*-tolualdehyde group per acetal.

Registry No.—*dl*-**1**, 55145-51-2; **2a**, 36871-89-3; **2s**, 55176-81-3; **13**, 55145-52-3; benzaldehyde, 100-52-7; *p*-tolualdehyde, 104-87-0.

References and Notes

(1) (a) Taken in part from the Ph.D. Dissertation of Armand B. Pepperman, Jr., Louisiana State University in New Orleans, 1973; (b) one of the facilities of the Southern Region, Agricultural Research Service, U.S. Department of Agriculture; (c) formerly Louisiana State University in New Orleans.
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Steric Effects in the Hydrolysis of Methyl- and *tert*-Butylphenylphosphinic Chloride and Fluoride[1]

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In aqueous acetone methylphenylphosphinic chloride and fluoride are much more reactive than the corresponding *tert*-butylphenylphosphinic halides in solvolysis and reaction with hydroxide ion. With the *tert*-butyl compounds, the fluoride is the more reactive toward hydroxide ion, but the chloride is more reactive in solvolysis, and solvolysis of the fluoride is very slow and autocatalyzed. All the reactions appear to be SN2 (P) displacements and have negative $\Delta S^{\ddagger}$, and steric hindrance by the *tert*-butyl group markedly increases $\Delta H^{\ddagger}$. Solvolysis of methylphenylphosphinic fluoride follows the Grunwald–Winstein equation with $m \sim 0.4$, but plots of log k against Y are curved for *tert*-butylphenylphosphinic chloride, although in the more aqueous solvents the plot is linear with $m \sim 0.6$.

Nucleophilic displacement at a phosphinyl group generally follows an associative, SN2 (P) mechanism, for both solvolysis and reaction in the presence of good nucleophiles, e.g., hydroxide ion.[2] However, it is sometimes possible to use bulky substituents to force a change to a dissociative, SN1 (P) mechanism.[5]

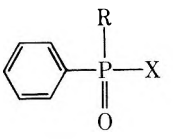
Part of the evidence for this mechanistic change came from markedly different solvent effects upon dissociative and associative reactions, based upon solvent nucleophilicities and the use of the Winstein–Grunwald mY equation. This equation was initially applied to SN reactions at saturated carbon.[6]

Substituent effects upon reaction rates and activation parameters have been rationalized in terms of steric and electronic effects upon nucleophilic attack on phosphorus. Inversion of configuration at phosphorus has been demonstrated,[7] although there is evidence in some reactions for build-up of a pentacovalent intermediate.[8]

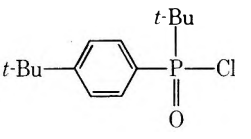
Electrophilic catalysis is often observed, and reactions of esters and fluorides are catalyzed by Brønsted and Lewis acids.[3-5,9a,b]

The aim of the present work was to compare reactions of phosphinyl chlorides and fluorides, because the strength of the P–F bond should make a dissociative mechanism less probable, but strong electron withdrawal by fluoride should assist a reaction in which bond making dominates, and the difference in the importance of bond making and breaking should make the fluorides much more discriminating than the chlorides to nucleophilic attack.

The compounds used were



Ia, X = F
b, X = Cl
R = Me, *t*-Bu



II

so that steric effects were varied, but electronic effects were approximately constant.

We had earlier found that *tert*-butylphenylphosphinic chloride (Ib, R = *t*-Bu) and *tert*-butyl-*p*-*tert*-butylphenylphosphinic chloride (II) were relatively unreactive in hydroxylic solvents,[10] and it seemed possible that these slow reactions might be dissociative. It was necessary to use a range of solvent compositions, in part because some of the substrates are sparingly soluble, and we used aqueous acetone to avoid reaction with the organic component of the solvent.

Experimental Section

Materials. The chlorides were prepared from the phosphinic acids using freshly distilled thionyl chloride,[11] but *tert*-butylphenylphosphinic chloride (Ib, R = *t*-Bu) was also prepared from phenyldichlorophosphine in CH_2Cl_2–$AlCl_3$ and *tert*-butyl chloride. Both samples had identical properties. The preparation of *tert*-butyl-*p*-*tert*-butylphenylphosphinic chloride (II) has been described.[10]

The phosphinic acids were prepared by standard methods. Methyl methylphenylphosphinate was prepared from dimethyl phenylphosphonite and methyl iodide and was saponified (1 *M* NaOH) to give methylphenylphosphinic acid, mp 135.5–136° (lit.[12] mp 136–136.5°). *tert*-Butylphenylphosphinic acid was prepared from phenylphosphonic dichloride and *tert*-butylmagnesium chloride, mp 155–157° (lit.[10,13] mp 154–156°). It proved to be more convenient to make *tert*-butylphenylphosphinic chloride directly.

The fluorides were obtained by heating the chloride under reflux with dried KF in dry MeCN.[14] The reaction was followed by withdrawing samples and examining the ir spectrum, using the bands: for Ia, R = Me, 825 (P–F), 1260 (P=O of the fluoride), 1237 (P=O for the chloride), and 695 cm^{-1} (Ph–P); and for Ia, R = *t*-Bu, ca. 835 (P–F), 1256 (P=O of the fluoride), 1230 (P=O of the chloride), and 634 and 698 cm^{-1} (Ph–P). The fluorides were isolated by vacuum distillation. Methylphenylphosphinic fluoride (Ia, R = Me) had bp 80–82° (0.5 mm) [lit.[14] bp 101–102.5° (4 mm)], and *tert*-butylphenylphosphinic fluoride (Ia, R = *t*-Bu) had mp 40–42°, bp 73° (0.03 mm) in a molecular still. (Anal. Calcd for $C_{10}H_{14}FOP$: C, 60.0; H, 7.0. Found: C, 59.8; H, 6.8.) *p*-*tert*-Butylphenyl-*tert*-butylphosphinic fluoride was prepared in the same way, mp 100–102°. It was unreactive in solvolysis and its reactions were not studied quantitatively.

The NMR and mass spectra of the *tert*-butyl derivatives and their chlorides have been reported.[10] The evidence for structure, based on the NMR spectra, is given below. All the spectra are at 60 MHz (Varian T-60), and except where noted are in $CDCl_3$ and are relative to Me_4Si. The values in parentheses are peak areas. Methyl methylphenylphosphinate: doublet (Me), δ 1.58, 1.80 (3) doublet (OMe), 3.52, 3.74 (3), multiplet 7.6–7.95 (5). Dimethyl phenylphosphonite: doublet (OMe) δ 3.42, 3.60 (6), multiplet 7.3–7.7 (5). Methylphenylphosphinic acid in D_2O with external Me_4Si: doublet (Me), δ 1.60, 1.84 (3.2) (J = 14.4 Hz), multiplet 7.7–8.1 (5). Methylphenylphosphinic chloride: doublet (Me) δ 2.08, 2.33 (3) (J = 15.0 Hz), multiplet 7.4–8.1 (5.2). Methylphenylphosphinic fluoride: doublet of doublets δ 1.68, 1.80 (J = 7.2 Hz, FH) and 1.93, 2.05 (J = 7.2 Hz, FH), and for PH (J = 15 Hz), area 3, multiplet 7.5–8.1 (5.1). *tert*-Butylphenylphosphinic fluoride: doublet of doublets, δ 1.08, 1.10 (J = 1.2 Hz, FH) and 1.37, 1.39 (J = 1.2 Hz, FH), and for PH, J = 17.4 Hz (area 9.3), multiplet 7.42–8.00 (5.0). *tert*-Butyl-*p*-*tert*-butylphenylphosphinic fluoride: doublet (*t*-Bu) δ 1.05, 1.30 (9) (J = 15 Hz), singlet (*t*-Bu) 1.33 (9), multiplet 7.5 (4).

Kinetics. Where possible, reactions of the chlorides were followed conductimetrically. The cells had ground joints which were sealed with Apiezon-W wax to prevent evaporation. This method was not always applicable and several others were also used. Solvolysis of the fluorides was followed using polyethylene or Teflon bottles from which aliquots were removed using a polyethylene pipette, and for most reactions were titrated against NaOH. Reaction of *tert*-butylphenylphosphinic chloride and fluoride with hydroxide ion was also followed by acid–base titration after quenching in cold acetone, and reaction of *tert*-butylphenylphosphinic chloride with hydroxide ion was also followed by potentiometric titration of chloride ion with $AgNO_3$. Reaction of methylphenylphosphinic fluoride with hydroxide ion was followed using a Radiometer pH Stat, with 0.1 *M* KOH as titrant. The reaction of *tert*-butylphenylphosphinic fluoride with hydroxide ion was also followed using an Orion fluoride ion electrode. The pH was brought to 8–9 (HNO_3) and EtOH (20 ml) was added to the 10-ml aliquot. Lanthanum nitrate was used as titrant. We were unable to obtain consistent results with this procedure unless we kept the electrolyte concentration constant, and the equivalence point of the titration depended on the nitrate ion concentration, but this might have been a vagary of the particular electrode which we used.

No single method could be used under all conditions, but the agreement was reasonable where comparisons could be made. In particular the *tert*-butyl derivatives are sparingly soluble in solvents of high water content, and because of the very different reactivities of the substrates we had to use a range of solvents and temperatures, and comparisons then involved large extrapolations, usually using the Arrhenius equation.

The kinetic solvents (aqueous acetone) were made up by weight to correspond to the quoted volume–volume composition. The observed first-order rate constants, k_ψ, are in reciprocal seconds.

Results

Methylphenylphosphinic Fluoride. In water–acetone (90:10 v/v) at 20.0° pK_w = 14.28,[15] and this value was used to calculate the hydroxide ion concentration in the reaction mixture. The values of k_ψ are in Table I, and they fit eq 1

$$k_\psi = k_0 + k_{OH}C_{OH^-} \quad (1)$$

where $k_0 = 3.1 \times 10^{-4}$ sec^{-1} and $k_{OH} = 9.0 \times 10^3$ l. mol^{-1} sec^{-1}.

For reactions in water–acetone (95:5 v/v) we assumed that the small amount of acetone (<1 mol %) would not materially affect K_w, and calculated C_{OH^-} using K_w for water at various temperatures.[16] The values of k_0 and k_{OH} are given in Table II.

Table I
Reaction of Methylphenylphosphinic Fluoride (Ia, R = Me) in Water–Acetone (90:10 v/v)[a]

pH	$10^4 k_\psi$, sec^{-1}	pH	$10^4 k_\psi$, sec^{-1}
5.5	3.00	6.5	4.45
6.0	4.27	7.0	8.27
6.25	4.30	7.5	17.7

[a] At 20.0° and 2×10^{-3} *M* substrate.

Table II
Rate Constants for Reactions of Methylphenylphosphinic Fluoride in Water–Acetone (95:5 v/v)

Temp, °C	$10^4 k_0$, sec^{-1}	$10^{-3} k_{OH}$, l. mol^{-1} sec^{-1}
0.0	1.49	2.73
10.0	2.50	4.44
15.0	3.22	5.50
20.0	4.3[a]	6.8[a]
25.0	5.50	8.43

[a] Interpolated using the Arrhenius equation.

The values of k_0 obtained over a range of solvents and temperatures, and usually by acid–base titration, are given in Table III.

Table III
Solvolysis of Methylphenylphosphinic Fluoride[a]

	% H_2O (v/v)						
Temp, °C	20	30	40	50	70	90	95
20.0						3.10	4.3
25.0	0.40	0.99	1.50	2.93			5.50
35.0		1.65		4.78	8.63		
50.0		3.84		10.4			

[a] Values of $10^4 k$

***tert*-Butylphenylphosphinic Chloride.** Solvolysis of this chloride is relatively slow and could be followed conductimetrically over a range of temperatures and aqueous acetone solvents (Table IV). The reaction with hydroxide ion was followed by acid–base titration or by potentiometric titration of chloride ion (Table V). A plot of k_ψ against hydroxide ion concentration in water–acetone (90:10 v/v) at 20.0° is slightly curved, presumably because of a salt effect at high hydroxide ion concentration, and the second-order rate constant, $k_{OH} = 2.8 \times 10^{-4}$ l. mol^{-1} sec^{-1}, is calculated from the initial slope of the plot.

Table IV
Solvolysis of *tert*-Butylphenylphosphinic Chloride (Ib, R = *t*-Bu) in Aqueous Acetone[a]

	% H_2O (v/v)			
Temp, °C	50	70	90	95
35.0	0.047	0.119	0.333	0.424
50.0	0.163	0.420	1.20	1.55
60.0	0.340	0.901	2.46	3.23

[a] Values of $10^4 k_\psi$, sec^{-1}.

Table V
Reaction of *tert*-Butylphenylphosphinic Chloride with Hydroxide Ion[a]

c_{OH^-}, *M*	$10^5 k_\psi$, sec^{-1}	c_{OH^-}, *M*	$10^5 k_\psi$, sec^{-1}
	0.87[b]	0.1	0.67[e]
	0.11[c]	0.3	11.9
0.01	1.28[d]	0.5	20.7
0.1	3.13		

[a] In water-acetone (90:10 v/v) at 20.0° with KOH followed by titration of chloride ion unless specified. [b] Extrapolated from results in Table IV. [c] Extrapolated to 0°. [d] Acid–base titration. [e] At 0°.

***tert*-Butyl-*p*-*tert*butylphenylphosphinic Chloride.** Solvolysis of this chloride was followed conductimetrically (Table VI) in order to estimate the effect of a *tert*-butyl group in the para position. Comparison of the results in Tables IV and VI show that the rate of solvolysis is halved by the para substituent.

Table VI
Solvolysis of *tert*-Butyl-*p*-*tert*-butylphenylphosphinic Chloride (II)[a]

	% H_2O (v/v)					
Temp, °C	30	40	50	70	90	95
25.0					0.058	0.083
35.0			0.022	0.054	0.161	0.204
50.0	0.027	0.047	0.070	0.182	0.620	0.829
60.0			0.171	0.478		

[a] Values of $10^4 k_\psi$, sec^{-1}.

***tert*-Butylphenylphosphinic Fluoride.** In the presence of hydroxide ion, plots of k_ψ against hydroxide ion (Table VII) are linear with very small intercepts. The values of 10^3 k_{OH} are ca. 1.5 l. mol^{-1} sec^{-1} at 0° and 7.44 l. mol^{-1} sec^{-1} at 20.0° in water–acetone (90:10 v/v).

Solvolysis is very slow and was followed by acid–base titration, but with substrate concentrations sufficient for analysis the product precipitated during the run. These solvolyses gave curved first-order plots and the values of k_ψ given in Table VIII are calculated from the initial slopes of the plots and are less accurate than the other rate constants. The curvature may be due to autocatalysis rather than to product precipitation because 0.05 *M* perchloric acid strongly catalyzes the reaction, and at 60.0° $10^5 k_\psi$ = 1.3 sec^{-1} in water–acetone (40:60 v/v) and 2.5 sec^{-1} in water–acetone (80:20 v/v). (In the absence of strong acid the solvolysis is too slow to be followed in 40% water.)

Table VII
Reaction of *tert*-Butylphenylphosphinic Fluoride with Hydroxide Ion in Water–Acetone (90:10 v/v)[a]

	c_{OH^-}, *M*		
Temp, °C	0.01	0.02	0.025
0.0		3.00	3.72
20.0	8.42	14.7	19.7, 17.9[b]

[a] Values of $10^5 k_\psi$, sec^{-1}, determined by acid–base titration except where specified. [b] Followed by potentiometric titration of fluoride ion.

Table VIII
Solvolysis of *tert*-Butylphenylphosphinic Fluoride[a]

	% H_2O (v/v)	
Temp, °C	80	90
60.0	2.3	6.0

[a] Values of $10^7 k_\psi$, sec^{-1}, followed by acid–base titration.

Solvent Effects upon Solvolytic Reactions. Solvent effects often depend on mechanism, and we therefore compared the solvent effects upon the solvolyses of some of these phosphinic halides using the Winstein–Grunwald equation.[6] There is no a priori reason why this equation should apply accurately to these solvolyses, but the *Y* solvent parameter gives a good indication of the ionizing power of a solvent and has been applied to other solvolyses of phosphorus compounds.[5]

The relations between log k_ψ and *Y* are shown in Figure 1 for solvolysis of methylphenylphosphinic fluoride at 25°, of *tert*-butyl-*p*-*tert*-butylphenylphosphinic chloride at 50°, and of *tert*-butylphenylphosphinic chloride over a temperature range. The plot is linear only for solvolysis of

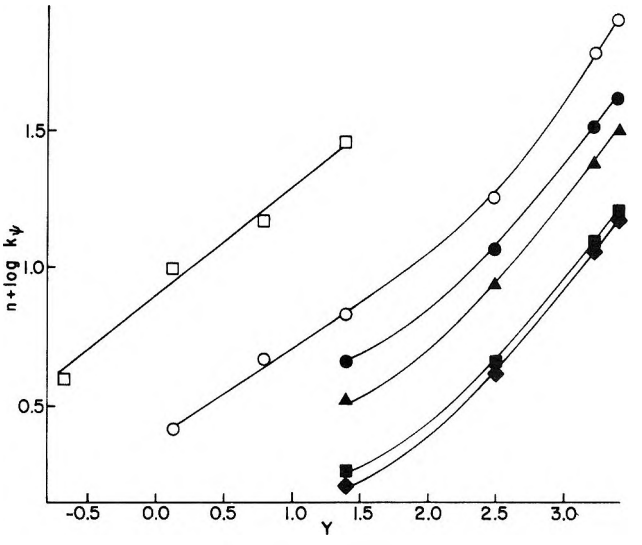


Figure 1. Solvent effects upon solvolysis: □, methylphenylphosphinic fluoride at 25.0°, *n* = 5; ○, *tert*-butyl-*p*-*tert*-butylphenylphosphinic chloride at 50.0°, *n* = 6. Solid points (*tert*-butylphenylphosphinic chloride): ■, at 25.0°, *n* = 6; ● at 35.0°, *n* = 6; ♦, at 50.0°, *n* = 5; ▲, at 60.0°, *n* = 5.

Table IX
m Values for Solvolyses

Substrate	Temp, °C	m
t-BuP(Ph)OCl	25	0.62
	35	0.60
	50	0.60
	60	0.62
p-*t*-BuPhP(*t*-Bu)OCl	50	0.66 (0.34[a])
MeP(Ph)OF	25	0.36

[a] From the slope at lower *Y* values.

methylphenylphosphinic fluoride. However, the slopes of the plots are insensitive to temperature changes. The plots are approximately linear for solvolyses of the chlorides in the more aqueous solvents, and the values of *m* given in Table IX are calculated from these linear portions; for the *p*-*tert*-butyl compound (II) the value of *m* given in parentheses is the approximate slope for the region 20–40% water.

The solvolysis of methylphenylphosphinic chloride is too fast, and that of *tert*-butylphenylphosphinic fluoride is too slow, for estimation of solvent effects on rate.

For similar substrates a solvolytic dissociative mechanism would be expected to have a higher *m* value than a bimolecular reaction with lyate ion,[6] but it is difficult to make a prediction of the probable *m* value for attack by solvent upon a phosphinyl group. The use of solvents of similar *Y* values but different nucleophilicities suggested that *m* values tended to be lower (ca. 0.2) for bimolecular solvent attack upon phosphorus than for a dissociative mechanism ($m \sim 0.5$),[5a] but the range of *m* values was small. Our values tend toward those considered to be characteristic of dissociative mechanisms (Table IX), but all our other evidence supports an associative SN2 (P) mechanism, and because some of our *mY* plots are curved we feel that this rate–solvent relationship is not a good mechanistic test for solvolysis of these phosphinic halides.

Activation Parameters for Solvolysis. The activation parameters given in Table X are not markedly dependent upon solvent composition, but the large differences between the solvents used in our work and the relatively nonaqueous solvent used for the solvolysis of methylphenylphosphinic chloride[17] complicate comparisons. Some of the parameters were determined over small temperature ranges, and their values are therefore not accurate.

Table X
Activation Parameters for Solvolysis

Substrate	% H_2O	$\Delta H^{\ddagger}$, kcal mol^{-1}	$\Delta S^{\ddagger}$, eu
MeP(Ph)OCl[a]	5	6.0	−26
MeP(Ph)OF	30	9.7	−44
	50	9.2	−44
	95	7.9	−47
t-BuP(Ph)OCl	50	16	−32
	70	16	−30
	90	16	−28
	95	16	−27
p-*t*-BuPhP(*t*-Bu)OCl	50	16	−33
	70	17	−27
	90	17	−24
	95	17	−25

[a] Reference 17.

For solvolysis of the *tert*-butylphenylphosphinic chlorides the kinetic solvent effect is largely on $\Delta S^{\ddagger}$, which becomes more negative as the solvent becomes drier (Table X), but for solvolysis of methylphenylphosphinic fluoride it is $\Delta H^{\ddagger}$ which increases as the solvent becomes drier with $\Delta S^{\ddagger}$ becoming slightly less negative. These differences could be related to hydrogen bonding between water and a departing fluoride ion, which should lower $\Delta H^{\ddagger}$. Unfortunately, we could not obtain activation parameters for the other substrates to test this hypothesis. The *tert*-butylphosphinic chlorides have much higher activation enthalpies than the methyl compounds, because of the steric bulk of the *tert*-butyl group.

Comparison of Reactivities toward Hydroxide Ion. The *tert*-butyl group considerably hinders nucleophilic attack, so that the reactions with hydroxide ion had to be followed at different temperatures, and where necessary extrapolations were made using the Arrhenius equation. The second-order rate constants are summarized in Table XI, and the activation parameters are in Table XII. These parameters are in the range expected for SN2 (P) reactions, and steric hindrance by the *tert*-butyl group shows up in both the enthalpy and entropy terms, as for solvolysis (Table X).

Table XI
Reactions with Hydroxide Ion[a]

Substrate	Temp, °C	k_{OH}, l. mol^{-1} sec^{-1}
MeP(Ph)OF	20.0	9030
	0.0	2730[b]
	10.0	4440[b]
	15.0	5500[b]
	20.0	6800[b]
	25.0	8430[b]
t-BuP(Ph)OF	0.0	1.5×10^{-3}
	20.0	7.4×10^{-3}
t-BuP(Ph)OCl	0.0	5.6×10^{-5}
	20.0	2.8×10^{-4}

[a] In water-acetone (90:10 v/v) except where specified. [b] In water-acetone (95:5 v/v).

Table XII
Activation Parameters for Reaction with Hydroxide Ion

Substrate	% H_2O (v/v)	$\Delta H^{\ddagger}$, kcal mol^{-1}	$\Delta S^{\ddagger}$, eu
MeP(Ph)OF	95	6.7	−18
t-BuP(Ph)OF	90	12	−34
t-BuP(Ph)OCl	90	12	−40

Activation enthalpies for attack of hydroxide ion upon fluorophosphonates, dialkylfluorophosphates, and diethylphosphonic fluoride and the corresponding unhindered chlorides are generally in the range 6–12 kcal mol^{-1}, and the activation entropies are negative, and in the range −15 to −35 eu. This pattern is typical of the attack of hydroxide ion on phosphorus.[3,4,17-19]

Although acid chlorides are generally more reactive than fluorides in solvolysis, the opposite is often found for reaction with hydroxide ion because the stronger electron withdrawal by a fluoride substituent overcomes the easier loss of chloride.[20] This pattern is observed with the *tert*-butylphenylphosphinic halides (Table XI).

The *tert*-butyl group has a very large effect on the attack of hydroxide ion and in water–acetone (90:10 v/v) methylphenylphosphinic fluoride (Ia, R = Me) is more reactive than the *tert*-butyl compound (Ia, R = *t*-Bu) by a factor of approximately 10^6 (Table XI). We could not make a rate

comparison for the chlorides because of the very high reactivity of methylphenylphosphinic chloride.[17]

Solvolytic Reactions. Our hope of comparing directly the reactivities of the methyl and *tert*-butyl compounds (Ia,b, II) under solvolytic conditions was frustrated by the very low reactivity of *tert*-butylphenylphosphinic fluoride in the absence of hydroxide ion and the very high reactivity of methylphenylphosphinic chloride,[17] and indirect comparisons involve large extrapolations over a range of solvent composition or temperature.

The hydrolysis of many acid fluorides is acid catalyzed because of the basicity of fluoride,[9] and autocatalysis is often observed, for example with dialkyl fluorophosphates and phosphonates[9a] but not with methylphenylphosphinic fluoride, probably because of the smaller dissociation constant of a phosphinic as compared with a phosphonic acid. The hydrolysis of *tert*-butylphenylphosphinic fluoride was autocatalyzed. suggesting that the spontaneous hydrolysis is more subject to steric hindrance by the *tert*-butyl group than the acid hydrolysis, because we found no autocatalysis with the methyl compound. However, conditions were not directly comparable because reaction of the *tert*-butyl compound was followed using a substrate concentration of ca. 10^{-2} *M* as compared with that of ca. 10^{-3} for the methyl compound.

The solvolytic reactivities of *tert*-butylphenylphosphinic chloride and fluoride can be compared directly at 60° in water–acetone (90:10 v/v) (Tables IV and VIII) where the chloride is more reactive than the fluoride by a factor of 410. This difference between the solvolytic reactivities of chlorides and fluorides is general, for example with benzenesulfonyl halides.[20]

Comparison of the solvolytic reactivities of methylphenylphosphinic chloride and fluoride requires considerable extrapolation. The first-order rate constant for the hydrolysis of methylphenylphosphinic chloride at 25° in water–acetone (95:5 v/v) is 0.18 sec^{-1}, calculated using the Arrhenius parameters given in ref 17. Extrapolation of the rate constants of solvolysis of the fluoride (Table III) using the Grunwald–Winstein equation[6] gives the corresponding value of 5.6×10^{-6} sec^{-1}. [Solvolysis of methylphenylphosphinic fluoride gives a linear plot of log k against Y (Figure 1).] Thus in this solvent of low water content the reactivity difference between methylphenylphosphinic chloride and fluoride is 3×10^4. This reactivity difference is much greater than for the *tert*-butyl compounds, but the difference could be related to differences in solvent and temperature rather than structure.

The *tert*-butyl compounds are much less reactive than the corresponding methyl compounds in solvolysis, and again because of problems due to high reactivity of some compounds and the low solubility of others, we cannot make all the rate comparisons for the methyl and *tert*-butyl compounds under the same conditions. For the chlorides we have to use a solvent of low water content, because of the very high reactivity of methylphenylphosphinic chloride. A very approximate estimate of the relative reactivities can be made on the following basis. In 5% water at 35° the extrapolated rate constant for solvolysis of methylphenylphosphinic chloride[17] is 0.26 sec^{-1}, and in 50% water at 35° $k_0 = 4.7 \times 10^{-6}$ sec^{-1} for the *tert*-butylphenylphosphinic chloride (Table IV). Although log k vs. Y plots are curved for solvents of low water content (Figure 1), $m \sim 0.3$ in these solvents, giving an approximate extrapolated value of $k_0 \simeq 2 \times 10^{-7}$ sec^{-1} at 35° in 5% water, so that the methyl would be more reactive than the *tert*-butyl compound by a factor of approximately 10^6 under these conditions.

Comparison of the reactivities of the fluorides has to be made using an aqueous solvent and a relatively high temperature. From the solvent and temperature effects upon the solvolysis of methylphenylphosphinic fluoride (Table III) we estimate $k_0 \simeq 1.7 \times 10^{-3}$ sec^{-1} at 60° in water–acetone (90:10 v/v), and under these conditions $k_0 = 6 \times 10^{-7}$ sec^{-1} for the *tert*-butyl compound (Table VIII), giving a reactivity difference of 3×10^3. This large difference in the relative effects of methyl and *tert*-butyl groups on hydrolyses of the fluoride and chloride may not be mechanistically significant, in part because different solvent compositions were used, but also because reactions of the *tert*-butyl compounds have higher activation energies than those of the methyl compounds (Table X), so that increasing temperature will reduce the reactivity difference.

Although a *tert*-butyl group sterically deactivates *tert*-butylphenylphosphinic chloride and fluoride strongly, the chloride ($k_0 = 3 \times 10^{-4}$ sec^{-1} at 60° in 95% water) is very much more reactive than di-*tert*-butylphosphinic chloride ($k_0 = 9 \times 10^{-7}$ sec^{-1} at 100° in water). The di-*tert*-butyl compound is believed to react by a dissociative SN1 (P) mechanism,[5a] suggesting that *tert*-butylphenylphosphinic chloride does not react by a dissociative mechanism.

Selectivities of Fluorides and Chlorides toward Nucleophiles. Although all the compounds which we examined appear to react by SN2 (P) mechanisms, a sterically hindered fluoride (Ia, R = *t*-Bu) discriminates very strikingly in favor of reaction with a strong nucleophile, OH^-, as compared with a weak one, H_2O, and this type of selectivity is important in the biological activity of fluorophosphorus compounds. This behavior of fluorides as compared with chlorides toward good nucleophiles appears to be general,[20,21] and can be viewed in terms of Pearson's distinction between hard and soft reagents.[22] This "hardness" of a fluoride as compared with a chloride is also evident in the differences in the P=O stretching frequencies of the phosphorus halides.[14,23] The relative importance of bond making and breaking is also important in that the latter should be easier with a chloride than a fluoride.

Registry No.—Ia (R = Me), 657-37-4; Ia (R = *t*-Bu), 55236-56-1; Ib (R = Me), 5761-97-7; Ib (R = *t*-Bu), 4923-85-7; II, 25097-44-3; *tert*-butyl-*p*-*tert*-butylphenylphosphinic fluoride, 55236-57-2; phenyldichlorophosphine, 644-97-3; *tert*-butyl chloride, 507-20-0; methyl methylphenylphosphinate, 6389-79-3; dimethyl phenylphosphonite, 2946-61-4; methylphenylphosphinic acid, 4271-13-0.

References and Notes

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Regiochemistry and Stereochemistry in the Hydralumination of Heterosubstituted Acetylenes. Interplay of Inductive and Resonance Effects in Electron-Rich Alkynes[1]

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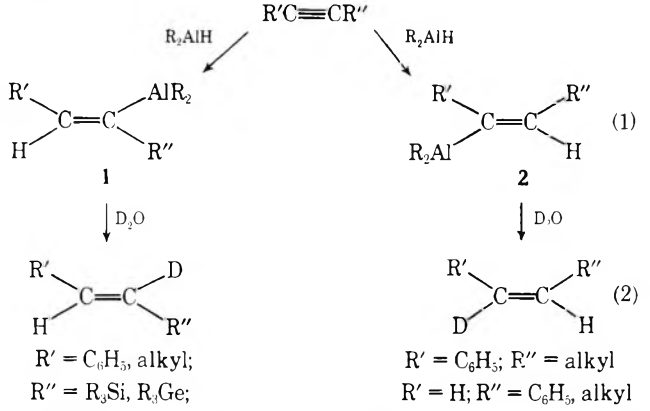
The hydralumination of certain electron-rich alkynes with diisobutylaluminum hydride was studied, in order to determine the influence of inductive and resonance factors on the regiochemistry and stereochemistry of the addition. Dimethyl(phenylethynyl)amine underwent an overall trans hydralumination, which placed the R_2Al group α to the phenyl group. In addition, one-third of the amine was consumed in a competing reductive dimerization. In additions moderated by *N*-methylpyrrolidine, no reductive dimerization of the alkyne was observed, but the initial cis adduct was detected by NMR spectroscopy. Ethyl phenylethynyl sulfide gave only the cis hydralumination adduct with the R_2Al attached to the phenyl-substituted vinyl carbon and the thio-substituted vinyl carbon in a 17:83 ratio. 1-Ethoxy-1-hexyne gave principally the cis hydralumination adduct with the R_2Al group exclusively α to the butyl group. In contrast, both phenylethynyllithium and diphenyl(phenylethynyl)aluminum underwent mono- and bishydraluminations to yield adducts having all metallo groups β to the phenyl group. Finally, chloro- and bromo(phenyl)acetylenes were relatively unreactive toward R_2AlH; at higher temperatures, addition did occur but with concurrent loss of halogen. The foregoing observations are interpreted in terms of a mechanism involving (a) electrophilic attack by R_2AlH on the triple bond; (b) addition of the Al–H bond, in accord with developing p_π–p_π or p_π–d_π polarizations, to yield the cis adduct; (c) isomerization to the trans adduct, where feasible; and (d) for those cases where the corresponding 1-alkyne is also formed, the cis elimination of R_2AlE (where E = Br, Cl, SEt, or OEt) from this trans adduct.

The addition of alkylaluminum hydrides to alkynes, with subsequent hydrolysis, constitutes a mild, convenient method for the cis reduction[2,3] or, in certain cases, the trans reduction[4] of the C≡C group (eq 1). Since the position of the alkylalumino group on the resulting C=C linkage is readily labeled by treatment with D_2O, both the stereochemistry and the regiochemistry of hydralumination can be determined by NMR spectroscopy (eq 2).[3-6]



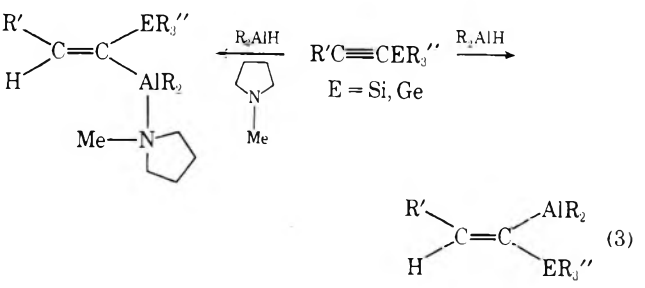
R′ = C_6H_5, alkyl; R″ = R_3Si, R_3Ge;

R′ = C_6H_5; R″ = alkyl

R′ = H; R″ = C_6H_5, alkyl

The hydralumination of heterosubstituted acetylenes, considered in the present study, was deemed worth investigating on several counts. First of all, the interplay of inductive and resonance effects for the heterosubstituent E in R′C≡CE (where E = R_2N, RO, RS, X, or M) could give rise to varying proportions of the four possible aluminum products, adducts 1 and 2 in eq 1 and their two regioisomers. Thus, analysis of these product ratios in terms of electronic effects for group E promised further insight into the nature of the transition state. Secondly, the hydralumination of acetylenic ethers and amines seemed to be a feasible synthetic route to vinylic ethers and enamines, respectively, of defined stereochemistry. Since such hydraluminations occur at or below room temperature and the hydrolytic work-up ensues under mildly basic conditions, these hydrolysis-sensitive olefins were expected to remain intact.

Finally, it was of interest to learn whether the cis or trans stereochemistry of such additions might be subject to kinetic or thermodynamic control. As with the cases of trialkylsilyl- and trialkylgermylacetylenes[5,6] (eq 3), the prospect of achieving cleanly either a cis or a trans hydralumination of these heterosubstituted acetylenes was most attractive.



Results

As model systems, the following available electron-rich acetylenes were subjected to the action of diisobutylaluminum hydride (3): dimethyl(phenylethynyl)amine (4); 1-eth-

oxy-1-hexyne (5); ethyl phenylethynyl sulfide (6); phenylethynyllithium (7); and diphenyl(phenylethynyl)aluminum (8). The behavior of chloro(phenyl)acetylene (9) and bromo(phenyl)acetylene (10) was also examined, even though the halogen atom was expected to exert a −I effect on the C≡C bond. However, since hydralumination of alkynes is now known to involve electrophilic attack by monomeric R_2AlH,[6,7] it was of interest to learn whether the halogen would show a +T effect in the transition state.

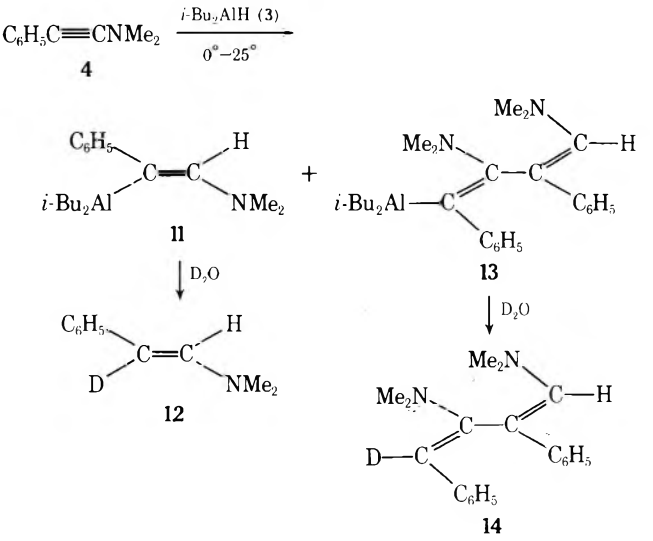
With the exception of the halo(phenyl)acetylenes, all the heterosubstituted acetylenes, RC≡CE, underwent hydraluminations more rapidly than their corresponding 1-alkynes. For example, by competitive hydralumination[8] at 35° the initial reaction rate of dimethyl(phenylethynyl)amine was shown to be ca. 1600 times that of phenylacetylene. In fact, the high reactivity of the acetylenic amine (4), ether (5), and sulfide (6) permitted their smooth hydralumination, even in the presence of 1 equiv of *N*-methylpyrrolidine. The complex of diisobutylaluminum hydride with the latter amine is a less reactive reagent[4] but the presence of the amine suppressed competing reactions. Hydraluminations without *N*-methylpyrrolines led, in certain cases, to (a) isomerization of cis adducts to trans adducts (cf. eq 3); (b) reductive dimerization of RC≡CE to yield 1,3-alkadienylaluminum adducts;[5] and (c) reductive scission of RC≡CE to produce RC≡CH.

The stereochemistry of the olefins obtained by the hydrolysis of the aluminum adducts (cf. eq 1 and 2) was assigned upon the basis of the magnitude of the vinylic proton NMR coupling constants and the characteristic ir C–H bending vibrations. The position of the R_2Al group in the adduct and hence the regiochemistry were determined by the D_2O-labeling technique (eq 2) and an NMR analysis as to which vinylic proton signals were decreased. Crucial to this method was the umambiguous assignment of the observed NMR vinylic proton signals to the protons α and β to the group E in RCH=CHE. By use of tabulated group contributions to the chemical shifts of such protons for both cis and trans 1,2-disubstituted ethylenes,[9] estimates of the expected chemical shifts for the protons in each geometrical isomer could be obtained. Such calculated values gave good assurance that the observed signals were ascribed to their proper vinylic protons.

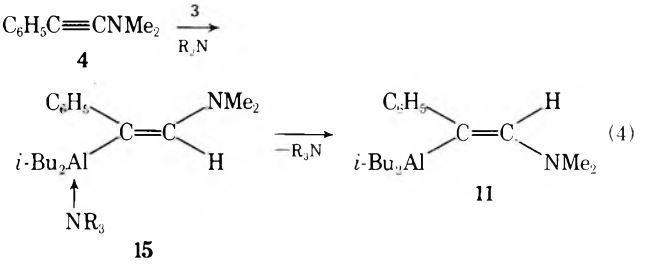
Dimethyl(phenylethynyl)amine. By far the most reactive of the heterosubstituted acetylenes examined in this work was dimethyl(phenylethynyl)amine (4). When admixed with the hydride 3 at 0–25° the reaction is not only rapid but reductive dimerization consumes ca. one-third of the starting amine. The only isolable monoamine proved to be dimethyl[(*E*)-β-styryl]amine (12), showing that a net trans hydraluminum had resulted. Deuterium labeling showed, furthermore, that the dialkylalumino group was attached exclusively to the vinylic carbon α to the phenyl group (11). An NMR spectral analysis of the reduced dimer obtained by hydrolysis showed it to be a 1,3-bis(dimethylamino)-2,4-diphenyl-1,3-butadiene (14). Treatment of the aluminum precursor of this butadiene with D_2O led to the disappearance of the vinylic proton at C_4 in 14. Finally, with the assumption that the stereochemistry in 14 and its aluminum precursor 13 will parallel that found for 12 (i.e., trans), the most reasonable stereochemistry of 13 and 14 seems to be *Z,Z* for 13 and *Z,E* for 14 (Scheme I).

In order to learn whether the trans adduct 11 was formed directly or by the isomerization of an initial cis adduct, a mixture of the amine 4 and the hydride 3 was monitored at −20° by NMR spectroscopy. Under these conditions only the vinylic signal attributable to 11 was detected; in fact, even after 40% of 4 was consumed, barely any of 13 was ob-

Scheme I



servable. In hopes of trapping any initially formed cis adduct by complexing with an external amine, the NMR spectral monitoring of 3 and 4 at −20° was repeated in the presence of *N*-methylpyrrolidine. Indeed, a new vinylic proton signal of modest intensity was observed at 6.28 ppm, 0.28 ppm downfield from that of 11. Since there are tertiary amine sites available in 11 and unconsumed 4, it seems unlikely that this new vinyl proton is due to a complex of 11 with a tertiary amine. Such complexation could also have occurred in the former NMR experiment where no *N*-methylpyrrolidine was present. The new downfield signal at 6.28 ppm is, on the other hand, consistent with the signal expected for the cis adduct 15. From chemical shift parameters a vinyl proton β,cis to a phenyl group would be expected to absorb at lower fields than one that is β,trans.[9] Although the chemical shift parameter for the free R_2Al or the complexed $R_2Al{:}NR_3$ substituent is not known, NMR studies of triphenylaluminum in C_6D_6 and in THF have shown that the ortho protons are markedly deshielded, compared with the meta and para protons.[18] This finding supports the suggestion that the cis proton in 15 would also be deshielded by the R_2Al group. These considerations lead to the suggestion that 4 undergoes intitial cis hydralumination to produce 15 and that, in the absence of an external amine, this adduct isomerizes rapidly to the trans adduct 11 (eq 4). Attempts to obtain evidence for the presence of



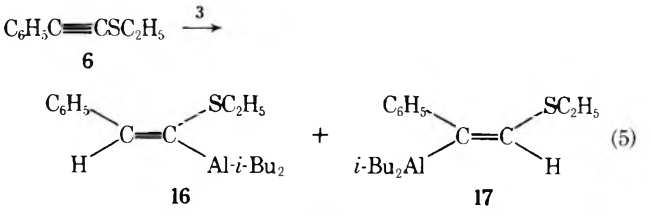
(4)

15 by means of low-temperature protolysis of the reaction mixture and the isolation of dimethyl[(*Z*)-β-styryl]amine have thus far failed. Possibly the ready isomerizability of such cis enamines may account for this failure.

Finally, it is noteworthy that 11, which is probably an associated molecule, did not show any tendency to split out i-Bu_2Al–NMe_2 and form phenylacetylene when heated at 100°. As will be seen later on, such cis eliminations are considerably easier with other heteroatoms.

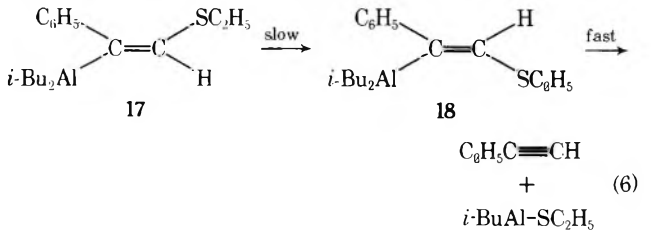
Ethyl Phenylethynyl Sulfide. In contrast with the acetylenic amine, this sulfide (6) underwent smooth and ex-

clusive cis hydralumination, without any sign of reductive dimerization. By deuterium labeling, however, the reaction was shown to be regioselective, rather than regiospecific; the isomeric aluminum compounds, **16** and **17**, were formed in a 83:17 ± 2 ratio (eq 5).



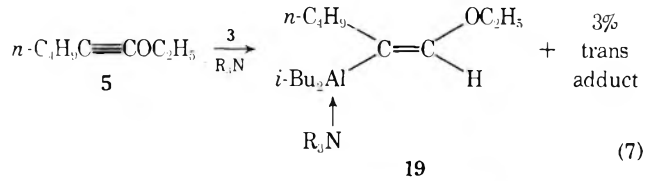
16 **17** (5)

Attempted isomerization of **16** and **17** to their trans adduct by heat, addition of a Lewis acid (i-Bu_2AlCl),[4] or Ni(0)[10,11] failed; no new vinylic proton signals could be detected by NMR spectroscopy. Prolonged heating at 80–90°, however, did give gradually increasing amounts of phenylacetylene. These results can be explained by proposing a slow isomerization of **17** to its trans adduct (**18**), followed by a relatively rapid cis elimination of i-Bu_2Al–SC_2H_5 (cf. eq 6 and below).



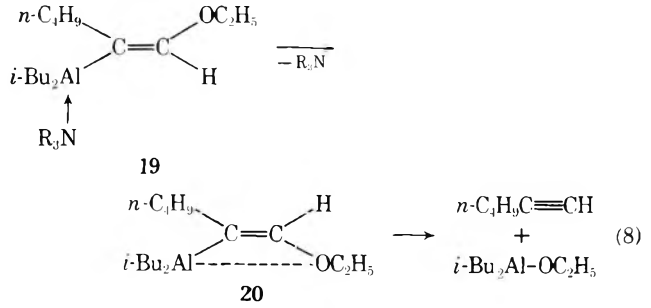
17 **18** (6)

1-Ethoxy-1-hexyne. Hydralumination of this acetylenic ether (**5**) in the absence of N-methylpyrroldine gives an uncontrolled series of reactions, involving extensive reductive cleavage of the C≡C—O linkage.[12,13] A much cleaner reaction was achieved in the presence of N-methylpyrrolidine, where again the stereochemistry and regiochemistry differ essentially from those of the acetylenic amine or sulfide. Here, the hydralumination is highly stereoselective, with the cis adduct composing >97% of the addition products.[13] By deuterium labeling, on the other hand, the reaction was shown to be regiospecific, with the alumino group attached exclusively to the vinylic carbon α to the n-butyl group (**19**) (eq 7).



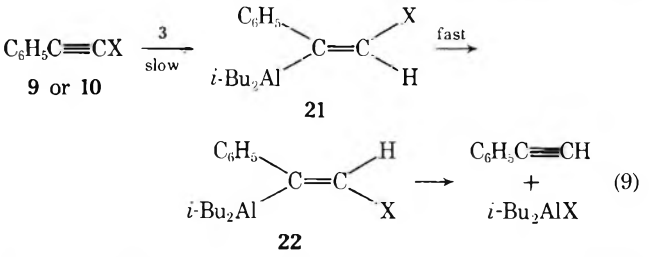
5 **19** (7)

Even in the presence of N-methylpyrrolidine, however, ca. 30% of **5** is cleaved to yield 1-hexyne. Since the amount of 1-hexyne formed is larger in the absence of the amine, the reductive cleavage seems to be due to the isomerization of **19** to its trans adduct **20** and the subsequent cis elimination of i-Bu_2Al–OC_2H_5 (eq 8).



19 **20** (8)

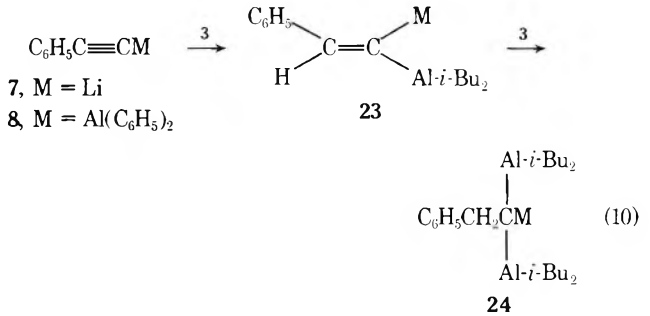
Halo(phenyl)acetylenes. Neither the chloro (**9**) nor the bromo (**10**) derivative reacts with hydride **3** in cyclohexane at 25°. This ranks their reactivity toward **3** lower than that of diphenylacetylene, one of the least reactive alkynes.[8] Heating **9** or **10** with **3** does effect hydralumination, but, thus far, no β-halostyrenes have been detected upon hydrolysis. Instead, varying amounts of styrene and ethylbenzene have been isolated. Interestingly, when mixtures of **10** and **3** are monitored by ir spectroscopy, it can be shown that phenylacetylene is formed during the early stage of reaction.[13] In light of the pattern emerging for the reductive cleavage of acetylenic sulfides (eq 6) and ethers (eq 8), it is reasonable to suggest a mechanism involving a slow cis addition of **3** to **9** or **10**, followed by isomerization to the trans adduct and subsequent elimination (eq 9). Attempts



9 or **10** **21** **22** (9)

to detect either of the postulated intermediates, **21** and **22**, have thus far been unsuccessful.

Phenylethynylmetallic Derivatives. Both phenylethynyllithium (**7**) and diphenyl(phenylethynyl)aluminum (**8**) underwent prompt reaction with hydride **3**. In fact, bishydralumination of either **7** or **8** competed seriously with monohydralumination, such that even 1 equiv of **3** led, upon hydrolysis, to mixtures of styrene and ethylbenzene. Although stereochemical information could obviously not result from these reactions, the regiochemistry could be obtained by deuterium labeling. The mono- and bishydraluminations were, in fact, regiospecific: the resulting styrene was exclusively the β,β-dideuterio isomer and the ethylbenzene was the β,β,β-trideuterio compound. Accordingly, for both **7** and **8**, the aluminum precursors are of the type **23** and **24** (eq 10).



7, M = Li
8, M = $Al(C_6H_5)_2$
23 **24** (10)

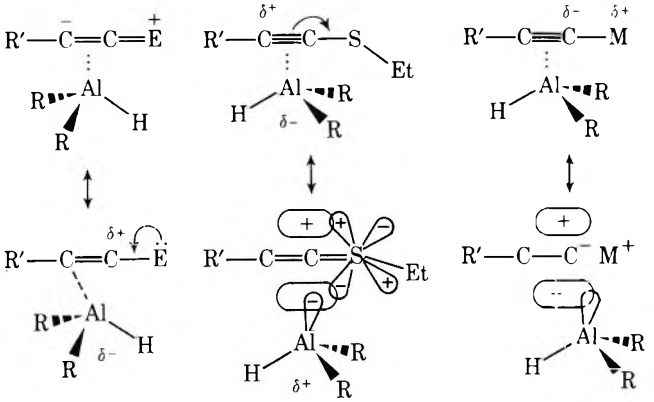
Discussion

From consideration of relative rates[8] and the experimental conditions required for hydralumination, the following order of decreasing reactivity can be established for these heterosubstituted alkynes: $C_6H_5C{\equiv}CNMe_2 \gg C_4H_9C{\equiv}COC_2H_5 > C_6H_5C{\equiv}CM$ [M = $Al(C_6H_5)_2$ or Li] > $C_6H_5C{\equiv}CSC_2H_5 \gg C_6H_5C{\equiv}CX$ (X = Cl or Br). Since all except the halo(phenyl)acetylenes are much more reactive than their corresponding 1-alkynes, they may be viewed as "electron-rich" alkynes, whose E group donates electron density to the C≡C group in the transition state of hydralumination. Such an interpretation is consonant with the known electrophilic character of R_2AlH attack on alkynes.[6,7] However, the exact nature of the electron donation by group E should be analyzed, since it clearly exerts a pro-

found influence on the stereochemistry and regiochemistry of the addition.

The only known cases where the hydralumination of alkynes leads principally to the trans adduct are those involving acetylenic silanes,[4] germanes,[4] and amines. For the first two types, a recent study has demonstrated that the cis adduct is actually the first-formed product and that the trans product results by isomerization.[4,6] In the case of dimethyl(phenylethynyl)amine, the presence of *N*-methylpyrrolidine did permit detection of what appears to be the cis adduct (**15**). Just as with the acetylenic silanes and germanes, the external amine seems to be able to complex with the cis adduct and thereby slow down its isomerization. Thus, it would appear warranted to conclude that probably all hydraluminations of alkynes are kinetically controlled cis additions.[6,7,14]

The variation in regiochemistry with the nature of group E is most instructive: (a) the dimethylamino and ethoxy groups direct the dialkylalumino group to their β carbon; (b) the metallo groups give exclusively α attachment of R_2Al groups; and (c) the ethylthio group displays ca. a fivefold preference for α attachment over β. Since all these substituents enhance the reactivity of the C≡C group, it is more logical to ascribe the changes in orientation to differing polarizations of the triple bond, rather than to electron donation or withdrawal by E. The operation of p_π–p_π delocalization in the transition state of reaction with the acetylenic amine or ether (**25**) would account nicely for the observed regiospecificity; likewise, the polarization fostered



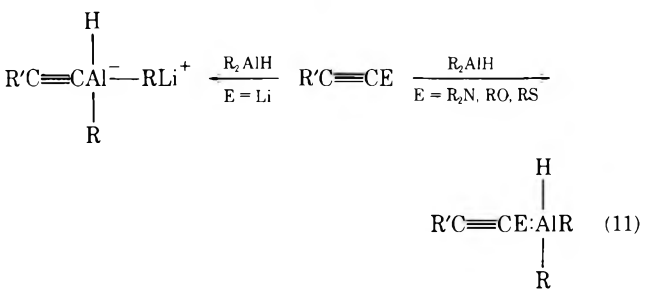
25 E = Me_2N, EtO

26

27 M = $(C_6H_5)_2Al$, Li

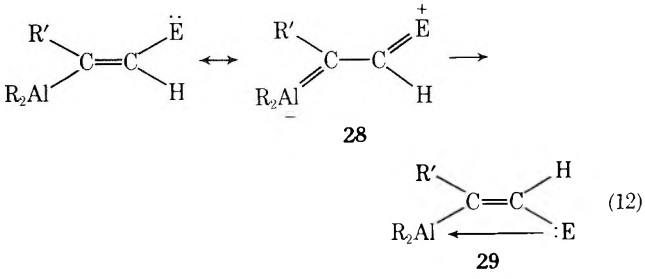
by d_π–p_π delocalization in the transition state for the acetylenic sulfide (**26**) rationalizes the regioselectivity. Finally, the metallo group apparently polarizes its C–M σ bond markedly, enlarging the π cloud at the α carbon (**27**). Thus, it can be concluded that in the transition state the +T effect dominates with the Me_2N and EtO groups; with EtS, the −T effect is definitely larger and with the M group the +I effect takes precedence.[15]

It might be noted that all these acetylenes have potential Lewis basic sites on group E. Consequently, preliminary coordination of the hydride R_2AlH at these sites can be assumed. However, as with other coordination complexes of organoaluminum compounds, such complexes are likely to be in equilibrium with the free acetylenes. Various studies have shown that uncomplexed alkynes and organoaluminum reagents undergo hydralumination and carbalumination more readily.[3,7]



(11)

The isomerization of cis adducts and the loss of R_2AlE from the resulting trans adducts were detected in the case of 1-ethoxy-1-hexyne and were inferred for the cases of ethyl phenylethynyl sulfide and the halo(phenyl)acetylenes (eq 6, 8, and 9). The ease of these cis, trans isomerizations seems to be related to the importance of the same +T effect of group E invoked in explaining the regiospecificity (**25**). Operation of such electron delocalization in cis adduct **28** should lower the barrier to rotation about the C=C bond (eq 12).[16] Once the trans adduct is formed, direct



28

(12)

29

coordination of electrons on E with the aluminum is possible (**29**, or a dimer thereof). Such direct interaction can set the stage for the elimination of R_2Al–E, if energetically favorable. Since various amines and mercaptans add readily to alkynes with metal salt catalysts, elimination of R_2AlNMe_2 or R_2AlSEt from **29** would not be expected to occur readily. On the other hand, eliminations of MOR and MX from various aromatic and olefinic systems are richly precedented. Hence, the large amounts of 1-alkyne obtained from the acetylenic ether and halides seem to be best explained by an addition–isomerization–elimination sequence.

Finally, the preparative possibilities of these hydraluminations should be borne in mind. Vinylic ethers and sulfides of cis configuration can be prepared in good or excellent yields. Enamines of trans configuration are likewise accessible. Trimethylamine can be used in place of *N*-methylpyrrolidine for moderating the reaction; the former amine can more readily be removed upon work-up. In addition, the bishydralumination of lithium acetylides provides a convenient route to interesting α,α,α-trimetalloalkanes and the CD_3 group.

Experimental Section

Melting points were determined with a Thomas-Hoover Unimelt apparatus and are corrected. Infrared spectra were recorded of samples as potassium bromide disks, mineral oil suspensions, or solutions in pure solvents, by means of a Perkin-Elmer spectrophotometer, Model 457. Proton magnetic resonance spectra were measured with Varian spectrometers, either a Model A-60 or a Model HA-100D, the latter being equipped with a Varian variable temperature control, Model V-6040, and a Hewlett-Packard audiofrequency generator, Model HP-205AG, for proton and deuterium spin decoupling. The samples were measured as solutions 10% by weight in pure solvents and tetramethylsilane was added as an internal standard. Such data are reported using the δ scale in parts per million, followed by the integrated intensities of the proton signals and the coupling constants (J) in hertz. Gas chromatographic analyses were performed with an F & M instrument, Model 720, equipped with dual columns of 10% silicone gum rubber on 60–80 mesh Chromosorb W (12 ft × 0.25 in). Elemental analyses were carried out by the Spang Microanalytical Laboratory, Ann Arbor, Mich.

All preparations and reactions involving substances sensitive to moisture and oxygen, such as organometallics and certain of the

acetylenic compounds, were conducted under an atmosphere of dry, oxygen-free nitrogen. Appropriate techniques for such manipulations, including the necessary purification of solvents and the measurement of spectra for sensitive substances, have already been described.[6,7]

Preparation of Starting Materials. The diisobutylaluminum hydride, as obtained from Texas Alkyls, Inc., was 94% pure. Its purification to a 99% grade and its analysis by a modified isoquinoline titration procedure were done in accordance with published methods.[7]

Chloro(phenyl)acetylene was prepared from phenylethynylsodium and *p*-toluenesulfonyl chloride, bp 23–24° (0.35 mm).[17] Phenylethynyllithium was prepared as a colorless suspension in cyclohexane by admixing equimolar quantities (18.2 mmol) of freshly distilled phenylacetylene and a 2.2 *M* hexane solution of *n*-butyllithium in 20 ml of cyclohexane. Diphenyl(phenylethynyl)aluminum was prepared from triphenylaluminum and phenylacetylene by adherence to a known procedure,[18] mp 142–144°, recrystallized from benzene and cyclopentane. Dimethyl(phenylethynyl)amine was prepared by heating bromo(phenyl)acetylene with trimethylamine for 50 hr at 55° in a sealed tube, bp 45–47° (0.07 mm).[19] Ethyl phenylethynyl sulfide was prepared by allowing sodium thioethoxide to react with bromo(phenyl)acetylene in DMF at lower temperatures,[20] bp 75–76° (0.35 mm). Because alkoxy(phenyl)acetylenes are difficult to synthesize in the pure state and are prone to polymerization,[21] the acetylenic ether chosen for this study was the commercially available 1-ethoxy-1-hexyne (Farchan Chemical Co.), bp 60–61° (0.9 mm).

Reactions of the 1-Substituted Alkynes with Diisobutylaluminum Hydride. General Procedure. The alkyne was dissolved or suspended in an anhydrous saturated hydrocarbon at the chosen temperature. In those cases where anhydrous *N*-methylpyrrolidine was used, it was admixed with the alkyne before reaction. The reaction vessel was equipped with a reflux condenser surmounted by a nitrogen gas inlet, a neck provided with a rubber septum, and a magnetic stirring bar. The diisobutylaluminum hydride was then added, either dropwise or in one portion, by means of a gas-tight syringe. After spectral monitoring or the hydrolysis of aliquots had shown the reaction to be complete, the chilled reaction mixture was cautiously treated with small amounts of degassed H_2O or D_2O (99.9%), in a dropwise manner, to yield a fine, granular suspension of aluminum hydroxide, which could be filtered off and washed with solvent to give directly a dry organic filtrate. (In some runs, dilute, degassed hydrochloric acid was used for effecting homogeneous hydrolysis. Thereafter, the separated organic layer was dried over anhydrous calcium sulfate.) Removal of solvent on a rotary film evaporator, gas chromatographic analysis, purification by distillation or preparative GLC, and spectral characterization completed the procedure.

Trans Hydralumination of Dimethyl(phenylethynyl)amine (4). A. Without *N*-Methylpyrrolidine. To 3.3 g (22.8 mmol) of **4** in 10 ml of dry cyclopentane was added 4.0 ml (22.5 mmol) of the hydride in a dropwise manner, while the solution was cooled to 0°. The solution gradually turned yellow but no gas evolution could be observed. After 10 min of stirring at 25° an aliquot was withdrawn for NMR spectral analysis. The spectrum, recorded at 30° after a total reaction time of 35 min, showed that **4** was already consumed and that the trans hydralumination adduct, $C_6H_5(i\text{-}Bu_2Al)_2$-C=C($NMe_2$)H (**11**), and the hydraluminated dimer, $C_6H_5(i\text{-}Bu$-Al)C=C(NMe_2)(C_6H_5)C=C(NMe_2)H (**13**) (cf. infra), had been formed in a ratio of 2:1. (Integrated signals for the respective vinylic and NMe_2 signals of **11** and **13** were in agreement with this ratio; the composite phenyl signal area between 6.8 and 7.3 ppm also corresponded to that to be expected.) Spectral data (cyclopentane) for **11**: δ 2.8 (d, NMe peaks separated by 2.0 Hz) and 6.08 (s, with shoulder peak of ca. one-third intensity at 6.06). For **13**: δ 2.32 (s, NMe_2), 2.52 (s, NMe_2, with a shoulder at 2.48), 2.68 (s, NMe_2), and 6.47 (s). For complexed diisobutylaluminum hydride: δ 3.63 (br, AlH) and 3.78 (sharp, AlH). After a reaction time of 50 hr the NMR spectrum of the mixture recorded at 0° displayed sharp signals without shoulders at δ 2.23, 2.47, 3.09, 3.20, and 3.27 (NMe_2) and at 6.01 and 6.43 (vinylic C–H).

The main reaction solution was slowly treated with water after a total reaction time of 4 hr. The color of the mixture changed from yellow to orange-red upon completion of hydrolysis. Upon extraction with ether the red color was adsorbed by the aluminum hydroxide and the filtered ether solution then became yellow. The NMR spectrum ($CDCl_3$) of the pale yellow distilled product [3.0 g, bp 50–53° (0.1 mm)] showed it to be dimethyl [(*E*)-β-styryl]amine[22] (**12**): δ 2.5 (s, NMe_2), 5.04 (d, =CH, *J* = 14 Hz), 6.58 (d, C=CH, *J* = 14 Hz), 6.85–7.25 (m, 5 H); ir (neat) significant bands at 695, 790, 935 (s, trans CH=CH out-of-plane bending) and 1635 cm^{-1} (s, C=C stretch).

The distillation residue consisted of 1.5 g of a viscous brown oil: NMR ($CDCl_3$) δ 2.58 and 2.62 (s, 6 H each, NMe_2 groups), 5.48 and 6.18 (s, 1 H each, C=CH), and 6.80–7.4 (m, 10 H); ir (neat) 698 (s), 760 (s), 975 (m), 1070 (s), 1090 (s), 1130 (s), 1335 (s), 1380 (s), 1415 (s), 1432 (s), 1480 (s), 1560–1630 (s, broad set of bands), and 2795–3075 cm^{-1} (s, broad set of bands). This product appeared to be (*Z,E*)-1,3-bis(dimethylamino)-2,4-diphenyl-1,3-butadiene (**14**).

Another run of the hydralumination was carried out and then the reaction mixture (after 4 hr of reaction time) was treated slowly with D_2O (99.9% pure) and the hydrolysate was worked up in the standard manner. The distilled dimethyl[(*E*)-β-styryl]amine obtained was analyzed spectroscopically: NMR (neat) δ 2.42 (s, NMe_2) 6.56 (t, =CH, *J* = 2 Hz), 6.82–7.25 (m, 5 H); ir (neat) bands at 790 and 935 cm^{-1} had essentially disappeared; bands at 695 and 1620 cm^{-1} were still strong.

Calculations of the chemical shifts for the vinyl protons[9] result in an estimate of 5.44 ppm for the proton adjacent to the phenyl group (observed, 5.04) and of 6.34 for that adjacent to the NMe_2 group (observed, 6.58). Thus, the signal assignment for these protons should be the reverse of those made in the literature.[22] Accordingly, then, the deuterium labeling showed that the aluminum in the hydralumination adduct was attached to the phenyl-substituted vinyl carbon.

Furthermore, the NMR spectrum of the dimeric **14**, which was isolated as a distillation residue from the run with a D_2O work-up, had only the vinyl singlet at 6.18 ppm. Since the vinyl singlet at 5.48 ppm had disappeared, the aluminum precursor of **14** must have been of the general structure $C_6H_5(i\text{-}Bu_2Al)C{=}C(NMe_2)$-$(C_6H_5)C{=}C(NMe_2)H$.

Another run was conducted with 2.31 g (16 mmol) of **4** and 3.0 ml (17 mmol) of the hydride in 6.0 ml of cyclopentane at −20° and the reaction was followed by NMR spectroscopy. Under these conditions the aminoacetylene was 50% consumed in 40 min and little dimerization took place.

B. With *N*-Methylpyrrolidine. A solution of 1.15 g (8 mmol) of **4** and 2.0 ml (8 mmol) of anhydrous *N*-methylpyrrolidine dissolved in 10 ml of dry heptane was cooled in a Dry Ice–acetone bath (−78°). To this chilled suspension was slowly added 2.1 ml (12 mmol) of the hydride. An aliquot was withdrawn and its NMR spectrum recorded at −23° after different periods of time. At −23° no vinyl proton ascribable to the aluminum precursor of the reduced dimer **13** (=CH at 6.42 ppm with =CH of $C_6H_5(i\text{-}Bu_2$-Al)C=C(NMe_2)H taken as 6.0 ppm) was discernible but there was a singlet at 6.28 ppm, which was ca. 15% of the signal of the diisobutyl[(*Z*)-β-dimethylamino-α-styryl]aluminum (**11**) at 6.0 ppm. The signal at 6.28 ppm might have been due to the (*E*)-β-dimethylamino-α-styryl isomer (**15**) of **11**.

Finally, the temperature was raised to 30° and under these conditions the reaction was complete in ca. 5 min. Here, only the monomeric product was detectable; no dimeric vinyl protons were present. The usual hydrolytic work-up showed that the resulting product was pure **12**.

Heating a sample of the hydralumination adduct in heptane solution for 45 min and working up in the usual manner gave only **12**, with no detectable amount of phenylacetylene.

Cis Hydralumination of Ethyl Phenylethynyl Sulfide (6). A. Hydrolytic Work-up. Stirring a solution of 1.82 g (11.2 mmol) of **6** and 2.0 ml (11.2 mmol) of the hydride in 10 ml of dry cyclopentane at 25° for 12 hr and hydrolytic work-up gave almost a quantitative yield of ethyl *cis*-β-styryl sulfide.[23,24] By GLC analysis on a 12-ft column packed with silicone gum rubber only ca. 0.1% of phenylacetylene was detected. Spectral data for ethyl *cis*-β-styryl sulfide: NMR ($CDCl_3$) δ 1.30 (t, CH_3, *J* = 7.0 Hz), 2.72 (q, CH_2, *J* = 7.0 Hz), 6.20 (d, =CH, *J* = 11 Hz), 6.46 (d, =CH, *J* = 11 Hz), 6.97–7.70 (m, 5 H); ir (neat) 698 (s), 725 (m), 770 (s), 850 (s), 910 (m), 970 (m), 1030 (m), 1055 (m), 1070 (m), 1265 (s), 1365 (s), 1445 (s), 1490 (s), 1565 (m), 1595 (s), 2870 (m), 2925 (s), 2970 (s), 3020 (m), and 3050 cm^{-1} (m).

Calculation of the chemical shifts for the vinyl protons,[9] whose coupling constant showed them to be cis,[25] yielded values of 6.59 and 6.18 ppm for the hydrogens α and β, respectively, to the phenyl group. These estimates compare fairly well with the observed values of 6.46 and 6.20 ppm and they help to secure the attribution of the signals to the proper vinylic proton. In addition, infrared correlations[26] for 1-alkylthio-1-alkenes lead one to expect a strong

out-of-plane bending vibration at 935 cm^{-1} for a trans CH=CH group or a strong in-plane bending vibration at 1330–1350 cm^{-1} for a cis CH=CH group. The absence of the former band and the presence of a strong band at 1365 cm^{-1} confirmed the assignment of the cis configuration.

B. Work-up with Deuterium Oxide. The foregoing hydralumination was repeated: in one case, with 2 equiv of the hydride in cyclopentane at 25° for 5 hr; and, in the other case, neat, with 3 equiv of the hydride. Addition of D_2O and usual work-up yielded ethyl *trans*-β-styryl sulfide, which was examined by NMR spectroscopy (neat): both vinylic doublets had disappeared and now two broad singlets (with hint of triplet character, $J_{HD} \simeq 2.0$ Hz) appeared at 6.08 and 6.33 ppm in an intensity ratio of (a) 82:19, for the run with 2 equiv of hydride; and (b) 85:15, for that with 3 equiv. These results showed that $C_6H_5CH{=}C(SEt)Al\text{-}i\text{-}Bu_2$ was the principal regioisomer and $C_6H_5(Al\text{-}i\text{-}Bu_2)C{=}C(SEt)H$ the minor.

C. Attempted Isomerization. When 1.82 g (11.2 mmol) of **6** and 6.0 ml (33 mmol) of the hydride were heated in 15 ml of dry cyclohexane for 5 hr, ca. 1–2% of phenylacetylene was detected upon hydrolytic work-up, but the sulfide isolated had not isomerized to the trans configuration. Also, neither the addition of diisobutylaluminum chloride to such a hydralumination reaction, followed by heating, nor the addition of a small amount of bis(1,5-cyclooctadiene)nickel(0)[10] caused any isomerization.

Cis Hydralumination of 1-Ethoxy-1-hexyne (5) in the Presence of *N*-Methylpyrrolidine. A solution of 3.50 g (28 mmol) of freshly distilled **5** and 2.4 g (28 mmol) of anhydrous *N*-methylpyrrolidine in 20 ml of dry pentane was cooled to −78° and then slowly treated with 5.6 ml (31 mmol) of the hydride. The temperature of reaction mixture was gradually allowed to come to room temperature and to remain there for 10 hr. One-half of the resulting mixture was worked up in the usual manner with water, the other half with D_2O.

The organic layer from the hydrolysis was shown by GLC to contain 1-hexyne (ca. 30%) and 1-ethoxy-1-hexene; the latter was chiefly (>97%) the cis isomer, bp 65–66° (0.9 mm). Spectral data: NMR (neat) δ 0.75–1.5 (m, $OCCH_3$, $n\text{-}C_3H_7$), 2.07 (br q, $CH_2C{=}$, J = 7.0 Hz), 3.69 (q, OCH_2, J = 7.0 Hz), 4.27 (ca. q, =CH, $J \simeq$ 6.5–8.0 Hz), 5.86 (d of t, =CH, J = 6.5 and 1.2 Hz); ir (neat) 600–1100 clear, 1115 (s), 1660 cm^{-1} (s). By the magnitude of the coupling constant for the vinyl protons, it is clear that the double bond had the cis configuration. Calculation of the expected chemical shifts for the vinyl protons gave a value of 4.44 ppm for the proton α to the *n*-butyl group and 6.17 ppm for that β to this group. These agree reasonably well with the observed values of 4.27 and 5.86 ppm.

Similar work-up of the other portion of the reaction mixture with D_2O gave a deuterated *cis*-1-ethoxy-1-hexene with these spectral properties: NMR (neat) the quartet centered at 4.27 had almost disappeared and the doublet of triplets at 5.86 had collapsed to a broad singlet. Hence, the aluminum precursor was preponderantly $(n\text{-}Bu)(i\text{-}Bu_2Al)C{=}C(OEt)H$.

Anal. Calcd for $C_8H_{16}O$: C, 74.94; H, 12.59. Found: C, 74.73; H, 12.64.

Attempted Hydralumination of Halo(phenylethynyl)acetylenes [Cl (9) and Br (10)]. A solution of 1.40 g (10.2 mmol) and **9** and 1.85 ml (10.5 mmol) of the hydride in 20 ml of dry cyclohexane was allowed to stand at 25° for 4 hr. Usual work-up revealed the presence of the starting chloro(phenyl)acetylene and *ca.* 3% of phenylacetylene.

A solution of 3.0 g (16.5 mmol) of **10** and 8.25 ml (49.5 mmol) of the hydride in 80 ml of dry cyclohexane was allowed to stand at room temperature for 5 days and then worked up with water. A GLC analysis on a 12-ft column packed with silicone SE-30 on firebrick showed the presence of styrene (59%), ethylbenzene (22%), and phenylacetylene (19%); this analysis was confirmed by NMR spectroscopy.

Hydralumination of Phenylethynyllithium (7). Phenylacetylene (930 mg, 9.1 mmol) in 20 ml of dry heptane was treated with 4.2 ml of *n*-butyllithium in hexane (2.21 *M*, 9.3 mmol) to yield a colorless suspension of **7**. Then 3.25 ml (18.2 mmol) of the hydride was added with stirring, after which the precipitate dissolved within 30 min. After a further 90 min at room temperature, the usual hydrolytic work-up led only to phenylacetylene; no styrene or ethylbenzene could be detected.

When another run with the foregoing proportions of reagents was heated at 80° for 60 min before hydrolysis, subsequent work-up yielded an oil and a solid (2:1). A NMR spectral analysis of the former revealed the presence of phenylacetylene and ethylbenzene in a ratio of 2:3, with only traces of styrene. The solid appeared to be polystyrene, based upon its solubility in acetone and its ir and NMR spectra.

When 18.2 mmol of **7** was heated with 73 mmol of the hydride in 20 ml of dry cyclohexane for 24 hr at 80°, subsequent work-up with D_2O and GLC analysis showed the presence of only ethylbenzene. A NMR spectrum of this hydrocarbon in $CDCl_3$ displayed broad singlets at 2.62 and 7.2 ppm, but essentially no absorption at 1.0 ppm. Thus, the product was preponderantly β,β,β-trideuterioethylbenzene.

Hydralumination of Diphenyl(phenylethynyl)aluminum (8). A solution of 1.27 g (4.5 mmol) of **8** and 0.80 ml (4.5 mmol) of the hydride in 10 ml of dry benzene was maintained at 20° for 0.5 hr and then at 40° for 22 hr. Work-up with D_2O and GLC analysis showed the products to be phenylacetylene (55%), styrene (18%), and ethylbenzene (27%). A NMR spectral examination showed that the products to be deuterated thus: $C_6H_5C{\equiv}CD$ (absence of absorption at 2.75 ppm); $C_6H_5CH{=}CD_2$ (broad singlet at 6.6 and absence of absorptions in the region 5.0–5.8 ppm); and $C_6H_5CH_2CD_3$ (broad singlet at 2.62 ppm and absence of absorptions in the region 0.95–1.25 ppm).

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Registry No.—**3,** 1191-15-7; **4,** 4604-65-3; **5,** 2806-51-1; **6,** 14476-62-1; **7,** 4440-01-1; **8,** 1157-32-0; **9,** 1483-82-5; **10,** 932-87-6; **11,** 55133-72-7; **12,** 14846-39-0; **13,** 55133-73-8; **14,** 55133-74-9; phenylethynylsodium, 1004-22-4; *p*-toluenesulfonyl chloride, 98-59-9; phenylacetylene, 536-74-3; *n*-butyllithium, 109-72-8; *N*-methylpyrrolidine, 120-94-5; ethyl *cis*-β-styryl sulfide, 20890-79-3; ethyl *trans*-β-styryl sulfide, 20890-80-6; *cis*-1-ethoxy-1-hexene, 50849-04-2.

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(15) Alternatively, the regiospecificity of hydralumination observed with **7** and **8** could be interpreted in terms of $p_\pi\text{-}p_\pi$ dispersal of π-electron density onto the metal center: $R'C^+{=}C{=}M^-$. However, it is likely that, in the presence of R_2AlH, both **7** and **8** are tetracoordinate and that no np_z metal orbital is available for such delocalization.
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A Stereoselective Synthesis of Cycloalkene-Fused Butyrolactones via Cyclopropylcarbinol Solvolysis

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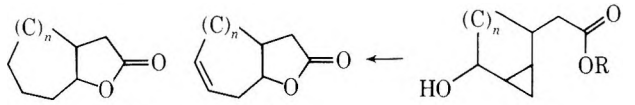
Various isomeric cyclohexanols and cyclopentanols bearing fused cyclopropane rings at the 2,3 position and acetic acid chains at the 4 position were synthesized by unambiguous routes. These cyclopropylcarbinols were then subjected to solvolysis in aqueous acid to give cycloheptene- and cyclohexene-fused γ-butyrolactones. These reactions proceeded in high yield with retention of C-3/C-4 stereochemistry and did not appear to be sensitive to the steric orientation of the carbinol grouping.

Fused ring γ-butyrolactones are widely distributed among natural products of plant origin, especially the sesquiterpene family.[1] The majority of these substances contain cis- or trans-fused lactones derived from 2-hydroxycyclohexyl- and 2-hydroxycycloheptylacetic acid moieties (part structure I). A reasonable route to (potentially more useful) unsaturated derivatives of such lactones (part structure II) can be envisioned as indicated (III → II) via solvolysis of a cyclopropylcarbinol (part structure III)

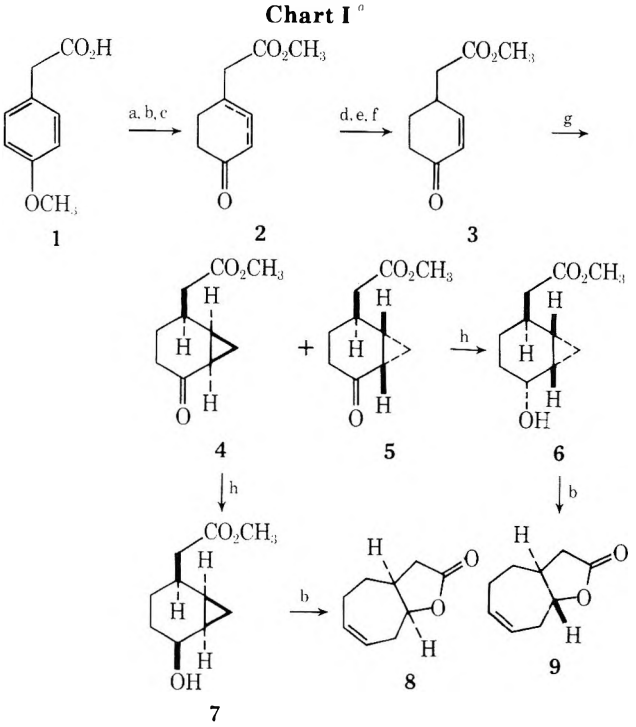


I ($n = 1$ or 2) II III

with participation of an appropriately positioned acetic acid appendage.[2] In fact, preliminary work along these lines showed great promise.[3] However, before this methodology could be applied to natural product synthesis, additional studies were needed to probe the regio and stereo aspects of the solvolysis reaction. These studies are reported herein.

In our preliminary work we examined the solvolysis of the bicyclo[4.1.0]heptanol **6**.[3] This substance and an isomer (**7**) were obtained as an 85:15 mixture by the route outlined in Chart I. Birch reduction of *p*-methoxyphenylacetic acid

Chart I[a]



(1) followed by acidic hydrolysis of the resulting enol ether and subsequent acidic esterification with methanol afforded the unsaturated keto ester **2** as a nearly 1:1 mixture of double bond isomers. The desired α,β isomer **3** was purified through the piperidine adduct.[4] Addition of dimethylsulfoxonium methylide[5] to enone **3** proceeded smoothly to give an 85:15 mixture of the cyclopropyl ketones **5** and **4**. This mixture could not be separated and was therefore used as such for the subsequent steps. Our stereochemical assignments are based on the expectation of favored attack by the methylide on the less hindered face of enone **3**.[6]

Reduction of the ketone mixture **5** and **4** with sodium borohydride led to the alcohols **6** and **7**. Again our stereochemical assignments presuppose favored attack by hydride on the less hindered face of the ketone carbonyl in a kinetically controlled process.[7] The alcohol mixture **6** and **7** upon treatment with aqueous perchloric acid in methanol at room temperature afforded an 85:15 mixture of the trans and cis lactones **9** and **8**. The identity of these products was ascertained by comparison of their dihydro derivatives, secured by catalytic hydrogenation, with authentic samples.[8]

An unequivocal synthesis of the cyclopropylcarbinol **6** and its carbinyl epimer **12** (as the acid) is shown in Chart II. Oxidation of the tricyclic ketone **10** of known stereochemistry[9] with *m*-chloroperoxybenzoic acid in methylene chloride gave rise to the lactone **11**. Saponification followed by esterification of the acid **12** with diazomethane and oxidation with the chromium trioxide–pyridine reagent in methylene chloride[10] yielded the keto ester **5** identical with the major methylide adduct of enone **3**. Reduction either with sodium borohydride or K-Selectride afforded the previously obtained hydroxy ester **6**. Both this hydroxy ester and the epimeric hydroxy acid **12** were smoothly converted to the trans lactone **9** in aqueous perchloric acid. Lactone **11** could also be directly rearranged to lactone **9** under these reaction conditions.

Efforts at obtaining the *syn-cis-syn*-bicyclo[4.1.0]heptanol **16** along the lines described above were less rewarding owing to an unfavorable isomer distribution in the Baeyer–Villiger oxidation of the tricyclic ketone **13**. Despite numerous trials with a variety of peroxy acids we were able to realize only a 1:9 mixture of lactones **15** and **14**. Lactone **15**, however, could be purified by column chromatography, thereby permitting an examination of its solvolysis. Initial attempts at conversion of this lactone to hydroxy acid **16** by saponification and subsequent acidification gave mainly the cis-fused lactone **8**. Evidently the intermediate hydroxy acid **16** solvolyzes with exceptional ease. Lactone **8** was most efficiently prepared via acid-catalyzed rearrangement of lactone **15**. This rearranged lactone was identified by comparison of its hydrogenation product with an authentic sample.[8] It was also found to have gas chromatographic characteristics identical with those of the minor solvolysis

Chart II[a]

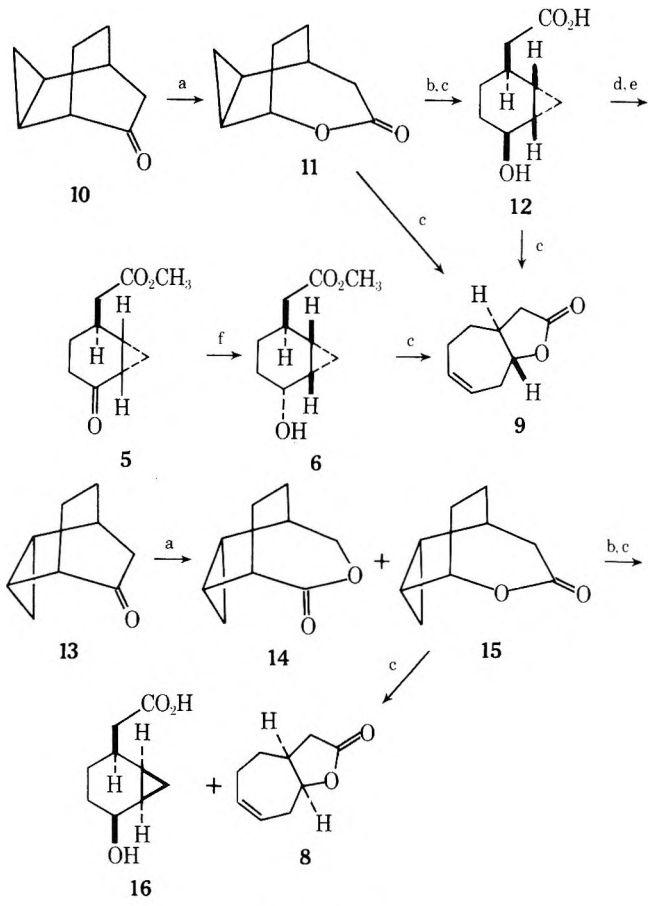
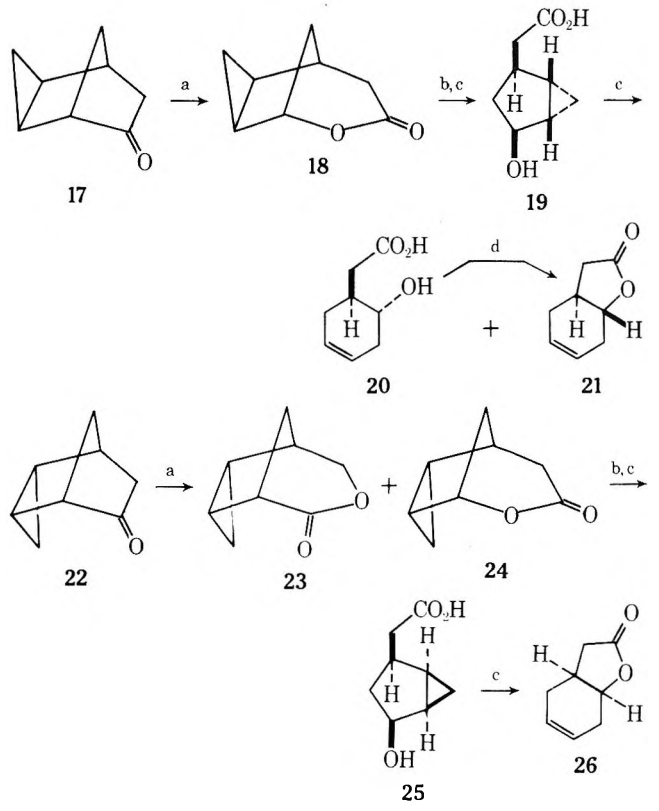


Chart III[a]



product of the hydroxy ester mixture (**6** and **7**) described above.

Parallel studies to those just detailed were next undertaken to examine the possible conversion of bicyclo[3.1.0]hexanols to cyclohexene-fused γ-butyrolactones (Chart III). Accordingly, the known tricyclic ketone **17**[11] was oxidized with *m*-chloroperoxybenzoic acid in methylene chloride to the lactone **18**. Saponification then gave the hydroxy acid **19**, which was converted to a mixture of hydroxy acid **20** and lactone **21** upon treatment with aqueous perchloric acid. Control experiments indicated that hydroxy acid **20** was formed via hydrolysis of lactone **21** rather than as a direct solvolysis product. Lactone **21** was identified through comparison of its hydrogenation product with an authentic sample.[12]

Oxidation of tricyclic ketone **22** with *m*-chloroperoxybenzoic acid in methylene chloride afforded the lactone **24**. Interestingly this oxidation, like its *endo*-bicyclo[2.2.2]octanone counterpart **13**, gave a significant amount of the isomeric lactone (**23**). However, this undesired isomer comprised a considerably smaller proportion of the product (20% vs. 90%) than in the aforementioned case. Lactone **24** could be purified by fractional crystallization, thus allowing for the preparation of pure hydroxy acid **25** by saponification. Solvolysis in aqueous perchloric acid led to the cis lactone **26**, identified by comparison of its hydrogenation product with an authentic sample.

Our findings indicate that the cyclopropylcarbinol solvolysis route to fused-ring γ-butyrolactones is efficient and highly stereoselective. It is tempting to speculate that the acetic acid (ester) side chain plays an important anchimeric part in the solvolysis reaction. The fact that both epimeric carbinols **6** and **12** afford the same lactone suggest that alcohol stereochemistry is not a critical factor. Thus an initial dissociative process followed by a carboxyl-assisted collapse of the intermediate ion would seem to best fit the results to date.

Experimental Section[13]

Methyl 2-(4-Oxo-2-cyclohexenyl)acetate (3). To a stirred solution of 101 g (0.61 mol) of *p*-methoxyphenylacetic acid in 200 ml of ethanol, 750 ml of ether, and 1.5 l. of liquid ammonia at −78° was added 27.3 g (3.9 g-atoms) of lithium wire in 2–3-cm pieces over a period of 3 hr. The ammonia was allowed to evaporate, water (500 ml) and concentrated hydrochloric acid (300 ml) were added, and the crude product was isolated by extraction with ether, affording 84 g of yellow oil (ca. 90% yield).

A 57.8-g portion of the above oil in 120 ml of 1,2-dichloroethane and 50 ml of methanol containing 3 ml of concentrated sulfuric acid was stirred at reflux for 6 hr. The cooled mixture was poured into water and the keto ester **2** (62.1 g), a 1:1 mixture of double bond isomers according to NMR analysis, was extracted with ether.

The crude keto ester **2** (62.1 g) was dissolved in 105 ml of piperidine. After 32 hr, the mixture was poured into 500 ml of 20% aqueous hydrochloric acid. The acidic solution was extracted with ether, cooled, and made basic with cold 20% sodium hydroxide. Ether extraction afforded 31.9 g of an orange solid piperidine adduct of enone **3**. This material was combined with 4.5 g of adduct from another run and the whole was treated with 80 ml (ca. 1.3 mol) of methyl iodide added at a rate to maintain reflux. The mixture was stirred for 24 hr and the excess methyl iodide was removed under reduced pressure. Pyridine (40 ml) was added and the mixture was heated on a steam bath for 3 hr, cooled, and poured into water. The product was isolated with ether and distilled to give 12 g of keto ester **3**, bp 105–110° (0.02 mm), which crystallized on standing. Recrystallization from ether afforded material: mp 51.5–53°; λ_{max} ($CHCl_3$) 5.78, 5.98 μ; δ_{TMS} (CCl_4) 6.36 (doubled AB pattern, J_{AB} = 10 Hz, $\Delta\nu_{AB}$ = 54 Hz), 3.70 ppm (OCH_3). The analytical sample, mp 51.5–53°, was secured by recrystallization.

Anal. Calcd for $C_9H_{12}O_3$: C, 64.27; H, 7.19. Found: C, 64.15; H, 7.19.

Methyl 2-(5-Oxo-*r*-2-*H*,*c*-1-*H*,*c*-6-*H*-bicyclo[4.1.0]hept-2-yl)acetate (4) and Methyl 2-(5-Oxo-*r*-2-*H*,*t*-1-*H*,*t*-6-*H*-bicyclo[4.1.0]hept-2-yl)acetate (5). The ylide was prepared from 5.42 g (24.6 mmol) of trimethylsulfoxonium iodide[5] and 0.59 g (24.6 mmol) of pentane-washed sodium hydride (from 1.04 g of 57% oil dispersion) in 28 ml of dimethyl sulfoxide (DMSO). After stirring

at 50° for 2 hr the milky suspension was cooled to room temperature and treated with a solution of 3.93 g (23.4 mmol) of keto ester 3 in 10 ml of DMSO. After stirring at room temperature for 3 hr and at 50° for 1 hr the mixture was treated with saturated brine and the product was isolated by extraction with ether to give 3.62 g (85%) of yellow oil. NMR and gas chromatographic analysis in conjunction with later synthetic work showed this to be a roughly 85:15 mixture of the anti (5) and syn (4) isomers, λ_{max} (film) 5.78, 5.92 μ, δ_{TMS} (CCl_4) 3.62 ppm (OCH_3).

Methyl 2-(5-Oxo-*r*-2-*H*,*t*-1-*H*,*t*-6-*H*-bicyclo[4.1.0]hept-2-yl)acetate (5). A solution of 1.63 g (9.6 mmol) of hydroxy acid 12 in 60 ml of ether was added to an ethereal solution of diazomethane generated from 3.2 g (30 mmol) of *N*-nitroso-*N*-methylurea.[14] After standing overnight the solution was washed with saturated aqueous sodium bicarbonate and dried over magnesium sulfate. Distillation afforded 1.71 g (96%) of hydroxy ester, bp 105° (bath temperature) (0.05 mm), which was 95% pure according to gas chromatography.

A 1.48-g sample of this material was oxidized with 4.83 g of CrO_3 and 7.75 ml of pyridine in 110 ml of methylene chloride (Collin's reagent)[10] at room temperature for 30 min. The product was isolated with ether and distilled to give 1.23 g (84%) of keto ester 5: bp 105° (bath temperature) (0.05 mm); λ_{max} (film) 5.78, 5.92 μ; δ_{TMS} (CCl_4) 3.63 ppm (OCH_3). The analytical sample was secured by preparative layer chromatography (silica gel) and redistillation.

Anal. Calcd for $C_{10}H_{14}O_3$: C, 65.92; H, 7.74. Found: C, 66.09; H, 7.90.

This material was found to coincide with the major dimethylsulfoxonium methylide adduct of enone 3 according to NMR and GC comparisons.

Methyl 2-(*c*-5-Hydroxy-*r*-2-*H*,*t*-1-*H*,*t*-6-*H*-bicyclo[4.1.0]-hept-2-yl)acetate (6). A solution of 0.22 g (1.2 mmol) of keto ester 5 in 20 ml of THF at 0° was treated with 4 ml of 0.5 *M* K-Selectride[15] in THF. After 1 hr, 1.5 ml of 20% aqueous sodium hydroxide and 1.5 ml of 30% hydrogen peroxide were added and stirring was continued for 15 min. The product was isolated by extraction with ether and distillation, which gave 0.22 g (98%) of hydroxy ester 6: bp 105° (bath temperature) (0.05 mm); λ_{max} (film) 2.96, 5.76 μ; δ_{TMS} (CCl_4) 4.05 (H-5, m), 3.63 (OCH_3), 3.45 ppm (OH). The analytical sample was secured by preparative layer chromatography (silica gel) and redistillation.

Anal. Calcd for $C_{10}H_{16}O_3$: C, 65.19; H, 8.75. Found: C, 64.97; H, 8.97.

Methyl 2-(*c*-5-Hydroxy-*r*-2-*H*,*t*-1-*H*,*t*-6-*H*-bicyclo[4.1.0]-hept-2-yl)acetate (6) and Methyl 2-(*t*-5-Hydroxy-*r*-2-*H*,*c*-1-*H*,*c*-6-*H*-bicyclo[4.1.0]hept-2-yl)acetate (7). The crude 85:15 mixture of keto esters 5 and 4 described above (3.62 g, 19.9 mmol) in 30 ml of methanol at 0° was treated with 0.75 g (20 mmol) of solid sodium borohydride. The mixture was stirred for 15 min, poured into brine, and extracted with ether to give 2.87 g (66.5% based on enone 3) of hydroxy esters 6 and 7, bp 120° (bath temperature) (0.05 mm), a roughly 85:15 mixture. The spectral properties attributable to the major component matched those of an authentic sample of the anti-cis-syn isomer 6 prepared as described above.

***cis*-2-(2-Hydroxy-4-cycloheptenyl)acetic Acid Lactone (8).** A solution of 54 mg (0.35 mmol) of lactone 15 (98% pure according to gas chromatography) in 5 ml of 7% aqueous perchloric acid and 0.5 ml of acetone was stirred for 24 hr at room temperature. The product was isolated with ether and distilled, affording 47 mg (87%) of lactone 8: bp 130° (bath temperature) (0.05 mm); λ_{max} (film) 5.59 μ; δ_{TMS} (CCl_4) 5.48–5.68 (H-4, H-5, m), 4.50–4.87 ppm (H-2, m). The analytical sample was secured by preparative layer chromatography (silica gel) and redistillation.

Anal. Calcd for $C_9H_{12}O_2$: C, 71.03; H, 7.95. Found: C, 71.05; H, 8.14.

Hydrogenation of a 40-mg sample over 20 mg of 5% platinum on carbon in 10 ml of ethanol afforded material with identical spectral (infrared, NMR) and chromatographic properties with those of an authentic sample.[8]

***trans*-2-(2-Hydroxy-4-cycloheptenyl)acetic Acid Lactone (9). A. From Hydroxy Ester 6.** A solution of 0.21 g (1.1 mmol) of hydroxy ester 6 in 10 ml of 7% aqueous perchloric acid and 3 ml of acetone was stirred at room temperature for 24 hr. The product was isolated with ether and distilled, affording 0.15 g (85%) of white solid, mp 44–46.5° after recrystallization from ether.

Solvolysis of the 85:15 mixture of hydroxy esters 6 and 7 under similar conditions afforded an 85:15 mixture of lactones 9 and 8 according to gas chromatographic analysis.

B. From Hydroxy Acid 12. A solution of 0.30 g (1.76 mmol) of hydroxy acid 12 in 8 ml of 7% aqueous perchloric acid and 1 ml of methanol was stirred for 24 hr at room temperature. The product was isolated with ether and distilled, affording 0.251 g (94%) of white solid: mp 41–43°; λ_{max} (KBr) 5.62 μ; δ_{TMS} (CCl_4) 5.63–5.96 (H-4, H-5, m), 3.61–4.09 ppm (H-2, m). The analytical sample, mp 44–46°, was obtained after several recrystallizations from ether–hexane.

Anal. Calcd for $C_9H_{12}O_2$: C, 71.03; H, 7.95. Found: C, 70.91; H, 8.00.

Hydrogenation of this material over 5% platinum on carbon in ethyl acetate afforded *trans*-2-(2-hydroxycycloheptyl)acetic acid lactone, identified by comparison with an authentic sample.[8]

C. From Lactone 11. A solution of 0.20 g (1.31 mmol) of lactone 11 in 10 ml of 7% aqueous perchloric acid and 1 ml of acetone was stirred for 24 hr at room temperature. The product was isolated with ether and distilled, affording 150 mg (75%) of lactone 9, mp 43–45° after recrystallization from ether.

2-(*t*-5-Hydroxy-*r*-2-*H*,*t*-1-*H*,*t*-6-*H*-bicyclo[4.1.0]hept-2-yl)acetic Acid Lactone (11). A mixture containing 0.80 g (5.9 mmol) of ketone 10,[9] 1.33 g (7.7 mmol) of *m*-chloroperoxybenzoic acid,[16] and 0.49 g (5.9 mmol) of sodium bicarbonate in 40 ml of methylene chloride was stirred at room temperature for 2 days. The solution was washed with 10% aqueous sodium hydroxide and saturated brine and dried over magnesium sulfate. After removal of solvent under reduced pressure the solid residue was distilled to give 0.55 g (62%) of waxy solid lactone 11: bp 160° (bath temperature) (0.05 mm); λ_{max} (film) 5.84 μ; δ_{TMS} ($CDCl_3$) 4.67 (H-5, m), 2.98 ppm (H-2, m). The analytical sample, mp 96–100.5°, was secured by recrystallization from hexane and sublimation (70°, 0.05 mm).

Anal. Calcd for $C_9H_{12}O_2$: C, 71.03; H, 7.95. Found: C, 70.89; H, 8.05.

2-(*t*-5-Hydroxy-*r*-2-*H*,*t*-1-*H*,*t*-6-*H*-bicyclo[4.1.0]hept-2-yl)acetic Acid (12). A solution of 0.77 g (5.1 mmol) of lactone 11 and 0.85 g of potassium hydroxide in 25 ml of methanol was heated at reflux for 4 hr. Most of the methanol was distilled under reduced pressure, water was added, and the aqueous phase was washed with ether and acidified with cold 10% aqueous hydrochloric acid. The acidic product was isolated with ethyl acetate, affording 0.85 g (98%) of solid. Recrystallization from chloroform afforded 0.72 g (84%) of acid 12: mp 113–116°; λ_{max} (KBr) 3.05, 3.8–4.0, 5.81 μ; δ_{TMS} (acetone-d_6) 5.52–6.58 (OH), 4.13 ppm (H-5, m). The analytical sample, mp 115–116.5°, was secured after an additional recrystallization and sublimation (80°, 0.05 mm).

Anal. Calcd for $C_9H_{14}O_3$: C, 63.51; H, 8.29. Found: C, 63.50; H, 8.23.

***t*-5-Hydroxymethyl-*r*-2-*H*,*c*-1-*H*,*c*-6-*H*-bicyclo[4.1.0]heptane-2-carboxylic Acid Lactone (14) and 2-(*t*-5-Hydroxy-*r*-2-*H*,*c*-1-*H*,*c*-6-*H*-bicyclo[4.1.0]hept-2-yl)acetic Acid Lactone (15).** A mixture containing 1.72 g (12.7 mmol) of ketone 13,[9] 4.38 g (25.4 mmol) of *m*-chloroperoxybenzoic acid,[16] and 1.09 g (13 mmol) of sodium bicarbonate in 150 ml of methylene chloride was stirred at room temperature for 5 days. The mixture was diluted with ether, washed with 20% aqueous sodium hydroxide, dried over magnesium sulfate, and concentrated under reduced pressure to give 1.87 g of yellow solid. Analysis by gas chromatography indicated a 90:10 mixture of lactones 14 and 15. This mixture could be partially separated by chromatography on silica gel. Lactone 14 was eluted in the earlier fractions. Material thus obtained was recrystallized from ether–petroleum ether to give a white solid: mp 190–192°; λ_{max} (KBr) 5.82 μ; δ_{TMS} ($CDCl_3$) 4.08 ($-CH_2O-$, d, J = 2 Hz), 3.3 (H-2), 2.46 (H-5), 1.84 ppm ($-CH_2CH_2-$).

Anal. Calcd for $C_9H_{12}O_2$: C, 71.03; H, 7.95. Found: C, 71.12; H, 8.00.

The later fractions were further purified by high-pressure liquid chromatography on a Corasil-2 column using 15% ethyl acetate–hexane as eluent. Lactone 15 was thus secured as a white solid, mp 124–127°, after recrystallization from ether–petroleum ether: λ_{max} (KBr) 5.74 μ; δ_{TMS} ($CDCl_3$) 4.77 ppm (H-5, m).

Anal. Calcd for $C_9H_{12}O_2$: C, 71.03; H, 7.95. Found: C, 71.16; H, 8.02.

2-(*t*-4-Hydroxy-*r*-2-*H*,*t*-1-*H*,*t*-5-*H*-bicyclo[3.1.0]hex-2-yl)-acetic Acid Lactone (18). A 3.37-g (27.6 mmol) sample of ketone 17[11] was oxidized with 7.1 g (41.5 mmol) of *m*-chloroperoxybenzoic acid[16] as described above to give 3.04 g (80%) of waxy solid, bp 110° (bath temperature) (0.05 mm). The analytical sample was secured by preparative layer chromatography (silica gel) and short-path distillation: λ_{max} (film) 5.80 μ; δ_{TMS} (CCl_4) 4.63 ppm (H-4).

Anal. Calcd for $C_8H_{10}O_2$: C, 69.55; H, 7.30. Found: C, 69.30; H, 7.46.

2-(*t*-4-Hydroxy-*r*-2-*H*,*t*-1-*H*,*t*-5-*H*-bicyclo[3.1.0]hex-2-yl)-acetic Acid (19). A solution of 1.16 g (8.40 mmol) of lactone 18 and 1.4 g of potassium hydroxide in 40 ml of methanol was stirred at reflux for 4 hr. Most of the methanol was removed under reduced pressure and the aqueous residue was washed with ether and acidified with cold 10% hydrochloric acid. Extraction with ethyl acetate afforded 1.14 g (87%) of solid acid. Recrystallization from ether afforded 0.93 g: mp 107.5–109°; λ_{max} (KBr) 2.99, 3.2–3.8, 5.83 μ; δ_{TMS} (acetone-d_6) 5.25–7.1 (OH), 4.17 ppm (H-4). The analytical sample, mp 108–109°, was secured by recrystallization from ether.

Anal. Calcd for $C_8H_{12}O_3$: C, 61.52; H, 7.75. Found: C, 61.59; H, 7.86.

***trans*-2-(2-Hydroxy-4-cyclohexenyl)acetic Acid Lactone (21).** A solution of 200 mg of hydroxy acid **19** in 10 ml of 7% aqueous perchloric acid and 0.5 ml of acetone was stirred at room temperature for 24 hr. The product was extracted with ethyl acetate and separated into acidic material (**20**, 140 mg) and neutral material (**21**, 60 mg) by base washing (10% sodium hydroxide) and acidification. The acidic material was stirred at reflux for 4 hr with 10 mg of *p*-toluenesulfonic acid in 10 ml of benzene to give 90 mg of lactone **21**. The combined material (150 mg) was distilled to give 136 mg (77%) of waxy solid: bp 100° (bath temperature) (0.05 mm); λ_{max} (KBr) 5.62 μ; δ_{TMS} (CCl_4) 5.58–5.79 (H-4, H-5), 3.75–4.22 ppm (H-2). The analytical sample, mp 54–55.5°, was secured by recrystallization from hexane.

Anal. Calcd for $C_8H_{10}O_2$: C, 69.55; H, 7.30. Found: C, 69.51; H, 7.13.

Hydrogenation of this material over 5% platinum on carbon in ethyl acetate afforded the known *trans*-2-(2-hydroxycyclohexyl)acetic acid lactone.[12]

2-(*t*-4-Hydroxy-*r*-2-*H*,*c*-1-*H*,*c*-5-*H*-bicyclo[3.1.0]hex-2-yl)acetic Acid Lactone (24). The oxidation of 1.87 g (15.3 mmol) of ketone **22**[11] was carried out with 3.98 g of *m*-chloroperoxybenzoic acid[16] for 60 hr as described above to give 1.76 g (83%) of solid lactone **24** contaminated with ca. 20% of the isomeric hydroxymethylcyclopentanecarboxylic acid lactone **23** according to NMR spectral analysis. Purification was effected by five successive recrystallizations from ether–hexane to give material with mp 77–80°: λ_{max} (KBr) 5.80 μ; δ_{TMS} ($CDCl_3$) 4.90 ppm (H-4, m).

Anal. Calcd for $C_8H_{10}O_2$: C, 69.55; H, 7.30. Found: C, 69.56; H, 7.42.

2-(*t*-4-Hydroxy-*r*-2-*H*,*c*-1-*H*,*c*-5-*H*-bicyclo[3.1.0]hex-2-yl)acetic Acid (25). Saponification of 1.20 g (8.70 mmol) of lactone **24** was effected with 2.9 g of potassium hydroxide in 50 ml of methanol as described above to give 1.37 g of solid acid **25**. Recrystallization from ethyl acetate afforded 1.1 g (81%) of material: mp 133–135°; λ_{max} (KBr) 3.08, 3.6–4.1, 5.90 μ.

The analytical sample, mp 134–135°, was secured after three additional recrystallizations from ethyl acetate.

Anal. Calcd for $C_8H_{12}O_3$: C, 61.52; H, 7.75. Found: C, 61.51; H, 7.91.

***cis*-2-(2-Hydroxy-4-cyclohexenyl)acetic Acid Lactone (26).** A solution of 0.19 g (1.2 mmol) of hydroxy acid **25** in 10 ml of 7% aqueous perchloric acid and 1 ml of acetone was stirred at 80° for 24 hr. The product was isolated with ether and distilled, affording 0.14 g (81%) of lactone **26**: bp 85° (bath temperature) (0.05 mm); λ_{max} (film) 5.61 μ; δ_{TMS} (CCl_4) 5.57–5.80 (H-4, H-5, m), 4.54–4.77 ppm (H-2, m). The analytical sample was secured by preparative layer chromatography (silica gel) and redistillation.

Anal. Calcd for $C_8H_{10}O_2$: C, 69.55; H, 7.30. Found: C, 69.37; H, 7.31.

Hydrogenation of this material over 5% platinum on carbon in ethyl acetate afforded the known *cis*-2-(2-hydroxycyclohexyl)acetic acid lactone.[12]

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Registry No.—**1**, 104-01-8; **3**, 52294-81-2; **4**, 55156-65-5; **5**, 52294-82-3; **6**, 52294-83-4; **7**, 55177-23-6; **8**, 55156-66-6; **9**, 52294-84-5; **10**, 51260-37-8; **11**, 55156-67-7; **12**, 55156-68-8; **12** Me ester, 55177-24-7; **13**, 51260-38-9; **14**, 55156-69-9; **15**, 55177-25-8; **17**, 2443-85-8; **18**, 55156-70-2; **19**, 55156-71-3; **21**, 34905-87-8; **22**, 2443-86-9; **23**, 55156-72-4; **24**, 55177-26-9; **25**, 55177-27-0; **26**, 55156-73-5; dimethylsulfoxonium methylide, 5367-24-6; *m*-chloroperoxybenzoic acid, 937-14-4.

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Cyclopropanes. XXXVI. Stereochemistry of the Decomposition of an Optically Active 1-Pyrazoline[1]

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The diastereomeric 3-carbomenthoxy-3-methyl-5,5-diphenyl-1-pyrazolines have been prepared and their absolute configurations established. Thermal and photochemical decomposition of the optically active pyrazoline produced the corresponding cyclopropane derivative with overall *retention of configuration* and in optical yields of 73 and 90%, respectively.

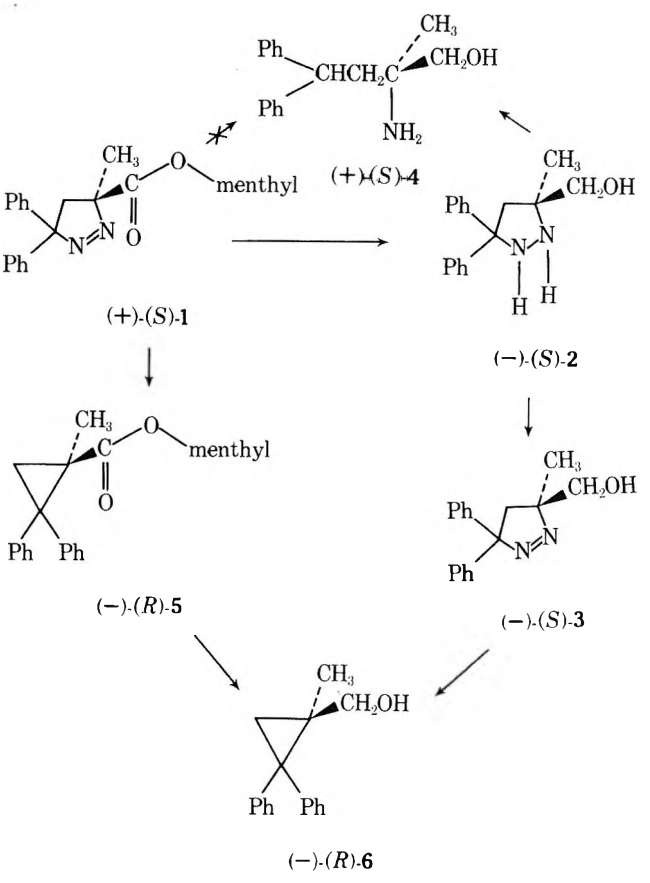
Previous work has indicated that a small amount of asymmetric synthesis occurs when diphenyldiazomethane is added to (−)-(1*R*,2*S*,5*R*)-menthyl methacrylate to produce in diastereomeric excess (−)-(1*R*,2*S*,5*R*)-menthyl (*R*)-1-methyl-2,2-diphenylcyclopropanecarboxylate.[2,3] It was postulated that the reaction proceeded by an initial 1,3-dipolar addition[4] to form a 1-pyrazoline intermediate which decomposed to the cyclopropyl derivative. The 1-pyrazoline was not isolated in this early work. In this article we will report on the synthesis, the determination of absolute configuration, and on the thermal and photochemical decomposition of the optically active 1-pyrazoline, (+)-(1*R*,2*S*,5*R*)-menthyl (*S*)-3-methyl-5,5-diphenyl-1-pyrazoline-3-carboxylate (**1**).

Synthesis and Absolute Configuration of 1. After a number of abortive attempts it was found that **1** could readily be obtained by mixing (−)-(1*R*,2*S*,5*R*)-menthyl methacrylate[2] with solid diphenyldiazomethane at subambient temperature and allowing this mixture to remain at −13° for 5 days. Purification of **1** led to some problems owing to heat sensitivity which caused decomposition at room temperature in a matter of hours. This necessitated working up the reaction mixture below 0°. Moreover, in order to prevent acid-catalyzed decomposition, all glassware was washed with a solution of alcoholic potassium hydroxide before use. Taking these precautions the method of synthesis developed was to treat the acrylate with excess diphenyldiazomethane and to successively wash the solid residue formed with cold methanol (−13°) until the diphenyldiazomethane color was removed. The resulting white solid, $[\alpha]_{Hg}^{23}$ 118.5°, melted sharply at 83–84° with loss of nitrogen and gave NMR and ir spectra consistent with the proposed structure (see Experimental Section).

The absolute configuration of (+)-**1** was established as *S*. The configurational assignment is based on two pieces of evidence. Neither datum by itself can be considered absolute but the internal consistency of both provides a convincing argument for the assignment.

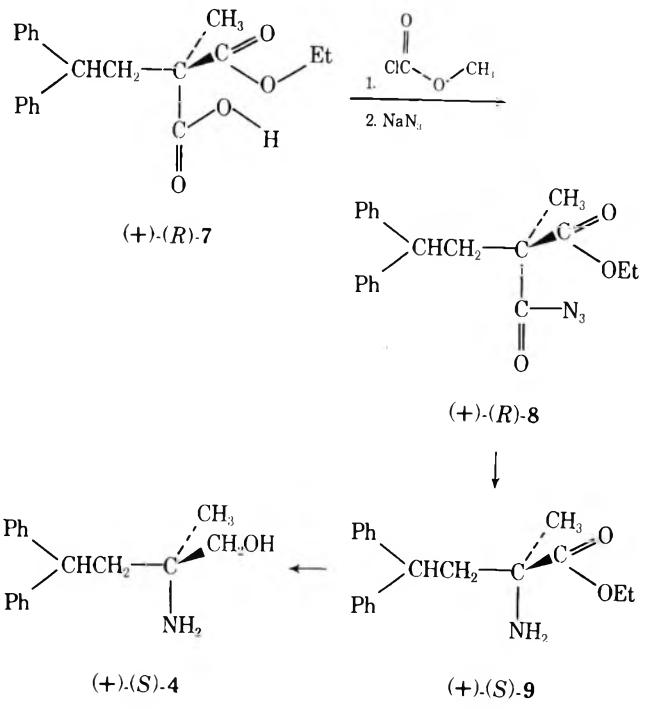
Applying the chiroptical correlations obtained by Snatzke and coworkers[5] for a number of 1-pyrazolines one would assign the *S* configuration to (+)-**1**. The pyrazoline (+)-**1** gave a positive CD band ($\Delta\epsilon$ +6.11) at 332 nm which corresponds to the n → π^* absorption of the azo chromophore.[5,6] A positive Cotton effect was also observed. Reduction of **1** with lithium aluminum hydride[7] in tetrahydrofuran at −78° led to the formation of (−)-(*S*)-3-hydroxylmethyl-3-methyl-5,5-diphenylpyrazolidine (**2**) (Chart I). The configurational assignment for **2** as *S* is based on the configuration assigned to its precursor **1**. Air oxidation[8] of **2** produced (−)-(*S*)-3-hydroxylmethyl-3-methyl-5,5-diphenyl-1-pyrazoline (**3**), which gave a negative CD band ($\Delta\epsilon$ −3.32) at 332 nm as well as a negative Cotton effect. The change in sign and magnitude of the CD band in going from **1** to **3** is characteristic and consistent with the configurational assignments given.[5]

Chart I



It was hoped to convert the pyrazoline **1**, by chemical means, to a compound whose absolute configuration was either known or could be established. Attempts to reduce **1** directly to an acyclic derivative were futile since **1** decomposed to **5** so readily. The method which proved successful was to first reduce **1** to the pyrazolidine **2** and then to catalytically reduce **2** directly to **4**. This involved not only the reduction of the nitrogen–nitrogen bond but also the hydrogenolysis of the diphenyl carbinyl–nitrogen bond. This was finally achieved by using a large excess of 5% palladium on charcoal as the catalyst and carrying out the reduction in an autoclave which permitted rapid stirring. Under these conditions (−)-(*S*)-**2** was converted to (+)-2-amino-2-methyl-4,4-diphenyl-1-butanol (**4**). Since the reduction of **2** to **4** does not involve the asymmetric center the configuration of **4** is related to **2**. Optically active **4** was independently synthesized as shown in Chart II. The absolute configuration was determined by the Nakanishi and Dillon[9]

Chart II



correlation of CD for α-amino alcohols using $Pr(dpm)_3$ reagent. The α-amino alcohol (+)-4 showed a $\Delta\epsilon$ +1.45 at 314 nm and a $\Delta\epsilon$ −1.45 at 293 nm[9] and on the basis of this CD the *S* configuration is assigned to (+)-**4**. This designation is consistent with the previous assignment of the *S* configurations to (+)-**1** and (−)-**2**.

Thermolysis. The thermal decomposition of optically active 3-carbomenthoxy-3-methyl-5,5-diphenyl-1-pyrazoline [(+)-(*S*)-**1**] was carried out at 50° in the dark under a nitrogen atmosphere for a period of 1 hr. To assess the effect of changing the polarity of the solvent on the stereochemical result two solvents of widely divergent polarity, cyclohexane and *N*,*N*-dimethylformamide, were used. The results showed that there was no significant difference in the product formed. In both cases 1-carbomenthoxy-1-methyl-2,2-diphenylcyclopropane [(−)-(*R*)-**5**] was produced as the sole product, in quantitative yield. Moreover, the optical rotation, $[\alpha]_{Hg}^{23}$ −64°, of **5** obtained from either solvent was identical, showing the absence of a solvent effect on the optical yield.

In order to determine the optical purity of the thermolysis product **5** a direct method was thought desirable.[10] This was achieved in the following manner. If a molecule contains two asymmetric centers, four diastereomers are possible: *R,R*, *R,S*, *S,S*, and *S,R*. If one center is held to one configuration, as in this case with (−)-(1*R*,2*S*,5*R*)-menthol, then only two diastereomers are possible, (*R,R*)-**5** and (*S,R*)-**5**. Since (*R*)-(+)-1-methyl-2,2-diphenylcyclopropanecarboxylic acid (**10**) was obtained[2] by the saponification of **5**, then the rotation of the mixture of diastereomeric esters should lie on the line between the rotation of (±)-(*RS*)-(−)-(*R*)- and pure (+)-(*R*)-(−)-(*R*)-**5**. The two menthyl esters were synthesized by converting (±)-**10** to the acid chloride followed by reaction with (−)-(*R*)-menthol to yield the (±)-(*RS*)-(−)-(*R*)-menthyl ester, $[\alpha]_{Hg}^{24}$ −58.1°. Repeating this process with optically pure (+)-(*R*)-**10** produced the (+)-(*R*)-(−)-(*R*) diastereomer, $[\alpha]_{Hg}^{24}$ −66.2°. Comparing the rotation of the ester obtained from the thermolysis, $[\alpha]_{Hg}^{24}$ −64°, with the above values gives an optical purity for the thermolysis product (**5**) of 73%.

In order to check the accuracy of the above method in one run the product was reduced with lithium aluminum hydride to give a mixture of 1-hydroxymethyl-1-methyl-2,2-diphenylcyclopropane (**6**) and menthol. Separation of this mixture by ordinary means proved difficult. The method which finally proved successful was to convert the mixture of alcohols to their trimethylsilyl derivative by reaction with *N*-trimethylsilylacetamide[11] and using GLC to separate them. The siloxane derivative was hydrolyzed to yield (−)-(*R*)-**6**, $[\alpha]_{Hg}^{23}$ −32.2° (c 2.1, $CHCl_3$), which corresponds to an optical purity[12] of 70% and agrees well with the value obtained from the previous method. The pyrolysis of **1** therefore proceeds with ~85% *retention of configuration.*

Pyrolysis of pyrazoline (−)-(*S*)-**3**, $[\alpha]_{Hg}^{23}$ −23.4°, produced (−)-(*R*)-**6**, $[\alpha]_{Hg}^{23}$ −25.5° (c, 2.0, $CHCl_3$), with an optical purity of 56% which represents 78% *retention of configuration.*

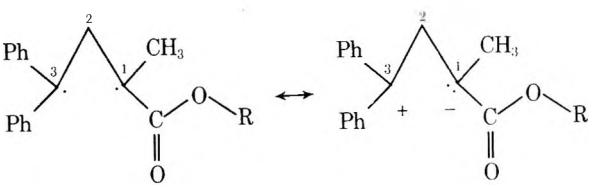
The direct photolysis of (+)-(*S*)-**1** was carried out to determine if there would be a change in stereochemistry of the product, **5**. The 1-pyrazoline **1** with λ_{max} 330 nm (N=N, ϵ 150) was dissolved in methylcyclohexane and irradiated at −4° using a high-pressure mercury lamp and a Pyrex filter. The main products obtained were (−)-(*R*)-**5** (79%) and 1,1-diphenylethylene[13] (13%). The rotation of the ester **5** produced was $[\alpha]_{Hg}^{24}$ −65.6° and **5** was shown to be stable under these irradiation conditions. This result shows that this reaction proceeds with over 95% *retention of configuration.*

Irradiation of (+)-(*S*)-**1** using benzophenone as a sensitizer[14] produced **5** in only trace amounts; the major products appeared to be formed by fragmentation.[15] No attempt was made to identify the many olefinic products produced.

Discussion

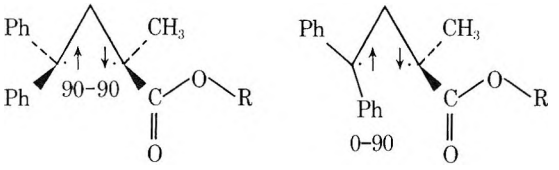
Our results show that in both the photolysis and pyrolysis of pyrazolines **1** and **3** the corresponding cyclopropane derivative is formed with a high retention of configuration and optical activity. Such results have been observed by other workers. Overberger[16] found that the thermal decomposition of *trans*-3,5-diphenyl-1-pyrazoline gave 89% *trans*-1,2-diphenylcyclopropane and that photolysis gave a similar result. Rinehart[17] showed that *cis*- and *trans*-1-carbomethoxy-3,4-dimethyl-1-pyrazoline produced cyclopropanes of corresponding stereochemistry and that photolysis was even more selective. Similar observations have been made by Nozaki[18] in the decomposition of *cis*- and *trans*-9,10-diazabicyclo[6.3.0]undec-9-ene. In an analysis of the stereochemistry of pyrazoline decomposition McGreer[19] has demonstrated that, in general, the decomposition proceeds with overall retention of configuration, although there are notable exceptions.[19,20]

It is generally believed that thermal and photochemical decomposition of a 1-pyrazoline leads to the formation of a cyclopropane by way of a trimethylene diradical intermediate.[21,22] The state of the diradical formed under these conditions is believed to be singlet. The amount of zwitterionic character associated with the singlet diradical, due to resonance, is not known but the amount would undoubtedly be structure dependent.[23] The diradical formed from **1** should



have an appreciable ionic contribution since it would have two phenyl groups at C-3 which would delocalize the positive charge and a carbomenthoxy at C-1 which would delocalize the negative charge. However, the absence of a solvent effect in the decomposition of 1 would indicate that the zwitterionic contribution is not very large.[23]

The high-temperature pyrolysis of cyclopropane derivatives presumably also results in the formation of singlet diradical intermediates. The stereochemistry of this ring opening–ring closing reaction has been studied by Berson,[24] Bergman,[25] and Cram[23] and has been the subject of a recent review.[21] The results show that the trimethylene radical produced under their conditions ring closes 5–11 times faster than it can rotate. In the case of the trimethylene radical produced in the decomposition of 1 and based on the percent retention of configuration observed, the rate of ring closure is seven times faster than rotation for the thermolysis and 19 times faster for the photolysis reaction. The configuration of the diradical that best accommodates our results is the one suggested by Bergman,[25] which has been referred to as 90-90 and by others as face-to-face.[23]



face-to-face edge-to-face

We cannot eliminate the 0-90 based on our observation but we can eliminate all intermediates which are achiral, such as 90-0 and 0-0. The small amount of inversion of confguration that is found is probably due to the latter type of intermediate, which is the result of rotation around the C_1–C_2 bond. Steric hindrance to such rotations is produced by the substituents at C_1 and C_3 which may enhance the rate of ring closure.[24,25] The rate of ring closure vs. rotation of the trimethylene radical would also be expected to be sensitive to temperature. The lower retention of configuration bound in the thermolysis of 1 (50°) to that of the photolysis of 1 (−3°) may well be due to a temperature effect. This effect may also account for the lowered retention of configuration in the pyrolysis of 3 (130°) although reduced steric interactions may also be playing a role.

Finally, it should be noted that our attempts to isolate cyclopropane derivatives from the benzophenone-sensitized photolysis of 1 were abortive and only a number of unsaturated compounds (not identified) were obtained. It was also shown that the cyclopropane 5 decomposed under these conditions. Apparently in this system the triplet diradical, presumably produced from 1 or 5, decomposed by other pathways[15] before triplet–singlet interconversion leading to ring closure could occur.

Experimental Section

Melting points were measured with a Mel-Temp apparatus and both melting and boiling points are uncorrected. Infrared spectra were determined using a Perkin-Elmer Model 257 spectrophotometer. Nuclear magnetic resonance spectra were recorded on a Varian A-60 or Bruker 90-MHz spectrophotometer; chemical shifts are reported in parts per million downfield from tetramethylsilane and coupling constants are in hertz. Optical rotatory and circular dichroism spectra were recorded with a Jasco 5 and optical rotations at 5461 A with a Bendix-Ericson Model 143A polarimeter. Microanalyses were performed by the Beller Laboratories, Gottingen, Germany.

Synthesis of Optically Active 2-Amino-2-methyl-4,4-diphenyl-1-butanol. 2,2-Diphenylethanol. To a stirred solution of 17.9 g (0.46 mol) of lithium aluminum hydride in 250 ml of dry ether was added a solution of 100 g (0.46 mol) of diphenylacetic acid in 250 ml of dry ether at such a rate so as to maintain a steady reflux. After the completion of addition the reaction mixture was allowed to stir for 30 min, and was hydrolyzed with water and 150 ml of 10% sulfuric acid. The ether layer was separated and washed twice with water and finally with saturated salt solution and dried over anhydrous sodium sulfate. Evaporation of ether gave 85 g (91%) of 2,2-diphenylethanol. Recrystallization from *n*-hexane gave colorless crystals: mp 54–55°; ir ($CHCl_3$) 3588 (m), 3120–2980 (m), 1730 (s), 1607 (m), 1498 (s), 1458 (s), 1390 (m), 1025 cm^{-1} (s); NMR ($CDCl_3$) δ 1.7 (s, 1 H), 4.0 (s, 3 H), 7.1 (s, 10 H).

2,2-Diphenylethyl Toluenesulfonate. To a stirred solution of 40.0 g (0.20 mol) of 2,2-diphenylethanol in 150 ml of dry pyridine at 0° was added dropwise a solution of 44.7 g (0.20 mol) of *p*-toluenesulfonyl chloride in 150 ml of dry pyridine. After stirring the reaction mixture for 6 hr at 0°, it was poured into 1 l. of ice water and the product, 2,2-diphenylethyl toluenesulfonate, was filtered. Recrystallization from acetone–water gave colorless needles: mp 93–95°; ir ($CHCl_3$) 3010 (w), 1600 (m), 1495 (w), 1450 (w), 1370 (s), 1175 (s), 1100 (m), 970 (s), and 875 cm^{-1} (m); NMR ($CDCl_3$) δ 2.36 (s, 3 H), 4.4 (m, 3 H), 7.1–7.55 (m, 14 H).

Diethyl (2,2-Diphenylethyl)methylmalonate. Sodium hydride–mineral oil dispersion (5.0 g, 0.12 mol) was washed free of oil with dry diethyl ether, 150 ml of distilled dimethylformamide was added under a dry atmosphere, and 22 g (0.13 mol) of diethyl methylmalonate was added dropwise with stirring at 0° until gas evolution ceased. To this solution 40 g (0.114 mol) of 2,2-diphenylethyl toluenesulfonate in 150 ml of dimethylformamide was added dropwise and the reaction mixture was heated at 110° for 30 hr. Upon cooling, the reaction mixture was diluted with water and extracted with diethyl ether several times which, upon combination, was washed with saturated salt solution and dried over anhydrous sodium sulfate. Evaporation of ether gave 50 g of crude yellow oil. Vacuum distillation of this oil gave 13 g (0.03 mol) of diethyl (2,2-diphenylethyl)methylmalonate: bp 176° (0.5 mm); yield 31.6% (based on converted tosylate); ir (CCl_4) 3080–2980 (m), 1755 (shoulder), 1740 (s), 1600 (m), 1495 (m), 1452 (m), 1150 (s), 1030 (m), and 690 cm^{-1} (s); NMR ($CDCl_3$) δ 1.1 (t, 3 H), 1.36 (s, 3 H), 3.86 (m, 5 H), 7.1 (s, 10 H). The major side product was identified by infrared and NMR as 1,1-diphenylethylene.

Anal. Calcd for $C_{22}H_{26}O_4$: C, 74.55; H, 7.39. Found: C, 74.99; H, 7.54.

(±)-2-Carbethoxy-2-methyl-4,4-diphenylbutanoic Acid. To a stirred solution of 14 g (0.039 mol) of diethyl (2,2-diphenylethyl)methylmalonate in 100 ml of 95% ethanol and 25 ml of water was added 2.2 g (0.039 mol) of potassium hydroxide and the solution was allowed to stir overnight at room temperature. The reaction mixture was then diluted with water and extracted several times with diethyl ether. The aqueous layer was acidified and extracted with diethyl ether, which, upon evaporation of ether extracts, gave 8.4 g (65%) of 2-carbethoxy-2-methyl-4,4-diphenylbutanoic acid: mp 90–92°; ir ($CHCl_3$) 3500–2500 (broad), 1725 (s), 1601 (w), 1495 (w), 1385 (w), 1115 cm^{-1} (m); NMR ($CDCl_3$) δ 1.1 (t, 3 H), 1.4 (s, 3 H), 2.75 (d, 2 H), 3.85 (q, 2 H, 2.05 (t, 1 H), 7.19 (s, 10 H), 10.25 (s, 1 H).

Anal. Calcd for $C_{20}H_{22}O_4$: C, 73.60; H, 6.79. Found: C, 73.72; H, 6.94.

(−)-(*S*)-Carbethoxy-2-methyl-4,4-diphenylbutanoic Acid.[26] To a solution of 19.7 g (0.056 mol) of (±)-2-carbethoxy-2-methyl-4,4-diphenylbutanoic acid in 50 ml of ethyl acetate was added a solution of 2.58 g (0.028 mol) of (−)-ephedrine in 50 ml of ethyl acetate and the solution was kept at 0 to −5° for 48 hr. The salt was recrystallized five more times from ethyl acetate to give $[\alpha]_{Hg}^{25}$ −14.1° (2.5%, EtOH). Another recrystallization from chloroform gave the value $[\alpha]_{Hg}^{25}$ −14.7° (2%, EtOH); mp 131–132°; ir and NMR spectra identical with those of racemic compound.

(±)-Ethyl 2-Carbazido-2-methyl-4,4-diphenylbutanoate. A solution of 2 g (0.0062 mol) of ethyl 2-carboxy-2-methyl-4,4-diphenylbutanoate in 12 ml of acetone and 2 ml of water was cooled to −15° and 0.72 g (1 ml, 0.007 mol) of triethylamine dissolved in 6 ml of acetone was added. To this mixture, 0.78 g (0.7 ml, 0.007 mol) of ethyl chlorocarbonate in 2 ml of acetone was added dropwise. The mixture was stirred for 30 min and then 0.6 g (0.01 mol) of sodium azide in 5 ml of water was added slowly and the reaction mixture was stirred overnight at room temperature. Dilution with water and extraction with several portions of diethyl ether followed by evaporation on an aspirator yielded 2.15 g (quantitative yield) of crude ethyl 2-carbazido-2-methyl-4,4-diphenylbutanoate: mp 72–74° dec; ir (CCl_4) 2140 (s), 1750 (s), 1720 (s), 1601 (w), 1499 (m), 1457 (m), 1182 (s), 1030 (m), 692 cm^{-1} (m); NMR ($CDCl_3$) δ

1.02 (t, 3 H), 1.33 (s, 3 H), 2.75 (d, 2 H), 3.80 (m, 2 H), 4.02 (t, 1 H), 7.18 (s, 10 H).

(−)-Ethyl (*S*)-2-Carbazido-2-methyl-4,4-diphenylbutanoate. A solution of 2 g (0.006 mol) of (−)-2-carbethoxy-2-methyl-4,4-diphenylbutanoic acid in 12 ml of acetone and 2 ml of water was cooled to −15° and 0.72 g (1 ml, 0.007 mol) of triethylamine in 5 ml of acetone was added with stirring. To this mixture, 0.78 g (0.7 ml, 0.007 mol) of ethyl chlorocarbonate in 2 ml of acetone was added dropwise. The reaction mixture was stirred for 30 min at −15° and then 0.6 g (0.01 mol) of sodium azide in 5 ml of water was added slowly and the reaction mixture was stirred overnight at room temperature. Dilution with water and extraction with diethyl ether followed by evaporation of diethyl ether gave 2.0 g (93%) of ethyl 2-carbazido-2-methyl-4,4-diphenylbutanoate as a yellow oil: ir ($CHCl_3$) 2145 (s), 1750 (s), 1720 (s), 1605 (w), 1499 (m), 1457 (m), 1178 (s), 1128 (m), 1025 cm^{-1} (m); NMR (CCl_4) δ 1.02 (t, 3 H), 1.33 (s, 3 H), 2.71 (d, 2 H), 3.90 (m, 3 H), 7.17 (s, 10 H); $[\alpha]_{Hg}^{23}$ −23.5° (2.4%, $CHCl_3$).

(±)-Ethyl 2-Isocyanato-2-methyl-4,4-diphenylbutanoate. Heating ethyl 2-carbazido-2-methyl-4,4-diphenylbutanoate neat on a steam bath gave a quantitative yield of ethyl 2-isocyanato-2-methyl-4,4-diphenylbutanoate as a yellow liquid: bp 353° dec; ir (CCl_4) 2255 (s), 1790 (s), 1601 (w), 1210 (s), 1110 (m), 695 cm^{-1} (m); NMR (CCl_4) δ 1.04 (t, 3 H), 1.3 (s, 3 H), 2.7 (d, 2 H), 3.8 (m, 3 H), 7.1 (s, 10 H).

Anal. Calcd for $C_{20}H_{21}NO_3$: C, 74.28; H, 6.55; N, 4.33. Found: C, 74.66; H, 6.73; N, 4.48.

(±)-Ethyl 2-Amino-2-methyl-4,4-diphenylbutanoate. A benzene solution (20 ml) of 1.8 g (0.005 mol) of ethyl 2-carbazido-2-methyl-4,4-diphenylbutanoate and 0.6 ml (0.58 g, 0.005 mol) of benzyl alcohol was refluxed for 48 hr, at which time the benzene was removed under vacuum, leaving a yellow, oily residue. This residue was dissolved in 50 ml of anhydrous diethyl ether and gaseous hydrogen bromide was passed through the stirred solution for 3 hr. The ether solution was then extracted several times with water and the water layers were combined and neutralized with solid sodium carbonate. Extraction with several portions of diethyl ether and evaporation of the combined ether layers after drying (Na_2SO_4) gave 1.27 g (86%) of ethyl 2-amino-2-methyl-4,4-diphenylbutanoate: bp 150° (0.5 mm); ir (CCl_4) 3382 (w), 3310 (w), 3100–2820 (broad), 1734 (s), 1610 (m), 1498 (m), 1456 (m), 1379 (m), 1200 (s), 1115 (s), 1080 (m), 1032 (m), and 693 cm^{-1} (s); NMR (acetone-d_6) 0.98 (t, 3 H), 1.21 (s, 3 H), 2.22 (s, 2 H), 2.49 (dd, 2 H), 3.64 (m, 2 H), 4.20 (1 H), 7.17 (m, 10 H).

Anal. Calcd for $C_{19}H_{23}NO_2$: C, 76.73; H, 7.80; N, 4.71. Found: C, 76.83; H, 7.40; N, 5.04.

(−)-Ethyl (*R*)-2-Amino-2-methyl-4,4-diphenylbutanoate. A benzene solution (25 ml) of 1.8 g (0.005 mol) of ethyl-2-carbazido-2-methyl-4,4-diphenylbutanoate and 0.6 ml (0.58 g, 0.005 mol) of benzyl alcohol was refluxed for 48 hr. The reaction mixture was cooled and benzene was removed under reduced pressure to give yellow oil. This was dissolved in 50 ml of dry diethyl ether and gaseous hydrogen bromide was passed through the stirred solution for 3 hr. The ether solution was then extracted several times with water and combined water layer was neutralized with sodium carbonate. Extraction with several portions of diethyl ether and evaporation of combined ether layers after drying over anhydrous sodium sulfate gave 1.5 g (90.6%) of ethyl 2-amino-2-methyl-4,4-diphenylbutanoate. Recrystallization from diethyl ether–hexane gave colorless crystals: mp 101–103°; ir ($CHCl_3$) 3365 (w), 3310 (w), 3100–2800 (broad), 1733 (s), 1605 (m), 1085 (w), 1028 cm^{-1} (w); $[\alpha]_{Hg}^{25}$ −47.9° (2.06%, $CHCl_3$).

(±)-2-Amino-2-methyl-4,4-diphenylbutanoic Acid. Refluxing a solution of 9 g (0.03 mol) of α-amino ester with 4.2 g (0.075 mol) of potassium hydroxide in 20 ml of 50% ethanol–water overnight, followed by acidification and evaporation of solvent, yielded a yellow residue. Trituration with ethanol followed by removal of solvent gave 9 g of 2-amino-2-methyl-4,4-diphenylbutanoic acid hydrochloride as a yellow glass: ir (KBr) 3300–2600 (s, broad), 1740 (s, broad), 1600 (m), 1495 (s), 1455 (m), 1390 (w, broad), 1220–1180 (s, broad), 1130 (m), 1080 (w), 1032 (w), 740 (m), 693 cm^{-1} (m).

Neutralization of the hydrochloride using a slight excess of silver carbonate in ethanol, filtering, treatment with hydrogen sulfide, followed by filtration and evaporation gave 2-amino-2-methyl-4-diphenylbutanoic acid: mp >220° (sublimes); ir (KBr) 3200–2800 (broad, m), 2500 (broad, w), 1600 (broad, s), 1494 (m), 1452 (m), 1398 (m), 1360 (m), 1247 (w), 1231 (w), 1125 (w), 1080 (w), 1030 (w), 885 (w), 842 (w), 804 (w), 792 (w), 739 (m), 690 cm^{-1} (s).

Anal. Calcd for $C_{17}H_{19}NO_2$: C, 75.81; H, 7.11; N, 5.20. Found: C, 75.73; H, 7.04; N, 5.35.

(±)-2-Amino-2-methyl-4,4-diphenyl-1-butanol. Lithium aluminum hydride (1 g, 0.027 mol) was suspended in 15 ml of anhydrous diethyl ether and a solution of 0.8 g (0.0027 mol) of ethyl 2-amino-2-methyl-4,4-diphenylbutanoate in 15 ml of ether was slowly added. After refluxing for 4 hr the excess lithium aluminum hydride was hydrolyzed with saturated ammonium chloride solution and the ether layer was extracted several times with 10% hydrochloric acid. Neutralization of the combined water layers and extraction with diethyl ether, followed by drying over anhydrous sodium sulfate, gave upon evaporation 0.603 g (88%) of 2-amino-2-methyl-4,4-diphenyl-1-butanol: mp 108–110°; ir (CCl_4) 3640 (w), 3500–3200 (broad). 3100–2810 (broad m), 1601 (w), 1498 (m), 1457 (m), 1053 (m), 1034 (m), and 692 cm^{-1} (s); NMR (acetone-d_6) δ 0.86 (s, 3 H), 2.24 (d, 2 H), 3.20 (s, 2 H), 1.8–3.6 (m, 3 H), 4.26 (t, 1 H), and 6.9–4.5 (m, 10 H).

Anal. Calcd for $C_{17}H_{21}NO$: C, 79.96; H, 8.29; N, 5.49. Found: C, 80.01; H, 8.41; N, 5.51.

(−)-(*R*)-2-Amino-2-methyl-4,4-diphenyl-1-butanol. Lithium aluminum hydride (1 g, 0.027 mol) was suspended in 25 ml of dry diethyl ether and a solution of 1.2 g (0.004 mol) of ethyl 2-amino-2-methyl-4,4-diphenylbutanoate in 25 ml of dry diethyl ether was added slowly with stirring. After refluxing for 4 hr, the excess lithium aluminum hydride was hydrolyzed with saturated ammonium chloride solution and the ether layer was separated and washed several times with 10% hydrochloric acid. Neutralization of combined water layer and extraction with diethyl ether, followed by drying over anhydrous sodium sulfate, gave upon evaporation of diethyl ether 1.0 g (92%) of 2-amino-2-methyl-4,4-diphenyl-1-butanol. Recrystallization from diethyl ether–hexane gave colorless needles: mp 83–85°; ir and NMR identical with those of racemic compound, $[\alpha]_{Hg}^{24}$ −1.82 ± 0.8° (0.6%, EtOH).

(−)-Menthyl Methacrylate.[27] A mixture of 172 g (2 mol) of methacrylic acid and 90.8 g (0.66 mol) of phosphorus trichloride was heated at 65–70° for 75 min. After cooling to room temperature, the upper layer was distilled at atmospheric pressure to give 107 g (51.2%) of methacrylyl chloride as a colorless liquid, bp 96–98°.

This methacrylyl chloride (107 g, 1.02 mol) was added slowly to a solution of 160 g (1.03 mol) of (−)-1-menthol in 250 ml of dry pyridine at 0°. After stirring at room temperature overnight the reaction mixture was diluted with water and extracted several times with diethyl ether. The combined ether layers were washed twice with water and once with saturated sodium chloride solution and then dried over anhydrous sodium sulfate. Evaporation of the solvent gave crude menthyl methacrylate, which on vacuum distillation gave 106 g (46%) of pure menthyl methacrylate: bp 89–90° (2 mm); $[\alpha]_{Hg}^{24}$ −117.9° (0.78%, $CHCl_3$); ir (film) ν 2958 (s), 2930 (s), 2870 (s), 1645 (m), 1460 (m), 1325 (m), 1305 (m), 1175 (s), 1150 cm^{-1} (m); NMR (CCl_4) δ 0.81 (d, 3 H), 0.90 (d, 6 H), 0.6–2.3 (unresolved, 9 H), 1.92 (q, 3 H), 4.73 (m, 1 H), 5.48 (m, 1 H), and 6.03 (m, 1 H).

(+)-(*S*)-3-Carbomenthoxy-3-methyl-5,5-diphenyl-1-pyrazoline. Freshly prepared diphenyldiazomethane (30 g, 0.15 mol) was added to 22.4 g (0.1 mol) of (−)-menthyl methacrylate at 0°. After thorough mixing the reactants were allowed to stand at −10 to −15° for 5 days, yielding a red gum. This gum was triturated repeatedly with cold absolute methanol at −10 to −15° until all trace of pink color was removed. Approximately 50–60% of the crude mixture was lost during this process. Upon drying the residue under vacuum, 14 g (25%) of white solid 3-carbomenthoxy-3-methyl-5,5-diphenyl-1-pyrazoline was obtained: mp 83–83.5° dec; $[\alpha]_{Hg}^{23}$ +111.7 ° (0.75%, $CHCl_3$) [optically pure pyrazoline has $[\alpha]_{Hg}^{23}$ +118.46° (2%, $CHCl_3$); this represents an optical purity of 94.3%]; ir (CCl_4) ν 3080 (w), 3060 (w), 3025 (w), 2960 (s), 2930 (s), 2875 (m), 1737 (s), 1595 (w), 1560 (broad, w), 1500 (m), 1455 (m), 1395 (w), 1377 (w), 1315 (m), 1270 (m), 1185 (s), and 700 cm^{-1} (s); NMR (CCl_4) δ 0.66 (d, 3 H), 0.90 (d, 3 H), 1.45 (s, 3 H), 0.45–1.9 (broad, no fine structure), 2.45 (dd, 2 H), 4.57 (broad, 1 H), 7.23 (d, 10 H); ORD (*c* 0.68, $CHCl_3$), 23° $[\Phi]_{400}$ +789.8°, $[\Phi]_{343}$ +5346.5°, $[\Phi]_{315}$ −3706.1°, $[\Phi]_{280}$ −972.1°; CD (*c* 0.40, dioxane), 23° $[\theta]_{360}$ 0, $[\theta]_{332}$ +20,180, $[\theta]_{280}$ 0 ($\Delta\epsilon$ 6.11).

(−)-(*S*)-3-Hydroxymethyl-3-methyl-5,5-diphenylpyrazolidine. To 3.0 g (0.079 mol) of lithium aluminum hydride slurried in 200 ml of dry tetrahydrofuran at −78° under nitrogen atmosphere was added 13.2 g (0.032 mol) of 1-pyrazoline in 125 ml of dry tetrahydrofuran. The solution was stirred and allowed to come to room temperature overnight, after which the solution was dark

green. Excess lithium aluminum hydride was hydrolyzed with saturated ammonium chloride solution. The solution was then filtered and diluted with 500 ml of water, which was extracted with three 100-ml portions of diethyl ether. The combined ether layers were extracted with three 50-ml portions of 5% hydrochloric acid which upon treatment with potassium hydroxide and extraction with diethyl ether followed by evaporation of solvent gave 6.7 g (85%) of 3-hydroxymethyl-3-methyl-5,5-diphenylpyrazolidine as an oil: $[\alpha]_{Hg}^{24}$ −31.57° (0.98%, EtOH); ir (CCl_4) ν 3620 (w), 3060 (w), 3030 (w), 2980 (s), 2880 (m), 1600 (w), 1498 (m), 1455 (m), 1080 (m), 1060 (m), and 705 cm^{-1}; NMR (acetone-d_6) δ 0.90 (s, 3 H), 2.80 (s, 3 H), 3.37 (s, 2 H), 4.0 (broad s, 3 H), 7.43 (m, 10 H).

Anal. Calcd for $C_{17}H_{20}ON_2$: C, 76.09; H, 7.51; N, 10.44. Found: C, 76.39; H, 7.62; N, 10.33.

(+)-(*S*)-2-Amino-2-methyl-4,4-diphenyl-1-butanol. A mixture of 6.7 g (0.025 mol) of pyrazolidine and 7.0 g of 5% palladium on charcoal catalyst in 200–300 ml of 95% ethyl alcohol was changed into a 1-l. Magnadash autoclave. The autoclave was then flushed six times with hydrogen at 500 psi, pressurized to 900 psi with hydrogen, heated at 60°, and stirred for 24 hr. Cooling and venting followed by filtration and evaporation of solvent gave 5.7 g (90%) of yellow, oily residue. Thin layer chromatography on a 1 mm × 20 cm × 40 cm silica gel plate with diethyl ether as eluent gave three bands. The band with lowest R_f value yielded 40% of oily material which had has an ir and NMR identical with those of authentic 2-amino-2-methyl-4,4-diphenyl-2-butanol, $[\alpha]_{Hg}^{24}$ +2.28 ± 0.8° (0.6%, EtOH). The other bands corresponded to starting material and oxidized starting material.

(−)-(*S*)-3-Hydroxymethyl-3-methyl-5,5-diphenyl-1-pyrazoline. A 4.0-g portion (0.015 mol) of 3-hydroxymethyl-3-methyl-5,5-diphenyl-1-pyrazoline, $[\alpha]_{Hg}^{24}$ +113.7° (0.7%, $CHCl_3$), was dissolved in 50 ml of tetrahydrofuran. This solution was exposed to atmospheric oxygen for 3 days by allowing it to stand at room temperature. Evaporation of solvent gave an almost quantitative yield of 3-hydroxymethyl-3-methyl-5,5-diphenyl-1-pyrazoline as a yellowish residue. Preparative thin layer chromatography on a 20 cm × 40 cm × 1 mm plate of silica gel with diethyl ether as eluent gave 3.0 g (75%) of pure 1-pyrazoline: mp 98–99° dec; $[\alpha]_{Hg}^{24}$ −26.3° (0.92%, $CHCl_3$); ir (CCl_4) ν 3600 (w), 3400 (w, broad), 3060 (w), 3030 (m), 1455 (m), 1390 (w), 1315 (w), 1060 (m), 1040 (w), 890 (w), 705 cm^{-1} (s); NMR ($CDCl_3$) δ 1.11 (s, 3 H), 2.29 (dd, 2 H), 3.20 (s, broad, 1 H), 3.81 (dd, 2 H), and 7.3 (s, 10 H); ORD (*c* 0.1, $CHCl_3$), 23° $[\Phi]_{400}$ −4522°, $[\Phi]_{340}$ −16,492°, $[\Phi]_{302}$ +16,359°, $[\Phi]_{270}$ +14,098°; CD (*c* 0.04, dioxane), 23° $[\theta]_{280}$ 0, $[\theta]_{332}$ −10,970, $[\theta]_{360}$ 0 ($\Delta\epsilon$ −3.32).

Anal. Calcd for $C_{17}H_{18}ON_2$: C, 76.69; H, 6.78; N, 10.52. Found: C, 76.58; H, 6196; N, 10.35.

(−)-(*R*)-1-Hydroxymethyl-1-methyl-2,2-diphenylcyclopropane. Heating 0.5 g (0.0019 mol) of 3-hydroxymethyl-3-methyl-5,5-diphenyl-1-pyrazoline at 130° until bubbling ceased (about 10 min) gave a quantitative yield of 1-hydroxymethyl-1-methyl-2,2-diphenylcyclopropane. This product was sublimed at 60° and reduced pressure (0.25 mm) to give pure compound: mp 98–99°; $[\alpha]_{Hg}^{23}$ −25.3° (0.82%, $CHCl_3$); ir (CCl_4) ν 3630 (m), 3090 (w), 3070 (m), 3030 (m), 2960 (w), 2940 (m), 2880 (m), 1605 (m), 1500 (s), 1455 (s), 1398 (w), 1385 (w), 1090 (w), 1050 (s), 1025 (s), and 705 cm^{-1} (s); NMR (CCl_4) δ 1.06 (s, 3 H), 1.18 (dd, 2 H), 1.43 (s, 1 H), 3.28 (d, 2 H), 7.26 (m, 10 H).

Synthesis of Menthyl 1-Methyl-2,2-diphenylcyclopropanecarboxylate. From Racemic Acid. A catalytic amount of anhydrous *N,N*-dimethylformamide (2 drops) was added to a solution of 1 g (0.004 mol) of 1-methyl-2,2-diphenylcyclopropanecarboxylic acid in 2 ml (0.027 mol) of thionyl chloride and allowed to react at room temperature for 3 hr. The excess thionyl chloride was removed under vacuum and the yellow oil was crystalized from pentane to give 0.83 g of light yellow solid acid chloride. This material was added to a solution of 0.54 g (0.003 mol) of (−)-1-menthol in 25 ml of dry benzene and the mixture was refluxed overnight. Removal of solvent and preparative thin layer chromatography on two 2 cm × 40 cm × 1 mm silica gel plates with 1:1 ether–hexane eluent gave 1.049 g of menthyl 1-methyl-2,2-diphenylcyclopropanecarboxylate, an overall yield of 67% from starting acid: mp 88–90°; $[\alpha]_{Hg}^{24}$ −58.07° (1%, $HCCl_3$); ir (CCl_4) 3070 (w), 3050 (w), 3015 (w), 2945 (s), 2920 (s), 2860 (m), 1720 (s), 1497 (w), 1495 (m), 1446 (m), 1385 (w), 1368 (w), 1315 (m), 1255 (m), 1160 (s), 1145 (s), 695 (m), 686 cm^{-1} (m); NMR ($CDCl_3$) δ 0.83 (m, 9 H), 1.20 (s, 3 H), 1.37 (d, 1 H), 0.4–2.0 (unresolved m, 9 H), 2.30 (poorly resolved m, 1 H), 7.30 (m, 10 H).

Anal. Calcd for $C_{27}H_{34}O_2$: C, 83.03; H, 8.77. Found: C, 82.92; H, 8.74.

From Optically Active Acid. The same procedure as above was used starting with 0.160 g (6.3 × 10^{-4} mol) of (−)-*R*-1-methyl-2,2-diphenylcyclopropanecarboxylic acid, $[\alpha]_{Hg}^{24}$ +41.8° (2.2%, $HCCl_3$). Optically pure acid has $[\alpha]_{Hg}^{25}$ +43.5° (2.2%, $HCCl_3$). This represents an optical purity of 96%. The ester was isolated following the above procedure in 70% overall yield, mp 120–122°, $[\alpha]_{Hg}^{24}$ −65.89° (1%, $HCCl_3$). Correcting for optical purity gives a maximum rotation of $[\alpha]_{Hg}^{24}$ −66.2°; ir same as mixture but C=O at 1710 cm^{-1}; NMR better resolved.

Anal. Calcd for $C_{27}H_{34}O_2$: C, 83.03; H, 8.77. Found: C, 83.01; H, 8.80.

Pyrolysis of Purified 1-Pyrazoline. In Methylcyclohexane. A cold solution of 1 g (0.0024 mol) of 1-pyrazoline ($[\alpha]_{Hg}^{23}$ 118.48) in 20 ml of methylcyclohexane was injected by syringe into 100 ml of methylcyclohexane at 50° under a nitrogen atmosphere in the dark. Removal of solvent under vacuum after 1 hr gave 0.935 g (quantitative yield) of 1-carbomethoxy-1-methyl-2,2-diphenylcyclopropane, mp 115–117°, $[\alpha]_{Hg}^{24}$ −64.06 ± 0.25° (1%, $HCCl_3$). This represents an optical purity of 73.5%. Ir and NMR are essentially identical with that of pure diastereomer reported earlier. Repeat of this run gave $[\alpha]_{Hg}^{24}$ −63.94 ± 0.25° (1%, $HCCl_3$). To check these results the ester was reduced with excess lithium aluminum hydride in ether reflux for 3 hr. Hydrolysis with saturated ammonium chloride solution, dilution with water, and extraction with ether gave a mixture of 1-menthol and 1-hydroxylmethyl-1-methyl-2,2-diphenylcyclopropane. Treatment of this mixture with excess *N*-bis(trimethylsilyl)acetamide in hexane at room temperature followed by gas–liquid chromatography with a 0.25 in. × 4 ft 20% SE-30 on 60/80 Chromosorb P at 190° gave 1-methyl-1-trimethylsiloxymethyl-2,2-diphenylcyclopropane in approximately 80% yield overall: ir (CCl_4) 3100 (m), 3000 (m), 2900 (m), 1600 (w), 1495 (m), 1443 (m), 1248 (s), 1100 (m), 1078 (s), 880 (s), 846 (s), 707 (s), 696 cm^{-1} (m); NMR (CCl_4) δ 0.0 (s, 9 H), 1.0 (s, 3 H), 1.09 (dd, 2 H), 3.16 (dd, 2 H), 7.0 (m, 10 H). Hydrolysis of this material by refluxing in methanol–water with a catalytic amount of potassium hydroxide followed by dilution with water and extraction with ether gave a quantitative yield of 1-hydroxymethyl-1-methyl-2,2-diphenylcyclopropane, mp 101–103°, $[\alpha]_{Hg}^{23}$ −32.13 ± 0.12° (2%, $HCCl_3$). Alcohol prepared from optically pure acid has a rotation of $[\alpha]_{Hg}^{24}$ −45.54 ± 0.12° (2%, $HCCl_3$) and this represents an optical purity of 70.3%. Ir and NMR are identical with those of authentic alcohol. This material was shown not to racemize under these conditions.

Pyrolysis in *N,N*-Dimethylformamide. The same procedure was used as above. Two runs gave ester of $[\alpha]_{Hg}^{23}$ −64.00 ± 0.25° (1%, $HCCl_3$), mp 114–117°. Conversion of one run to 1-hydroxymethyl-1-methyl-2,2-diphenylcyclopropane gave $[\alpha]_{Hg}$ −31.60 ± 0.12° (25%, $HCCl_3$). This represents an optical purity of 69.3%. Ir and NMR are identical with those of authentic materials.

Photolysis of Purified 1-Pyrazoline. The equipment for these experiments was a Pyrex reactor with a glass frit gas inlet at the base and fitted with a water-jacketed Pyrex probe into which a 450-W Hanovia high-pressure mercury lamp was inserted. Nitrogen gas, which was prepurified and bubbled through a solution of benzophenone ketyl, was passed through a solution of 0.50 g (0.0012 mol) of 3-carbomenthoxy-3-methyl-5,5-diphenyl-1-pyrazoline in 120 ml of purified methylcyclohexane at −3° for 1 hr. Irradiation for 9 hr gave nearly complete reaction as indicated by the disappearance of N=N absorbance at 330 mμ. Evaporation of the solvent in vacuo left behind 0.3859 g of white solid. Thin layer chromatography on a 1 mm × 20 cm × 40 cm silica gel plate gave four bands which were isolated. In increasing order of R_f band 3 gave 0.3148 g of 1-carbomenthoxy-1-methyl-2,2-diphenylcyclopropane, mp 116–118°, $[\alpha]_{Hg}^{24}$ −65.72 ± 0.25° (1%, $HCCl_3$). This represents an optical purity of 93.8%. Ir and NMR are identical with those of pure diastereomeric ester. Band 4 consisted of 0.0245 g of colorless liquid identified by ir and NMR as 1,1-diphenylethylene. Ester accounts for 79.1% of starting pyrazoline and 1,1-diphenylethylene accounts for 13.3%. The remaining products were not identified.

A repeat of this experiment with 0.51 g of 3-carbomenthoxy-3-methyl-5,5-diphenyl-1-pyrazoline in 150 ml of methylcyclohexane irradiating for 3 hr gave 1-carbomenthoxy-1-methyl-2,2-diphenylcyclopropane (0.2791 g): $[\alpha]_{Hg}^{24}$ −65.42 ± 0.25° (1%, $HCCl_3$); optical purity 90.4%; mp 117–118°; major side product was 1,1-diphenylethylene.

Registry No.—(+)-(*S*)-**1**, 55124-19-1; (−)-(*S*)-**2**, 55124-20-4; (−)-(*S*-**3**, 55124-21-5; (±)-**4**, 55124-22-6; (−)-(*R*)-**4**, 55156-06-4; (+)-(*S*)-**4**, 55156-07-5; (±)-**5**, 55124-23-7; (*R*)-**5**, 55124-24-8; (−)-

(*R*)-**6**, 55124-25-9; (±)-**7**, 55124-26-0; (−)-(*S*)-**7**, 55156-08-6; (±)-**8**, 55124-27-1; (−)-(*S*)-**8**, 55156-09-7; (±)-**9**, 55124-28-2; (−)-(*R*)-**9**, 55156-10-0; 2,2-diphenylethanol, 614-29-9; 2,2-diphenylacetic acid, 117-34-0; 2,2-diphenylethyl toluenesulfonate, 6944-27-0; *p*-toluenesulfonyl chloride, 98-59-9; diethyl (2,2-diphenylethyl)methylmalonate, 55124-29-3; diethyl methylmalonate, 609-08-5; ethyl (±)-2-isocyanato-2-methyl-4,4-diphenylbutanoate, 55124-30-6; (±)-2-amino-2-methyl-4,4-diphenylbutanoic acid, 55124-31-7; (±)-2-amino-2-methyl-4,4-diphenylbutanoic acid hydrochloride, 55124-32-8; (−)-menthyl methacrylate, 2231-91-6; methacrylic acid, 79-41-4; phosphorus trichloride, 7719-12-2; methacrylyl chloride, 920-46-7; (−)-*l*-menthol, 2216-51-5; (±)-1-methyl-2,2-diphenylcyclopropanecarboxylic acid, 35389-12-9; (*R*)-1-methyl-2,2-diphenylcyclopropanecarboxylic acid, 4542-84-1; (*R*)-1-methyl-1-trimethylsiloxymethyl-2,2-diphenylcyclopropane, 55124-33-9.

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Synthesis of Stereoisomeric 4-Hydroxymethyl-4-methyl-3β-hydroxycholestanes, -androstanes, and -10-methyl-*trans*-decalins

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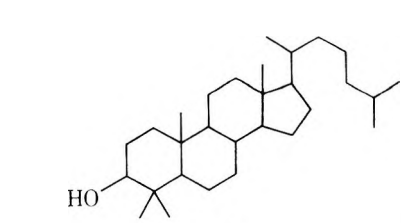
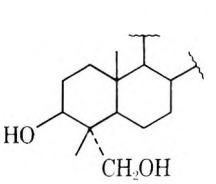
Reductive carbomethoxylation of enones **8**, **9**, and **10** was used as the key step in the preparation of 3β-hydroxycholestanes, 3β-hydroxyandrostanes, and 3β-hydroxy-10β-methyl-*trans*-decalins with 4α-hydroxymethyl-4β-methyl and 4β-hydroxymethyl-4α-methyl substituents (compounds **2**–**7**). Alkylation of the β-keto esters (**11**–**13**) resulting from reductive carbomethoxylations of enones **8**–**10** led to both 4β- and 4α-methyl compounds with the 4β isomer as the major product (~55%) in each case. Stereochemical assignments were made principally on the basis of the shielding effect that a 4β-carbomethoxyl group has on the NMR signal of the 10β-methyl group. Reduction of the methylated β-keto esters led to diols **2**–**7**, which were desired for study as possible intermediates in enzymic oxidative demethylation.

As part of a study of oxidative demethylation at C-4 during steroid biosynthesis,[1-3] we required derivatives of 4,4-dimethylcholestan-3β-ol (**1**) with the 4α or 4β methyl group in various stages of oxidation, particularly 4α-hydroxymethyl and 4β-hydroxymethyl compounds **2** and **3**.[1] The analogous derivatives **4** and **5** in the androstane series and **6** and **7** in the 10-methyl-*trans*-decalin[4] series were also needed for studies intended to determine the effect which substrate truncation would have on the enzymic demethylation process.[5] In this paper the details of the syntheses of these six diols and several related compounds are described.



1



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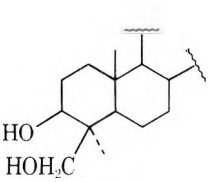
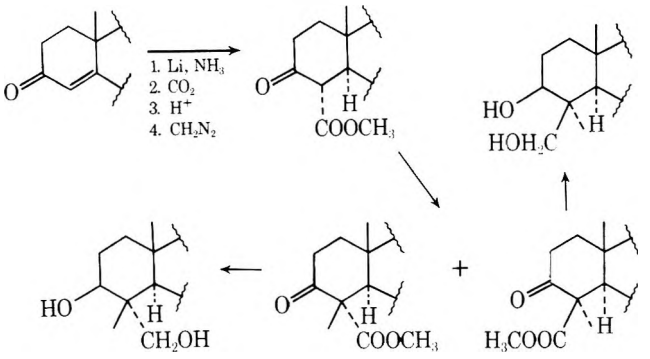


3

Scheme I shows the pathway used for preparation of each of the three sets of diols. The same approach had been used previously for the synthesis of naturally occurring di-

Scheme I



terpenes of the abietic acid[6-8] and podocarpic acid[9] series. The key step is reductive carbomethoxylation[10] of the appropriate enone followed by methylation of the resulting β-keto esters, which leads in all three cases to both stereoisomers at C-4. After separation and identification, these were reduced to the desired diols.

The requisite starting materials, unsaturated ketones **8**, **9**, and **10** (Scheme II), were prepared by known methods (see Experimental Section). Reductive carbomethoxylation of enone **10** has been reported by Stork[10] to afford β-keto ester **13** as an oil in 34% yield. In our hands a slightly different procedure gave 44% of **13** as an oil from which 37% of pure **13**, mp 60–64°, was obtained. The same procedure applied to **9** afforded 43% of **12**.

With enone **8**, however, the yield of 4α-carbomethoxycholestan-3-one (**11**)[11] from reductive carbomethoxylations never exceeded 33% and was often extremely low. Usually isolated in greater amount was the dimeric substance **14**, produced by reductive coupling.[12] This "cholestenone pinacol" has previously been isolated by a variety of procedures, including electrochemical reduction of **8**.[13,14]

Efforts were made to minimize the formation of **14** by varying reaction conditions. For instance, various nonpolar solvents were added in large amounts to test the hypothesis that the undesired reductive coupling was being promoted by a tendency for the fatty **8** to be associated with itself in liquid ammonia. These experiments failed, and the reasons why **14** tends to form remains obscure. However, even taking into account the low yield (typically around 20%), reductive carbomethoxylation of **8** is more convenient than the previous preparation of **11**.[11]

Certain C-4 monosubstituted steroids were also needed for our biochemical studies,[2] so some β-keto ester from each series was reduced rather than methylated. Since β-keto esters **11–13** were, as expected,[15,7] completely nonenolic, reduction to diol could be effected without difficulty using lithium aluminum hydride. It was anticipated[16] that a preponderance of the desired equatorial alcohol **15** would be formed. However, $LiAlH_4$ reduction of **11** afforded the 3α isomer **16** and **15** in approximately a 2:1 ratio. Assignment of stereochemistry at C-3 was made on the basis of the NMR spectra of the diacetates derived from **15** and **16**, which showed the expected differences between the C-3 protons bonded to carbons bearing equatorial and axial acetoxyl groups, respectively.[17]

In an effort to obtain a greater proportion of the desired diols **17** and **18** in the other two series, reduction of β-keto esters **12** and **13** was tried with sodium borohydride, despite the fact that $NaBH_4$ usually affords a larger fraction of axial alcohol than $LiAlH_4$.[18] As it turned out, 3β-hydroxy esters **19** and **20** were obtained as the dominant products (ca. 65% crude yield) from $NaBH_4$ reduction of **12** and **13**. These in turn were reduced with $LiAlH_4$ to **17** and **18**. Consistent with these results was $NaBH_4$ reduction of **11**, which afforded 65% of a hydroxy ester convertible to **15** by treatment with $LiAlH_4$ and 20% of a hydroxy ester convertible to **16**. No further exploration was made of the interesting effect that the 4α-carbomethoxyl group has on the stereochemical course of the $LiAlH_4$ reduction of **11**.

Table I
NMR Chemical Shifts (δ, $CDCl_3$) of Methyl Group Singlets in Seven Pairs of Isomers with Methyl and Carbomethoxyl Groups at C-4

Compound	C-18	10β-CH_3	4α-CH_3	4β-CH_3	-$COOCH_3$
21	0.67	1.06		1.35	3.68
22	0.66	0.97	1.32		3.65
23	0.65	0.90		1.15	3.64
24	0.64	0.69	1.18		3.62
25	0.73	1.08		1.37	3.70
26	0.70	0.96	1.26		3.62
27		1.10		1.25	3.70
28		0.99	1.26		3.61
37	0.65	0.87		1.16	3.70
38	0.65	0.71	1.40		3.62
39	0.70	0.90		1.14	3.75
40	0.70	0.74	1.37		3.72
41		0.95		1.10	3.66
42		0.75	1.35		3.70

Methylation of β-keto esters **11–13** was accomplished by treatment with sodium hydride and a trace of *tert*-butyl alcohol in dimethoxyethane, followed by methyl iodide.[7] From **11** there was obtained after chromatography 56% of the 4β-methylated compound **21** and 19% of 4α-methylated **22**. The stereochemical assignments to **21** and **22** were based on the previously documented fact[7,19] that an axial carbomethoxyl group at C-4, as in **22**, causes the NMR signal of the 10β-methyl group to be shifted upfield. In Table I are compiled the pertinent data on the seven pairs of compounds prepared in this study for which this shielding effect is evident in the 4β-carbomethoxy isomer.

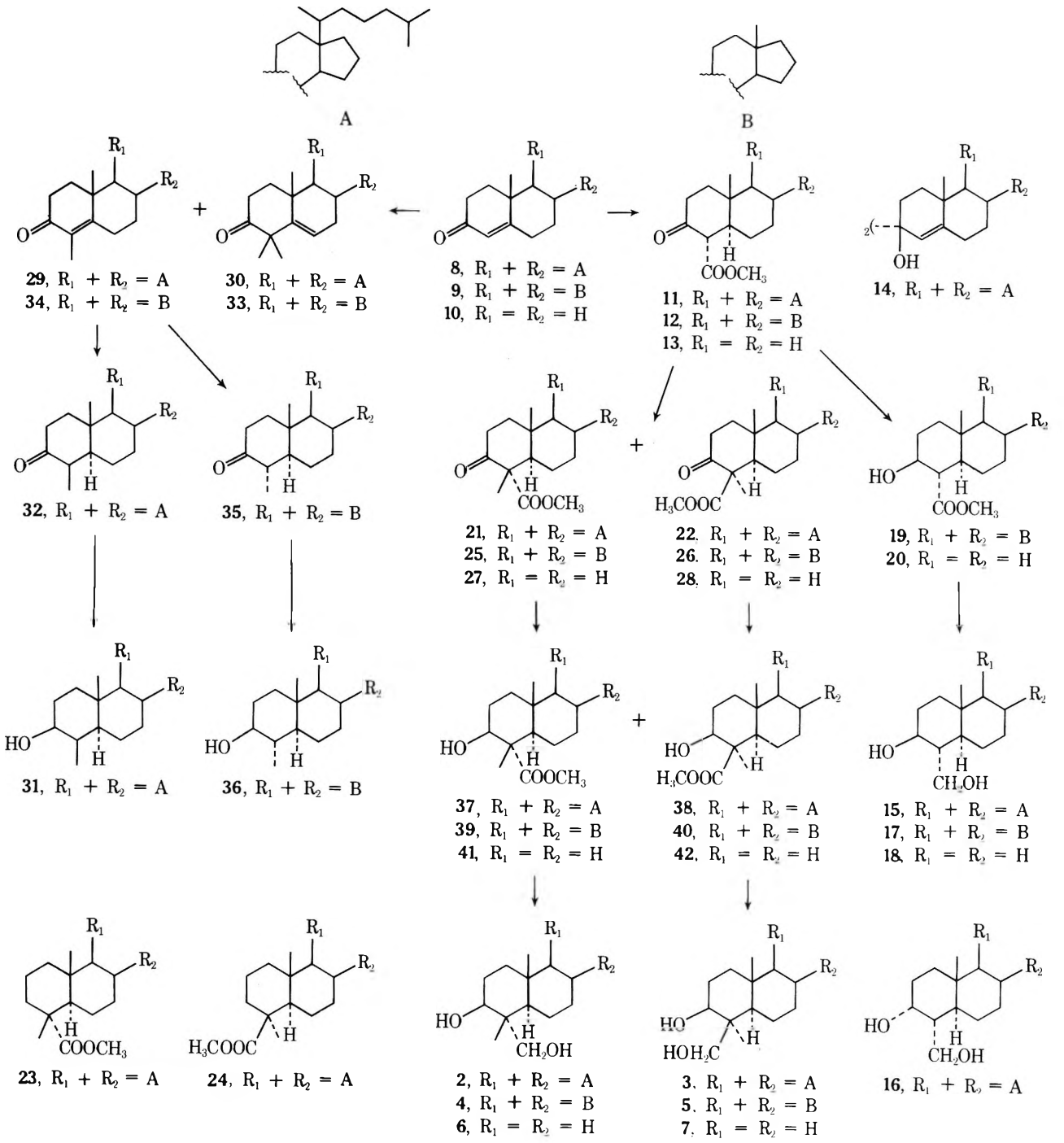
It had been previously noticed[7] that compounds which lacked the C-3 carbonyl group exhibited a considerably enhanced shielding of the angular methyl group by a 4β-carbomethoxyl. To see if this would also be observed in the cholestane series, **21** and **22** were subjected to Clemmensen reduction conditions of Wenkert.[20] The product from the Clemmensen reduction of **21** was contaminated with a large amount of unsaturated material[21] (NMR vinyl proton absorption) but pure **23** was obtained by hydrogenation of the mixture. Clemmensen reduction of **22** gave **24** directly. The expected enhanced shielding in **24** (0.21 ppm vs. 0.09 ppm in **22**) was indeed observed, in confirmation of the stereochemical assignments.[22]

Methylation of the β-keto esters in the androstane and decalin series proceeded analogously. From **12** was obtained 54% of **25** and 33% of **26**; from **13**, 56% of **27** and 28% of **28**. The preference for β alkylation in all three cases was expected on the basis of previous work,[7,20] and the β:α ratio was roughly the same in all cases.

Similar alkylations were performed on enones **8** and **9**. Methylation of **8** was conducted by the procedure of Atwater[23] to afford a separable mixture of **29** and **30**. Monomethylated **29** was converted to 4β-methylcholestan-3β-ol (**31**) by hydrogenation to **32**,[24] followed by reduction with lithium tri-*tert*-butoxyaluminum hydride.[25] Methylation of **9** gave the known[26] **33** and the monomethylated **34**, mp 100–103°. Lithium–ammonia reduction of **34** yielded **35**, which was converted to **36** by sodium borohydride.

The desired diols **2–7** were readily obtained from the methylated β-keto esters. Treatment of **21**, **22**, and **25–28**

Scheme II



with $NaBH_4$ led to the corresponding 3β-hydroxy esters **37–42.** Assignment of the β configuration to the hydroxyl group in each of these substances was made by NMR.[17] Finally, treatment of each hydroxy ester with $LiAlH_4$ led to diol: **37** → **2,** mp 219–220°; **38** → **3,** mp 209–210°; **39** → **4,** mp 203–204°; **40** → **5,** mp 143–144°; **41** → the previously reported[27] **6,** mp 97–98°; and **42** → **7,** an oil.

Experimental Section

Melting points were determined in open capillaries using a Thomas-Hoover apparatus and are uncorrected. Unless otherwise specified, ir spectra of solids were obtained as KBr pellets and liquids as neat films on a Perkin-Elmer 137 spectrophotometer. Unless otherwise specified, NMR spectra were determined in $CDCl_3$ on a Perkin-Elmer R-24 spectrometer with Me_4Si as an internal standard. Elemental analyses were performed by Spang Microanalytical Laboratory, Ann Arbor, Mich. Preparative TLC was performed on 20 × 20 cm plates coated with 1.45-mm thick layers of silica gel $PF_{254+366}$ (Brinkmann Instruments, Inc., Westbury, N.Y.) which had been mixed with 0.002% Rhodamine 6G dye (Eastman Kodak Co., Rochester, N.Y.). Uv light was used to visualize TLC plates. Brine refers to saturated aqueous sodium chloride solution.

4α-Carbomethoxycholestan-3-one (11). To a 2-l., three-necked flask, equipped with a mechanical stirrer and a reflux condenser, was added 800 ml of liquid ammonia followed by 1.12 g (0.16 mol) of lithium wire which had been cut into 1-cm lengths and washed with hexane to remove mineral oil. The resulting blue mixture was stirred for 15 min and a solution of 15.39 g (0.040 mol) of Δ^4-cholesten-3-one[28] (8) in 200 ml of anhydrous ether was added over a 1-hr period while vigorous stirring was maintained. The mixture was stirred for another 1 hr and then a steam bath was applied to the flask to speed evaporation of the ammonia. When the coating of ice on the flask melted, 600 ml of anhydrous ether was added and a Drierite tube was attached to the condenser. The mixture was refluxed for 30 min to drive off any residual ammonia and then was cooled to Dry Ice–acetone temperature.

During this cooling period a piece of Dry Ice (ca. 50 g) was pul-

verized in a cloth bag enclosed in a plastic bag. This fine powder was then added to the cold reaction mixture through a powder funnel which was also encased in a larger plastic bag. Care was taken to exclude moisture. The reaction flask was removed from the cooling bath and stirred for 30 min, and then was placed in a room-temperature water bath and stirred for 30 min. The mixture was cooled again in a Dry Ice–acetone bath and 100 g of powdered Dry Ice was added, followed by slow addition of 30 ml of 95% ethanol (to destroy excess lithium metal) and 200 ml of cold water. The contents of the flask were cooled to −10° under nitrogen and 20% hydrochloric acid was added until the reaction mixture was acidic. The mixture was quickly transferred to a separatory funnel which contained ice. The aqueous layer was separated and washed once with ether. The combined organic layers were washed once with cold brine and then added dropwise to a rapidly stirred solution of excess, freshly distilled diazomethane in ether at −78°. After 2 hr the excess diazomethane was destroyed by careful addition of acetic acid, and the mixture was concentrated in vacuo. The residue was dissolved in 400 ml of hexane and cooled to 0° for 4 hr. During this time a precipitate formed which was collected by filtration and washed with hexane to afford 3.4 g (22%) of **14**. Two recrystallizations from hexane gave an analytical sample: mp 215–217° (lit.[14] mp 225–227°); ir 3400 cm^{-1}; NMR δ 2.50 (s, HO–) and 5.25 ppm (s, HC=C–); M^+ *m/e* 770.

Anal. Calcd for $C_{54}H_{90}O_2$: C, 84.09; H, 11.76. Found: C, 83.79; H, 11.88.

The hexane filtrate was evaporated and the residue was dissolved in 100 ml of ether and stored at −10° for 48 hr. During this time a precipitate formed which was collected by filtration and washed with a small amount of cold ether to afford 3.66 g (21%) of **11**. Recrystallization from ether afforded 3.02 g (17%) of **11**: mp 170–172° (lit.[11] mp 170–172°); ir 1740 and 1720 cm^{-1} [lit.[11] ir (Nujol) 1740 and 1710 cm^{-1}]; NMR δ 0.67 (s, H_3C_{18}–), 1.03 (s, 10 β-H_3C–), 3.23 (d, J = 12 Hz, 4β-H), and 3.73 ppm (s, H_3COOC–). The yield of **11** varied from 0 to 33%. It was often necessary to use column chromatography (elution with 9:1 hexane–ether from acid-washed alumina) to isolate pure **11**.

Concentration of the ethereal filtrate afforded 8.15 g of a solid mixture of **8**, cholestan-3-one, and a trace of **11**.

4α-Carbomethoxyandrostan-3-one (12). Reductive carbomethoxylation of **9** was conducted by the following, simpler procedure. Into an oven-dried 500-ml three-necked flask, equipped with a Dewar condenser, a glass paddle mechanical stirrer, and a dropping funnel, was placed 200 ml of liquid ammonia and 150 mg (0.0214 mol) of lithium wire which had been wiped witlh a hexane-soaked cloth. The resulting blue mixture was stirred for 1 hr and a solution of 1.000 g (0.0037 mol) of **9**,[29] which had been dried in vacuo at 78° for 48 hr, in 15 ml of dry tetrahydrofuran was added dropwise rapidly. Vigorous stirring was continued for 1 hr. The ammonia was evaporated with a warm water bath and 75 ml of dry ether was added. The mixture was then refluxed for 30 min to ensure evaporation of any residual ammonia. The system was cooled and ca. 200 g (4.5 mol) of pulverized Dry Ice (taken from the center portion of a 50-lb block) was rapidly added. The slurry was stirred vigorously until it warmed to −10° (ca. 2 hr). Large pieces of residual lithium were removed with tweezers and then cold 10% sulfuric acid was added dropwise until the mixture became homogeneous (pH ~2). The solution was poured into a separatory funnel and quickly washed with two 50-ml portions of brine. The ethereal layer was dripped into cold excess ethereal diazomethane with stirring. The excess diazomethane was removed by blowing a stream of nitrogen into the flask; the resulting organic layer was dried ($MgSO_4$) and concentrated in vacuo to give 1.22 g of a crude yellow solid. This was distributed among five preparative TLC plates which were developed four times with 4:1 hexane–ether. Elution of the fastest moving band gave 0.178 g (18%) of androstan-3-one. The next band gave 0.390 g (43%) of **12**. The third band gave 0.250 g of **9**; the fourth band gave 0.048 g (5%) of androstan-3β-ol. The last band afforded 0.114 g (6%) of polar material which was recrystallized from 1:1 methanol–chloroform to give a substance with mp 225–230°; ir (KBr) 3400 cm^{-1}; NMR δ 5.62 ppm (br s, vinyl H). This material, thought to be the dimeric diol analogous to **14**, was not characterized further.

Recrystallization of **12** from ether afforded 0.300 g (25%) of white cubes: mp 160–162°; ir 1745 and 1710 cm^{-1}; NMR δ 0.69 (s, 3, H_3C_{18}–), 1.01 (s, 3, 10β-H_3C–), 3.22 (d, 1, J = 15 Hz, 4β-H), and 3.69 ppm (s, 3, H_3COOC–).

Anal. Calcd for $C_{21}H_{32}O_3$: C, 75.86; H, 9.70. Found: C, 75.91; H, 9.73.

4α-Carbomethoxy-10β-methyl-*trans*-decal-3-one (13). Reductive carbomethoxylation of enone **10**[30] was carried out in the same manner as that of **9**, which differs slightly from the published procedure for this conversion.[10] From 10.000 g (0.0610 mol) of **10** there was obtained 11.031 g of crude product which was chromatographed on 500 g of silica gel activated at 110° for 5 hr. Elution with 1:10 ether–petroleum ether (bp 37–48°) gave 0.514 g (4%) of 2α-carbomethoxy-10β-methyl-*trans*-decal-3-one;[31] elution with 1:4 ether–petroleum ether gave 5.918 g (44%) of **13**, followed by 0.685 g of **10**.

The semisolid **13** was recrystallized thrice from hexane to afford 4.992 g (37%) of pure **13**: mp 60–64°; ir 1745 and 1705 cm^{-1}; NMR δ 1.1 (s, 3, 10β-H_3C–), 3.16 (d, 1, J = 11 Hz, 4β-H), and 3.75 ppm (s, 3, H_3COOC–).

Anal. Calcd for $C_{13}H_{20}O_3$: C, 69.61; H, 8.99. Found: C, 69.72; H, 8.88.

4α-Hydroxymethylcholestan-3β-ol (15) and 4α-Hydroxymethylcholestan-3α-ol (16). To a stirred suspension of 0.19 g (0.005 mol) of $LiAlH_4$ in 20 ml of dry tetrahydrofuran (distilled from $LiAlH_4$), a solution of 0.675 g (0.0015 mol) of **11** in 25 ml of dry tetrahydrofuran was added over a period of 10 min. The mixture was heated at reflux for 1.5 hr and cooled, and ice and dilute sulfuric acid were added. It was then partitioned between 50 ml of water and ether. The ether extracts were washed with water, dilute $NaHCO_3$ solution, and brine, dried over $MgSO_4$, and evaporated to afford 0.670 g of white, crystalline material, mp 207–215°, which TLC (ether) indicated was a mixture of two compounds. This product was chromatographed over 125 g of Merck acid-washed alumina. Elution with ether removed pale yellow gummy material. Elution with ethyl acetate afforded 0.234 g (39%) of **16**, which was recrystallized successively from ether and methanol to give an analytical sample: mp 195–197°; ir 3320 cm^{-1}. NMR data were determined on the crude diacetate of **16** prepared by treatment with acetic anhydride in pyridine at room temperature for 24 hr: δ 2.00 (s, H_3CCOO–), 2.02 (s, H_3CCOO–), 4.05 (br m, $-H_2COOCCH_3$), and 5.13 ppm (br s, 3β-H).

Anal. Calcd for $C_{28}H_{50}O_2$: C, 80.32; H, 12.04. Found: C, 80.41; H, 12.26.

Elution with 9:1 ethyl acetate–methanol afforded 0.160 g (17%) of **15**, which was recrystallized from ether to give material with mp 228–231°, and then from methanol to give an analytical sample: mp 211–213°; ir 3240 cm^{-1}. NMR data were determined on the crude diacetate of **15** prepared in the same manner: δ 2.02 (s, 2 H_3CCOO–), 4.08 (br s, $-H_2COOCCH_3$), and 4.65 ppm (br m, 3α-H).

Anal. Calcd for $C_{28}H_{50}O_2$: C, 80.32; H, 12.04. Found: C, 80.01; H, 12.01.

Preparative TLC using 3:2 hexane–ether twice of the product from another $LiAlH_4$ reduction of **11** afforded 54% of **16** and 27% of **15**. Reduction of 0.200 g (0.45 mmol) of **11** with $NaBH_4$ as described below for 12 afforded, after preprative TLC using 2:1 hexane–ether twice, 0.039 g (20%) of a hydroxy ester (ir 3550 and 1730 cm^{-1}) which was converted exclusively to **16** by $LiAlH_4$, and 0.130 g (65%) of a hydroxy ester (ir 3450 and 1725 cm^{-1}) which was converted exclusively to **15** by $LiAlH_4$.

4α-Carbomethoxyandrostan-3β-ol (19). A mixture of 0.100 g (0.3 mmol) of **12**, 0.010 g (0.26 mmol) of $NaBH_4$, and 10 ml of methanol was stirred for 2 hr at room temperature. The methanol was evaporated in vacuo and the resulting solid was partitioned between 25 ml of ether and 10 ml of 5% sulfuric acid. The ether layer was separated, dried ($MgSO_4$), and concentrated in vacuo to give 0.110 g from which preparative TLC, using 1:1 ether–hexane twice, afforded 0.040 g of material presumed to be crude 4α-carbomethoxyandrostan-3α-ol on the basis of its NMR spectrum [δ 3.65 (s, 3, H_3COOC–) and 4.05 ppm (br s, 3β-H)], 0.064 g (63%) of crude **19**, and 0.002 g of polar material, presumably diol. Recrystallization of **19** from isopropyl alcohol afforded 0.039 g (38%) of white, silky crystals: mp 173–174°; ir 3300 and 1740 cm^{-1}; NMR δ 0.67 (s, 3, H_3C_{18}–), 0.82 (s, 3, 10β-H_3C–), 3.70 (s, 3, H_3COOC–), and 3.5–3.8 ppm (m, 2, 4β-H and 3α-H).

Anal. Calcd for $C_{21}H_{34}O_3$: C, 75.41; H, 10.25. Found: C, 75.45; H, 10.32.

4α-Carbomethoxy-10β-methyl-*trans*-decal-3β-ol (20). Reduction of 0.400 g (1.8 mmol) of **13** with $NaBH_4$ in exactly the same manner as **12** afforded 0.120 g of material presumed to be crude 4α-carbomethoxy-10β-methyl-*trans*-decal-3α-ol on the basis of its NMR spectrum [δ 3.51 (br s, 4β-H), 3.65 (s, 3, H_3COOC–), and 4.11 ppm (br s, 3β-H)], 0.281 g (69%) of oily **20**, and 0.023 g of polar material, presumably diol. Purification of **20** was effected by sublimation twice at 63° (65 mm) to afford 0.183 g (48%) of **20** as white, silky crystals: mp 69°; ir 3400 and 1735 cm^{-1}; NMR δ 0.91

(s, 3, 10β-H_3C–) and 3.5–4.0 ppm (m and s overlapping, 5, H_3COOC–, 3α-H and 4β-H).

Anal. Calcd for $C_{13}H_{22}O_3$: C, 68.99; H, 9.79. Found: C, 69.08; H, 9.77.

4α-Hydroxymethylandrostan-3β-ol (17). A mixture of 0.066 g (0.19 mmol) of **19**, 0.020 g (0.52 mmol) of $LiAlH_4$, and 10 ml of ether was stirred for 2 hr at room temperature. Excess $LiAlH_4$ was destroyed with 2 drops of ethyl acetate followed by 5 ml of 10% sulfuric acid. Standard work-up with ether and concentration in vacuo afforded 0.042 g of a white solid, which was recrystallized from ether to give 0.027 g (46%) of pure **17** as white plates: mp 194–196°; ir ($CHCl_3$) 3300 cm^{-1}; NMR δ 0.70 (s, 3, H_3C_{18}–), 0.90 (s, 3, 10β-H_3C–), and 3.0–4.5 ppm (m, 5).

Anal. Calcd for $C_{20}H_{34}O_2$: C, 78.38; H, 11.18. Found: C, 78.20; H, 11.10.

4α-Hydroxymethyl-10β-methyl-*trans*-decal-3β-ol (18). Reduction of 0.073 g (0.32 mmol) of **20** with $LiAlH_4$ in exactly the same manner as **19** afforded 0.081 g of a crude product which was sublimed at 100° (15 mm) to give 0.056 g (88%) of **18** as white plates: mp 117–118°; ir 3300 cm^{-1}; NMR δ 0.88 (s, 3, 10β-H_3C–) and 3.4–4.2 ppm (m, 5).

Anal. Calcd for $C_{12}H_{22}O_2$: C, 72.68; H, 11.18. Found: C, 72.72; H, 11.09.

4α-Carbomethoxy-4β-methylcholestan-3-one (21) and 4β-Carbomethoxy-4α-methylcholestan-3-one (22). To a stirred solution of 1.51 g (3.4 mmol) of keto ester **11** in 100 ml of dimethoxyethane, which had been distilled from sodium and redistilled from $LiAlH_4$, was added 0.35 g (4.2 mmol) of NaH (55% dispersion in mineral oil) and 8 drops of dry *tert*-butyl alcohol under a nitrogen atmosphere. After the evolution of gas ceased, 19.4 g (8.5 ml, 0.13 mol) of methyl iodide was added and the mixture was heated at 70° for 4 hr and at 85° for 1 hr. The mixture was cooled, diluted with 15 ml of cold water, concentrated to a volume of ca. 50 ml in vacuo, diluted with water, and extracted with ether. The ether extracts were washed with water and brine, dried ($MgSO_4$), and evaporated to afford 1.87 g of pale yellow oil which was chromatographed on 130 g of acid-washed alumina. Elution with hexane removed mineral oil (0.27 g). Elution with 9:1 hexane–ether afforded 0.29 g (19%) of **22**, mp 110–111°. Recrystallization from methanol afforded an analytical sample as needles: mp 117–118°; ir 1740 and 1720 cm^{-1}; NMR δ 0.66 (s, H_3C_{18}–), 0.97 (s, 10β-H_3C–), 1.32 (s, 4α-H_3C–), and 3.65 ppm (s, H_3COOC–).

Anal. Calcd for $C_{30}H_{50}O_3$: C, 78.55; H, 10.99. Found: C, 78.54; H, 10.91.

Further elution with 5:1 hexane–ether afforded 0.854 g (56%) of **21**, mp 95–96°. Recrystallization from methanol afforded an analytical sample as small plates: mp 100–101°; ir 1745 and 1720 cm^{-1}; NMR δ 0.67 (s, H_3C_{18}–), 1.06 (s, 10β-H_3C–), 1.35 (s, 4β-H_3C–), and 3.68 ppm (s, H_3COOC–).

Anal. Calcd for $C_{30}H_{50}O_3$: C, 78.55; H, 10.99. Found: C, 78.52; H, 10.93.

4α-Carbomethoxy-4β-methylandrostan-3-one (25) and 4β-Carbomethoxy-4α-methylandrostan-3-one (26). To a stirred solution of 0.250 g (0.75 mmol) of **12** in 30 ml of dimethoxyethane was added 1 drop of *tert*-butyl alcohol and 0.033 g (0.78 mmol) of sodium hydride (57% dispersion in mineral oil). This mixture was heated at reflux for 2 hr and then a solution of 0.226 g (1.6 mmol) of methyl iodide in 10 ml of dimethoxyethane was dripped in over 30 min. The resulting mixture was stirred at reflux for an additional 3 hr, cooled, and poured into a mixture of 50 ml of ether and 20 ml of water. The aqueous layer was reextracted with 10 ml of ether and the combined organic layers were washed once with 20 ml of 10% HCl and once with 20 ml of water, dried ($MgSO_4$), and evaporated in vacuo to give 0.307 g of a white solid. Preparative TLC, using 4:1 hexane–ether, afforded 0.006 g (2%) of overalkylated material, 0.085 g (33%) of **26**, 0.140 g (54%) of **25**, and 0.042 g (12%) of **12**.

Recrystallization twice from methanol gave 0.042 g (16%) of pure **26**: mp 128–129°; ir 1730 and 1705 cm^{-1}; NMR δ 0.70 (s, 3, H_3C_{18}–), 0.96 (s, 3, 10β-H_3C–), 1.26 (s, 3, 4α-H_3C–), and 3.62 ppm (s, 3, H_3COOC–).

Anal. Calcd for $C_{22}H_{34}O_3$: C, 76.25; H, 9.89. Found: C, 76.19; H, 9.80.

Recrystallization twice from ether gave 0.093 g (36%) of pure **25**: mp 146–147°; ir 1740 and 1705 cm^{-1}; NMR δ 0.73 (s, 3, H_3C_{18}–), 1.08 (s, 3, 10β-H_3C–), 1.37 (s, 3, 4β-H_3C–), and 3.70 ppm (s, 3, H_3COOC–).

Anal. Calcd for $C_{22}H_{34}O_3$: C, 76.25; H, 9.89. Found: C, 76.31; H, 9.73.

4α-Carbomethoxy-4β,10β-dimethyl-*trans*-decal-3-one (27) and 4β-Carbomethoxy-4α,10β-dimethyl-*trans*-decal-3-one (28). Methylation of β-keto ester **13** was conducted in exactly the same manner as methylation of **12**, except that the reaction was allowed to proceed for an additional 1 hr. The same work-up afforded, from 0.500 g (2.2 mmol) of **13**, 0.673 g of crude product, which upon preparative TLC using 4:1 hexane–ether afforded 0.019 g (3.6% based on 518 mg of recovered material) of overalkylated material which was not characterized, 0.146 g (28%) of **28**, 0.289 g (55%) of **27**, and 0.064 g (12%) of **13**.

Compound **28** was purified by preparative TLC using 4:1 hexane–ether to an oil which was homogeneous by TLC: ir 1735 and 1710 cm^{-1}; NMR δ 0.99 (s, 3, 10β-H_3C–), 1.26 (s, 3, 4α-H_3C–), and 3.61 ppm (s, 3, 4β-H_3COOC–); M^+ *m/e* 238.1571 (calcd for $C_{14}H_{22}O_3$, 238.1568).

Compound **27** was purified by preparative TLC using 4:1 hexane–ether to an oil which was homogeneous by TLC: ir 1745 and 1705 cm^{-1}; NMR δ 1.10 (s, 3, 10β-H_3C–), 1.25 (s, 3, 4β-H_3C–), and 3.70 ppm (s, 3, H_3COOC–); M^+ *m/e* 238.1569 (calcd for $C_{14}H_{22}O_3$, 238.1568).

4α-Carbomethoxy-4β-methylcholestane (23). According to a Clemmensen reduction procedure reported by Wenkert,[20] a suspension of amalgamated zinc (prepared by shaking 9.0 g of zinc moss in a solution of 0.6 g of mercuric chloride and 0.5 ml of concentrated hydrochloric acid in 6 ml of water for 15 min, and then washing the undissolved zinc with water) and 0.28 g (0.61 mmol) of **21**, mp 101–102°, in 6 ml of 15% hydrochloric acid was refluxed for 60 hr. During this time 0.5 ml of concentrated hydrochloric acid was added to the reaction mixture every 8 hr. The cooled mixture was extracted with ether. The organic layer was washed with water, sodium bicarbonate solution, and brine, dried ($MgSO_4$), and evaporated to give 0.27 g of a viscous oil. The crude oil was purified by preparative TLC, using 9:1 hexane–ether, to give 0.23 g of crystalline material. Recrystallization from ethanol afforded 0.16 g: mp 73–78°; ir 1740 cm^{-1}; NMR δ 5.5 ppm (m);[21] TLC on silica gel G impregnated with 12% $AgNO_3$, using 19:1 hexane–ether, showed two components; GLC (Varian 2100 instrument, 3% QF-1, 6 ft × 4 mm column, 220°) indicated (disc chart integration) the mixture to be 1.6 parts **23** to 1 part presumably unsaturated material.

The entire 0.23 g of crystalline product was hydrogenated over 0.08 g of 10% Pd/C in 85 ml of ethanol for 1.5 hr at atmospheric pressure. The catalyst was removed by filtration and the filtrate was evaporated to give 0.21 g of a white solid which TLC and GLC indicated was homogeneous. Recrystallization from ethanol afforded 0.17 g (63% from **21**) of **23**, mp 80–82°. Further recrystallization from ethanol afforded an analytical sample: mp 81–82.5°; ir 1740 cm^{-1}; NMR δ 0.65 (s, H_3C_{18}–), 0.90 (s, 10β-H_3C–), 1.15 (s, 4β-H_3C–), and 3.62 ppm (s, H_3COOC–).

Anal. Calcd for $C_{30}H_{52}O_2$: C, 81.02; H, 11.79. Found: C, 81.13; H, 11.78.

4β-Carbomethoxy-4α-methylcholestane (24). Exactly as in the preparation of **23** from **21**, 0.080 g (0.17 mmol) of **22**, mp 115–116°, was subjected to Clemmensen reduction. There was obtained 0.077 g of solid, mp 70–78°. One recrystallization from hexane gave 0.066 g (84%) of **24**: mp 78–80°; NMR, no vinyl proton absorption. Further recrystallization from hexane afforded an analytical sample: mp 79.5–80.5°; ir 1740 cm^{-1}; NMR δ 0.64 (s, H_3C_{18}–), 0.69 (s, 10β-H_3C–), 1.18 (s, 4α-H_3C–), and 3.62 ppm (s, H_3COOC–).

Anal. Calcd for $C_{30}H_{52}O_2$: C, 81.02; H, 11.79. Found: C, 81.33; H, 11.86.

4β-Methylcholestan-3β-ol (31). To a stirred solution of 0.500 g (1.29 mmol) of 4β-methylcholestan-3-one (**32**)[24] in 25 ml of dry tetrahydrofuran at 0° was added, dropwise, a slurry of 1.50 g of lithium tri-*tert*-butoxyaluminum hydride in 40 ml of tetrahydrofuran. This mixture was stirred at 0° for 2 hr and at room temperature for 2 hr. It was then acidified with dilute hydrochloric acid, concentrated in vacuo, and extracted with ether. The organic layer was washed with water, dried ($MgSO_4$), and evaporated to give 0.490 g (98%) of **31**, mp 157–161°. Recrystallization from methanol afforded an analytical sample, mp 160.5–162.5°,[25] ir 3360 cm^{-1}.

Anal. Calcd for $C_{28}H_{50}O$: C, 83.51; H, 12.51. Found: C, 83.65; H, 12.47.

4-Methyl-Δ⁴-androsten-3-one (34). To a mixture of 70 ml of dry *tert*-butyl alcohol and 0.500 g (11 mmol) of NaH (57% dispersion in mineral oil), under nitrogen, was added 2.00 g (7.3 mmol) of **9**. The resulting mixture was refluxed for 1 hr and then a solution of 1.50 g (10.5 mmol) of methyl iodide in 10 ml of dry *tert*-butyl alcohol was added dropwise over 30 min. After being refluxed for an additional 1 hr, the mixture was cooled and evaporated in vacuo. The resulting yellow gum was dissolved in 150 ml of ether and washed with two 50-ml portions of 5% sulfuric acid and two 50-ml

portions of water. The organic layer was dried ($MgSO_4$) and evaporated in vacuo to give 2.9 g of a yellow solid, which was chromatographed on 60 g of silica gel in hexane. Elution with ether–hexane gave 0.657 g (30%) of **33**. Recrystallization from acetone afforded 0.432 g (20%) of pure **33**: mp 174–175° (lit.[26] mp 178–180°); ir 1705 cm^{-1}; NMR δ 0.71 (s, 3, H_3C_{18}–), 0.85 (s, 3, 10β-H_3C–), 1.22 (s, 6, 4α- and 4β-H_3C–), and 5.55 ppm (m, 1, 6-H).

Next eluted was 0.808 g of solid which was recrystallized from methanol to give 0.583 g (28%) of pure **34**: mp 100–103°; ir 1675 cm^{-1}; NMR δ 0.85 (s, 3, H_3C_{18}–), 1.24 (s, 3, 10β-H_3C–), and 1.88 ppm (s, 3, 4 H_3C–).

Anal. Calcd for $C_{20}H_{30}O$: C, 83.85; H, 10.55. Found: C, 83.76; H, 10.43.

Further elution afforded 0.489 g of **9**.

4α-Methylandrostan-3-one (35). To a 100-ml three-necked flask equipped with a Dewar condenser, an addition funnel, and a glass paddle mechanical stirrer was added 55 ml of liquid ammonia and 0.055 g (7.8 mmol) of lithium wire which had been wiped with a hexane-soaked cloth. After this blue mixture had been stirred for 30 min, a solution of 0.400 g (1.4 mmol) of **34** in 15 ml of ether was added rapidly and stirring was continued for 10 min. The ammonia was evaporated with the aid of a warm water bath and 30 ml of ether, 5 ml of 95% ethanol, and 5 ml of water were added. This solution, plus an additional 30 ml of ether, was poured into 50 ml of water. The aqueous layer was extracted with 3 × 20 ml of ether and the combined extracts were washed with 30 ml of water, dried ($MgSO_4$), and evaporated in vacuo to give 0.390 g of white solid. This material was dissolved in 25 ml of acetone and oxidized with 1 ml of Jones reagent.[32] A standard ether work-up gave 0.373 g of white solid, which was chromatographed on 15 g of silica gel. Elution with hexane containing increasing amounts of ether afforded **35**, which was recrystallized twice from 95% ethanol to afford 0.164 g (41%) of **35** as white plates: mp 130–132°; ir 1710 cm^{-1}; NMR δ 0.80 (s, 3, H_3C_{18}–), 1.00 (s, 3, 10β-H_3C–), and 1.12 ppm (d, 3, J = 6 Hz, 4α-H_3C–).

Anal. Calcd for $C_{20}H_{32}O$: C, 83.27; H, 11.18. Found: C, 83.18; H, 11.15.

Further elution afforded 0.110 g of **34**.

4α-Methylandrostan-3β-ol (36). A mixture of 0.130 g (0.45 mmol) of **35**, 40 ml of methanol, and 0.050 g (1.3 mmol) of $NaBH_4$ was stirred at room temperature while the disappearance of **35** was monitored by TLC. After 1 hr, the reaction mixture was worked up as in the preparation of **19** to afford 0.140 g of white solid which was purified by preparative TLC using 3:1 hexane–ether. Two substances were eluted. The first, 0.006 g (5%), is tentatively identified as 4α-methylandrostan-3α-ol: mp 147–151°; NMR δ 0.70 (s, 3, H_3C_{18}–), 0.80 (s, 3, 10β-H_3C–), 0.95 (d, 3, J = 4 Hz, 4α-H_3C–), and 3.7 ppm (br s, 1, 3β-H). The second was recrystallized twice from 3:1 methanol–water to afford 0.040 g (31%) of **36**: mp 158–160°; ir 3400 cm^{-1}; NMR δ 0.69 (s, 3, H_3C_{18}–), 0.85 (s, 3, 10β-H_3C–), 1.0 (d, 3, J = 6 Hz, 4α-H_3C–), and 2.9–3.4 ppm (br m, 1, 3α-H).

Anal. Calcd for $C_{20}H_{34}O$: C, 82.69; H, 11.79. Found: C, 82.58; H, 11.82.

4α-Carbomethoxy-4β-methylcholestan-3β-ol (37). Reduction of 0.400 g (0.87 mmol) of **21** with $NaBH_4$ was performed in exactly the same manner as **12**, except that the reaction was allowed to proceed for 12 hr, to afford 0.430 g of crude product which was recrystallized from methanol to give 0.357 g (89%) of **37**, mp 171–173°. Further recrystallization from methanol gave an analytical sample as white needles: mp 173–173.5°; ir 3500 and 1720 cm^{-1}; NMR δ 0.65 (s, H_3C_{18}–), 0.81 (s, 10β-H_3C–), 1.16 (s, 4β-H_3C–), 3.70 (s, H_3COOC–), and 3.9–4.1 ppm (br m, 3α-H).

Anal. Calcd for $C_{30}H_{52}O_3$: C, 78.21; H, 11.38. Found: C, 78.33; H, 11.42.

4β-Carbomethoxy-4α-methylcholestan-3β-ol (38). Reduction of 0.286 g (0.62 mmol) of **22** with $NaBH_4$ in exactly the same manner as **12** except that the reaction was allowed to proceed for 12 hr afforded 0.278 g of crude product which was recrystallized from ether to give 0.211 g (74%) of **38**, mp 145–147°. Further recrystallization from ether gave an analytical sample: mp 147–148°; ir 3550 and 1700 cm^{-1}; NMR 0.65 (s, H_3C_{18}–), 0.71 (s, 10β-H_3C–), 1.40 (s, 4α-H_3C–), 2.75–3.50 (br m, 3α-H), and 3.62 ppm (s, H_3COOC–).

Anal. Calcd for $C_{30}H_{52}O_3$: C, 78.21; H, 11.38. Found: C, 78.29; H, 11.47.

4α-Carbomethoxy-4β-methylandrostan-3β-ol (39). Reduction of 0.050 g (0.14 mmol) of **25** with $NaBH_4$ in exactly the same manner as **12** afforded 0.055 g of crude product which was purified by preparative TLC, using 1:1 hexane–ether twice, to afford 0.008 g (16%) of material tentatively identified as 4α-carbomethoxy-4β-methylandrostan-3α-ol, 0.039 g (78%) of **39**, and 4 mg of polar material, presumably diol. Recrystallization of **39** from ether afforded 0.022 g (45%) of white cubes: mp 188–189°; ir 3700 and 1730 cm^{-1}; NMR δ 0.70 (s, 3, H_3C_{18}–), 0.90 (s, 3, 10β-H_3C–), 1.14 (s, 3, 4β-H_3C–), 3.75 (s, 3, H_3COOC–), and 4.02 ppm (m, 1, 3α-H).

Anal. Calcd for $C_{22}H_{36}O_3$: C, 75.81; H, 10.41. Found: C, 75.78; H, 10.48.

4β-Carbomethoxy-4α-methylandrostan-3β-ol (40). Reduction of 0.042 g (0.12 mmol) of **26** with $NaBH_4$ in exactly the same manner as **12** afforded 0.043 g of crude product which was purified in the same manner used in the preparation of **39** to afford 0.035 g (83%) of **40** and 0.007 g of polar material, presumably diol. Recrystallization from isopropyl alcohol afforded 0.020 g (48%) of **40**: mp 129–130°; ir 3600 and 1730 cm^{-1}; NMR δ 0.70 (s, 3, H_3C_{18}–), 0.74 (s, 3, 10β-H_3C–), 1.37 (s, 3, 4α-H_3C–), 2.95–3.25 (m, 1, 3α-H), and 3.72 ppm (s, 3, H_3COOC–).

Anal. Calcd for $C_{22}H_{36}O_3$: C, 75.81; H, 10.41. Found: C, 75.70; H, 10.44.

4α-Carbomethoxy-4β,10β-dimethyl-*trans*-decal-3β-ol (41). Reduction of 0.399 g (1.7 mmol) of **27** with $NaBH_4$ in exactly the same manner as **12** afforded 0.411 g of crude oily product which was purified by preparative TLC, using 2:1 hexane–ether twice, to afford 0.088 g (21%) of material tentatively identified as 4α-carbomethoxy-4β,10β-dimethyl-*trans*-decal-3α-ol, 0.29 g (72%) of **41**, and 0.020 (5%) of polar material, presumably diol. Compound **41** was sublimed thrice at 70° (15 mm) to yield 0.150 g (37%) of white needles: mp 87–88°; ir 3400 and 1740 cm^{-1}; NMR δ 0.95 (s, 3, 10β-H_3C–), 1.10 (s, 3, 4β-H_3C–), 3.66 (s, 3, H_3COOC–), and 4.00 ppm (br t, 1, 3α-H).

Anal. Calcd for $C_{14}H_{24}O_3$: C, 69.96; H, 10.06. Found: C, 70.05; H, 10.04.

4β-Carhomethoxy-4α,10β-dimethyl-*trans*-decal-3β-ol (42). Reduction of 0.200 g (0.9 mmol) of **28** with $NaBH_4$ in exactly the same manner as **12** afforded 0.264 g of crude product which was purified by preparative TLC, using 2:1 hexane–ether twice to afford 0.043 g of material tentatively identified as 4β-carbomethoxy-4α,10β-dimethyl-*trans*-decal-3α-ol, 0.212 g of crude **42**, and 0.008 g of polar material, presumably diol. Compound **42** was sublimed twice at 65° (15 mm) to yield 0.120 g (56%) of white needles: mp 70–71°; ir 3500 and 1730 cm^{-1}; NMR δ 0.75 (s, 3, 10β-H_3C–), 1.35 (s, 3, 4α-H_3C–), 2.95–3.25 (br m, 1, 3α-H), and 3.70 ppm (s, 3, H_3COOC–).

Anal. Calcd for $C_{14}H_{24}O_3$: C, 69.96; H, 10.06. Found: C, 70.16; H, 9.90.

4α-Hydroxymethyl-4β-methylcholestan-3β-ol (2). Diol **2** was prepared by treatment of both **37** and **21** with $LiAlH_4$. Reduction of 0.050 g (0.11 mmol) of **21** with $LiAlH_4$ was performed exactly as with **11** to afford 0.047 g of crude product, mp 195–216°. One recrystallization from ether gave 0.034 g (78%) of **2**, mp 215–217°. Further recrystallization from ether afforded an analytical sample as glistening plates: mp 219–220°; ir 3350 cm^{-1}; NMR δ 0.64 (s, H_3C_{18}–), 0.80 (s, 10β-H_3C–), and ~3.5 ppm (br m, 3α-H and 4β-HOH_2C–).

Anal. Calcd for $C_{29}H_{52}O_2$: C, 80.49; H, 12.11. Found: C, 80.54; H, 12.27.

4β-Hydroxymethyl-4α-methylcholestan-3β-ol (3). Diol **3** was prepared by treatment of both **38** and **22** with $LiAlH_4$. Reduction of 0.58 g (1.5 mmol) of **22** with $LiAlH_4$ was performed exactly as with **11** to afford 0.58 g of a crude product, mp 187–199°, which was purified by chromatography on 12 g of acid-washed alumina. Elution with ethyl acetate afforded 0.52 g (93%) of **3**, which tends to gel in many solvents, but can be recrystallized from ethyl acetate to afford an analytical sample: mp 209–210°; ir 3300–3200 cm^{-1}; NMR δ 0.63 (s, H_3C_{18}–), 0.82 (s, 10β-H_3C–), 1.18 (s, 4α-H_3C–), and ~3.8 ppm (br m, 3α-H and 4β-HOH_2C–).

Anal. Calcd for $C_{29}H_{52}O_2$: C, 80.49; H, 12.11. Found: C, 80.46; H, 12.02.

4α-Hydroxymethyl-4β-methylandrostan-3β-ol (4). Reduction of 0.020 g (0.05 mmol) of **39** with $LiAlH_4$ was performed exactly as with **12** to afford 0.020 g of crude product which was recrystallized from ether to give 0.010 g (63%) of pure **4** as white needles: mp 203–204°; ir ($CHCl_3$) 3400 cm^{-1}; NMR δ 0.69 (s, 3, H_3C_{18}–), 0.91 (s, 6, 4β-H_3C– and 10β-H_3C–), and 3.0–4.0 ppm (br m, 3α-H and 4α-HOH_2C–).

Anal. Calcd for $C_{21}H_{36}O_2$: C, 78.69; H, 11.32. Found: C, 78.54; H, 11.34.

4β-Hydroxymethyl-4α-methylandrostan-3β-ol (5). Reduction of 0.018 g (0.05 mmol) of **40** with $LiAlH_4$ was performed exactly as with **12** to afford 0.017 g of crude product which was recrys-

tallized from 20:1 ether–isopropyl alcohol to give 0.008 g (48%) of pure **5** as white prisms: mp 197–199°; ir 3400–3300 cm^{-1}; NMR δ 0.68 (s, 10β-H_3C– and H_3C_{18}–), 1.30 (s, 4α-H_3C–), and 3.25–4.10 ppm (complex m, 3α-H and 4β-HOH_2C–).

Anal. Calcd for $C_{21}H_{36}O_2$: C, 78.69; H, 11.32. Found: C, 78.71; H, 11.35.

4α-Hydroxymethyl-4β,10β-dimethyl-*trans*-decal-3β-ol (6). Reduction of 0.045 g (0.19 mmol) of **41** with $LiAlH_4$ was performed exactly as with **12** to afford 0.048 g of crude product which was sublimed at 80° (15 mm) to give 0.030 g (74%) of **6** as white plates: mp 97–98° (lit.[27] mp 107°); ir 3300 cm^{-1}; NMR δ 0.85 (s, 3, 10β-H_3C–), 0.95 (s, 3, 4β-H_3C–), and 2.75–3.70 ppm (complex m, 5).

Anal. Calcd for $C_{13}H_{24}O_2$: C, 73.53; H, 11.39. Found: C, 73.62; H, 11.42.

4β-Hydroxymethyl-4α,10β-dimethyl-*trans*-decal-3β-ol (7). Reduction of 0.042 g (0.18 mmol) of **42** with $LiAlH_4$ was performed exactly as with **12** to afford 0.032 g (86%) of crude **7**. Preparative TLC using 1:1 hexane–ether twice gave 0.015 g (40%) of pure **7** as a colorless oil: ir (neat) 3350 cm^{-1}; NMR δ 0.89 (s, 3, 10β-H_3C–), 1.19 (s, 3, 4α-H_3C–), and 3.1–4.25 ppm (br m, 5); M^+ *m/e* 212.1779 (calcd for $C_{13}H_{24}O_2$, 212.1776).

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References and Notes

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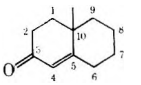

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A Remarkable Methyl Substituent Effect in a Twistane Aldol Synthesis

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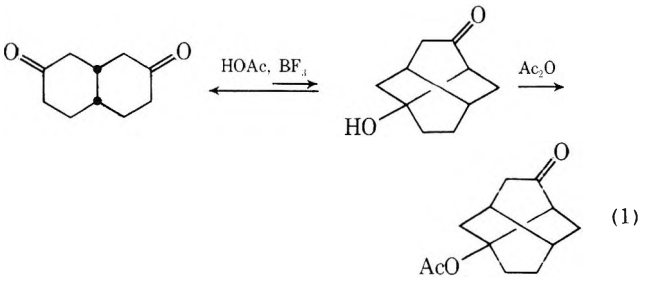
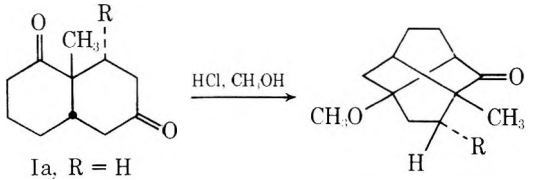
An internal aldol cyclization of 1-methyl-*cis*-bicyclo[4.4.0]decane-2,8-dione derivatives (I) to substituted twistanones (II) is described. The presence of a *trans*-methyl substituent at C-10 enhances this cyclization in a striking manner. Indeed, the resulting aldol product (III) predominates in the base-catalyzed equilibrium. The *p*-bromobenzenesulfonate derivative of III was analyzed by X-ray diffraction.

The twistane ring system (the tricyclo[4.4.0.0^{5,8}]decane system) has intrigued organic chemists since its initial synthesis by Whitlock in 1962.[1] Because of its D_2 symmetry, twistane is an ideal model for studying the chiroptical properties of twist-boat structures.[2] Furthermore, twistane is a highly efficient precursor to adamantane,[3] and its 4-keto derivative is reported to be an antiviral agent.[4] For these and other reasons, effective methods for synthesizing twistane and its derivatives have been sought and developed by many research groups. One of the most interesting new methods for preparing such compounds involves the intramolecular aldol condensation of *cis*-bicyclo[4.4.0]decane-3,9-dione discovered by Deslongchamps and coworkers.[5,6] In their approach an unfavorable aldol equilibrium was displaced by derivatization of the aldol hydroxyl function.



(1)

In this paper we report our investigations of a similar intramolecular aldol condensation of the 1-methyl-*cis*-bicyclo[4.4.0]decane-2,8-dione system (eq 2), and call attention to a remarkable methyl substituent effect on the aldol equilibrium. The C-1 angular methyl substituent in these diketones is necessary to maintain a cis configuration of the fused six-membered rings. However, we find that other methyl groups may exert profound but less easily explained influences.



Ia, R = H
b, R = CH$_3$

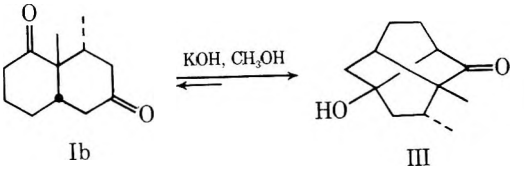
IIa, R = H (25%)
b, R = CH$_3$ (98%)

(2)

On treatment with a methanolic potassium hydroxide solution, Ia remained unchanged insofar as TLC analysis could determine. Although the trapping procedure used by Deslongchamps (eq 1) did not work well in this case, we were able to obtain a methyl ether derivative of the twistane aldol (IIa) in modest yield by treating Ia with a solution of hydrogen chloride in anhydrous methanol (eq 2). A sample of pure IIa was obtained by preparative GLC and identified by comparing its characteristic ir, NMR, and mass spectra (Experimental Section) with those of the methyl homolog IIb.

The introduction of a second methyl substituent at C-10 resulted in a surprising enhancement of twistane ether formation when this methyl was oriented trans to the angular methyl, but not when it was cis. Thus Ib was converted to IIb in almost quantitative yield by treatment with methanolic hydrogen chloride. Both IIa and IIb exhibited a characteristic carbonyl absorption at 1726 cm^{-1} and displayed parent ions at *m/e* 194 and 208 in their respective mass spectra. It proved possible to crystallize IIb from wet ether, mp 45–46°, but the product appeared to be a hydrate (infrared absorption at 3410 cm^{-1}).

An even more striking influence of the methyl substituent in Ib was observed in its reaction with base, a mixture of Ib (29%) and its internal aldol isomer III (71%) being generated by treatment of either pure Ib or III with methanolic potassium hydroxide (eq 3).



Ib III

(3)

A pure sample of III, obtained by GLC, proved to be a crystalline solid, mp 106–107° having spectroscopic properties consistent with the assigned structure (Experimental Section). Pure III proved to be sensitive to moisture and decomposed in part to Ib on silica gel chromatography. Treatment of III with a benzene solution of *p*-toluenesulfonic acid also gave Ib.

A crystalline *p*-bromobenzenesulfonate derivative of III, mp 124–125°, gave excellent single crystals, having the space group $P1$-cell constants a = 11.949 (2), b = 12.475 (2), c = 6.683 (1) Å, α = 108.48 (1), β = 100.86 (1), γ = 108.48 (1)°, with two molecules per unit cell. Analysis of such a crystal by means of a Picker FACS-1 four-circle diffractometer established the twistane configuration of III,[7] as shown in Figure 1. Interestingly, the carbonyl bond angle (C-1–C-2–C-3) disclosed by this study is 108.9 (4)°, indicating a degree of angle strain also reflected in the infrared stretching frequency of this function (1725 cm^{-1}).

The influence of the C-10 methyl substituent on the internal aldol cyclization of Ib appears to be due in part to extreme nonbonded interactions in one of the decalin conformations (eq 4).

Methyl substituents in other locations on the *cis*-bicyclo[4.4.0]decane-2,8-dione system may also influence the course of intramolecular aldolization. For example, our initial investigation of the 7-methyl derivative IV suggests that four-membered aldol products such as V and VI are formed. No products having ^{1}H NMR, ir, and mass spectra consistent with a twistane structure were obtained.

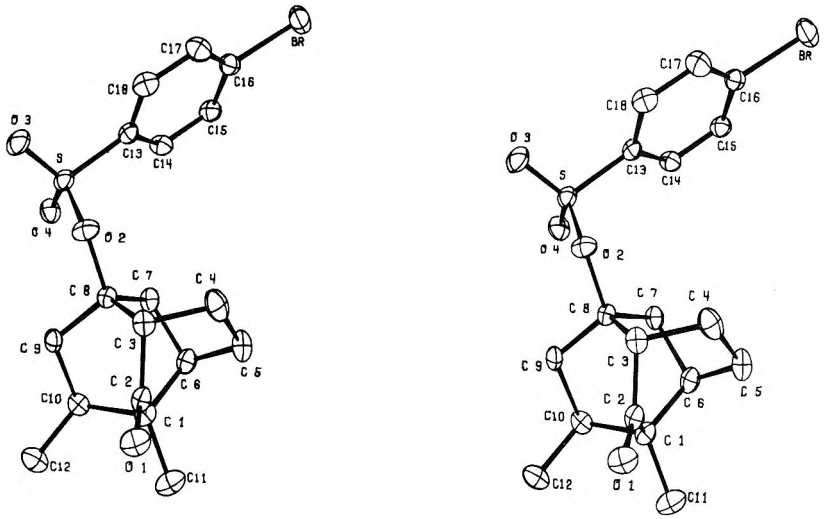
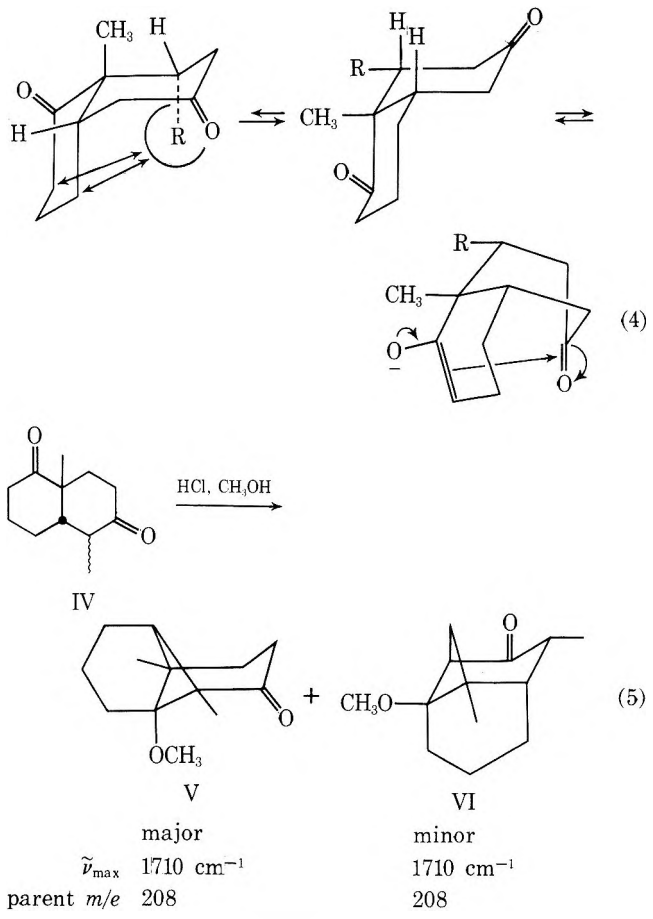


Figure 1. Stereodrawings illustrating the brosylate of III as determined by X-ray analysis. The 30% probability ellipsoids represent the thermal motions of each nonhydrogen atom.



Experimental Section[8]

***cis*-8a-Methyl-3,4,4a,7,8,8a-hexahydronaphthalene-1,6(2*H*,5*H*)-dione Derivatives (I).** The Wieland–Miescher ketone[9] and its 8-methyl derivatives[10] were prepared by established variations of the Robinson annelation procedure.[10,11] Reduction of the Wieland–Miescher ketone over a palladium catalyst yielded Ia.[12] Reduction of an ethanol solution of *trans*-8,8a-dimethyl-3,4,8,8a-tetrahydronaphthalene-1,6(2*H*,7*H*)-dione[10] over palladium on charcoal (10%) with 50 psi of hydrogen gave 94% Ib as a colorless oil: ir (CCl_4) 1720, 1705, 1085 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.23 (3 H, d, J = 6.0 Hz), 1.43 (3 H, s), 1.52–3.20 (12 H); mass spectrum (70 eV) *m/e* (rel intensity) 194 (35), 179 (3), 161 (10), 123 (20), 110 (91), 95 (28), 81 (29).

Anal. Calcd for $C_{12}H_{18}O_2$: C, 74.19, H, 9.34. Found: C, 74.11; H, 9.20.

(1*R,3*R**,6*S**,8*R**,10*R**)-8-Methoxy-1,10-dimethyltricyclo-[4.4.0.0^{3,8}]decan-2-one (IIb).** A solution of 22.5 mg (0.108 mmol) of Ib in 4 ml of absolute methanol was maintained at 0° while anhydrous hydrogen chloride was added over a 2-min period. The reaction mixture was then allowed to warm to room temperature with stirring, and an hour later the solvent was removed at reduced pressure. The residue was dissolved in ether, washed sequentially with saturated sodium chloride solution and saturated sodium bicarbonate solution, and dried. The resulting solution was passed through a short silica gel column, and subsequent removal of the solvent gave 23.8 mg (98%) of IIb as an oil with the following physical properties: ir (neat) 1726, 1451, 1135, 1110, 1090, and 1074 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.80 (3 H, d, J = 6.0 Hz), 0.91 (3 H, s), 1.00–2.42 (11 H), 3.23 (3 H, s); mass spectrum (70 eV) *m/e* (rel intensity) 208 (13), 193 (4), 176 (8), 110 (100), 99 (63).

Anal. Calcd for $C_{13}H_{20}O_2$: C, 74.96; H, 9.68. Found: C, 74.96, H, 9.72.

The oil thus obtained could be crystallized from wet ether (mp 45–46°); however, ir absorption at 3410 cm^{-1} suggested that water was incorporated in the crystal lattice. The carbonyl absorption appeared unchanged.

(1*R,3*R**,6*S**,8*R**10*R**)-8-Hydroxy-1,10-dimethyltricyclo-[4.4.0.0^{3,8}]decan-2-one (III).** To 2 ml of methanol–water (50:50) which contained one pellet of potassium hydroxide was added 20 mg (0.10 mmol) of Ib. This solution was stirred overnight at room temperature and then diluted with water and extracted with benzene. The organic extract was washed with water and evaporated at reduced pressure, giving a quantitative recovery of an oil. GLC analysis (4% QF-1, 195°) of this oil indicated that it was a mixture of ketol III (71%) and unreacted starting material (29%). Preparative GLC gave an analytical sample (mp 106–107°) which rapidly lost its crystalline properties on exposure to the air and which could not be recrystallized. The spectroscopic properties of III were observed to be ir (CCl_4) 3590, 3400, 1725, 1455, 1378, 1315, and 1070 cm^{-1}; ^1H NMR (DMSO-d_6) δ 0.67 (3 H, d, J = 6.5 Hz), 0.81 (3 H, s), 0.85–2.40 (11 H), 4.96 (1 H, s); mass spectrum (70 eV) *m/e* (rel intensity) 194 (35), 110 (91), 95 (28), 81 (29), 69 (75), 55 (47), 41 (100).

Anal. Calcd for $C_{12}H_{18}O_2$: C, 74.19; H, 9.34. Found: C, 74.14; H, 9.51.

Overnight treatment of a benzene solution of III with *p*-toluenesulfonic acid gave a 92% yield of Ib, identified by ir spectroscopy and GLC retention time.

Preparation of a *p*-Bromobenzenesulfonate Derivative of III. A solution of 90 mg (0.22 mmol) of ketol III in 2 ml of dry pyridine was treated at 0° with a large excess of *p*-bromobenzenesulfonyl chloride. After complete dissolution the resulting solution was stirred at room temperature for 3 days and then poured into water at 0°, stirred, and extracted with ether. The organic phase was washed sequentially with dilute hydrochloric acid, water, and saturated sodium bicarbonate solution and dried over anhydrous sodium sulfate. Careful evaporation gave 133 mg (70%) of white crystals. A portion of these were dissolved in ether and placed in a closed vial from which very slow evaporation of the solvent gave

excellent single crystals appropriate for collecting three-dimensional X-ray data. An analytical sample had mp 124–125°; ir (CCl_4) 1734, 1325–1380, 1178, 920, 868 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.88 (3 H, d, J = 6.5 Hz), 0.92 (3 H, s), 1.20–2.86 (11 H), 7.78 (4 H, s); mass spectrum (70 eV) m/e (rel intensity) 414 (3), 412 (3), 221 (6), 219 (6), 193 (45), 176 (24), 157 (14), 155 (14), 148 (28), 133 (12), 120 (12), 110 (100), 93 (17), 81 (41), 69 (21), 55 (21).

Anal. Calcd for $C_{18}H_{21}BrO_4S$: C, 52.31, H, 5.12. Found: C, 52.29; H, 5.21.

(1*R,3*R**,6*S**,8*R**)-8-Methoxy-1-methyltricyclo-[4.4.0.0^{3,8}]decan-2-one (IIa).** A solution of 194 mg (1.0 mmol) of Ia in 5 ml of absolute methanol saturated with hydrogen chloride was stirred overnight and worked up by quenching with saturated sodium bicarbonate solution. The ether extracts of this solution yielded an oil which GLC analysis showed to be a mixture of Ia, IIa, and several other components. The component assigned structure IIa (about 20% of the mixture) was collected by preparative GLC (4% QF-1 at 170°): ir (neat) 2930, 2855, 2820, 1730, 1460, 1325, 1135, 1115, 1100 cm^{-1}; mass spectrum (70 eV) m/e 194, 179, 95, 85, 55. The parent ion (m/e 194) exhibited isotope peaks at m/e 195 (14.5% P) and 196 (ca. 2% P); the isotopic abundance calculated for $C_{12}H_{18}O_2$ is 14.45 and 1.37%, respectively.

Acknowledgments. We thank the National Institutes of Health for their support of this work (Grant AM-10849). We also thank Dr. B. L. Barnett for his help in conducting the X-ray crystal analysis.

Registry No.—Ia, 4707-05-5; Ib, 55090-34-1; IIa, 55090-35-2; IIb, 55090-36-3; III, 55090-37-4; III brosylate, 55090-38-5; *trans*-8,8a-dimethyl-3,4,8,8a-tetrahydronaphthalene-1,6(2*H*,7*H*)-dione, 17566-22-2; *p*-bromobenzenesulfonyl chloride, 95-58-8.

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(7) This appears to be the first reported X-ray structure determination of a twistane derivative. Full details of this work (with Dr. B. L. Barnett) have been submitted: *J. Cryst. Mol. Struct.*, in press.
(8) All reactions were conducted under a nitrogen or argon atmosphere. Infrared spectra were recorded on a Perkin-Elmer 237B grating spectrophotometer. Proton magnetic spectra were obtained using a Varian T-60 high-resolution spectrometer. Mass spectra were obtained by Mrs. Lorraine Guile with a Hitachi RMU-6 mass spectrometer. Gas–liquid partition chromatography (GLC) was carried out using Varian Aerograph 1200 and A-90P3 instruments. Microanalyses were performed by Spang Microanalytical Laboratory, Ann Arbor, Mich.
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Synthesis and Substituent Effects in the Nuclear Magnetic Resonance and Mass Spectra of Dimethyl- and Dihaloxanthones

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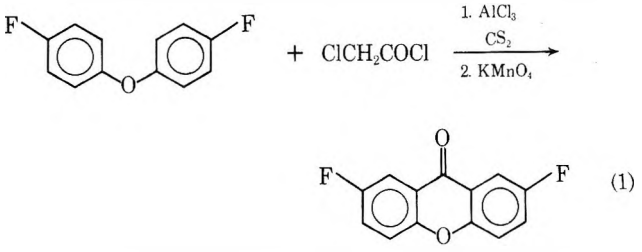
Halogen- and methyl-substituted xanthones have been prepared by three routes. The main approach has been Friedel–Crafts acylation–cyclization of aromatic ethers with oxalyl chloride or with chloroacetyl chloride followed by permanganate oxidation. The substituent shifts in the ^1H NMR spectra of the compounds studied are in good agreement with those predicted for substituted benzene derivatives. The typical electron-impact-induced CO expulsion from the molecular ion of xanthone decreases or even disappears in the halogenated derivatives owing to the competing halogen elimination.

In a preliminary communication by one of us, it was shown that the Friedel–Crafts acylation–cyclization reaction can be used to synthesize substituted xanthones (xanthen-9-ones) from aromatic ethers and chloroacetyl chloride,[1] e.g., from *p,p'*-difluorodiphenyl ether. This reaction,



(1)

which is a variation of a similar procedure using oxalyl chloride,[2–4] has also been used to prepare phenoxaphosphines[5] and phenothiaphosphines,[6] starting with phosphorus trichloride and aromatic ethers and sulfides, respectively. Whereas these earlier papers have dealt with the synthesis of substituted xanthones,[2–4] practically no comparative studies which might demonstrate the generality of this reaction have appeared. With this goal in mind, we have synthesized ten xanthone derivatives, some of which are new, and studied their properties by mass spectrometry, nuclear magnetic resonance spectrometry, and infrared absorption spectroscopy. This report provides syntheses of xanthones and some correlations of various spectral parameters with the structures of the xanthone derivatives.

Experimental Section

Melting points were taken with a Thomas-Hoover capillary apparatus and are uncorrected. Proton NMR spectra were run in $CDCl_3$ with Me_4Si and $CHCl_3$ as internal standards with a Jeol C-60 HL high-resolution spectrometer. Mass spectra were obtained with a Hitachi Perkin-Elmer RMU-6 instrument at 70 eV using the direct insertion probe and a source temperature of 150–200°. Peaks with intensities greater than 10% of the base peak are

given and isotope peaks are excluded. Infrared spectra were recorded for solutions in $CHCl_3$ with a Perkin-Elmer Infracord 137B spectrophotometer.

The syntheses and some spectral properties of **1d,g** and **2c,d,g** (vide infra) have been recently reported.[1,2] All the other aromatic ethers 1 were either commercially available (**1c,i**) or prepared by standard methods.[7,8]

Preparation of Substituted Xanthones by the Oxalyl Chloride Method. General Procedure. Oxalyl chloride (6.4 g, 0.05 mol) was added rapidly to a mechanically stirred mixture of carbon disulfide (150 ml), the substituted aromatic ether (0.05 mol), and aluminum chloride (8.6 g, 0.065 mol). The mixture was refluxed for 3 hr, oxalyl chloride (6.0 g) was again added, and the reflux was continued for 3 hr. Hydrolysis, chloroform extraction, and washing the resulting solution with 10% sodium hydroxide gave the substituted xanthone in 50–60% yield (recrystallized from ethanol). **1a** was an exception, giving only 5% yield of **2a.** The following compounds were prepared from the corresponding aromatic ethers.

3,6-Dimethylxanthone (2a) was prepared from *m*-tolyl ether, mp 167°. Anal. Calcd for $C_{15}H_{12}O_2$: C, 80.4; H, 5.4. Found: C, 80.2; H, 5.6. Spectra: NMR ($CDCl_3$) δ 2.50 (6 H, s, Me), 7.18 (2 H, d, H-2, 7), 7.26 (2 H, d, H-4, -5, J = 1.5 Hz), 8.20 (2 H, d, H-1, -8, J = 9 Hz); mass spectrum *m/e* (rel intensity) 224 (100, M^+), 223 (15, M − H^+), 195 (23, M − CHO^+), 97 (14, M − CH_2O^{2+}).

2,7-Dimethylxanthone (2b) was prepared from *p*-tolyl ether, mp 141°. Anal. Calcd for $C_{15}H_{12}O_2$: C, 80.4; H, 5.4. Found: C, 80.3; H, 5.3. Spectra: NMR ($CDCl_3$) δ 2.44 (6 H, s, Me), 7.28 (2 H, d, H-4, -5, J = 9 Hz), 7.48 (2 H, dd, H-3, -6, J = 9 and 2 Hz), 8.08 (2 H, m, H-1, -8); mass spectrum *m/e* (rel intensity) 224 (100, M^+), 223 (19, M − H^+), 195 (23, M − CHO^+), 181 (13, M − CO − CH_3^+).

2-Bromo-7-fluoroxanthone (2e) was prepared from 4-bromo-4′-fluorodiphenyl ether, mp 181°. Anal. Calcd for $C_{13}H_6BrFO_2$: C, 53.2; H, 2.1; Br, 27.3; F, 6.5. Found: C, 53.2, H, 2.2, Br, 27.0; F, 6.7. Spectra: NMR ($CDCl_3$) δ 7.40 (4 H, m, Ar), 7.93 (1 H, m, H-8), 8.38 (1 H, d, H-1, J = 2.5 Hz); mass spectrum *m/e* (rel intensity) 292 (100, M^+), 213 (19, M − Br^+), 185 (11, M − Br − CO^+), 157 (46, M − Br − CO^+), 106.5 (11, M − Br^{2+}), 78.5 (28, M − Br − $2CO^{2+}$).

2,7-Dichloroxanthone (2f) was prepared from 4,4′-dichlorodiphenyl ether, mp 219°. Anal. Calcd for $C_{13}H_6Cl_2O_2$: C, 58.9; H, 2.3; Cl, 26.8. Found: C, 59.1; H, 2.3; Cl, 26.6. Spectra: NMR ($CDCl_3$) δ 7.39 (2 H, d, H-4, -5, J = 9 Hz), 7.66 (2 H, dd, H-3, -6, J = 9 and 2 Hz), 8.23 (2 H, d, H-1, -8, J = 2 Hz); mass spectrum *m/e* (rel intensity) 264 (100, M^+), 236 (28, M − CO^+), 173 (28, M − Cl − $2CO^+$).

2-Bromo-7-chloroxanthone (2h) was prepared from 4-bromo-4′-chlorodiphenyl ether, mp 210°. Anal. Calcd for $C_{13}H_6BrClO_2$: C, 50.4; H, 1.9. Found: C, 50.7; H, 2.0. Spectra: NMR ($CDCl_3$) δ 7.34 (1 H, d, H-4), 7.40 (1 H, d, H-5), 7.66 (1 H, dd, H-6), 7.79 (1 H, dd, H-3), 8.23 (1 H, d, H-8), 8.38 (1 H, d, H-1); mass spectrum *m/e* (rel intensity) 308 (77, M^+), 173 (30, M − Br − $2CO^+$), 138 (13, M − Br − Cl − 2 CO^+).

2,7-Dibromoxanthone (2i) was prepared from 4,4′-dibromodiphenyl ether, mp 211°. Anal. Calcd for $C_{13}H_6Br_2O_2$: C, 44.1, H, 1.7; Br, 45.2. Found: C, 44.4; H, 2.0; Br, 45.2. Spectra: NMR ($CDCl_3$) δ 7.33 (2 H, d, H-4, −5, J = 9 Hz), 7.77 (2 H, dd, H-3, −6, J = 9 and 2 Hz), 8.36 (2 H, d, H-1, −8, J = 2 Hz); mass spectrum *m/e* (rel intensity) 352 (53, M^+), 273 (11, M − Br^+), 217 (28, M − Br − 2 CO^+), 138 (46, M − 2 Br − 2 CO^+), 108.5 (12, M − Br − 2 CO^{++}).

Preparation of Substituted Xanthones by the Chloroacetyl Chloride Method. General Procedure. Chloroacetyl chloride (12.4 g, 0.11 mol) was added to a mechanically stirred mixture of carbon disulfide (300 ml), the aromatic ether (0.1 mol), and aluminum chloride (20.0 g, 0.15 mol). The mixture was refluxed for 5 hr, cooled, decomposed with cold water, and extracted with chloroform. The crude substituted 9-chloromethylenexanthene (4) was either recrystallized and identified or dissolved in 85% aqueous pyridine, and oxidized by potassium permanganate (30 g), added portionwise. The latter mixture was heated to boiling and filtered hot. Dilution of the filtrate with water precipitated the substituted xanthone in 50–70% yield (recrystallized from ethanol). This method gave the same compounds described under the oxalyl chloride method, excluding **2a.** Examination of the NMR spectrum of the expected intermediate in an attempted synthesis of **2a** by this method showed that it was **5.**

2-Bromo-7-fluoro-9-chloromethylenexanthene (4 and 7, X = F; Y = Br) were prepared according to the general procedure for the chloroacetyl chloride method excluding the oxidation. The 1:1 mixture of geometrical isomers was obtained from 4-bromo-4′-fluorodiphenyl ether (**1e**), mp 112–116°. Anal. Calcd for $C_{14}H_7BrClFO$: C, 51.6; H, 2.2; F, 5.8. Found: C, 51.9; H, 2.1; F, 6.1. This isomer mixture was separated by repeated fractional crystallization from ethanol.

4, X = F; Y = Br. This was the more soluble isomer: mp 97°; NMR ($CDCl_3$) δ 6.50 (1 H, s, H-11), 7.13 (4 H, m, HAr), 7.50 (1 H, dd, H-3, J = 9 and 2 Hz), 8.55 (1 H, d, H-1, J = 2 Hz).

7, X = F; Y = Br. This high-melting isomer was the first to crystallize from the ethanol mother liquor: mp 141°; NMR ($CDCl_3$) δ 6.50 (1 H, s, H-11), 7.30 (5 H, m, HAr) 8.13 (1 H, m, H-8).

3,3′-Dimethyl-4,4′-di(chloroacetyl)diphenyl ether (5) was prepared from *m*-tolyl ether in 30% yield, as described above, excluding the oxidation, mp 113° (recrystallized from CCl_4). Anal. Calcd for $C_{18}H_{16}Cl_2O_3$: C, 61.5; H, 4.6; Cl, 20.2. Found: C, 61.3; H, 4.5; Cl, 19.9.

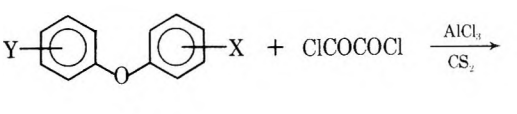
Spectra: NMR ($CDCl_3$) δ 2.54 (6 H, s, Me), 4.60 (4 H, s, $ClCH_2CO$), 6.93 (4 H, m, Ar), 7.70 (2 H, d, H-5,5′, J = 10 Hz); mass spectrum *m/e* (rel intensity) 350 (19, M^+), 301 (100, M − CH_2Cl^+), 225 (11), 224 (11, M − 2 CH_2Cl − CO^+), 126 (16, M − $2CH_2Cl^{2+}$).

2,7-Diiodoxanthone (2j). A solution of xanthone (6.2 g) in concentrated sulfuric acid (100 ml) was added gradually to a stirred mixture of iodine (20 g), potassium iodate (5.0 g), and sulfuric acid (150 ml). After 48 hr, the mixture was decomposed with crushed ice (600 g), extracted with chloroform, and washed with aqueous sodium thiosulfate, giving eventually 2.1 g of **2j,** mp 241° (ethanol). Anal. Calcd for $C_{13}H_6I_2O_2$: C, 34.8; H, 1.3; I, 56.7. Found: C, 34.9; H, 1.3; I, 57.0. Spectra: NMR ($CDCl_3$) δ 7.20 (2 H, d, H-4, −5, J = 9 Hz), 7.95 (2 H, dd, H-3, −6, J = 9 and 2.5 Hz), 8.58 (2 H, d, H-1, −8, J = 2.5 Hz); mass spectrum *m/e* (rel intensity) 448 (100, M^+), 321 (49, M − I^+), 265 (40, M − I − 2 CO^+), 224 (19, M^{2+}), 194 (13, M − 2 I^+), 166 (20, M − 2 I − CO^+), 160.5 (16, M − I^{2+}), 138 (71, M − 2 I − $2CO^+$).

Xanthone-^{18}O (2k) was prepared by the photooxidation of xanthene in the presence of 99.98% $^{18}O_2$ as previously described.[9] From its mass spectral analysis and infrared spectrum, we have determined its purity to be 95%. Sufficient quantity for NMR was not available. The mass spectrum was similar to that of xanthone except that ions containing ^{18}O were shifted by 2 mass units with respect to the parent ion peaks.

Results and Discussion

Synthesis. The application of the Friedel–Crafts acylation–cyclization reaction for the preparation of substituted xanthones from aromatic ethers and oxalyl chloride has been briefly reported.[1–4] The main advantages of this route (eq 2) are the use of simple starting materials and easy ma-



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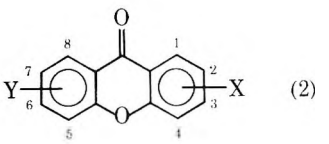
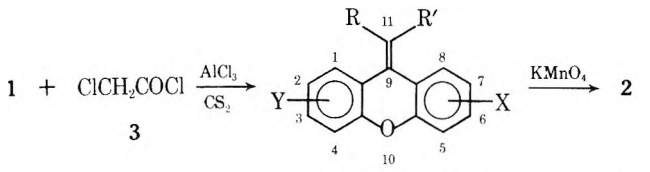


(2)

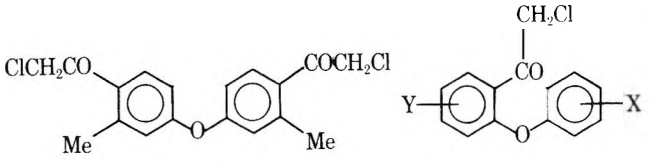
2

1a, X = 3-Me; Y = 3′-Me	**2a**, X = 3-Me; Y = 6-Me
b, X = 4-Me; Y = 4′-Me	b, X = 2-Me; Y = 7-Me
c, X = 4-F; Y = 4′-F	c, X = 2-F; Y = 7-F
d, X = 4-F; Y = 3′-Br	d, X = 2-F; Y = 6-Br
e, X = 4-F; Y = 4′-Br	e, X = 2-F; Y = 7-Br
f, X = 4-Cl; Y = 4′-Cl	f, X = 2-Cl; Y = 7-Cl
g, X = 4-Cl; Y = 3′-Br	g, X = 2-Cl; Y = 6-Br
h, X = 4-Br; Y = 4′-Cl	h, X = 2-Br; Y = 7-Cl
i, X = 4-Br; Y = 4′-Br	i, X = 2-Br; Y = 7-Br

nipulations. Oxalyl chloride is known to be decomposed by aluminum chloride.[10] Thus, using 50–100% excess of the former reagent is profitable in terms of yields. The 4,4′-disubstituted **1** gave ca. 50% yield of the appropriate **2.** Similarly, meta-brominated **1** was well protected[2] in the para position, leading to the synthesis of **2d,g.** However, a meta methyl allowed only 5% yield of **2a.**



4, R = Cl; R′ = H
7, R = H; R′ = Cl (3)



5 6

In a preliminary communication,[1] we have described an alternative route leading to **2c**. This sequence (eq 3) has now been studied in some detail. In some cases (**2e,h**), it provided even better overall yields than those obtained by the oxalyl chloride method (eq 2). However, for the transformation **1a** → **2a**, again only 5% of **2a** was produced, while the main product of the reaction of **1a** with **3** was **5**. The structures of both **2a** and **5** have been elucidated from their ^{1}H NMR and mass spectra.

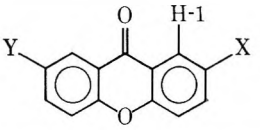
The aluminum chloride must be dry and in ca. 50% excess, or otherwise a mixture of **4** and the intermediate *ketone* **6** is obtained. In any event, the latter mixture is easily converted to **4** upon heating with phosphorus oxychloride. Best yields of **2** are achieved when the crude **4** is treated with potassium permanganate in pyridine–water. When X ≠ Y, the two geometrical isomers **4** and **7** are produced in 1:1 ratio. In the case of **1e**, the resulting isomers **4** and **7** (X = 7-F; Y = 2-Br) could not be separated by column chromatography. Repeated fractional crystallization gave eventually the pure isomers. The isomer ratio determination in the mixtures of **4** and **7** as well as monitoring isomer separation were achieved from the ^{1}H NMR spectra. This was based on the different signals of H-1 and H-8. The proton closer to the vinylic chloride is deshielded and resonates at a relatively low field. A clear separation of the signals due to the two geometrical isomers is aided by the substituent shift (vide infra). The 9-chloromethylenexanthenes (**4**) are thermally unstable (decompose at ca. 150°) and light sensitive.

One of the desired xanthones, i.e., **2j** (X = 2-I; Y = 7-I), has been prepared from xanthone by direct iodination in sulfuric acid in the presence of potassium iodate. In addition to the expected melting point, as reported[11] for a sample prepared by a multistep procedure, the structure of **2j** has been established from its mass spectrum and the ^{1}H NMR spectrum, typical of 2,7-disubstituted xanthones.

^{1}H NMR Spectra. The ^{1}H NMR spectra of the substituted xanthones have been used to characterize these compounds and to determine the substitution pattern for **2a** and **2j** in particular (Table I). H-1 and H-8 resonate at a relatively low field owing to the typical deshielding effect by the ortho cyclic carbonyl function.[12] The series of 2,7-disubstituted xanthones enables one to verify the validity and accuracy of predicted[13] substituent shielding effects in benzene derivatives for this ring system. Predicted and observed substituent shifts along with the chemical shift of H-1 (or H-8) in the substituted xanthones are given in Table I. The shielding constant of H-2 on H-1 in xanthone is taken as 0.00 ppm, and those of the other functional groups as additive.

Indeed, there seems to be a very good agreement between the calculated and actual substituent shifts. This verification suggests that this technique may be useful[14] in the structural analysis of other complex aromatic systems justifying the current interest in the tool.[15,16] In addition to the expected chemical shifts of H-1,8 in the ^{1}H NMR spectra of **2a** and **2j**, the substituents' positions have been further confirmed from the lines' shapes and integration of the NMR signals, (see Experimental Section).

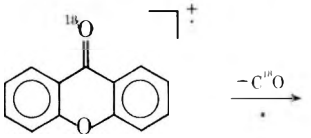
Table I
Substituent Effects on the Chemical Shift of H-1 in Xanthones



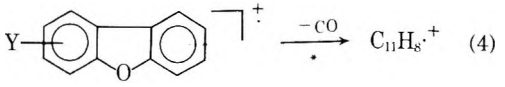
Substituent X	Y	δH-1, ppm	Substituent shift constant, ppm: Observed	Predicted[8]
H	H	8.25	0.00	0.00
Me	Me	8.08	0.17	0.17
F	F	7.92	0.33	0.30
F	Br	7.93	0.32	0.30
Cl	Cl	8.23	0.02	−0.02[a]
Cl	Br	8.23	0.02	−0.02
Br	F	8.39	−0.14	−0.22
Br	Cl	8.39	−0.14	−0.22
Br	Br	8.36	−0.11	−0.22
I	I	8.58	−0.33	−0.40
3-Me[b]	6-Me	8.20	0.05	0.09

[a] Negative sign denotes downfield shift. [b] In 3,6-dimethylxanthone.

Mass Spectra. The electron-impact-induced decomposition of xanthone has been reported,[17] and the influence of hydroxy and methoxy substituents on the fragmentation patterns has been studied in detail.[18] The main reactions of xanthone in the mass spectrometer are the successive eliminations of two molecules of CO. By ^{18}O labeling of the carbonyl in xanthone, we have now confirmed that the first lost molecule of CO is totally derived from the carbonyl function (eq 4), as suggested intuitively earlier.[18] Further-



2k



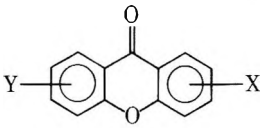
(4)

more, the ion at *m/e* 92, though not abundant, is completely shifted to *m/e* 94 after incorporation of ^{18}O into the carbonyl group of xanthone. This ion must be $C_6H_4O^{\cdot+}$. It is probably formed by a minor, but specific, rearrangement involving the carbonyl oxygen in a portion of the molecular ions which do not lose CO.

The halogenated xanthones allowed the examination of the gas-phase simple bond (C–halogen) cleavage vs. the competing rearrangement reaction, namely the CO expulsion, both from the molecular and from M − CO$^{\cdot+}$ ions. The relative intensities of the relevant ions are shown in Table II.

Generally, the halogenated xanthones show similar fragmentation patterns, while the dimethyl derivatives behave

Table II
Relative Intensities[a] of the Ions Involved in CO Elimination in the 70 eV Mass Spectra of A



A

X	Y	M − CO	M − Y	M − YCO[b]	M − 2 CO	M − Y − 2 CO[b]	M − Y − X	M − YCO − X[b]	M − YCO − XCO[b]
H	H	50	4		7	40			
2-F	7-F	40			7	5			
2-Cl	7-Cl	28	4	3	3	15			
2-Cl	7-Br	10	6	4		20			
2-Cl	6-Br	13	3	6		20			
2-F	7-Br	15	9	6		23			
2-F	6-Br	15	5	9		24			
2-Br	7-Br	8	11	5		28			23
2-I	7-I		49	9		40	13	20	71
2-Me	7-Me	5	7	13		3			
3-Me	6-Me	9	5	9		5			

[a] Isotopic ions are included in the calculation of the relative intensities to enable comparison with xanthones having negligible isotopic ions. [b] The loss of YCO as one entity in the mass spectral fragmentations of oxygen heterocycles where Y = H[18], Cl[19] has been established. Here, both the one-step and two-step reactions are included, since they are indistinguishable.

somewhat differently. The three pairs of isomeric xanthones studied exhibit practically indistinguishable spectra within each pair. Thus, mass spectrometry is not very useful for structure elucidation of the positional isomers studied.

The competing C–Y bond cleavage and CO expulsion in the molecular ions of the halogenated xanthones depend on the C–Y bond energy. The stronger this bond, the higher is the ratio M − CO/M − Y. Thus, no fluorine elimination is observed from a fluorinated xanthone, while CO loss from the molecular ion of **2j** is entirely quenched by the energetically more favorable C–I bond rupture. A similar trend is found for M − CO − YCO^+ ions where Y elimination after successive loss of two CO molecules is also competing with the expulsion of a hydrogen atom. It has been established that rearrangement reactions are relatively low energy processes,[19] as compared with direct bond cleavages. However, it should be noted that a simple weak bond cleavage, such as the C–I bond, may be favored over a competing rearrangement. The labile nature of the C–I bond is further demonstrated by the observation that photolysis of **2j** in isooctane leads to the formation of I_2 and another product whose identity was not determined.[20]

Summary. Ten dimethyl- or dihaloxanthone derivatives have been synthesized mainly by the acylation–cyclization of aromatic ethers with oxalyl- or chloroacetyl chloride in the presence of aluminum chloride, followed by permanganate oxidation in the latter route. The yields are typically in the range of 50–70%. The mass spectral data show that loss of CO is an important process except when elimination of the higher atomic weight halogen atoms can effectively compete with the latter process. The ^1H NMR spectra of the xanthones can readily be predicted on the basis of the substituent shift constants reported for benzene derivatives.

Acknowledgment. We thank Professor Jack B. Levy of the University of North Carolina at Wilmington for his gift of *m*-tolyl ether.

Registry No.—**1a,** 19814-71-2; **1b,** 1579-40-4; **1c,** 330-93-8; **1d,** 50904-38-6; **1e,** 55102-99-3; **1f,** 2444-89-5; **1g,** 6842-61-1; **1h,** 30427-95-3; **1i,** 2050-47-7; **2a,** 19814-69-8; **2b,** 7573-15-1; **2c,** 37611-32-8; **2d,** 50904-46-6; **2e,** 55103-00-9; **2f,** 55103-01-0; **2g,** 50904-47-7; **2h,** 55103-02-1; **2i,** 40102-85-0; **2j,** 55103-03-2; **2**(X = Y = H), 90-47-1; **3,** 79-04-9; **4**(X = 7-F; Y = 2-Br), 55124-07-7; **5,** 55103-04-3; **7**(X = 7-F; Y = 2-Br), 55103-05-4; oxalyl chloride, 79-37-8.

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Synthesis of 3-Alkyl-2,6-dicyanopyridines by a Unique Rearrangement. Preparation of Fusaric Acid Analogs

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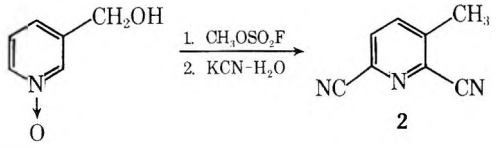
The reaction of 3-hydroxymethylpyridine 1-oxide with methyl fluorosulfonate and potassium cyanide produced a simple, direct synthesis of 2,6-dicyano-3-methylpyridine. The mechanism and scope of this reaction are discussed. Chemical transformations of 2,6-dicyano-3-methylpyridine produced 6-cyano-5-methylpicolinic acid and, by acid hydrolysis, methyl 6-cyano-5-methylpicolinate via an imino ester and dimethyl 3-methyl-2,6-pyridinedicarboxylate through a bis imino ester. In a similar fashion 3-α-hydroxy-*n*-butylpyridine 1-oxide gave 3-*n*-butyl-2,6-dicyanopyridine, which was converted to 6-cyano-5-*n*-butylpicolinic acid and 2,6-biscarbamyl-3-*n*-butylpyridine, analogs of fusaric acid.

The reaction of 1-alkoxypyridinium quaternary salts with cyanide ion to give α- and γ-cyanopyridine derivatives is a general reaction.[1,2] Thus far, there are no reports on the use of methyl fluorosulfonate[3] to generate such 1-alkoxypyridinium salts by alkylation of pyridine 1-oxides. Moreover, methyl fluorosulfonate is such a powerful alkylating agent that it will react with a variety of functional groups such as amides, nitriles, ethers, esters, etc.[4] The question then arises as to what reactions would occur when a pyridine 1-oxide bearing such a functional group is allowed to react with methyl fluorosulfonate and cyanide ion. We wish to report the novel reaction of 3-hydroxymethylpyridine 1-oxide (**1**)[5] with these reagents to form 2,6-dicyano-3-methylpyridine (**2**) and to comment on the scope of this reaction and its utilization for the synthesis of fusaric acid analogs.



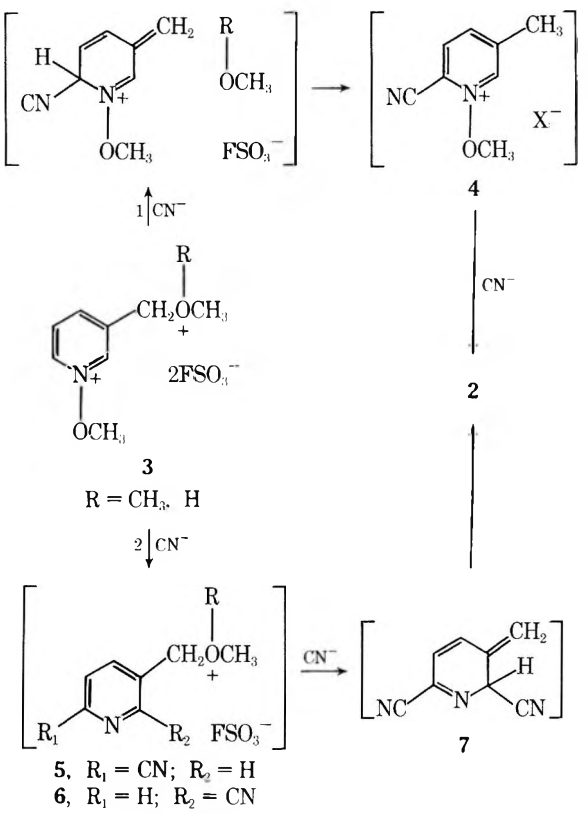
1 **2**

Treatment of **1** with 3 equiv of methyl fluorosulfonate under anhydrous conditions resulted in a mildly exothermic reaction, leaving a liquid product. Addition of an aqueous solution of potassium cyanide to this liquid resulted in a vigorously exothermic reaction. The product **2** was easily isolated, the yield being consistently in the 30–35% range. While the exothermic reaction upon the addition of potassium cyanide could be controlled on a small scale, this procedure was not feasible for the preparation of larger quantities of **2**. Thus, the product from the reaction of **1** and methyl fluorosulfonate was dissolved in a limited[6] amount of methylene chloride and added to a cooled mixture of an aqueous potassium cyanide solution and methylene chloride. The reaction was easily controlled and the yield of **2** remained the same as above.

The structure of **2** was established from its NMR spectral data, which consisted of only a methyl absorption at δ 2.72 and two pyridine proton absorptions, H_4 and H_5, as an AB quartet with overlapping inner lines and a coupling constant of 9 Hz. Thus, a 2,3,4- or a 2,4,5-trisubstituted pyridine is ruled out on the basis of the coupling constants as well as chemical shifts of the pyridine protons.

The reaction to form **2** can be rationalized by assuming alkylation of the *N*-oxide to form a 1-methoxypyridinium salt and alkylation of the primary alcohol to form a methyl ether with liberation of fluorosulfonic acid. The ether moiety would in turn be either alkylated with methyl fluorosulfonate to form an oxonium ion or protonated with fluorosulfonic acid to give intermediate **3** (see Scheme I). The product **2** would then arise from two distinct reactions of

Scheme I



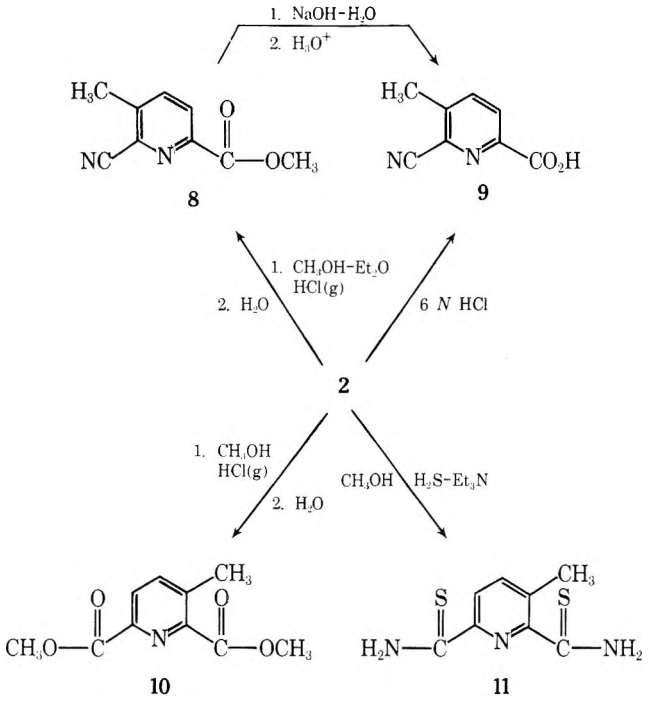
cyanide ion with **3**, namely, nuclear substitution with expulsion of dimethyl ether (or methanol) and nuclear substitution with expulsion of methoxide. The order in which these reactions occur is unknown but, for reasons to be discussed shortly, we favor pathway 1. Cyanide attack on **3** could occur at either the 2 or 6 position of the pyridine ring, expelling dimethyl ether or methanol. Aromatization would then give **4** or its equivalent for purposes of our argument, the 1-methoxy-2-cyano-3-methylpyridinium salt. A second ring attack by cyanide ion with expulsion of methoxide would give **2**. There is some evidence to support the driving forces operative in this mechanism. It has been shown that 1-alkoxypyridinium salts bearing a cyano,[7] methoxycarbonyl,[7] or keto[8] function in the 2 position direct cyanide ion exclusively to the 6 position. In pathway 2 nuclear substitution by cyanide ion would give either **5** or **6** with expulsion of methoxide. Further ring substitution by cyanide ion would give **7**, but the driving force in this

mechanism favoring ring over side-chain substitution is not obvious.

The yield of **2** is undoubtedly reduced by competing reactions which are possible under these alkaline conditions. Abstraction of a proton from the *N*-methoxyl would generate formaldehyde and a pyridine.[9,10] Dealkylation of an oxonium ion or neutralization of a protonated ether, as in **3**, would result in only monosubstitution of the pyridine ring by cyanide ion.

Some of the chemistry of 2,6-dicyano-3-methylpyridine (**2**) is depicted in Scheme II.

Scheme II

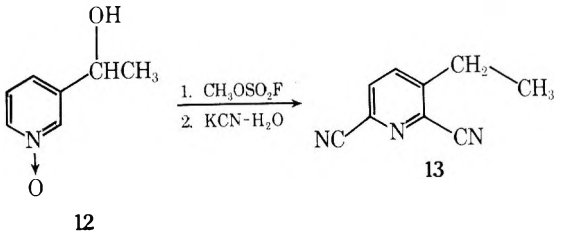


Treatment of **2** with 3 equiv of methanol in diethyl ether and saturation with anhydrous hydrogen chloride resulted in precipitation of an imino ester hydrochloride. Hydrolysis of this salt gave a solid, methyl 6-cyano-5-methylpicolinate (**8**), in 52% yield. The presence of the ester function affected the chemical shifts of the pyridine ring protons, which now appeared as two well-separated doublets at δ 7.93 and 8.27. Relative to **2** one of the ring protons experienced a slight downfield shift ($\Delta\delta$ 0.05) while the other proton showed a significantly greater downfield shift ($\Delta\delta$ 0.31), indicating that the methoxycarbonyl group was adjacent to this proton. Saponification of **8** gave the carboxylic acid **9.**

The methyl group in **2** conferred some protection upon the adjacent nitrile. After heating **2** with dilute hydrochloric acid and cooling, 6-cyano-5-methylpicolinic acid (**9**) spontaneously crystallized. Prolonged heating in acid, however, reduced the yield of **9.**

The bis imino ester dihydrochloride of **2** was formed by treating a methanolic solution of **2** with anhydrous hydrogen chloride. Hydrolysis gave the diester **10,** the NMR spectrum of which exhibited a methoxycarbonyl absorption (six protons) at δ 4.05. The chemical shifts of the two ring protons were again affected relative to **2** and appeared as two doublets at δ 7.82 and 8.19.

To determine the scope of this reaction, pyridine 1-oxides bearing secondary and tertiary alcohol functions in the 3 position were synthesized. 3-α-Hydroxyethylpyridine 1-oxide (**12**), prepared from 3-α-hydroxyethylpyridine[11] by oxidation with aqueous hydrogen peroxide in acetic acid, reacted with methyl fluorosulfonate and potassium cyanide and gave **13** in 30% yield. The NMR spectrum of **13** displayed the methyl and methylene absorptions at δ 1.45 and



3.09, respectively, and the ring proton absorptions as an AB quartet with overlapping inner lines.

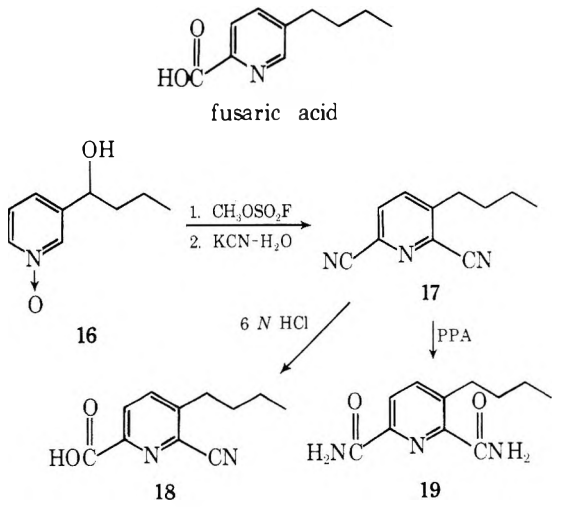
3-α-Hydroxyisopropylpyridine[12] was converted to its *N*-oxide **14** with aqueous hydrogen peroxide in acetic acid. TLC analysis of the crude product from the reaction of **14** with methyl fluorosulfonate and potassium cyanide on silica gel showed three major and three minor components. We did not pursue the identification of these components.

3-α-Hydroxybenzylpyridine[11] was oxidized with aqueous hydrogen peroxide to 3-α-hydroxybenzylpyridine 1-oxide (**15**). Reaction of **15** with methyl fluorosulfonate and potassium cyanide gave a dark, viscous oil but no identifiable products.

A consequence of the successful reaction of **12** with methyl fluorosulfonate and potassium cyanide was the synthesis of a number of analogs of fusaric acid (5-*n*-butylpicolinic acid), an antibiotic produced by the fungus *Fusarium oxysporum.* Fusaric acid is a potent noncompetitive inhibitor of dopamine-β-hydroxylase, both in vitro and in vivo.[13] 5-*n*-Butylpicolinamide was also reported to be an effective dopamine-β-hydroxylase inhibitor with hypotensive properties.[14]

3-α-Hydroxy-*n*-butylpyridine 1-oxide (**16**) was prepared by oxidation of 3-α-hydroxy-*n*-butylpyridine[15] with aqueous hydrogen peroxide in acetic acid. The product from the reaction of **16** with methyl fluorosulfonate and cyanide ion was obtained by distillation and 3-*n*-butyl-2,6-dicyanopyridine (**17**) was isolated as an oil by silica gel column chroma-

Scheme III



tography. In the NMR spectrum of **17** the pyridine ring protons appeared as an AB quartet with overlapping inner lines. Heating **17** with 6 *N* hydrochloric acid for 5 hr and cooling resulted in the spontaneous crystallization of **18.** The crystalline bisamide **19** was prepared by treating **17** with polyphosphoric acid at 120° and quenching with water.[16] These fusaric acid analogs are currently being evaluated for possible pharmacological properties.

Experimental Section

2,6-Dicyano-3-methylpyridine (2). A. In a dry one-neck, 100-ml, round-bottom flask protected with a $CaCl_2$ drying tube was placed 4.0 g (0.032 mol) of 3-hydroxymethylpyridine 1-oxide.[5] While this solid was stirred with a magnetic bar 10.72 g (0.094 mol) of methyl fluorosulfonate[3] was added in one portion, resulting in a mildly exothermic reaction, and the solution was stirred for 20 min. A solution of 10 g (0.154 mol) of KCN in 30 ml of water was added to the above solution in portions over a 5-min period, resulting in a very rigorous exothermic reaction which was moderated with a cold water bath. After stirring for several hours, the solution was extracted with CH_2Cl_2 and dried ($MgSO_4$) and the solvent was removed in vacuo to give an oil which was Kugelrohr distilled. After a small forerun was discarded, the product was collected at 115–120° (0.01–0.15 mm) as an oil which solidified to yield 1.7 g; TLC on silica gel with CH_2Cl_2 showed a major component (R_f 0.25) with some impurities at the origin. Recrystallization from 4 ml of EtOH gave, after drying, 1.5 g (32.7%): mp 78–80°, homogeneous by TLC; ir max (melt) 4.46 μ; NMR ($CDCl_3$) δ 2.72 (s, 3 H, 3-CH_3) and 7.75, 7.90, 7.93, and 8.07 (AB quartet, J = 9 Hz, 2 H, pyridine H_4, H_5, calcd[17] δ_{AB} 7.88 and 7.96).

Anal. Calcd for $C_8H_5N_3$: C, 67.12; H, 3.52; N, 29.36. Found: C, 66.94; H, 3.47; N, 29.48.

B. In a dry two-neck, 200-ml, round-bottom flask protected with a $CaCl_2$ drying tube and equipped with an addition funnel (equilibrating side arm) was placed 25 g (0.20 mol) of 3-hydroxymethylpyridine 1-oxide.[5] While this solid was stirred with a magnetic bar, 75.2 g (0.66 mol) of methyl fluorosulfonate was added in portions from the addition funnel. After completion of the addition, the product was stirred for 1 hr at ambient temperature. This liquid was dissolved in 50 ml of CH_2Cl_2[6] and transferred to a dry addition funnel (without equilibrating side arm), protected with a $CaCl_2$ drying tube. This addition funnel was attached to a three-neck, 1-l., round-bottom flask equipped with a condenser and mechanical stirrer with a Teflon paddle. The flask was charged with 65 g (1.0 mol) of KCN, 100 ml of water, and 100 ml of CH_2Cl_2 and cooled in ice. The solution from the addition funnel was then added portionwise with stirring. After stirring overnight at room temperature the contents of the flask were diluted with 100 ml of water and 100 ml of CH_2Cl_2 and filtered through Celite. The organic phase was separated, the aqueous phase was again extracted with CH_2Cl_2, and the combined organic extract was dried ($MgSO_4$). Removal of solvent in vacuo left a dark oil which was Kugelrohr distilled at 125–135° (0.1–0.4 mm). The resulting oil solidified to yield 15.11 g of a brown solid; TLC analysis on silica gel with CH_2Cl_2 showed a major component with R_f 0.25 along with some material at the origin. Recrystallization from 5 ml of EtOH gave 12.0 g which by TLC still indicated a slight impurity at the origin. A second recrystallization from 10 ml of EtOH gave, after drying, 10.2 g (35.66%), mp 77–79°, homogeneous by TLC (conditions cited).

6-Cyano-5-methylpicolinic Acid (9). A. 2,6-Dicyano-3-methylpyridine (**2**, 1.0 g, 0.007 mol) was treated with 6 ml of 6 *N* HCl, heated in an oil bath at 115° for 5 hr, and left at room temperature overnight. The resulting solid was collected by filtration and dried to yield 0.79 g (69.6%), mp 190–193°. This material was recrystallized from 10 ml of *n*-BuOH and dried to yield 0.63 g, mp 192–194°, ir max (Nujol) 5.86 μ (s).

Anal. Calcd for $C_8H_6N_2O_2$: C, 59.26; H, 3.73; N, 17.28. Found: C, 58.99; H, 3.72; N, 17.13.

B. Methyl 6-cyano-5-methylpicolinate (**8**, 0.65 g, 0.0037 mol) was dissolved in 5 ml of MeOH, treated with 0.18 g (0.0045 mol) of NaOH in 4 ml of water, and stirred overnight at room temperature. The MeOH was removed in vacuo using a Büchi evaporator and a water bath at room temperature. The residue, upon treatment with 0.4 ml of concentrated HCl, gave a precipitate which was collected and dried to yield 0.33 g, mp 192.5–193°. The infrared spectrum was entirely superimposable with that of the acid above.

Methyl 6-Cyano-5-methylpicolinate (8). In a dry three-neck, 100-ml, round-bottom flask equipped with a condenser ($CaCl_2$ drying tube) and gas inlet tube was placed 4.3 g (0.030 mol) of **2**, 2.37 g (0.075 mol) of MeOH, and 50 ml of Et_2O. The solution was cooled in ice and treated with HCl(g) for 30 min, causing a yellow solid to separate. The heterogeneous solution was stirred at room temperature overnight and the solid was collected and dried to yield 6.9 g of the imino ester hydrochloride, mp 75–76° dec. Of this material 4.4 g (0.021 mol) was dissolved in 6 ml of water and heated on a steam bath. After 2 min a solid separated and after 10 min the solution was cooled and the solid was collected, washed with water, and dried to yield 1.90 g (51.4%): mp 108–109°; ir max (Nujol) 4.49 (w) and 5.75 μ (s); TLC analysis on silica gel with diethyl ether showed a single component. Recrystallization of 0.40 g from a minimum of *n*-BuOH gave, after drying, the analytical specimen of 0.30 g: mp 107–108.5°; ir max (Nujol) 4.48 (w) and 5.75 μ (s); NMR ($CDCl_3$) δ 2.80 (s, 3 H, 5-CH_3), 4.15 (s, 3 H, -CO_2CH_3), 7.85, 7.99, 8.22, and 8.35 (AB quartet, J_{AB} = 8 Hz, 2 H, pyridine H_3 and H_4, calcd[17] δ_{AB} 7.93 and 8.27).

Anal. Calcd for $C_9H_8N_2O_2$: C, 61.36; H, 4.58; N, 15.90. Found: C, 61.04; H, 4.58; N, 15.78.

Dimethyl 3-Methyl-2,6-pyridinedicarboxylate (10). A dry, three-neck, 100-ml, round-bottom flask equipped with a condenser ($CaCl_2$ drying tube) and gas inlet tube was charged with 5.8 g (0.040 mol) of **2** and 60 ml of MeOH and then cooled in ice and saturated with HCl(g) for 1 hr. The stoppered flask was refrigerated overnight and the MeOH was removed in vacuo. Trituration of the residue with Et_2O gave 9.4 g (theory 9.14 g) of a solid which was dissolved in 20 ml of water and warmed on a steam bath. After 2 min an oil separated. The cooled solution was treated with $NaHCO_3$, diluted with water, extracted with Et_2O, and dried ($MgSO_4$). Removal of solvent in vacuo gave an oil which solidified to yield 5.1 g: mp 67–71.5°; ir max (Nujol) 5.82 μ; TLC on silica gel with Et_2O showed a major component and a small amount of less mobile material. Of the above material, 4.0 g was recrystallized from 16 ml of *n*-BuOH to yield, after drying, 3.1 g: mp 75–77°; TLC analysis now showed a single component; ir max (Nujol) 5.82 μ (s); NMR ($CDCl_3$) δ 2.66 (s, 3 H, 3-CH_3), 4.05 (s, 6 H, O=C-OCH_3), 7.74, 7.89, 8.15, 8.27 (2 H, pyridine H_4, H_5, AB quartet with J = 8 Hz, calcd[17] δ_{AB} 7.82 and 8.19).

Anal. Calcd for $C_{10}H_{11}NO_4$: C, 57.41; H, 5.32; N, 6.70. Found: C, 57.15; H, 5.32; N, 6.69.

2,6-Bisthiocarbamyl-3-methylpyridine (11). Compound **2**, (3.4 g, 0.024 mol) was dissolved in 25 ml of MeOH and treated with 1 ml of triethylamine. This solution was saturated with H_2S for 20 min and then stirred overnight at room temperature. During this time a yellow solid separated, redissolved, and separated again. The solvent was removed in vacuo and the residue was dissolved in 100 ml of EtOH, concentrated to 50 ml where a solid started to separate, and left at room temperature. The resulting solid was collected and dried to give 3.0 g but had a strong odor of H_2S. This material was recrystallized from 75 ml of EtOH to give 2.1 g after drying in vacuo over refluxing water: mp 194–198° dec; ir max (Nujol) 3.05 (s), 3.15 (s), 6.20 μ (s).

Anal. Calcd for $C_8H_9N_3S_2$: C, 45.50; H, 4.30; N, 19.90; S, 30.31. Found: C, 45.45; H, 4.57; N, 19.82; S, 30.70.

3-α-Hydroxyethylpyridine 1-Oxide (12). 3-α-Hydroxyethylpyridine[11] (84 g, 0.68 mol) in 200 ml of glacial AcOH was treated with 50 ml of 35% aqueous H_2O_2 and heated at 70° in an oil bath for 3 hr. An additional 34 ml of H_2O_2 was added and heating was continued overnight. Excess solvent was removed in vacuo and the residue was treated with $CHCl_3$ and excess solid K_2CO_3. After stirring, the $CHCl_3$ was decanted and the residual salts were again extracted with $CHCl_3$. The combined organic extract was dried with $MgSO_4$ and concentrated in vacuo to give an oil which crystallized upon trituration with Et_2O. This solid was dried in vacuo to yield 88 g (93%), mp 108–110°. The analytical sample was obtained by dissolving 3.0 g in 10 ml of EtOH and treating this solution with 75 ml of Et_2O to yield 2.9 g after drying, mp 108–110°.

Anal. Calcd for $C_7H_9NO_2$: C, 60.42; H, 6.52; N, 10.07. Found: C, 60.61; H, 6.51; N, 9.99.

2,6-Dicyano-3-ethylpyridine (13). A dry one-neck, 100-ml, round-bottom flask with a $CaCl_2$ drying tube was charged with 5.0 g (0.036 mol) of **12** and 14.25 g (0.125 mol) of methyl fluorosulfonate was added in one portion, resulting in a mildly exothermic reaction. This solution was stirred with a magnetic bar for 30 min, dissolved in 20 ml of CH_2Cl_2, and transferred to an addition funnel (without a side arm) which was protected with a $CaCl_2$ drying tube. This addition funnel was attached to a three-neck, 100-ml, round-bottom flask equipped with a condenser and stirring bar. A solution of 16.5 g (0.254 mol) of KCN in 25 ml of water was placed in the flask, which was cooled with cold water. The solution from the addition funnel was then added over 5 min, resulting in a mildly exothermic reaction. Stirring was continued for 3 hr and the solution was extracted with additional methylene chloride and dried with $MgSO_4$. Removal of solvent in vacuo and Kugelrohr distillation of the residue up to 140° (0.25 mm) gave an oil which partially solidified on scratching; TLC on silica gel with CH_2Cl_2 showed a major component and two minor, less mobile impurities near the origin. This solid was dissolved with warming in 2 ml of *n*-BuOH and crystallization was induced, after cooling, by scratching. After

standing at room temperature for 10 min and refrigeration for 15 min, the solid was collected and dried in a drying pistol in vacuo without heating to yield 1.70 g (30.1%): mp 40.5–42°; homogeneous by TLC; ir max (Nujol) 4.46 μ (m); NMR ($CDCl_3$) δ 1.45 (t, 3 H, CH_2CH_3), 3.09 (q, 2 H, CH_2CH_3), 7.87, 8.01, 8.05, and 8.18 (AB quartet, J = 8.1 Hz, 2 H, pyridine H_4H_5, calcd[17] δ_{AB} 7.97 and 8.08).

Anal. Calcd for $C_9H_7N_3$: C, 68.77; H, 4.49; N, 26.74. Found: C, 68.74; H, 4.60; N, 26.61.

3-α-Hydroxyisopropylpyridine 1-Oxide (14). A solution of 41.0 g (0.30 mol) of 3-α-hydroxyisopropylpyridine[12] in 80 ml of glacial AcOH was treated with 25 ml of 35% aqueous H_2O_2 and warmed at 70° in an oil bath for 3 hr. An additional 15 ml of H_2O_2 was added and heating was continued overnight. The solvent was removed in vacuo and the residue was stirred with $CHCl_3$ and excess solid K_2CO_3. The $CHCl_3$ was decanted and three extractions of the residual salts followed. The combined $CHCl_3$ extract was dried ($MgSO_4$) and concentrated in vacuo to yield an oil which crystallized upon trituration with Et_2O. The solid was collected, washed with Et_2O, and dried in vacuo to yield 44.1 g (96.1%), mp 90–94°. An analytical specimen was obtained by dissolving 4.0 g in 10 ml of EtOH and adding Et_2O gradually until an oil started to separate. Crystallization was induced by scratching, and more Et_2O was added. The solid was collected and dried to yield 3.2 g, mp 93.5–95°.

Anal. Calcd for $C_8H_{11}NO_2$: C, 62.72; H, 7.24; N, 9.14. Found: C, 62.62; H, 7.37; N, 9.11.

3-α-Hydroxybenzylpyridine 1-Oxide (15). A solution of 87.0 g (0.47 ml) of 3-α-hydroxybenzylpyridine[11] in 200 ml of glacial AcOH was treated with 50 ml of 35% aqueous H_2O_2 and heated at 70° for 3 hr. Another 37 ml of H_2O_2 was added and heating was continued overnight. The solvent was removed in vacuo and the residue was treated with aqueous K_2CO_3 solution and extracted twice with $CHCl_3$ which was then dried ($MgSO_4$). Removal of solvent in vacuo gave an oil and trituration with Et_2O gave a solid which was dried to yield 87.1 g (92.1%), mp 102–105°. The analytical specimen was obtained by treating a solution of 4.0 g in 10 ml of EtOH with 75 ml of Et_2O. The resulting solid was collected and dried in vacuo to yield 2.5 g, mp 105–106°.

Anal. Calcd for $C_{12}H_{11}NO_2$: C, 71.62; H, 5.51; N, 6.96. Found: C, 71.60; H, 5.50; N, 6.87.

3-α-Hydroxy-n-butylpyridine 1-Oxide (16). A solution of 113.9 g (0.75 mol) of 3-α-hydroxy-n-butylpyridine[15] in 225 ml of glacial AcOH was treated with 70 ml of 35% aqueous H_2O_2 and warmed at 70° in an oil bath for 3 hr. An additional 45 ml of H_2O_2 was added and heating was continued overnight. Solvent was removed in vacuo and the residue was treated with excess solid K_2CO_3, diluted with water, extracted twice with $CHCl_3$, and dried ($MgSO_4$). Concentration in vacuo gave an oil which crystallized upon trituration with Et_2O to yield after drying in vacuo 121.6 g (97.1%), mp 98–102°. The analytical specimen was obtained by dissolving 3.0 g in 10 ml of EtOH and adding 100 ml of Et_2O to yield a flocculent precipitate. This solid was dried in vacuo to yield 2.2 g, mp 107–108°.

Anal. Calcd for $C_9H_{13}NO_2$: C, 64.65; H, 7.84; N, 8.38. Found: C, 64.59; H, 7.82; N, 8.46.

3-n-Butyl-2,6-dicyanopyridine (17). In a dry one-neck, 100-ml, round-bottom flask protected with a $CaCl_2$ drying tube was placed 16.7 g (0.10 mol) of **16** and 39.9 g (0.35 mol) of methyl fluorosulfonate, resulting in a mildly exothermic reaction. After being stirred at room temperature for 45 min, the viscous material was dissolved in 50 ml of CH_2Cl_2 and transferred to an addition funnel (without a side arm) and protected with a $CaCl_2$ drying tube. This addition funnel was attached to a three-neck, 500-ml, round-bottom flask containing a magnetic stirring bar and equipped with a condenser. The flask, charged with 32.5 g (0.50 mol) of KCN and 50 ml of water, was cooled with cold water and the CH_2Cl_2 solution was added to the cyanide solution over 30 min. The reaction mixture was diluted with 100 ml of water, stirred overnight at room temperature, and extracted with additional CH_2Cl_2. This extract was filtered through Celite, dried with $MgSO_4$, and concentrated in vacuo to give an oil. Kugelrohr distillation at 115–150° (0.06–0.45 mm) gave 9.5 g of a red oil which by TLC on silica gel with CH_2Cl_2 showed a major mobile component with some material at the origin. This oil was dissolved in 25 ml of C_6H_6 and applied to a column of silica gel (100 g) packed in C_6H_6 and 15-ml fractions were collected using a fraction collector. Elution with 525 ml of C_6H_6 and with 400 ml of 25% CH_2Cl_2–C_6H_6 gave 3.80 and 2.20 g, respectively, of an oil which was homogeneous by TLC. Elution with 250 ml of 50% C_6H_6–CH_2Cl_2 gave 0.55 g which on TLC showed some material on the origin in addition to a single mobile component. Elution with 500 ml of CH_2Cl_2 gave only a slight amount of material. The above homogeneous material, 6.0 g, (32.4%), was Kugelrohr distilled at 110° (0.04 mm) in quantitative yield: ir max (film) 4.44 μ; NMR ($CDCl_3$) δ 7.83, 7.98, 8.00, and 8.15 (AB quartet, J_{AB} = 9 Hz, 2 H, pyridine H_4H_5; calcd[17] δ_{AB} 7.95 and 8.04).

Anal. Calcd for $C_{11}H_{11}N_3$: C, 71.33; H, 5.99; N, 22.69. Found: C, 71.50; H, 6.37; N, 22.73.

5-n-Butyl-6-cyanopicolinic Acid (18). Compound **17** (1.0 g, 0.0054 mol) was heated with 6 ml of 6 *N* HCl (aqueous) at 115° for 5 hr, cooled, and stirred at room temperature overnight to deposit 0.90 g (81.6%), mp 104–110°. This material was dissolved in 15 ml of C_6H_6, concentrated to 3 ml, and left at room temperature. The resulting solid was collected by filtration and dried in vacuo to yield 0.59 g (53.5%), mp 111–113°, ir max (Nujol) 5.87 μ (s).

Anal. Calcd for $C_{11}H_{12}N_2O_2$: C, 64.69; H, 5.92; N, 13.72. Found: C, 64.86; H, 5.98; N, 14.04.

2,6-Biscarbamyl-3-n-butylpyridine (19). Compound **17** (2.0 g, 0.08 mol) was mixed with 35 g of polyphosphoric acid in a one-neck flask equipped with a mechanical stirrer with a Teflon blade. The viscous solution was heated at 120° in an oil bath for 1.25 hr, cooled, and quenched with cold water. The resulting solid (2.0 g) was dissolved in 75 ml of hot EtOH and concentrated to 15 ml, where a solid started to separate. After standing overnight the solid was collected and dried in vacuo to yield 1.62 g (67.8%): mp 220–222°; ir max (Nujol) 2.96 (m), 3.15 (m), 5.94 (s), and 5.96 μ (sh, s).

Anal. Calcd for $C_{11}H_{15}N_3O_2$: C, 59.71; H, 6.83; N, 18.99. Found: C, 59.92; H, 6.95; N, 19.00.

Acknowledgment. The author wishes to thank Dr. Thomas Wickersham for the NMR spectra.

Registry No.—**1**, 6968-72-5; **2**, 55267-66-8; **8**, 55267-67-9; **8** HCl, 55267-68-0; **9**, 55267-69-1; **10**, 55267-70-4; **11**, 55267-71-5; **12**, 4319-52-2; **13**, 55267-72-6; **14**, 55267-73-7; **15**, 39585-76-7; **16**, 55267-74-8; **17**, 55267-75-9; **18**, 55267-76-0; **19**, 55267-77-1; methyl fluorosulfonate, 421-20-5; KCN, 151-50-8; 3-α-hydroxyethylpyridine, 4754-27-2; 3-α-hydroxyisopropylpyridine, 15031-77-3; 3-α-hydroxybenzylpyridine, 6270-47-9; 3-α-hydroxy-n-butylpyridine, 18085-85-3.

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Halogen–Hydrogen Halide Catalysis of the Oxidation of Thiols to Disulfides by Sulfoxides

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Halogens and hydrogen halides (not including fluorine and hydrogen fluoride) have been found to be exceptional catalysts for the oxidation of aliphatic and araliphatic thiols to disulfides by sulfoxides. They are significantly more effective catalysts than ordinary (nonhydrohalic) acids. A given halogen and its hydrogen halide provide an equivalent catalytic effect. Water has a retarding effect. A mechanism in which the halogen and hydrogen halide are coupled is suggested. Catalytic ability is in the order Br > I > Cl. HCl in combination with a minor amount of iodine is a particularly effective catalyst. In the analogous oxidation of aromatic thiols, these catalysts are not distinctive from ordinary acids, and the oxidation is not retarded by water. This is interpreted as the aforementioned mechanism having diminished applicability for the oxidation of aromatic thiols. Iodine–HI catalysis provides a vivid indicator for completion of oxidation. With bromine–HBr catalysis, this is less so.

Wallace and Mahon[1] have reported acid catalysis of the oxidation of aliphatic and araliphatic thiols to disulfides by sulfoxides (1). The catalysis was observed at 100° and found to be mild. No hydrogen halide (hydrohalic acid) was included in the study.

On the other hand, I observed ready oxidation at significantly lower temperatures in the presence of hydrogen halides (HX) or halogens. When iodine or HI is used as the catalyst, there is a pronounced color change from colorless to amber when the thiol is exhausted. A similar but much less intense color change can be observed with bromine or HBr.

These observations suggested the operation of reactions 2[2] and 3.[3] Reaction 2 may provide the acid for catalysis when halogen is used. On the other hand, a coupling of reactions 2 and 3 could provide an alternative form of catalysis.

$$2RSH + R'\overset{\overset{O}{\|}}{S}R' \longrightarrow RSSR + R'SR' + H_2O \quad (1)$$

$$2RSH + X_2 \longrightarrow RSSR + 2H^+ + 2X^- \quad (2)$$

$$2H^+ + 2X^- + R'\overset{\overset{O}{\|}}{S}R' \longrightarrow X_2 + H_2O + R'SR' \quad (3)$$

For the study of halogen and HX catalysis, the determination of completion time based on color appearance seemed convenient but only proved practical with iodine species. To provide a basis for comparison of catalytic ability of all halogens and acids in general, a test based upon reaction 2 using iodine in dimethyl sulfoxide (DMSO) was devised. Though not as satisfactory as the in situ appearance of iodine color, lack of decolorization in this test established when 98–99% of the thiol had reacted. Also, because of the generally diminished solubility of disulfides in sulfoxides and higher melting points as compared with thiols, there were other indications of reaction extent.

Solutions of a thiol in excess sulfoxide containing minor amounts of halogen or acid were heated until completion was indicated by the in situ appearance of amber (iodine) color, if applicable, or by the no-decolorization test or for an otherwise meaningful length of time. With solutions of 2-methyl-2-propanethiol (MPT) in DMSO heated at 65°, the catalytic effect of iodine and concentrated hydriodic acid was readily apparent in the inverse effect of concentration on completion time (Table I). Bromine and concentrated hydrobromic acid had the same effect but were more efficient.

The discrepancy in the catalytic effect of equivalent amounts of the halogen and its HX is due to the retarding effect of water introduced through the use of an aqueous HX, for adding water to the halogen in amount equal to that present with the HX gave equal completion times (Table II). Increased water caused still more retardation.

Table I[a]
Oxidation of 2-Methyl-2-propanethiol by Dimethyl Sulfoxide

Catalyst	Catalyst concn	Completion time, hr
I_2	0.68	8.2
I_2	1.36	2.0
I_2	1.36	1.9[b]
I_2	1.36	1.7[c]
I_2	2.48	0.3
HI	1.37	3.5
HI	2.74	0.9
Br_2	0.48	4.8
Br_2	0.72	1.7
Br_2	1.44	0.2
HBr	0.91	1.8
HBr	1.40	0.8
HCl	1.42	Inc_7
HCl	2.84	8.0
HCl	1.42	4.5[d]
HF	1.42	NAR_7[d]
CH_3SO_3H	1.39	NAR_7[d]
HNO_3	1.42	NAR_7[d]

[a] Thiol/sulfoxide molar ratio, 0.41; temperature, 65°. Catalyst concentration and water concentration (Table II) are expressed in moles/100 mol of sulfoxide. Where the catalyst is a halogen, its concentration is expressed as HX equivalents. Inc_n indicates an apparent reaction as evidenced by separation (crystallization) of product disulfide but otherwise incomplete in n hours. NAR_n indicates no apparent reaction in n hours. [b] Oxidation conducted under a nitrogen atmosphere. [c] Completion time determined by the no-decolorization test. [d] Thiol/sulfoxide ratio is half of that indicated for the table.

With concentrated hydrochloric acid as the catalyst, completion did not occur readily except with a high HCl concentration (Table I). Alternatively, ready completion was attained with a moderate HCl concentration when the amount of thiol was reduced. With hydrofluoric, methanesulfonic, or nitric acid, there was no apparent reaction even with a low MPT concentration, apparent reaction being indicated by the appearance of a new, bis(*tert*-butyl) disulfide phase.[4]

Completion time on admixture of halogen species and of nonhydrohalic acids with halogen or HX was also investigated (Table III). HCl with a minor amount of iodine was a

Table II[a]
Effect of Water on Oxidation of 2-Methyl-2-propanethiol by Dimethyl Sulfoxide

Catalyst (concn)	Water concn	Completion time, hr
I_2 (1.36)	Nil	2.0
I_2 (1.36)	7.4	3.5
57% HI (1.37)	7.4	3.5
Br_2 (1.44)	Nil	0.2
Br_2 (1.44)	6.8	0.8
48% HBr (1.40)	6.7	0.8
29% HBr (1.40)	15.5	2.0

[a] Thiol/sulfoxide molar ratio, 0.41; temperature 65°.

Table III[a]
Mixed Catalysis, Oxidation of 2-Methyl-2-propanethiol by Dimethyl Sulfoxide

Principal catalyst (concn)	Enhancer catalyst (concn)	Completion time, hr
HCl (1.42)	None	Inc_7
HCl (0.95)	I_2 (0.067)	0.8
HBr (0.91)	None	1.8
HBr (0.91)	I_2 (0.063)	1.5
H_2SO_4 (1.13)	I_2 (0.062)	NAR_3
CH_3SO_3H (1.40)	I_2 (0.065)	NAR_5
HF (1.42)	I_2 (0.070)	NAR_7[b]
I_2 (0.68)	None	8.2
I_2 (0.62)	CH_3SO_3H (0.73)	6.8
I_2 (1.24)	None	2.3
I_2 (1.24)	CH_3SO_3H (1.40)	1.0
I_2 (2.48)	None	0.3
HCl (1.42)	None	4.5[b]
HCl (1.42)	CH_3SO_3H (1.40)	3.0[b]

[a] Thiol/sulfoxide molar ratio, 0.41; temperature, 65°. [b] See footnote *d*, Table I.

markedly more effective catalyst than HCl alone. The analogous addition of iodine to HBr gave only a minor enhancement. Similar trace addition of iodine to sulfuric, methanesulfonic, and hydrofluoric acids did not produce effective catalysts. The addition of 1 equiv of a strong acid, methanesulfonic acid, to iodine or HCl produced an enhancement, though the effect was less than that of another 1 equiv of the halogen species.

Catalysis of the oxidation of MPT by sulfoxides was also checked using tetramethylene sulfoxide (TMSO) and dipropyl sulfoxide (DPSO) (Table IV). Results completely paralleled those obtained with DMSO, including a slightly longer completion time relative to halogen where an aqueous HX was used. With TMSO oxidation could be conducted at 25°.

The oxidation of dodecanethiol by DMSO was similarly investigated (Table V). Again, oxidation of the thiol went to completion within a number of hours at 60–75° when a minor amount of halogen or HX was present. With methanesulfonic acid present, completion was not attained in 10 hr at 75° even with half the usual thiol concentration, nor was apparent reaction indicated by crystallization of didodecyl disulfide on cooling. As in the oxidation of MPT, an admixture of HCl and a minor amount of iodine had a marked catalytic effect. Use of methanesulfonic acid along with iodine showed an increase in catalytic effect over that of iodine alone.

Results for the oxidation of α-toluenethiol by DMSO at 60° are given in Table V. Again, halogen species were effective catalysts; methanesulfonic acid was not.

There is a definite distinction between halogen–HX catalysis (not including fluorine–HF catalysis) and ordinary (nonhydrohalic) acid catalysis in that the former occurs readily at moderately elevated temperatures at which the latter is not particularly apparent. This along with equivalent catalytic effect of a halogen and its HX, retardation by water, and acceleration by ordinary acid, supports the probability that halogen–HX catalysis is a consequence of the coupling of reactions 2 and 3. It would seem that halogen is in the HX or other colorless form initially. Acceleration by nonhydrohalic acid may be through a common ion effect in reaction 3. Increase in the reverse of reaction 3[3,5] may account for retardation by water, which would indicate progressive retardation since water is a product.

The pronounced catalysis by HCl in the presence of a minor amount of iodine may be due to the formation of a mixed halogen.

The situation is entirely different in the oxidation of aromatic thiols, which, even without catalyst, may be oxidized by sulfoxides at room temperature[6] though Whiting[7] has reported acid catalysis. Halogen, HX, and methanesulfonic acid were all found to be effective catalysts for the DMSO oxidation of benzene- and 2-naphthalenethiol (Table VI). There was no great variation in completion time and no readily apparent trend. Addition of water to the HBr-catalyzed reaction did not slow the oxidation. Thus, it would

Table IV
Oxidation of 2-Methyl-2-propanethiol by Other Sulfoxides

Catalyst	Catalyst concn	Temp, °C	Completion time, hr
By TMSO (Thiol/Sulfoxide Molar Ratio, 0.47)			
I_2	1.55	50	0.4
I_2	1.55	25	9.5
HI	1.55	50	0.8
Br_2	1.60	25	0.1[a]
HBr	1.60	50	0.1[a]
HBr	1.60	25	0.3
HCl	3.22	50	7.0
CH_3SO_3H	3.18	50	NAR_{14}
By DPSO (Thiol/Sulfoxide Molar Ratio, 0.49)			
I_2	1.62	50	1.5
HBr	1.66	50	0.8
HCl	3.36	65	8.8
CH_3SO_3H	3.31	65	NAR_{20}

[a] Noticeably exothermic.

Table V
Oxidation of Thiols by Dimethyl Sulfoxide

Catalyst	Catalyst concn	Temp, °C	Completion time, hr
Dodecanethiol (Thiol/Sulfoxide Molar Ratio, 0.40)			
I_2	1.24	60	8.8
HBr	1.40	60	2.2
HCl	1.42	75	4.5[a]
CH_3SO_3H	1.39	75	NAR_{10}[a]
HCl + I_2	0.95, 0.067[b]	60	1.2
CH_3SO_3H + I_2	1.39, 1.24[b]	60	3.5
α-Toluenethiol (Thiol/Sulfoxide Molar Ratio, 0.40)			
I_2	1.36	60	1.6
HBr	1.40	60	0.9
HCl	1.42	60	1.7[a]
CH_3SO_3H	1.39	60	NAR_9[a]

[a] See footnote *d*, Table I. [b] Respectively.

Table VI
Oxidation of Aromatic Thiols by Dimethyl Sulfoxide

Catalyst	Catalyst concn	Completion time, hr
Benezenethiol (Thiol/Sulfoxide Molar Ratio, 0.46; Temperature 25°)[a]		
I_2	1.36	4.0[b]
I_2	1.36	8.0
HBr	1.40	2.9
HBr	1.40	2.7[c]
HCl	1.42	3.5
CH_3SO_3H	1.39	4.2
none		Inc_{21}
2-Naphthalenethiol (Thiol/Sulfoxide Molar Ratio, 0.25; Temperature, 25°)[a]		
HBr	1.40	2.0
HBr	1.40	1.5[c]
HCl	1.42	1.5
CH_3SO_3H	1.39	2.5
none		25.

[a] Noticeably exothermic. [b] See footnote *c*, Table I. [c] Additional water added so that its total initial concentration was 15.5 mol/100 mol of DMSO.

seem that here a true or proper acid catalysis[8] competes favorably with the sequence represented by reactions 2 and 3. These may do little more than respectively provide the acid when a halogen is used and signal completion.

With each MPT–sulfoxide combination, a preparative experiment was undertaken. Through isolation and determination of properties, it was ascertained that bis(*tert*-butyl) disulfide and a reduced sulfoxide (a sulfide) were products in reasonable amount consistent with the expected stoichiometry. The disulfide was obtained in 80–87% of the theoretical yield; the sulfide, 76–84%. For dodecane-, α-toluene-, benzene-, and 2-naphthalenethiol, completed oxidations were checked for the disulfide product and its yield by work-up and isolation. In each case, the anticipated disulfide was obtained in about 90% of the theoretical yield.

Halogen–HX catalysis significantly enhances the ease with which aliphatic and araliphatic thiols may be oxidized to disulfides by sulfoxides and can be expected to be synthetically useful. Yields are excellent and possibly quantitative except for crystallization and mechanical losses. The catalysis seems to be applicable for oxidation of a wide variety of aliphatic thiols. Indeed, the tertiary thiol MPT, which otherwise oxidizes with difficulty,[9] served as a useful model for much of this study.

Experimental Section

Reagents. The DMSO, halogens, hydrohalic acids, nitric acid, and sulfuric acid were reagent grade. TMSO and DPSO were dried over molecular sieves and distilled. The concentration of the acids was as follows unless otherwise indicated: HI, 57%; HBr, 48%; HCl, 37%; HF, 48%; HNO_3, 70%; and H_2SO_4, 96%. The methanesulfonic acid was redistilled; hence, essentially 100%. Commercial thiols were used directly unless of practical grade, in which case they were redistilled.

General Procedure for Determination of Completion Time. Experiments were run with 0.10–0.13 mol of sulfoxide and a thiol/sulfoxide molar ratio of less than 0.50. A mixture of the thiol, sulfoxide, catalyst, and any added water was heated under reflux within 1° of the temperature indicated while stirring magnetically.

Completion times were determined as follows. When no iodine-containing catalyst was used, a drop (0.03 ml) of the reacting mixture was periodically withdrawn and added to 1 ml of a 0.025% solution of iodine in DMSO until decolorization no longer occurred (limit of thiol detection in this test, about 0.026 *M*). When an iodine-containing catalyst was used, reaction was continued until the in situ appearance of iodine color unless otherwise indicated. (Completion occurs later on the basis of in situ color appearance when the no-decolorization test is applied). When two phases were present, the no-decolorization test was applied to both phases except when the second phase was a crystalline solid. Results are given in Tables I–VI.

Bis(*tert*-butyl) Disulfide (Preparative Example). A solution of 18 ml (0.157 mol) of MPT and 0.66 g of iodine (0.0052 mol as HI) in 30 ml of TMSO was cautiously heated[10] under reflux at 50° until a deep amber color appeared (about 0.5 hr). After cooling, the mixture was shaken with 50 ml of water containing sufficient sodium carbonate to remove the amber color. The organic phase was extracted twice with 25 ml of water. Combined aqueous extracts were then extracted thrice with 20-ml portions of ether. Combined organic phases were dried over anhydrous potassium carbonate and distilled. Obtained was 5.8 g of tetramethylene sulfide (84% of theory). The boiling point and melting point of the mercuric chloride derivative were in agreement with reported values.[11] Further distillation at a pressure of 22 mm gave 11.4 g of bis(*tert*-butyl) disulfide (82% of theory). The melting point and boiling point agreed with reported values.[12]

Recovery of Disulfide from Completion Experiments (Dodecane-, α-Toluene-, Benzene- and 2-Naphthalenethiol). Following completion, dimethyl sulfide was removed by subjecting the reaction mixture to vacuum. Twenty milliliters of water was stirred in to completely precipitate the disulfide, which was then collected and recrystallized from an appropriate solvent. Identity was confirmed by melting point.

Registry No.—I_2, 7553-56-2; HI, 10034-85-2; Br_2, 7726-95-6; HBr, 10035-10-6; HCl, 7647-01-0; CH_3SO_3H, 75-75-2; MPT, 75-66-1; DMSO, 67-68-5; TMSO, 1600-44-8; DPSO, 4253-91-2; dodecanethiol, 112-55-0; α-toluenethiol, 110-53-8; benzenethiol, 108-98-5; 2-naphthalenethiol, 91-60-1; bis(*tert*-butyl) disulfide, 1518-72-5.

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Polar Effects in Radical Reactions. V. Homolytic Aromatic Substitution by Methyl Radicals[1]

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Methyl radicals, produced by thermolysis of *tert*-butyl peracetate at 110°, effect substitution reactions with benzene and substituted benzenes. Partial rate factors were calculated using the relative reactivities of methyl radicals with substituted benzenes and the isomer distribution of the toluenes produced. A Hammett equation plot of the partial rate factors vs. σ gives $\rho = 0.1 \pm 0.1$, indicating that the methyl radical, like the phenyl radical, shows little polar character. This ρ value is very similar to the ρ found for reaction of methyl radicals with the methyl group of substituted toluenes, supporting the suggestion previously made by us that the ρ values are very similar for addition to benzenes and for abstraction from toluenes by any given radical. This similarity had not been noticed previously since in ionic or polar reactions, an electrophilic species which adds to aromatic rings generally does not also react as the benzylic position. The assumption which is inherent in most homolytic aromatic substitution studies, that the relative amounts of substituted benzenes formed are proportional to the relative rates of attack at the three positions of a monosubstituted benzene, is discussed and its limitations noted. The inadequacy of the correlation coefficient as a measure of goodness of fit of points to a line with a small slope is discussed.

The quantitative treatment of homolytic aromatic substitution reactions using the technique of partial rate factors[3,4a,5] provides insight into the nature both of the attacking radical[6,7] and of the aromatic system undergoing attack.[8] Radicals whose addition to benzene has been studied include the phenylethynyl,[9] benzoyloxy and substituted benzoyloxy,[10] isopropoxycarboxy,[11] and 1-cyclohex-1-enyl[12] radicals, and the oxygen atom,[13] all of which are electrophilic; the cyclohexyl,[14] *n*-propyldimethylsilyl,[15] and pentamethylsilanyl[15] radicals, which are nucleophilic; and the cyano,[16] cyclopropyl,[17] phenyl,[4b,9,18] and substituted phenyl[18] radicals and the hydrogen atom,[6] all of which are nearly electroneutral.

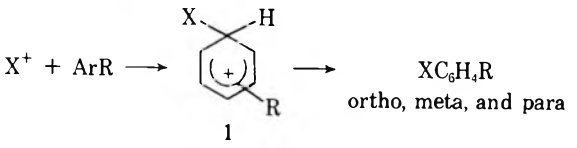
Homolytic substitution by methyl radicals has been the subject of numerous studies. The influence of substituents on reactivity in methylation was originally reported by Szwarc and coworkers[19] as a methyl affinity scale and later studied by Williams.[20] Substituent effects on orientation have been given by Eliel[21] (for toluene), Waters,[22] and Williams.[23] Surprisingly, however, no single reference describes the influence of a substituent on both reactivity and product distribution. Although Williams reported both types of data, he does not report a ρ value, and a Hammett correlation of his data is rather unsatisfactory.[24] We have studied substituent effects on both reactivities and orientations in the reaction of methyl radicals with five benzene derivatives and find $\rho \simeq 0.1$.

Our kinetic system involved the competitive reaction of methyl radicals, produced by thermolysis of *tert*-butyl peracetate at 110°, with either a substituted benzene or benzene.[28] The relative reactivities of methyl addition (k_H^X), determined from yields of the substituted toluene to toluene formed, are given in Table I. From these data and the isomer distribution of substituted toluenes listed in Table I, partial rate factors (F_i^X), given in Table II, were calculated from eq 1,[3,4a,5] where s, a statistical correction factor,

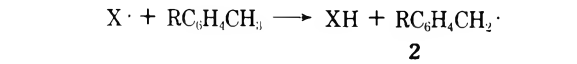
$$F_i^X = s(k_H^X)\,(\text{fraction substitution at } i\text{th position in } XC_6H_4CH_3) \quad (1)$$

equals 6 for F_p^X and 3 for F_m^X and F_o^X, and k_H^X is the total rate constant for the addition of methyl to all positions in C_6H_5X relative to the total rate constant for reaction with benzene.

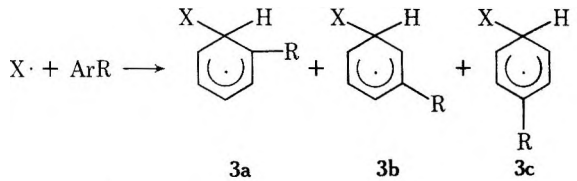
Inherent in our analysis is the requirement that the relative amounts of substituted toluenes formed are proportional to the relative rates of attack at the three positions of a monosubstituted benzene. Although this assumption is made in all homolytic aromatic substitution studies[3,4a,5] and appears to be satisfactorily fulfilled,[4c,29] it is probably not strictly true in all these systems. It should be noted that in *ionic* electrophilic aromatic substitution, a reaction which generally is excellently correlated by linear free energy relations (LFER),[30] the analogous assumption is surely valid. The rate of attack by the electrophile X^+ at meta or para positions would be expected to closely parallel the ultimate yield of meta- or para-substituted products since the substituent R in intermediate **1** does not divert intermediate **1** from its expected aromatization to XC_6H_4R (eq 2). Similarly, in abstraction of hydrogen atoms from substituted toluenes by the radical X·, the conversion of the intermediate radicals **2** to the ultimate products would not be expected to be influenced markedly by the substituent R (eq 3). However, in homolytic aromatic substitution (eq 4),



(2)



(3)



(4)

the nature and position of the substituent R in intermediate radicals **3a**, **3b**, or **3c** probably exerts an influence on the relative rates at which these radicals dimerize, disproportionate, or are oxidized to ortho, meta, or para XC_6H_4R by a radical present in the system.[4c,7,31]

In our system, we tested this assumption that the substituent R does not influence the partition of intermediates **3a–c** by varying the rate of production of intermediates **3** and **3** (R = H), and consequently their concentrations, and observing the effect on k_H^X and isomer distribution. The constancy of both k_H^X (Table I) and isomer distribution

Table I
Relative Rates and Isomer Distributions of Methylation of C_6H_5X at 110°

X	[TBA][a]	$[C_6H_6]/[C_6H_5X]$	k_H^X [b]	% $XC_6H_4CH_3$ Ortho	Meta	Para
NO_2	0.05	1.1	4.3	71	6	23
	0.05	3.4	3.8	70	7	22
	0.05	5.7	4.2	70	8	21
	0.1	1.1	4.6	69	7	23
	0.1	3.4	6.1	68	9	23
	0.1	5.7	5.4	71	6	23
		Av[c] 4.6 ± 1.0		70	7	22
CN	0.05	1.1	4.2	58	10	32
	0.05	3.4	6.0			
	0.05	5.7	4.9	61	11	29
	0.1	1.1	5.2	57	12	32
	0.1	3.4	5.3			
	0.1	5.7	5.3			
		Av[c] 5.1 ± 0.6		59	11	31
Br	0.05	1.2	1.4	66	22	12
	0.05	3.5	1.6			
	0.05	5.9	1.6	66	23	11
	0.1	1.2	1.8	65	24	11
	0.1	3.5	1.7			
	0.1	5.9	1.9	66	22	12
		Av[c] 1.7 ± 0.2		66	23	12
Cl	0.05	1.2	1.2	69	20	11
	0.05	3.5	1.5			
	0.05	5.8	1.6			
	0.1	1.2	1.7	69	21	10
	0.1	3.5	1.6			
	0.1	5.8	1.5			
		Av[c] 1.5 ± 0.2		69	20	10
CH_3	0.1	*d*	0.8			
	0.1	*d*	1.2			
	0.1	0		53	31	15
	0.1	1.0		51	32	15
		Av[c] 1.0 ± 0.2		52	32	15

[a] Molar concentration of *tert*-butyl peracetate. [b] Relative reactivity of C_6H_5X to C_6H_6 toward methyl addition. [c] Average k_H^X ± one standard deviation, and average isomer distribution. [d] Indirectly determined. See Experimental Section for discussion.

Table II
Partial Rate Factors for Methylation of C_6H_5X at 110°

X	F_o^X	F_m^X	F_p^X	Registry no.
NO_2	9.7	0.97	6.1	98-95-3
CN	9.0	1.7	9.5	100-47-0
Br	3.4	1.2	1.2	108-86-1
Cl	3.1	0.90	0.90	108-90-7
H	(1.0)	(1.0)	(1.0)	71-43-2
CH_3	1.6	0.96	0.90	108-88-3

(Table I) as the initiator concentration and ratio of reactants are varied over the limited range studied supports the assertion that this assumption is satisfactorily obeyed in our system.[32] However, this is negative evidence and does not establish the general applicability of the partial rate factor approach in radical systems. Furthermore, in our system, as in most others that have been studied, the range over which the variables can be altered to test the constancy of the partial rate factors is rather narrow. At present, it appears that an adequate test of the assumption that the rates of formation of **3a–c** parallel the rates of formation of final ortho-, meta-, and para-substituted products may not be possible. In theory, the direct measurement of the rates

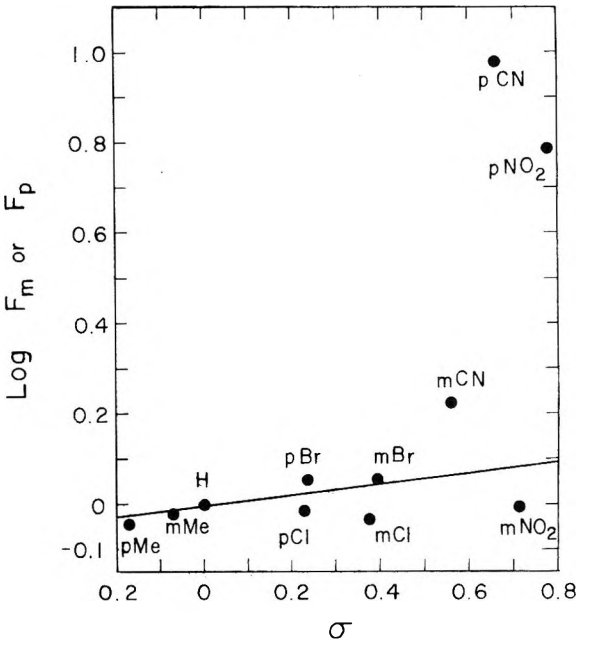


Figure 1. A plot of the partial rate factors for substitution by methyl radicals in monosubstituted benzenes at 110° vs. σ constants. The least-squares treatment gives $\rho = 0.1 \pm 0.1$ for meta substituents only and $\rho = 0.14 \pm 0.9$ for all points except *p*-CN and *p*-NO_2.

of formation of **3a–c** is possible using pulse techniques; however, the one application of this technique of which we are aware found that the absorption peaks of three isomers of **3** could not be resolved so that only the sum of the three could be determined.[33] In the final analysis, the most striking testimonial to the utility of the partial rate factor method is the fact that it works. This is not totally satisfactory because, among other things, it may work because of the fortuitous cancellation of influences from several factors. We suspect that this probably is the case: LFER correlations of homolytic aromatic substitution generally are not as satisfactory as those of hydrogen abstraction from toluenes; for one thing, they appear more susceptible to the influence of "extra" resonance.[6,34]

A Hammett treatment (Figure 1) of the partial rate factors of Table II vs. σ gives the following: meta substituents only, $\rho = 0.1 \pm 0.1$ (six points); meta and para substituents $\rho = 0.1 \pm 0.1$ (nine points).[35,36] The *p*-NO_2 and *p*-CN points are not included in this analysis because these points lie far from the least-squares lines. In fact, in homolytic aromatic substitution reactions, the *p*-NO_2 and *p*-CN groups always have partial rate factors which are much different from the values predicted by the linear regression line.[4b,6,14,17-19,22] Apparently these deviations arise because the "extra" resonance of these groups is far beyond that accommmodated by their σ constants.[34] A "σ-dot" scale is needed, but the reaction series on which to base this scale remains a mystery.[6]

Since the methyl radical is considered to be nearly electroneutral, the ρ for homolytic aromatic methylation, like that for phenylation,[4b,9,18] should be about zero. However, the values which can be obtained from the literature are surprisingly large; the ρ calculated by combining data of Szwarc,[19] Eliel,[21] and Waters[22] is 1.4 ± 0.4[6] and the value obtained from the data of Williams[20,23] is 0.8 ± 0.4.[24] The data on which both these ρ values are based suffer from the fact that relative rates and isomer distributions were measured at different temperatures, and often in different laboratories. Furthermore, the isomer distributions were determined by ir analyses of fractions obtained by subjecting the reaction mixtures to distillation and preparative VPC,

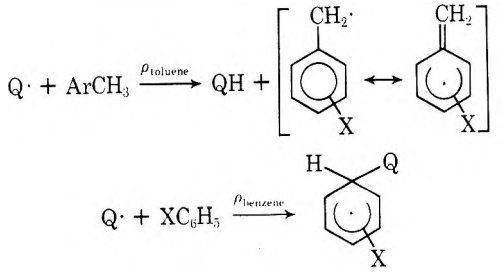
Table III
Comparison of ρ Values for Hydrogen Abstraction from Ring-Substituted Toluenes and for Addition to Substituted Benzenes[a]

Radical	H abstraction from toluenes ρ	Temp, °C	Addition to benzenes ρ	Temp, °C
Methyl	−0.2[b]	100	0.1[c]	110
Hydrogen atom	−0.1[d]	35	−0.3[e]	40
Phenyl	−0.5[f]	60	0.1[h]	80
Phenyl	−0.2[g]	60	0.0[i]	*i*
Phenyl			0.1[j]	20
p-$CH_3C_6H_4$·	−0.1[f]	60	0.0[j]	20
p-XC_6H_4·	−0.3[f,k]	60	−0.3[j,l]	20
p-$NO_2C_6H_4$·	−0.6[f]	60	−0.7[j]	20
Cyclopropyl	0.2[m,n]	100	0.1[m]	100
Cyclohexyl			1.1[o]	90
3-Heptyl	0.7[p]	80		
Isopropyl	0.9[q]	35		

[a] This correlation is based on meta substituents, except for a few cases in which an insufficient number of meta derivatives were studied. In those instances the ρ values are based on both meta- and para-substituted compounds. [b] W. A. Pryor, U. Tonellato, D. L. Fuller, and S. Jumonville, *J. Org. Chem.*, **34**, 2018 (1969). [c] This work. [d] R. W. Henderson and W. A. Pryor, submitted for publication. [e] W. A. Pryor, T. H. Lin, J. P. Stanley, and R. W. Henderson, *J. Am. Chem. Soc.*, **95**, 6993 (1973). [f] W. A. Pryor, J. T. Echols, and K. Smith, *J. Am. Chem. Soc.*, 88, 1189 (1966). [g] R. F. Bridger and G. A. Russell, *ibid.*, **85**, 3754 (1963). [h] Data summarized by G. H. Williams, *Chem. Soc., Spec. Publ.*, **24**, 36 (1970). [i] G. Martelli, P. Spagnolo, and M. Tiecco, *J. Chem. Soc. B*, 1413 (1970) (temperature not given). [j] R. Itó, T. Migita, N. Morikawa, and O. Simamura, *Tetrahedron*, **21**, 955 (1965). [k] X is bromine. [l] X is chlorine. [m] T. Shono and I. Nishiguchi, *Tetrahedron*, **30**, 2183 (1974). [n] Value for 2-phenylcyclopropyl radical. [o] J. R. Shelton and C. W. Uzelmeier, *Intra-Sci. Chem. Rep.*, **3**, 293 (1969). [p] R. W. Henderson, *J. Am. Chem. Soc.*, **97**, 213 (1975). [q] W. A. Pryor and W. H. Davis, Jr., unpublished results.

rather than by analytical VPC of the reaction mixture itself as we have done. The ρ value we report here, 0.1, certainly is more indicative of the expected electroneutrality of the methyl radical.

Our interest in the Hammett ρ value for the homolytic methylation of benzenes was kindled not by the failure of previous ρ values to reflect the methyl radical's nonpolar character but rather by the failure of these values to substantiate a proposal we made. We suggested that for a given radical, Q·, the ρ for hydrogen abstraction from the side chain of substituted toluenes ($\rho_{toluene}$) is very similar



to ρ for additions to benzenes ($\rho_{benzene}$).[6] At the time we made this suggestion, the most significant difference in $\rho_{toluene}$ and $\rho_{benzene}$ was for the methyl radical; $\rho_{toluene}$ = −0.2[39] and $\rho_{benzene} \sim 1$. However, the ρ we report here, $\rho_{benzene}$ = 0.1, is very close to that for reaction of methyl with toluene, and thus supports our suggestion. Table III lists radicals for which both $\rho_{toluene}$ and $\rho_{benzene}$ are known. Although it is not obvious that there need be a relation between these sets of ρ values, evidently, $\rho_{toluene} \simeq \rho_{benzene}$.

The correlation coefficient, r, of our data (r = 0.4[35]) is much smaller than 0.9, which is the minimum value which has been recommended as acceptable.[27,38b] The value of r, however, is a poor measure of the "goodness of fit" of the experimental points to the least-squares line in linear free energy relations, since r is related to the slope of the line, ρ.[40] The numerators of r and ρ are the same (eq 6), where x

$$r = \frac{\Sigma xy}{(\Sigma x^2 \Sigma y^2)^{1/2}} \qquad (6)$$

$$\rho = \frac{\Sigma xy}{\Sigma x^2}$$

$= X_i - \bar{X}$, $y = Y_i - \bar{Y}$, and the averages of the coordinates of the points (X_i, Y_i) are $\bar{X}$ and $\bar{Y}$.[26b] Lines of zero slope (ρ = 0 and Σxy = 0) give r = 0 regardless of whether all points lie on the line or are widely scattered from it. It is not surprising, therefore, that when Hammett correlations result in small ρ values, small r's have been obtained even though the points fall close to the line; e.g., see Figure 1 of ref 9, in which ρ = 0.03 ± 0.03 but r = 0.17; and Figure 1 of ref 17, in which ρ = 0.09 ± 0.07 but r = 0.57.

Experimental Section

Benzene (MCB Chromatoquality) and toluene (Baker Ultrex) were used as received. No toluene in the benzene was observed by VPC. The other substituted benzenes were vacuum distilled before use. Benzene-free *tert*-butyl peracetate (TBA, Lucidol) was obtained by vacuum distillation. All VPC analyses were performed on a Varian 1440 flame ionization gas chromatograph using a 10 ft × 2 mm glass column of 10% OV-1 on 100/120 Chromosorb W AW-DMCS (column A) or a 10 ft × 2 mm glass column consisting of 8 ft of 15% 4,4′-azoxydianisole on 100/120 Chromosorb W AW with 1 ft of 10% OV-1 on 100/120 Chromosorb W AW-DMCS on each end (column B). Liquid crystals, such as 4,4′-azoxydianisole, are excellent stationary phases to affect the VPC separation of ortho, meta, and para isomers of disubstituted benzenes.[41]

General Procedure. Solutions of various benzene/substituted benzene ratios (1, 3, and 5 to 1 by volume) and different TBA concentrations (0.1 and 0.05 *M*) were prepared in glass ampoules. After degassing by three freeze–pump–thaw cycles, the tubes were sealed and heated at 110 ± 0.5° for 10 hr. The ampoules were opened and samples were analyzed by VPC. Column A was employed to determine the substituted toluene to toluene ratio (relative reactivity) for all the substituted benzenes (except toluene) and to determine the isomer distribution of nitrotoluene from nitrobenzene. The other isomer distributions (ortho-, meta-, para-substituted toluenes) were measured using column B. Since methylation of benzene gives toluene, the relative reactivity of toluene to benzene, k_H^{Me}, cannot be evaluated by direct competition. Instead, the relative reactivity of toluene to bromobenzene, k_{Br}^{Me}, was determined from the amount of xylene to bromotoluene produced in a competition experiment involving toluene and bromobenzene. Multiplying this value, k_{Br}^{Me}, by the relative reactivity of bromobenzene to benzene, k_H^{Br}, gives k_H^{Me}.

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(25) The ρ values are reported as follows: $\rho = b \pm s_b$ (n points, r, s_{yx}), where b is the slope of the least-squares line, s_b is the standard deviation of the slope, n is the number of points, r is the correlation coefficient, and s_{yx} is the standard deviation from regression.[26a]
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(28) (a) Since the reactions were only run for 1 initiator half-life, the yield of toluenes must be less than 0.05 *M*. After decomposition of 0.1 *M tert*-butyl peracetate in chlorobenzene and benzene ($[C_6H_6]/[C_6H_5Cl] = 3.5$), the total concentration of the toluenes formed in this reaction was 0.031 *M*. Once formed, these toluenes are not significantly consumed by benzylic hydrogen abstraction by methyl radicals because the ratio of rate constants for this abstraction to addition to the aromatic ring is less than 10^{28b} while the concentration ratio [toluenes]/[benzenes] is less than 0.005. (b) W. A. Pryor, D. L. Fuller, and J. P. Stanley, *J. Am. Chem. Soc.*, **94**, 1632 (1972); M. Szwarc and J. H. Binks, "Theoretical Organic Chemistry", Kekule Symposium, Butterworths, London, 1958, p 262; S. H. Wilen and E. L. Elliel, *J. Am. Chem. Soc.*, **80**, 3309 (1958).
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(34) "Extra" resonance is the ability of a substituent to stabilize an odd electron by direct interaction with the reaction site. This effect of substituents is more likely to be observed in nuclear substitution than in side chain substitution by ions as well as by radicals. For example, nucleophilic aromatic substitution rates are best correlated by σ^- and electrophilic aromatic substitution by σ^+, substituent parameters which include "extra" resonance considerations.[5b] Side chain reactions, however, are usually correlated by σ, a parameter which has only a limited resonance dependency.[5c] (Also see K. Wiberg, "Physical Organic Chemistry", Wiley, New York, N.Y., 1964, pp 285–290.)
(35) The complete analysis of our methylation data gives, for meta only, $\rho = 0.1 \pm 0.1$ (six points, $r = 0.37$, $s_{yx} = 0.1$); meta and para, $\rho = 0.1 \pm 0.1$ (nine points, $r = 0.44$, $s_{yx} = 0.09$).[25]
(36) Partial rate factors for *p*-nitro and *p*-cyano substituents are not included in these correlations because they lie far off the line determined by the meta substituents alone. The suggestion of van Bekkum and Taft[37,38a] has been followed; meta substituents are used to determine a line and the fit of para substituents to this line is examined. Also see discussion in ref 6.
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Stable Carbocations. CLXXVIII. Carbon-13 Nuclear Magnetic Resonance Spectroscopic Study of Protonated and Diprotonated Acyclic and Cyclic Diketones in FSO_3H–SbF_5–SO_2 Solution[1]

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The carbon-13 NMR chemical shifts for a series of protonated acyclic and cyclic diketones were determined in FSO_3H–SbF_5–SO_2 solution at −60° together with those of their parent diketones. Phenyl-substituted diketones were studied in FSO_3H–SO_2ClF solution at −80° to avoid protonation of the aromatic ring. Protonation of acyclic and cyclic diketones results in deshielding of the carbonyl resonances of the order of 10 ppm and the carbons α to the carbonyl carbons by 5 ppm. The results are discussed in view of other substituent effects and provide an insight into the extent of keto–enol tautomerism operating for the ions and precursors at low temperatures. Diprotonated diketones can also serve as model systems for carbodications.

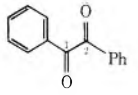
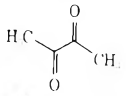
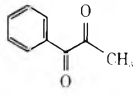
Keto–enol tautomerism is well recognized in 1,2- and 1,3-dicarbonyl compounds.[4] Physical measurements of the extent of keto–enol tautomeric equilibria of acyclic and cyclic diketones is of interest since both tautomers can be observed under suitable conditions. Extensive research efforts have been carried out along these lines utilizing bromine titrations,[5] infrared[6] and ultraviolet spectroscopy,[7] and proton[8] and ^{17}O nuclear magnetic resonance.[9] ^{13}C NMR carbonyl chemical shifts for some acyclic diketones were reported by Stothers and Lauterbur.[10] Proton magnetic resonance studies of protonated 1,3-diketones have been reported by Brouwer.[11]

In our previous investigation of protonated heteroaliphatic compounds, we reported a proton NMR study of protonated diones in FSO_3H–SbF_5–SO_2 solution.[12] We felt it, therefore, of interest to extend this study by undertaking a systematic ^{13}C NMR investigation of protonated 1,2-, 1,3- and 1,4-diketones (as well as their parent compounds) using the Fourier transform method. As protonated ketones can serve as model compounds for carbenium ions, diprotonated diketones are expected to provide similar information about carbodicationic systems. The study of these ions is being reported in detail in a forthcoming paper.

Results and Discussion

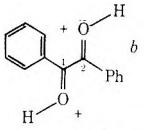
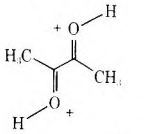
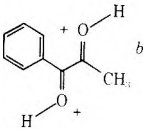
We undertook the ^{13}C NMR study of a series of protonated diketones in the FSO_3H–SbF_5–SO_2 superacid system, and for comparison also studied their neutral parent compounds. FSO_3H–SO_2ClF solution was used for aromatic diketones sensitive to the stronger "Magic Acid" system.

Table I
Carbon-13 Chemical Shifts of Acyclic 1,2-Diketones[a]

Precursor	Registry no.	C-1, C-2	Phenyl				CH_3
			Ipso	o-	m-	p-	
	134-81-6	195.4	131.9	130.2	130.7	136.4	
	431-03-8	198.0					22.8
	579-07-7	192.1, 202.5	*b*	130.6	129.3	135.6	25.8

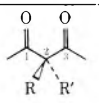
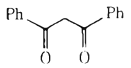
[a] In parts per million from external Me_4Si (capillary). Recorded in SO_2 at −60°. [b] Ipso carbon appears as a small shoulder downfield from ortho carbon.

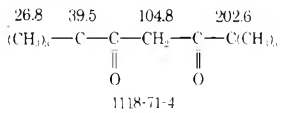
Table II
Carbon-13 Chemical Shifts of Protonated 1,2-Acyclic Diketones[a,c]

Ion	Registry no.	C-1, C-2	Phenyl				CH_3
			Ipso	o-	m-	p-	
	55236-79-8	197.3	128.3	136.2	131.4	145.6	
	55236-80-1	204.0					25.5
	55236-81-2	197.2, 198.3	124.5	139.3	132.0	149.3	29.1

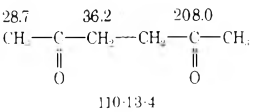
[a] In parts per million from external Me_4Si (capillary). Protonated in FSO_3H-SbF_5-SO_2 at −60°. [b] Protonated in FSO_3H-SO_2ClF. [c] Peaks may be the result of equilibration between several mono- and diprotonated forms. See text.

Table III
Carbon-13 Chemical Shifts of Acyclic 1,3- and 1,4-Diketones[a]

	Registry no.	Carbonyls C-1, C-3	C-2	R'	Phenyl				CH_3
					Ipso	o-	m-	p-	
R = R' = H	600-14-6	189.4	98.9						23.3
R = H; R' = CH_3	815-57-6	198.0, 209.3	60.5, 105.9	12.1					23.0, 28.8
R = R' = CH_3	3142-58-3	211.1	62.3	20.6					25.9
R = H; R' = Ph	5910-25-8	193.7	115.3		136.4	131.5	129.2	127.9	23.6
	120-46-7	185.6	93.4		134.3	127.5	129.2	133.6	



1118-71-4



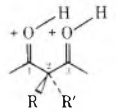
110-13-4

[a] In parts per million from external Me_4Si (capillary). Recorded in SO_2 at −60°. [b] Both diketo and keto-enolic tautomers are present; δ ^{13}C value for enolic tautomers is represented by a shielded carbonyl carbon. See text.

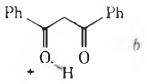
The ^{13}C NMR chemical shift data obtained using the Fourier transform (FT) techniques[13,14] are summarized in Tables I–VI.

The assignment of resonances was made by the now-familiar procedures of Grant and coworkers.[15,16] These include the observation that a polar group exerts a large inductive effect on the shift of a directly attached carbon, and, if symmetry elements are present in a molecule, it is possible to assign signals on the basis of relative intensities. To be assured of the correct assignment, in a number of cases, it was necessary to conduct "off-resonance" proton-decoupling experiments.

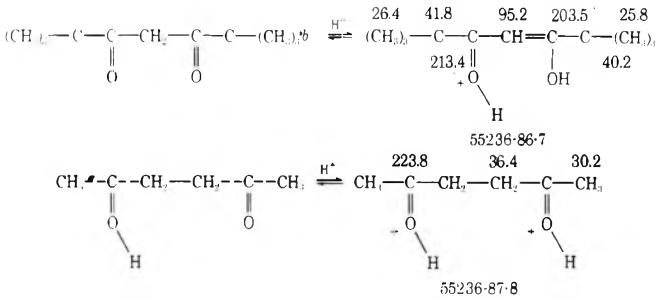
Table IV
Carbon-13 Chemical Shifts of Protonated 1,3- and 1,4-Acyclic Diketones[a]



R R′	Registry no.	Carbonyls C-1, C-3	C-2	R′	Phenyl Ipso	Phenyl o-	Phenyl m-	Phenyl p-	CH_3
R = R′ = H mono-[d]	16962-62-2	198.8	103.1						25.4
R = R′ = H di-[d]	55236-82-3	206.2	52.6						33.2
R = H; R′ = CH_3	55236-83-4	226.9	57.6	16.3					31.4
R = R′ = CH_3	55236-84-5	223.4	62.8	22.9					29.4
R = H; R = Ph[b]	55236-85-6	204.1 193.1	116.6		131.8	130.1	*c*	*c*	



b	16292-64-4	188.9 185.3	95.9		128.9	137.6	130.2	138.9	

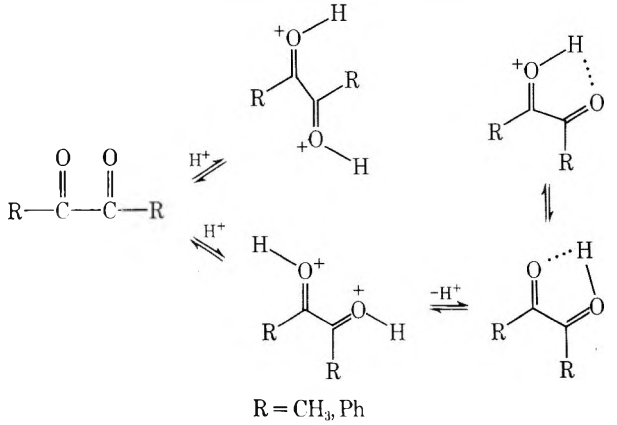


[a] In parts per million from external Me_4Si (capillary). Protonated in FSO_3H-SbF_5-SO_2 at −60°. [b] Protonated in FSO_3H-SO_2ClF at −80°. [c] Protonated 3-phenyl-2,5-pentanedione showed a broad singlet at δ 130.1 making meta and para aromatic carbon shifts. [d] Abbreviations mono- and di- refer to monoprotonation and diprotonation, respectively.

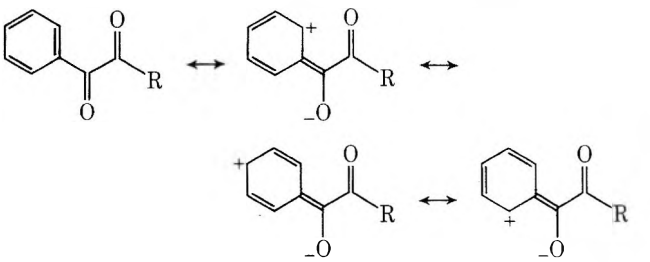
Solvent effects on carbonyl carbon-13 shifts in aprotic solvents have been interpreted in terms of carbonyl π-bond polarity as influenced by polar and van der Waals interactions with the solvent.[17] Our present experimental results may indicate slight solvent–solute interaction between diketone carbonyl groups and sulfur dioxide, but the effect is small and is not a major contribution to the deshieldings that occur for the carbonyl carbon-13 shift upon oxygen protonation.

Carbon-13 chemical shifts of the protonated diketones were measured at −60° in excess of FSO_3H–SbF_5 solution, using SO_2 as diluent. The carbon-13 chemical shifts of protonated aromatic diketones were measured at −80° in SO_2ClF–FSO_3H solution.

1,2-Diketones. Inspection of data in Tables I and II for precursor and protonated aliphatic 1,2-diketones reveals several interesting features. For diacetyl, the adjacent acetyl groups with their significant inductive effect cause shielding of the carbonyl carbons with respect to the carbonyl carbon of acetone. Upon protonation (on oxygen) of diacetyl with FSO_3H–SbF_5–SO_2, a deshielding of 6 ppm is observed for the carbonyl resonance, while the methyl carbon shows a deshielding of 3.3 ppm. Owing to the symmetrical nature of diacetyl, the exact structural geometry of its protonated form is difficult to ascertain. Several protonated forms could be formed which represent mono- and diprotonated cisoid or transoid arrangements of the 1,2-dicarbonyl structure in a rapidly equilibrating system.



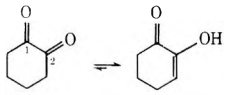
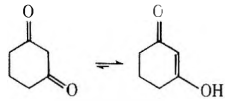
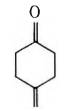
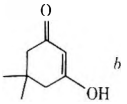
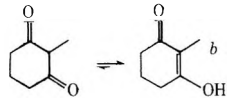
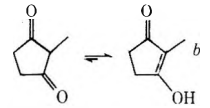
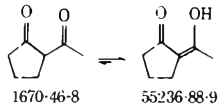
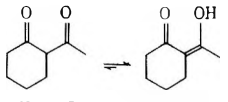
An especially interesting observation is the effect of adjacent dicarbonyl groups on aromatic ring carbons. Maciel reported significant deshielding for carbon-1 of benzophenone presumably as a result of considerable inductive electron withdrawal from the neighboring PhCO substituent.[18] Our results indicate that the para ring carbon is more deshielded than carbon-1 when COCOR (R = CH_3, Ph) is the neighboring substituent. These results are best understood when one considers the following mesomeric structures as contributors to the overall molecular structure. ^{13}C NMR



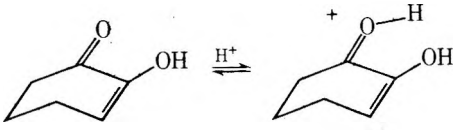
assignments were clarified by off-resonance experiments. [^{13}C–^{1}H coupling observed for the para carbon (doublet), no coupling expected for the ipso carbon (singlet)].

At low temperatures, 1,2-cyclohexanedione shows keto–enol tautomerism. Owing to its position in a closed cyclic system only the cisoid conformation is achieved. The carbonyl resonance is shielded by 11.4 ppm when compared to a monocarbonyl compound, i.e., cyclohexanone. The shielding effect is expected, however, since previous results show a shielding effect of adjacent sp^2 centers.[19] Structure I best represents this tautomer. Unlike its acyclic analog, protonated 1,2-cyclohexanedione can be represented only by I-H^+.

Table V
Carbon-13 Chemical Shifts of Cyclic 1,2-, 1-3-, and 1,4-Diketones[a]

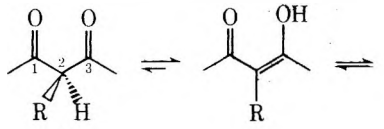
Precursor[b]	C-1	C-2	C-3	C-4	C-5	C-6	$COCH_3$	CH_3
 765-87-7 10816-66-2	197.6	145.3	122.2	22.4	23.2	35.5		
 504-02-9 30182-67-3	209.2	103.7	194.8	31.9	21.9	31.9		
 637-88-7	214.2	34.9						
 3471-13-4	187.5	103.8	187.5	47.4	33.5	47.4		29.4
 1193-55-1 32774-63-3	185.1	110.6		33.4	21.6	33.4		8.1
 765-69-5 5870-63-3	202.5	112.5	142.0	31.1				8.1
 1670-46-8 55236-88-9	216.1 209.6 205.8 174.5	110.8 62.9	36.5	29.8	38.4			25.1 25.0 20.3
 874-23-7 55236-89-0	192.1	108.0	23.8	22.4	24.8	30.5	182.0	21.3

[a] In parts per million from external Me_4Si (capillary). Recorded in SO_2 at −60°. [b] C-1 and C-3 appear as a broad peak in DMSO-d_6 solvent. [b] Registry no. is given below the compound.

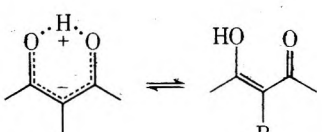


I I-H$^+$

1,3-Diketones. Tables III and IV list the carbon-13 chemical shift data for the protonated 1,3-diketones and their precursors. An important feature of these data is the significant deshielding of carbon-2 indicating significant sp^2 character of this carbon. The position of tautomeric



II IIa



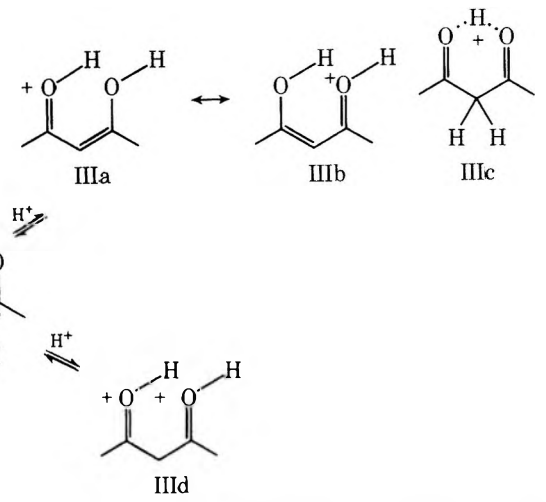
IIb IIc

equilibria is clearly in the direction of the keto–enol form whenever a labile proton is present α to two carbonyl groups in the molecule (as shown by structures IIa–c). However, both tautomers (II and IIa–c) were observed for 3-methyl-2,4-pentanedione, since the carbon α to both carbonyls could be detected as both sp^3 (δ 60.5) and sp^2 (δ 105.9) hybridized forms. Since the carbonyl resonance appears as a singlet absorption for the diketones studied, the precursor can be represented by symmetrical structure IIB indicating significant hydrogen bonding or, equally, by rapid equilibration of IIa with IIc.

By proper variation of molecular structure, the pure diketo tautomer can be observed as in the case of 3,3-dimethyl-2,4-pentanedione. Protonation of the diketo tautomer causes a deshielding of 10 ppm for the carbonyl carbons.

It is significant to note the marked deshielding of aromatic carbon 1 of 3-phenyl-2,4-pentanedione (relative to benzene) at these temperatures due to the enolic contribution of this tautomer which renders the structure to a substituted styrene.

One further interesting aspect of protonation of 1,3-dicarbonyl compounds was the observation of mono- and diprotonated forms. Since the exact nature of the position of

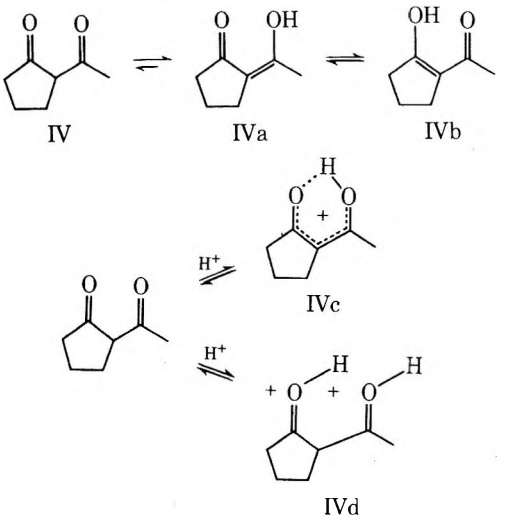


equilibrium was established by measuring the carbon-13 NMR of the precursors (vide supra) the anticipated result was monoprotonation. For example, 2,4-pentanedione shows a deshielding effect of approximately 10 ppm after monoprotonation, and is best represented by resonance structures IIIa,b which account for the observation of one carbonyl resonance. Structure IIIc can be discounted as a monoprotonated contributor III-H^+ since carbon 2 appears as a doublet upon ^1H decoupling.

Using excess superacid, diprotonated structure IIId was obtained which shows a carbonyl singlet 16 ppm deshielded from the neutral parent. Similar results were obtained for 3-methyl-2,4-pentanedione and 3,3-dimethyl-2,4-pentanedione with deshielded absorption for the protonated carbonyls of 23.3 and 12 ppm, respectively.

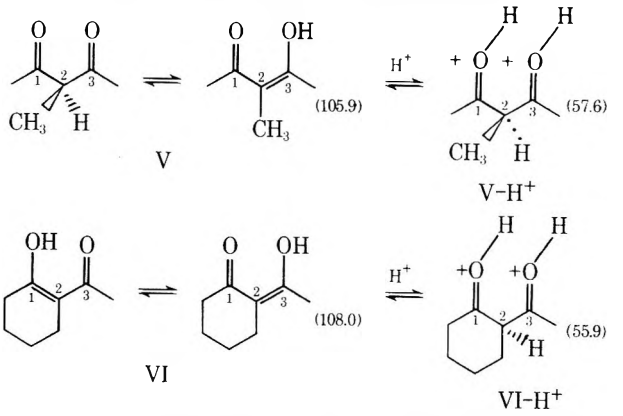
Cyclic 1,3-dicarbonyl compounds demonstrate similar trends both in degree of enolic contribution and in deshielding of charge upon protonation, as can be seen in Tables V and VI. Incorporation of more than one carbonyl in a ring system showed varied results (see also cycloalkanones studied by Roberts).[20,21] One example in this series of cyclic 1,3-dicarbonyl compounds, 5,5-dimethyl-1,3-cyclohexanedione, shows this preference for the keto–enolic tautomeric form, as indicated by the olefinic type absorption of the α carbon relative to both carbonyls (δ ^{13}C 103.8).

Examples of 1,3-dicarbonyl compounds representing α-acetylated cycloalkanones were also studied. ^{13}C NMR parameters for 2-acetylcyclopentanone and 2-acetylcyclohexanone can be seen in Table V. For 2-acetylcyclopentanone, an equilibrating tautomeric system can be best represented by structures IVa and IVb, since four different keto–enolic carbons were observed in the carbon-13 spectrum.



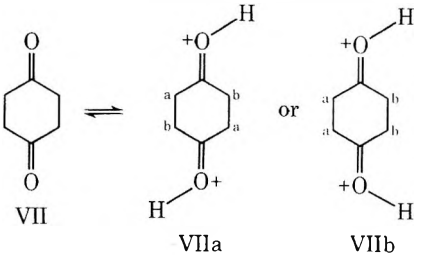
^{13}C NMR parameters for monoprotonated 2-acetylcyclopentanone (IVc) and diprotonated 2-acetylcyclopentanone (IVd) are also shown in Table VI.

^{13}C NMR data indicate the preference of keto–enolic tautomeric forms for 2-acetylcyclohexanone (VI) at the temperatures employed. As previously mentioned, both tautomers were observed for 3-methyl-2,4-pentanedione (V), the acyclic analog of VI. Numerical values in parentheses indicate ^{13}C NMR chemical shifts for carbon 2 of precursors and ions; values for precursors show typical olefinic carbon shieldings. Although monoprotonation of VI was



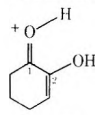
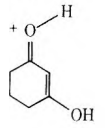
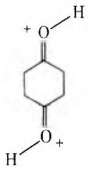
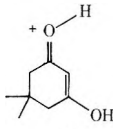
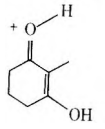
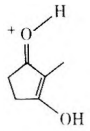
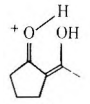
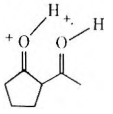
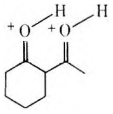
anticipated, the ^{13}C NMR chemical shift data for V-H^+ reveal carbon 2 as δ ^{13}C 57.6 and carbon 2 for VI-H^+ δ ^{13}C 59.9, results which best describe diprotonated ions. Diprotonated structures would thus explain the highly deshielded carbonyl resonances of the order of 35.1 ppm for the ring carbonyl and 43.8 ppm for the acetyl carbonyl carbon for VI-H^+. The larger deshielded value for the acetyl carbonyl carbon could then be explained by the additional deshielding effect of a directly attached methyl group. Diprotonated species V-H^+ shows a deshielding of 23.3 ppm from the precursor (an average value is reported since two carbonyl absorptions are observed when both tautomers are present).

1,4-Diketones. 1,4-Cyclic and acyclic diketones were also studied by ^{13}C NMR spectroscopy. The ^{13}C NMR chemical shift data for the studied compounds can be found in Tables III and IV. According to ^{13}C NMR assignments, it was determined that neither cyclic nor acyclic 1,4-diketones exist in the enolic form when compared to 1,2- and 1,3-dicarbonyl compounds, where the preference for the keto–enol tautomeric forms predominates at these temperatures. α methylene carbons appear at the expected resonance positions as well as the carbonyl carbons. Diprotonation of the carbonyl carbons occurs for both cyclic and acyclic 1,4-diketones studied. A deshielding of 15 ppm was observed for 2,5-hexanedione and 30 ppm for 1,4-cyclohexanedione. If one considers diprotonation of 1,4-cyclohexanedione, two structures (VIIa and VIIb) can be formed



where a and b designate the equivalent carbons. An exact differentiation between structures VIIa and VIIb cannot be made, since both structures would exhibit two methylene signals in the ^{13}C NMR spectrum.

Table VI
Carbon-13 Chemical Shifts of Protonated 1,2-, 1,3-, and 1,4-Cyclic Diketones[a]

Ion	Registry no.	C-1	C-2	C-3	C-4	C-5	C-6	$COCH_3$	CH_3
	55236-90-3	215.9		106.4	66.0	45.8	66.0		
	55236-91-4	206.8	106.0		32.0	21.7	32.0		
	55236-92-5	245.5	35.4	34.6					
	55236-93-6	203.2	103.1	203.2	43.2	34.7	43.2		26.6
	55336-94-7	200.7	113.3	200.7	31.1	19.7	31.1		6.0
	55236-95-8	203.8	115.5	203.8	30.0	30.0			4.4
	55236-96-9	200.2	110.3	26.0	22.0	36.7		188.2	18.4
	55236-97-0	248.1	62.3	29.0	31.6	43.9		237.9	21.3
	55236-98-1	227.7	59.9	32.3	30.8	36.4	42.3	225.8	27.0

[a] In parts per million from external Me_4Si (capillary). Protonated in FSO_3H–SbF_5–SO_2 at −60°. [b] Abbreviations mono- and di- refer to monoprotonation and diprotonation, respectively.

Conclusions

Keto–enol equilibrating tautomers were generally observed at low temperatures for 1,2- and 1,3-acyclic and cyclic diketones. Only 1,4-diketones and suitably substituted 1,3-diketones (e.g., 3,3-dimethyl-2,4-pentanedione) could be observed in pure diketo tautomeric forms. Monoprotonation of these keto–enol tautomers (on oxygen) results in only relatively significant deshielding for the carbonyl carbon, while more significantly deshielded resonances are observed for the diprotonated species in excess of "Magic Acid" solutions.

Experimental Section

Materials. All diketones were commercially available materials and were purified prior to use.

Preparation of Protonated Diketones. Protonated diketones were prepared by adding the diketone (0.5 ml) to a stirred solution of 1:1 FSO_3H–SbF_5 (1.5 ml) in an equal volume of SO_2 at −76°. Samples prepared in this manner gave spectra which showed no appreciable chemical shift differences with temperature or small concentration variations. The acid was always in excess as indicated by an acid peak at about δ 10.9 ppm in the ^1H NMR spectrum. The ^{13}C NMR spectra of protonated diketones were recorded only if the ^1H NMR data matched the reported values in the literature.[22] For diketones not yet reported, the structure of the protonated forms could be established from the ^1H NMR spectral data (chemical shifts, multiplicity patterns, and peak area integration). After the ^{13}C NMR spectrum of a protonated diketone was obtained, the sample was again checked by ^1H NMR spectroscopy to determine if any decomposition had occurred. Samples of protonated aromatic diketones were prepared by dissolving the diketone (0.5 ml) in SO_2ClF (0.5 ml). This solution was added dropwise to a rapidly stirred solution of FSO_3H (2 ml)–SO_2ClF (1 ml) at −76°. The acid was always in excess as indicated by an acid peak at about δ 10.4 ppm in the ^1H NMR spectrum. The ^{13}C NMR spectra of protonated aromatic diketones were recorded at −80°.

NMR Spectroscopy. ^1H NMR spectra were obtained on a Varian Associates Model A56/60-A spectrometer equipped with a variable temperature probe.

^{13}C NMR spectra were obtained in part on a modified Varian Associates Model HA-100 spectrometer equipped with a FT-100 Fourier transform accessory (V-4357 pulsing and control unit); a broad-band proton decoupler of 25.14 MHz was derived from a gated power amplifier capable of putting out approximately 80 W into the transmitter coils. The pulse width used was 35 μsec, and

the pulse interval 1.5 sec. The available computer memory (4000 input channels) and the need to provide multichannel excitation over the region of interest (seeep width 6800 Hz) limited the data acquisition time to 0.2 sec.

The free induction signal derived after each pulse was signitized and accumulated in a Varian 620/i computer (8K). Approximately 5000–7000 accumulations were made to obtain each spectrum. Field frequency regulation was maintained by a homonuclear internal lock system. The lock used was the proton-decoupled carbon-13 resonance of a 60% carbon-13 labeled methyl iodide sample contained in a precision coaxially spaced capillary (o.d. ca. 0.2 and 0.4 mm) inserted in the sample NMR tube (5 mm o.d.).

Fourier transformation of the accumulated free induction signal gave the frequency spectrum,[23,24] from which was measured the chemical shift of each signal, relative to the reference methyl iodide signal. All the chemical shifts reported here have been corrected to a Me_4Si reference by the relationship

$$\text{ppm } (Me_4Si) = \frac{H_2(\text{obsd}) - 977 - T\,(^\circ\text{C}) \times 0.70}{25.2}$$

The ^{13}C NMR spectra for the remaining protonated diketones and precursors were obtained on a Varian Associates Model XL-100 spectrometer equipped with a broad decoupler and variable temperature probe. The instrument operates at 25.2 MHz for ^{13}C, and is interfaced with a Varian 620L computer. The combined system was operated in the pulse Fourier transform mode, employing a Varian Fourier transform accessory. Typically 3000–5000 pulses, each of width 20–30 μsec, needed to be accumulated in order to give a satisfactory signal to noise ratio for all signals of interest. Field frequency stabilization was maintained by locking on the ^{19}F external sample of fluorobenzene. Chemical shifts were measured from the ^{13}C signal of 5% ^{13}C enriched tetramethylsilane in a 1.75-mm capillary held concentrically inside the standard 12-mm sample tube.

Acknowledgment. Support of our work by the National Institutes of Health is gratefully acknowledged.

Registry No.—FSO_3H–SbF_5, 33843-68-4; SO_2ClF, 13632-84-8; SO_2, 7446-09-5.

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Stable Carbocations. CLXXXI.[1] Dihydrodibenzotropylium and Dibenzotropylium Ions. Neighboring Methyl, Cyclopropyl, and Phenyl Substituent Effects in Geometrically Constrained Systems

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A series of dihydrodibenzotropylium and dibenzotropylium ions have been prepared under stable ion conditions and characterized by NMR spectroscopy. Neighboring methyl, cyclopropyl, and phenyl substituent effects are discussed in terms of ^{13}C NMR shift changes. The relative ability of neighboring methyl, cyclopropyl, and phenyl substituents in stabilizing carbenium ions via either inductive or conjugative charge-delocalizing effects is further discussed.

Methyl, cyclopropyl, and phenyl groups stabilize carbenium ions by inductive and/or resonance (conjugative) effects.[2–5] The degree of conjugation between π or σ bonds in phenyl or cyclopropyl rings with a neighboring empty p orbital on a carbenium center is significant in the degree of delocalization it can exercise and depends upon the orientation of these substituents. Since a phenyl group is larger than a cyclopropyl group, in a given sterically crowded system the former might be affected more in its ability for conjugative stabilization (i.e., effective overlap between p and π orbitals) than the latter. Therefore, if steric inhibition of conjugation becomes significant or overwhelming, phenyl-substituted carbenium ions might become less stable than either the parent (unsubstituted) or alkyl-substituted analogs. A typical example is seen in the case of dibenzotropylium ions.[6] The parent (unsubstituted) ion ($pK_{R^+} = -3.7$) is found to be considerably more stable than the phenyl-substituted ion ($pK_{R^+} = -5.7$) based on comparison of the corresponding pK_{R^+} values.[6a] The decrease in stability of the lattter ion is explained by the fact

Table I
^{1}H NMR Parameters of Dihydrodibenzotropylium (1-R) and Dibenzotropylium (2-R) Ions[a]

Ion	$H_{1,9}$	$H_{2,8}$	$H_{3,7}$	$H_{4,6}$	H_5	$H_{10,11}$	Others
1-H	8.22[b]	8.64	8.22	8.64	9.82	3.78	
1-CH_3	7.92[b]	8.40	7.92	8.88		3.88	3.44 (CH_3)
1-CH_2CH_3	8.02[c]	8.42	8.02	8.92		3.52	4.30 (CH_2), 1.92 (CH_3)
1-C_3H_5		← 7.50-8.10 →				3.40	4.40 (CH), 3.16 (CH_2)
1-C_6H_5	7.70	← 7.5-8.0 →		8.50		3.60	7.8-8.4 (aromatic)
1-OH		← 7.50-8.50 →		8.76		3.56	11.6 (OH)
2-H		← 8.9-9.4 →		9.54[d]	10.98	9.65	
2-CH_3		← 8.2-8.8 →		9.40[e]		9.20	4.25 (CH_3)
2-CH_2CH_3		← 8.4-9.0 →		9.62[f]		9.19	4.56 (CH_2), 2.22 (CH_2)
2-C_3H_5		← 9.4-8.8 →		9.92[f]		9.12	3.95 (CH), 2.00 (CH_3), 0.82 (CH)
2-C_6H_5		← 7.8-8.5 →				9.60	8.5-9.3 (aromatic)
2-OH		← 8.2-8.6 →		9.15[e]		8.40	11.20 (OH)
2-Cl		← 8.4-9.0 →		9.90[d]		9.20	

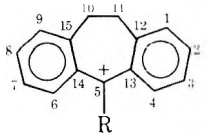
[a] ^{1}H chemical shifts (δ) are in parts per million (ppm) from external tetramethylsilane (capillary Me_4Si). [b] $J_{1,2}$ = 7.60, $J_{2,3}$ = 8.00, $J_{3,4}$ = 8.00 Hz. [c] $J_{1,2}$ = 7.60, $J_{2,3}$ = 8.00, $J_{3,4}$ = 8.80 Hz. [d] $J_{3,4}$ = 7.80 Hz. [e] $J_{3,4}$ = 8.00 Hz. [f] $J_{3,4}$ = 8.20 Hz.

that the phenyl group in this ion is kept from achieving coplanarity with the conjugated system and therefore cannot have much influence on the resonance stabilization of the ion, while the electron-withdrawing ability (inductive effect) of the phenyl ring still plays a major role and thus destabilizes the ion. Deno, Jaruzelski, and Schriesheim[7] also measured the stability of the parent and phenyl-substituted dibenzotropylium ions in aqueous sulfuric acid and found that the fusion of two benzene rings to the tropylium ion strongly destabilized the ion; likewise did a third phenyl group, as indicated by Berti.[6]

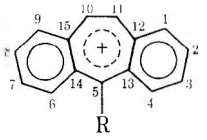
In addition to the unusual stability of dibenzotropylium ions, dihydrodibenzotropylium ions were also reported in the literature to show similar behavior.[6] Several stable dibenzo- and dihydrodibenzotropylium type ions have been reported by Looker,[6b] who also found that the dihydro systems were markedly stabilized by substituents. Many of these compounds were noticed to possess pharmacological activity characteristic of psychotropic agents.[8] The substituent effect of cyclopropyl groups[9] in these systems was not previously investigated. We have now chosen the geometrically constrained dibenzo- and dihydrodibenzotropylium ions as models for a further better understanding of substituent effects on carbenium ions bearing phenyl, cyclopropyl, and alkyl (methyl and ethyl) groups, and report their preparation and NMR spectroscopic study.

Results

Preparation of Dibenzotropylium (2-R) and Dihydrodibenzotropylium (1-R) Ions). The parent (R = H)

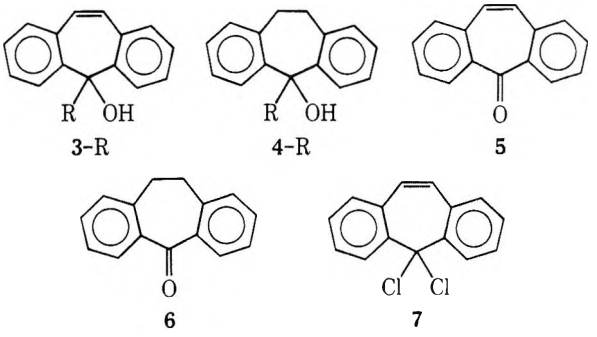


1-R



2-R

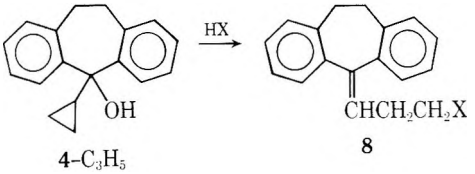
and tertiary alkyl (and phenyl) (R = CH_3, CH_2CH_3, C_3H_5, and C_6H_5) dibenzotropylium and dihydrodibenzotropylium ions, as well as the related protonated ketones (R = OH), were prepared from the corresponding secondary and tertiary alcohols, R = H, CH_3, CH_2CH_3, C_3H_5 and (or Cl), OH, and ketones, respectively, in FSO_3H–SO_2ClF solution at −78°. The chlorine-substituted dibenzotropylium ion (2-Cl) was prepared from its geminal dichloride precursor **7**.



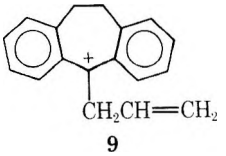
3-R 4-R **5** **6** **7**

All the ions were stable under the reaction conditions studied and their solutions generally showed deep-red color.

When the solution of ion 2-C_3H_5 was warmed (above −45°), a mixture of two ions were formed. One of them has been identified (by ^{1}H NMR) as **9**; the other was not yet identified and is still under further investigation. Likewise a cyclopropyl-substituted derivative of dihydrodibenzocycloheptenol (4-C_3H_5) which has been noted owing to its relation to psychotherapeutic drugs,[8] upon treatment with hydrogen halides[8a] underwent homoallylic rearrangement to quantitatively yield the corresponding γ-halopropenylcycloheptene derivative **8**, via homoallylic ion 2-C_3H_5.[10]



4-C_3H_5 **8**



9

Proton and Carbon-13 Nuclear Magnetic Resonance Spectra. Tables I and II summarize the ^{1}H (60 MHz) and ^{13}C (25.16 MHz) NMR parameters for the studied dibenzotropylium and dihydrodibenzotropylium ions. [Both proton and carbon shifts are reported in parts per million from capillary tetramethylsilane (Me_4Si)]. Figures 1 and 2 show ^{1}H NMR spectra of both secondary and tertiary ions for 1-R and 2-R (R = H, CH_3, c-C_3H_5, C_6H_5), respectively. The ^{13}C NMR spectrum of the particularly interesting cy-

Table II
^{13}C NMR Parameters of Dihydrodibenzotropylium (1-R) and Dibenzotropylium (2-R) Ions[a]

Ion	$C_{1,9}$[b]	$C_{2,8}$(para)	$C_{3,7}$[b]	$C_{4,6}$(ortho)	Δ_1[c]	C_5	Δ_2[c]	$C_{10,11}$	$C_{12,15}$	$C_{13,14}$	Δ_3[c]	Others
1-H	132.5	150.6	130.5	150.6	0.0	195.1	0.0	31.7	156.6	137.3	19.3	
1-CH_3	132.5	148.1	129.8	141.2	6.9	218.4	23.3	35.8	157.5	140.0	17.5	33.4 (CH_3)
1-CH_2CH_3	132.5	151.2	130.5	140.8	10.4	221.2	26.1	35.8	157.2	140.2	17.0	33.7 (CH_2), 22.9 (CH_3)
1-C_3H_5	133.5	150.0	131.6	141.6	8.4	217.1	22.0	36.6	158.4	141.2	17.2	42.1 (CH), 37.0 (CH_2)
1-C_6H_5	131.7	148.4	128.8	148.4	0.0	205.2	10.1	35.4	158.0	140.1	17.9	144.2 (C_i), 129.4 (C_o), 137.8 (C_m), 136.8 (C_p)
1-OH	130.9	135.2	130.2	134.7	0.5	202.0	6.9	35.5	144.5	132.9	11.6	
2-H	136.2	144.9	135.0	143.6	1.3	170.7	0.0	138.3	147.1	142.5	4.6	
2-CH_3	133.3	143.0	133.3	140.9	2.1	190.3	19.6	134.4	144.6	139.5	5.1	30.8 (CH_3)
2-CH_2CH_3	135.1	144.8	134.6	141.7	3.1	193.3	22.6	137.0	146.6	139.6	7.0	37.2 (CH_2), 21.2 (CH_3)
2-C_3H_5	134.7	145.3	132.8	141.0	4.3	191.8	21.1	135.6	143.5	140.6	2.9	25.0 (CH), 13.1 (CH_2)
2-C_6H_5	134.2	145.8	130.5	140.9	4.9	183.7	13.0	137.4	148.2	140.1	8.1	145.8 (C_i), 129.8 (C_o), 142.4 (C_m), 131.4 (C_p)
2-OH	134.9	140.4	132.9	137.6	2.8	190.2	19.5	131.0	142.6	129.3	3.3	
2-Cl	137.4	146.0	136.8	143.3	2.7	195.3	24.6	137.8	146.3	139.3	7.0	

[a] ^{13}C chemical shifts (δ ^{13}C) are in parts per million from external Me_4Si (capillary). [b] Interchangeable values. [c] $\Delta_1 = \delta_{13}$ $- \delta_{^{13}C_4}$, $\Delta_2 = \delta_{^{13}C_5}$ (tertiary ion) $- \delta_{^{13}C_5}$ (secondary ion), $\Delta_3 = \delta_{^{13}C_{12}} - \delta_{^{13}C_{13}}$.

clopropyl-substituted dibenzotropylium ion is shown in Figure 3. (^{13}C NMR spectra were obtained by using the Fourier transform method. See Experimental Section for details.) Assignment of carbon shifts was made with the aid of off-resonance spectra.

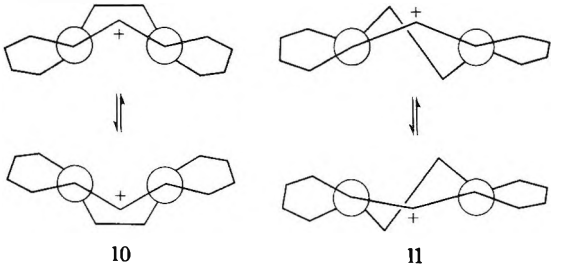
The ortho protons (H_4 and H_6's) in both ions **1**-R and **2**-R are deshielded from the rest of the ring protons, which are less resolved in the latter. The proton attached directly at the carbenium center (C_5) in **2**-H is more deshielded than that in **1**-H. The methylene and methyne bridge protons (H_{10} and H_{11}) in **1** and **2**, respectively, are sharp singlets, indicating that the ions are symmetrical.

Assignments for the ^{13}C NMR shifts are more complicated than those for the ^1H NMR shifts. The lowest field shifts are naturally assigned to the carbenium carbons. In off-resonance spectra, the secondary carbenium carbons for both **1**-H and **2**-H are doublets. The two sets of carbons at the ring junctions (C_{12} and C_{15}, C_{13} and C_{14}) are easily identified, since they are singlets in their off-resonance spectra. C_{12}'s (and C_{15}) which are at ortho positions to the electron-deficient center are assigned to the lower field singlet, while the higher field singlets are assigned to C_{13}'s (and C_{14}'s). The differences in carbon shifts between C_{12} and C_{13} in dihydrodibenzotropylium ions (**1**-R), $\Delta_3 = \delta_{^{13}C_{12}} - \delta_{^{13}C_{13}}$, are generally larger than those in the dibenzo analogs (**2**-R). Carbons (C_1 and C_3) at positions meta to the carbenium center are assumed to have more shielded shifts than those at ortho and para positions. Assignments for C_1 (and C_9) and C_3 (and C_7) are, however, tentative and could be reversed. The carbon shifts for the ortho positions (C_4 and C_6), which are assigned upfield from that of the para carbons (C_2 and C_8), vary more substantially upon substitution than those of the rest of the molecule except the carbenium carbons (C_5's).

Discussion

Dihydrodibenzotropylium Ions. The ^1H NMR pattern of the aromatic ring protons in substituted dihydrodibenzotropylium ions **1**-R varies with the substituents. Ring protons for both secondary and tertiary ions **1**-R generally show deshielded coupling patterns as found in diphenylcarbenium ions, with one exception, i.e., the cyclopropyl-substituted ion **1**-C_3H_5 (Figure 1). The cyclopropyl ring protons in this ion are considerably deshielded in comparison with those of the precursor (**4**-C_3H_5), indicating that substantial positive charge has been conjugatively drawn into the cyclopropane ring or alternatively inductive electron withdrawal by a neighboring, but nonconjugative, cation center (for the latter case the cyclopropylammonium ion c-C_3H_5-NH_3^+ was studied as a suitable model). In addition, the methylene-bridge protons in **1**-C_3H_5 are less deshielded, but these carbons are more deshielded than those in other analogous ions. In contrast benzo ring protons in the phenyl-substituted ion **1**-C_6H_5 show normal splitting patterns (Figure 1), similarly as in methyl- or ethyl-substituted ions. Thus apparently the phenyl group could not reach coplanear alignment with the empty p orbital for effective p–π overlap. The cyclopropane ring, on the other hand, can achieve a certain degree of conjugation between the empty p orbital and C–C bonds of cyclopropane ring, even if steric restriction would prevent the most favorable bisected arrangement.

Consideration of models show that the dihydrodibenzotropylium skeleton itself cannot be planar.[11] It should adopt either a boat form **10** or skew conformation **11**. Either form should, however, undergo rapid conformational transformation with minimum nuclear movement, therefore making the molecule symmetrical as indicated by NMR studies.



10 **11**

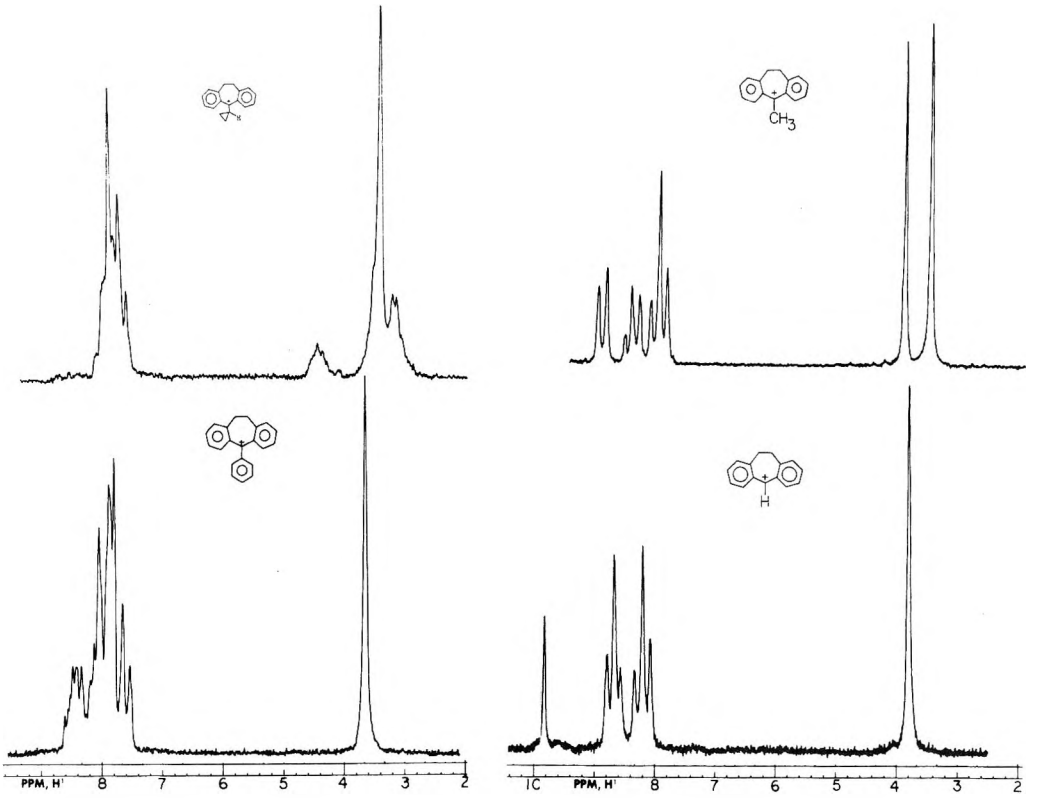


Figure 1. 60-MHz ^1H NMR spectra of the 9,10-dihydro-5-dibenzotropylium ions (a) 1-H, (b) 1-CH_3, (c) 1-C_3H_5, and (d) 1-C_6H_5, in FSO_3H–SO_2ClF solution at −78°.

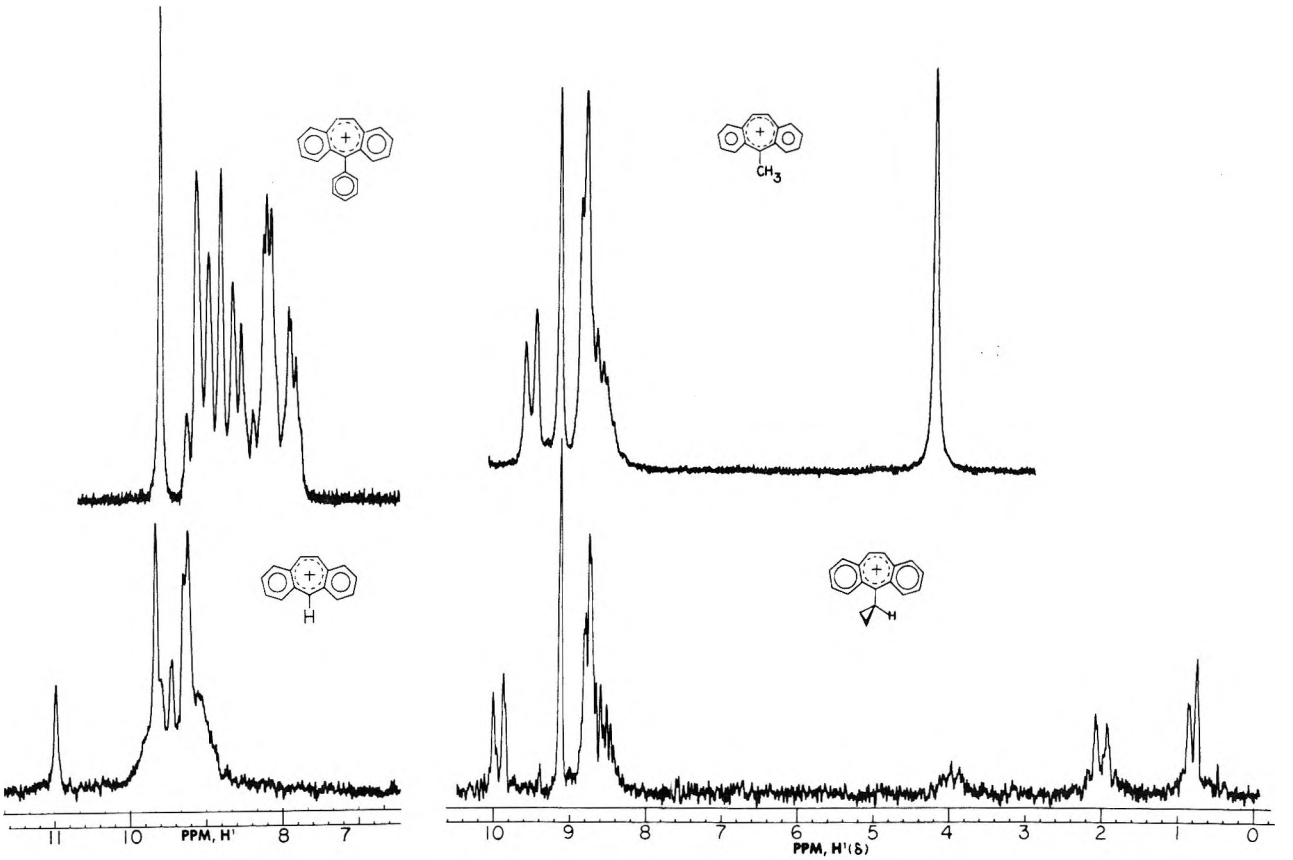


Figure 2. 60-MHz ^1H NMR spectra of the 5-dibenzotropylium ions, (a) 2-H, (b) 2-C_3H_5, (c) 2-C_6H_5, (d) 2-CH_3, in FSO_3H–SO_2ClF solution at −78°.

The ^{13}C NMR studies, through deshielding effects, indicate that substantial positive charge has been delocalized into the dihydrodibenzotropylium ring system. In the case of the cyclopropyl-substituted ion 1-C_3H_5 both methine and methylene carbons of the cyclopropane ring are substantially deshielded, indicating that the positive charge has also been shared by the cyclopropyl ring. Thus the cyclopropyl ring in the sterically constrained systems delo-

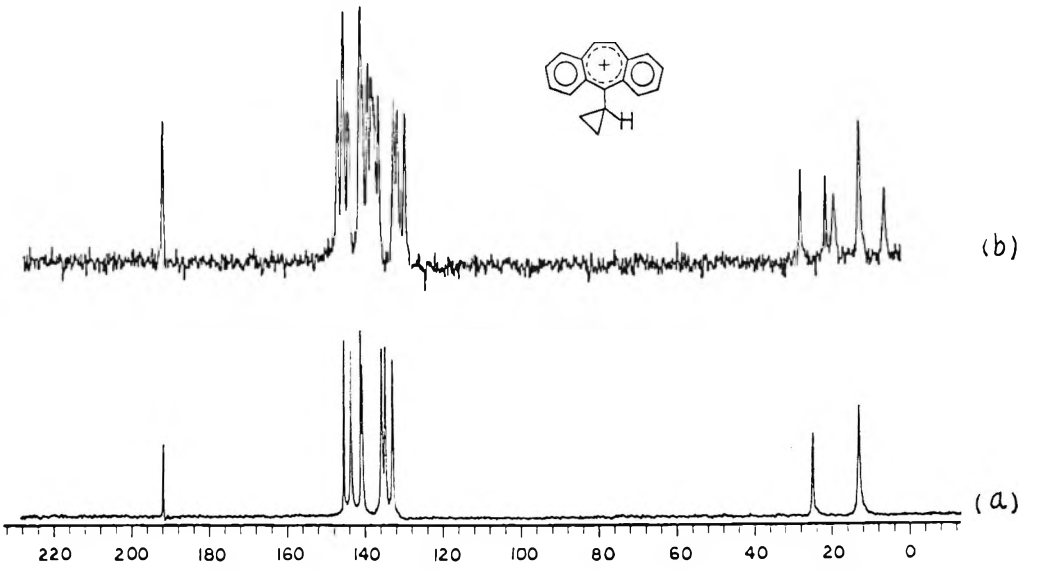
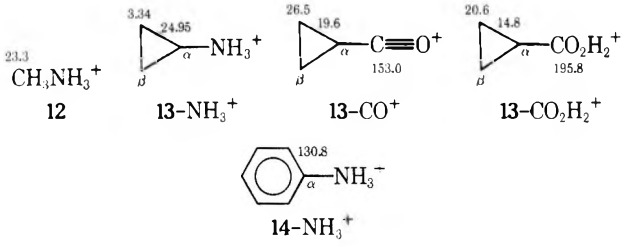


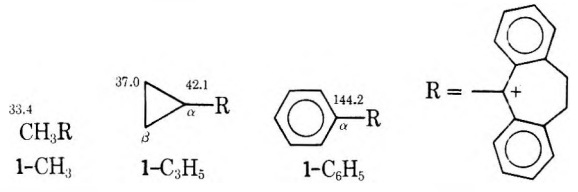
Figure 3. Carbon-13 NMR spectra (25.16 MHz) of the 5-cyclopropyl-5-dibenzotropylium ion (2-C_3H_5) in FSO_3H–SO_2ClF solution at −78°: (a) proton noise decoupled; (b) proton coupled.

calizes charge better than the phenyl group, probably also since the latter cannot achieve planarity for suitable overlap with the empty 2p orbital.

A neighboring positive center also could cause either shielding or deshielding effect on an attached cyclopropyl group. The effect on C_β seems to be particularly dependent on the nature of the substituent bearing positive charge. This is shown by comparing the ^{13}C NMR shifts for cyclopropanes bearing different positively charged ligands. C_β in the cyclopropylammonium ion ($\delta_{^{13}C}$ 3.34) is hardly deshielded, while C_α is deshielded.[12] On the other hand, C_β in



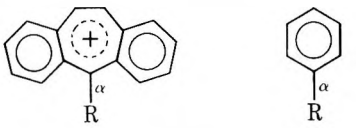
cyclopropylacylium ion becomes even more deshielded than C_α. The same trend is also found in protonated cyclopropanecarboxylic acid.[12] Apparently when the C–C bonds in cyclopropane are conjugatively able to share positive charge with a neighboring positively charged center, ring carbons are usually deshielded. This is the case in systems such as cyclopropylcarbinyl-type cations.[9,13] In contrast, C_α will experience mostly inductive deshielding effect from neighboring groups bearing positive charge, while C_β is hardly affected when resonance conjugation becomes unlikely. Table II shows that both C_α and C_β of the cyclopropyl ring in 1-C_3H_5 are deshielded. Clearly the dihydrodibenzotropylium moiety in 1-R causes deshielding of C_α in 1-C_3H_5 via mostly inductive effect, but also deshielding on C_β via a certain degree of conjugative effect. If only the inductive deshielding effect would operate, C_β in 1-C_3H_5 should not be deshielded to any great extent.



In the parent, secondary dihydrodibenzotropylium ion 1-H, ortho and para carbons (C_2, C_4, and C_{12}) show resonances deshielded from that of meta carbons (C_1, C_3). This is also in accordance with the ^1H NMR observations (Table I). Substituents at C_{12} (and C_{15}) cause a small deshielding effect. Proton and carbon-13 data, therefore, indicate that positive charge in the secondary ion is very evenly distributed among the ortho and para positions. When an *alkyl* substituent is introduced unto the carbenium center (C_5), the latter becomes deshielded. Carbon resonances of the rest of the molecule are, however, not much affected. When a phenyl group is introduced unto the carbenium ion center, carbon resonances in the dihydrodibenzotropylium moiety do not show significant changes, except C_5, which experiences a moderate deshielding (10 ppm) effect. Both ortho and para carbons in 1-C_6H_5 are experiencing the same degree of deshielding effect as found in 1-H. The deshielding effects upon substitution, directly reflected by the C_5 resonances, are small for phenyl substitution ($\Delta_2 \simeq$ 10 ppm) and larger for alkyl substitutions ($\Delta_2 >$ 22 ppm). The shielding effect at C_4 induced by alkyl substituents, as shown in Table II, is about 7–10 ppm (Δ_1) and practically zero in the case of phenyl substitution (which cannot conjugatively interact).

For the presently studied series of dihydrodibenzotropylium ions 1-R, ^{13}C NMR data reveal (Table III) that alkyl (or even aryl) substituents exert only minimal effect at the meta positions (C_1 and C_3). Such substitution, however, causes a shielding effect at the ortho (C_4) positions ranging from 6.9 ppm for methyl and 8.4 ppm for cyclopropyl to 10.4 ppm for ethyl, similar to γ substituent effects observed in aliphatic hydrocarbons.[14] These effects in the presently investigated dihydrodibenzotropylium ions apparently show the decreasing order ethyl > cyclopropyl > phenyl. The substituent effects observed for shielding the ortho positions in 1-R indicates the following order: ethyl > cyclopropyl > methyl > phenyl. The same trend is also found in the deshielding effect of the carbenium centers (Δ_2 values in Table II) with slight modification, i.e., methyl $\simeq$ cyclopropyl. The change in shifts of the ortho carbons or carbenium carbon upon substitution, especially by cyclopropyl group, cannot wholly be explained by substituent effects, since the cyclopropyl ring in 1-C_3H_5 also shares positive charge via σ–p conjugation. In addition, the deshielding effect at the carbenium center (α carbon) upon

Table III
Carbon-13 NMR Shifts in Methyl-, Ethyl-, Cyclopropyl-, and Phenyl-Substituted Dibenzotropylium Ions and Related Substituted Benzenes



2-R 14-R

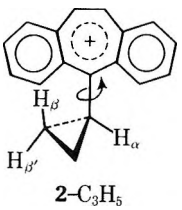
R	C_α^+	CH	CH_2	CH_3	C_α	CH	CH_2	CH_3
H	170.7				129.7			
CH_3	190.3			30.8	138.0			22.4
CH_2CH_3	193.7		37.2	21.2	145.1		29.3	16.8
C_3H_5	191.8	25.0	13.1		144.3	16.4	9.8	
C_6H_5	183.7				142.2			

phenyl substitution in 1-C_6H_5 (Δ_2 = 10.1 ppm) is very similar to that observed (12.5 ppm) between diphenyl- and triphenylcarbenium ions.[9]

Dibenzotropylium Ions. Several dibenzotropylium ions have been studied previously,[6] but no systematic NMR studies were carried out. We have now obtained detailed ^1H and ^{13}C NMR parameters for a series of dibenzotropylium ions. The parent, secondary dibenzotropylium ion (2-H) shows a more deshielded methine proton (δ 10.98) than that in its dihydro analog, 2-H (δ 9.82). The carbon shift for the carbenium center (C_5) in the former is, however, about 25 ppm less deshielded than that in the latter. This might be the result of a stronger ring current effect involved in the former seven-membered aromatic ring (tropylium)[15] system. This is also in accord with the fact that both methyl and ethyl groups are more deshielded in dibenzotropylium ions than those in their dihydro analogs.

When the C_5 position in 1-H is consecutively substituted by phenyl, methyl, ethyl, cyclopropyl, chloro, or hydroxy groups, the two equivalent olefinic protons (H_{10} and H_{11}) become less deshielded. Carbon shifts for the carbenium center (C_5) show shielding in the order of H > C_6H_5 > CH_3 (~OH) > C_3H_5 > CH_2CH_3 > Cl. The substituent effects in dibenzotropylium and dihydrodibenzotropylium ions are also generally in accord with this sequence. C_5 is more shielded in the secondary than in tertiary ions, and alkyl substituents cause a greater deshielding than aryl groups. The cyclopropyl group generally causes a similar deshielding effect as the methyl and ethyl groups.

Particularly interesting is the NMR spectrum of the cyclopropyl-substituted dibenzotropylium ion 2-C_3H_5. In its ^1H NMR spectrum (Figure 2b) the cyclopropyl ring protons do not show a typical deshielding pattern due to substantial charge delocalization into the three-membered ring. Normally, when positive charge is delocalized into the cyclopropane ring in cyclopropyl-substituted carbenium ions, both α and β protons are deshielded,[9,14] as seen in the case of 1-C_3H_5. The ^1H NMR chemical shift difference between H_α and H_β in 1-C_3H_5 is only 1.24 ppm. The difference in 2-C_3H_5 is much bigger (1.95 and 3.13 ppm, respectively, for the two different kinds of β protons). In addition, the dibenzotropylium framework in ion 2-C_3H_5 shows a similar charge-delocalization pattern as in its other analogs. This indicates that the cyclopropane ring bears a minimum amount of positive charge (i.e., minimum degree of charge delocalization). Apparently, the cyclopropane ring in 2-C_3H_5 does not significantly affect the aromatic nature of tropylium ion systems, i.e., the dibenzotropylium framework. Since two sets of cyclopropane protons are observed at the β position, having a chemical shift difference of 1.18 ppm, the cyclopropane ring is considered in ion 2-C_3H_5 to be perpendicular relative to the rest of the molecule. Models show that two of the hydrogens, H_β's, are closely located in the deshielding region of the benzene ring, while the two others, $H_{\beta'}$, are further away. A deshielding effect caused by ring current must therefore account for the slight difference in chemical shifts between these two types of hydrogens. Furthermore, restricted rotation around the C_5–C_α bond always should put the two H_β atoms into the deshielding region and the two $H_{\beta'}$ hydrogens away from it.



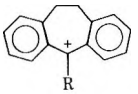
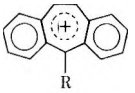
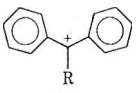
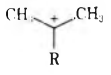
2-C_3H_5

The fact that the cyclopropane ring in 2-C_3H_5 does not delocalize positive charge to any substantial degree is also seen from the corresponding ^{13}C NMR parameters. Both the C_α and C_β carbons of the cyclopropane ring in 2-C_3H_5 are substantially less deshielded than those in 1-C_3H_5. We have previously reported several cyclopropyl-substituted carbocations[9,13] in which substantial charge delocalization takes place as indicated by the substantial deshielding of C_α and C_β in the cyclopropane rings. In certain cases, C_β even becomes more deshielded than C_α.[13] Considering these ^{13}C NMR parameters, ion 2-C_3H_5 can be considered as a further example of a cyclopropylcarbinyl cation in which the cyclopropane ring does not substantially delocalize charge. At the same time it must also be realized that the aromatic dibenzotropylium ion should be considerably less susceptible to substituent effects than its more localized dehydro analog.

In comparing the carbon shifts of the carbenium centers in dibenzotropylium ions and their dihydro analogs (Table II), one notices that the carbenium ion centers in the former are less deshielded than those in the latter. For example, the secondary, parent dibenzotropylium ion (2-H) shows a carbenium shift shielded by about 25 ppm from that in its dihydro analog, 1-H. The presence of the additional two π electrons in 2-R must allow retaining of a substantial degree of aromatic tropylium ion character so that positive charge becomes more delocalized into the seven-membered ring, making C_5's less deshielded. The aromatic nature of dibenzotropylium ions must resist any substantial delocalization which would substantially weaken the six π electron system. The cyclopropane ring can therefore not effectively compete with the tropylium ion systems in sharing (delocalizing) the positive charge.

One further notices that carbon chemical shift differences between the two quaternary carbons (C_{12} and C_{13}) in dibenzotropylium ions are much smaller than those in the dihydro analogs. This also can be accounted for as a consequence of the fact that the positive charge has been further spread out over the seven-membered tropylium ring in 2, in order to maintain six-π aromaticity. It is therefore of interest to compare dibenzotropylium ions with other aromatic six π electron systems. We have chosen the corresponding substituted benzenes as models for comparison. Table III summarizes the relevant ^{13}C NMR data for these two systems: the dibenzotropylium ions and related substituted benzenes 14. Carbon deshielding effects caused by substitution in 2-R exhibit the order ethyl > cyclopropyl > methyl > phenyl. A slightly different order is observed in 14: ethyl ≥ cyclopropyl ≥ phenyl > methyl. All carbon resonances in 2-R are substantially deshielded from the corre-

Table IV
Comparison of Carbenium Center Carbon-13 Shifts

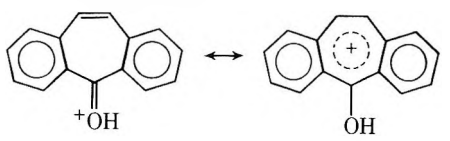
	 1-R		 2-R		 15-R		 16-R	
R	δ_{C^+}	Δ^a	δ_{C^+}	Δ	δ_{C^+}	Δ	δ_{C^+}	Δ
H	195.1	0.0	170.7	0.0	200.7	0.0	318.8	0.0
CH_3	218.4	(23.3)	190.3	(19.6)	229.3	(28.6)	329.4	(10.6)
C_3H_5	217.1	(22.0)	191.8	(21.1)	235.1	(34.4)	280.6	(−38.2)
C_6H_5	205.2	(10.1)	183.7	(13.0)	211.9	(11.2)	264.6	(−54.2)
OH	202.0	(6.9)	190.2	(19.5)	209.2	(8.5)	249.5	(−69.3)

$^a \Delta = \delta_{C_R^+} - \delta_{C_H^+}$.

sponding shifts in **14**-R. The dibenzotropylium ions, when substituted, can be considered as substituted six-π aromatic systems without substantial charge delocalization into the substituents. For example, the carbon shift difference between CH_2 and CH_3 in **2**-CH_2CH_3 is about 16 ppm, and that in ethylbenzene is 12.5 ppm. Apparently, the six-π aromatic systems in both dibenzotropylium ions and substituted benzenes produce a similar inductive deshielding effect toward substituents.

We have already suggested that the cyclopropyl group in **2**-C_3H_5 does not show significant charge delocalization, as in other cyclopropylcarbenium ions.[13] It thus might behave merely as a substituent experiencing inductive electronic effect from the adjacent electron-deficient center. This is indeed indicated when comparing cyclopropyl-substituted dibenzotropylium ion **2**-C_3H_5 and benzene **14**-C_3H_5.

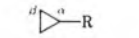
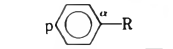
Comparison of Dibenzotropylium, Dihydrodibenzotropylium, and Diphenylcarbenium Ions. Although we cannot directly compare two series of ions having different steric environment, a comparison of substituent effects within a given series of closely related ions is reasonable. Table IV summarizes the ^{13}C NMR shifts for the carbenium centers in a series of related ions bearing hydrogen, methyl, cyclopropyl, and phenyl groups as substituents. For the three series of ions shown, one recognizes that a similar trend of substituent effects exists, i.e., carbenium centers in secondary ions are less deshielded than those of the phenyl-substituted tertiary ions, which in turn are less deshielded than those in alkyl- (or hydroxy-) substituted ions. When one makes comparison between secondary and tertiary ions within a given series, methyl substitution generally causes deshielding of the carbenium center (Δ's in Table IV) to a more or less similar degree as cyclopropyl, while phenyl substitution causes a smaller deshielding effect. The effect produced by hydroxy group is even smaller (Δ 7–9 ppm), with one exception, i.e., the 5-hydroxydibenzotropylium ion **2**-OH (Δ 19.5 ppm). The larger deshielding effect of the carbenium ion center in the latter might be due to the greater stability of the tropylium (or dibenzotropylium) moiety.[15] Structure such as **2**-OH should be more suitable to represent the ion.



2-OH

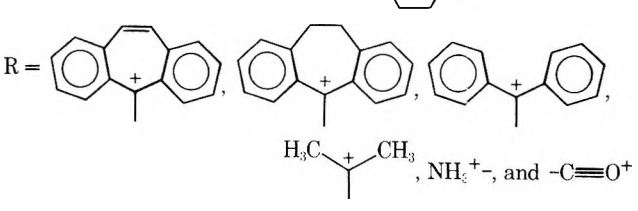
In our preceding paper[1] we have shown similar deshielding effects in a series of methyl-, cyclopropyl-, and phenyl-substituted allylic ions. Carbon resonances of carbenium centers are not only affected by the inductive deshielding

Table V
Comparison of C_α(and C_β) Carbon-13 Shifts in Substituted Methanes, Cyclopropanes, and Benzenes

					
R	C_α	C_α	C_β	C_α	C_p
1. Dihydrodibenzotropylium	33.4	42.1	37.0	144.2	136.8
2. Dibenzotropylium	30.8	25.0	13.1	145.8	131.4
3. Diphenylcarbenium	31.3	41.0	36.0	140.9	144.1
4. Dimethylcarbenium	48.5	56.8	53.5	140.1	156.0
5. Ammonium	23.3	24.95	3.34	130.8	130.8
6. Acylium	7.5	19.6	20.6	87.7	149.9
7. 3-Methylallyl	29.8	45.8	42.2	135.1	149.9

effects, but also by the resonance shielding effects of the substituents. A methyl substituent in presently studied systems causes similar shielding of carbenium centers; a phenyl substituent causes a smaller effect. In **1**-R and **2**-R the methyl substituents cause deshielding of the carbenium centers of about 20 ppm. A similar deshielding is observed for cyclopropyl substituents. Both methyl and cyclopropyl substituents, however, cause larger deshielding of carbenium centers (≥30 ppm) in diphenylcarbenium ions **15**-R (Table IV). Phenyl substituents cause about 12 ppm deshielding effects in all three series of ions.

The present NMR spectroscopic data no doubt indicate that positive charge has mainly been delocalized into the dibenzo rings in **1**-R and **2**-R. For comparison and to obtain further information, attention should be also given to C_α (and C_β) carbon resonances in the following series of substituted methanes, cyclopropanes, and benzenes. Table



V summarizes carbon-13 shifts for comparable carbon atoms in these compounds.

Neighboring charged groups can produce either shielding or deshielding effects on C_α (and/or C_β). Substituents

carrying positive charge generally cause deshielding of carbon atoms to which they are directly attached. Both C_α and C_β in substituted cyclopropanes, however, are also deshielded, except in the cyclopropylammonium ion, in which C_β is hardly affected. The $-C\equiv O^+$ substituent causes an unusual shielding effect on C_α in all three series. The particularly interesting ketene-type resonance stabilization in acylium ions has recently been noted.[17]

$$R-\overset{+}{C}\equiv O \leftrightarrow {}^{+}R=C=O$$

The deshielding on C_β in substituted cyclopropanes is generally observed in cases where the cyclopropyl C–C bonds can share positive charge with neighboring electron-deficient centers via a certain degree of conjugation.[13] Similar deshielding is not observed in the cyclopropylammonium ion, where only inductive effect operates.

Methyl, cyclopropyl, and phenyl groups are clearly three different types of neighboring groups for charge delocalization in carbocations. The effectiveness of the π-electron system of the phenyl group in delocalizing neighboring electron-deficient centers (i.e., carbenium ions) is well known.[3,4] σ electrons of saturated bonds (i.e., C–H in methyl and C–C in cyclopropyl groups) can, however, also delocalize neighboring positive charge to various degrees. The nucleophilicity of C–H bonds is known to be weaker than that of C–C bonds.[18] We have recently shown that neighboring cyclopropyl groups can delocalize charge to substantially differing degree depending on the internal strain involved in the cyclopropyl ring.[13] Cyclopropyl groups which do not possess other internal strain than that initially present in the three-membered ring delocalize charge to a lesser degree than do more strained systems. For example, the C_β shifts for cyclopropyl carbons in the methylcyclopropylcarbenium ion[13a] and the 3-methyl-3-nortricyclyl[13a] and the 2-methyl-8,9-dehydro-2-adamantyl[13b] cations are δ ^{13}C 53.5, 83.7, and 100.7, respectively, while carbon shifts for C_α are of comparable magnitude, i.e., δ ^{13}C 56.8, 67.5, and 71.8, respectively. Carbenium ions having neighboring cyclopropyl groups apparently show varied carbon resonances of the carbenium centers depending on how strained the C–C bonds are in the cyclopropyl group and the substituent effect caused by the cyclopropyl group.

Methyl, cyclopropyl, and phenyl substituents, in the presently studied systems, generally cause deshielding of the carbenium ion centers (C_5's) and a slight shielding at ortho positions (C_4 and C_6) of the dibenzo moiety. The methyl group causes a net deshielding of about 20 ppm of the carbenium centers in **1**-R and **2**-R. Similar replacement of hydrogen by methyl causes an about 30 and 10 ppm deshielding at carbenium centers in the diphenyl- and dimethylcarbenium ions, respectively. Replacement of hydrogen in secondary diphenylcarbenium type ions (**1**-R, **2**-R, and **15**-R) by cyclopropyl or phenyl groups causes an opposite effect (i.e., deshielding) than that observed at the carbenium ion centers of dimethylcarbenium ions (Table IV). It is apparent that cyclopropyl and phenyl substituents not only cause inductive deshielding but also conjugative shielding effects at neighboring carbenium ion centers depending upon the steric crowding of the system.[19]

It is difficult to divide the total effect of substituents at carbenium centers into the corresponding inductive and conjugative components, particularly when one attempts to directly compare cyclopropyl and phenyl groups. A reversed trend is observed in diphenylcarbenium type ions and dimethylcarbenium ions, indicating that steric inhibition of conjugation in the former system renders the cyclopropyl and phenyl groups unable to share positive charge as fully as in the latter case, where no severe steric crowding exists. These effects are more significant for phenyl than for cyclopropyl substituents. When conjugation between the phenyl group and the empty 2p orbital is possible, positive charge is nearly equally distributed among the ortho and para positions of the phenyl ring. However, ortho shifts are also easily affected by steric effects of substituents.[14] Para shifts, which are not similarily affected, have been utilized as a reliable indicator for the extent of charge delocalization into the phenyl ring in phenylcarbenium ions.[14,16] For example, the para shift in the dimethylphenylcarbenium ion is substantially deshielded (δ ^{13}C 156, Table V), while the corresponding carbenium ion center is shielded by about 54 ppm (Table IV) when the methine hydrogen in the dimethylcarbenium ion is replaced by a phenyl group. In cases where conjugation is not possible, the para shift of the phenyl ring is much less deshielded. Examples are found in the protonated aniline and the 5-phenyl-5-dibenzotropylium ion **2**-C_6H_5. The more shielded para shifts of the phenyl-substituted carbenium ions seems to indicate that less positive charge has been delocalized into the phenyl ring.

It is interesting to notice that para carbon shifts in phenyl-substituted dihydrodibenzo- and dibenzotropylium ions (**1**-C_6H_5 and **2**-C_6H_5, respectively), although are both shielded, differ by about 5 ppm. The para shift (δ ^{13}C 131.4) in the latter approaches that in the protonated aniline (δ ^{13}C 130.8). It seems to indicate that the phenyl group in **1**-C_6H_5 still experiences a limited degree of conjugation, while in **2**-C_6H_5 it does not. Although the replacement of hydrogen in **1**-H by a phenyl group does not change much the carbon shifts of the dihydrodibenzotropylium moiety, the deshielding of the carbenium center (10 ppm) caused by phenyl substitution might be a net result of the combined inductive deshielding and conjugative shielding effects. Comparison of the para shifts of the phenyl substituents in **1**-C_6H_5 and **15**-C_6H_5 (Table V) shows that the phenyl ring in the former experiences more steric repulsion than that in the latter. Carbon shifts for C_α and C_β of the cyclopropyl rings in **1**-C_3H_5 and **15**-C_3H_5, respectively, are of equal magnitude, indicating that the cyclopropyl ring, being smaller in size than the phenyl group, can share positive charge to a relatively similar degree (even if not necessarily in the most favorable bisected in-plane configuration) in these two ions while the phenyl groups cannot. Cyclopropyl rings in **1**-C_3H_5 and **15**-C_3H_5 experience, however, less conjugative deshielding from neighboring electron-deficient centers than does that in **16**-C_3H_5 (dimethylcyclopropylcarbenium ion) owing to a difference in charge demand. When the conjugation of cyclopropyl groups is further reduced (or limited) as in the cases of **2**-C_3H_5 and cyclopropylammonium ion (**13**-NH_3^+), both C_α and C_β of the cyclopropyl ring are becoming much less deshielded. As para shifts of adjacent phenyl rings in carbenium ion have been utilized as a measurement of charge delocalization into the phenyl ring in phenylcarbenium ions, C_β shifts of cyclopropyl rings can also be used as an indicator of charge delocalization into the cyclopropyl ring in cyclopropylcarbenium ions, although obviously our present understanding of charge effects on the overall chemical shifts in cyclopropyl rings is still inadequate.

Experimental Section

Materials. Secondary alcohols (**3**-H and **4**-H) and ketones (**5** and **6**) used in the present study were obtained from the Aldrich Chemical Co., and were used without further purification. The tertiary alcohols (**3**-R and **4**-R) were prepared by the reaction of the appropriate Grignard reagent with the related ketones **5** and **6**, respectively, in the usual manner.[6,8,16] The dichloride **7** was prepared according to the reported procedure.[20]

Preparation of Carbocations. Freshly distilled FSO_3H was dissolved in an appropriate amount of SO_2ClF as solvent at Dry Ice–acetone temperature (ca. −78°). To this was slowly added with vigorous stirring a cold solution of appropriate precursor dissolved in SO_2ClF, to give an approximately 15–20% solution of the ion. Except for the protonated ketones **1**-OH and **2**-OH, both secondary and tertiary dihydrodibenzotropylium and dibenzotropylium ions generally gave deep-red colored solutions.

Proton and Carbon-13 NMR Spectroscopy. Both proton and carbon-13 NMR spectra were obtained as previously reported.[21]

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Registry No.—**1**-H, 55090-25-0; **1**-CH_3, 55090-26-1; **1**-CH_2CH_3, 55090-27-2; **1**-C_3H_5, 55124-05-5; **1**-C_6H_5, 30880-08-1; **1**-OH, 55090-28-3; **2**-H, 55090-18-1; **2**-CH_3, 55090-19-2; **2**-CH_2CH_3, 55090-20-5; **2**-C_3H_5, 55090-21-6; **2**-C_6H_5, 55090-22-7; **2**-OH, 55090-23-8; **2**-Cl, 55090-24-9; **3**-H, 10354-00-4; **3** (R = CH_3), 10354-00-4; **3** (R = CH_2CH_3), 18259-45-5; **3** (R = C_3H_5), 55124-06-6; **3** (R = C_6H_5), 55090-29-4; **3** (R = OH), 55090-30-7; **4**-H, 1210-34-0; **4** (R = CH_3), 15323-25-8; **4** (R = CH_2CH_3), 55090-31-8; **4** (R = C_3H_5), 3241-97-2; **4** (R = C_6H_5), 55090-32-9; **4** (R = OH), 55090-33-0; **7**, 13099-45-1; FSO_3H, 7789-21-1.

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Delocalized Carbanions. V.[1] A Tetraanion from the Lithium Reduction of *cis,cis*-1,2,3,4-Tetraphenylbutadiene

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The reduction of *cis,cis*-1,2,3,4-tetraphenylbutadiene with lithium in tetrahydrofuran yields 1,2,3,4-tetralithio-1,2,3,4-tetraphenylbutane, which upon hydrolysis with D_2O gives *dl*- and *meso*-1,2,3,4-tetradeuterio-1,2,3,4-tetraphenylbutane in yields up to 86%. The progress of the reduction was followed through the radical anion and dianion stages to the tetraanion by EPR and uv–visible spectroscopy. No trianion radical intermediate was detected. The tetraanion is apparently stable for weeks in the presence of excess lithium, but gradually cyclizes to give 3-benzyl-1,2,-diphenylindene upon hydrolysis. This amazing stability is attributed to a cyclic reaction scheme which regenerates tetraanion from partially protonated species. In ether, reduction with Li for 4 hr, Na for 24 hr, or K for 50 hr yielded *cis*- and *trans*-1,2,3,4-tetraphenyl-2-butene in 4:1, 5:1, and 1.4:1 ratios, respectively. Reduction for 24 hr with Li or Na for 20 days yielded 1,4-dihydro-1,2,3-triphenylnaphthalene. Reduction for 4 days with Li yielded 9,14-dihydro-9-phenyldibenz[*a*,*c*]anthracene.

Brook, Tai, and Gilman[2] have reported the reduction of *cis,cis*-1,2,3,4-tetraphenylbutadiene (**1**) with lithium metal, followed be ethanolysis to yield *dl*- and *meso*-1,2,3,4-tetraphenylbutanes.[3] The intriguing possibility of a 1,2,3,4-tetralithio-1,2,3,4-tetraphenylbutane (**2**) intermediate in this reaction prompted the present investigation. Although West and coworkers[4] have prepared several polylithium derivatives of acetylenes containing four or more lithium atoms, the tetralithium compound (**2**) differs from these compounds in that each carbon–lithium bond is benzylic in nature, and may give rise to delocalized carbon–metal bonding. Since delocalization greatly affects the physical and chemical properties of organometallic compounds, the preparation of **2** and the investigation of its properties were of considerable interest.

Our case for the intermediacy of **2** in the reduction of **1** rests primarily upon obtaining *dl*- and *meso*-1,2,3,4-tetradeuterio-1,2,3,4-tetraphenylbutanes (**3a**-d_4 and **3b**-d_4) in up to 86% yield when **1** is reduced with lithium in tetrahydrofuran (THF) and hydrolyzed with D_2O. In addition to the detection of **2** and the investigation of the reaction sequence leading to it, preparatively useful reductions of **1** with lithium, sodium, and potassium are here reported.

Reduction of *cis,cis*-1,2,3,4-Tetraphenylbutadiene (1) with Li in THF. When a solution of **1** in THF was treated with a large excess of lithium under argon, reduc-

Table I
Reaction Products vs. Time

Run	Reaction time, hr	Butadienes	Butanes[a]		Butanes[b]	
			Cis (4a)	Trans (4b)	*dl* (3a) and meso (3b)	Indene (5)
1	1.3	3	39	7	49	
	4.0		21	9	58	
	7.0		19	9	61	
	22		8	2	74	5
	46		20	7	58	5
	78		19	7	54	10
	123		32		5	35
2	0.083	95	5			
	0.50	7	93			
	1.67		17		83	
	6.0		13		87	
3[c]	4.25		5		95	
	22		7		93	1
	168		8		76	15
	264		16		67	17
	432		25		56	19

[a] Individual butenes are estimated from the NMR spectra of the crude reduction products. [b] NMR spectra of the crude products gave an invariant 1.2:1 rough estimate of the *dl* (**3a**) to meso (**3b**) isomer ratio. [c] Hydrolyzed with D_2O. Yields are percentages of the volatile material only.

tion occurred with accompanying color changes from colorless to bluish-purple, then to a dark brown-black with the precipitation of a black solid. After removal of the excess lithium, hydrolysis yielded *cis*- (**4a**)[5] and *trans*-1,2,3,4-tetraphenyl-2-butene (**4b**), *dl*- (**3a**) and *meso*-1,2,3,4-tetraphenylbutane[3] (**3b**), 3-benzyl-1,2-diphenylindene[6] (**5**), and hydrogen in varying amounts depending upon the reaction time. The general classes of compounds (butenes, butanes, and indene) were separated and quantified by GLC, but separation of the configurational isomers within the groups was not accomplished by this method. Fortunately, the *cis*- and *trans*-2-butenes and *dl* and meso butanes were easily separated by fractional crystallization. The products separated by GLC and crystallization were identified by comparing their retention times, spectroscopic properties, and melting points with those of authentic samples. In addition to the products listed, some of the GLC analyses indicated the presence of two additional unidentified products which did not amount to more than 8% of the total products.

Typical product ratios in the reduction are shown as a function of time in Table I. In runs 1 and 2 the yields are actual yields obtained by GLC analysis with an internal standard, whereas in run 3 the yields are reported as percentages of the volatile fraction of the product only. In other reductions (run 1 and others not reported), it was ascertained that even with very long reaction times, the volatile material accounted for 70–90% of the product, so absolute yields do not differ greatly from the reported yields. The butadiene recovered in run 2 was a mixture of 1 and the trans,trans isomer.[7] Estimation of the yields of cis and trans butenes **4a** and **4b** was accomplished using a combination of GLC analysis and NMR integration to estimate isomer ratios. The same technique was more difficult to apply to the butane isomers **3a** and **3b** because the aliphatic proton signals in these compounds overlap; however, the ratio of *dl* (**3a**) and meso (**3b**) isomers appeared to remain invariant at about 1.2:1. The poor reproducibility of the yields with time probably results from agitation and metal surface differences in the heterogeneous reactions.

When reduction times exceeded 12 hr, hydrogen was evolved upon hydrolysis. A 24-hr reduction mixture, for example, liberated 14 ml of gas when hydrolyzed with D_2O (after removal of excess lithium), and titration of the hydrolyzed mixture with acid indicated that 4.38 g-atoms of lithium had reacted per mole of starting diene. Mass spectrometric analysis of the gas evolved showed it to be 2% H_2, 97% HD, and 1% D_2. The preponderance of HD indicates that lithium hydride is the source of the gas upon hydrolysis.

Table II
Deuterium Analyses[a] of the Butane Fractions from the D_2O-Hydrolyzed Reduction (Run 3)

Time, hr	d_1	d_2	d_3	d_4
4.25	1	2	6	90
22.0	0	2	9	88
168	1	5	19	74
264	0	16	61	24
432	1	44	41	14

[a] These results are accurate to approximately ±3%.

Having shown that approximately 4 g-atoms of lithium was consumed during the reduction of **1**, the case for the production of a tetraanion rests upon establishing that four deuterium atoms were incorporated into the hydrolyzed product. In run 3 (Table I), aliquots of the reduction mixture were hydrolyzed with D_2O and the butane fractions were separated by GLC and analyzed for deuterium content by mass spectrometry,[8] the results being shown in Table II. The intervention of a tetralithio species was inferred from the high (95%) yield of 1,2,3,4-tetraphenylbutanes in the 4.25-hr reduction mixture and the fact that 90% of it was tetradeuterated (**3a**-d_4 and **3b**-d_4). Although alternative mechanisms for the production of tetradeuteriobutanes may be envisioned, these involve either abstraction of protons or hydrogen atoms from the solvent or disproportionation of odd-electron species, neither of which is consistent with the 86% overall yield of tetradeuteriobutanes. Since **3b** does not undergo H–D exchange when treated with LiOD in D_2O, the only reasonable source of tetradeuteriobutanes would seem to be the deuterolysis of a tetralithio species. It is not clear at this point, however, whether 1,2,3,4-tetralithio-1,2,3,4-tetraphenylbutane (**2**) is actually the intermediate, since migration of anionic sites

Table III
Relative Uv, Visible, and EPR Absorptions

Reaction time, hr	650 nm	550 nm	425 nm[a]	305 nm	EPR
0.17	1.0	2.0	1.0	50	Strong
2.0	0.058[b]	*c*	1.0[d]	*e*	Medium
4.0	0.0	0.0	1.0	*e*	Weak
20.0	0.0	0.0	1.0	*e*	Very weak
20.0[f]	1.6	2.8	1.0	1.0	Strong

[a] There is a 340-nm shoulder on each of these peaks. [b] λ_{max} was 685 nm. [c] The 550-nm peak was masked by the 425-nm absorption and appeared as a slight shoulder on the tail of this peak. [d] λ_{max} was 435 nm. [e] A minimum between the 425-nm band and end absorption occurs at 265 nm. The intensity of this minimum increased from 0.2 at 2.0 hr to 0.5 at 4.0 hr, and then remained at 0.5 in the 20.0-hr spectrum. [f] With 3 molar equiv of *cis,cis*-1,2,3,4-tetraphenylbutadiene added.

within a molecule are not uncommon. Similar analysis of the butene fraction of the product (**4a**-d_2 and **4b**-d_2) showed it to be almost exclusively dideuterated, indicating that its precursor is indeed the dianion of **1**.

Evidence for the 1,2,3,4 disposition of anionic sites was obtained from the NMR spectra of the tetradeuteriobutanes. The *dl* (**3a**-d_4) and meso (**3b**-d_4) butane isomers[9] from the same 4.25-hr reduction were separated by fractional crystallization and examined by NMR spectroscopy. The *dl* isomer (**3a**-d_4) showed two broad (3-Hz half-width) singlets from the aliphatic hydrogens at δ 2.83 and 3.12 ppm and a complex multiplet at δ 6.65–7.2 ppm from the aromatic hydrogens. The meso isomer **3b**-d_4 showed broad (3.5 Hz) singlets at δ 2.53 and 2.76 ppm and a complex multiplet at δ 6.5–7.3 ppm. Integration of the aromatic and aliphatic proton signals in both *dl* (**3a**-d_4) and meso (**3b**-d_4) isomers gave the proper 10:1 ratio, indicating that no ring deuteration occurred. The NMR spectra show conclusively that the products were actually the 1,2,3,4-tetradeuterio-1,2,3,4-tetraphenylbutanes **3a**-d_4 and **3b**-d_4. In order to explain the 1:1 double singlet nature of the aliphatic proton spectra, it would be useful to first consider what the spectrum of a 1,2,3,4-tetraphenylbutane-2,3-d_2 ($PhCH_2$-CDPhCDPhCH_2Ph) would look like. Since the 2 and 3 carbons are chiral, the methylene protons would be magnetically nonequivalent and would give rise to an AB quartet. If we now randomly substitute deuterium for one of the A or B hydrogens in each methylene, J_{AB} would not be observed and two singlets are expected, exactly as found in the spectra of **3a**-d_4 and **3b**-d_4. The singlets are broadened owing to coupling with deuterium. If the hydrogens were 1,3 to each other, a similar argument would predict three peaks, two peaks of ½ proton intensity each for H-1 and a singlet of unit intensity for H-3. A 1,2 and 1,1 disposition of the hydrogens is eliminated by the absence of coupling. Thus, one infers from the 1,2,3,4 deuterium positions in the product that the anionic sites had a similar disposition in **2**.

The progress of the reduction was also followed qualitatively by uv–visible and EPR spectroscopy, with the results being tabulated in Table III. The intensities of the absorptions in the electronic spectrum are presented relative to the intensity of the dianion–tetraanion band at 425 nm, which is arbitrarily assigned a value of 1.0. Doran and Waack[7] reported absorptions at 585 and 435 nm for the tetraphenylbutadiene radical anion and dianion, respectively. We assign the two bands at 550 and 650 nm (intensity ratio about 2:1) to the radical anion because they rose and then fell proportionately during the early phase of the reaction as expected of the radical anion spectrum. The band at approximately 305 nm is attributed to tetraphenylbutadienes.[7] It was disturbing not to find a separate band directly attributable to the tetraanion **2**. A small red shift was observed between the 2.0-hr sample (435 nm, in agreement with the data of Doran and Waack[7] for the dianion) and those with longer reduction times (425 nm). This is in the expected direction since there is less conjugation in the tetraanion than the dianion, but the shift is close to the limit of detectability because of the extreme broadness of the 425-nm band. Another indication of change, however, was an increase in the minimum at 265 nm between the 425-nm band and end absorption from a relative intensity of 0.2 to 0.5.

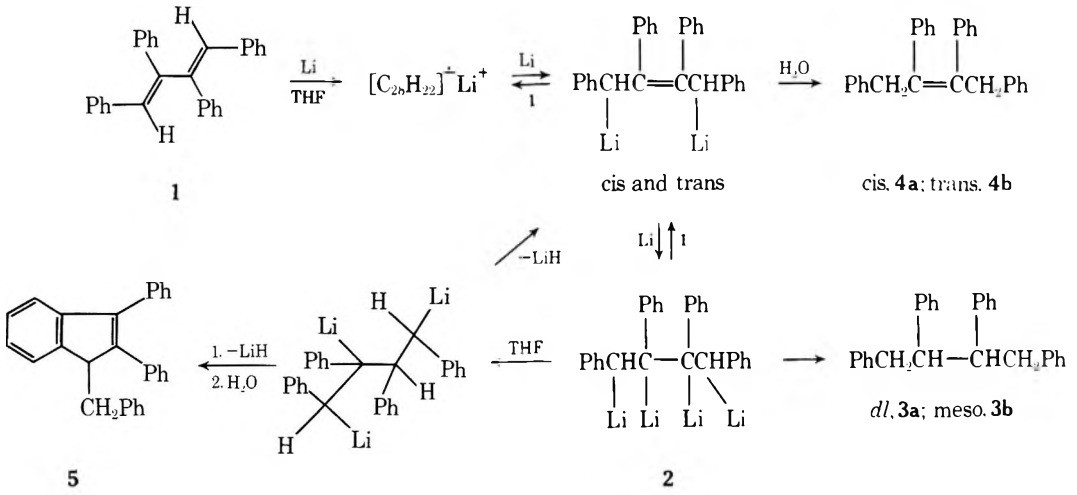
The EPR spectrum consisted of a single line about 7 G in width[7] which was most intense in the 0.17-hr sample, and whose intensity decreased progressively with longer reaction times. The progressive decay of the EPR signal after the radical anion stage suggests that the trianion radical is unstable and either disproportionates or is rapidly reduced to tetraanion. Reversibility of the reduction process was demonstrated by adding 3 molar equiv of tetraphenylbutadiene (**1**) to the reaction mixture after reduction for 20 hr, whereupon the EPR signal returned and the uv–visible spectrum showed the same bands (although in different intensities) as the 0.17-hr sample. This ready reversibility of the reduction illustrates the strong electron-donating property of the tetraanion.

The stability of **2** in THF was surprising. Even after 168 hr at room temperature an overall yield of 56% of tetradeuteriobutanes was obtained (Tables I and II), which implies that a similar amount of tetraanion survived the extended reaction time. In comparison, Gillman and McNinch[10] found the initial half-life of benzyllithium in THF to be approximately 5 hr, although the long-term decomposition rate decreased to 0.44%/hr. Thus, it appears as though **2** has roughly the same, or perhaps even greater, stability in THF than benzyllithium. Recall, however, that lithium hydride was one of the products in the reductions with long reaction times. The apparent stability of **2** and the production of lithium hydride may both be explained by a cyclic process in which **2** is regenerated from its partially protonated analogs by splitting out LiH and reverting back to dianion as shown in Scheme I. Evidence for this lies in the fact that LiH is formed in reaction mixture even when the only organic products are butenes and butanes.

Another source of lithium hydride in the system is ring closure to **5** under long reaction times. Although the precursor of **5** is not known, its appearance so late in the reduction scheme suggests that it may not be the tetraanion. Perhaps a more likely candidate would be the trianion formed upon monoprotonating **2** at the more basic 2 position. This would preclude delocalization of charge into the 2-phenyl ring and make it more susceptible to nucleophilic aromatic substitution. A suggested reduction scheme which is in accord with the experimental data is presented in Scheme I.

Variation of Reducing Metal and Solvent. A cursory investigation of the effects of cation solvation on the reduction of **1** was carried out by varying the solvent and reducing metal. When the reduction of **1** is carried out with sodium in THF, very little butane is obtained. Treatment of the diene **1** with excess sodium for 18 hr yielded 37% butadienes, 62% butenes, and only 1% butanes (identified by GLC retention times). Thus, it is apparent that the tetraanion forms far less readily when sodium is the reducing agent, and may not form at all. The small amount of butane formed could have arisen by electron transfer from the

Scheme I



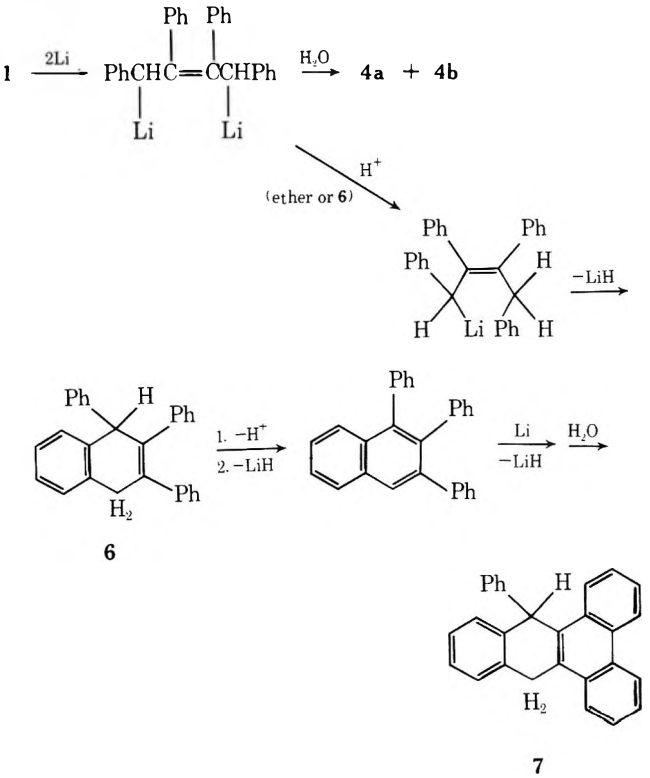
dianion to tetraphenylbutene during hydrolysis. An analogous reaction was reported by Levin, Jogur-Grodzinski, and Szwarc,[11] who obtained bibenzyl from the methanolysis of the diphenylacetylene dianion. Alternatively, the butane could result from protonation of the dianion by THF, followed by further reduction. The greater reducing ability of lithium compared to sodium is undoubtedly due to the greater energy of solvation of the organolithium compounds in THF.

In ether the reduction of **1** with Li for 4 hr, with Na for 24 hr, or with K for 50 hr yields *cis*- and *trans*-1,2,3,4-tetraphenyl-2-butene (**4a** and **4b**, respectively). Apparently only the lower melting (78°) isomer has been described in the literature,[5] and no assignment of configuration is made. We tentatively assign the cis geometry to the 78° melting isomer because it is thermodynamically less stable than the 194° isomer (equilibrium ratio of the 194° isomer and the 78° isomer is 1.93:1), and because the phenyl protons of the 2- and 3-phenyl rings appear as singlets in the NMR spectrum similar to those of *cis*-stilbene, whereas the pattern from the corresponding protons in the 194° isomer are a complex multiplet similar to *trans*-stilbene. Unfortunately, attempts to confirm this assignment by stereospecific reduction to the known *dl* and meso butanes (**3a** and **3b**) by hydrogenation and hydroboration were unsuccessful. The ratio of cis:trans isomers of **4** obtained in the reduction of **1** appeared to be metal dependent. Typical ratios are: Li, from 4:1 to 2:1, with the higher ratio being obtained with shorter reduction times; Na, 5:1, K, 1.4:1. Hydrolysis of the reduction mixtures with D_2O yielded **4a**-d_2 and **4b**-d_2 as expected from a dianion intermediate.

When the reductions of **1** were carried out with lithium in ether for 24 hr, 1,4-dihydro-1,2,3-triphenylnaphthalene[12] (**6**) was obtained in addition to the butenes. **6** was also obtained in better yield by treating **1** in ether with excess sodium for 20 days, followed by hydrolysis. When **1** was treated with lithium metal in ether for 4 days, further cyclization occurred, yielding nearly pure 9,14-dihydro-9-phenyldibenz[*a*,*c*]anthracene (**7**) upon hydrolysis. The structure of the product was confirmed by dehydrogenation to 9-phenyldibenz[*a*,*c*]anthracene.[12]

It is interesting that the first ring closure in ether yields a six-membered ring, whereas in THF a five-membered ring was obtained. In both cases, the direction of ring closure may be determined by the position of monoprotonation of the polyanions. Earlier we mentioned that monoprotonation of the tetraanion at the more basic secondary site could direct ring closure to the phenyl ring attached to the same carbon. In a similar manner, protonation of the dianion might be expected to occur at the 1 position, yielding the allylic monoanion in which the 1-phenyl is now most susceptible to nucleophilic aromatic substitution. The source of the proton may be solvent, or the cyclization product **6**. A suggested reduction scheme consistent with the products obtained is presented in Scheme II.

Scheme II



Experimental Section

Melting points are uncorrected. The nuclear magnetic resonance spectra were recorded on either Varian A-60 or HA-100 spectrometers. The ultraviolet–visible spectra were obtained using a Cary 14 spectrophotometer, and the electron paramagnetic resonance spectra were recorded using 100-kHz modulation on a Varian V-4560 spectrometer equipped with a 12-in. magnet.

Reduction of 1,2,3,4-Tetraphenylbutadiene (1) with Lithium in Tetrahydrofuran (THF). The preparative reactions were carried out under a positive pressure argon atmosphere. The THF

solvent used was reagent grade dried over KOH pellets and freshly distilled from the radical anion of anthracene before each experiment. In a typical reduction, 3.0 g (8.4 mol) of **1** in 50 ml of THF was stirred at 22° with 0.07 g of Li metal cut into four pieces 2 × 4 × 4 mm. Periodically samples of the solution were withdrawn by syringe and run into degassed H_2O or D_2O. Each sample was extracted with CH_2Cl_2, dried over Na_2SO_4, and evaporated. The samples were analyzed by NMR and GLC at 265° using an F & M Model 500 chromatograph with a 2-ft column packed with Apiezon L on Chromosorb P. The GLC peaks were identified by trapping the exiting materials in capillaries and running their ir and mass spectra. These were compared with the retention times and spectra of authentic samples.

In run 3 of Table I, the tetradeuterated *dl* (mp 82–85°, lit.[3] mp 89–90° undeuterated) and *meso*-1,2,3,4-tetraphenylbutane-d_4 (mp 179–180°, lit.[3] mp 183–185° undeuterated) from the 4.25-hr reduction sample were separated by fractional crystallization from ethanol.

The reductions in which the uv–visible and EPR spectra were monitored were carried out under vacuum in a sealed glass system having a 1.0-mm absorption cell and an EPR sample tube attached. In the run leading to the data in Table III, 0.025 g of **1** in 8.0 ml of THF was treated with a 1 × 5 × 10 mm piece of lithium in a reaction compartment. Periodically the solution was decanted from the metal into an adjacent compartment from which it was transferred to either the absorption or EPR cell to record its spectra. For the uv–visible spectra the samples had to be diluted considerably. After the solution had contacted the metal for 20 hr it was decanted into the adjacent compartment, 0.075 g of **1** was added via a break-seal tube, and the spectra were again recorded. The solution was then allowed to react with the metal again for another 18 hr, after which the metal was removed and H_2O was added via another break-seal tube. GLC analysis of the product showed it to consist of 83% tetraphenylbutanes and 17% tetraphenylbutenes.

Attempted H–D Exchange in *meso*-1,2,3,4-Tetraphenylbutane (3b). A 26-mg sample of **3b** in 2 ml of THF was stirred with 4 ml of 1.2 *M* LiOD in D_2O for 1.5 hr at 22°, then heated on a steam bath for 5 min. The recovered **3b** showed no detectible H–D exchange when analyzed by mass spectrometry.

Preparation of *cis*- (4a) and *trans*-1,2,3,4-Tetraphenylbutene (4b). Reductions of **1** with Li in ether for 4 hr, with Na for 24 hr, and with K for 50 hr were carried out using about a threefold excess of metal. The reactions were hydrolyzed by removing the solution from the metal via syringe and introducing it into degassed H_2O. Extraction with CH_2Cl_2, drying over Na_2SO_4, and evaporation yielded crude products which were analyzed by NMR for the relative amounts of high- and low-melting 1,2,3,4-tetraphenyl-2-butenes. The isomers were separated by fractional crystallization from ethanol.

Isomer A, mp 194–195°. Anal. Calcd for $C_{28}H_{24}$: C, 93.29; H, 6.71. Found: C, 93.05; H, 6.83. NMR ($DCCl_3$) δ 3.60 (s, 4), 6.9–7.4 ppm (m, 20).

Isomer B, mp 77–78° (lit.[5] mp 80°). Anal. Found: C, 93.11; H, 6.71. NMR ($DCCl_3$) δ 4.03 (s, 4), 7.03 (s, 10), 7.25 (s, 10).

Equilibration of *cis*- and *trans*-1,2,3,4-Tetraphenyl-2-butene. In separate experiments, isomers A and B were heated at 280° in an evacuated sealed tube for 17 hr. NMR analysis of the product in both cases yielded a ratio A:B of 1.93:1.

Preparation of 1,4-Dihydro-1,2,3-triphenylnaphthalene (6). The title compound was the predominant product along with butenes **4a** and **4b** when **1** was reduced with Li in ether for 24 hr. The products were readily separated by fractional crystallization from CH_2Cl_2–ethanol. From 2.0 g of **1** was obtained 0.5 g of pure **6**, mp 168–169.5° (lit.[12] mp 165°).

6 was also obtained when 3.0 g of **1** was treated with excess Na in ether for 20 days, followed by hydrolysis. Crystallization from CH_2Cl_2–ethanol yielded 2.3 g, mp 153–161°. Two more recrystallizations from the same solvent gave 1.3 g of **6**, mp 168–169.5°.

Preparation of 9,14-Dihydro-9-phenyldibenz[*a,c*]anthracene (7). The reduction of **1** with excess Li in ether for 4 days followed by hydrolysis, extraction with CH_2Cl_2, and evaporation of the solvent yielded crude **7**. The NMR spectrum of this crude product showed no detectable impurities. Recrystallization from CH_2Cl_2–ethanol yielded **7** melting at 192–194° (lit.[12] mp 192°).

Dehydrogenation of 7. The method of Bergmann and Zwecker[12] was used. A mixture of 0.40 g of **7** and 0.40 g of Se was heated for 21 hr at 290–320°. The crude product was extracted with $CHCl_3$ and decolorized with Norit, ethanol was added, and the solution was concentrated until brown crystals began to form. Cooling the solution yielded 0.120 g of 9-phenyldibenzo[*a,c*]anthracene, mp 225–230° (lit.[12] mp 227°).

Registry No.—**1**, 1608-10-2; **2**, 55255-17-9; **3a**, 35341-52-7; **3b**, 5271-40-9; **4a**, 55255-18-0; **4b**, 55255-19-1; **5**, 55255-20-4; **6**, 55255-21-5; **7**, 55255-22-6; lithium, 7439-93-2.

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(7) M. A. Doran and R. Waack, *J. Organomet. Chem.*, **3**, 94 (1965).
(8) We are indebted to Professor F. W. McLafferty for the mass spectral analyses.
(9) The terms *dl* and meso are no longer strictly correct when applied to **3a**-d_4 and **3b**-d_4 because two new chiral centers are created by the introduction of deuterium on the 1 and 4 carbons. This complication is ignored in the discussion since the properties of **3a**-d_4 and **3b**-d_4 roughly correspond to those of the undeuterated *dl* and meso butanes, respectively.
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(11) G. Levin, J. Jagur-Grodzinski, and M. Szwarc, *J. Am. Chem. Soc.*, **92**, 2268 (1970).
(12) von E. Bergmann and O. Zwecker, *Justus Liebigs Ann. Chem.*, **487**, 155 (1931).

Geometry-Optimized INDO Calculations on 1,3-Donor–2,4-Acceptor-Substituted Cyclobutadienes

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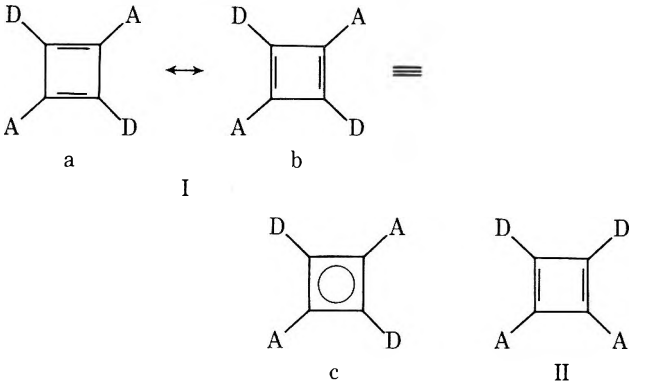
Geometry-optimized SCF–MO calculations, in the INDO approximation, were performed on a series of donor–acceptor substituted cyclobutadienes to include 1,3-diamino-2,4-dicyanocyclobutadiene (III), 1,3-dihydroxy-2,4-dicyanocyclobutadiene (IV), 1,3-difluoro-2,4-dicyanocyclobutadiene (V), 1,3-diaminocyclobutadiene (VI), 1,3-dicyanocyclobutadiene (VII), and 1,2-diamino-3,4-dicyanocyclobutadiene (VIII). The most stable geometry of III–VII was D_{2h} parallelograms and not the D_{2h} square or C_{2h} rectangular geometries. Electron-donating groups caused the ring angles at that point to be >90° while electron-withdrawing groups caused a decrease in the ring angle <90°. Using III and VIII as model systems, it was shown that 1,3-donor–2,4-acceptor cyclobutadienes are more stable than their 1,2-donor–3,4-acceptor analogs in the square, rectangular, and parallelogram geometries. These results are compared to previous calculations and experimental results.

Unlike highly unstable cyclobutadiene, donor–acceptor substituted cyclobutadienes are stable molecules whose chemistry has been established.[1–3] However, the structure of these derivatives is a topic of somewhat more controversy. The reported X-ray structure of diethyl 2,4-bis(diethylamino)cyclobutadiene-1,3-dicarboxylate (I where D = $-NEt_2$ and A = –COOEt) found all the ring carbon–carbon bond lengths to be equal,[4] in agreement with resonance hybrid Ic. Furthermore, the NCH_2 proton NMR signals were



equivalent down to −46° in accordance with Ic.[5,6] On the other hand, the strongly nonvertical uv spectrum[5,6] spanning 8000 cm^{-1} (λ_{max} 25,500 cm^{-1}, ϵ_{max} 2.37) suggested that the ground and first excited state potential surfaces were markedly different. Also, the photoelectron spectrum of this molecule showed that the shape and binding energies of C_{1s}, N_{1s}, and O_{1s} were very similar to those of β-diethylaminoethyl acrylate. Further, the low-energy π bands of these molecules (7.55 and 7.63 eV, respectively) are only trivially different. These observations are incompatible with the D_{2h} (square) structure and were explaned on the basis of localized double bonds linked through single bonds.[5]

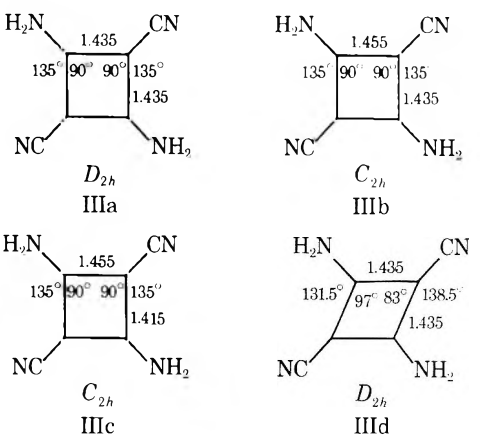
MINDO/2 calculations of Weiss and Murrell indicate that a low barrier exists for the interconversion of the energetically equivalent valence tautomers Ia and Ib.[7] These calculations on donor–acceptor molecules I and II (where D = $-NEt_2$ and A = –COOEt) showed that distortion of geometry toward double bond fixation (pseudo D_{2h} to C_{2h} symmetry) lowered the energy in both, but that the effect was appreciably larger in II than in I. Furthermore, these calculations predicted a 3 kcal/mol energy difference between D_{2h} (delocalized) and C_{2h} (localized) 1,3-diamino-2,4-dicyanocyclobutadiene. The MINDO/2 results differ from calculations of Hoffman,[8] who predicted I to be more stable than II based on a greater symmetry-favored splitting of the frontier orbital pair which is degenerate in square cyclobutadiene itself. Hoffman had assumed that the ring bond lengths remained the same (D_{2h}).[8]

In view of the results described above, we performed a series of SCF-MO calculations in the INDO[9,10] approximation on the five model systems: 1,3-diamino-2,4-dicyanocyclobutadiene (III), 1,3-dihydroxy-2,4-dicyanocyclobutadiene (IV), 1,3-difluoro-2,4-dicyanocyclobutadiene (V), 1,3-diaminocyclobutadiene (VI), and 1,3-dicyanocyclobutadiene (VII). The geometry of these compounds was optimized with respect to energy to establish the ground state structure. The use of optimized geometries stands in sharp contrast to that of previous studies.[7,8] In addition the stabilities of diaminodicyanocyclobutadienes of types I and II were compared.

Results

The CNINDO program QCPE no. 141 was employed, as described earlier,[11–18] with a model builder program. Both were modified for use on a Univac 110 computer. Figure 1 summarizes the optimized geometries and gives the charge densities for III–V. For donor–acceptor cyclobutadienes the following procedure was used. The relative energies of various geometries of III–VIII are summarized in Table I.

Starting with D_{2h} symmetry (optimized bond lengths were obtained for that symmetry, IIIa) the ring was modified to a rectangle, C_{2h}, by elongating one parallel pair of the ring CC bonds (see IIIb). Then the other parallel pair was shortened as shown in IIIc. Then the entire structure was optimized without restrictions. This resulted in a parallelogram geometry with D_{2h} symmetry. For IIIa–c all lengths used were optimized (except for the ring bonds in IIIb and IIIc). The substituents' axes bisected the ring an-



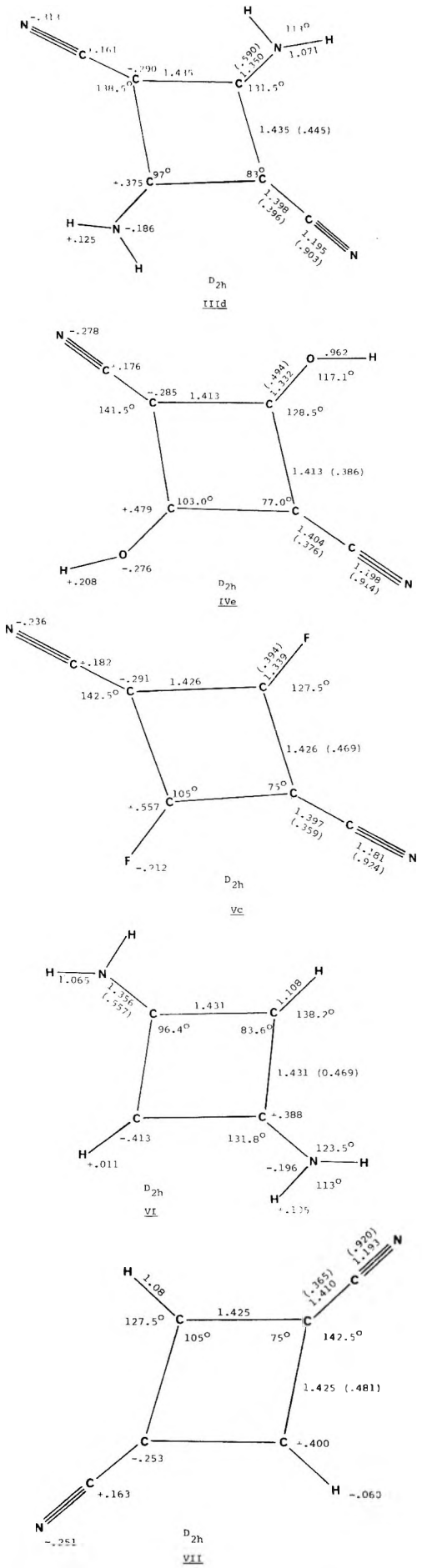


Figure 1. Optimized geometries, charge densities, and π-bond orders for donor and acceptor substituted cyclobutadienes III–VII. π-bond orders are given in parentheses.

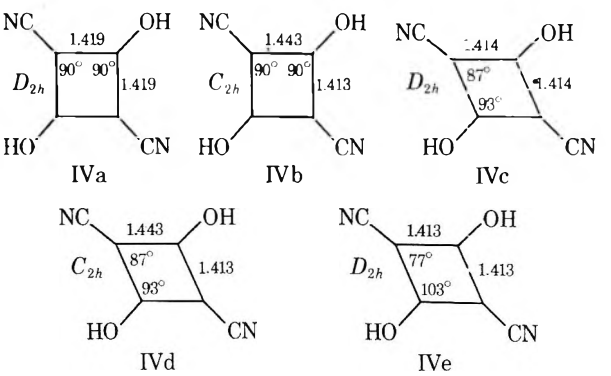
Table I
Relative Energies of Different Geometries of Donor–Acceptor Substituted Cyclobutadienes[a]

Structure	Symmetry	Shape	Relative energy,[b] kcal/mol
IIIa	D_{2h}	Square	7.8
IIIb	C_{2h}	Rectangle	8.0
IIIc	C_{2h}	Rectangle	8.1
IIId	D_{2h}	Parallelogram	0
IVa	D_{2h}	Square	12.7
IVb	C_{2h}	Rectangle	21.6
IVc	D_{2h}	Parallelogram	8.8
IVd	C_{2h}	Parallelogram	9.0
IVe	D_{2h}	Parallelogram	0
Va	D_{2h}	Square	29.5
Vb	C_{2h}	Rectangle	26.0
Vc	D_{2h}	Parallelogram	0
VI	D_{2h}	Square	3.6
VI	D_{2h}	Parallelogram	0
VII	D_{2h}	Square	20.6
VII	D_{2h}	Parallelogram	0
VIIIa	C_{2v}	Square	19.3
VIIIb	C_{2v}	Rectangle	0
VIIIc	C_s	Parallelogram	11.4
VIIId	C_{2v}	Trapezoid	82.3
VIIIe	C_{2v}	Trapezoid	58.7

[a] Structures have each been geometry optimized with the exception of the bonds and angles being distorted to give the various geometries (see text for details). [b] The energies above 0 kcal mol^{-1} are less stable structures relative to the most stable structure (the one with a relative energy of zero). Comparison is only valid with other structures of the same molecule (i.e., IIIa with IIIb,c, or d but not IIIa with IVe, etc.)

gles. Optimizations all gave smooth paraboloid type potential wells. In the D_{2h} parallelogram geometry all the ring angles and lengths were optimized followed by complete optimization without restriction to IIId. Figure 1 summarizes the final optimized geometries and gives their total charge distributions and π-bond orders.

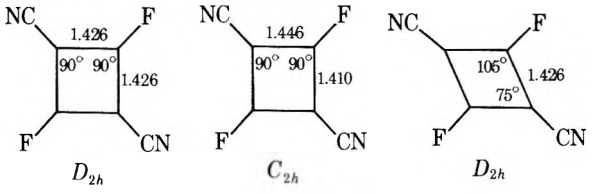
In contrast to the MINDO calculations of Weiss,[7] the optimized square geometry, IIIa, was 0.2 and 0.3 kcal/mol *more stable* than rectangular geometries IIIb and IIIc. More important, the square and rectangular geometries were significantly *less stable* than the parallelogram geometry IIId by 7.8, 8.0, and 8.1 kcal mol^{-1}, respectively. A similar analysis was performed on 1,3-dihydroxy-2,4-diaminocyclobutadiene (IV). The optimized square geometry IVa was more (8.9 kcal mol^{-1}) stable than the rectangular distortion IVb. Slight deformation of IVa to IVc parallelogram



resulted in 3.9 kcal mol^{-1} increase in stability, but elongating one pair of sides (to IVd) caused only a tiny energy change (0.2 kcal mol^{-1}). However, deformation of the IVa to the completely optimized parallelogram geometry IVe

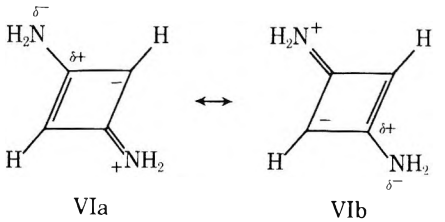
resulted in the most stable (12.7 kcal mol^{-1} more stable than IVa) structure.

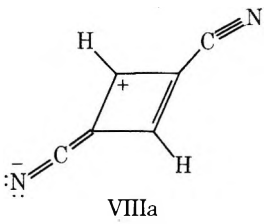
1,3-diaminocyclobutadiene (VI), and 1,3-dicyanocyclobutadiene (VII), also were predicted to distort from the square D_{2h} to the parallelogram D_{2h} symmetry. Their optimized structures are given in Figure 1. In VI a small distortion of the ring angles (96.4 and 83.6°) occurs compared to VII, where the deviation is larger (75 and 105°). The ring angle increases when substituted at that point with an electron-donating group and contracts when substituted with an electron-withdrawing group. This trend in VI and VII is the same as that found in donor–acceptor cyclobutadienes III–V. The energy difference between square and parallelo-



gram D_{2h} geometries in VI was 3.6 kcal mol^{-1}, while for VII a larger difference (20.6 kcal mol^{-1}) was found.

The charge distribution in VI shows a significant build-up of negative charge at the unsubstituted carbons (−0.413), while the amino-substituted carbons are significantly positive (+0.388). The nitrogen atoms contain significant negative charge (−0.196) owing to strong σ polarization of the C–N bond toward N. However, examination of the π system confirms that the nitrogen p orbital (perpendicular to the molecular plane) is back donating electron density to the ring. The C–N π-bond order (0.557) is greater than the ring C–C π-bond orders (0.469). Thus, π-delocalization can be represented by hybrids VIa,b and VIIa below.



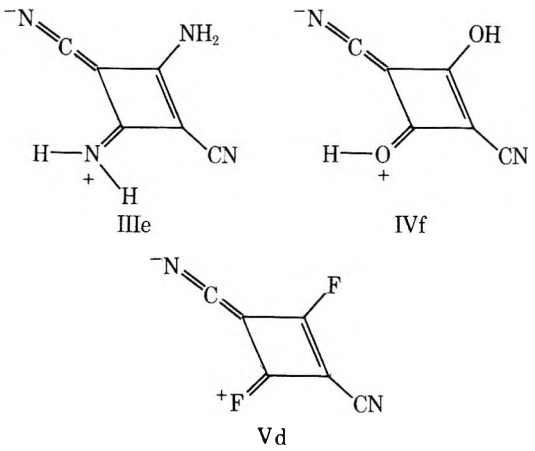


In contrast to VI, a significant positive charge density exists at the unsubstituted ring carbons in VII (+0.400) whereas the substituted ring carbons are negative (−0.253) to about the same extent as the cyano group nitrogens are (−0.250). Examining the σ and π systems carefully shows that an extensive depletion of the π-electron density from the unsubstituted carbon largely accounts for this. The π-bond orders follow: ring C–C, 0.481; the ring C–CN, 0.365; and the CN, 0.920.

The equal-sided parallelogram geometry was also favored in V. Deforming Va to Vc resulted in a 29.5 kcal mol^{-1} lowering of the energy. Va was 3.55 kcal mol^{-1} less stable than Vb.

Thus a clear picture emerges within the framework of the INDO SCF–MO modification. Donor–acceptor cyclobutadienes of type I are most stable in the equal-sided parallelogram geometries shown in Figure 1. Furthermore, confining the ring angles to 90°, one sees that distortion from square (delocalized) to rectangular (localized) geometry results in a small destabilization. This is in conflict with the results of Weiss, but in his reported calculations geometry optimizations were not made.[7] Thus, it is not possible to be sure if MINDO favors the square, rectangular, or parallelogram structure, because it is necessary to optimize geometry to obtain the inherent results predicted by any calculational model.

Charge Distributions in III–V. Significant contribution by resonance structures such as IIIe were not supported by the calculations. In III the amino nitrogen's charge (−0.186) and cyano nitrogen's charge (−0.313) were similar to the charges on the corresponding atoms of VI and VII (−0.196 and −0.250), suggesting only a modest contribution by IIIe. However, π donation to the ring by amino nitrogen (in III), hydroxy oxygen (in IV), and fluorine (in V) was occurring.[20] Also the cyano nitrogens were accepting π



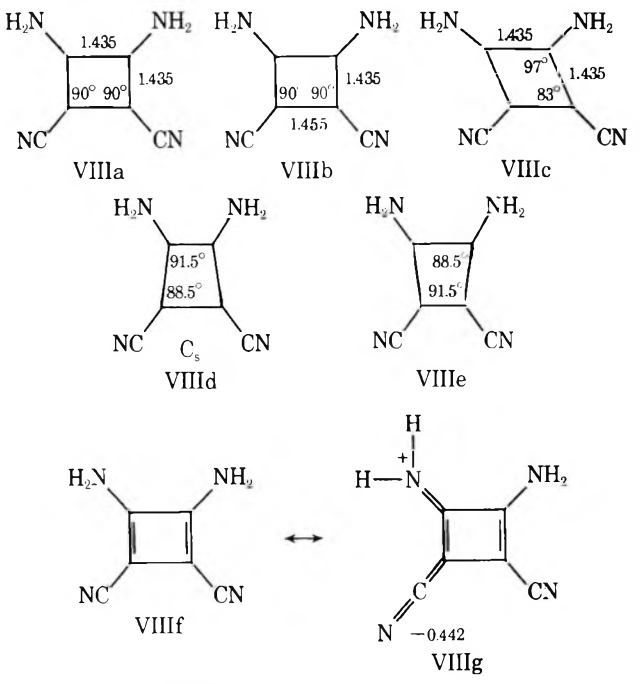
electrons from the ring. This was counteracted by polarization of the ring carbon σ bonds toward amino nitrogen, oxygen, and fluorine in III–V, respectively. In each case the ring, taken as a whole, was positively charged and the order of this effect was V > IV > III.

π-Bond Orders III–V. The π-bond orders also support the contention that resonance hybrids IIIe, IVf, and Vd do not significantly contribute. For example, in III the π-bond orders of H_2N–C (0.590) and C–CN (0.396) may be compared to those of VI (H_2N–C = 0.557) and VII (NC–C = 0.365). The slightly larger values in III, relative to VI and VII, argue for very small contributions by hybrid structure IIIe. A similar comparison of the C–CN π-bond orders in IV and V vs. that in VII suggests that IVf and Vd contribute only slightly. The π-bond orders are listed in Figure 1.

Relative Stability of Type I and Type II Donor–Acceptor Cyclobutadienes. Preliminary calculations were made on several geometries of 1,2-diamino-3,4-dicyanocyclobutadiene (VIII), as a model type II molecule. Complete optimization of all bond lengths and angles was not carried out and the total energy surfaces were not completely established. However, the lengths and angles employed were not far from the optimized structures, and further optimization would not be expected to change the trends established below. The C–NH_2, C–CN, C≡N, and N–H lengths employed were 1.350, 1.398, 1.195, and 1.072 Å, respectively, and an H–N–H angle of 113° was used.

The rectangular, C_{2v}, geometry VIIIb was 19.3 kcal mol^{-1} more stable than the C_{2v} square, VIIIa. The C_s parallelogram, VIIIc, was 7.9 kcal mol^{-1} more stable than square VIIIa. Since in VI, VII, and the type I molecules, III–V, it was clear that the ring angles were >90° where a

donor substituent was attached and <90° where an acceptor was attached, it was considered possible that VIII might favor a C_{2v} trapezoid geometry such as VIIId. Thus, VIIIa was deformed by slightly closing the ring angles at the position of the cyano substituents to give VIIId. However, this geometry was far less stable (by 63 kcal mol^{-1}) than VIIIa. Also, the trapezoid geometry VIIIe, where the angles at the cyano groups were opened to 92°, was examined and found to be 23.6 kcal mol^{-1} more stable than trapezoid VIIId (but still less stable than rectangle VIIIb). Thus, it would appear that localization as represented by VIIIf was favored in VIII as a model type II structure. Analysis of the charge distributions, π-bond orders, and p_z orbital electron densities suggest that VIIIg contributes more strongly to VIII than IIIe did to III.



Next, the stabilities of the model donor–acceptor diaminodicyanocyclobutadienes of type I and II were compared in various geometries. In all comparisons, the type I molecules were more stable than their type II counterparts. Thus, IIIa, IIIb, and IIId were more stable than VIIIa, VIIIb, and VIIIc by 91.3, 71.0, and 90.6 kcal mol^{-1}, respectively. The greater stability of IIIa vs. VIIIa agrees with the predicted thermodynamic stabilities of Hoffman. However, it must be remembered that IIId is the favored geometry of III and VIIIb for VIII. Since IIId is more stable than VIIIb, we predict (within the limits of INDO theory) that type I molecules will be thermodynamically more stable than type II.

Questions concerning a rigorous comparison of MINDO/2 and INDO methods still exist. Currently, it is not clear if INDO and MINDO/2 results differ because previous MINDO/2 studies[7] failed to use optimized geometries or because the methods inherently differ.

Finally, it might be expected that type I cyclobutadienes, with strong donor and acceptor groups, will have D_{2h} parallelogram geometries in the gas phase and possibly in the solid phase. Carefully performed electron diffraction, microwave spectroscopy, and X-ray crystallographic studies on such molecules are needed to test this prediction. Already, one interesting study is available. Rausch et al.[19] found that the cyclobutadienyl ring, in (π-C_5H_5)-[*trans*-diphenyldi(trimethylsilyl)cyclobutadiene]cobalt, was planar with the four C–C distances equal. However, the internal angles were not 90°. Instead, a parallelogram geometry with 88.1° (at site of phenyl groups) and 91.8° (at site of silicons) was found.

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Registry No.—III, 55208-71-4; IV, 55208-72-5; V, 55208-73-6; VI, 25723-65-3; VII, 55208-74-7; VIII, 55208-75-8.

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Catalysis of the Hydrolysis of Aryl Sulfonyl Fluorides by Acetate Ion and Triethylamine[1a]

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The ability of (1) acetate and (2) triethylamine to catalyze the hydrolysis of aryl sulfonyl fluorides in aqueous dioxane has been explored kinetically. Acetate ion does catalyze the hydrolysis, and the solvent isotope effect associated with the acetate-catalyzed reaction indicates that this is due to nucleophilic catalysis (eq 1). The relative effectiveness of acetate as a catalyst, as measured by the ratio of the rate constant for the acetate-catalyzed reaction to that for spontaneous hydrolysis of the sulfonyl fluoride under the same conditions, appears to be closely comparable to its relative effectiveness as a catalyst for the hydrolysis of aryl sulfonyl chlorides and α-disulfones. Catalysis by triethylamine, while detectable in competition with the normal alkaline hydrolysis of $ArSO_2F$ in 1:1 Et_3N–Et_3NH^+ buffers, is relatively much less important compared to the normal alkaline hydrolysis under these conditions than in the hydrolysis of aryl α-disulfones, but considerably more important than in the hydrolysis of *p*-nitrophenyl *p*-toluenesulfonate. The possible mechanistic significance of this result is discussed.

Although they react readily with hydroxide ion, sulfonyl fluorides hydrolyze very slowly in neutral or acidic aqueous solution.[2,3] On the other hand, when complexed to a macromolecule such as an enzyme[4] or cellulose,[5] sulfonyl fluorides can undergo rapid covalent bond formation with OH groups on the macromolecule. Catalysis of the hydrolysis of the sulfonyl fluoride by the enzyme can also occur.[4] In view of the very slow rate of spontaneous hydrolysis of sulfonyl fluorides, it would appear that there must be very effective intramolecular catalysis by functional groups on the macromolecule in each of the reactions mentioned.

This suggested to us that a study of the possible catalysis of the hydrolysis of sulfonyl fluorides by such simple species as carboxylate ions and nitrogen bases might prove interesting and informative. Functional groups of these types are present in the side chains of protein amino acid residues and have often been implicated in the catalytic activity of various enzymes. We also knew that such species as acetate ion and triethylamine are able to catalyze the hydrolysis of sulfonyl derivatives with better leaving groups than F, namely, sulfonyl chlorides[6] ($ArSO_2Cl$) and α-disulfones[7] ($ArSO_2SO_2Ar$), and so it seemed quite reasonable that catalysis by those species might also be important for the hydrolysis of aryl sulfonyl fluorides.

We have therefore investigated the hydrolysis of several aryl sulfonyl fluorides in the presence of a representative carboxylate ion, acetate ion, and in the presence of a typical tertiary amine, triethylamine, in order to see whether there was marked catalysis of the hydrolysis by either species, and to then determine, if significant catalysis was observed, whether this catalysis was nucleophilic or general base catalysis.

Results

Catalysis of the Hydrolysis of Aryl Sulfonyl Fluorides by Acetate Ion. The disappearance of the aryl sulfonyl fluoride was followed spectrophotometrically in acetate buffers in 20% dioxane (v/v) as solvent using added potassium chloride to maintain a constant ionic strength of 0.04. In runs with *m*-nitrobenzenesulfonyl fluoride a wavelength of 275 nm was used to follow the reaction; with *p*-toluenesulfonyl fluoride the wavelength used was 235 nm. Depending on the sulfonyl fluoride, the data were plotted as either log $(A - A_\infty)$ or log $(A_\infty - A)$ vs. time. Plots of this type were linear and the experimental first-order rate constant, k_1, for the disappearance of the sulfonyl fluoride was evaluated in the usual way from the slope of such plots.

Our initial studies were conducted with *p*-toluenesulfonyl fluoride as the substrate. However, the disappearance of this sulfonyl fluoride, even in the presence of 0.04 *M* acetate at 90°, was rather slow ($t_{1/2} \simeq 5$ hr), and there seemed to be difficulty in determining the infinity value of the absorbance accurately and getting reproducible rate constants. For this reason the decision was made to switch to *m*-nitrobenzenesulfonyl fluoride as the substrate. This reacts about 30 times faster than the *p*-tolyl compound, just as it undergoes spontaneous hydrolysis much more readily than $p\text{-}CH_3C_6H_4SO_2F$.[3]

Table I
Hydrolysis of *m*-Nitrobenzenesulfonyl Fluoride in Acetate Buffers in 20% Dioxane at 91°

10^5 [$ArSO_2F$]$_0$, *M*	[AcO^-], *M*	[AcOH], *M*	[KCl], *M*[a]	$10^4 k_1$, sec^{-1}
8.0	0.00	0.00	0.04	0.51 ± 0.03
	0.01	0.01	0.03	3.4 ± 0.3
				2.3 (D_2O)
	0.02	0.02	0.02	4.7 ± 0.4
				4.6 (D_2O)
	0.03	0.03	0.01	6.1 ± 0.5
				6.4 (D_2O)
	0.04	0.04	0.00	8.7 ± 0.6
				8.9 (D_2O)
	0.04	0.02	0.00	9.9

[a] The same rates were obtained when $LiClO_4$ was used in place of KCl to maintain ionic strength in the AcO^-–AcOH buffers.

The *m*-nitro compound underwent hydrolysis in 1:1 acetate–acetic acid buffers at a convenient rate at 91°. The results are shown in Table I, along with the rates of hydrolysis under identical conditions in 20% dioxane–80% D_2O. Evidence that acetate, and *not* acetic acid, is the species responsible for the catalysis of the hydrolysis of the sulfonyl fluoride in these buffers was provided by an experiment using a 2:1 AcO^-–AcOH buffer containing 0.04 *M* AcO^-. The rate of hydrolysis was not less than that found for a 1:1 buffer containing 0.04 *M* AcO^-.

Salomaa and coworkers[8] have pointed out that in mixed dioxane–water solvents apparent catalysis by a buffer component can *sometimes* result from accidental salt effects involved with the control of ionic strength. Their results, however, indicate that, if one gets the same rates for a series of experiments of the type shown in Table I when the ionic strength is maintained with an alkali metal perchlorate as when it is maintained with an alkali metal chloride, one can feel quite confident that an effect of this type is

Table II
Hydrolysis of Aryl Sulfonyl Fluorides in Triethylamine Buffers in 60% Dioxane at 25°

$ArSO_2F$, Ar =	10^4 $[ArSO_2F]_0$, M	$[Et_3N]$, M	$[Et_3NH^+]$, M	$[LiClO_4]$, M	$10^4 k_1$, sec^{-1}
m-$O_2NC_6H_4$	8.0	0.01	0.01	0.2375	7.2 ± 0.1
		0.02	0.02	0.2275	8.3 ± 0.3
		0.04	0.04	0.2075	9.8 ± 0.2
		0.06	0.06	0.1875	11.0 ± 0.1
p-BrC_6H_4	6.0	0.02	0.02	0.2275	0.95 ± 0.07
		0.04	0.04	0.2075	1.10 ± 0.01
		0.06	0.06	0.1875	1.21 ± 0.01

not operating and that one is observing true catalysis by the buffer component. In the present work we observed no change in rate when lithium perchlorate was used instead of potassium chloride to maintain ionic strength in the AcO^-–AcOH buffers. Therefore we are confident that the catalysis being observed here with acetate ion is in fact either nucleophilic or general base catalysis, and *not* an accidental salt effect.

Plots of k_1 vs. $[AcO^-]$ for both the runs in 20% dioxane–80% H_2O and 20% dioxane–80% D_2O are satisfactorily linear, indicating a first-order dependence of the rate of the catalyzed reaction on acetate concentration. From the slopes of the plots $k_{OAc}(H_2O)$ is estimated to be 0.020 ± 0.002 M^{-1} sec^{-1}, and $k_{OAc}(D_2O)$ as 0.022 ± 0.001 M^{-1} sec^{-1}, giving a solvent isotope effect for catalysis by acetate, $k_{OAc}(H_2O)/k_{OAc}(D_2O)$, of 0.9 ± 0.2.

Hydrolysis of Aryl Sulfonyl Fluorides in Triethylamine Buffers. Rates of disappearance of the sulfonyl fluorides were followed spectrophotometrically in 1:1 Et_3N–Et_3NH^+ buffers in 60% dioxane (v/v) at 25°, using lithium perchlorate to maintain a constant total ionic strength of 0.25. The triethylamine concentration was varied between 0.01 and 0.06 *M*. *m*-Nitrobenzenesulfonyl fluoride and *p*-bromobenzenesulfonyl fluoride were used as substrates. The disappearance of the sulfonyl fluorides followed good first-order kinetics, and the experimental first-order rate constants, k_1, for the different conditions are shown in Table II.

Figure 1 shows a plot of k_1 vs. $[Et_3N]$ for the data in Table II. One can see that, while there is some increase in rate with increasing $[Et_3N]$, the intercept on the k_1 axis at $[Et_3N]$ = 0.00, which represents the contribution to k_1 from the reaction of the sulfonyl fluoride with hydroxide ion present in the Et_3N–Et_3NH^+ buffers, is in both cases equal to, or larger than, the increase in rate brought on by the addition of 0.06 *M* Et_3N. Because in each case the triethylamine-catalyzed reaction constituted only a relatively modest portion of the total rate of disappearance of the sulfonyl fluoride, even at high triethylamine concentrations, we did not attempt to determine the solvent isotope effect associated with it. From the slopes of the plots in Figure 1 k_{Et_3N} is estimated to be about 7×10^{-3} M^{-1} sec^{-1} for the reaction involving *m*-$O_2NC_6H_4SO_2F$ and $\sim 6 \times 10^{-4}$ M^{-1} sec^{-1} for the *p*-bromo compound.

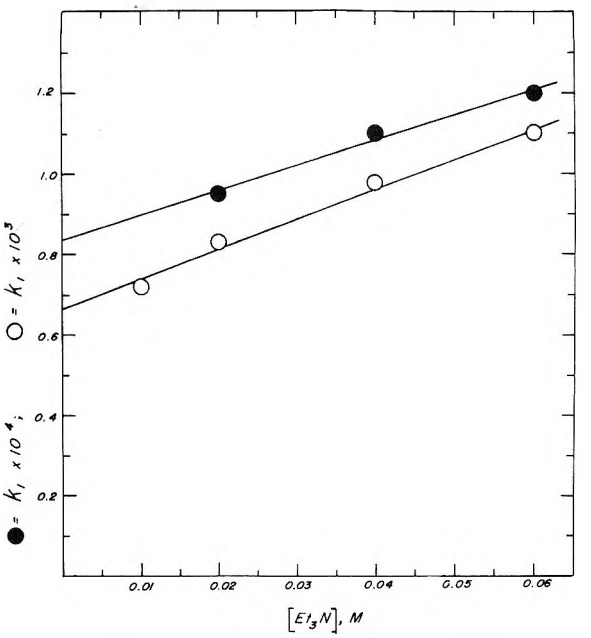

Figure 1. Rates of hydrolysis of aryl sulfonyl fluorides in 1:1 Et_3N–Et_3NH^+ buffers in 60% dioxane at 25° as a function of $[Et_3N]$: data for *m*-nitrobenzenesulfonyl fluoride, O; data for *p*-bromobenzenesulfonyl fluoride, ●.

Discussion

Catalysis of the Hydrolysis of Aryl Sulfonyl Fluorides by Acetate Ion. The results in Table I show that the hydrolysis of an aryl sulfonyl fluoride can definitely be catalyzed by acetate ion. In principle, this could be either general base catalysis or nucleophilic catalysis, but the observation that the solvent isotope effect associated with the acetate-catalyzed reaction is 0.9 ± 0.2 suggests that nucleophilic catalysis (eq 1) is what is involved in the present case.[9] This is the same type of catalysis observed with acetate in the hydrolysis of aryl sulfonyl chlorides[6] and α-disulfones.[7a]

$$AcO^- + ArSO_2F \xrightarrow{k_{OAc}} F^- + ArSO_2OAc \xrightarrow[\text{fast}]{H_2O} ArSO_3^- + AcO^- + 2H^+ \quad (1)$$

Presumably the reason that $ArSO_2OAc$ hydrolyzes more rapidly than either $ArSO_2F$, $ArSO_2Cl$, or $ArSO_2SO_2Ar$ is because attack of water on the *carbonyl* group of $CH_3C(O)OSO_2Ar$ is much faster than attack of water on the sulfonyl group of any of the sulfonyl substrates. That this should be the case is not surprising, since $ArSO_2O$ represents an excellent leaving group, and nucleophilic attack on a carbonyl carbon is generally much more rapid than attack on an equivalent sulfonyl sulfur.[10]

The relative effectiveness of acetate as a catalyst for the hydrolysis of an aryl sulfonyl fluoride seems to be very similar to its effectiveness as a catalyst for the hydrolysis of aryl sulfonyl chlorides[6] or α-disulfones.[7a] Thus, using as a measure of effectiveness the ratio k_{OAc}/k_{H_2O}, where k_{H_2O} is the rate constant for the spontaneous hydrolysis of the sulfonyl derivative under the same reaction conditions, the values of k_{OAc}/k_{H_2O} are 400, 500, and 2000 for the hydrolyses of the sulfonyl fluoride, sulfonyl chloride,[6] and α-disulfone,[7a] respectively. Clearly, then, while acetate, and presumably other carboxylate ions, can catalyze the hydrolysis of a sulfonyl fluoride, their ability to do this parallels their ability to catalyze the hydrolyses of other sulfonyl derivatives having better leaving groups, and there is no special synergism associated with the carboxylate ion–sulfonyl fluoride system. The origin of the rapid rate of reaction of sulfonyl fluorides with OH groups in certain macromolecules vis-à-vis their slow rate of spontaneous hydrolysis does not therefore have its origin in some unusual rate enhancement due to neighboring carboxylate groups in the macromolecule, at least insofar as being the result of some particularly favorable rate for reaction of a carboxylate ion with a sulfonyl fluoride, as compared to the ease of reaction of $RCOO^-$ with hydrolytically more reactive sulfonyl derivatives.

Hydrolysis of Aryl Sulfonyl Fluorides in Triethyl-

amine Buffers. As is evident from Figure 1, most of the rate of hydrolysis of an aryl sulfonyl fluoride in a 1:1 Et_3N–Et_3NH^+ buffer in 60% dioxane is due to the reaction of hydroxide ion with the sulfonyl fluoride (eq 2) and not to a

$$HO^- + ArSO_2F \xrightarrow{k_{OH}} F^- + ArSO_3H \xrightarrow[\text{fast}]{OH^-} ArSO_3^- \quad (2)$$

triethylamine-catalyzed reaction. This contrasts with the behavior of phenyl α-disulfone under the same conditions,[7b] where most of the rate was due to a triethylamine-catalyzed reaction. On the other hand, while a kinetic term dependent on $[Et_3N]$ is still clearly detectable in the hydrolyses of the two sulfonyl fluorides in Table II, no triethylamine-dependent term could be observed in the hydrolysis of *p*-nitrophenyl *p*-toluenesulfonate, $ArSO_2OC_6H_4NO_2$-*p*, in the same buffer and solvent medium.[11] These several results suggest that as the leaving group gets poorer it becomes more difficult for a triethylamine-catalyzed reaction to compete kinetically in a 1:1 Et_3N–Et_3NH^+ buffer with the normal alkaline hydrolysis of the sulfonyl derivative (eq 2 for $ArSO_2F$).

This would seem to be more consistent with the idea that any catalysis of the hydrolysis of these sulfonyl derivatives by triethylamine involves nucleophilic catalysis, rather than general base catalysis, as was originally suggested,[7b] since, with general base catalysis, all else being equal, one normally finds that such catalysis is more important the poorer the leaving group.[12]

We had originally hoped that the hydrolysis of aryl sulfonyl fluorides might prove just as good a system in which to explore catalysis of the hydrolysis of sulfonyl derivatives as the hydrolysis of sulfonyl chlorides[6] or α-disulfones.[7] The experiments outlined in the present paper strongly suggest, however, that this is not so, and have discouraged us from undertaking any further current work in this area. Despite their somewhat esoteric nature the aryl α-disulfones appear to provide a considerably more versatile system in which to study catalysis[7] of substitution at sulfonyl sulfur, as well as nucleophilic reactivity.[13]

Experimental Section

Preparation and Purification of Reagents. *p*-Bromobenzenesulfonyl fluoride was prepared by the method of Aberlin and Bunton,[3] mp 64–65° (lit.[3] mp 65–66°). The other sulfonyl fluorides were obtained from commercial sources, *m*-nitrobenzene- (Alfred Bader) and *p*-toluene (Aldrich), and were recrystallized from ethanol–water prior to use. Triethylamine and dioxane were purified by previously described procedures.[11] Sodium acetate, acetic acid, lithium perchlorate, and potassium chloride were all analytical reagent grade and were used without further purification.

Procedure for Kinetic Runs in Acetate Buffers. The runs were carried out under nitrogen in a reaction vessel of a type previously used[14] which permits an aliquot of the reaction solution to be withdrawn without exposing the rest of the solution to the atmosphere. Fifty milliliters of a solution containing the proper amounts of sodium acetate, acetic acid, and either potassium chloride or lithium perchlorate in 20% dioxane (v/v) as solvent was placed in the reaction vessel, 0.5 ml of a 0.008 *M* solution of the sulfonyl fluoride in pure dioxane was added and thoroughly mixed with the acetate buffer, and the final reaction solution was then deaerated by passing a stream of nitrogen through the cooled solution for a number of minutes. The flask containing the reaction solution was then placed in a constant-temperature bath at 91° and aliquots of the reaction solution were removed at appropriate time intervals, stoppered, and quickly cooled in ice to stop further reaction, and then kept at 0° until all the aliquots that were going to be taken in that particular run had been removed. Their absorbance, and that of the aliquot removed after reaction was complete, was then measured at an appropriate wavelength using either a Cary Model 14 or Perkin-Elmer Model 402 spectrophotometer. Runs involving *m*-nitrobenzenesulfonyl fluoride were followed at 275 nm, those with *p*-toluenesulfonyl fluoride at 235 nm.

Procedure for Kinetic Runs with Triethylamine Buffers. The kinetics of the hydrolyses in the 1:1 Et_3N–Et_3NH^+ buffers were followed by monitoring continuously the absorbance of a solution of the sulfonyl fluoride in the appropriate buffer in a thermostatted 1-cm cell in the cell compartment of either a Cary Model 14 or Perkin-Elmer Model 402 spectrophotometer. For each run the proper volume of a stock solution containing 0.12 *M* Et_3N and 0.12 *M* $Et_3NH^+ClO_4^-$ in 60% dioxane was pipetted into the reaction cell, followed by the necessary amount of a 0.75 *M* stock solution of lithium perchlorate in the same solvent. After mixing, the cell containing the solution was placed in the thermostatted cell holder in the spectrophotometer and allowed to come to 25°. A small, known amount of a freshly prepared stock solution of the sulfonyl fluoride, which had also been brought to 25°, was then quickly added to the spectrophotometer cell, the cell was shaken vigorously to ensure complete mixing and quickly replaced in the cell holder, and measurements of absorbance vs. time were then started.

Registry No.—*p*-Bromobenzenesulfonyl fluoride, 498-83-9; *m*-nitrobenzenesulfonyl fluoride, 349-78-0; *p*-toluenesulfonyl fluoride, 455-16-3; acetate ion, 71-50-1; triethylamine, 121-44-8.

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(9) A referee has noted that an extrapolation from known room temperature data to 91° would suggest that general base catalysis by acetate ion at that temperature would generate a solvent isotope effect in the range 1.4–1.8. He feels that the lower limit of this range is close enough to the upper limit of the actual measured solvent isotope effect of 0.9 ± 0.2 so that drawing the conclusion from the solvent isotope effect that the catalysis by acetate is nucleophilic in character rather than general base, while probably correct, is subject to some risk.
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(12) It is possible, of course that a change in the leaving group might have a larger effect on k_{OH} than it does on the rate constant for a general base catalyzed reaction involving triethylamine, although, since attack of OH^- on the sulfonyl compound should almost certainly be rate determining for reaction of hydroxide ion with each substrate, we find this rather difficult to believe. A decrease in k_{Et_3N}/k_{OH} with nature of the leaving group is, however, readily explicable if triethylamine catalysis is nucleophilic catalysis.[11]
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Notes

Absence of Catalysis of the Hydrazinolysis of Phenyl α-Disulfone by Triethylamine and Its Mechanistic Implications for the Ordinary Hydrazinolysis[1a]

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Kice and Legan[2] studied the kinetics of the reaction of various amino compounds with phenyl α-disulfone (1), $PhSO_2SO_2Ph$, in 60% aqueous dioxane as solvent at a constant ionic strength of 0.04, with the amino compound present in large stoichiometric excess over the α-disulfone. With most amino compounds the experimental first-order rate constant, k_{exp}, was, as expected, strictly proportional to the first power of the concentration of the amino compound, i.e., $k_{exp} = k_a$[amino], but with hydrazine k_{exp} appeared to have a different form (eq 1)

$$k_{exp} = k_a[NH_2NH_2] + k_b[NH_2NH_2]^2 \quad (1)$$

with the k_b term contributing about one-third of the total value of k_{exp} at 0.04 *M* NH_2NH_2 in a 1:1 NH_2NH_2–$NH_2NH_3^+$ buffer. Kice and Legan[2] suggested that the k_b term probably represented general base catalysis by a second molecule of hydrazine of the attack of a molecule of hydrazine on 1.

If this interpretation is correct then hydrazinolysis of 1 in the presence of the much stronger base triethylamine ought to lead to marked catalysis of the hydrazinolysis by Et_3N, with k_{exp} being given by

$$k_{exp} = k[NH_2NH_2][Et_3N] \quad (2)$$

We have now determined the kinetics of the hydrazinolysis of 1 in a series of 1:1 Et_3N–Et_3NH^+ buffers containing 0.01 *M* NH_2NH_2 and 0.01–0.04 *M* triethylamine. The results are shown in Table I. It is evident that there is no dependence of k_{exp} on [Et_3N] and that the rate is the same as that found[2] in the absence of triethylamine at the same hydrazine concentration. Clearly, then, the *apparent* $k_b[NH_2NH_2]^2$ term in eq 1 observed by Kice and Legan[2] was *not* the result of general base catalysis by hydrazine of the reaction of hydrazine with 1.

Table I
Kinetics of the Hydrazinolysis of Phenyl α-Disulfone in Et_3N–Et_3NH^+ Buffers in 60% Dioxane at 25°[a]

[NH_2NH_2], *M*	[Et_3N], *M*	[Et_3NH^+], *M*	[$LiClO_4$], *M*	k_{exp}, sec^{-1}
0.01	0.01	0.01	0.03	0.18
	0.02	0.02	0.02	0.20
	0.04	0.04	0.00	0.19

[a] All runs with initial concentration of 1.3×10^{-5} *M*.

To explore the matter further we have reexamined the hydrazinolysis of 1 in both 1:1 and 2:1 NH_2NH_2–$NH_2NH_3^+$ buffers, but using a significantly higher total ionic strength of about 0.10, so that $NH_2NH_3^+$ was always present at a lower concentration than Li^+, something that was not true in the earlier study.[2] The results are shown in Table II. It is clear that under these conditions $k_{exp}/[NH_2NH_2]$ is effectively constant and that there is no significant contribution to the rate from a term of the form $k_b[NH_2NH_2]^2$.

Table II
Kinetics of the Hydrazinolysis of Phenyl α-Disulfone in NH_2NH_2–$NH_2NH_3^+$ Buffers in 60% Dioxane at 25°[a]

[NH_2NH_2], *M*	[$NH_2NH_3^+$], *M*	[$LiClO_4$], *M*	k_{exp}, sec^{-1}	$k_{exp}/[NH_2NH_2]$, M^{-1} sec^{-1}
0.02	0.01	0.09	0.37	19
0.04	0.02	0.08	0.75	19
0.08	0.04	0.06	1.55	19
0.01	0.01	0.095	0.18	18
0.02	0.02	0.09	0.40	20
0.04	0.04	0.08	0.81	20

[a] All runs with initial concentration of 1.3×10^{-5} *M*.

Salomaa and coworkers[3] have shown that *apparent* catalysis by a buffer component is *sometimes* observed in experiments in dioxane–water solvents, as a consequence of salt effects, when maintenance of a constant ionic strength is achieved by a systematic variation in the concentration of both buffer component and inert salt, rather than by use of a large constant excess of inert salt. The results in Table II suggest that an effect of this type might well have been responsible for the apparent $k_b[NH_2NH_2]^2$ term observed by Kice and Legan,[2] although a more extensive investigation of the salt effects associated with the hydrazinolysis would, of course, be necessary to establish this with certainty.

In any event, the important point of the present work is that the variation in $k_{exp}/[NH_2NH_2]$ with [NH_2NH_2] observed by Kice and Legan[2] under their particular reaction conditions actually has nothing to do with the concentration of free hydrazine base and is definitely not the result of general base catalysis of the hydrazinolysis of 1 by a second hydrazine molecule, as was originally suggested.[2]

Experimental Section

The kinetics of the reactions were followed by the same stopped-flow procedure described by Kice and Legan.[2] The triethylamine was purified in the manner described by Kice, Walters, and Burton.[4] The purification of the other reagents followed previously described procedures.[2]

Registry No.—Phenyl α-disulfone, 10409-06-0; NH_2NH_2, 302-01-2; Et_3N, 121-44-8.

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A Novel Heterocycle. Crystal Structure and Formation of *N*-Chloro-3-aza-3*H*,2,1-benzoxiodol-1-yl Chloride from the Dichloride of *o*-Iodobenzamide

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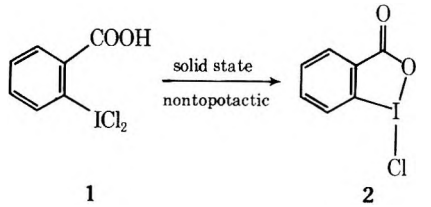
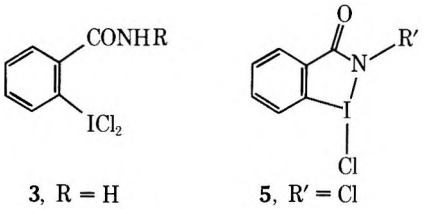
During the course of our studies of topotactic transformations involving organic polyvalent iodine compounds[1] we investigated the solid state cyclization of the iododichloride 1 to the chlorobenzoxiodole 2.[2,3] However, 2 was found to form as a polycrystalline phase[4] of no preferred orientation relative to the single crystal structure of the parent dichloride 1 (a nontopotactic transformation) and we therefore examined the behavior of the corresponding iododichlorides 3 and 4. These studies led to the isolation of a novel heterocycle, *N*-chloro-3-aza-3*H*,2,1-benzoxiodol-1-yl chloride (5), the crystal structure of which is described in this report.



1 2



3, R = H
4, R = CH_3

5, R′ = Cl
6, R′ = H
7, R′ = CH_3

Results and Discussion

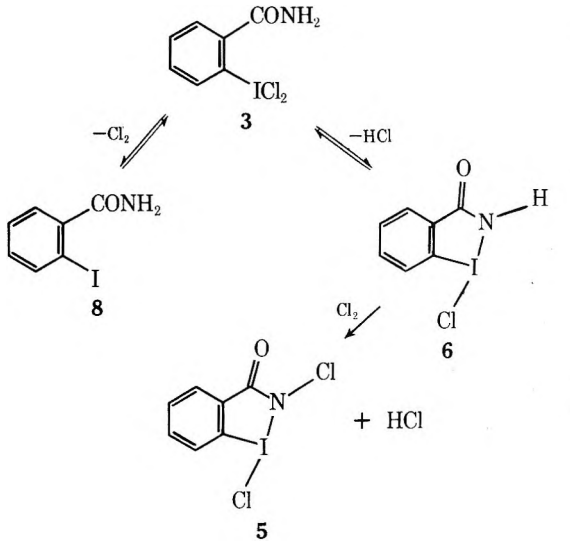
In contrast to the facile formation of crystalline 2 with loss of HCl from single crystals of 1 at room temperature, single crystals of 3 slowly lose chlorine when exposed to the atmosphere and are transformed to polycrystalline *o*-iodobenzamide (8). Crystals of 4, and also the methyl ester of 1, similarly evolve chlorine at room temperature and are converted to the parent monovalent iodine compounds.

The mode of decomposition of the crystalline dichlorides also is variable in the presence of pure solvents in which they have some solubility. Thus, the formation and subsequent crystallization of 2 occurs within a few seconds after the addition of methanol (~22°) to crystalline 1. 4 is relatively insoluble at this temperature, but it dissolves readily in boiling methanol. The bright yellow color of 4, which is common to all of these iododichlorides, fades upon dissolution and a nearly colorless substance, 7, crystallizes upon cooling. Both 2 and 7 can be recrystallized from boiling methanol without appreciable decomposition. We have tentatively formulated 7 as the trivalent iodine heterocycle rather than as the isomeric *N*-chloro-*N*-methyl-o-iodobenzamide, primarily on the basis of its infrared carbonyl absorption which is bathochromically shifted by 26 cm^{-1} relative to that of *N*-methyl-*o*-iodobenzamide (1636 cm^{-1}). The crystal structure and solid state behavior of 7 are under investigation.

Attempts to dissolve 3 in boiling methanol or chloroform led to isolation of only 8. However, 3 dissolves slowly in warm (<60°) methanol or chloroform to give clear yellow solutions which deposit the intensely yellow monoclinic crystals of 5 when stored at room temperature for several days, or overnight at −20°. Variable amounts of 3 and/or 8 also crystallize from the cooled solutions but the direct cyclization product, 6, could not be isolated in this manner. An impure, nearly colorless precipitate which appears to consist primarily of 6 was obtained by acidification of an aqueous buffered solution of 3. Attempts to recrystallize the precipitate have been unsuccessful. It disproportionates in warm methanol and approximately equal amounts of 5 and 8 are formed.

These observations are consistent with the equilibria shown in Scheme I. Similar equilibria between 1, 2, and *o*-IC_6H_4COOH have been proposed by Andrews and Keefer.[2]

Scheme I



Crystal Structure of 5. The intramolecular bond distances and angles observed in the crystal structure of 5 are shown in Figure 1. The distorted T-shape geometry of the three covalent bonds to iodine in this essentially planar molecule is similar to that in 2[4] and several other closely related benzoxiodole structures.[5] The crystal structures of trivalent iodine compounds in our studies invariably have been found to contain intermolecular coordination bonds between the relatively electropositive trivalent iodine and some nucleophilic atom in a neighboring molecule. In most structures an oxygen coordinates with iodine, as is the case in the three polymorphs of 1 which, despite their different crystal structures, contain similar coordination bonds involving the carbonyl oxygen atom. The geometry of oxygen coordination has been found to be remarkably constant.[6] Monovalent halogen atoms also can coordinate with the trivalent iodine[5] and it is this coordination mode which is present in the crystal structure of 5. Atom Cl-2 closely approaches (3.36 Å) the iodine of a screw-related molecule resulting in an approximately square planar arrangement of the four atoms, C-1, N, Cl-2, and Cl-2 (intermolecular) about iodine (Figure 1).

Since these coordination bonds are established between molecules related by a screw axis, the crystal structure consists of infinite chiral chains of coordinated molecules extending along the crystallographic *b* axis. The space group is $P2_1$ and therefore a single crystal is *chiral* and contains only one of the enantimorphs of the chiral chains; however,

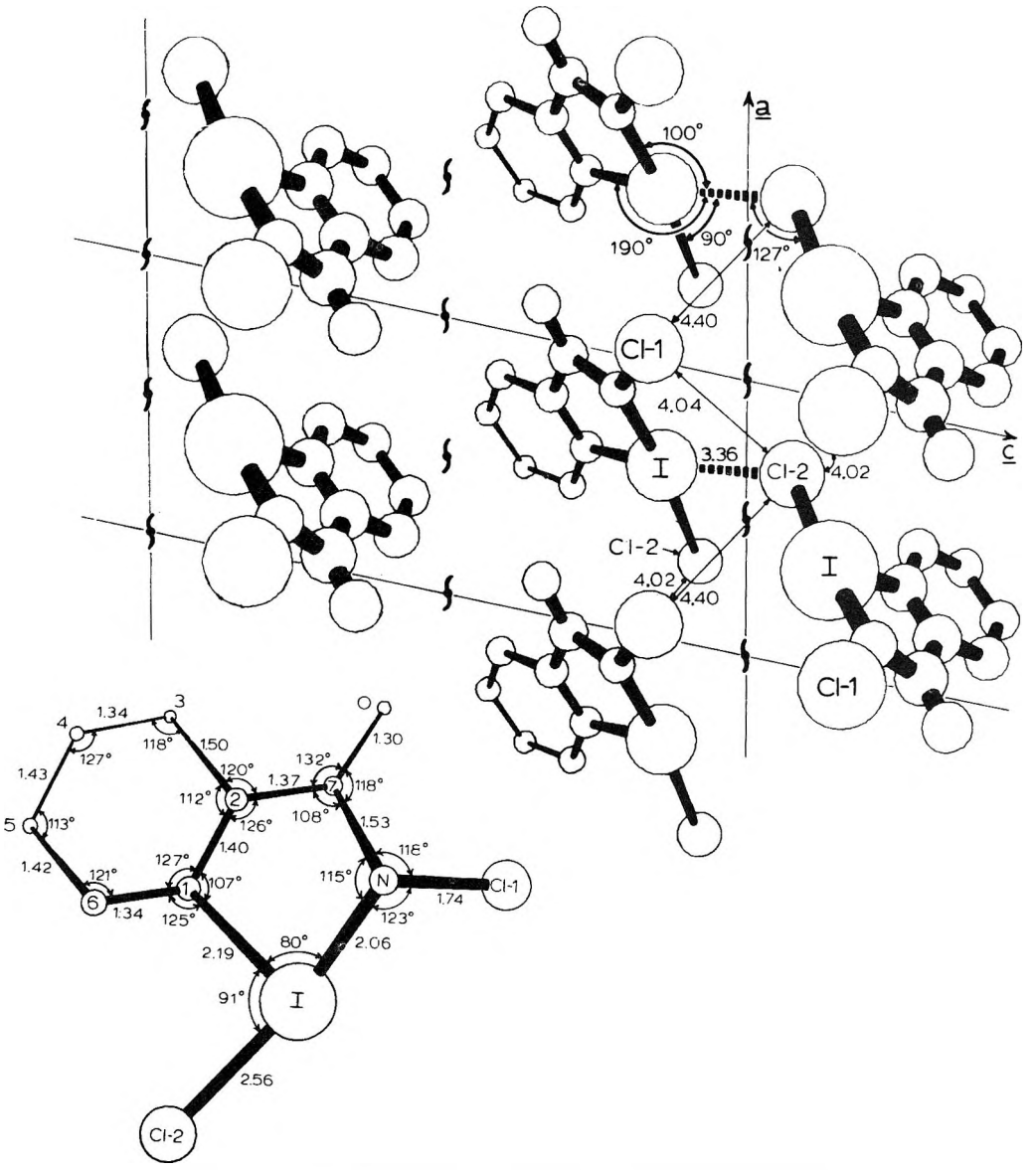


Figure 1. The crystal structure of **5**, viewed along the *b* axis. The coordination bond between I and Cl-2 of a screw related molecule is indicated by a broken line. Distances are given in ångstroms. Lower left: bond distances and angles in **5**. Esd values for bonds to I fall in the range 0.02–0.05 Å. The esd is 0.05 Å for the N–Cl bond, and 0.07–0.11 Å for the other bonds. Esd values for bond angles about I are ~1°, while those about the lighter atoms are 2–5°.

we have not attempted to establish the absolute configuration of the crystal used in the analysis. Intermolecular contacts between chains are dominated by Cl–Cl contacts ranging from 3.33 to 4.40 Å.

Experimental Section

Preparation of the Dichlorides 3 and 4. The preparation of **3** from **8** by chlorination in chloroform has been reported;[7] **4** was prepared in an analogous manner, mp 135–142° dec. Anal. Calcd: I, 38.25. Found: I, 38.9.

Formation of 5 from 3. **3** (50 mg) was dissolved slowly in 5 ml of warm (<60°) methanol. Yellow plates (8 mg) of **5** were isolated after cooling the methanolic solution overnight at −20°: mp 187–192° dec; ir (KBr) no λ_{max} from 4000 to 3100 cm^{-1}, 1660 (s), 1588 (m), 1565 (m), 1452 (s), 1440 (s), 1283 (s), 1234 (s), 1142 (s), 1114 (m), 1000 (m), 780 (m), 730 (s), 650 cm^{-1} (m). The mass spectrum exhibited the molecular ion peak at 315. Anal. Calcd: I, 40.19. Found: I, 39.90.

Preparation of 6. **3** (0.5 g) was dissolved slowly in aqueous pH ~7 phosphate buffer. The solution was filtered to remove a small amount of insoluble material. Acidification of the filtrate with dilute HCl gave a nearly colorless precipitate which was dried over P_2O_5 in vacuo, mp 127–129°. The mass spectrum exhibited a peak (*m/e* 281) corresponding to the molecular ion of **6**. This material rapidly oxidized a KBr disk which then displayed an ir spectrum similar to that of **8**.

Formation of 5 from 6. Fifty milligrams of the above precipitate (**6**) were dissolved in 8 ml of hot methanol and the solution was allowed to evaporate to dryness at room temperature. The crystalline residue was contained in two separate zones on the walls of the test tube. The first, 21 mg (75%) of yellow crystals, was identified as **5** by ir and TLC. The second zone consisted of ~18 mg (80%) of colorless crystals of **8**.

Preparation of 7. **4** dissolves readily in boiling methanol. Colorless needles of **7** were obtained after cooling the solution overnight: mp 182–186°; ir (KBr) 1610 (s), 1586 (m), 1568 (m), 1455 (m), 1439 (m), 1356 (m), 1028 (w), 1008 (m), 975 (m), 772 (w), 728 (s), 653 cm^{-1} (m). The mass spectrum exhibited the molecular ion peak for **7** at 295. Anal. Calcd: I, 42.98. Found: I, 42.81.

Crystal Structure Determination. The unit cell constants a = 5.78 (1), b = 6.49 (1), c = 12.88 (2) Å, and β = 101.7 (1)° were determined from Al-calibrated Weissenberg photographs. The diffraction symmetry and systematically absent reflections ($0k0$, k odd), together with the measured crystal density (2.27 g cm^{-3}), suggested either space group $P2_1$ or $P2_1/m$ with Z = 2. Of the 731 intensities measured on a Pailred diffractometer (monochromatic Cu Kα), 597 with intensity $\geq 3\sigma(I)$ were used for the solution and refinement of structure. The statistical distribution of these intensities (corrected for absorption, μ = 330 cm^{-1}) and the successful progress of the structure analysis verified our initial assignment of crystalline **5** to space group $P2_1$.

The structure was solved by Patterson and Fourier methods but no attempt was made to locate the hydrogen atoms. Least-squares

refinements of the atomic coordinates and thermal parameters (anisotropic for I and Cl and isotropic for C, N, and O) converged to R = 0.07. Various refinements of the multiplicities of C-7, O, and N in the final stages of the analysis confirmed the presence of the N-chloro lactam moiety in **5**.

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Registry No.—**3**, 5152-34-1; **4**, 27305-20-0; **5**, 27305-23-3; **6**, 3580-04-9; **7**, 27305-21-1.

Supplementary Material Available. Tables of fractional coordinates and temperature factors will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 24× reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 16th St., N.W., Washington D. C. 20036. Remit check or money order for $4.00 for photocopy or $2.50 for microfiche, referring to code number JOC-75-2129.

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Unusual Reaction of 4-Mercapto-1,2,3-benzotriazine with *N*-(2,4-Dibromophenyl)benzohydrazonyl Bromide

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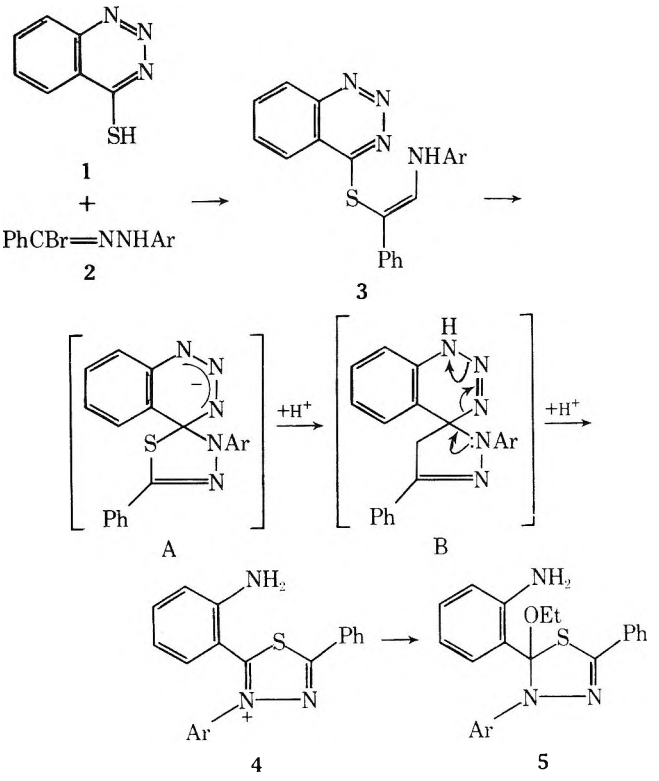
During the course of studies on hydrazonyl halides, we have noted an unusual reaction between 4-mercapto-1,2,3-benzotriazine (**1**), *N*-(2,4,-dibromophenyl)benzohydrazonyl bromide (**2**, Ar = 2,4-$Br_2C_6H_3$), and ethanol in the presence of triethylamine.

Reactions of aryl mercaptans with hydrazonyl halides in the presence of base give aryl thiohydrazonates which are normally stable under the conditions of formation.[1] In the present case we envisage deprotonation by triethylamine of the thiohydrazonate **3** formed from **1** and **2**, followed by intramolecular nucleophilic addition of the anion to C-4 of the triazine.[2] Reversible protonation of the spirocyclic intermediate A at N-1 or N-3 of the triazine to give, e.g., B may now be followed by aromatization of the newly formed ring, opening of the triazine ring with loss of N-3 and N-2 as nitrogen, and protonation of N-1 to give the thiadiazolium ion **4**. We have confirmed[3] that such thiadiazolium ions add ethoxide ion equivalent at C-2(5) when treated with ethanolic sodium ethoxide or ethanol–triethylamine and so progression of **4** to the observed product **5** is readily understood. The ease of reaction is notable in view of the stability of simple aryl thiohydrazonates.[1]

This case and the recently reported[4] formation of 2-(2-aminophenyl)-5-mercapto-1,3,4-thiadiazole from 4-hydrazinoquinazoline and CS_2 in the presence of KOH represent unusual Smiles-type rearrangements[5] in which the migrating aryl ring (1,2,3-benzotriazin-4-yl or quinazolin-4-yl) collapses while the cyclic transition state for the migration is consolidated as a new ring (1,3,4-thiadiazole), closure occurring by C–N or C–S bond formation as appropriate.



Experimental Section

NMR data were obtained with a Varian A-60 spectrometer (tetramethylsilane as internal standard).

4-Mercapto-1,2,3-benzotriazine was conveniently prepared from 1,2,3-benzotriazin-4-one and phosphorus pentasulfide in pyridine or toluene.[6]

5-(2-Aminophenyl)-4-(2,4-dibromophenyl)-5-ethoxy-2-phenyl-Δ^2-1,3,4-thiadiazoline (5). A mixture of 1.63 g (0.01 mol) of **1**, 4.33 g (0.01 mol) of **2**,[7] and 30 ml of ethanol was stirred at room temperature and 2 ml of triethylamine was added. There was an immediate evolution of gas. After 30 min, solvent was removed in vacuo and the pale brown solid was washed with water and dried to give 2.8 g (53%) of **5** which crystallized from hexane as fawn needles: mp 136–137°; ir (Nujol–hexachlorobutadiene mulls) 3500 and 3400 (NH), 1600, 1570, 1550, and 1480 (aromatic C=C and C=N),[8] 1460 and 1375 (aliphatic CH), 1325, 1300, 1220, 1150, 1105, 1075, 1060, 1050, 980, 970; 870, 820, 765, 745, 725, and 690 cm^{-1} (aromatic C–H; mono-, 1,2-di-, and 1,2,4-trisubstituted benzene); NMR ($CDCl_3$) δ 7.90–6.42 (m, 12 H), 4.39 (s, br, 2 NH, exchangeable with D_2O), 3.82 (m, 2 H), and 1.35 ppm (t, 3 H).

Anal. Calcd for $C_{22}H_{19}Br_2N_3OS$: C, 49.5; H, 3.6; Br, 30.0; N, 7.9. Found: C, 49.8; H, 3.8; Br, 30.5; N, 7.7.

Registry No.—**1**, 2536-88-1; **2** (Ar = 2,4-$Br_2C_6H_3$), 2516-46-3; **5** (Ar = 2,4-$Br_2C_6H_3$), 55298-74-3.

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1,2-Hydride Shift in the 2-Phenylvinyl Cation[1]

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Recently, degenerate 1,2-aryl shifts across the double bond in triarylvinyl cations were investigated in this laboratory using the ^{14}C label as tracer or ^{13}C labeling coupled with ^{1}H NMR and ^{13}C NMR analyses. The reactions studied were the solvolyses of triphenylvinyl-2-^{14}C triflate,[2] the reaction of triphenylvinyl-2-^{14}C or triphenylvinyl-2-^{13}C bromide with HOAc–AgOAc,[3] and the acetolysis and trifluoroacetalysis of trianisylvinyl-2-^{13}C bromide.[4] As an extension of this work, it was thought that the possibility of a 1,2-phenyl shift in the 2-phenylvinyl cation might be similarly studied using labeling with isotopic carbon. However, when either *cis*- or *trans*-β-bromostyrene (*cis*-**1** or *trans*-**1**) was treated with HOAc–AgOAc, the product obtained was acetophenone (**2**). The reaction was very slow. For example, when the heterogeneous mixture of 3.8 mmol of *cis*-**1** or *trans*-**1** and a 10% excess of AgOAc in 100 ml of HOAc was refluxed with stirring for 3 weeks, the ratio of product **2** to unreacted *cis*-**1** or *trans*-**1**, as measured by VPC, was about 20:80. When the AgOAc was replaced by NaOAc, no reaction was detected after 3 weeks, indicating that the presence of Ag^+ ion was essential and suggesting that the reaction was a cationic process.

The formation of **2** from *cis*-**1** or *trans*-**1** likely is attributable to a 1,2-hydride shift in the 2-phenylvinyl cation.

$$\underset{\mathbf{3}}{PhCH{=}\overset{+}{C}H} \longrightarrow \underset{\mathbf{4}}{Ph\overset{+}{C}{=}CH_2}$$

The driving force for the reaction, as in many reported rearrangements of vinyl cations,[5] is the formation of the more stable 1-phenylvinyl cation (**4**) from the less stable 2-phenylvinyl cation (**3**). Recently, Jäckel and Hanack[6] have reported the first observation of a 1,2-hydride shift in a vinyl cation in the formation of cyclopropyl ethyl ketone from the solvolysis of *cis*- or *trans*-3-cyclopropyl-2-propen-2-yl triflate in aqueous trifluoroethanol. The present finding is another example of a 1,2-hydride shift in a vinyl cationic system.

Although the use of labeled *cis*-**1** and *trans*-**1** as a means of studying degenerate 1,2-phenyl shifts no longer applies, *cis*- and *trans*-β-bromostyrene-α-^{14}C are utilized in the present work so that data on yields may be obtained by isotope dilution. The results are summarized in Table I. Moreover, from the reactions with labeled substrates, oxidation of the active acetophenone product, as expected, gave a benzoic acid with essentially no loss of ^{14}C activity. This finding thus also eliminated the remote possibility that a 1,2-phenyl shift might have occurred prior to the 1,2-hydride shift.

$$Ph^{14}CH{=}\overset{+}{C}H \not\rightleftharpoons PhCH{=}\overset{+}{^{14}C}H \longrightarrow Ph\overset{+}{C}{=}{}^{14}CH_2$$

From Table I, it is seen that phenylacetylene was detected by isotope dilution as a minor product. The yields of **2** at different stages of the reactions, as summarized in Table I, showed no significant difference with either *cis*-**1**-α-^{14}C or *trans*-**1**-α-^{14}C as reactant. Thus the stereochemical difference in the initial substrate has been lost during the reaction, indicating that the 1,2-hydride shift took place via classical vinyl cations **3** and **4**, rather than via a hydrogen-bridged ion. A similar conclusion was drawn by Jäckel and Hanack[6] for the rearrangement of the 2-cyclopropyl-1-methylvinyl cation to the 1-cyclopropyl-2-methylvinyl cation.

Table I
Yields from Isotope Dilution Experiments in the Reaction of *cis*- or *trans*-β-Bromostyrene-α-^{14}C (*cis*- or *trans*-1-α-^{14}C) with HOAc–AgOAc at 120°

Reactant	Reaction time, days	Yield, % $PhCOCH_3$	Yield, % $PhC{\equiv}CH$
cis-1-α-^{14}C	4	5.7[a]	0.6
	8	9.1	0.5
	14	14.2	0.6
	21	19.4	0.5
	29	29.4	0.5
trans-1-α-^{14}C	4	5.3	0.5
	8	9.4	0.8
	14	15.4	0.3
	21	16.8	0.5
	29	33.8	0.5

[a] As an illustration, in this experiment, the specific activity of the 1.769 mmol of reactant was 2.32×10^6 dpm/mmol. The amount of $PhCOCH_3$ carrier added was 3.02 mmol and the specific activity of the diluted $PhCOCH_3$ product was 7.90×10^4 dpm/mmol. Calculation from these data gave the yield of 5.7%.

Experimental Section

Reaction of *cis*- or *trans*-β-Bromostyrene (*cis*-1 or *trans*-1) with HOAc–AgOAc. In a typical run, 7.0 g (38 mmol) of *cis*-**1** or *trans*-**1** and 7.0 g (42 mmol) of AgOAc in 100 ml of HOAc were placed in a 200-ml flask equipped with a magnetic stirrer and fitted with a reflux condenser and $CaCl_2$ tube. All the AgOAc did not dissolve and the heterogeneous mixture was gently refluxed with stirring for 21 days. The resulting material was poured into a saturated NaCl solution and then extracted several times with petroleum ether (bp 40–60°). The extract was washed with 10% $NaHCO_3$ solution and with H_2O and then dried over $MgSO_4$. After removal of the solvent, the only product recovered from the residue by preparative VPC (12 ft × 0.375 in. copper column packed with 20% FFAP on Chromosorb W at 150°), besides the unreacted bromide, was acetophenone (**2**), which showed identical NMR and ir spectra with those of an authentic sample. From a number of experiments, the ratio of **2** to unreacted *cis*-**1** or *trans*-**1** was found to average about 20:80, with individual values ranging from 17:83 to 22:78.

Acetophenone also was the only isolable product when the reaction with HOAc–AgOAc was carried out in the presence of Ac_2O or when the reaction mixture was worked up by distilling off most of the HOAc and extracting with petroleum ether without being poured into saturated NaCl solution. If the initial product was 1-phenylvinyl acetate, during the reaction, this product must have been cleaved to the vinyl alcohol which ketonized to **2**. A similar cleavage of the expected product ester to the corresponding ketone was observed in the formolysis of triphenylvinyl triflate[2] and in the formolysis of *cis*- or *trans*-1,2-dianisyl-1-phenylvinyl bromide.[7]

***cis*- and *trans*-β-Bromostyrene-α-^{14}C (*cis*-1-α-^{14}C and *trans*-1-α-^{14}C).** $Ph^{14}COOH$ was converted by standard procedures to the acid chloride and then reduced to $Ph^{14}CHO$,[8a] in yields of 95 and 84%, respectively. The aldehyde, through the Perkin reaction, was converted in 50% yield to the labeled *trans*-cinnamic acid, $Ph^{14}CH{=}CHCOOH$.[8b] Conversion of the *trans*-cinnamic acid to the dibromide followed by dehydrobromination in H_2O–NaOH as described by Grovenstein and Lee[9] gave predominantly *trans*-1-α-^{14}C. After recrystallization from pentane at −20°, pure *trans*-1-α-^{14}C, as indicated by VPC, was obtained. When the dehydrobromination of the labeled *trans*-cinnamic acid dibromide was carried out with $NaHCO_3$ in dry acetone,[10] the product was *cis*-1-α-^{14}C.

Determination of Yields by Isotope Dilution. The reactions were carried out in sealed tubes. Each tube, equipped with a small magnetic stirring bar, contained 1.769 mmol of *cis*-1-α-^{14}C or 1.795 mmol of *trans*-1-α-^{14}C, 2.0 mmol of AgOAc, and 5.0 ml of a 9:1 (v/v) mixture of HOAc–Ac_2O. The tubes were heated with stirring in an oil bath at 120 ± 2°. At different intervals ranging from 4 to 29 days, samples were quenched by cooling in an ice bath, appro-

priate amounts of ordinary acetophenone and phenylacetylene were added as carriers, and the reaction mixtures poured into saturated NaCl and worked up as described earlier. Samples of the diluted acetophenone and phenylacetylene were recovered by preparative VPC and their specific activities determined. From the known weights of carriers added and the known specific activities before and after dilution, the yields of acetophenone and phenylacetylene were calculated. The results are summarized in Table I.

Registry No.—*cis*-**1**, 588-73-8; *trans*-**1**, 588-72-7; **3**, 24343-35-9.

References and Notes

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Stereochemistry of Electrophilic Additions to Linear Enol Ethers

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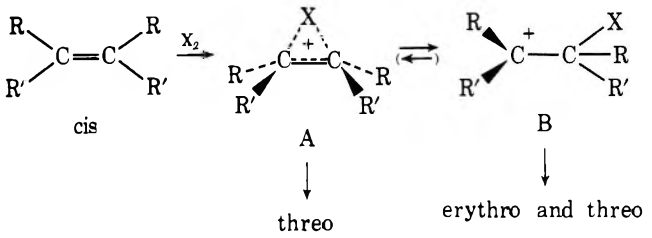
The stereospecific electrophilic anti addition of halogen to alkenes results from the existence of the bridged halonium ion A, generally more stable than the classical carbonium ion B.



Syn-addition products appear whenever the ion B is stabilized. A well-known illustration of this case is when an oxygen nonbonding electron pair stabilizes the carbocation by conjugation through the benzene ring, as in the case of anethole.[1]

The effect of an oxygen atom directly bound to the cationic carbon has been the subject of stereochemical studies in cyclic unsaturated ethers; in these cases, by adding chlorine to dihydropyrans[2] or dihydrofurans,[3] 70 and 78% of syn addition was obtained. Surprisingly, very few studies have been made on the stereochemistry of electrophilic addition to linear ethers as simple as $ROCH{=}CHCH_3$ (**1**, isomers *Z* and *E*).

In the present study, the results found when R = C_2H_5 (**1a**) or R = $CH_2C_6H_5$ (**1b**) are reported. In order to examine if it was possible to control the stereochemistry of the addition on this type of olefin by modifying the availability of the oxygen nonbonding electrons to the carbocation, the study of para-substituted phenol ethers (**2**) was simultaneously undertaken. In this case, the stabilization of the

$$p\text{-}YC_6H_4OCH{=}CHCH_3$$

2

c, Y = OMe; d, Y = Me; e, Y = H; f, Y = Cl

carbocation by oxygen electrons depends upon the nature of Y.

Experimental Section

The halogenation of ethers was carried out by adding chlorine, bromine, or iodine monochloride to a 10% solution of olefin in CCl_4 at −20° in the dark. The halogens reacted rapidly and gave the expected products, as revealed by NMR spectroscopy and chemical results. There were no by-products except in the case of ether **1a**,

$$R\,(\text{or Ar})OCH{=}CHCH_3 \xrightarrow{X_2} R\,(\text{or Ar})OCHXCHX'CH_3$$
(A) (M) (X)

for which, even under these experimental conditions, some products due to radical reactions appeared. The reaction of iodine addition did not proceed at low temperature and polymerization occurred at higher temperature.

The mixtures obtained were periodically analyzed by NMR spectroscopy while being maintained at −20°, thus avoiding an excess of halogen, which catalyzes the isomerization between erythro and threo dihalogenated ethers.[3]

The ratio of erythro to threo isomers depended on the configuration (*Z* or *E*) of the starting olefin (Table I). Because the product mixtures were not in the equilibrium ratio and were stable in all cases under the experimental conditions, it appeared that the reaction proceeded by kinetic control.

Table I
Stereospecificity of the Addition of Halogens to *Z* or *E* Olefins[a]

R (or Ar) OCH=CHCH$_3$

Olefin, R or Ar	Cl_2 addition, % T		Br_2 addition, % T		ICl addition, % T	
	Z	*E*	*Z*	*E*	*Z*	*E*
1a, C_2H_5	50	37	71[b]	68[b]	74	
1b, $C_6H_5CH_2$	55	40	74	65	75	
2c, *p*-$MeOC_6H_4$	58	46	83	78	90	87
2d, *p*-MeC_6H_4	60	48	92	84	98	
2e, C_6H_5	61	50	95	86	100	
2f, *p*-ClC_6H_4	62	51	100	100	100	100

[a] Percent anti addition, reproducible within 2% (threo ether from the *Z* olefin, and erythro from the *E* olefin). [b] Approximate values owing to the presence of by-products.

In the NMR spectra of the addition products, the proton H_A signal appeared as two doublets, one having a coupling constant of 2 Hz and the other one having a coupling constant of 6–8 Hz (Table II). It was noticed, as in other well-known cases,[4] that the isomer having the smallest J_{AM} value appeared at a lower field.

These data allowed us to classify the isomers in two well-characterized families: in the present study, the isomer having the smallest coupling constant (lower field signal) is the threo isomer (vide infra).

Discussion

The assignment of the erythro or threo configuration to each of the two spectroscopic families is based on the two following criteria.

(a) The anti addition becomes more or less stereospecific depending on the nature of the electrophilic reagent: $I^+ > Br^+ > Cl^+$ (Table I).

Table II
NMR Spectra of Erythro and Threo Dihalogenated Ethers[c]

R (or Ar) OCHXCHX′CH$_3$
(A) (M) (X)

R or Ar	X	X′	δH$_A$, ppm (J_{AM}, Hz) Erythro[d]	δH$_A$, ppm (J_{AM}, Hz) Threo[e]	δH$_X$, ppm[a] Erythro	δH$_X$, ppm[a] Threo	δH$_M$, ppm[b]
C_2H_5	Cl	Cl	5.5 (5.8)	5.7 (2.8)	1.63	1.63	
	Br	Br	5.86 (7.8)	6.20 (2)	1.85	1.85	
	Cl	I	5.5 (7.6)	5.9 (2)	2.03	1.97	4.35
$C_6H_5CH_2$	Cl	Cl	5.45 (5.8)	5.63 (2.4)	1.59	1.63	4.17
	Br	Br	6.01 (7.6)	6.12 (2)	1.84	1.88	4.38
	Cl	I	5.42 (7.6)	5.8 (2)	1.97	1.97	4.44
p-$MeOC_6H_4$	Cl	Cl	5.87 (6.2)	6.00 (2.4)	1.72	1.76	4.33
	Br	Br	6.13 (8)	6.45 (2)	1.97	2.03	4.55
	Cl	I	5.85 (8)	6.17 (2)	2.07	2.07	4.50
p-MeC_6H_4	Cl	Cl	5.90 (6.2)	6.05 (2.4)	1.70	1.75	4.33
	Br	Br	6.12 (8)	6.43 (2)	1.95	2.02	4.55
C_6H_5	Cl	Cl	5.97 (6.2)	6.08 (2.4)	1.67	1.73	4.33
	Br	Br	6.20 (8)	6.50 (2)	1.98	2.02	4.55
	Cl	I		6.30 (2)		2.10	4.50
p-ClC_6H_4	Cl	Cl	5.91 (6.2)	6.07 (2.4)	1.72	1.76	4.33
	Br	Br	6.21 (8)	6.50 (2)	1.97	2.02	4.55
	Cl	I	5.90 (8)	6.20 (2)	2.08	2.08	4.50

[a] Doublet (J_{MX} = 7 Hz). [b] Signals of the two isomers together. [c] Chemical shifts were expressed relative to tetramethylsilane used as internal reference for a 10% solution of dihalogenated products in CCl_4. [d] Registry no. are, respectively, 54912-01-5, 54912-03-7, 54912-05-9, 54912-07-1, 54912-09-3, 54934-05-3, 54912-12-8, 54912-14-0, 54912-16-2, 54912-18-4, 54912-20-8. 54912-22-0, 54912-24-2, 54934-06-4, 54912-28-6, 54934-07-5. [e] Registry no. are, respectively, 54912-02-6, 54912-04-8, 54912-06-0, 54912-08-2, 54912-10-6, 54912-11-7, 54912-13-9, 54912-15-1, 54912-17-3, 54912-19-5, 54912-21-9, 54912-23-1, 54912-25-3, 54912-26-4, 54912-27-5, 54912-29-7, 54912-30-0.

Table III[a]
NMR Spectroscopy of Enol Ethers. Chemical Shift of ^{13}C in the Propenyl Group

R (or Ar) OCH=CHCH$_3$
(α) (β)

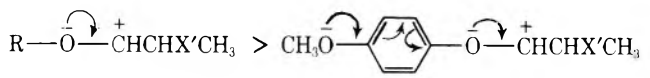
	1a R = C_2H_5		1b R = $CH_2C_6H_5$		2c Y = OMe		2d Y = CH_3		2e Y = H		2f Y = Cl	
	Z	E	Z	E	Z	E	Z	E	Z	E	Z	E
δC$_\alpha$	145.23	146.27	145.0	146.12	141.81	143.23	141.19	142.25	140.69	141.83	140.38	141.68
δC$_\beta$	100.84	98.41	101.73	99.29	105.95	106.68	106.48	107.32	107.18	108.08	108.07	109.01
δCH$_3$	9.22	12.59	9.32	12.58	9.32	12.18	9.35	12.25	9.34	12.23	9.37	12.13

[a] ^{13}C NMR spectra were determined using a Varian XL-100-12 NMR spectrometer, operating at 25.20 MHz in pulsed Fourier transform mode with proton noise decoupling (precision ±0.04 ppm). Chemical shifts are expressed in parts per million relative to tetramethylsilane used as internal reference for $CDCl_3$ solutions (0.4–0.5 *M*).

(b) By changing the substituent Y in olefins **2**, the availability of the oxygen electrons toward the carbocation decreases in the order *p*-MeO > *p*-Me > H > *p*-Cl. For any given halogen and a series of olefins **2** with configuration *Z* or *E* stated, the stereospecificity of the anti addition must increase from Y = *p*-MeO to Y = Cl (Table I).

Those two criteria coincide when the erythro structure is attributed to dihalogenated ethers having a coupling constant J_{AM} = 6.4–8 Hz and the threo structure is attributed to the ones having a coupling constant J_{AM} = 2–2.4 Hz.

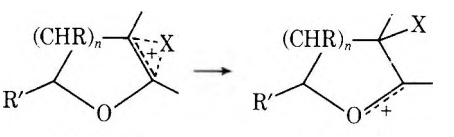
It is noteworthy that with olefins **2**, even when Y = MeO, the anti addition always remains more stereospecific than for the olefins **1** in spite of the resonance hybrid which greatly favors the opening of the bridged ion A.



In all cases, the nonbonding electrons of a phenol ether **2** remain less available than those of an alcohol ether **1**.

On the other hand, the observed results for the *Z* or *E* olefins show that the *Z* isomer systematically yields more anti addition than the *E* isomer (the contrary is usually noticed with simple olefins[5]). That result means that an attractive effect exists between OR and CH_3 in the bridged cis ion A, as has been already noticed in the original enol ethers.[6] The bridged trans ion A is less stable than its cis isomer and is more prone to open.

It is interesting to compare these results with those obtained with cyclic ethers[2,3] (which may be classified as alcohol ether **1** of *Z* configuration). The higher yields observed in syn addition indicate in fact that the corresponding bicyclic halonium ions are even less stable than in the linear series.



n = 1, 2 *n* = 1, 2

The study of the spectroscopic properties of the olefins **2** shows that a good correlation exists between the chemical shift $\delta\ ^{13}C_\beta$ in NMR spectroscopy (Table III) and the Hammett constants σ (Y): $\delta\ ^{13}C_\beta = 107.18 + 0.436\sigma$ (Y) for the *Z* olefins ($|\delta_{calcd} - \delta_{obsd}| \leq 0.08$ ppm); $\delta\ ^{13}C_\beta = 108.08 + 0.436\sigma$ (Y) for the *E* olefins ($|\delta_{calcd} - \delta_{obsd}| \leq 0.15$ ppm). It is well known that in unsaturated systems, the contribution of the π electron density is an important component in the ^{13}C chemical shift, especially for analogous ring-substituted phenyl vinyl ethers.[7] Therefore the chemical shift of C_β seems to be a good criterion to evaluate the availability of the oxygen nonbonding electrons toward the benzene ring, whatever be the series.

In Figure 1, the percent of anti addition found when adding chlorine, bromine, and iodine monochloride is reported against the chemical shift of C_β. A rough linear relationship is found for chlorine: it appears that the same phenomenon occurs with the alcohol ether or the phenol ether, the six points falling on the same empirically derived straight line.

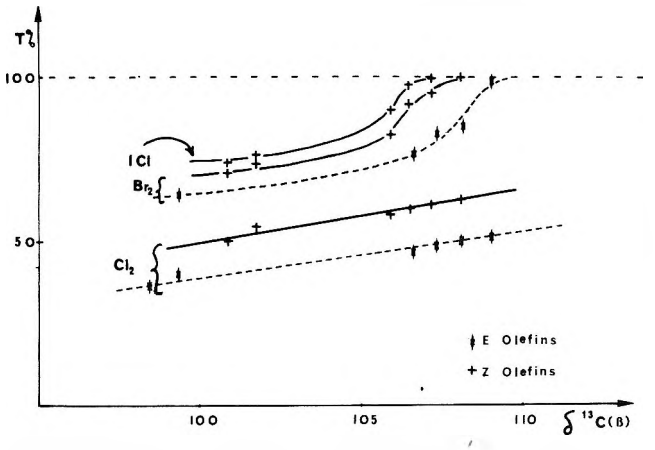


Figure 1. Correlation between the selectivity of electrophilic anti addition and the availability of π electron on C_β (evaluated by means of its chemical shift, see Hammett correlation in text).

When adding bromine or iodine monochloride, different curves tending towards the asymptotic value of 100% anti addition for electron-withdrawing groups are observed. In these cases, there is a stabilization of A due to the electrophilic reagent and a destabilization of B due to the electron-withdrawing groups. Since the concentration of B (at equilibrium) is an exponential function of $-\Delta G/RT$, its contribution to the reaction becomes negligible. In fact, the equilibrium conditions are not attained, as the *Z* and *E* isomeric enol ethers do not give the same erythro:threo ratio.

In conclusion, the electrophilic addition simultaneously involves the two intermediate species A and B, the bridged halonium ion and the classical carbonium ion.

Registry No.—(*Z*)-**1a**, 4696-25-7; (*E*)-**1a**, 4696-26-8; (*Z*)-**1b**, 32426-80-5; (*E*)-**1b**, 32426-79-2; (*Z*)-**2c**, 51896-37-8; (*E*)-**2c**, 51896-38-9; (*Z*)-**2d**, 51896-41-4; (*E*)-**2d**, 51896-42-5; (*Z*)-**2e**, 4696-23-5; (*E*)-**2e**, 4696-24-6; (*Z*)-**2f**, 51896-45-8; (*E*)-**2f**, 54912-31-1; Cl_2, 7782-50-5; Br_2, 7726-95-6; ClI, 7790-99-0.

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1-Phenylpiperidine-2,4,6-trione

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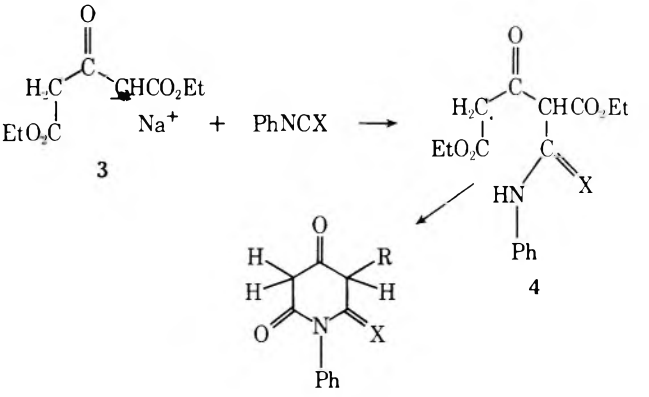
The synthesis of the title compound has been the subject of several papers that have appeared in the chemical literature. The compound identified by Kaushal[1] as **5c** was subsequently shown[2] to be an adduct of aniline and zinc chloride. Later, Nakhre and Deshapande[3] reported that **5c** may be obtained by the reaction of 3-oxoglutaric anhydride with aniline in anhydrous ether. Repetition of this reaction yielded the anilic acid **1**, which readily lost carbon dioxide upon heating, with the formation of acetoacetanilide (**2**).

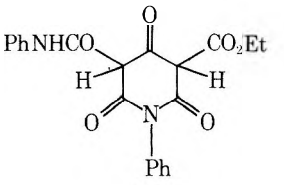
$$\underset{\mathbf{1}}{PhNHCOCH_2COCH_2CO_2H} \xrightarrow{-CO_2} \underset{\mathbf{2}}{PhNHCOCH_2COCH_3}$$

More recently, Junek, Metallidis, and Ziegler[4] described the reaction of the sodium salt of diethyl 3-oxoglutarate (**3**) with phenyl isothiocyanate[5] to give the ester **5a** via the intermediate formation of **4**.



5a, R = CO_2Et; X = S
b, R = CO_2Et; X = O
c, R = H; X = O

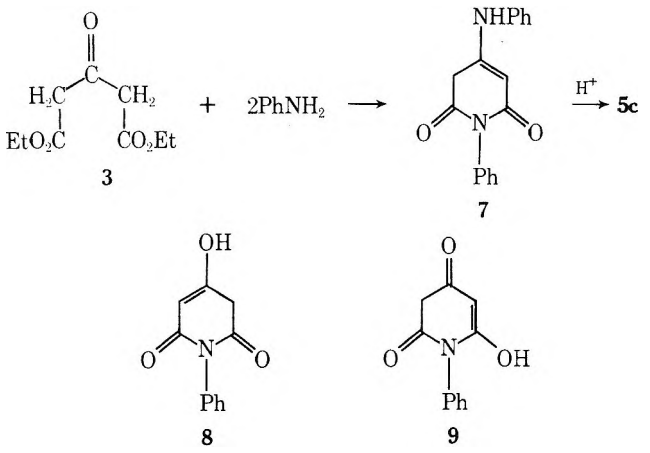
When the reaction was conducted using phenyl isocyanate, it was reported[4] that the product was not the expected ester **5b**, but **5c**, in which an ethoxycarbonyl group had been lost. We have re-examined this reaction, but have been unable to find any trace of **5c** among the products. The ester **5b** was obtained, accompanied by a small amount of a compound formed by reaction of **5b** with a second molecule of phenyl isocyanate, for which **6** is a probable structure.



6

Finally, we have been able to synthesize the required trione **5c** by acidic hydrolysis of **7**, which is obtained by reaction of diethyl 3-oxoglutarate with aniline.[6]

The NMR spectrum of **5c** in DMSO-d_6 indicates three types of exchangeable protons, with singlets at δ 3.65 (2 H), 5.42 (1 H), and 17.1 (1 H, broad). Such a spectrum is consistent only with one of the two possible monoenol tautomers, **8** or **9**.



Experimental Section

3-Oxoglutaranilic Acid (1). A solution of 1.88 g (0.02 mol) of aniline in 20 ml of anhydrous ether was added at a slow drop rate to a stirred suspension of 2.56 g (0.02 mol) of 3-oxoglutaric anhydride in 20 ml of the same solvent. After the addition was complete, the mixture was stirred for a further 2 hr. The resulting solid was collected and washed with anhydrous ether to give 3.80 g (86%) of a white powder: mp 105–106°; ir (KBr) 3300, 1730, and 1660 cm^{-1}.

Anal. Calcd for $C_{11}H_{11}NO_4$: C, 59.7; H, 5.0; N, 6.4. Found: C, 59.9; H, 5.0; N, 6.5.

Decarboxylation of 1. Compound 1 (0.5 g, 0.0023 mol) was heated at 120° for 5 min, as CO_2 was evolved. On cooling, the reaction mixture solidified to give 0.40 g (100%) of 2: mp (benzene) 84–85°, undepressed on admixture with an authentic sample; ir (KBr) identical with that of an authentic sample.

Reaction of Phenyl Isocyanate with 3. Sodium (2.3 g, 0.1 mol) was added to a solution of 20.2 g (0.1 mol) of diethyl 3-oxoglutarate in 120 ml of anhydrous ether and the mixture was warmed gently until all the sodium had dissolved. The resulting solution was stirred at 0–5° as 11.9 g (0.1 mol) of phenyl isocyanate was added dropwise. The suspension thus obtained was heated at reflux temperature on a steam bath for 2 hr. After cooling, 500 ml of water was added and the mixture was stirred until all the solid had dissolved. The aqueous layer was separated and acidified with 5 *N* HCl, and the precipitated solid was collected and washed with water. Extraction of the solid with 300 ml of benzene, followed by evaporation of the solvent, yielded 0.75 g of **6**. An analytical sample, obtained by recrystallization from ethanol, decomposed on heating, with no clearly defined melting point: mass spectrum *m/e* (rel intensity) 394 (29), 348 (27), 322 (4), 302 (11), 256 (38), 174 (5), 120 (12), 119 (5), 93 (100), 77 (8).

Anal. Calcd for $C_{21}H_{18}N_2O_6$: C, 64.0; H, 4.6; N, 7.1. Found: C, 63.7; H, 4.5; N, 6.8.

The undissolved material was again washed with benzene to give crude **5b**, 10.8 g (39%): mp (EtOH) 198–200°, undepressed by admixture with an authentic sample;[7] ir (KBr) identical with that of an authentic sample.

1-Anilino-1-phenyl-2,6(1*H*,3*H*)-pyridinedione (7). This compound was prepared by the following modification of the method described by Emery.[6] A mixture of 40.1 g (0.2 mol) of diethyl 3-oxoglutarate and 37.2 g (0.4 mol) of aniline was heated at 120° for 4 hr in an open flask. After it had cooled, a vacuum distillation apparatus was attached and a pressure of about 50 mm was maintained as the bath temperature was raised to 180° over a 30-min period. The reaction was completed by heating for a further 1.5 hr at 180° under reduced pressure. After cooling, the reaction mixture was warmed with 100 ml of ethanol to obtain a suspension of yellow solid, which was filtered from the hot mixture. The solid was dissolved in a solution of 16 g of sodium hydroxide in 400 ml of 50% methanol. After filtration, the solution was acidified with acetic acid to obtain 6.7 g (12%) of **7**: mp (DMF–methanol) 281–283° dec (lit.[6] mp 275° dec); NMR (DMSO-d_6) δ 9.20 (s, 1), 7.0–7.6 (m, 10), 5.45 (s, 1), 3.81 (s, 2).

1-Phenylpiperidine-2,4,6-trione (5c). Compound 7 (5 g, 0.018 mol) was added to a boiling mixture of 50 ml of 50% acetic acid and 5 ml of concentrated HCl. The mixture was heated at reflux temperature for 5 min and a small amount of undissolved solid was removed by filtration of the hot mixture. The filtrate was evaporated to dryness under reduced pressure, the residue was dissolved in 35 ml of water, and the solution was made basic by dropwise addition of 40% KOH. After extraction with ether (2 × 10 ml), the aqueous solution was acidified with acetic acid and the small amount of precipitated solid was removed by filtration. The solution was acidified to pH 3–4 with concentrated HCl and chilled, and the precipitated solid was collected. The yield of crude **5c** was 2.0 g (55%): mp (CH_3CN) 183–184° dec; ir (KBr) 3110 (broad), 1711, 1670, 1640, 1370, 1255, 1208, 841, and 700 cm^{-1}; NMR (DMSO-d_6) δ 17.1 (broad s, 1), 7.0–7.6 (m, 5), 5.42 (s, 1), 3.65 (s, 2); mass spectrum *m/e* (rel intensity) 203 (55), 175 (18), 119 (100), 93 (38), 91 (37), 84 (55), 77 (9), 64 (19), 63 (10), 51 (11), 42 (21), 39 (12).

Anal. Calcd for $C_{11}H_9NO_3$: C, 65.0; H, 4.5; N, 6.9. Found: C, 64.6; H, 4.6; N, 7.2.

Registry No.—**1**, 55267-57-7; **2**, 102-01-2; **3**, 105-50-0; **5b**, 55267-58-8; **5c**, 55267-59-9; **6**, 55267-60-2; **7**, 55267-61-3; 3-oxoglutaric anhydride, 10521-08-1; phenyl isocyanate, 103-71-9.

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Bufadienolides. 30. Synthesis of the Ch'an Su Component 15β-Hydroxybufalin[1,2]

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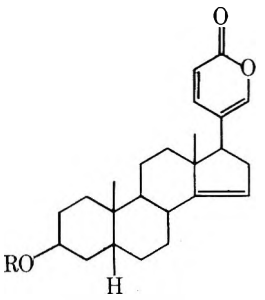
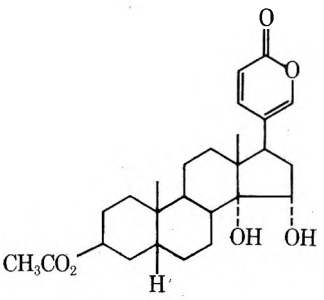
Venom from the toad *Bufo bufo gargarizans* is generally employed to prepare the Chinese medicinal preparation, Ch'an Su.[4] The first bufadienolide component was isolated from Ch'an Su some 63 years ago,[5] and a number of later investigations produced most of the bufadienolides now considered representative of toad venoms. In a recent continuation of their very careful toad venom isolation studies the Meyer group[6] has succeeded in isolating 11 new bufadienolides from Ch'an Su. One of these new bufadienolides was found to be 15β-hydroxybufalin (**3d**). The structure of the substance was determined by instrumental methods and comparison with the higher melting cis diol obtained by osmium tetroxide hydroxylation of 14-dehydrobufalin acetate (**1a**). The mixture of diols **2** and **3a** obtained by this procedure amounted to a 10% yield. Interestingly, the β-cis glycol was obtained in about 2% yield.

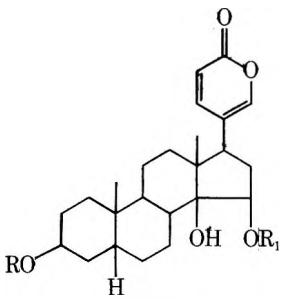
Since 15β-hydroxybufalin may be a component of other toad venoms and possess potentially useful biological properties, we have developed a new synthesis of this substance based on our prior route to 15β-hydroxy digitoxigenin.[7] To begin with, we subjected 14-dehydrobufalin acetate to a modified osmium tetroxide hydroxylation procedure. By this means, α-cis diol **2** was obtained in up to 28% yield and β-cis diol **3a** was isolated in about 5% yield. The most efficient route to the β-cis diol was realized using a Woodward cis-hydroxylation procedure.[7] Treatment of 14-dehydrobufalin (**1b**) or its 3-acetate derivative **1a** with iodine and silver acetate led to 21% yields of 15β-acetate **3b** and **3c**. Next, an acid-catalyzed hydrolysis procedure was utilized to convert the acetate derivatives **3a–c** to 15β-hydroxybufalin (**3d**). By this approach yields of triol **3d** ranged from



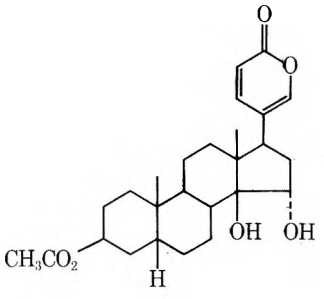
1a, R = $COCH_3$
b, R = H



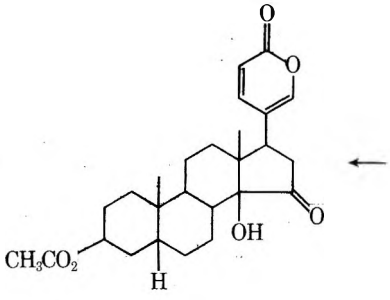
2



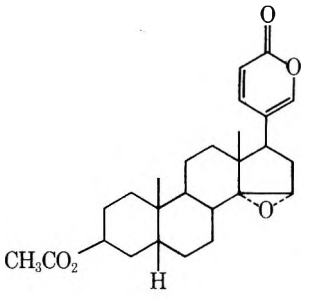
3a, R = $COCH_3$; R_1 = H
b, R = H; R_1 = $COCH_3$
c, R = R_1 = $COCH_3$
d, R = R_1 = H



5



4



6

about 30% starting with diacetate **3c** to over 50% starting with monoacetate **3a**.

Additional evidence for the structure assigned to 15β-hydroxybufalin (**3d**) was obtained by oxidizing 3β-acetate **3a** to 15-ketone **4**.[8] As part of an earlier study we synthesized 15α-hydroxybufalin from 14-dehydrobufalin acetate (**1a**) and by oxidation of the 15α-alcohol obtained 15-ketone **4**. The specimens of 15-ketone **4** obtained from the 15β- and 15α-alcohols **3a** and **5** were identical. The same 15-ketone (**4**) was more conveniently obtained by chromium trioxide oxidation of α-epoxide **6**, as previously reported.[8]

In summary, the Woodward cis-hydroxylation approach to 15β-hydroxybufalin has provided a workable means of obtaining the substance for biological evaluation. The route from 14-dehydrobufalin (**1b**) also completes a formal total synthesis[9] of this rare toad venom constituent.

Experimental Section

A summary of equipment, chromatographic substrates, and general techniques has been provided in the introduction to the Experimental Section of Part 23.[10] Bufalin employed as starting material for preparation of 14-dehydrobufalin was isolated from the Chinese medicinal preparation Ch'an Su. The mutual identity of all comparison specimens was established by mixture melting point and infrared spectral and TLC determination.

The purity of each specimen was ascertained by thin layer chromatography on silica gel (E. Merck, Darmstadt) using 3:3:4 acetone–chloroform–hexane as solvent.

3β-Acetoxy-14α,15α-dihydroxy-5β-bufa-20,22-dienolide (2) and 3β-Acetoxy-14β,15β-dihydroxy-5β-bufa-20,22-dienolide (3a). Selective hydroxylation of 14-dehydrobufalin acetate (**1a**, 0.6 g) was performed in dry ethyl ether (120 ml)–pyridine (12 ml) with osmium tetroxide (0.6 g) at 10° over 12 hr as previously described employing 14-dehydrodigitoxigenin.[7] The crude product was chromatographed on a column of silica gel. The fraction eluted with 3:1 hexane–acetone weighed 0.25 g and corresponded to a mixture of diols **2** and **3a**. Careful rechromatography using the same solvent gave 0.172 g (mp 225–237°) of α-diol **2** as prisms from chloroform–hexane and 0.033 g of β-diol **3a** (mp 275–279°) as prisms from chloroform–hexane.

The preceding experiment was repeated using 0.3 g of 14-dehydrobufalin acetate (**1a**) and 0.3 g of osmium tetroxide. After diluting the reaction mixture with methanol (40 ml) the resulting solution was treated with hydrogen sulfide.[11] The osmium sulfides were removed by filtration and evaporation of the solvent afforded a 0.28-g residue which was purified as described above. By this means, 0.075 g (mp 222–235°) of α-diol **2** and 0.016 g (271–278°) of β-diol **3a** was obtained. Melting points of 170–240° for α-diol **2** and 273–277° for β-diol **3a** have been reported.[6]

An analytical sample of α-diol **2** exhibited ir ν_{max} (KBr) 3560, 3440 (OH), 1740 (ester CO), 1712, 1700, 1680 (conjugated CO), 1637, 1540 (conjugated C=C), 1244, 1215 (ester C–O), 1135, 1033, 954, 904, 835, 748 cm^{-1}; NMR (10% solution in $CDCl_3$) δ 0.72 (3 H, s, 18-CH_3), 0.93 (3 H, s, 19-CH_3), 2.03 (3 H, s, 3-$OCOCH_3$), 4.28 (1 H, broad t, J = 7.5 Hz, 15-H), 5.02 (1 H, broad peak, 3α-H), 6.18 (1 H, d, J = 9.5 Hz, 23-H), 7.27 (1 H, d, J = 2.5 Hz, 21-H), and 7.90 (1 H, dd, J = 9.5 and 3 Hz, 22-H); mass spectrum m/e 444 (M^+), 426 ($M^+ - H_2O$), 408 ($M^+ - 2H_2O$), 384 (M^+ – AcOH).

Anal. Calcd for $C_{26}H_{36}O_6$: C, 70.24; H, 8.16. Found: C, 70.36; H, 8.13.

A pure sample of β-diol **3a** displayed ir ν_{max} (KBr) 3580, 3450 (OH), 1740 (ester CO), 1713, 1700, 1690 (conjugated CO), 1638, 1540 (conjugated C=C), 1244, 1215 (ester C–O), 1135, 1035, 955, 905, 837, 748 cm^{-1}; NMR (10% solution in $CDCl_3$) δ 0.70 (3 H, s, 18-CH_3), 0.92 (3 H, s, 19-CH_3), 2.04 (1 H, s, 3-$OCOCH_3$), 4.27 (1 H, broad t, J = 7.5 Hz, 15α-H), 5.06 (1 H, broad peak, 3α-H), 6.26 (1 H, d, J = 9.5 Hz, 23-H), 7.23 (1 H, d, J = 3 Hz, 21-H), and 7.65 (1 H, dd, J = 9.5 and 3 Hz, 22-H); mass spectrum m/e 444 (M^+), 426 ($M^+ - H_2O$), 408 ($M^+ - 2H_2O$), 384 (M^+ – AcOH).

Anal. Calcd for $C_{26}H_{36}O_6$: C, 70.24; H, 8.16. Found: C, 70.49; H, 8.17.

15β-Acetoxy-14β-hydroxy-5β-bufa-20,22-dienolide (15β-Acetoxybufalin, 3b). To a solution of 14-dehydrobufalin (**1b**, 0.3 g) in acetic acid (72 ml)–water (3.6 ml) was added iodine (2.4 g) and silver acetate (2.4 g). The mixture was stirred at room temperature for 24 hr and the solution was filtered. The solvent was evaporated and the yellow residual solid was chromatographed on a column of silica gel. The fraction eluted by hexane–acetone (3:1) was recrystallized from acetone–hexane to afford 0.252 g (21%) of 15β-acetoxy-β-diol **3b** as prisms melting at 213–216°: TLC R_f 0.23 (light blue color with sulfuric acid); uv λ_{max} (MeOH) 297.5 nm (log ϵ 3.24); ir ν_{max} (KBr) 3460, 3430 (OH), 1760 (ester CO), 1710, 1700, 1698 (conjugated CO), 1636, 1540 (conjugated C=C), 1258, 1244, 1214 (ester C–O), 1135, 1045, 1033, 1007, 953, 938, 903, 834, 800, 747 cm^{-1}; NMR (10% solution in $CDCl_3$) δ 0.75 (3 H, s, 18-CH_3), 0.93 (3 H, s, 19-CH_3), 2.09 (3 H, s, 15-OAc), 4.10 (1 H, broad s, 3α-H), 5.56 (1 H, t, J = 7.5 Hz, 15α-H), 6.25 (1 H, d, J = 9.5 Hz, 23-H), 7.24 (1 H, d, J = 2.5 Hz, 21-H), 7.86 (1 H, dd, J = 9.5 and 2.5 Hz, 22-H); mass spectrum m/e 444 (M^+), 426 ($M^+ - H_2O$), 408 ($M^+ - 2H_2O$), 384 (M^+ – AcOH).

Anal. Calcd for $C_{26}H_{36}O_6$: C, 70.24; H, 8.16. Found: C, 70.31; H, 8.13.

A 0.474-g amount of unreacted starting material was also isolated accompanied by 0.418 g of an amorphous substance which was not identified.

3β,15β-Diacetoxy-14β-hydroxy-5β-bufa-20,22-dienolide (15β-Acetoxybufalin Acetate, 3c). Method A. From 14-Dehydrobufalin Acetate (1a). Olefin **1a** (0.6 g) in acetic acid (36 ml)–water (1.8 ml) was allowed to react with iodine (1.3 g) and silver acetate (1.3 g) as described for the Woodward cis hydroxylation of 14-dehydrobufalin (**1b**). Chromatography of the crude product on silica gel and elution with 5:1 hexane–acetone yielded 0.123 g (20.5%) of diacetate **3c** as an amorphous solid: TLC R_f 0.37 (green to light blue color with sulfuric acid); uv λ_{max} (EtOH) 297 nm (log ϵ 3.22); ir ν_{max} (KBr) 3420 (OH), 1755 (ester CO), 1740–1710 (ester CO and conjugated CO), 1635, 1537 (conjugated C=C), 1260, 1250, 1240, 1230 (ester CO), 1120, 1025, 950, 830, 790, 750 cm^{-1}; NMR (10% solution in $CDCl_3$) δ 0.76 (3 H, s, 18-CH_3), 0.97 (3 H, s, 19-CH_3), 2.03 (3 H, s, 3-OAc), 2.11 (3 H, s, 15-OAc), 5.02 (1 H, broad peak, 3α-H), 5.54 (1 H, broad t, 15α-H), 6.27 (1 H, d, J = 9.5 Hz, 23-H), 7.22 (1 H, d, J = 2.5 Hz, 21-H), 7.84 (1 H, dd, J = 9.5 and 2.5 Hz, 22-H); mass spectrum m/e 486 (M^+), 468 ($M^+ - H_2O$), 426 ($M^+ - AcOH$), 408 ($M^+ - H_2O - AcOH$), 348 ($M^+ - 2AcOH$).

Anal. Calcd for $C_{28}H_{38}O_7$: C, 69.11; H, 7.87. Found: C, 69.37; H, 7.91.

In addition to 15β-acetate **3c**, a 0.231-g amount of unreacted starting material was recovered.

Method B. From 15β-Hydroxybufalin Acetate (3a). A 0.05-g sample of acetate **3a** was acetylated with acetic anhydride (0.7 ml)–pyridine (1.2 ml) at room temperature over 18 hr. The crude product (0.06 g) was purified as described in method A to afford 0.043 g (86%) of diacetate **3c** identical with the specimen obtained by method A.

Method C. From 15β-Acetoxybufalin (3b). Acetylation of acetate **3b** (0.06 g) was conducted as described in method B above and 0.041 g (84%) of diacetate **3c** was isolated and found identical with the product of method A.

15β-Hydroxybufalin (3β,14β,15β-Trihydroxy-5β-bufa-20,22-dienolide, 3d). Method A. From 15β-Hydroxybufalin 3-Acetate (3a). A solution of 3β-acetate **3a** (0.059 g) in 80% ethyl alcohol (33 ml) containing sulfuric acid (0.22 ml) was allowed to remain at room temperature for 5 days. The solution was poured into water, neutralized with dilute sodium bicarbonate, and extracted with chloroform and the combined extract was washed with water. After removal of solvent the residue (0.05 g) was chromatographed on a column of silica gel and the fractions eluted with 3:1 to 2:1 hexane–acetone were recrystallized from acetone–hexane to provide 0.032 g of 15β-hydroxybufalin melting at 267–269° (lit.[6] mp 266–269°) as needles: TLC R_f 0.15 (light blue color with sulfuric acid); uv λ_{max} (MeOH) 297.5 nm (log ϵ 3.23); ir ν_{max} (KBr) 3460, 3428 (OH), 1720, 1700 (conjugated CO), 1635, 1540 (conjugated C=C), 1130, 1040, 1030, 950, 835, 745 cm^{-1}; NMR (10% solution of $CDCl_3$) δ 0.71 (3 H, s, 18-CH_3), 0.91 (3 H, s, 19-CH_3), 4.11 (1 H, broad peak, 3α-H), 4.26 (1 H, broad peak, 15α-H), 6.27 (1 H, d, J = 9.5 Hz, 23-H), 7.22 (1 H, d, J = 2.5 Hz, 21-H), 7.83 (1 H, dd, J = 9.5 and 2.5 Hz, 22-H), mass spectrum m/e 402 (M^+), 384 ($M^+ - H_2O$), 366 ($M^+ - 2H_2O$).

Anal. Calcd for $C_{24}H_{34}O_5$: C, 71.61; H, 8.51. Found: C, 71.55; H, 8.48.

Method B. From 15β-Acetoxybufalin (3b). The preceding experiment was repeated employing 15β-acetate **3b** (0.05 g) in 80% methyl alcohol (60 ml) containing 0.2 ml of 35% hydrochloric acid. The product was purified to yield 15β-hydroxybufalin weighing 0.019 g and melting at 265–268°.

Method C. From 15β-Acetoxybufalin Acetate (3c). The acid hydrolysis reaction of method A was applied to diacetate **3c** (0.025 g) using 30 ml of either 80% ethyl alcohol or methyl alcohol containing sulfuric acid (0.1 ml). In this experiment the 15β-hydroxybufalin (0.008 g, mp 263–267°) was isolated by preparative thin layer chromatography.

The specimens of 15β-hydroxybufalin (**3b**) obtained by means of methods A–C were found to be identical.

3β-Acetoxy-14β-hydroxy-15-oxo-5β-bufa-20,22-dienolide (4). A solution of 15β-hydroxybufalin 3-acetate (**3a**, 0.075 g) in acetic acid (1.5 ml) was treated with a solution of chromium trioxide (0.028 g) in acetic acid (0.5 ml)–water (0.05 ml). After 1.5 hr, stirring was discontinued and 3.5 hr later methyl alcohol (0.3 ml) was added. The mixture was poured into ice–water and extracted with chloroform and the combined extract was washed with water. Solvent was removed and the residue (0.077 g) was chromatographed on a column of silica gel. Elution with 6:1 hexane–acetone and recrystallization of this fraction from acetone led to 0.049 g of 15-ketone **4** as needles melting at 259–261°. The ketone **4** was identical with specimens obtained by analogous oxidation of trans diol **5** and α-epoxide **6**.[8]

Registry No.—**1a**, 22612-50-6; **1b**, 7439-77-2; **2**, 39844-84-3; **3a**, 39844-82-1; **3b**, 55156-32-6; **3c**, 39844-83-2; **3d**, 39844-81-0; **4**, 31444-12-9; osmium trioxide, 20816-12-0; silver acetate, 563-63-3; acetic anhydride, 108-24-7; chromium trioxide, 1333-82-0.

References and Notes

(1) Part 93 of the series, Steroids and Related Natural Products. For Part 92 refer to Y. Kamano, G. R. Pettit, and M. Tozawa, *J. Chem. Soc.*, in press. For Part 29 of the bufadienolide series, see Y. Kamano, G. R. Pettit, and M. Inoue, *J. Org. Chem.*, **39**, 3007 (1974).

(2) We are pleased to acknowledge support of this investigation by the National Cancer Institute, National Institutes of Health (performed pursuant to Contract N01-CM-12308 with the Division of Cancer Treatment, NCI, Department of Health, Education and Welfare), the J. W. Kieckhefer Foundation, and the Fannie E. Rippel Foundation.

(3) (a) Department of Chemistry, School of Medicine, Premedical Course, The Jikei University, Kokuryomachi, Chofushi, Tokyo, 182, Japan; (b) Department of Chemistry, Faculty of Science, Tokyo Metropolitan University, Fukazawa, Setagayaku, Tokyo 158, Japan.

(4) On a recent visit to the People's Republic of China one of us (GRP) saw specimens of *Bufo bufo gargarizans* prominently displayed in medical collections and learned of current applications of Ch'an Su in traditional medical treatment, particularly for its anesthetic, cardiac, and antiinflammatory effects. These interesting observations were made while a member of the National Academy of Sciences Pharmacology Delegation to the People's Republic of China, June 1974.

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A New Method for the Dehydration of Nitro Alcohols

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Received February 26, 1975

While synthesizing a variety of nitro compounds for use in connection with our recent study of nitro group reduction by titanous ion,[1] we attempted to prepare several nitroolefins by dehydration of the corresponding 2-nitro alcohols. These nitro alcohols are, of course, readily available by aldol-type addition of nitroalkanes to aldehydes and ketones.[2,3] A search of the literature reveals that, although a number of methods have been employed using such reagents as phosphorus pentoxide[4] and phthalic anhydride,[5] such dehydrations are normally carried out by first acetylating the hydroxyl and then effecting elimination with sodium acetate.[6] In our experience, however, yields obtained using this method were low and variable, perhaps because of the severe reaction conditions (5 hr, 120°). We have therefore devised a new, mild method of dehydration which we wish to report here.

We reasoned that the key to effecting dehydration lay simply in transforming the hydroxyl into a better leaving group, and we therefore treated the representative nitro alcohol, 2-nitro-3-pentanol, with 1 equiv of methanesulfonyl chloride in methylene chloride at 0°.[7] After addition of triethylamine and stirring for 15 min at 0°, 2-nitro-2-pentene could be isolated in 80% yield.[8]

Some of our results are given in Table I.

Table I
Dehydration of Nitro Alcohols with Methanesulfonyl Chloride–Triethylamine[a]

Reaction	Yield, %
$CH_3CHOHCH_2NO_2 \longrightarrow CH_3CH{=}CHNO_2$ 3156-73-8 3156-70-5	30
$CH_3CHOHCH(NO_2)CH_3 \longrightarrow CH_3CH{=}C(NO_2)CH_3$ 6270-16-2 4812-23-1	67
$CH_3CH_2CHOHCH(NO_2)CH_3 \longrightarrow$ 20575-40-0 $CH_3CH_2CH{=}C(NO_2)CH_3$ 6065-19-6	80
$CH_3CH_2CHOHCH(NO_2)CH_2CH_3 \longrightarrow$ 5342-71-2 $CH_3CH_2CH{=}C(NO_2)CH_2CH_3$ 4812-22-0	70
$CH_3CH_2CH_2CHOHCH(NO_2)CH_2CH_3 \longrightarrow$ 5462-04-4 $CH_3CH_2CH_2CH{=}C(NO_2)CH_2CH_3$ 6187-24-2	78

[a] Registry no. are given below the compounds.

With the exception of the unhindered and sensitive (toward polymerization) 1-nitro-1-propene, generally good results were obtained. This fact, together with the mildness of the reaction conditions, should make the method of some use in synthesis.

Experimental Section

General Reaction Procedure. *Caution! Nitroolefins are lachrymatory and allergenic. The following procedures should be carried out in a fume hood by a gloved operator.* The nitro alcohol (0.040 mol) was dissolved in 40 ml of methylene chloride at 0° under a nitrogen atmosphere, and 1 equiv of methanesulfonyl chloride (4.6 g, 3.1 ml, 0.040 mol) was added in one portion. Triethylamine (16.0 g, 22 ml, 0.160 mol) was then added dropwise, and the reaction mixture was stirred for 15 min at 0°. The reaction mixture was then transferred to a separatory funnel with the aid of 40 ml of methylene chloride, then washed with water, 5% aqueous HCl, and brine. After concentration at the rotary evaporator, the residual oil was purified by Kugelrohr distillation. In this manner, the following compounds were prepared. Product purity was established by VPC in all cases.

2-Nitro-2-butene from 3-nitro-2-butanol: ir (neat) 1670, 1520 cm^{-1}; NMR (CCl_4) δ 1.88 (d, 3 H, J = 7 Hz), 2.15 (s, 3 H), 7.07 (q, 1 H, J = 7 Hz); bp 80° (20 mm) (Kugelrohr); 2.70 g (67%).

2-Nitro-2-pentene from 2-nitro-3-pentanol: ir (neat) 1670, 1520 cm^{-1}; NMR (CCl_4) δ 1.13 (t, 3 H, J = 7 Hz), 2.13 (s, 3 H), 7.0 (t, 1 H, J = 7 Hz); bp 85° (20 mm) (Kugelrohr); 3.70 g (80%).

3-Nitro-3-hexene from 4-nitro-3-hexanol: ir (neat) 1670, 1550, 1520 cm^{-1}; NMR (CCl_4) δ 6.92 (t, 1 H, J = 7 Hz); bp 90° (18 mm) (Kugelrohr); 3.63 g (70%). The product consisted of a 7:3 mixture of the conjugated and nonconjugated nitroolefins judging from NMR.

3-Nitro-3-heptene from 3-nitro-4-heptanol: ir (neat) 1670, 1550, 1520 cm^{-1}; NMR (CCl_4) δ 7.02 (t, 1 H, J = 7 Hz); bp 90° (20 mm) (Kugelrohr); 4.46 g (78%). The product consisted of 65:35 mixture of conjugated and nonconjugated nitroolefins judging from NMR.

1-Nitropropene from 1-nitro-2-propanol: ir (neat) 1655, 1520 cm^{-1} NMR (CCl_4) δ 1.95 (d, 3 H, J = 6 Hz), 6.83–7.55 (m, 2 H); bp 70° (20 mm) (Kugelrohr); 1.05 g (30%). This reaction worked best when only 0.08 mmol of triethylamine was used per 0.04 mmol of nitro alcohol.

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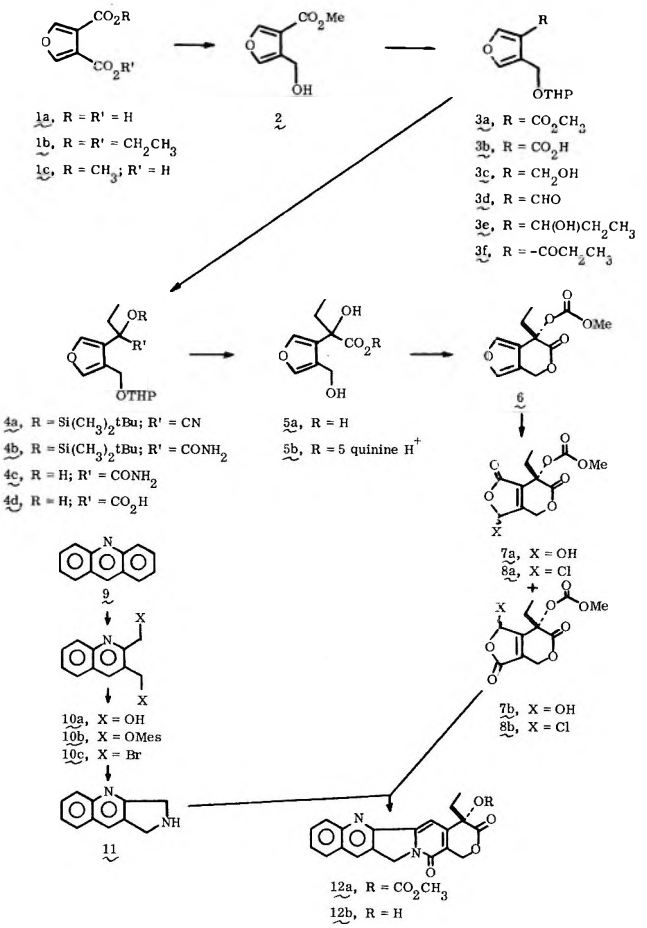
A Total Synthesis of Natural 20(*S*)-Camptothecin

Summary: A total synthesis of natural 20(*S*)-camptothecin (**12b**) is described by a sequence involving intermediates **1–11**; the furancarboxylic acid derivative **5a** was resolved using quinine and was converted to the lactone **6**; photooxidation and chlorination afforded **8b** which upon treatment with the tricyclic amine **11** led to the desired pentacyclic structure (**12**).

Sir: The alkaloid camptothecin (**12b**),[1,2] formerly considered of possible use as an antitumor agent, has attracted the attention of many synthetic groups with the result that several different pathways for synthesis of the racemic form have been demonstrated.[3] We describe herein another approach which actually represents the first successful synthesis of camptothecin in the *naturally occurring* form (*S* configuration at C-20).[2] The synthesis is convergent and involves a convenient resolution at the stage of a relatively early intermediate (**5a**). Since the 20(*S*)-camptothecin now has an important use as a biological reagent which inhibits selectively biosynthesis of ribosomal and messenger RNA's without preventing the biosynthesis of mitochondrial, 4*S* or 5*S* RNA's,[4] this synthesis of natural material may be of some use.

The acid ester **1c** could be prepared either from the diethyl ester **1b** by treatment with sodium methoxide (1 equiv) in 5% aqueous methanol at 25° for 2 hr (78% yield)[5] or from the acid **1a** by reaction with 1.06 equiv of methyl chloroformate and excess triethylamine in tetrahydrofuran (THF) with stirring at 25° for 3 days (75%). Reduction of **1c** with borane (1.2 equiv) in THF for 3 hr at 0° provided the hydroxy ester **2** in 65% yield.[6] The hydroxy ester **2** was protected as the tetrahydropyranyl ether (THP) (benzene–dihydropyran–toluenesulfonic acid) and hydrolyzed (11% potassium hydroxide–methanol) providing the crystalline acid **3b** (mp 64–66°) in an overall yield of 40% based on the acid ester **1c**. Reduction of the acid **3b** was effected quantitatively with 1.05 equiv of borane in THF for 30 hr at 0° to afford the monoprotected diol **3c** which in turn was oxidized to the aldehyde **3d** with manganese dioxide, ethylated to **3e** with ethylmagnesium bromide, and oxidized with Collins' reagent[7] to the keto furan **3f** (69% overall yield from the acid **3b**). The direct conversion of the lithium salt of the acid **3b** to afford **3f** in one step could be accomplished by reaction with 3.5 equiv of ethyllithium in THF at −40° to 0°, but the yield was lower (28%).[8] The ketone **3f** was heated (110°, neat) for 10 days with distilled *tert*-butyldimethylsilyl cyanide[9] (2 equiv), made from *tert*-butyldimethylsilyl chloride and dipotassium mercuric tetracyanide in hexamethylphosphoric triamide (HMPA).[10] Dicyclohexyl-18-crown-6-potassium cyanide was used as a catalyst[11] and was added in portions of 0.1 equiv on days 1, 2, 4, and 6 along with excess *tert*-butyldimethylsilyl cyanide (1 equiv each) added on days 3 and 6. The cyano silyl ether **4a** was isolated by column chromatography (silica gel–methylene chloride) in 85% yield, and the starting ketone **3f** (15%) was recovered for recycling.[12] Hydrolysis of **4a** to a mixture of amides **4b** and **4c** was effected with hydrogen peroxide (30%, 10 equiv) in basic (1.2 equiv of potassium carbonate) methanol at room temperature using 1-heptene (10 equiv) as an oxygen acceptor. Isolation of the acid-sensitive amides **4b** and **4c** required quenching at 0° with aqueous sodium bisulfite and immediate addition of pyrrolidine and potassium carbonate before extractive work-up. The mixture of **4b** and **4c** was heated at reflux in H_2O–KOH–CH_3OH (1.5:14:100) for 4 days to give the hydroxy acid **4d** in 73% overall yield from **3f**. The cleavage of the tetrahydropyranyl ether was then brought about in 30% aqueous acetic acid by heating for 4 hr at 45° to afford pure dihydroxy acid **5a** (65% yield).



The natural base quinine proved to be very satisfactory for the resolution of the acid **5a** via a nicely crystalline solid of composition dihydroxy acid (**5a**)–quinine–water in a ratio of 1:5:2. The use of 5 equiv of quinine trihydrate resulted in a 76% yield of resolved salt **5b** with $[\alpha]^{22}D$ −145° (EtOH) (three recrystallizations from benzene–heptane, 1:1). The chiral lactone **6** was generated by adding triethylamine and methyl chloroformate (34 equiv each) to a methylene chloride solution of **5b**. After 4 hr at room temperature the quinine salt was removed by quaternization with methyl iodide in nitromethane for 18 hr at room temperature. Column chromatography (neutral alumina–methylene chloride) gave a quantitative yield of the resolved lactone **6**,[13] $[\alpha]^{22}D$ +1.10° (MeOH).[14] Photooxidation of **6** was accomplished using 30% 2,6-lutidine in *tert*-butyl alcohol at 25° by irradiation in the presence of oxygen and eosine[16] to afford quantitatively a mixture of pseudo-acids **7a** and **7b** (ratio of 1:2.5)[17] which upon treatment with thionyl chloride and a catalytic amount of Vilsmeier reagent[18] at 50°

for 7 hr led quantitatively to a mixture of the pseudo-acid chlorides **8a** and **8b** (1:2.5, respectively).

The tricyclic diamine **11**[19] was synthesized from acridine by a simple three-step procedure. Oxidation of acridine with ozone (2.2 equiv) in methanol at −40° followed by sodium borohydride (4.4 equiv) reduction of the ozonide resulted in the crystalline diol **10a** (43% yield), mp 115–118°. The diol was converted into the dimesylate **10b** in benzene–triethylamine with methanesulfonyl chloride (3 equiv) at 0° for 1 hr (85% yield). Exposure of **10b** to 15% concentrated ammonium hydroxide in methanol for 2 hr at room temperature gave the tricyclic diamine **11** after work-up (careful exclusion of oxygen) and purification by column chromatography (silica gel–methanol) (48% yield of **11** as tan crystals, mp 92.5–95°).[20]

The mixture of pseudo-acid chlorides **8a** and **8b** (1:2.5) was stirred with the tricyclic diamine **11** (0.85 equiv) in 10% pyridine–acetonitrile for 10 hr at room temperature, and the resulting amide mixture was cyclized using as medium 10% sodium acetate–acetic acid for 20 hr at 25°. After column chromatographic purification (a) on silica gel using 20% CH_3OH in $CHCl_3$ and (b) on silica gel using 3% CH_3OH in CH_2Cl_2, and finally preparative TLC on silica gel plates using 3% CH_3OH in CH_2Cl_2, the pure camptothecin 20-methoxycarbonyl derivative (**12a**) was obtained: uv (20% MeOH in $CHCl_3$) 258 nm (ϵ 20,600), 295 (5000), and 362 (18,100); $[\alpha]^{22}D$ +31.7° ($CHCl_3$).[21] The methoxy carbonyl group of **12a** was removed by reaction with lithium mercaptide in HMPA[22] yielding 90% of 20(*S*)-camptothecin (**12b**) identical in every respect with natural material:[23] found for synthetic **12b**, $[\alpha]^{22}D$ +31.1° (20% MeOH in $CHCl_3$), mp 275–278° dec; found for naturally derived camptothecin, $[\alpha]^{25}D$ +31.3° (20% MeOH in $CHCl_3$),[1] mp 276–278° dec.[24] The NMR, ir, uv, TLC, MS, and mixture melting point all confirmed the identity of synthetic and natural camptothecins.[25]

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(12) The use of the stable *tert*-butyldimethylsilyl derivative was required to avoid desilylation in the next step which would lead to reversal of cyanohydrin formation; the trimethylsilyl cyanide analog of **4a** was not a satisfactory substrate.
(13) This procedure was found to be superior to the isolation of the resolved dihydroxy acid (**5a**) owing to the acid sensitivity and water solubility of **5a**.
(14) Both camptothecin {$[\alpha]^{25}D$ +31.3° (MeOH)} and (+)-atrolactic acid {$[\alpha]^{13.8}D$ +37.7° (EtOH)} have the *S* configuration[3,15] and a positive rotation; it was therefore anticipated that the (+)-lactone **6** should also be of the *S* configuration.
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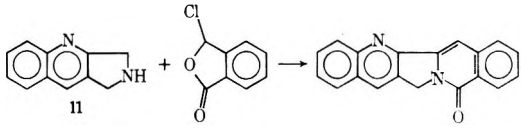
(20) See C. Dauth and H. G. O. Becker, *J. Prakt. Chem.*, **313**, 686 (1971).
(21) The yield of **12a** obtained in the coupling–cyclization process as described herein is ~6.5%. However, optimum conditions for this transformation have not been extensively studied owing to limitations of time and material (for example, a study of the variation of X in **7** may well be rewarding). It is noteworthy in this regard that the cyclization of the pseudo-acid chloride i with the tricyclic diamine (**11**) in a similar manner to that described for the production of **12a** yielded camptothecin analog ii in quantitative yield.



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(25) This research was assisted financially by grants from the National Institutes of Health and the National Science Foundation. We are grateful to Dr. Harold C. Kluender for experimental contributions on the synthesis of the tricyclic intermediate **11**.

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Dry Ozonation. A Method for Stereoselective Hydroxylation of Saturated Compounds on Silica Gel

Summary: A convenient preparative method is described for hydroxylation of tertiary carbon atoms by ozonation of saturated compounds adsorbed on silica gel.

Sir: Ozone reacts slowly with saturated hydrocarbons inserting oxygen atoms into their C–H bonds, resulting in alcohols and ketones.[1] This insertion occurs preferentially at the tertiary carbon atoms, with a retention of configuration.

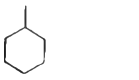
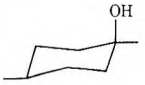
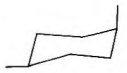
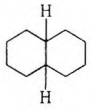
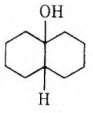
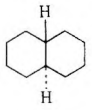
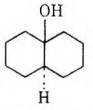
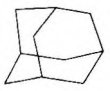
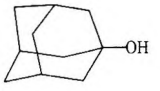
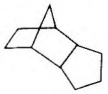
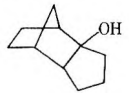
In spite of its preparative potentialities this reaction has been rarely used until now. One of the factors limiting the use of ozone as reagent for hydroxylation of saturated hydrocarbons is its low solubility in organic solvents. Even at low temperatures at which ozone forms stable solutions in saturated hydrocarbons and no reaction is observed, its solubility is slight (~0.1–0.3% by weight at −78°).[2] At higher temperatures necessary for reaction to proceed at reasonable rate, the solubility of O_3 is even smaller, necessitating prolonged ozonation periods.

Furthermore, the reactivity of ozone toward most of the organic solvents[3] limits its practical use as a hydroxylation reagent only to neat hydrocarbons.

Considering that silica gel adsorbs ozone efficiently at low temperatures[4] (its concentration being ~4.5% by weight at −78°), we have used the silica gel as the reaction matrix, thus overcoming the drawbacks arising from ozonations in solutions.

To perform the reaction we have pre-adsorbed the silica gel with the hydrocarbon[5] either by direct mixing or by im-

Table I
Reaction of Hydrocarbons with Ozone on Silica Gel

Substrate	Products	Yield,[a] %	Conversion,[a] %
		65[b]	>99.5
		79[c]	72
		76[d]	92
		99	>99.5
		72[e]	88
		99	>99.5
		90	>99.5

[a] Based on the quantity of the starting material consumed as determined by VPC analysis. [b] In addition to 34% of a mixture of the three methylcyclohexanones. [c] In addition to 0.6% of the epimeric alcohol. [d] In addition to 3.5% of the epimeric alcohol. [e] In addition to 10% *trans*-decal-1-one and 16% *trans*-decal-2-one.

pregnation using a volatile solvent. A stream of ozone was then passed through the silica gel containing ~1% by weight of the hydrocarbon at −78° [6] until it became saturated with ozone. It was then allowed to warm slowly, during ~0.5 hr, to room temperature, followed by elution of the organic material.

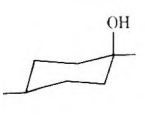
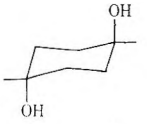
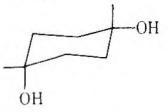
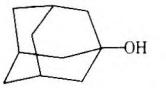
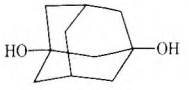
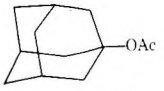
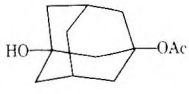
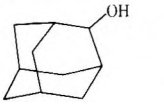
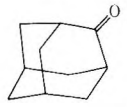
Using these reaction conditions, we have observed almost quantitative conversions of the hydrocarbons, resulting in a very high yield of the tertiary alcohols and an almost complete retention of configuration in the case of *cis*-decalin and the two isomeric *cis*- and *trans*-1,4-dimethylcyclohexanes (Table I).[5]

Thus the advantage of the dry ozonation is not only the almost quantitative conversions, but also practically exclusive formation of monooxygenated products. The alternative sweeping of hydrocarbon solutions with ozone for long periods of time may lead to reoxidation of the primarily formed products resulting in mixtures of polyoxygenated compounds as well as formation of impurities caused by oxidation of the solvent.[1,7]

The efficacy of the dry ozonation as a general method for stepwise hydroxylation of tertiary carbon atoms may be exemplified by hydroxylation of adamantan-1-ol, its acetate, and the two isomeric *cis*- and *trans*-1,4-dimethylcyclohexanols (Table II).

Under the same conditions secondary alcohols are oxidized to ketones as shown by a quantitative conversion of adamantan-2-ol to adamantanone.

Table II
Reaction of Substituted Hydrocarbons with Ozone on Silica Gel

Substrate	Product	Yield,[a] %	Conversion,[a] %
		>99.5	95
		76[b]	97
		99	43
		86	50
		>99.5	>99.5

[a] Based on the starting material consumed. [b] In addition to 5% of the trans diol.

We suggest that the mechanism of ozonation of saturated compounds in the adsorbed phase is the same as the one proposed by us for ozonation in solution.[2]

Acknowledgment. We thank Professor G. Krakower and Mr. Y. Barness from the Bar-Ilan University, Ramat-Gan, for the useful advise.

References and Notes

(1) (a) J. R. Durland and H. Adkins, *J. Am. Chem. Soc.*, **61**, 429 (1939); (b) M. C. Whiting, A. Z. N. Bolt, and J. H. Parish, *Adv. Chem. Ser.*, **77**, 4 (1968); (c) G. A. Hamilton, B. S. Ribner, and T. M. Heilman, *ibid.*, **77**, 15 (1968); (d) C. C. Schubert and R. N. Pease, *J. Am. Chem. Soc.*, **78**, 2044 (1956); (e) D. G. Williamson and R. J. Cvetanovic, *ibid.*, **92**, 2949 (1970); (f) T. M. Hellman and G. A. Hamilton, *ibid.*, **96**, 1530 (1974); (g) J. E. Batterbee and P. S. Bailey, *J. Org. Chem.*, **32**, 3899 (1967).
(2) H. Varkony, S. Pass, and Y. Mazur, *Chem. Commun.*, 437 (1974).
(3) Saturated solvents normally used in ozonolysis, like methyl acetate, ethyl acetate, methyl chloride, carbon tetrachloride, and trifluorochloromethane, were found to react with ozone even at low temperatures.
(4) G. A. Cook, A. D. Kiffer, C. V. Klumpp, A. H. Malik, and L. A. Spence, *Adv. Chem. Ser.*, **21**, 44 (1959).
(5) The hydrocarbons used were purified by conventional techniques; the liquid ones also by passing through an $AgNO_3$–HNO_3 alumina column [E. C. Murray and R. N. Keller, *J. Org. Chem.*, **34**, 2234 (1969)]. GLC analysis indicated in all compounds used <0.01% impurities.
(6) Below this temperature the concentration of ozone adsorbed on silica increases rapidly. However we want to warn that at temperatures below −112° ozone liquifies and there is a potential explosion danger when handling silica gel containing adsorbed ozone and organic material at temperatures lower than −100°
(7) W. H. Clingman, Jr., *Chem. Abstr.*, **53**, 3066*h* (1959); U.S. Patent 2,849,484 (1958).

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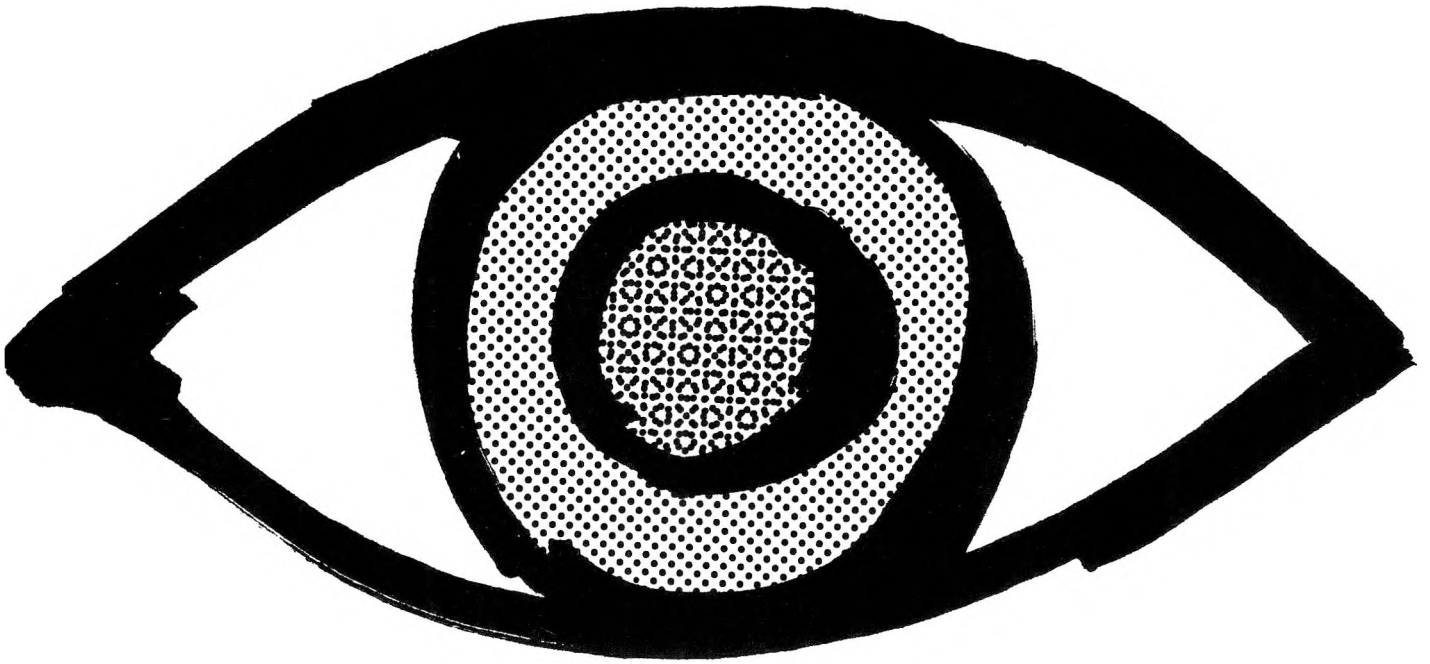

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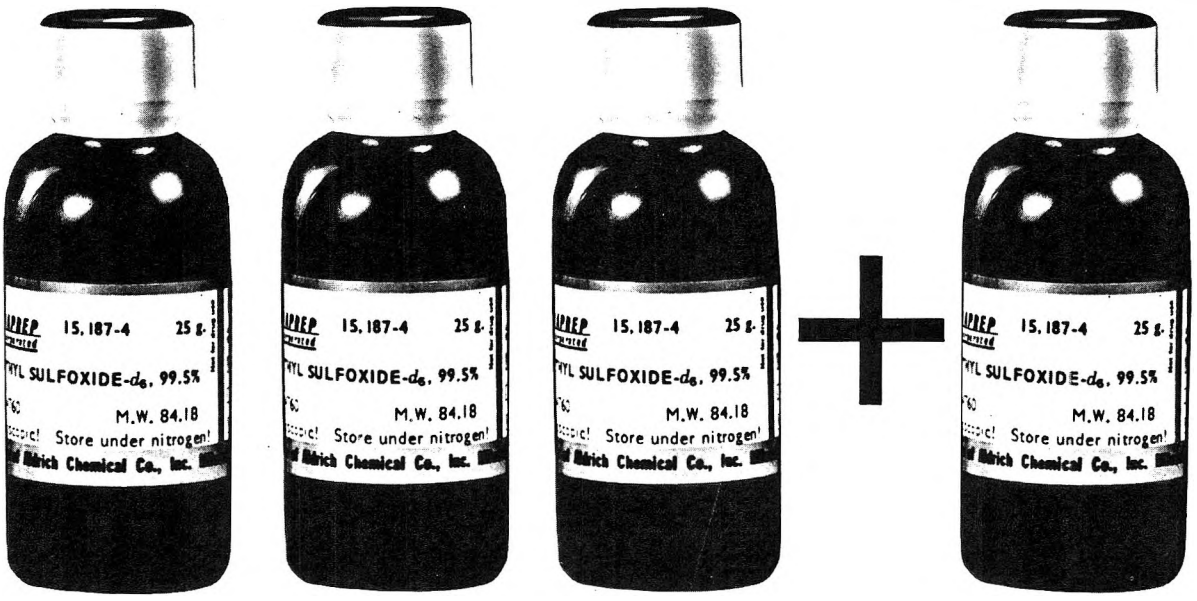

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