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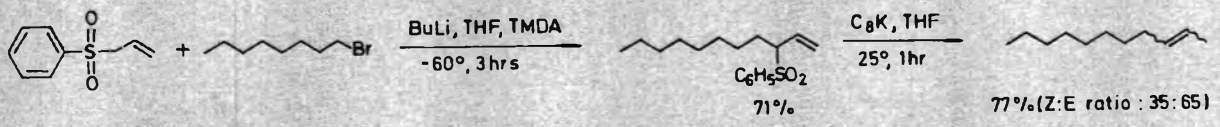

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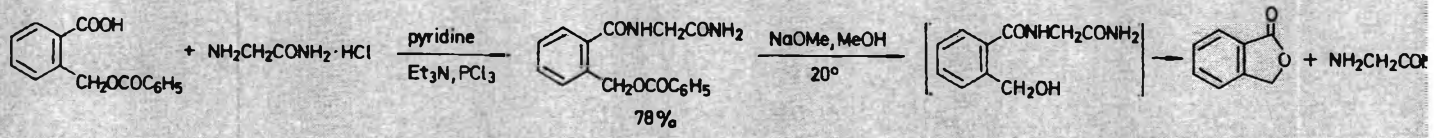

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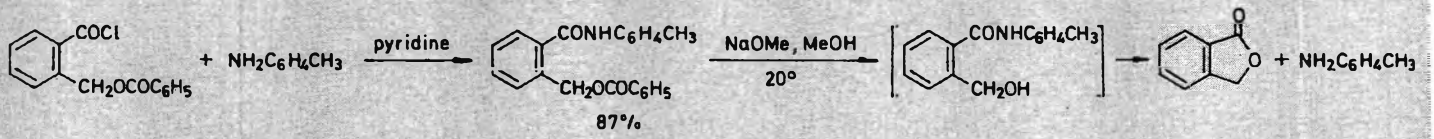

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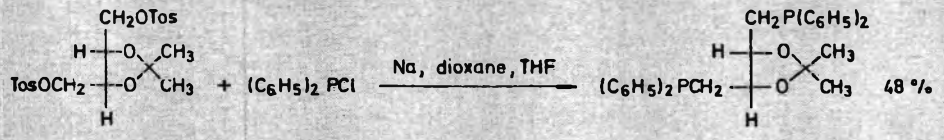

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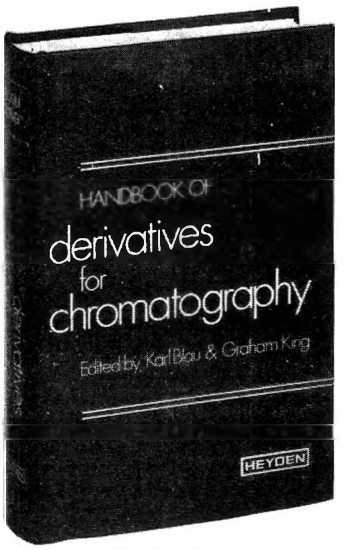

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THE JOURNAL OF Organic Chemistry®

VOLUME 43, NUMBER 11

MAY 26, 1978

Synthesis and Absolute Configuration of (−)-Methyl (*E*)-2,4,5-Tetradecatrienoate, the Sex Attractant of the Male Dried Bean Weevil

W. H. Pirkle* and Charles W. Boeder

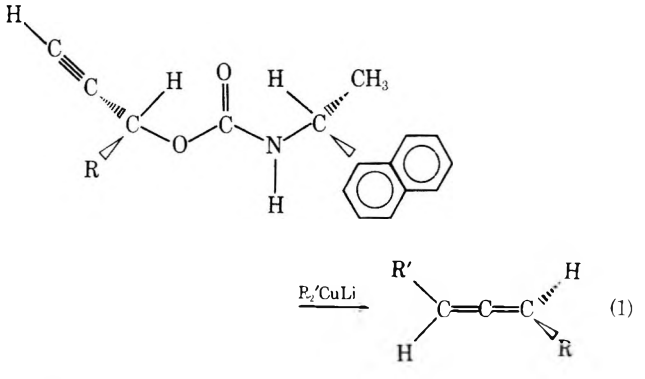
The Roger Adams Laboratory School of Chemical Sciences, University of Illinois, Urbana, Illinois 61801

Received November 15, 1977

(−)-Methyl (*E*)-2,4,5-tetradecatrienoate [(−)-**1**, $[\alpha]_D$ −98°] was synthesized from β-cyanopropionaldehyde dimethyl acetal. The key intermediates, (*R,R*)- and (*S,R*)-1-ethynyl-3-carbomethoxypropyl *N*-[1-(1-naphthyl)ethyl]-carbamates (**4a,b**) are separable using liquid chromatography. The low temperature reaction of **4b** with lithium di-*n*-octylcuprate affords (*R*)-(−)-methyl 4,5-tetradecadienoate [*R*-(−)-**5**] and this allene was then converted to (*R*)-(−)-**1**. Similarly, (*S*)-(+)-**1** is prepared from **4a**. The synthetic pheromone, (*R*)-(−)-**1**, has 77% the rotatory power of the natural product.

(−)-Methyl (*E*)-2,4,5-tetradecatrienoate [(−)-**1**] has been of synthetic interest since Horler determined it to be a sex attractant produced by the male bean weevil, *Acanthoscelides obtectus*.[1] While several syntheses of the racemic material have been described,[2-6] a synthesis of the chiral pheromone has not been reported nor has the absolute configuration of the natural product been determined. This paper describes the asymmetric synthesis of chiral **1** by a sequence which also enables determination of the absolute configuration of the natural pheromone.

Synthesis. We recently reported a simple two-step synthesis of chiral 1,3-dialkyl allenes of moderate to high enantiomeric purity.[7] This sequence involves the reaction of lithium dialkylcuprates with a single diastereomer of the carbamates derived from racemic secondary propargylic alcohols and (*R*)-1-(1-naphthyl)ethyl isocyanate (eq 1). Such carbamates are readily separable by means of liquid chromatography.[7,8] The operational simplicity, known stereochemical pathway, and substantial optical yield of this asymmetric synthesis made it attractive as the key step in the synthesis of (−)-**1**.



(1)

Scheme I outlines the synthesis of **1** from β-cyanopropionaldehyde. Treatment of the aldehyde with ethynylmagnesium bromide afforded racemic alcohol **2** in 72% yield. Cyanocarbamates **3a,b** were isolated as a 1:1 mixture in 90% yield from the reaction of (±)-**2** with (*R*)-1-(1-naphthyl)ethyl isocyanate. Treatment of **3a,b** with methanolic HCl at room temperature for 1 h affords diastereomeric carbamates **4a** and **4b** which are readily separable by liquid chromatography on silica gel. Once separated, these diastereomeric carbamates were treated with di-*n*-octylcuprate to afford chiral allene **5**. The *trans* double bond was introduced by the method of Kocienski et al.[6]

As previously noted,[7] the diastereomers of a propargylic carbamate may afford allenes of different enantiomeric purity and may require different mixing orders of reactants (i.e., normal vs. inverse addition) to optimize the enantiomeric yield. Table I outlines the results of the reaction of di-*n*-octylcuprate with **4a** and **4b** under various conditions. The reaction of **4b** with di-*n*-octylcuprate in diethyl ether using normal addition (adding carbamate to cuprate) afforded (−)-**5**, $[\alpha]_D$ −45° (2.9, hexane), in 62% yield. The pheromone, (−)-**1**, $[\alpha]_D$ −98° (3.9, hexane), was obtained in 83% yield from (−)-**5** and has 77% the rotatory power of the naturally occuring material. Similarly, (+)-**5** (therefore (+)-**1**) was obtained from **4a**. However, maximum enantiomeric yields were obtained from **4a** using inverse addition (cuprate added to carbamate).

Absolute Configuration of (−)-1. Introduction of the *trans* double bond in (−)-**5** to afford (−)-**1** does not change the absolute configuration of the allene. Since the stereochemical pathway of the allene forming reaction is known,[7,9] determination of the absolute configuration of **4b** also determines that of (−)-**5** and (−)-**1**. This is straightforward; the absolute configuration of the amine portion of **4b** is known and the realtive configuration (and hence, the absolute configuration) about the carbinyl carbon can be assigned based on NMR spectral differences between **4a** and **4b**.

0022-3263/78/1943-2091$01.00/0

Scheme I

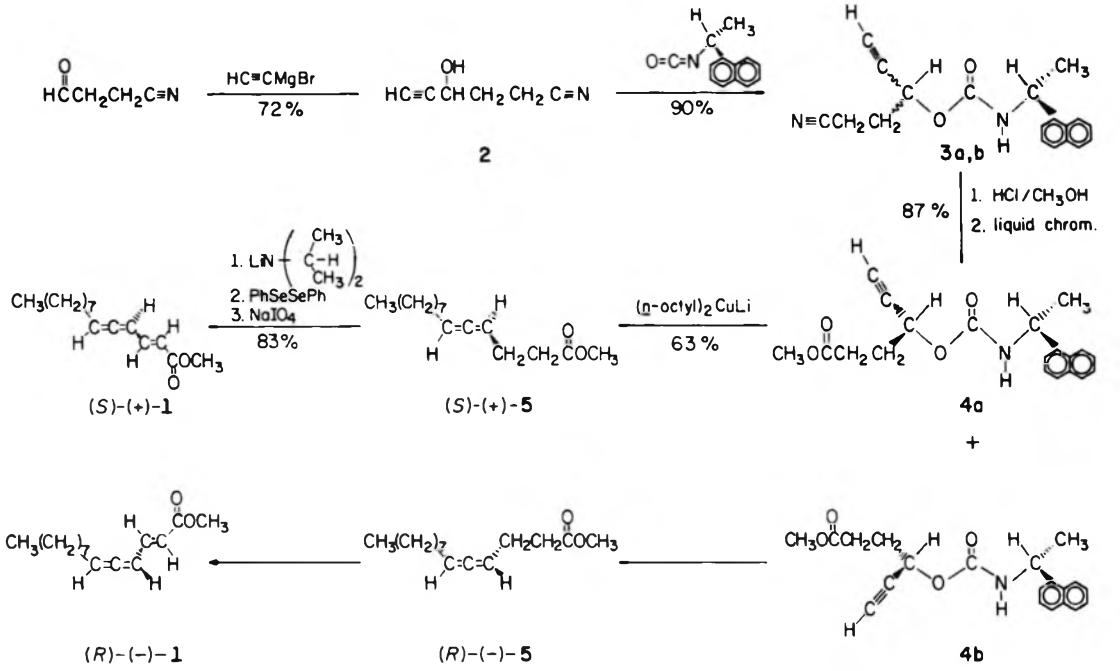


Table I. The Reaction of Diastereomeric Carbamates 4a and 4b with Di-*n*-octylcuprate for 7 h at −78 °C

Carbamate	Solvent	Order of addition	$[\alpha]_D$ of product 5
4a	Et_2O	Normal	+26.7° (4.6, hexane)
4a	Et_2O	Inverse	+43.5° (5.1, hexane)
4b	Et_2O	Normal	−45.0° (2.9, hexane)
4b	Et_2O	Inverse	−30.5° (7.5, hexane)
4b	THF	Normal	Racemic[a]
4b	Toluene	Normal	*b*

[a] Only 20% of the carbamate had undergone reaction under these conditions. [b] Starting material was quantatively recovered after 12 h.

A variety of carbamates derived from secondary alcohols and (*R*)-1-(1-naphthyl)ethyl isocyanate have been shown to preferentially populate conformations similar to those shown in Scheme I for **4a** and **4b**.[8] Owing to the shielding effect of the *cis*-α-naphthyl group, the methoxy resonance of **4a** would be expected to occur upfield of that of **4b.** For the same reason, the ethynyl doublet of **4a** would be expected to occur downfield of that of **4b.** These spectral differences are observed; **4a,** the high R_f diastereomer, is therefore assigned the (*R,R*) configuration; **4b** is assigned the (*S,R*) configuration. This assignment is consistant with NMR spectral differences observed for similar carbamates of configurationally known propargyl alcohols.[8]

Crabbé has shown that (*S*)-(−)-3-hydroxy-1-octyne acetate reacts with lithium dimethylcuprate at −10 °C to afford an (*R*)-allene.[9] Further, it has been demonstrated that acetates, tosylates, and carbamates of (*S*) secondary propargylic alcohols afford (*R*)-allenes when treated with dialkylcuprates and that similarly derivatized (*R*) secondary propargylic alcohols afford (*S*)-allenes.[7] Therefore, carbamate **4b,** having the (*S*) configuration about the carbinyl carbon, affords (*R*)-(−)-**5** when treated with di-*n*-octylcuprate. Hence, the natural product, (−)-**1,** derived from (*R*)-(−)-**5,** has the (*R*) configuration.

Summary. Both enantiomers of methyl (*E*)-2,4,5-tetradecatrienoate have been synthesized. The levorotatory isomer has 77% of the rotatory power of the natural product and has been determined to have the (*R*) configuration.

Experimental Section

Infrared spectra were recorded with a Beckman IR-12 spectrometer, NMR spectra with a Varian EM-390 instrument using Me_4Si as an internal standard, and mass spectra with a Varian CH-5 spectrometer. Melting points are uncorrected.

β-Cyanopropionaldehyde. To 500 mL of water was added 65 g (0.50 mol) of β-cyanopropionaldehyde dimethyl acetal[10] and 100 mg of *p*-toluenesulfonic acid. The stirred solution was heated at reflux for 2 h. The water was removed under reduced pressure (bath <50 °C) and the β-cyanopropionaldehyde was distilled under vacuum to afford 40 g (96%): bp 66–68 °C (2 mm); NMR (CCl_4) δ 2.6 (m, 2 H), 2.85 (m, 2 H), 9.75 (s, 1 H).

(±)-5-Cyano-1-pentyn-3-ol (2). To a stirred solution of ethynylmagnesium bromide[11] (0.15 mol) in 400 mL of dry THF at ambient temperature 8.3 g (0.10 mol) of β-cyanopropionaldehyde in 20 mL of dry THF was added dropwise over a 45-min period. The solution became slightly warm and was stirred for 3 h before the addition of saturated aqueous NH_4Cl (400 mL). The organic phase was separated and the aqueous phase was extracted with three 200-mL portions of Et_2O. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated at reduced pressure. The residue was vacuum distilled to afford 7.8 g (72%) of **2**: bp 85 °C (0.05 mm); NMR (CCl_4) δ 2.1 (m, 2 H), 2.55 (t, 2 H), 2.67 (d, 1 H), 3.1 (broad s, 1 H), 4.5 (dt, 1 H); IR ($CHCl_3$) 3600, 3460, 3310, 3030, 2260, 2120, 1425, 1235, 1070, 935 cm^{-1}; MS (70 eV) *m/e* (rel intensity) 110 [$(M + H)^+$], 55 (100), 54 (34), 41 (11), 39 (14).

1-Ethynyl-3-cyanopropyl *N*-[1-(1-naphthyl)ethyl]carbamates (3a,b). A mixture of **2** (5.0 g, 46 mmol), (*R*)-(−)-(1-naphthyl)-ethyl isocyanate (9.06 g, 46 mmol), and *N,N*-dimethylethanolamine (1 wt%) in toluene (200 mL) was heated at reflux for 60 h. The cooled solution was then washed with 1 N HCl (50 mL), saturated $NaHCO_3$ (50 mL), and water (100 mL). The organic layer was dried ($MgSO_4$) and filtered, and the solvent was removed under reduced pressure to afford a yellow syrup, 12.7 g (90%), of **3a,b** as a 1:1 mixture: NMR (CCl_4) δ 1.67 (d, 3 H), 2.1 (m, 2 H), 2.5 (m, 3 H), 5.0–5.8 (m, 3 H), 7.3–8.3 (m, 7 H); IR ($CHCl_3$) 3450, 3310, 3040, 2260, 2130, 1730, 1505, 1450, 1380, 1240, 1060 cm^{-1}; MS (70 eV) *m/e* (rel intensity) 360 (M^+, 44), 291 (31), 215 (15), 214 (100), 170 (30), 155 (11), 129 (14).

1-Ethynyl-3-carbomethoxypropyl *N*-[1-(1-Naphthyl)ethyl]carbamates (4a,b). These methyl esters were prepared from **3a,b** by the method of Betz and Daub.[12] Anhydrous HCl was bubbled into a stirred ice-cooled solution of 12.16 g (40 mmol) of **3a,b** in 100 mL of 1:1 methanol–ether for 1 h. After stirring at 25 °C for 1 h[13] 100 mL

of water was slowly added with cooling and air was bubbled rapidly through the solution for 30 min to remove HCl. The aqueous phase was extracted with ether (200 and 75 mL) and the combined extracts were washed with 10% $NaHCO_3$ and saturated NaCl. After drying ($MgSO_4$), the organic phase was filtered and the solvent was removed under reduced pressure to afford 11.7 g (87%) of **4a,b**. The mixture was then chromatographed on a multigram HPLC system[14] using benzene–ether (15:1) on silica gel. The effluent was monitored at 280 nm.

The first major fraction to be eluted was (*R,R*)-**4a** (5.9 g). Recrystallization from hexane afforded a white solid: mp 104–105 °C; NMR (CCl_4) δ 1.6 (d, 3 H), 2.0 (m, 2 H), 2.3 (d, 1 H), 2.2–2.4 (m, 2 H), 3.50 (s, 3 H), 5.1–5.7 (m, 3 H), 7.2–8.1 (m, 7 H); IR ($CHCl_3$) 3450, 3320, 3020, 2130, 1730, 1510, 1250, 1175, 1065 cm^{-1}; MS (70 eV) *m/e* (rel intensity) 339 (M^+, 14), 214 (00), 182 (25), 170 (57), 156 (23), 155 (88), 154 (23), 153 (22), 129 (46), 127 (24), 125 (29), 97 (26). Anal. Calcd for $C_{20}H_{21}NO_4$: C, 70.78; H, 6.24; N, 4.13. Found: C, 70.92; H, 6.19; N, 3.94.

The second major fraction to be eluted was (*S,R*)-**4b** (5.8 g). Crystallization from hexane afforded a white solid: mp 78.5–80.5 °C; NMR (CCl_4) δ 1.6 (d, 3 H), 2.0 (broad, 2 H), 2.24 (d, 1 H), 2.15–2.6 (broad, 2 H), 3.57 (s, 3 H), 4.9–5.7 (m, 3 H), 7.2–8.1 (m, 7 H); IR ($CHCl_3$) 3460, 3320, 3020, 2130, 1740, 1510, 1250, 1175, 1065 cm^{-1}; MS (70 eV) *m/e* (rel intensity) 339 (M^+, 9), 214 (98), 197(21), 182 (52), 170 (63), 156 (43), 155 (100), 154 (36), 153 (41), 129 (71), 128 (33), 127 (44), 125 (28), 97 (26). Anal. Calcd for $C_{20}H_{21}NO_4$: C, 70.78; H, 6.24; N, 4.13. Found: C, 70.66; H, 6.04; N, 4.37.

(*R*)-(−)-Methyl 4,5-Tetradecadienoate [(*R*)-(−)-5]. This compound was prepared from the reaction of lithium di-*n*-octylcuprate with **4b** by two procedures.

Normal Addition. Carbamate **4b** (1.20 g, 3.5 mmol) in diethyl ether (25 mL) was added dropwise over a 10-min period to a stirred solution of lithium di-*n*-octylcuprate[15] (3.85 mmol) in diethyl ether (40 mL) cooled to −78 °C. After stirring the solution for an additional 7 h at −78 °C, the cooling bath was removed and the reaction mixture was allowed to come to 0 °C. Saturated NH_4Cl (10 mL) was then added and the mixture was stirred for 15 min to allow the copper salts to precipitate. The resulting slurry was filtered and the organic layer was separated, washed with 1 N HCl (10 mL) and saturated $NaHCO_3$ (15 mL), dried ($MgSO_4$), filtered, and concentrated at reduced pressure. Vacuum distillation of the residue afforded 0.52 g (62%) of (*R*)-(−)-**5**, $[\alpha]_D$ −45.0° (2.9, hexane): NMR (CCl_4) δ 0.87 (t, 3 H), 1.25 (broad s, 12 H), 1.9 (m, 2 H), 2.27 (m, 4 H), 3.54 (s, 3 H), 5.0 (m, 2 H); IR ($CHCl_3$) 2940, 1965, 1740 cm^{-1}; MS (70 eV) *m/e* (rel intensity) 238 (M^+, 21), 140 (92), 98 (37), 85 (40), 83 (85), 81 (61), 80 (100), 79 (40), 71 (61), 67 (33).

Inverse Addition. Lithium di-*n*-octylcuprate (3.85 mmol) in diethyl ether (25 mL) cooled to −78 °C was added portionwise over 5 min to a cold (−78 °C) stirred solution of **4b** (1.20 g, 3.5 mmol) in diethyl ether (40 mL). The reaction mixture was stirred for 7 h at −78 °C and worked up as described above to afford 0.54 g (64%) of (*R*)-(−)-**5**, $[\alpha]_D$ −30.5° (7.5, hexane).

(*S*)-(+)-Methyl 4,5-Tetradecadienoate [(*S*)-(+)-5]. This compound was prepared from the reaction of lithium di-*n*-octylcuprate with **4a** by the procedures described for the preparation of (*R*)-(−)-**5**.

Use of inverse addition afforded (*S*)-(+)-**5** (65%), $[\alpha]_D$ +43.5° (5.1, hexane). Use of normal addition afforded (*S*)-(+)-**5** (61%), $[\alpha]_D$ +26.7° (4.6, hexane).

(*R*)-(−)-Methyl (*E*)-2,4,5-Tetradecatrienoate [(*R*)-(−)-1]. This compound was prepared from (*R*)-(−)-**5**, $[\alpha]_D$ −45.0°, by the method of Kocienski.[6] Allene (*R*)-(−)-1 was isolated (83%) as a light yellow oil, $[\alpha]_D$ −98.3° (3.8, hexane): NMR (CCl_4) δ 0.87 (t, 3 H), 1.3 (broad s, 12 H), 2.03 (m, 2 H), 3.65 (s, 3 H), 5.3 (m, 1 H), 5.6–5.9 (m, 1 H), 5.72 (d, 1 H), 7.1 (dd, 1 H); IR ($CHCl_3$) 2950, 2880, 1950, 1730, 1635, 1440, 985 cm^{-1}; MS (70 eV) *m/e* (rel intensity) 236 (M^+, 2),138 (67), 137 (21), 107 (21), 82 (28), 79 (100), 78 (39), 67 (21).

(*S*)-(+)-Methyl (*E*)-2,4,5-Tetradecatrienoate [(*S*)-(+)-1]. This compound was prepared from (*S*)-(+)-**5**, $[\alpha]_D$ +43.5°, by the method of Kocienski.[6] Allene (*S*)-(+)-1 was isolated as a light yellow oil, $[\alpha]_D$ +94.9° (3.3, hexane).

Acknowledgment. This work has been partially funded by grants from the National Science Foundation and the National Institutes of Health.

Registry No.—(*R*)-(−)-**1**, 28066-21-9; (*S*)-(+)-**1**, 65451-10-7; **2**, 65414-51-9; **3a**, 65414-52-0; **3b**, 65414-53-1; **4a**, 65414-54-2; **4b**, 65414-55-3; (*R*)-(−)-**5**, 65451-09-4; (*S*)-(+)-**5**, 65494-90-8; β-cyanopropionaldehyde, 3515-93-3; β-cyanopropionaldehyde dimethyl acetal, 14618-78-1; ethynyl bromide, 593-61-3; *R*-(−)-(1-naphthyl)ethyl isocyanate, 42340-98-7; lithium di-*n*-octylcuprate, 38317-57-6.

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Total Synthesis of 3-Oxa-4,5,6-trinor-3,7-*inter-m*-phenylene Prostaglandins. 1. Photochemical Approach

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The total syntheses of optically active 3-oxa-4,5,6-trinor-3,7-*inter-m*-phenylene prostaglandins **3**, **28**, **29**, and **30** are described. The synthetic route to these novel and biologically active prostaglandin analogues involved the photochemical cycloaddition of *m*-acetoxybenzaldehyde (**16**) and optically active acetal **5** to give the tricyclic oxetane **17** as the key step. The structure and optical purity of oxetane **17** were supported by model studies and NMR chiral shift reagent studies as well as subsequent transformations to the desired end products.

During the past several years, a number of prostaglandin analogues have been synthesized which have incorporated an aromatic ring at some location in the basic prostaglandin structure. Two such examples are the 17-phenyl-18,19,20-trinor- and the 16-phenoxy-17,18,19,20-tetranor-substituted prostaglandins represented by **1** and **2**, respectively. These

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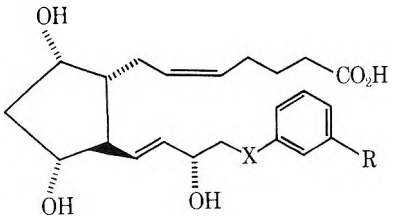
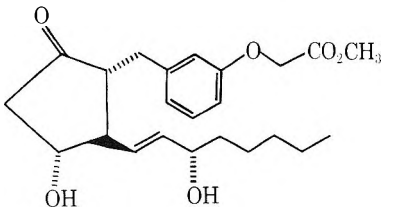


1, X = CH_2; R = H
2, X = O; R = CF_3

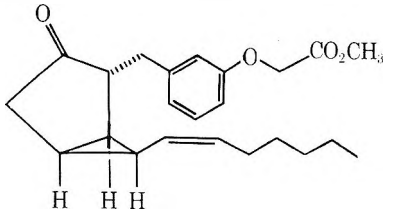


3

compounds belong to analogue families which have displayed not only structural diversity but also significant biological activity.[1] Although these examples involve modification of the lower, aliphatic side chain, other prostaglandin analogues have been synthesized which have incorporated an aromatic ring in the upper, carboxylic acid side chain. A specific example of this type of modification is illustrated by 3-oxa-4,5,6-trinor-3,7-*inter*-*m*-phenyleneprostaglandin E_1 methyl ester (**3**),[2] the racemate of which has been demonstrated to be a potent inhibitor of ADP-induced human platelet aggregation in vitro.[3] Because of continued interest in the biological properties of *dl*-**3**, a method for the synthesis of the pure enantiomeric form of **3** of natural prostaglandin configuration was sought.

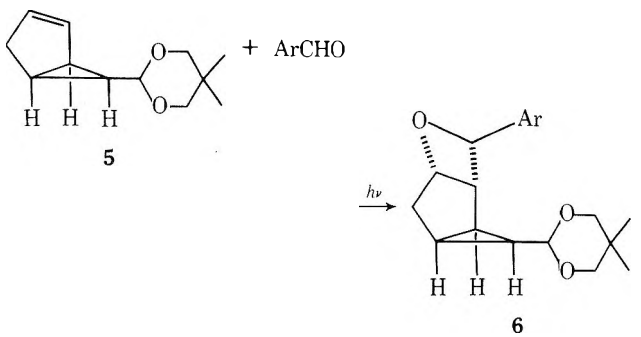
Results and Discussion

Strategy. The original synthesis of *dl*-**3** involved the preparation of the racemic bicyclo[3.1.0]hexanone intermediate *dl*-**4b** which was subsequently transformed into *dl*-**3** by



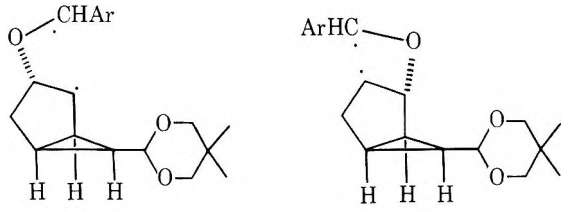
4b

way of a solvolytic ring opening reaction.[3] A successful synthesis of enantiomerically pure **3** would therefore be formally achieved by the synthesis of enantiomerically pure **4b.** To this end, use was made of *l*-bicyclo[3.1.0]hex-2-ene-6-*endo*-carboxaldehyde neopentyl glycol acetal **5,** which had been previously demonstrated to be the enantiomer which would lead to prostaglandins of natural configuration.[4] It was envisaged that a suitable aromatic aldehyde could be photochemically cycloadded to **5** to afford an oxetane **6** possessing the indicated



5 6

orientation and configuration. That **6** would be preferentially formed over other isomeric oxetanes was predicted on the following grounds: (1) the endo orientation of the neopentyl glycol acetal group of **5** essentially excludes approach to the β face of the molecule and thereby assures predominant cycloaddition from the α face; (2) extensive literature precedent for the photochemical formation of oxetanes from aromatic aldehydes or ketones with olefins[5] suggests that the reaction usually occurs by way of the most stable biradical intermediate. For the case in point, intermediate **7** should therefore

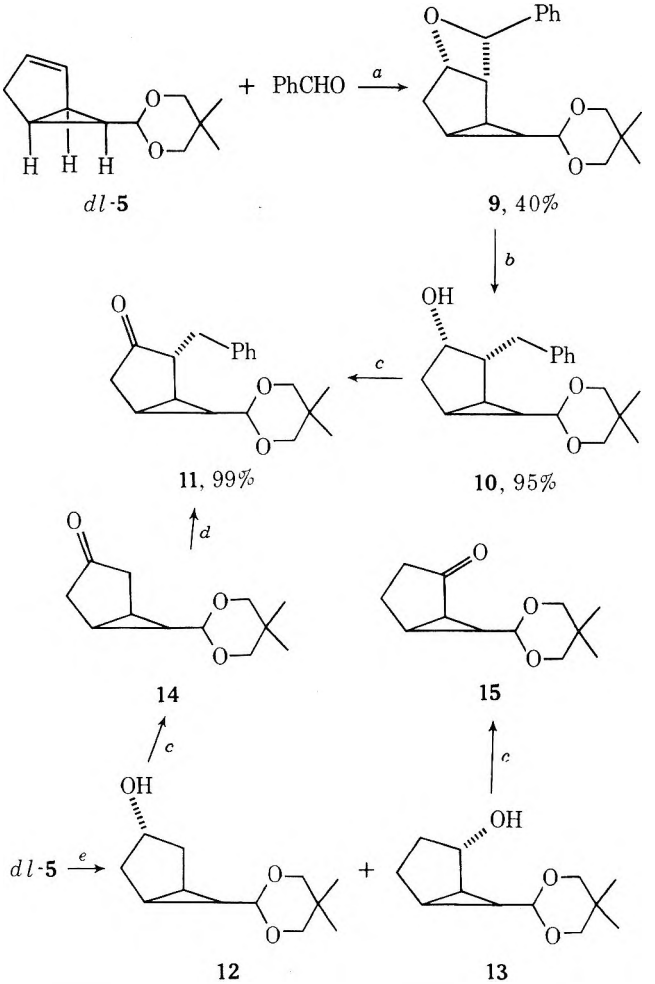


7 8

be favored over **8** since the former is stabilized by a cyclopropyl carbinyl interaction with the radical center on the ring.

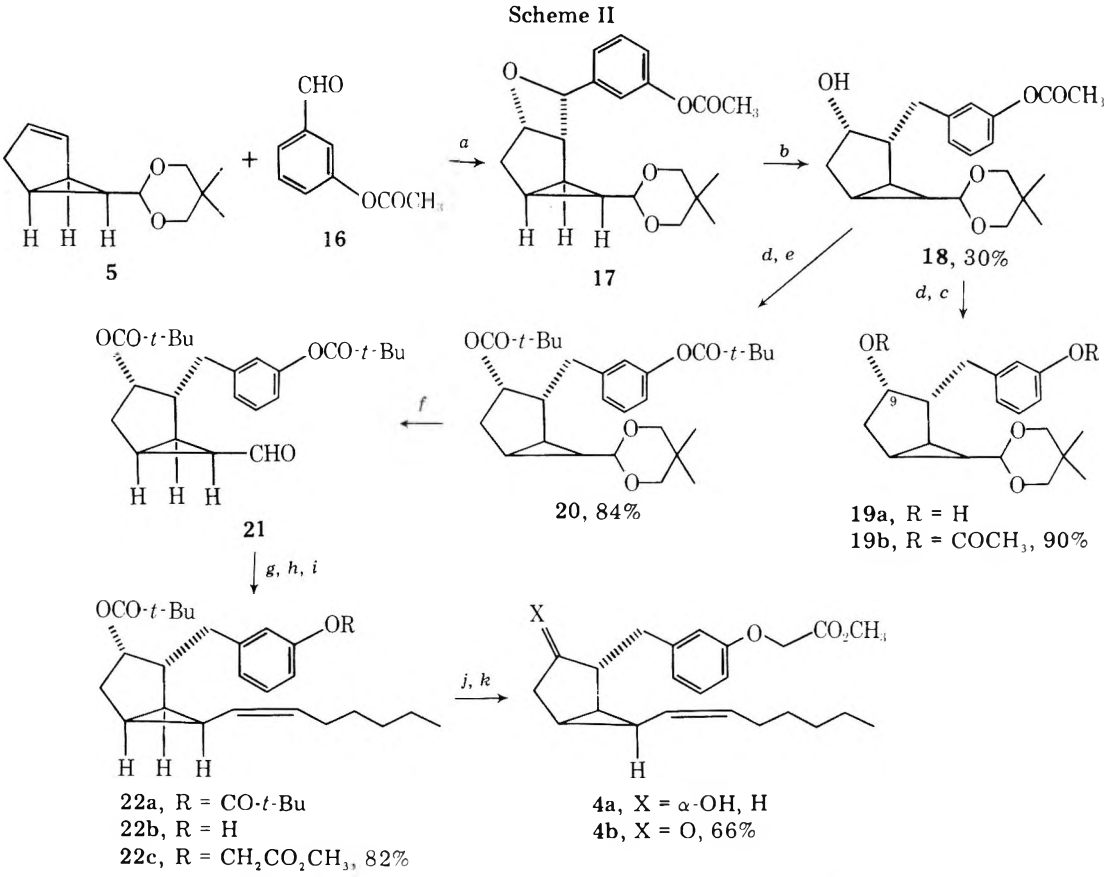
Model Studies. To test the correctness of the above reasoning, the model series of reactions illustrated in Scheme I were carried out with *dl*-**5.** Irradiation of a solution of *dl*-**5** and benzaldehyde (molar ratio 3:1) in benzene afforded oxetane *dl*-**9** as the major product in addition to more polar impurities. Dissolving metal reductive cleavage of the benzylic carbon–

Scheme I



[a] $h\nu$, 350 nm, C_6H_6, N_2. [b] Na, *n*-BuOH, $C_6H_5CH_3$, reflux. [c] $CrO_3 \cdot 2pyr$, CH_2Cl_2, 25 °C. [d] *t*-BuOK, THF; $PhCH_2Br$, 25 °C. [e] BH_3, THF, 0 °C; H_2O_2, NaOH.

Scheme II

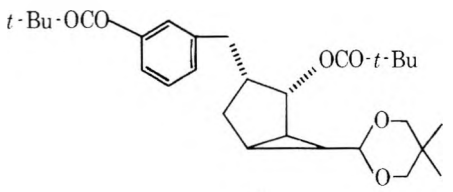


[a] $h\nu$, 350 nm, C_6H_6, 25 °C, N_2. [b] H_2, 10% Pd-C, EtOH, 25 °C. [c] Ac_2O, pyridine. [d] K_2CO_3, CH_3OH, H_2O, 25 °C. [e] *t*-BuCOCl, pyridine. [f] 88% HCO_2H, 0 °C, 4 h. [g] $Ph_3P{=}CH(CH_2)_4CH_3$, C_6H_6. [h] K_2CO_3, CH_3OH, H_2O. [i] NaH, $BrCH_2CO_2CH_3$, CH_3O–CH_2CH_2–OCH_3, 25 °C. [j] $NaOCH_3$, CH_3OH. [k] $CrO_3 \cdot 2$ pyr, CH_2Cl_2, 25 °C.

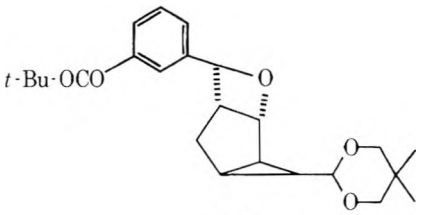
oxygen bond afforded alcohol *dl*-**10**, and subsequent oxidation of this material gave ketone *dl*-**11** in 94% overall yield from **9**. To confirm the structure assigned to *dl*-**11**, its synthesis was carried out by an independent route. Thus, hydroboration of *dl*-**5** gave secondary alcohols *dl*-**12** and *dl*-**13** (ratio ca. 3:1 by TLC) which were separated with some difficulty by chromatography. Oxidation of each alcohol separately gave the ketones *dl*-**14** (from *dl*-**12**) and *dl*-**15** (from *dl*-**13**). These isomers were distinguished by their respective infrared and ultraviolet spectra. Thus, the cyclopropyl conjugated ketone *dl*-**15** exhibited absorptions at ν_{max} (mull) 1710 cm^{-1} in the infrared and $\lambda_{max}^{n\rightarrow\pi^*}$ 278 nm (ϵ 41) in ethanol in the ultraviolet regions, while the nonconjugated isomer *dl*-**14** exhibited corresponding absorptions at ν_{max} (mull) 1740 cm^{-1} and $\lambda_{max}^{n\rightarrow\pi^*}$ 270 nm (ϵ 28) in ethanol. Finally, alkylation of *dl*-**14** with benzyl bromide gave *dl*-**11**, identical in all respects with the specimen of *dl*-**11** derived from oxetane *dl*-**9**.

Synthesis. The application of the above methods to the synthesis of optically pure **4b** is illustrated in Scheme II. Irradiation of a solution of *l*-**5** and *m*-acetoxybenzaldehyde[6] (**16**) (molar ratio 3:1) in benzene for 24 h afforded oxetane **17** which was subsequently converted to alcohol 18 in ca. 30% overall yield based on 28% of recovered **16**. Extended photolysis times did not significantly increase the yield of oxetane **17**, and the maximum conversion obtainable was ca. 70%. The structure proof of **17** rested primarily on its NMR spectrum. In particular, the oxetane proton pattern (δ 4.97–5.52) was essentially superimposable on that for *dl*-**9**. Further evidence for the assigned structure was gained by its eventual conversion to optically active **3** and **4b** and comparison with authentic racemic materials (vide infra). Accepting that the structure of the oxetane is correct as shown, the optical purity of **17** became of prime importance. Clearly, for the synthetic route to optically pure **4b** to be viable, the high level of optical purity of *l*-**5** must be maintained in **17**. Two experiments have shown that **17** is of high optical purity. First, reisolation of unconsumed olefin *l*-**5** and measurement of its specific rotation confirmed that racemization had not occurred to any extent during photolysis (e.g., by hydrogen atom abstraction to afford a symmetrical allylic radical intermediate). Secondly, the optical purity of diacetate **19b** (derived from monoacetate **18**) was determined by NMR spectroscopy using the chiral shift reagent tris[3-(heptafluoropropylhydroxymethylene)-*d*-camphorato]europium(III).[7] For this experiment, a sample of *dl*-**19b** was prepared in analogous fashion from *dl*-**5**. Successive addition of the shift reagent to a deuteriochloroform solution of *dl*-**19b** (ca. 0.3 M) eventually produced an NMR spectrum in which the C-9 acetate methyl group (prostaglandin numbering[2]) was shifted downfield by 3.8 ppm and split into two singlets, $\Delta\nu$ = 5 Hz. For *d*-**19b** (prepared from *l*-**5**), the addition of an amount of shift reagent necessary to produce the same 3.8 ppm downfield shift of the C-9 acetate methyl group failed to split the acetate singlet. This result confirmed that the sample of *d*-**19b** and therefore **18** was of high optical purity (≥90%).

Continuing with the synthetic sequence in Scheme II, the monoacetate **18** is a crystalline solid which may be upgraded at this stage by recrystallization or carried on in crude form. Hydrolysis of the phenolic acetate and esterification of the resulting diol with pivaloyl chloride afforded dipivalate **20** as a solid after silica gel chromatography. At this stage, the NMR spectrum of **20** (homogeneous by TLC in several solvent systems) suggested the presence of an impurity to the extent of 10–20%. Multiple recrystallizations eventually afforded a pure specimen of **20**. The impurity was then crystallized from the combined mother liquors of **20** and was shown to be isomeric with **20**. The structure of this impurity was tentatively assigned as **23**: a structure which would be derived from oxetane

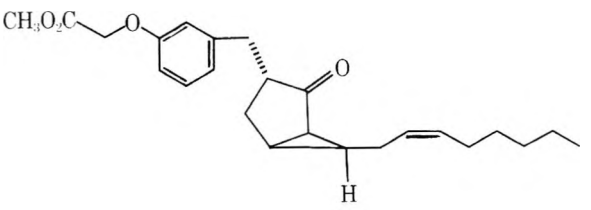


23



24

regioisomer **24** and one which will receive further support (vide infra). Dipivalate **20** may either be upgraded by recrystallization, or the mixture of **20** and **23** may be employed for the hydrolysis to **21** with concentrated (88%) formic acid. *endo*-Aldehyde **21** exhibited a doublet at 9.68 δ (J = 3 Hz). If the hydrolysis was allowed to proceed for longer reaction times (≥8 h at 0 °C) or at elevated temperatures (≥25 °C), significant quantities of the corresponding exo aldehyde (doublet at δ 9.05; J = 4 Hz) were formed. The aldehyde **21** was then condensed with *n*-hexylidenetriphenylphosphorane (to give **22a**), the phenolic ester of the Wittig product was then selectively hydrolyzed (to give **22b**), and the resulting phenol was finally alkylated with methyl bromoacetate to afford diester **22c** in 82% overall yield from aldehyde **21**. When a mixture of **20** and **23** was employed for the syntheses of **21** and **22c**, the isomer corresponding to **23** was carried through all steps. At no point was the isomeric impurity separated from the desired forms (i.e., **21** and **22a–c**) by TLC in several solvent systems. Finally, diester **22c** was treated with dry sodium methoxide to liberate the latent C-9 hydroxyl group which was then oxidized to afford ketone **4b**. At this stage, the isomeric impurity was chromatographically separable for the first time in the entire synthetic sequence. For **4b**, this impurity was tentatively assigned as **25**. That **4b** and **25** were isomeric was confirmed by high resolution mass spectrometry. Additionally, the infrared spectrum of **4b** exhibited carbonyl absorptions at 1765 and 1740 cm^{-1} while that for **25** exhibited absorptions at 1765, 1740 and 1720 cm^{-1} (the ester function in this type



25

of compound appears to exhibit two carbonyl stretches at 1765 and 1740 cm^{-1}). In the case of **4b**, the ketone carbonyl is coincident with the 1740-cm^{-1} ester band while in the case of **25** the ketone carbonyl absorbs at 1720 cm^{-1} due to conjugation with the cyclopropane ring.[8] These results implied that oxetane regioisomer **24** was formed as a by-product along with oxetane **17** in the photochemical cycloaddition reaction (ratio **17:24** ca. 9:1) for *l*-**5** and **16**, and literature precedent[9] for simple vinylcyclopropane systems supports this conclusion.

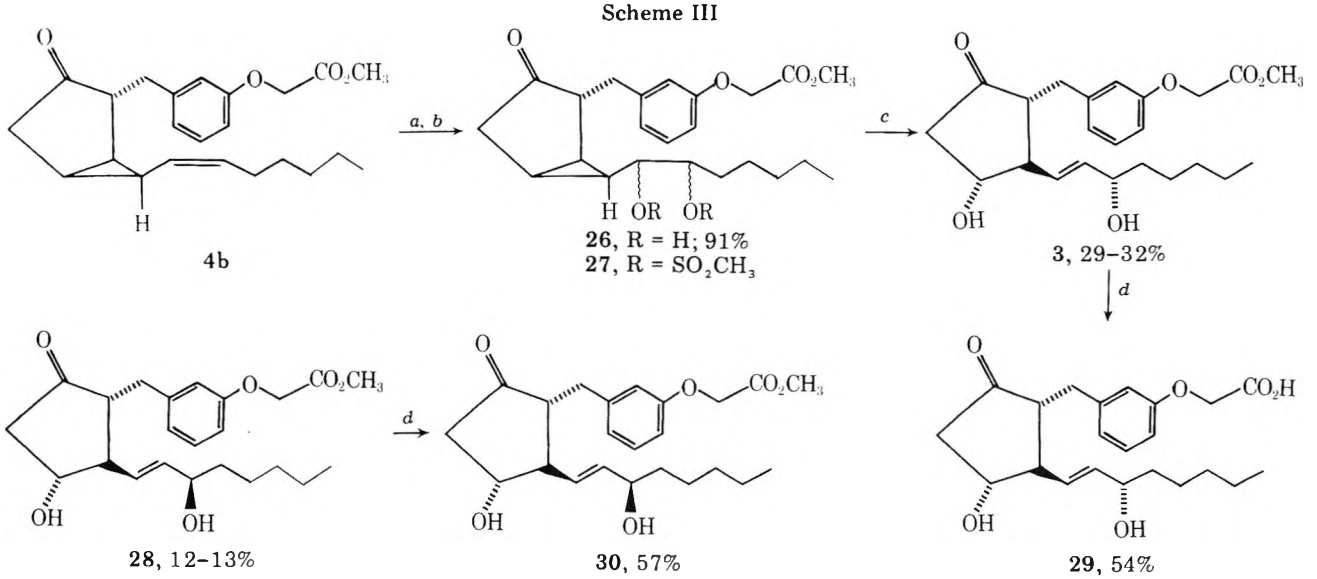
The transformations of **4b** into 3-oxa-4,5,6-trinor-3,7-*inter*-*m*-phenyleneprostaglandin E_1 (**29**) and (15*R*) -3-oxa-4,5,6-trinor-3,7-*inter*-*m*-phenyleneprostaglandin E_1 (**30**) are illustrated in Scheme III. *endo*-Olefin **4b** was hydroxylated catalytically with osmium tetroxide[10] to afford a mixture of *cis*-glycols **26**. This mixture was then esterified with methanesulfonyl chloride to give bismesylates **27**, which were then solvolyzed in aqueous acetone to give the epimeric esters **3** and **28** in 30–40% combined yield from **4b**. These isomers were separated by chromatography on silica gel, and the sample of **3** ([α]$_D$ −48 ° in ethanol) produced was identical by NMR and infrared spectroscopy and TLC (several systems) with an authentic sample of *dl*-**3**.[3] Methyl esters **3** and **28** were finally converted to their free acid forms **29** (mp 128.7–130.0 °C) and **30**, respectively, by enzymatic hydrolysis with the acetone-insoluble fraction from the sea whip, *Plexaura homomalla*.[11]

The biological evaluation of these novel prostaglandin analogues is in progress and will be reported elsewhere. However, it is interesting to note that free acid **29** is 30 times more potent than PGE_1 as an inhibitor of ADP-induced human platelet aggregation in vitro.[12]

Experimental Section

General. All melting points are corrected. All analytical data were obtained by the Physical and Analytical Chemistry Research Department of The Upjohn Co., with IR spectra being obtained either on neat samples (oils) or on Nujol mulls (crystalline samples). Mass spectra were recorded at high or low resolution for derivatized (Me_3Si)

Scheme III



[a] OsO_4, *N*-methylmorpholine oxide, acetone, H_2O, 25 °C. [b] CH_3SO_2Cl, pyridine, 0 °C. [c] Acetone–water (2:1), 25 °C. [d] *Plexaura homomalla* enzyme, H_2O.

or underivatized compounds at 70 eV. The NMR spectra were obtained on a Varian A-60D or T-60 spectrometer operating at 60 MHz on chloroform-*d* solutions containing internal tetramethylsilane. Thin-layer chromatography (TLC) was conducted using Analtech (Uniplate) glass plates precoated with silica gel GF (250 μm). Where mixed solvents were used for chromatography, the composition is expressed as a percent by volume of the former in the latter. The solvent system A-IX[13] is the organic layer from an equilibrated mixture of 90 mL of ethyl acetate, 20 mL of acetic acid, 50 mL of 2,2,4-trimethylpentane, and 100 mL of water. The TLC plates were visualized first by UV light (Mineralight UVS-11), then by spraying with a vanillin–phosphoric acid solution or 50% aqueous sulfuric acid, followed by heating. Unless otherwise noted, column chromatography utilized neutral silica gel (E. Merck), 70–230 mesh. Acid washed silica gel was Mallinckrodt CC-4. All solvents were reagent grade or reagent grade distilled from glass (Burdick and Jackson). All reagents were used as purchased and were reagent grade where available.

***dl*-7-Oxa-8-phenyltricyclo[4.2.0.0^{2,4}]octane-3-*endo*-carboxaldehyde Neopentyl Glycol Acetal (9).** A Pyrex photolysis vessel, equipped with an immersible, water-cooled cold-finger and fritted gas inlet, was charged with a solution of 5.82 g (30 mmol) of *dl*-**5** and 1.06 g (10 mmol) of benzaldehyde in 25 mL of benzene. Dry nitrogen was bubbled through the solution for 15 min to remove dissolved oxygen, and the reaction mixture was then irradiated at 350 nm with a Rayonet Type RS preparative photochemical reactor (The Southern New England Ultraviolet Co., Middletown, Conn.) equipped with six RUL 3500-Å lamps for 48 h. The photolysate was concentrated in vacuo to give 7.31 g of a pale yellow oil which was chromatographed as follows: a 28 mm × 48 in. column was slurry-packed with 300 g of silica gel in Skellysolve B. The sample was applied in Skellysolve B and eluted with 250 mL of Skellysolve B, 1500 mL of 10% ethyl acetate in Skellysolve B, 1000 mL of 20% ethyl acetate in Skellysolve B, and 500 mL of ethyl acetate. Fractions 1 and 2 were 500 mL each (discarded), and subsequent fractions were 20 mL each. Based on TLC homogeneity, fractions 12–25 were combined to give 4.20 g of recovered *dl*-**5**. Fractions 83–113 were combined to give 1.19 g (47% based on recovered **5**) of pure oxetane **9** as a pale tan oil which crystallized on standing at −19 °C. A small portion of this material was recrystallized from ethyl acetate–Skellysolve B (3×) to give colorless microcrystals: mp 103.0–105.0 °C. The IR showed bands at 3030, 1600, 1580, 1490, 1110, 1020, 1005, 750, and 700 cm^{-1}. The NMR showed absorptions at δ 0.68 (s, 3 H), 1.18 (s, 3 H), 0.9–2.7 (m, 5 H), 3.00 (t, J = 4 Hz, 1 H), 3.1–3.8 (m, 4 H), 3.50 (d, J = 8 Hz, 1 H), 5.13 (t, J = 4 Hz, 1 H), 5.40 (d, J = 4 Hz, 1 H), 7.33 (bd s, 5 H). The mass spectrum exhibited peaks at m/e 300 (M$^+$; very weak), 299, 115, 108, 107, 80, 79, 77, 70, 69, 45, and 41. TLC using 25% ethyl acetate in Skellysolve B showed one spot, R_f 0.31.

Anal. Calcd for $C_{19}H_{24}O_3$: C, 75.97; H, 8.05. Found: C, 75.67; H, 8.21.

***dl*-2-*exo*-Benzyl-3-*exo*-hydroxybicyclo[3.1.0]hexane-6-*endo*-carboxaldehyde Neopentyl Glycol Acetal (10).** A 50-mL round-bottom flask, equipped with magnetic stirring bar and reflux condenser, was charged with 10 mL of toluene and 0.07 g (3.03 mg-atoms) of sodium metal. After heating the mixture to reflux, a solution of 0.25 g (0.83 mmol) of oxetane **9** and 0.16 mL (ca. 1.8 mmol) of *n*-butyl alcohol in 1.0 mL of toluene was added dropwise with stirring from the top of the reflux condenser. The addition funnel was rinsed with toluene (2 × 0.5 mL) and the reaction mixture was refluxed for 2.5 h. Methanol (0.5 mL) was then added to destroy the unreacted sodium. The reaction mixture was cooled to room temperature, diluted with brine, and extracted with ethyl acetate (2×). After washing the combined extracts with brine (3×) and drying over magnesium sulfate, concentration in vacuo gave 0.277 g of crude product which was chromatographed as follows: a 19 mm × 24 in. column was slurry packed with 60 g of silica gel in 20% ethyl acetate in Skellysolve B. The sample was applied and eluted with 300 mL of 20% ethyl acetate in Skellysolve B and 500 mL of 50% ethyl acetate in Skellysolve B. The first fraction was 200 mL (discarded). Subsequent fractions were 20 mL each. Based on TLC homogeneity, fractions 13–23 were combined to give 0.213 g (85%) of pure **10** as a white crystalline solid. Recrystallization of this material from ethyl acetate–Skellysolve B gave a white powder: mp 119.8–122.8 °C. The IR showed bands at 3290, 3020, 1600, 1585, 1495, 1115, 1085, 1070 1020, 995, 985, 735, and 700 cm^{-1}. The NMR showed absorptions at δ 0.67 (s, 3 H), 1.18 (s, 3 H), 0.55–3.19 (m, 8 H), 2.23 (bd s, 1 H), 3.19–3.85 (m, 4 H), 4.10 (d, J = 7 Hz, 1 H), 3.85–4.37 (m, 1 H), 7.22 (bd s, 5 H). The mass spectrum exhibited peaks at m/e 115, 107, 105, 91, 79, 69, 55, 45, 43, and 41. TLC using 25% ethyl acetate in Skellysolve B showed one spot, R_f 0.08.

Anal. Calcd for $C_{19}H_{26}O_3$: C, 75.46; H, 8.67. Found: C, 75.54; H, 8.89.

***dl*-3-*exo*-Hydroxybicyclo[3.1.0]hexane-6-*endo*-carboxaldehyde Neopentyl Glycol Acetal (12) and *dl*-2-*exo*-Hydroxybicyclo[3.1.0]hexane-6-*endo*-carboxaldehyde Neopentyl Glycol Acetal (13).** A 500-mL three-neck, round-bottom flask, equipped with magnetic stirring bar, nitrogen inlet, and serum stopper, was charged with 5.82 g (30 mmol) of acetal *dl*-**5** and 100 mL of tetrahydrofuran. The resulting solution was stirred, alternately degassed and flushed with nitrogen several times, and then cooled to 0 °C. A solution of 25 mL of 1.0 M borane in tetrahydrofuran (25 mmol) was added, and the reaction mixture was then warmed to room temperature with stirring for 1 h. After cooling back down to 0 °C, excess borane was quenched by the cautious addition of 3 mL of water. The reaction mixture was then treated with 6.6 mL of 3 N aqueous sodium hydroxide followed by the dropwise addition of 6.6 mL of 30% hydrogen peroxide, and then allowed to stir at room temperature overnight. After dilution with brine, the product was extracted with chloroform (3×). The combined organic fractions were washed with brine, dried over magnesium sulfate, and concentrated in vacuo to give 7.17 g of crude product which was chromatographed as follows: a 28 mm × 48 in. column was slurry packed with 300 g of silica gel in 5% acetone in methylene chloride. The sample was applied in methylene chloride and eluted with 250 mL of 5% acetone in methylene chloride, 500 mL of 10% acetone in methylene chloride, 1000 mL of 20% acetone in methylene chloride, and 500 mL of 30% acetone in methylene chloride. The first fraction was 1000 mL (discarded), and subsequent fractions were 20 mL each. Based on TLC homogeneity, fractions 28–38 were combined to give 2.44 g (38%) of alcohol **12** as colorless crystals: mp 97–102 °C. Recrystallization from ethyl acetate–Skellysolve B gave pure **12** as colorless needles: mp 105.3–106.8 °C. The IR showed bands at 3480, 3050, 3030, 1110, 1105, 1070, 1020, 1000, and 975 cm^{-1}. The NMR showed absorptions at δ 0.70 (s, 3 H), 1.20 (s, 3 H), 0.6–2.4 (m, 7 H), 2.92 (bd s, 1 H), 3.20–3.81 (m, 4 H), 3.92 (d, J = 7.5 Hz, 1 H), 3.8–4.46 (m, 1 H). The mass spectrum exhibited peaks at m/e 212 (M$^+$; very weak), 115, 96, 69, 55, 45, and 41. TLC using 30% ethyl acetate in Skellysolve B showed one spot, R_f 0.48.

Anal. Calcd for $C_{12}H_{20}O_3$: C, 67.89; H, 9.50. Found: C, 67.81; H, 9.70.

Fractions 39–56 were combined to give 2.36 g (37%) of a mixture of **12** and **13**. Fractions 57–66 were combined to give 0.55 g (9%) of slightly impure acetal **13** as a colorless solid. Recrystallization of this material from ethyl acetate–Skellysolve B (2×) gave pure **13** as colorless needles: mp 117.8–119.5 °C. The IR showed bands at 3420, 3040, 3020, 1115, 1095, 1015, 1005, 990, and 980 cm^{-1}. The NMR spectrum showed absorptions at δ 0.70 (s, 3 H), 1.20 (s, 3 H), 0.5–2.6 (m, 7 H), 3.17 (bd s, 1 H), 3.17–3.80 (m, 4 H), 4.12 (d, J = 7 Hz, 1 H), 4.17–4.43 (m, 1 H). The mass spectrum exhibited peaks at m/e 212 (M$^+$; very weak), 115, 109, 96, 79, 55, 45, and 41. TLC using 30% ethyl acetate in Skellysolve B showed one spot, R_f 0.41.

Anal. Calcd for $C_{12}H_{20}O_3$: C, 67.89; H, 9.50. Found: C, 67.81, 67.50; H, 9.03, 9.38.

***dl*-2-Oxobicyclo[3.1.0]hexane-6-*endo*-carboxaldehyde Neopentyl Glycol Acetal (15).** A 250-mL flask, equipped with magnetic stirring bar and calcium sulfate drying tube, was flushed with dry nitrogen and charged with 40 mL of methylene chloride and 2.24 g (28.26 mmol) of pyridine followed by 1.41 g (14.13 mmol) of chromium trioxide. After stirring at room temperature for 30 min, the burgundy-colored reaction mixture was treated all at once with a solution of 0.50 g (2.36 mmol) of alcohol **13** in a minimal volume of methylene chloride. The reaction mixture was then stirred at room temperature for 30 min, diluted with 130 mL of ether, and washed with 5% aqueous sodium hydroxide (3 × 75 mL), water, saturated aqueous cupric sulfate (2 × 75 mL), and brine, and dried over magnesium sulfate. Concentration in vacuo gave 0.50 g (ca. 100%) of slightly impure product as an oily solid. Recrystallization of this material from ether–hexane (2×) gave pure **15** as colorless needles: mp 99.8–101.0 °C. The IR showed bands at 3060, 1710, 1185, 1110, 1095, 1015, 995, and 930 cm^{-1}. The NMR spectrum showed absorptions at δ 0.70 (s, 3 H), 1.20 (s, 3 H), 1.5–2.5 (m, 7 H), 3.1–3.8 (m, 4 H), 4.30 (d, J = 6 Hz, 1 H). The mass spectrum exhibited peaks at m/e 209 (M$^+$ − 1; very weak), 125, 115, 95, 69, 56, 55, 45, 41, 30, and 29. The ultraviolet spectrum showed $\lambda_{max}^{n\to\pi^*}$ 278 nm (ε 41) in ethanol. TLC using 50% ethyl acetate in Skellysolve B showed one spot, R_f 0.42.

Anal. Calcd for $C_{12}H_{18}O_3$: C, 68.54; H, 8.63. Found: C, 68.83; H, 8.89.

***dl*-3-Oxobicyclo[3.1.0]hexane-6-*endo*-carboxaldehyde Neopentyl Glycol Acetal (14).** In the same manner that **13** was oxidized to **15**, alcohol **12** (2.38 g, 11.21 mmol) was oxidized to ketone **14** using 175 mL of methylene chloride, 10.93 g (138.12 mmol) of pyridine, and 6.90 g (69.06 mmol) of chromium trioxide. Identical workup as before gave 2.54 g of crude **14** which was chromatographed as follows: a 19

mm × 24 in. column was slurry-packed with 60 g of silica gel in 5% ethyl acetate in Skellysolve B. The sample was applied in Skellysolve B and eluted with 350 mL of 5% ethyl acetate in Skellysolve B, 250 mL of 10% ethyl acetate in Skellysolve B, and 500 mL of 25% ethyl acetate in Skellysolve B. The first fraction was 300 mL (discarded), and subsequent fractions were 20 mL each. Based on TLC homogeneity, fractions 21–34 were combined to give 2.28 g (97%) of pure **14** as a waxy solid. Recrystallization from Skellysolve B at −19 °C gave colorless microprisms: mp 54.0–55.3 °C. The IR showed bands at 3050, 3030, 2750, 2650, 1740, 1150, 1115, 1015, 995, and 980 cm^{-1}. The NMR spectrum showed absorptions at δ 0.68 (s, 3 H), 1.20 (s, 3 H), 0.9–3.0 (m, 7 H), 3.15–3.82 (m, 4 H), 4.07 (d, J = 7 Hz, 1 H). The mass spectrum exhibited peaks at m/e 210 (M^+; very weak), 209 ($M^+ - 1$; very weak), 125, 115, 95, 69, 67, 56, 55, 45, 43, and 41. The ultraviolet spectrum showed $\lambda_{max}^{n-\pi^*}$ 270 nm (ε 28) in ethanol. TLC using 50% ethyl acetate in Skellysolve B showed one spot, R_f 0.50.

Anal. Calcd for $C_{12}H_{18}O_3$: C, 68.54; H, 8.63. Found: C, 68.02, 68.67; H, 8.92, 8.96.

***dl*-2-*exo*-Benzyl-3-oxobicyclo[3.1.0]hexane-6-*endo*-carboxaldehyde Neopentyl Glycol Acetal (11).** A 250-mL flask, equipped with magnetic stirring bar, was charged with 125 mL of tetrahydrofuran (Burdick and Jackson) and 2.66 g (12.65 mmol) of ketone **14**. After purging the reaction vessel with nitrogen for several minutes, solid potassium *tert*-butoxide (1.55 g; 13.81 mmol) was added, and the reaction mixture was stirred at room temperature for 5 min. The enolate containing solution was then treated dropwise with benzyl bromide (2.18 g; 12.74 mmol), stirred for 1 h, and quenched with 35 mL of water. The reaction mixture was concentrated in vacuo, diluted with brine, and extracted with ethyl acetate (2×). The combined extracts were washed with brine, dried over magnesium sulfate, and concentrated in vacuo to give 4.60 g of crude product as an oil which was chromatographed as follows: a 19 mm × 24 in. column was slurry-packed with 60 g of silica gel in 2% ethyl acetate in Skellysolve B. The sample was applied in Skellysolve B and eluted with 350 mL of Skellysolve B, 250 mL of 5% ethyl acetate in Skellysolve B, 250 mL of 10% ethyl acetate in Skellysolve B, and 500 mL of 20% ethyl acetate in Skellysolve B. The first fraction was 500 mL (discarded), and subsequent fractions were 20 mL each. Based on TLC homogeneity, fractions 6–17 were combined to give 0.65 g (13%) of dialkylated material. Fractions 18–25 were combined to give 1.07 g (28%) of pure **11** as a white crystalline solid. Recrystallization of this material from benzene–hexane (2×) and then acetone–ether gave pure **11** as colorless prisms: mp 130.3–132.8 °C. The IR showed bands at 3060, 1735, 1600, 1500, 1470, 1115, 1100, 1015, 990, 790, 765, and 710 cm^{-1}. The NMR spectrum showed absorptions at δ 0.64 (s, 3 H), 1.17 (s, 3 H), 1.03–1.83 (m, 3 H), 2.10–3.17 (m, 5 H), 3.17–3.77 (m, 4 H), 4.06 (d, J = 6.5 Hz, 1 H), 7.20 (s, 5 H). The mass spectrum exhibited peaks at m/e 300 (M^+), 219, 170, 128, 123, 115, 104, 91, 81, 69, 45, and 41. TLC using 25% ethyl acetate in Skellysolve B showed one spot, R_f 0.39. TLC using 10% acetone in benzene showed one spot, R_f 0.49.

Anal. Calcd for $C_{19}H_{24}O_3$: C, 75.97; H, 8.05. Found: C, 75.72; H, 8.11.

***dl*-2-*exo*-Benzyl-3-oxobicyclo[3.1.0]hexane-6-*endo*-carboxaldehyde Neopentyl Glycol Acetal (11).** A 50-mL round-bottom flask, equipped with magnetic stirring bar and calcium sulfate drying tube, was flushed with dry nitrogen and charged with 10 mL of methylene chloride and 0.278 g (3.5 mmol) of pyridine. Solid chromium trioxide (0.176 g, 1.76 mmol) was then added in one portion and the resulting mixture stirred at room temperature for 30 min. To this burgundy-colored solution was added a solution of 0.0884 g (0.293 mmol) of alcohol **10** in a minimal volume of methylene chloride. After stirring at room temperature for 45 min, the reaction mixture was transferred to a separatory funnel containing 100 mL of 5% aqueous sodium hydroxide and 100 mL of ether. The remaining chromium salts were washed with a little ether which was combined with the organic phase. After thorough mixing, the layers were separated and the organic phase was washed with 5% aqueous sodium hydroxide (2 × 100 mL), water, saturated aqueous cupric sulfate, water, and brine, and dried over $MgSO_4$. Concentration in vacuo gave 0.0872 g (99%) of crude product **11** as a white solid. The NMR and infrared spectra of this material were identical with those of an independently synthesized sample of **11**, as were its R_f values in three different solvent systems. Recrystallization of the crude oxidation product from benzene–hexane (2×) and then from acetone–ether gave colorless prisms: mp 128.5–131 °C, undepressed on admixture with authentic *dl*-**11**.

***m*-Acetoxybenzaldehyde (16).** The method of Bender and Nakamura[6] was employed. Thus, a 250-mL flask, equipped with a magnetic stirring bar and calcium sulfate drying tube, was charged with 25.0 g (0.205 mol) of *m*-hydroxybenzaldehyde and 100 mL of pyridine followed by 25.0 mL of acetic anhydride. After stirring at room temperature for 40 min, the reaction mixture was diluted with brine and ice and extracted with ethyl acetate (2×). The combined extracts were washed with 1.2 N aqueous hydrochloric acid (2×), saturated aqueous sodium bicarbonate (2×), and brine, and dried over magnesium sulfate. Concentration in vacuo gave 32.52 g of a red-orange oil which was distilled at reduced pressure to give 24.95 g (74%) of pure **16**: bp 100 °C (1.0 mm). The NMR spectrum showed absorptions at δ 2.25 (s, 3 H), 7.1–7.8 (m, 4 H), 9.78 (s, 1 H).

***d*-8-(*m*-Acetoxyphenyl)-7-oxatricyclo[4.2.2.0^{2,4}]octane-3-*endo*-carboxaldehyde Neopentyl Glycol Acetal (17).** A Pyrex photolysis vessel, equipped with an immersible, water-cooled cold-finger and fritted gas inlet, was charged with a solution of 5.82 g (30 mmol) of *l*-bicyclo[3.1.0]-hex-2-ene-6-*endo*-carboxaldehyde neopentyl glycol acetal **5**[4] ($[\alpha]_D$ − 227 ° in methanol) and 1.64 g (10 mmol) of *m*-acetoxybenzaldehyde in 25 mL of benzene. Dry nitrogen was bubbled through the solution for 15 min to remove dissolved oxygen, and the reaction mixture was then irradiated at 350 nm with a Rayonet Type RS preparative photochemical reactor (The Southern New England Ultraviolet Co., Middletown, Conn.) equipped with six RUL 3500-Å lamps for 24 h. Extended irradiation times did not significantly increase the yield of product. The photolysate was concentrated in vacuo to give 10 g of a pale yellow oil which was chromatographed as follows: a 28 mm × 48 in. column was slurry-packed with 300 g of silica gel in 10% ethyl acetate in Skellysolve B. The sample was applied and eluted with 700 mL of 15% ethyl acetate in Skellysolve B, 1000 mL of 25% ethyl acetate in Skellysolve B, 1000 mL of 35% ethyl acetate in Skellysolve B, 1000 mL of 50% ethyl acetate in Skellysolve B, and 1000 mL of 70% ethyl acetate in Skellysolve B. The first fraction was 500 mL (discarded), and subsequent fractions were 50 mL each. Based on TLC homogeneity, fractions 9–16 were combined to give 4.17 g of recovered olefinic acetal **5** as a white crystalline solid: mp 53–55 °C ($[\alpha]_D$ − 227 ° in methanol). The rotation of this material was identical with that of pure starting material which confirmed that racemization of *l*-**5** had not occurred during photolysis. Fractions 26–32 were combined to give 0.46 g (28%) of recovered *m*-acetoxybenzaldehyde. Fractions 33–58 were combined to give 1.50 g of impure **17** which was submitted to HPLC purification as follows: an LC-1-43 column (Chromatronix, Inc., Berkeley, Calif.) containing 241 g of "sized" Silica Gel H (mean particle diameter ca. 40 μm) was equilibrated with 30% ethyl acetate in Skellysolve B. The sample was diluted to 6 mL with methylene chloride, injected onto the column, and eluted with 30% ethyl acetate in Skellysolve B at 10.5 mL/min and 25 psi with a Milton Roy Co. pump (Model DC-1-60R Simplex Milroyal Pump, Milton Roy Co., Philadelphia, Pa.). The first fraction was 800 mL (discarded), and subsequent fractions were 20 mL each. Based on TLC homogeneity, fractions 24–45 were combined to give 0.86 g (33% based on recovered **16**) of pure *d*-**17** as a pale yellow oil; $[\alpha]_D$ + 55 ° (*c* 0.7505, 95% ethanol). The IR showed bands at 3040, 2950, 2860, 2840, 1765, 1610, 1590, 1485, 1470, 1370, 1205, 1115, 1020, 1005, 990, 790, and 700 cm^{-1}. The NMR spectrum showed absorptions at δ 0.68 (s, 3 H), 1.20 (s, 3 H), 0.8–2.5 (m, 5 H), 2.28 (s, 3 H), 2.99 (t, J = 4 Hz, 1 H), 3.12–3.88 (m, 4 H), 3.48 (d, J = 8 Hz, 1 H), 4.97–5.52 (m, 2 H), 6.78–7.60 (m, 4 H). The mass spectrum exhibited peaks at m/e 358 M^+; very weak), 116, 115, 108, 107, 79, 70, 69, 45, 43, and 41. TLC using 25% ethyl acetate in Skellysolve B showed a single spot, R_f 0.18.

***d*-2-*exo*-(*m*-Acetoxybenzyl)-3-*exo*-hydroxybicyclo[3.1.0]-hexane-6-*endo*-carboxaldehyde Neopentyl Glycol Acetal (18).** A glass Parr hydrogenation bottle (ca. 500 mL) was charged with 5.66 g of partially purified *d*-8-(*m*-acetoxyphenyl)-7-oxatricyclo[4.2.2.0^{2,4}]octane-6-*endo*-carboxaldehyde neopentyl glycol acetal **17**, 100 mL of absolute ethanol, and 0.30 g of 10% palladium on carbon. The resulting mixture was then hydrogenated on a Parr apparatus at 20 psi overnight (ca. 16–18 h). The mixture absorbed ca. 15 mmol of hydrogen, and longer reduction times resulted in no further absorption. The resulting mixture was filtered through Celite to remove the catalyst, and the filtrate was concentrated in vacuo to give 5.66 g of crude **18**. A 48 mm × 36 in. column was slurry-packed with 500 g of silica gel in 25% ethyl acetate in Skellysolve B. The sample of **18** was applied in methylene chloride and eluted with 1 L each of 30, 30, 40, 50, 60, 70, and 80% ethyl acetate in Skellysolve B. Fractions were 50 mL each. Based on TLC homogeneity fractions 72–89 were combined to give 3.65 g of **18** as a solid (30% yield overall from *l*-**5** based on recovered *l*-**5**). In a separate experiment, a sample of chromatographically pure **18** was recrystallized from ethyl acetate–*n*-hexane (2×) to give colorless needles: mp 122.2–125.9 °C; $[\alpha]_D$ + 31 ° (*c* 0.9188, ethanol). The IR showed bands at 3220, 1775, 1610, 1590, 1490, 1200, 1185, 1150, 1115, 1110, 1080, 1015, and 695 cm^{-1}. The NMR spectrum showed absorptions at δ 0.73 (s, 3 H), 1.25 (s, 3 H), 0.5–3.22 (m, 9 H), 2.30 (s, 3 H), 3.22–3.86 (m, 4 H), 4.00–4.37 (m, 2 H), 6.72–7.50 (m, 4 H). The mass spectrum exhibited peaks at m/e

360 (M^+; weak), 359, 342, 331, 317, 316, 304, 301, 300, 256, 214, 211, 125, 115, 107, and 69. TLC using 25% ethyl acetate in Skellysolve B showed one spot, R_f 0.32.

Anal. Calcd for $C_{21}H_{28}O_5$: C, 69.97; H, 7.83. Found: C, 69.98; H, 7.94.

***d*-2-*exo*-[*m*-(Pivaloyloxy)benzyl]-3-*exo*-(pivaloyloxy)bicyclo[3.1.0]hexane-6-*endo*-carboxaldehyde Neopentyl Glycol Acetal (20) and *l*-2-*exo*-(Pivaloyloxy)-2-*exo*-[*m*-(pivaloyloxy)benzyl]bicyclo[3.1.0]hexane-6-*endo*-carboxaldehyde Neopentyl Glycol Acetal (23).** A 500-mL flask, equipped with a magnetic stirring bar, was charged with 16.40 g (45.50 mmol) of chromatographically pure acetate **18** and 200 mL of methanol. The resulting solution was then treated with a solution of 6.0 g of potassium carbonate in 65 mL of water. The reaction mixture was stirred for 16 h at room temperature, diluted with 500 mL of ice-cold water, acidified to pH 5 with 1 M aqueous potassium bisulfate, and saturated with sodium chloride. The resulting aqueous mixture was extracted with chloroform (4 × 150 mL). The combined extracts were washed with brine, dried over sodium sulfate, and concentrated in vacuo to give 16.57 g of crude 2-*exo*-(*m*-hydroxybenzyl)-3-*exo*-hydroxybicyclo[3.1.0]hexane-6-*endo*-carboxaldehyde neopentyl glycol acetal (**19a**) as a pale yellow oil.

The above sample of diol **19a** was dissolved in 150 mL of pyridine and treated with 17.75 mL of pivaloyl chloride. The reaction mixture was stirred at room temperature for 2 days. Excess acid chloride was decomposed by the dropwise addition of 20 mL of water. The reaction mixture was diluted with 1000 mL of brine and extracted with ethyl acetate (2 × 200 mL). The combined extracts were washed with brine, water, saturated aqueous cupric sulfate (until all pyridine was removed), saturated aqueous sodium bicarbonate, and brine, and dried over sodium sulfate. Concentration in vacuo gave crude **20** which was chromatographed as follows: a 48 mm × 36 in. column was slurry-packed with 500 g of silica gel in 3% ethyl acetate in Skellysolve B. The sample was applied with Skellysolve B and eluted with 10% ethyl acetate in Skellysolve B. Fractions were 100 mL each. Based on TLC homogeneity, fractions 12–36 were combined to give 18.56 g (84%) of **20** as an oil which crystallized on standing at room temperature. This material was dissolved in 100 mL of methanol, heated to 40–45 °C on a steam bath, diluted with water to the point of incipient cloudiness, cooled, seeded, and allowed to crystallize overnight at 4 °C to give 8.81 g of essentially pure **20** as colorless needles: mp 106–112 °C. Subsequent recrystallizations from *n*-hexane (6×) gave analytically pure **20**: mp 112.4–115.1 °C; $[\alpha]_D$ +23° (*c* 0.8270, ethanol). The IR showed bands at 3040, 1755, 1725, 1610, 1590, 1285, 1235, 1160, 1150, 1120, 1100, 1020, and 990 cm^{-1}. The NMR showed absorptions at δ 0.72 (s, 3 H), 1.22 (s, 12 H), 1.36 (s, 9 H), 0.5–3.12 (m, 8 H), 3.25–3.83 (m, 4 H), 4.18 (d, J = 6.5 Hz, 1 H), 4.77–5.19 (m, 1 H), 6.70–7.37 (m, 4 H). The mass spectrum exhibited peaks at *m/e* 486 (M^+; weak), 384, 298, 214, 196, 193, 115, 107, 85, 69, 57, 45, and 41. TLC using 25% ethyl acetate in Skellysolve B showed one spot, R_f 0.50. GLPC using 6 ft × 1/8 in. 1% OV-17 on 80/100 Gas Chrom Q at 225 °C (60 mL/min), t_R = 8.4 min.

Anal. Calcd for $C_{29}H_{42}O_6$: C, 71.57; H, 8.70. Found: C, 71.47; H, 8.84.

The mother liquors from the above crystallization were combined. Recrystallization from methanol–water (2×) gave 1.0 g of isomeric dipivalate **23** as colorless microcrystals; mp 135.1–136.6 °C; $[\alpha]_D$ −25 ° (*c* 0.9000, ethanol). The IR showed bands at 3040, 1755, 1720, 1610, 1585, 1285, 1170, 1140, 1120, 1110, and 975 cm^{-1}. The NMR spectrum showed absorptions at δ 0.70 (s, 3 H), 1.20 (s, 3 H), 1.22 (s, 9 H), 1.33 (s, 9 H), 0.5–3.13 (m, 8 H), 3.15–3.82 (m, 4 H), 4.23 (d, J = 6 Hz, 1 H), 5.15–5.42 (m, 1 H), 6.71–7.54 (m, 4 H). The mass spectrum exhibited peaks at *m/e* 486 (M^+; weak), 384, 298, 214, 196, 193, 171, 115, 107, 85, 69, and 57. TLC using 25% ethyl acetate in Skellysolve B showed a single spot, R_f 0.50. GLPC using 6 ft × 1/8 in. 1% OV-17 on 80/100 Gas Chrom Q at 225 °C (60 ml/min), t_R = 7.4 min.

Anal. Calcd for $C_{29}H_{42}O_6$: C, 71.57; H, 8.70. Found: C, 71.32; H, 8.94.

***d*-2-*exo*-(*m*-Acetoxybenzyl)-3-*exo*-acetoxybicyclo[3.1.0]hexane-6-*endo*-carboxaldehyde Neopentyl Glycol Acetal (19b).** A sample of 1.01 g (ca. 3.17 mmol, prepared as previously described) of crude diol **19a** was dissolved in 25 mL of pyridine and treated with 5 mL of acetic anhydride. After stirring for 15.5 h at room temperature, the reaction mixture was diluted with 200 mL of brine and extracted with ethyl acetate (2 × 100 mL). The combined extracts were washed with saturated aqueous sodium bicarbonate (2 × 100 mL), water, saturated aqueous cupric sulfate (2 × 100 mL), water, and brine, and dried over sodium sulfate. Concentration in vacuo gave 0.75 g (90%) of nearly pure diacetate, which was further purified by passage through a 1-in. plug of silica gel to give pure *d*-**19b** as an oil; $[\alpha]_D$ +7° (c 0.7060, ethanol). The IR showed bands at 3030, 2950, 2860, 1765, 1735, 1610, 1590, 1490, 1470, 1450, 1395, 1370, 1240, 1205, 1145, 1115, 1100, 1065, 1040, 1015, 985, 960, 930, 790, and 695 cm^{-1}. The NMR showed absorptions at δ 0.72 (s, 3 H), 1.22 (s, 3 H), 1.98 (s, 3 H), 2.27 (s, 3 H), 0.8–3.0 (m, 8 H), 3.28–3.85 (m, 4 H), 4.17 (d, J = 6.5 Hz, 1 H), 4.75–5.22 (m, 1 H), 6.80–7.47 (m, 4 H). The mass spectrum exhibited peaks at *m/e* 402 (M^+; very weak), 401, 115, 107, 73, 69, 45, 44, 43, 42, 41, and 30. TLC using 50% ethyl acetate in Skellysolve B showed one spot, R_f 0.66.

Optical Purity Studies on *d*-19b and *dl*-19b. A sample of ca. 60 mg of *dl*-**19b** (prepared in the same manner as *d*-**19b**, except that *dl*-**5** was used in the preparation of *dl*-**17**) was dissolved in 0.5 mL of deuteriochloroform (Stohler Isotope Chemicals) and transferred to an NMR tube (5 × 180 mm). An NMR spectrum was recorded. Incremental amounts of tris[3-(heptafluoropropylhydroxymethylene)-*d*-camphorato]europium(III) (Willow Brook Laboratories, Inc. Eu-OPTI-SHIFT II) were then added (as the solid) by "small spatula tips" and the NMR spectrum of the resulting solution was recorded. After the addition of 28 spatula tips of shift reagent, the C-9 acetate signal was shifted downfield by 3.8 ppm and was split into two singlet resonances of equal intensity (one each for the *d* and *l* enantiomeric forms) with $\Delta\nu$ = 5 Hz. Correspondingly, the phenolic acetate signal was shifted downfield by 1.35 ppm and was split into two singlets with $\Delta\nu$ = 2 Hz.

The same experiment was then repeated with a sample of *d*-**19b** (ca. 120 mg) dissolved in 1.0 mL of deuteriochloroform. The shift reagent was added in increments until the C-9 acetate signal was shifted downfield by ca. 3.8 ppm. At this point, only *one* singlet was detected (>90% *d*-enantiomer by NMR). Similar results were obtained by monitoring the phenolic acetate signal.

Optically Active 2-*exo*-[*m*-(Pivaloyloxy)benzyl]-3-*exo*-pivaloyloxybicyclo[3.1.0]hexane-6-*endo*-carboxaldehyde (21). A 50-mL flask, equipped with a magnetic stirring bar, was charged with 0.48 g (0.97 mmol) of *d*-acetal **20** and immersed in an ice bath. Stirring was initiated, and 25 mL of 88% formic acid (precooled to 0 °C) was added all at once. The reaction mixture was stirred at 0 °C for 4 h, diluted with 200 mL of brine, and extracted with 150 mL of ethyl acetate. The extract was then washed with brine, and saturated aqueous sodium bicarbonate (2×), and dried over magnesium sulfate. Concentration in vacuo gave 0.55 g of crude **21** as an oil which was chromatographed as follows: a 19 mm × 24 in. column was wet-packed with 60 g of silica gel in 5% ethyl acetate in Skellysolve B. The sample was applied in Skellysolve B and eluted with 300 mL of 5% ethyl acetate in Skellysolve B, 500 mL of 10% ethyl acetate in Skellysolve B, and 500 mL of 15% ethyl acetate in Skellysolve B. The first fraction was 350 mL (discarded), and subsequent fractions were 20 mL each. Based on TLC homogeneity, fractions 19–35 were combined to give 0.37 g of pure, optically active **21** as an oil which partially solidified at −19 °C. The NMR spectrum showed absorptions at δ 1.20 (s, 9 H), 1.33 (s, 9 H), 0.6–3.2 (m, 8 H), 5.1–5.5 (m, 1 H), 6.6–7.5 (m, 4 H), 9.68 (d, J = 3 Hz, 1 H). TLC using 25% ethyl acetate in Skellysolve B showed one spot, R_f 0.50.

Optically Active 2-*exo*-{*m*-[(Methoxycarbonyl)methoxy]benzyl}-3-*exo*-(pivaloyloxy)-6-*endo*-(*cis*-1-heptenyl)bicyclo[3.1.0]hexane (22c). A 250-mL pointed flask, equipped with a magnetic stirring bar, was charged with 5.68 g (13.3 mmol) of *n*-hexyltriphenylphosphonium bromide and 75 mL of benzene. The system was stoppered with a serum cap and then alternately degassed and flushed with nitrogen (3×). *n*-Butyllithium (1.6 M in hexane) was added dropwise with stirring until a permanent yellow color was produced. An additional 8.24 mL (13.2 mmol) of *n*-butyllithium was then added. The reaction mixture was stirred at 25 °C for 45 min to generate the red ylide. The suspended lithium bromide was allowed to settle, and the supernatant was transferred to an oven-dry 500-mL three-neck flask via a cannula with positive nitrogen pressure. The lithium bromide was washed with 40 mL of benzene and allowed to settle, and the supernatant again transferred via cannula. The red benzene solution was cooled to 10 °C in a water bath, and a solution of 3.52 g (8.79 mmol) of aldehyde **21** in 10 mL of benzene was added all at once. Residual aldehyde was washed in with 2 × 3 mL of benzene, and the reaction mixture was stirred at 25 °C for 15 min. Acetone (5 mL) was added to react with excess Wittig reagent, and the reaction mixture was heated to 60 °C for 10 min, cooled to room temperature, and diluted with brine. The layers were mixed and separated. The aqueous phase was extracted with benzene (150 mL), and the combined extracts were dried over sodium sulfate. Concentration in vacuo gave 8.65 g of crude product. This material was suspended in Skellysolve B and filtered, washing well with Skellysolve B. The filtrate was concentrated in vacuo to give a brown oil which was filtered through 50 g of silica gel, eluting with 1000 mL of 10% ethyl acetate

in Skellysolve B. Fractions of 50 mL were collected. Based on TLC homogeneity, fractions 2 and 3 were combined to give 3.38 g (82%) of pure **22a** as an oil.

The above sample of **22a** was dissolved in 100 mL of methanol. A solution of 1.3 g of potassium carbonate in 15 mL of water was added, and the reaction mixture was stirred at 25 °C for 2 h. The major portion of methanol was removed in vacuo, and the residue was diluted with 300 mL of brine. The pH of this mixture was adjusted to 5–6 with 1 N aqueous hydrochloric acid, and the mixture was then extracted with diethyl ether (3×). The combined extracts were washed with saturated aqueous sodium bicarbonate and brine, and dried over sodium sulfate. Concentration in vacuo gave 3.00 g (~100%) of crude phenol **22b.**

The above sample of phenol **22b** was dissolved in 40 mL of 1,2-dimethoxyethane and 1.80 g (11.77 mmol) of methyl bromoacetate. The solution was alternately degassed and flushed witn nitrogen (2×), cooled to 0 °C, and treated in portions with 0.38 g of 57% sodium hydride dispersion (~9.03 mmol). The mixture was then stirred at 25 °C overnight (16 h). Excess hydride was destroyed by the dropwise addition of 2 mL of glacial acetic acid. The reaction mixture was diluted with 300 mL of brine and extracted with ethyl acetate (150 mL). The organic fraction was washed with saturated aqueous sodium bicarbonate and brine, and dried over sodium sulfate. Concentration in vacuo gave a yellow oil which was purified as follows: a 19 mm × 24 in. column was slurry-packed with 60 g of silica gel in 5% ethyl acetate in Skellysolve B. The sample was applied in Skellysolve B and eluted with 375 mL of 5% ethyl acetate in Skellysolve B and 500 mL of 10% ethyl acetate in Skellysolve B. Fractions were 20 mL each. Based on TLC homogeneity, fractions 12–25 were combined to give 3.29 g of diester **22c** as an oil (82% from **21**). The IR showed bands at 1775, 1750, 1735, 1620, 1590, 1480, 1450, 1439, 1281, 1208, and 1159 cm^{-1}. The NMR spectrum showed absorptions at δ 0.89 (t, J = 5 Hz, 3 H), 1.20 (s, 9 H), 0.6–3.0 (m, 16 H), 3.82 (s, 3 H), 4.65 (s, 2 H), 4.73–5.95 (m, 3 H), 6.62–7.43 (m, 4 H). TLC using 10% ethyl acetate in Skellysolve B showed on spot, R_f 0.27.

***l*-2-*exo*-{*m*-[(Methoxycarbonyl)methoxy]benzyl}-6-*endo*-(*cis*-1-heptenyl)bicyclo[3.1.0]hexan-3-one (4b).** A 100-mL flask, equipped with a magnetic stirring bar and reflux condenser, was charged with 2.83 g (6.20 mmol) of diester **22c** and 40 mL of absolute methanol. The resulting solution was alternately degassed and flushed with nitrogen (3×), treated with 10 mL of 25% sodium methoxide in methanol, and heated with stirring at 70 °C for 20 h. The reaction mixture was cooled to room temperature, acidified with 10 mL of glacial acetic acid, diluted with brine, and extracted with ethyl acetate (2×). The combined extracts were washed with saturated aqueous sodium bicarbonate and brine, and dried over sodium sulfate. Concentration in vacuo gave 1.50 g of crude **4a.** The aqueous fraction from above was acidified with 1 M aqueous potassium bisulfate and extracted with chloroform (2×). The combined extracts were washed with brine, dried over sodium sulfate, and concentrated in vacuo to give 0.87 g of the free acid of **4a** as an oil. This material was esterified with diazomethane and combined with the previous sample of **4a** and purified as follows: a 28 mm × 36 in. column was slurry-packed with 200 g of silica gel in 10% ethyl acetate in Skellysolve B. The sample was applied in methylene chloride and eluted with 450 mL of 10% ethyl acetate in Skellysolve B, 1000 mL of 20% ethyl acetate in Skellysolve B, 1000 mL of 30% ethyl acetate in Skellysolve B, and 500 mL of 40% ethyl acetate in Skellysolve B. The first fraction was 500 mL and subsequent fractions were 20 mL each. Based on TLC homogeneity, fractions 65–93 were combined to give 1.97g (85%) of alcohol **4a** as an oil.

A 250-mL flask, equipped with a magnetic stirring bar, was charged with 80 mL of methylene chloride and 5.02 g (63.46 mmol) of pyridine. Chromium trioxide (3.17 g, 31.7 mmol) was then added with stirring, and the burgundy-colored mixture was stirred at 25 °C under nitrogen for 30 min. A solution of 1.97 g (5.29 mmol) of the above alcohol in 5 mL of methylene chloride was added all at once. Residual alcohol was washed in with methylene chloride, and the resulting reaction mixture was stirred at 25 °C for 45 min. The mixture was then transferred to a separatory funnel, and the chromium salts were washed with diethyl ether (3 × 75 mL). The combined organic fractions were diluted with 50 mL of diethyl ether, washed with 1 N aqueous sodium hydroxide (3 × 100 mL), 1 N aqueous hydrochloric acid and brine, and dried over sodium sulfate. Concentration in vacuo gave 1.87 g of crude **4b** as an oil which was purified as follows: a 28 mm × 36 in. column was slurry-packed with 187 g of silica gel in 10% ethyl acetate in Skellysolve B. The sample was applied in Skellysolve B and eluted with 550 mL of 10% ethyl acetate in Skellysolve B, 530 mL of 15% ethyl acetate in Skellysolve B, and 1000 mL of 20% ethyl acetate in Skellysolve B. Fractions were 20 mL each. Based on TLC homogeneity, fractions 48–62 were combined to give 1.52 g of pure **4b** as an oil (66% overall from **22c**); $[\alpha]_D$ −39° (c 0.8380, ethanol). The IR showed bands at 3020, 2920, 2850, 1765, 1740, 1605, 1585, 1510, 1450, 1440, 1285, 1255, 1210, 1160, 1090, 780, and 695 cm^{-1}. The NMR spectrum showed absorptions at δ 0.87 (t, J = 5 Hz, 3 H), 0.6–3.3 (m, 16 H), 3.77 (s, 3 H), 4.60 (s, 2 H), 4.5–5.1 (m, 1 H), 5.37–5.95 (m, 1 H), 6.58–7.40 (m, 4 H). The mass spectrum exhibited peaks at m/e 370.2170 (M^+; calcd for $C_{23}H_{30}O_4$: 370.2144), 352, 342, 339, 311, 205, 204, 191, and 179. TLC using 25% ethyl acetate in Skellysolve B showed one spot, R_f 0.33.

Fractions 63–74 were combined to give 0.14 g of 3-*exo*-{*m*-[(methoxycarbonyl)methoxy]benzyl}-6-*endo*-(*cis*-1-heptenyl)bicyclo-[3.1.0]hexan-2-one (**25**) as an oil; $[\alpha]_C$ −37° (*c* 0.7915, ethanol). The IR showed bands at 3020, 3000, 2920, 2860, 1765, 1740, 1720, 1615, 1605, 1585, 1490, 1455, 1440, 1295, 1240, 1210, 1160, 1090, and 690 cm^{-1}. The NMR spectrum showed absorptions at δ 0.89 (t, J = 5 Hz, 3 H), 0.6–3.45 (m, 16 H), 3.82 (s, 3 H), 4.64 (s, 2 H), 4.95–6.00 (m, 2 H), 6.58–7.45 (m, 4 H). The mass spectrum exhibited peaks at m/e 370.2148 (M^+; calcd for $C_{23}H_{30}O_4$: 370.2144), 352, 339, 313, 299, 260, 220, 191, 179, and 150. TLC using 25% ethyl acetate in Skellysolve B showed one spot, R_f 0.27.

***l*-3-Oxa-4,5,6-trinor-3,7-*inter-m*-phenyleneprostaglandin E_1 Methyl Ester (3) and *l*-(15*R*)-3-Oxa-4,5,6-trinor-3,7-*inter-m*-phenyleneprostaglandin E_1 Methyl Ester (28).** A 500-mL flask, equipped with a magnetic stirring bar, was charged with 8.07 g (21.78 mmol) of ketone **4b,** 100 mL of acetone, and 6.4 mL of water. The resulting solution was then treated with 2.6 mL of osmium tetroxide in *tert*-butyl alcohol (concentration, 30 mg/mL). *N*-Methylmorpholine oxide dihydrate (33.3 g, 22 mmol) was added, and the reaction mixture was stirred under nitrogen at 25 °C for 2 h. A solution of 5.0 g of sodium bisulfite in 25 mL of water was added and stirring was continued for 30 min. The reaction mixture was concentrated in vacuo, diluted with brine, and extracted with ethyl acetate (2×). The combined extracts were washed with brine, dried over sodium sulfate, and concentrated in vacuo to give 9.08 g of crude **26** which was purified as follows: a 48 mm × 36 in. column was slurry-packed with 454 g of silica gel in 20% ethyl acetate in Skellysolve B. The sample was applied in CH_2Cl_2 and eluted with 1 L each of 35, 45, 55, 70, and 80% ethyl acetate in Skellysolve B. The first fraction was 500 mL and subsequent fractions were 50 mL each. Based on TLC homogeneity, fractions 50–77 were combined to give 8.06 g (91%) of pure **26** as 1:1 mixture of isomers. TLC using 50% ethyl acetate in Skellysolve B showed two equally intense spots, R_f = 0.20 and 0.15.

A 250-mL three-neck flask, equipped with a magnetic stirring bar, thermometer, addition funnel, and a nitrogen inlet, was charged with 8.06 g (19.93 mmol) of glycols **26** and 100 mL of pyridine. The resulting solution was alternately degassed and flushed with nitrogen (2×), cooled to 6 °C, and treated with 7.72 mL (ca. 100 mmol) of methanesulfonyl chloride. The addition was carried out with vigorous stirring and at a rate that allowed the internal temperature to be maintained at 3–8 °C. After 2.5 h, the reaction mixture was diluted with 500 mL of methylene chloride. The total organic phase was washed with brine, 1 N aqueous hydrochloric acid (ice-cold; 5×), saturated aqueous sodium bicarbonate and brine, and dried over sodium sulfate. Concentration in vacuo gave 13.09 g of crude bismesylates **27** as a viscous oil.

The above sample of **27** was dissolved in 250 mL of acetone and treated with 125 mL of water. The reaction mixture was stirred at room temperature (25 °C) for 10 h and 20 min. Solid sodium bicarbonate was then added to adjust the pH to 6–7. The reaction mixture was concentrated in vacuo (to remove the major portion of acetone), diluted with brine, and extracted with chloroform (3×). The combined extracts were washed with brine, dried over sodium sulfate, and concentrated in vacuo to give 8.58 g of crude solvolysis product. A 48 mm × 36 in. column was slurry-packed with 430 g of silica gel in 5% acetone in methylene chloride. The solvolysis product was applied in methylene chloride and eluted with 1 L each of 10, 20, 30, 40, 50, and 60% acetone in methylene chloride. Fractions were 50 mL each. Based on TLC homogeneity, fractions 25–38 were combined to give 3.17 g of an oil containing a monomesylate. TLC using 20% acetone in methylene chloride showed two major spots, R_f 0.64 and 0.57. Fractions 65–81 were combined to give 0.81 g of essentially pure (15*R*)-prostaglandin **28.** Fractions 81–100 were combined to give 1.90 g of pure (15*S*)-prostaglandin **3.**

The above monomesylate fraction (fractions 25–38) was recycled (mesylation followed by solvolysis and chromatography) to afford an additional 0.23 g of (15*R*)-prostaglandin **28** (total yield 1.04 g, 13% based on **26**) and 0.42 g of (15*S*)-prostaglandin **3** (total yield 2.32 g, 29% based on **26**). The (15*S*)-prostaglandin **3** was obtained as an oil which slowly solidified at −19 °C to a waxy mass. A portion of this sample was rechromatographed by HPLC (2% methanol in chloro-

form) to give 1.14 g of very pure **3** as an oil. This material was dissolved in 7 mL of diethyl ether, cooled to −14 °C, and treated with *n*-hexane to the point of incipient cloudiness. The solution was seeded with the above waxy solid and stored at 0 °C for 30 min, then at 4 °C for 3 h and finally at −19 °C overnight. The procedure afforded 0.296 g of **3** as a white, tacky solid: mp 45–53 °C; $[\alpha]_D$ −48° (c 0.8275, ethanol). The IR showed bands at 3380, 2960, 2920, 2860, 1765, 1740, 1725, 1615, 1605, 1585, 1490, 1460, 1375, 1285, 1210, 1165, 1085, 1005, 970, 880, 785, and 700 cm^{-1}. The NMR spectrum showed absorptions at δ 0.92 (t, J = 5 Hz, 3 H), 0.7–3.0 (m, 14 H), 3.78 (s, 3 H), 3.0–4.4 (m, 4 H), 4.60 (s, 2 H), 5.48 (m, 2 H), 6.52–7.42 (m, 4 H). The mass spectrum exhibited peaks at 548.2979 (M^+ of $(Me_3Si)_2$ derivative; calcd for $C_{29}H_{48}Si_2O_6$: 548.2989), 533, 477, 458, 387, 368, 361, 333, and 179. TLC using 30% acetone in methylene chloride showed one spot, R_f 0.32. TLC using 7.5% methanol in methylene chloride showed one spot, R_f 0.35.

Several combined samples of slightly impure (15*R*)-prostaglandin **28** were twice rechromatographed by HPLC (one chromatography using 5% methanol in chloroform and a second using 20% acetone in methylene chloride) to afford a pure specimen of **28** as an oil; $[\alpha]_D$ −44° (c 0.9325, ethanol). The IR showed bands at 3420, 1745, 1605, 1590, 1490, 1215, 1160, 1085, and 975 cm^{-1}. The NMR spectrum showed absorptions at δ 0.88 (t, J = 5 Hz, 3 H), 0.6–3.5 (m, 16 H), 3.78 (s, 3 H), 3.5–4.3 (m, 2 H), 4.59 (s, 2 H), 5.53 (m, 2 H), 6.47–7.45 (m, 4 H). The mass spectrum exhibited peaks at 548.3022 (M^+ of $(Me_3Si)_2$ derivative; calcd for $C_{29}H_{48}Si_2O_6$: 548.2989), 533, 477, 458, 387, 361, 333, 279, 217, and 179. TLC using 30% acetone in methylene chloride showed one spot, R_f = 0.37. TLC using 7.5% methanol in methylene chloride showed one spot, R_f = 0.38.

***l*-3-Oxa-4,5,6-trinor-3,7-*inter-m*-phenyleneprostaglandin E_1 (29).** A 500-mL flask, equipped with a magnetic stirring bar, was charged with 0.79 g (1.95 mmol) of methyl ester **3** and 30 mL of 95% ethanol. The resulting solution was then treated with 52 mL of water, followed by 7.90 g of purified coral enzyme powder[11] and 112 mL of water. The reaction mixture was stirred at 24 °C for 14.5 h, diluted with 500 mL of acetone, allowed to stand for 30 min, and finally filtered through Celite. The filtered material was washed with 1000 mL of acetone, and the total filtrate was concentrated in vacuo to remove the major portion of acetone. The resulting aqueous mixture was diluted with brine, equilibrated with 200 mL of ethyl acetate and acidified to pH ~ 3 with 1 M aqueous citric acid. The layers were mixed and separated and the aqueous phase was again extracted with ethyl acetate. The combined extracts were washed with brine, dried over sodium sulfate, and concentrated in vacuo to give 0.87 g of crude **29** as an oil. A 19 mm × 24 in. column was slurry-packed with 43 g of Silica Gel CC-4 (Mallinckrodt) in 50% ethyl acetate in *n*-hexane. The sample was applied in methylene chloride and eluted with 275 mL of 50% ethyl acetate in *n*-hexane, 500 mL of 60% ethyl acetate in *n*-hexane, and 500 mL of ethyl acetate. Fractions were 20 mL each. Based on TLC homogeneity, fractions 32–80 were combined to give 0.41 g (54%) of pure **29** as a white solid. This sample was recrystallized from ethyl acetate–*n*-hexane to give 0.2901 g of pure **29** as white microcrystals: mp 128.7–130.0 °C. (In a separate experiment, an apparent isomorphic form of **29** was obtained: mp 100.1–102.5 °C); $[\alpha]_D$ −61° (c 0.8155, ethanol.) The IR showed bands at 3540, 3360, 3000, 2740, 2680, 2600, 2540, 1760, 1740, 1605, 1585, 1490, 1300, 1200, 1175, 1165, 1100, 1065, 960, 760, and 690 cm^{-1}. The NMR spectrum showed absorptions at δ 0.90 (t, J = 5 Hz, 3 H), 0.6–3.52 (m, 14 H), 3.52–4.36 (m, 2 H), 4.62 (bd s, 2 H), 5.49 (m, 2 H), 6.08–7.42 (m, 7 H, aryl H + 2 OH + CO_2H). The mass spectrum exhibited peaks at *m/e* 606.3226 (M^+ of $(Me_3Si)_3$ derivative; calcd for $C_{31}H_{54}Si_3O_6$: 606.3228), 591, 589, 535, 516, 501, 445, 426, and 237. TLC using A-IX[13] showed one spot, R_f 0.13.

Anal. Calcd for $C_{22}H_{30}O_6$: C, 67.67; H, 7.74. Found: C, 67.64; H, 7.84.

Optically Active (15*R*)-3-Oxa-4,5,6-trinor-3,7-*inter-m*-phenyleneprostaglandin E_1 (30). A 500-mL flask equipped with a magnetic stirring bar was charged with 0.91 g (2.25 mmol) of slightly impure methyl ester **28** and 36 mL of 95% ethanol. The resulting solution was then treated with 60 mL of water, followed by 9.10 g of purified coral enzyme powder[11] and 129 mL of water. The reaction mixture was stirred at room temperature for 24 h and worked up as detailed in the previous experiment (for the preparation of **29**) to give 1.07 g of crude **30** as an oil. A 28 mm × 36 in. column was slurry-packed with 214 g of Silica Gel CC-4 (Mallinckrodt) in 30% ethyl acetate in *n*-hexane. The sample was applied in methylene chloride and eluted with 1 L each of 40, 45, and 55% ethyl acetate in *n*-hexane followed by 500 mL each of 70 and 85% ethyl acetate in *n*-hexane. The first fraction was 500 mL and subsequent fractions were 20 mL each. Based on TLC homogeneity, fractions 132–169 were combined to give 0.50 g (57%) of pure **30** as an oil; $[\alpha]_D$ −45° (c 0.8595, EtOH). The IR showed bands at 3420, 2620, 2560, 1740, 1605, 1585, 1490, 1240, 1160, 1080, and 975 cm^{-1}. The NMR spectrum showed absorptions at δ 0.88 (t, J = 5 Hz, 3 H), 0.6–3.35 (m, 14 H), 4.01 (m, 2 H), 4.60 (bd s, 2 H), 5.53 (m, 2 H), 6.28 (bd s, 3 H, 2 OH + CO_2H), 6.4–7.50 (m, 4H). The mass spectrum exhibited peaks at *m/e* 606.3202 (M^+ of $(Me_3Si)_3$ derivative; calcd for $C_{31}H_{54}Si_3O_6$: 606.3228), 591, 535, 516, 501, 445, 426, 419, 391, 313, 279, 237, and 199. TLC using A-IX[13] showed one spot, R_f 0.18.

Acknowledgment. The authors thank P. A. Meulman and R. J. Wnuk for IR and mass spectra. We especially acknowledge with gratitude Dr. H. A. Karnes and associates for the preparation of generous supplies of intermediates, and Dr. N. A. Nelson for helpful discussions and a sample of *dl*-**3**.

Registry No.—**3,** 59829-42-4; **4a,** 59751-50-7; **4a** acid, 59751-49-4; **4b,** 59751-51-8; *dl*-**5,** 39521-36-3; *l*-**5,** 59685-80-2; **9,** 65423-67-8; **10,** 65423-68-9; **11,** 65423-69-0; **12,** 65452-58-6; **13,** 65452-59-7; **14,** 65452-60-0; **15,** 65452-61-1; **16,** 34231-78-2; **17,** 59657-47-5; **18,** 59657-49-7; *d*-**19b,** 59657-50-0; *dl*-**19b,** 65494-92-0; **20,** 59657-48-6; **21,** 59751-47-2; **22a,** 59751-48-3; **22b,** 64313-68-4; **22c,** 64313-69-5; **23,** 65423-63-4; **25,** 65423-64-5; **26** isomer 1, 65451-53-8; **26** isomer 2, 65451-54-9; **27** isomer 1, 65451-55-0; **27** isomer 2, 65451-56-1; **28,** 65423-65-6; **29,** 65451-57-2; **29** $(Me_3Si)_3$ derivative, 65423-66-7; **30,** 65451-59-3; **30** $(Me_3Si)_3$ derivative, 65451-59-4; benzaldehyde, 100-52-7; benzyl bromide, 100-39-0; *m*-hydroxybenzaldehyde, 100-83-4; acetic anhydride, 108-24-7; pivaloyl chloride, 3282-30-2; *n*-hexyltriphenylphosphonium bromide, 4762-26-9; methyl bromoacetate, 96-32-2.

References and Notes

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Total Synthesis of 3-Oxa-4,5,6-trinor-3,7-*inter-m*-phenylene Prostaglandins. 2. Conjugate Addition Approach

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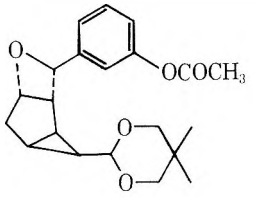
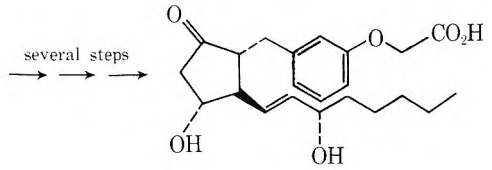
An alternative and more efficient total synthesis of optically active 3-oxa-4,5,6-trinor-3,7-*inter-m*-phenylene-prostaglandin E_1 (**2**) is described starting from the known protected lactone **7**. Lactone **7** was converted in six steps to α-methylenecyclopentanone (**13**), which was then condensed with lithium diarylcuprate (**16**) to give the 1,4-adduct **17** in good overall yield. Subsequent transformations (Scheme II) afforded **2** in 23–27% overall yield from **7**. The synthesis of enone **13** (Scheme I) involved the oxidative decarboxylation of an intermediary carboxylic acid (i.e., **10**), and the utility of **13** as an intermediate for the synthesis of the desired analogue was confirmed.

The preceding paper[1] in this series described the rationale for and the total synthesis of several optically active 3-oxa-4,5,6-trinor-3,7-*inter-m*-phenyleneprostaglandin analogues of the PGE_1 family (e.g., **2**) starting from the readily available and optically active tricyclic oxetane **1**. Although this



1

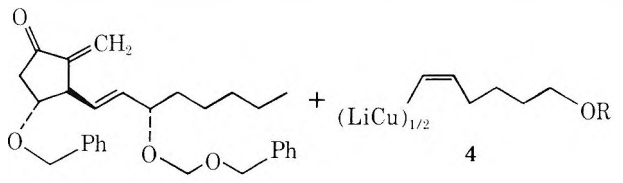


2

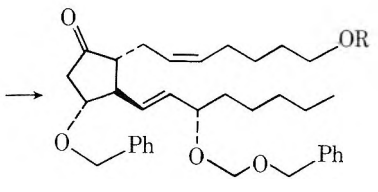
synthetic procedure was satisfactory for procuring initial quantities of the desired analogues for biological evaluation, it proved to have too many limitations. In particular, the final solvolytic ring-opening step to afford the methyl ester of **2** was low-yielding and required extensive chromatographic purification of the product mixture. For these reasons, an alternative and more efficient synthesis of *l*-3-oxa-4,5,6-trinor-3,7-*inter-m*-phenyleneprostaglandin E_1 (**2**) was developed and is reported herein.

Results and Discussion

Strategy. Recently, Stork and co-workers[2] described a novel total synthesis of prostaglandins which employed as a key step the conjugate addition of the lithium divinylcuprate **4** to the α-methylene ketone **3** to afford prostanoid **5**. It was



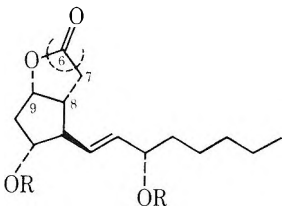
3 **4**



5

R = $CH(CH_3)(OCH_2CH_3)$

envisaged that if an optically active enone intermediate like **3** could be readily synthesized from an available and optically active intermediate (e.g., **6**[3,4]), then a new total synthesis of the biologically[1] and optically active 3-oxa-4,5,6-trinor-3,7-*inter-m*-phenyleneprostaglandins could be realized by the conjugate addition of an appropriate aryl organometallic reagent. The use of a suitably protected form of lactone diol **6** (e.g., **7**) to generate an α-methylenecyclopentanone moiety



6, R = H
7, R = THP

like **3** would necessarily require a one-carbon degradation (i.e., loss of C-6[5]) and subsequent oxidation of C-8 and C-9. Further, any degradation or oxidation conditions would have to be compatible with the other functional groups present in the molecule.

Synthesis. The successful synthesis of α-methylenecyclopentanone **13** is illustrated in Scheme I. Starting with the readily available and optically pure lactone bis(tetrahydropyranyl ether) **7**[3] the silylated acid **10** was prepared in 88% overall yield by (a) saponification of **7** to **8** with aqueous base, (b) silylation of **8** with *tert*-butyldimethylsilyl chloride[6] to **9**, and (c) selective basic hydrolysis of the silyl ester of **9**. The acid **10** was then subjected to the oxidative decarboxylation procedure of Kochi[7] to afford olefin **11** in 71% yield correcting for 45% of recovered starting acid **10**. The conversion of **10** to **11** was in general always in the range of 35–50%. This was attributed to the fact that acetic acid (a by-product of the reaction) effectively competed with acid **10** for coordination to lead(IV).[7] However, the reaction was relatively clean, and olefin **11** was easily separated from unreacted **10** by column chromatography and the acid was recycled. It is interesting to note that the oxidative decarboxylation conditions did not prove detrimental to the lower side chain of **10** or **11**. In addition, the procedure allowed the one-carbon degradation of C-6 and the oxidation at C-8 to be carried out simultaneously.

At this point, the latent hydroxyl function of C-9[5] was selectively liberated with tetra-*n*-butylammonium fluoride in tetrahydrofuran.[6] Alcohol **12** was then oxidized with Jones reagent at −20 °C to the α-methylenecyclopentanone **13** in high overall yield. This unsaturated ketone, like **3**,[2a] was stable to chromatography on silica gel; however, it was not necessary to further purify the crude sample of **13** obtained from the

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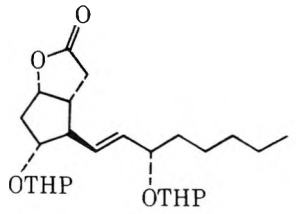
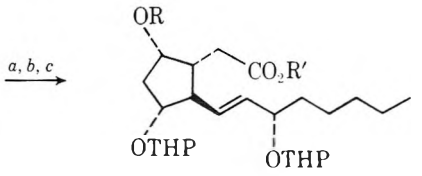
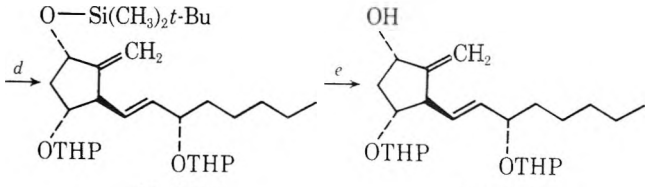
Scheme I



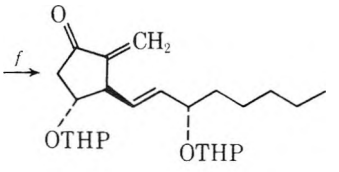
7



8, R = R′ = H
9, R = R′ = *t*-Bu(CH$_3$)$_2$Si
10, R = *t*-Bu(CH$_3$)$_2$Si; R′ = H; 88%



11, 71% 12, 95%



13

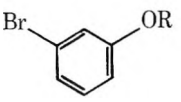
[a] NaOH, CH$_3$OH, H$_2$O; aq KHSO$_4$. [b] *t*-BuSi(CH$_3$)$_2$Cl, imidazole, DMF. [c] K$_2$CO$_3$, CH$_3$OH, H$_2$O. [d] Pb(OAc)$_4$, C$_6$H$_6$, Cu(OAc)$_2$, pyridine, 80 °C or *hν*. [e] (*n*-Bu)$_4$NF, THF. [f] H$_2$CrO$_4$, acetone, −20 °C.

oxidation reaction since it was ≥90% pure (by TLC and NMR spectroscopy).

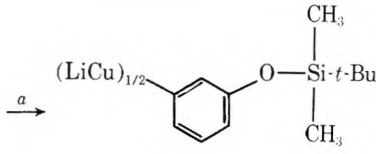
The synthesis of the requisite lithium diarylcopper reagent **16** and its condensation with α-methylenecyclopentanone **13** are illustrated in Scheme II. Commercially available *m*-bromophenol (**14**) was protected as its *tert*-butyldimethylsilyl ether **15**[6] and then metalated at −78 °C with 2 equiv of *tert*-butyllithium. The resulting aryllithium reagent was then added to a suspension of cuprous iodide–tri-*n*-butylphosphine complex in ether (−78 °C) to give the lithium diarylcuprate **16** as an orange-brown mixture. Addition of **13** to **16** at −78 °C followed by addition of the resulting enolate to a solution of glacial acetic acid in ether afforded ketone **17** in 74–89% isolated yield based on allylic alcohol **12**. The structure of **17** was supported by standard spectral data (see Experimental Section) and subsequent conversion to and comparison with known materials (vide infra).[1]

Continuing with the synthetic sequence in Scheme II, the phenol **20** was prepared from **17** in 98% overall yield by (a) reduction of the C-9 ketone function with sodium borohydride to give **18** as a mixture of epimers (ca. 1:1), (b) acetylation of **18** to give **19**, and (c) cleavage of the phenolic silyl ether with tetra-*n*-butylammonium fluoride. Alkylation of **20** with methyl bromoacetate gave diester **21** in essentially quantitative yield and this material was then transformed into optically active 3-oxa-4,5,6-trinor-3,7-*inter*-*m*-phenyleneprostaglandin E$_1$ (**2**) by (a) saponification with aqueous base to **22**, (b) Jones oxidation of the resulting C-9 alcohols to **23**, and (c) hydrolysis of the protecting groups in aqueous acid (40–50% overall from **21**). The sample of **2** so produced was identical

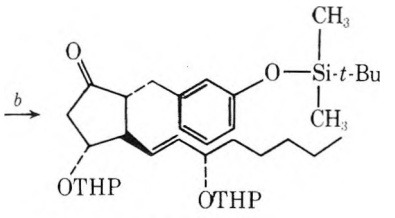
Scheme II



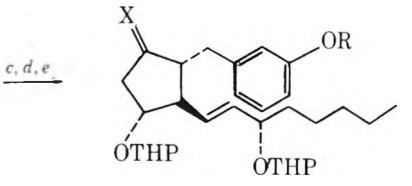
14, R = H
15, R = *t*-Bu(CH$_3$)$_2$Si; 81–88%



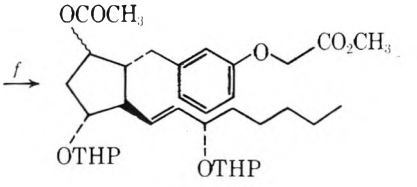
16



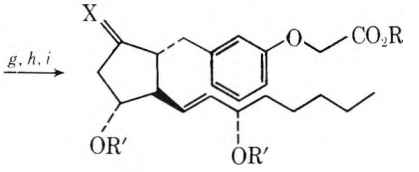
17, 74–89%



18, X = H, OH; R = *t*-Bu(CH$_3$)$_2$Si
19, X = H, OAc; R = *t*-Bu(CH$_3$)$_2$Si
20, X = H, OAc; R = H; 98%



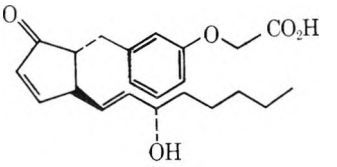
21, 99%



22, X = H, OH; R = H; R′ = THP
23, X = O; R = H; R′ = THP
2, X = O; R = R′ = H; 50%

[a] *t*-BuLi, Et$_2$O, −78 °C; CuI–(*n*-Bu)$_3$P, Et$_2$O, −78 °C. [b] Enone **13**, Et$_2$O, −78 °C; HOAc, Et$_2$O. [c] NaBH$_4$, CH$_3$OH, −25 to −5 °C. [d] Ac$_2$O, pyridine, 4-DMAP. [e] (*n*-Bu)$_4$NF, THF. [f] BrCH$_2$CO$_2$CH$_3$, NaH, CH$_3$OCH$_2$CH$_2$OCH$_3$, 0 °C. [g] KOH, CH$_3$OH, H$_2$O, 40 °C. [h] H$_2$CrO$_4$, acetone, −30 to −15 °C. [i] H$_3$PO$_4$, H$_2$O, THF, 35 °C.

in all respects with an authentic specimen of **2**,[1] including an undepressed mixture melting point. In addition to the prostaglandin E$_1$ analogue **2**, significant quantities of 3-oxa-4,5,6-trinor-3,7-*inter*-*m*-phenyleneprostaglandin A$_1$ (**25**) were also formed during the hydrolysis of **23** to **2**.



25

In summary, α-methylenecyclopentanone **13** has proved to be a versatile and useful intermediate for the total synthesis of 3-oxa-4,5,6-trinor-3,7-*inter*-*m*-phenyleneprostaglandins and is easily prepared in six steps from the known lactone **7** in ca. 60% overall yield.

Experimental Section

General. All melting points are corrected unless otherwise noted. Analytical data were obtained by the Physical and Analytical Chemistry Research Department of The Upjohn Co. IR spectra were obtained either on neat samples (oils) or on Nujol mulls (crystalline samples). Mass spectra were recorded at high or low resolution for derivatized (Me_3Si) or underivatized compounds at 70 eV. The NMR spectra were obtained on a Varian A-60D or T-60 spectrometer operating at 60 MHz on chloroform-*d* solutions containing internal tetramethylsilane. Thin layer chromatography (TLC) was conducted using Analtech (Uniplate) glass plates precoated with silica gel GF (250 μm). Where mixed solvents were used for chromatography, the composition is expressed as a percent by volume of the former in the latter. The solvent system A–IX[8] is the organic layer from an equilibrated mixture of 90 mL of ethyl acetate, 20 mL of acetic acid, 50 mL of 2,2,4-trimethylpentane, and 100 mL of water. The TLC plates were visualized first by UV light (Mineralight UVS-11), then by spraying with a vanillin–phosphoric acid solution or 50% aqueous sulfuric acid, followed by heating. Unless otherwise noted, column chromatography utilized neutral silica gel (E. Merck), 70–230 mesh. Acid-washed silica gel was Mallinckrodt CC-4. All solvents were reagent grade or reagent grade distilled from glass (Burdick and Jackson). All reagents were used as purchased and were reagent grade where available. Cuprous iodide was purified by the method of Kauffman and Teter[9] and dried in vacuo over phosphorus pentoxide before use.

3α,5α-Dihydroxy-2β-[3′(*S*)-hydroxy-*trans*-1′-octenyl]cyclopentane-1α-acetic Acid 3,3′-Bis(tetrahydropyranyl ether) 5-*tert*-Butyldimethylsilyl Ether (10). A 500-ml flask, equipped with a magnetic stirring bar, was charged with 10.30 g (23.59 mmol) of 3α,5α-dihydroxy-2β-[3′(*S*)-hydroxy-*trans*-1′-octenyl]cyclopentane-1α-acetic acid γ-lactone 3,3′-bis(tetrahydropyranyl ether) (**7**),[3] and 91 mL of methanol. The resulting solution was then treated with 91 mL of 1.0 N aqueous sodium hydroxide and stirred at 25 °C for 10–16 h. The reaction mixture was then concentrated in vacuo to one-half volume, diluted with 300 mL of brine, and cooled to 0 °C. The pH was then adjusted to 4–5 with ice-cold 1.0 N aqueous potassium bisulfate and the ice-cold aqueous mixture was quickly extracted with ethyl acetate (3 × 150 mL). The combined extracts were washed with brine, dried over sodium sulfate, and concentrated in vacuo to give 12.3 g of 3α,5α-dihydroxy-2β-[3′(*S*)-hydroxy-*trans*-1′-octenyl]cyclopentane-1α-acetic acid 3,3′-bis(tetrahydropyranyl ether) (**8**) as an oily foam.

The above sample of hydroxy acid **8** was immediately dissolved in 80 mL of *N,N*-dimethylformamide. The resulting solution was purged for several minutes with nitrogen and then treated with 14.32 g (95.00 mmol) of *tert*-butyldimethylsilyl chloride followed by 12.94 g (190.07 mmol) of imidazole. The reaction mixture was stirred at 40 °C for 4 h, cooled to 25 °C, diluted with 1000 mL of brine, and extracted with 1:1 diethyl ether–Skellysolve B (2 × 250 mL). The combined extracts were washed with ice-cold 1.0 N aqueous hydrochloric acid and brine, and dried over sodium sulfate. Concentration in vacuo gave crude 3α,5α-dihydroxy-2β-[3′(*S*)-hydroxy-*trans*-1′-octenyl]cyclopentane-1α-acetic acid *tert*-butyldimethylsilyl ester 3,3′-bis(tetrahydropyranyl ether) 5-*tert*-butyldimethylsilyl ether (**9**) as an oil.

The above sample of **9** was dissolved in 300 mL of methanol and 100 mL of tetrahydrofuran and then treated with a solution of 10 g of potassium carbonate in 100 mL of water. The reaction mixture was stirred at 25 °C for 1 h, concentrated in vacuo to one-quarter volume and diluted with 300 mL of brine. The resulting aqueous mixture was cooled to 0 °C, adjusted to pH 4–5 with 1.0 M aqueous potassium bisulfate, and extracted with diethyl ether (2 × 150 mL). The combined extracts were washed with brine, dried over sodium sulfate, and concentrated in vacuo to give 18 g of crude acid **10** as an oil. A 48 mm × 48 in. column was slurry-packed with 600 g of acid-washed silica gel in 3% ethyl acetate in Skellysolve B. The sample of **10** was applied in Skellysolve B and eluted with 1 L each of 10%, 15%, 20%, and 25% ethyl acetate in Skellysolve B. Fractions were 50 mL each, and based on TLC homogeneity fractions 22–49 were combined to give 11.83 g (88%) of pure **10** as a viscous oil. The IR showed bands at 3700–2480 (CO_2H), 2980, 2890, 1735, 1715, 1252, 1200, 1181, 1128, 1110, 1074, 1020, 982, 870, 838, and 777 cm^{-1}. The NMR showed absorptions at δ 0.3 (bd, s, 6 H, silyl CH_3), 0.89 (s, 9 H, silyl *tert*-butyl), 0.7–2.8 (m, 29 H), 3.2–4.47 (m, 7 H), 4.68 (m 2 H), 5.27–5.72 (m, 2 H), 9.63 (m, 1 H). The mass spectrum exhibited peaks at *m/e* 583.3452 ($M^+ - C_4H_9$ of Me_3Si derivative; calcd for $C_{30}H_{55}Si_2O_7$: 583.3486), 539, 499, 481, 397, 382, 322, 305, 187, and 85. TLC using ethyl acetate in Skellysolve B showed one spot, R_f 0.14. Anal. ($C_{31}H_{56}O_7Si$) C, H.

3α-5α-Dihydroxy-2β-[3′(S)-hydroxy-*trans*-1′-octenyl]-1-methylenecyclopentane 3,3′-Bis(tetrahydropyranyl ether) 5-*tert*-Butyldimethylsilyl Ether (11). A 100-mL, three-neck flask, equipped with a magnetic stirring bar, reflux condenser, and a nitrogen inlet (a glass pipet placed below the surface of the reaction mixture), was charged with 2.20 g (3.87 mmol) of acid **10** and 35 mL of benzene. The resulting solution was treated with a mixture of 0.19 g of cupric acetate monohydrate and 1.16 mL of pyridine and then stirred at 25 °C until a homogeneous blue-green solution was produced (ca. 1 h). Then 5.03 g (11.34 mmol) of lead tetracetate was added and the resulting mixture was stirred at 25 °C in the dark for 1.5 h while maintaining a gentle nitrogen purge. The reaction mixture was heated to 80 °C (oil bath) over 20–30 min and heated with stirring and nitrogen purge at 80 °C for an additional 30 min. The reaction mixture was then cooled to ambient temperature, diluted with 300 mL of brine, and extracted with ethyl acetate (2 × 150 mL). The combined extracts were washed with brine, dried over sodium sulfate, and concentrated in vacuo to give 2.25 g of crude product mixture as an oil. A 28 mm × 36 in. column was slurry-packed with 225 g of silica gel in 3% ethyl acetate in Skellysolve B. The sample was applied in Skellysolve B and eluted with 500 mL each of 5%, 10%, 15%, 25%, 35%, and 45% ethyl acetate in Skellysolve B. Fractions were 20 mL each, and based on TLC homogeneity, fractions 44–63 were combined to give 0.80 g (40%) of pure **11** as an oil. Fractions 101–125 were combined to give 0.98 g (45%) of recovered acid **10** as an oil. For **11**, the IR showed bands at 3080, 1665, 1255, 1200, 1130, 1115, 1075, 1035, 1020, 1005, 975, 870, 835, and 775 cm^{-1}. The NMR showed absorptions at δ 0.08 (s, 6 H, silyl methyl), 0.92 (s, 9 H, silyl *tert*-butyl), 0.75–2.9 (m, 26 H), 2.9–4.5 (m, 7 H), 4.72 (m, 2 H), 4.93 and 5.17 (2m, 2 H, *exo*-methylene H), 5.33–5.64 (m, 2 H). The mass spectrum exhibited peaks at *m/e* 465.3034 ($M^+ - C_4H_9$; calcd for $C_{26}H_{45}SiO_5$: 465.3036), 420, 394, 381, 363, 326, 319, 279, and 85. TLC using 25% ethyl acetate in Skellysolve B showed one spot, R_f 0.64. Anal. ($C_{30}H_{54}O_5Si$) C, H.

3α,5α-Dihydroxy-2β-[3′(*S*)-hydroxy-*trans*-1′-octenyl]-1-methylenecyclopentane 3,3′-Bis(tetrahydropyranyl ether) (12). A 500-mL flask, equipped with a magnetic stirring bar, was charged with 28.94 g (55.35 mmol) of silyl ether **11** and 70 mL of dry tetrahydrofuran. The resulting solution was alternatively degassed and flushed with nitrogen (3×), cooled in an ice bath and then treated with 100 mL of 1.0 M tetra-*n*-butylammonium fluoride[10] in tetrahydrofuran. The reaction mixture was stirred at 5 °C under nitrogen for 2 h, diluted with brine, and extracted with ethyl acetate (2 × 250 mL). The combined extracts were washed with brine, dried over magnesium sulfate, and concentrated in vacuo to give 32.71 g of crude **12** as a dark red-brown oil. A 48 mm × 48 in. column was slurry-packed with 654 g of silica gel in 10% ethyl acetate in Skellysolve B. The sample was applied in Skellysolve B and eluted with 1000 mL each of 25%, 35%, 45%, 55%, and 65% ethyl acetate in Skellysolve B. The first fraction was 1000 mL and subsequent fractions were 50 mL each. Based on TLC homogeneity, fractions 35–60 were combined to give 21.38 g (95%) of pure **12** as a pale yellow solid. This material was then recrystallized from 200 mL of Skellysolve B at −20 °C to give 17.79 g of very pure **12** as a white solid: mp 83–84.5 °C (uncorrected); $[\alpha]_D$ + 45° (*c* 1.3755, EtOH). The IR showed bands at 3220, 3140, 1660, 1125, 1080, 1065, 1040, 1020, 1000, 970, and 910 cm^{-1}. The NMR showed absorptions at δ 0.88 (t, $J \sim 5$ Hz, 3 H), 0.6–2.8 (m, 24 H), 3.0–4.5 (m, 7 H), 4.70 (m, 2 H), 5.02 (m, 1 H, *exo*-methylene H), 5.20–5.62 (m, 3 H, olefinic H and *exo*-methylene H). The mass spectrum exhibited peaks at *m/e* 378.2591 (M^+ − THPOH; calcd for $C_{22}H_{38}SiO_3$: 378.2590), 379, 352, 294, 252, and 85. TLC using 25% ethyl acetate in Skellysolve B showed one spot, R_f 0.19. Anal. ($C_{24}H_{40}O_5$) C, H.

3-(*tert*-Butyldimethylsilyloxy)-1-bromobenzene (15). A 250-mL flask, equipped with a magnetic stirring bar, was charged with 10.0 g (57.80 mmol) of *m*-bromophenol, 40 mL of *N,N*-dimethylformamide, 17.42 g (115.60 mmol) of *tert*-butyldimethylsilyl chloride, and 15.74 g (231.20 mmol) of imidazole. The reaction mixture was stirred at 23 °C overnight, diluted with brine, and extracted with 3:1 Skellysolve B–methylene chloride (2×). The combined extracts were washed with brine (3×), dried over sodium sulfate, and concentrated in vacuo to give 29.07 g of oil which was distilled at reduced pressure to give 13.47 g (81%) of pure **15** as an oil: bp 66 °C (0.28 mm). The IR showed bands at 1590, 1570, 1475, 1295, 1270, 1240, 930, 840, 825, 810, and 780 cm^{-1}. The NMR showed absorptions at δ 0.20 (s, 6 H), 0.98 (s, 9 H), 6.58–7.48 (m, 4 H). The mass spectrum exhibited peaks at *m/e* 288, 286 (M^+), 232, 231, 230, 229, 150, 139, 137, and 135. The ul-

traviolet spectrum showed λ_{max}(*n*-hexane) 218 (sh, ϵ 9250), 267 (sh, ϵ 937), 272 (ϵ 1300), and 278 (ϵ 1150). Anal. ($C_{12}H_{19}BrOSi$) C, H.

3α-Hydroxy-5-oxo-2β-[3′(*S*)-hydroxy-*trans*-1′-octenyl]-1α-[*m*-(*tert*-butyldimethylsilyloxy)benzyl]cyclopentane 3,3′-Bis(tetrahydropyranyl ether) (17). A. Synthesis of 3α-Hydroxy-5-oxo-2β-[3′(*S*)-hydroxy-*trans*-1′-octenyl]-1-methylenecyclopentane 3,3′-Bis(tetrahydropyranyl ether) (13). A 2000-mL, three-neck flask, equipped with a mechanical stirrer, addition funnel, thermometer, and a nitrogen–vacuum connection, was charged with 40.0 g (97.90 mmol) of allylic alcohol **12** and 800 mL of acetone. The resulting solution was alternately degassed and flushed with nitrogen (2×) and cooled to −35 °C (internal temperature). Then added with stirring, 50 mL of 2.67 M Jones reagent during 5–10 min maintaining the internal temperature at or below −20 °C. The reaction mixture was stirred at −25 to −20 °C for 30 min, treated with 30 mL of isopropyl alcohol, and stirred for an additional 30 min at −25 to −20 °C. The reaction mixture was concentrated in vacuo at ≤30 °C to one-half volume, diluted with brine, and extracted with diethyl ether (3 × 350 mL). The combined extracts were washed with saturated aqueous sodium bicarbonate and brine, and dried over magnesium sulfate. Concentration in vacuo gave 40 g of enone **13** as a pale yellow oil. The IR showed bands at 2980, 2890, 1735, 1647, 1200, 1129, 1112, 1076, 1035, 1020, and 978 cm^{-1}. The NMR showed absorptions at δ 0.91 (t, J = 5 Hz, 3 H), 0.8–3.1 (m, 23 H), 3.1–4.4 (m, 6 H), 4.68 (m, 2 H), 5.11 and 5.98 (2m, 2 H, *exo*-methylene H), 5.47 (m, 2 H). TLC using 25% ethyl acetate in Skellysolve B showed one spot, R_f 0.44. Enone **13** was not further purified but used directly in part B.

B. Generation of Lithium Bis(3-*tert*-butyldimethylsilyloxyphenyl)copper (16). A 3000-mL, three-neck flask, equipped with a mechanical stirrer, serum stopper, and a nitrogen–vacuum connection, was charged with 600 mL of anhydrous diethyl ether, 24.8 g (122.58 mmol) of tri-*n*-butylphosphine, and 23.2 g (121.82 mmol) of cuprous iodide. The resulting mixture was alternately degassed and flushed with nitrogen (3×), stirred at 25 °C for 1 h, and then cooled to −78 °C (solution I).

A 2000-mL, three-neck flask, equipped with a magnetic stirring bar, serum stopper, 500-mL addition funnel (pressure equilibrated and graduated with a serum stopper at the top) and a nitrogen–vacuum connection, was charged with 360 mL of anhydrous diethyl ether. The system was alternately degassed and flushed with nitrogen (3×) and the flask was cooled to −78 °C. The addition funnel was then charged with 258 mL of 1.90 M *tert*-butyllithium in pentane (490.20 mmol) via a double-tipped needle with positive nitrogen pressure.[11] The *tert*-butyllithium solution was then added dropwise with stirring to the ether solvent in the flask (solution II).

A 500-mL flask, equipped with a magnetic stirring bar, was charged with 70.4 g (245.07 mmol) of aryl bromide **15** and 240 mL of anhydrous diethyl ether. The resulting solution was alternately degassed and flushed with nitrogen (3×), cooled to −78 °C, and added over 15 min to solution II via a double-tipped needle with positive nitrogen pressure.[11] The reaction mixture was then stirred at −78 °C for 1.75 h (solution III).

Solution III was added to solution I with vigorous stirring via a double-tipped needle at −78 °C.[11] The addition was carried out over 45–60 min with the following color change: white → yellow → tan → orange-brown. After the addition was complete, the reaction mixture was stirred at −78 °C for an additional 30 min.

C. Synthesis of 17. A 1000-mL flask, equipped with a magnetic stirring bar, was charged with 40 g of enone **13** and 400 mL of anhydrous diethyl ether. The resulting solution was alternately degassed and flushed with nitrogen (3×), cooled to −78 °C, and added to the above mixture of cuprate **16** (vigorously stirred) via a double-tipped needle with positive nitrogen pressure.[11] The addition was carried out over 60–80 min and the reaction mixture was then stirred for an additional 30–40 min at −78 °C. The resulting reaction mixture was then transferred into a rapidly stirred solution of 1000 mL of 7.6% glacial acetic acid in diethyl ether (precooled to −40 °C) via a ⅛-in. o.d. Teflon cannula and positive nitrogen pressure. After the transfer was complete, the resulting mixture was washed with brine (2 × 1000 mL), saturated aqueous sodium bicarbonate (3 × 1000 mL), and brine (1000 mL), and dried over magnesium sulfate. Concentration in vacuo gave 197.6 g of crude **17** as an oil.

The above product was combined with similar products obtained from runs employing 1, 5, and 20 g of allylic alcohol **12** (total of 161.54 mmol of **12**) to give 231.82 g of crude product which was purified as follows: a 110 mm × 48 in. column was dry-packed with 3000 g of silica gel (previously equilibrated with 300 mL of ethyl acetate). The sample was applied in Skellysolve B and eluted with 2 L each of 3, 10, 15, 15, 20, 20, 25, 30, 40, and 50% ethyl acetate in Skellysolve B. Fractions were 500 mL each, and based on TLC homogeneity, fractions 27–40 were combined to give 75.11 g (76%) of pure **17** as an oil. The IR showed bands at 2970, 2890, 1750, 1612, 1583, 1485, 1470, 1440, 1272, 1258, 1200, 1160, 1132, 1129, 1112, 1080, 1037, 1020, 976, 843, and 784 cm^{-1}. The NMR showed absorptions at δ 0.18 (s, 6 H), 0.90 (t, J = 5 Hz, 3 H), 0.98 (s, 9 H), 0.6–3.1 (m, 26 H), 3.2–4.4 (m, 6 H), 4.68 (m, 2 H), 5.50 (m 2 H), 6.52–7.42 (m, 4 H). The mass spectrum exhibited peaks at *m/e* 614.3982 (M^+; calcd for $C_{36}H_{58}O_6Si$: 614.4002), 557, 530, 529, 513, 512, 463, 455, 428, 410, 371, 357, 355, 353, 317, 246, 221, 159, and 85. TLC using 25% ethyl acetate in Skellysolve B showed three to four spots (diastereomeric THP mixture), R_f 0.25–0.37.

5αβ-Acetoxy-3α-hydroxy-2β-[3′(*S*)-hydroxy-*trans*-1′-octenyl]-1α-(*m*-hydroxybenzyl)cyclopentane 3,3′-Bis(tetrahydropyranyl ether) (20). A. Synthesis of 3α,5αβ-Dihydroxy-2β-[3′(*S*)-hydroxy-*trans*-1′-octenyl]-1α-[*m*-*tert*-butyldimethylsilyloxy)benzyl]cyclopentane 3,3′-Bis(tetrahydropyranyl ether) (18). A 1000-mL, three-neck flask, equipped with a magnetic stirring bar, addition funnel, thermometer, and a nitrogen–vacuum connection, was charged with 150 mL of absolute methanol and 2.52 g (66.65 mmol) of sodium borohydride. The resulting solution was alternately degassed and flushed with nitrogen (3×) and cooled to −30 °C (internal temperature). A solution of 27.3 g (44.43 mmol) of ketone **17** in 50 mL of methylene chloride was then added with stirring while maintaining the temperature of the reaction mixture at −30 to −25 °C. Residual **17** was rinsed in with 25 mL of methylene chloride and the reaction mixture was stirred at −30 to −25 °C for 1.5 h, diluted with 1000 mL of brine, and extracted with ethyl acetate (2 × 300 mL). The combined extracts were washed with brine (2 × 300 mL), dried over sodium sulfate, and concentrated in vacuo to give 27.8 g of crude **18** as an oil (ca 1:1 mixture of epimers). TLC using 50% ethyl acetate in Skellysolve B showed two spots, R_f 0.64 and 0.51.

B. Synthesis of 5αβ-Acetoxy-3α-hydroxy-2β-[3′(*S*)-hydroxy-*trans*-1′-octenyl]-1α-[*m*-(*tert*-butyldimethylsilyloxy)-benzyl]cyclopentane 3,3′-Bis(tetrahydropyranyl ether) (19). A 500-mL, three-neck flask, equipped with a magnetic stirring bar, addition funnel, thermometer, and a nitrogen inlet, was charged with 27.8 g of alcohols **18** (from part A) and 200 mL of pyridine. The resulting solution was purged with nitrogen for several minutes, cooled to 0 °C, and treated with 80 mL of acetic anhydride and 0.50 g of 4-(*N*,*N*-dimethylamino)pyridine. The reaction mixture was stirred at 8–10 °C for 20 min then at 20–25 °C for 3 h. The flask was immersed in an ice bath and 75 mL of anhydrous methanol was added at a rate such that the internal temperature was maintained at or below 35 °C. After stirring for an additional 30 min, the reaction mixture was diluted with 1000 mL of brine and extracted with ethyl acetate (2 × 300 mL). The combined extracts were washed with brine (300 mL), ice-cold 1 N aqueous hydrochloric acid (5 × 300 mL), saturated aqueous sodium bicarbonate (300 mL), and brine (300 mL), and dried over sodium sulfate. Concentration in vacuo gave 29.4 g of crude **19** as an oil. The IR showed the absence of a hydroxyl band and the appearance of a carbonyl band at 1745 cm^{-1}.

C. Synthesis of 20. A 250-mL three-neck flask, equipped with a magnetic stirring bar, serum cap, thermometer, and a nitrogen–vacuum connection was charged with 29.4 g of acetates **19** (from part B) and 100 mL of dry tetrahydrofuran. The resulting solution was alternately degassed and flushed with nitrogen (3×), cooled to 0 °C, and treated with 115 mL of 0.5 M tetra-*n*-butylammonium fluoride[10] in tetrahydrofuran. The reaction mixture was stirred at 3–10 °C for 45 min, diluted with 1000 mL of brine, and extracted with ethyl acetate (350 mL). The extract was washed with brine (300 mL), dried over sodium sulfate, and concentrated in vacuo to give 35.4 g of crude **20** as a dark oil. A 48 mm × 36 in. column was slurry-packed with 500 g of silica gel in 25% ethyl acetate in Skellysolve B. The sample was applied in methylene chloride and eluted with 1000 mL each of 25%, 35%, 45%, and 55% ethyl acetate in Skellysolve B. Fractions were 60 mL each, and based on TLC homogeneity, fractions 25–39 were combined to give 23.8 g of pure **20** (ea. 1:1 mixture of epimers) as an oil (98% overall from **17**). The IR showed bands at 3400, 2970, 2890, 1745, 1725(sh), 1604, 1590, 1240, 1131, 1114, 1075, 1021, and 974 cm^{-1}. The NMR showed absorptions at δ 0.88 (t, J = 5 Hz, 3 H), 1.80, 1.82, 2.07 (3 s, 3 H total, acetate CH_3), 0.8–3.1 (m, 26 H), 3.18–4.42 (m, 6 H), 4.47–5.23 (m, 3 H), 5.23–5.90 (m, 2 H), 6.42–7.30 (m, 4 H), 7.07 (bd, s, 1 H, OH, shifts downfield on cooling). The mass spectrum exhibited peaks at *m/e* 616.3820 (M^+ of trimethylsilyl derivative; calcd for $C_{35}H_{56}SiO_7$: 616.3795), 532, 514, 430, 370, 352, 326, 259, 179, and 85. TLC using 25% ethyl acetate in Skellysolve B showed two spots, R_f 0.09 and 0.13.

9-Deoxy-9(*RS*)-acetoxy-3-oxa-4,5,6-trinor-3,7-*inter*-*m*-phenyleneprostaglandin $F_{1\alpha}$ Methyl Ester 11,15-Bis(tetrahydropyranyl ether) (21). A 1000-mL three-neck flask, equipped with a magnetic stirring bar, thermometer, and a nitrogen–vacuum con-

nection, was charged with 23.83 g (43.75 mmol) of phenols **20**, 300 mL of 1,2-dimethoxyethane, and 20.04 g (131 mmol) of methyl bromoacetate. The resulting solution was alternately degassed and flushed with nitrogen (3×), cooled to 3–5 °C in an ice bath, and treated with stirring with 2.76 g of 57% sodium hydride dispersion in mineral oil (65.5 mmol) in small portions during 10 min. The reaction mixture was stirred at 5–10 °C for 2 h and then cautiously treated with 1 mL of glacial acetic acid. The reaction mixture was diluted with 1000 mL of brine and extracted with ethyl acetate (300 mL). The extract was washed with brine (300 mL), dried over sodium sulfate, and concentrated in vacuo to give 36.4 g of crude **21** as an oil. A 48 mm × 36 in. column was slurry-packed with 500 g of silica gel in 5% ethyl acetate in Skellysolve B. The sample was applied in Skellysolve B and eluted with 750 mL of 5% ethyl acetate in Skellysolve B followed by 1000 mL each of 10%, 15%, 30%, and 30% ethyl acetate in Skellysolve B. The first fraction was 900 mL and subsequent fractions were 60 mL each. Based on TLC homogeneity fractions 50–82 were combined to give 26.91 g of pure **21** as an oil (99%). This sample was a mixture of C-9 epimers. The IR showed bands at 2970, 2890, 1765, 1740, 1612, 1590, 1239, 1200, 1158, 1130, 1112, 1076, 1020, and 973 cm^{-1}. The NMR showed absorptions at δ 0.88 (t, J = 5 Hz, 3 H), 1.78, 1.82, 2.07 (3 s, 3 H total, acetate CH_3), 0.8–3.0 (m, 26 H), 3.12–4.33 (m, 6 H), 3.77 (s, 3 H, OCH_3), 4.43–5.23 (m, 3 H), 4.60 (s, 2 H), 5.23–5.83 (m, 2 H), 6.50–7.42 (m, 4 H). The mass spectrum exhibited peaks at *m/e* 616.3654 (M^+; calcd for $C_{35}H_{52}O_9$: 616.3611), 532, 514, 430, 370, 352, 326, 179, and 85. TLC using 15% acetone in methylene chloride showed a single broad spot, R_f 0.64. Anal. ($C_{35}H_{52}O_9$) C, H.

3-Oxa-4,5,6-trinor-3,7-*inter-m*-phenyleneprostaglandin E_1 (2). A. Synthesis of 9-Deoxy-9(*RS*)-hydroxy-3-oxa-4,5,6-trinor-3,7-*inter-m*-phenyleneprostaglandin $F_{1\alpha}$ 11,15-Bis(tetrahydropyranyl ether) (22). A 500-mL flask, equipped with a magnetic stirring bar, was charged with 22.36 g (36.25 mmol) of diester **21**, 50 mL of water, and 150 mL of 5% aqueous potassium hydroxide. The resulting mixture was stirred at 25 °C for 14 h, heated at 35–40 °C for 4 h, cooled to room temperature, and then transferred to a 2-L flask equipped with a magnetic stirring bar. The flask and its contents were cooled to 0 °C, stirring was started, and 1 M aqueous potassium bisulfate was added until pH 3 was obtained. The resulting mixture was diluted to 1000 mL with ice-cold brine, saturated with solid sodium chloride, and extracted with ethyl acetate (3 × 200 mL). The combined extracts were washed with brine, dried over sodium sulfate, and concentrated in vacuo to give 19.83 g of crude **22** as an oil.

B. Synthesis of 3-Oxa-4,5,6-trinor-3,7-inter-*m*-phenyleneprostaglandin E_1 11,15-Bis(tetrahydropyranyl ether) (23). A 1000-mL three-neck flask, equipped with a magnetic stirring bar, thermometer, addition funnel, and a nitrogen–vacuum connection, was charged with 19.83 g of acid **22** (from part A) and 300 mL of acetone. The resulting solution was alternately degassed and flushed with nitrogen (3×), cooled to −25 °C (internal temperature), and treated with 38.6 mL of 2.67 M Jones reagent at a rate that maintained the internal temperature at −20 to −15 °C. The reaction mixture was stirred at −20 to −15 °C for 40 min, treated with 20 mL of isopropyl alcohol, and stirred for an additional 15 min at −20 to −15 °C. The reaction mixture was then diluted with ice-cold brine and extracted with diethyl ether (4 × 200 mL). The combined extracts were washed with brine (4 × 200 mL), dried over sodium sulfate, and concentrated in vacuo to give 20.68 g of crude **23** as a viscous oil. A 48 mm × 36 in. column was slurry-packed with 200 g of acid-washed silica gel in 50% ethyl acetate in Skellysolve B. The sample of **23** was applied in methylene chloride and quickly eluted with 50% ethyl acetate in Skellysolve B until 3000 mL of eluate were collected. Concentration in vacuo gave 17.46 g of semi-pure **23** as an oil. TLC using the A–IX system[8] showed a major spot at R_f 0.54.

C. Synthesis of 2. A 100-mL flask, equipped with a magnetic stirring bar, was charged with 17.46 g of acid **23** (from part B), and 260 mL of tetrahydrofuran. Then 140 mL of water was added followed by 21 mL of 85% phosphoric acid. The resulting solution was purged with nitrogen for 15 min, heated with stirring at 35 °C for 12 h, and cooled to room temperature. The reaction mixture was diluted with 1000 mL of brine, saturated with solid sodium chloride, and extracted with ethyl acetate (3 × 300 mL). The combined extracts were washed with brine (3 × 300 mL), dried over sodium sulfate, and concentrated in vacuo to give 17.38 g of crude product. A 48 mm × 36 in. column was slurry-packed with 520 g of acid-washed silica gel in 25% ethyl acetate in Skellysolve B. The sample was applied in methylene chloride and eluted with 1000 mL each of 25%, 35%, 45%, 65%, 75%, and 85% ethyl acetate in Skellysolve B followed by 2000 mL of acetone. The first fraction was 1000 mL and subsequent fractions were 60 mL each. Based on TLC homogeneity, fractions 25–65 were combined to give 8.98 g of a less polar mixture and fractions 67–94 were combined to give 5.62 g of pure **2** as a pale tan solid.

The less polar mixture from the above chromatography was recycled using 134 mL of tetrahydrofuran, 72 mL of water, and 11 mL of 85% phosphoric acid to give, after a similar chromatography, 5.4 g of a less polar mixture and an additional 1.45 g of pure **2** as a pale tan solid (total yield of 7.07 g; 50% overall from **21**).

The total sample of **2** (7.07 g) was dissolved in 100 mL of hot acetone, treated with 1.0 g of activated carbon for 10 min, and filtered through Celite washing well with acetone. The filtrate was then concentrated to ca. 100 mL total volume, heated to boiling, and treated with 200 mL of hot *n*-hexane. Pure **2** crystallized on standing at 25 °C to give 4.11 g of white microcrystals: mp 129.0–130.0 °C (undepressed on admixture with an independently synthesized sample of **2**[1]). Physical constants for **2** were reported in the preceding manuscript.[1]

3-Oxa-4,5,6-trinor-3,7-*inter-m*-phenyleneprostaglandin A_1 (25). The less polar chromatographic fractions from the previous experiment (part C) were rechromatographed over acid-washed silica gel with 30–50% ethyl acetate in Skellysolve B to give a pure specimen of **25** as an oil. The NMR showed absorptions at δ 0.88 (t, J = 5 Hz, 3 H), 0.6–1.9 (m, 8 H), 2.15–3.47 (m, 4 H), 3.97 (m, 1 H), 4.63 (s, 2 H), 5.28 (m 2 H), 6.12–6.33 and 7.38–7.60 (2 m, 2 H), 6.62–7.4 (m, 6 H, aryl H + CO_2H + OH). The mass spectrum exhibited peaks at *m/e* 516.2743 (M^+ of bistrimethylsilyl derivative; calcd for $C_{28}H_{44}Si_2O_5$: 516.2727), 501, 445, 426, 235, 199, and 173. TLC using the A–IX system[8] showed one spot, R_f 0.31.

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Registry No.—**2**, 65451-57-2; **7**, 37517-42-3; **8**, 65423-49-6; **9**, 65423-50-9; **10**, 65423-51-0; **10** Me_3Si ester, 65423-52-1; **11**, 65423-53-2; **12**, 65423-54-3; **12** Me_3Si derivative, 65423-48-5; **13**, 65423-55-4; **15**, 65423-56-5; **16**, 65453-04-5; **17**, 65423-57-6; 5α-**18**, 65423-58-7; 5β-**18**, 65451-49-2; 5α-**19**, 65423-59-8; 5β-**19**, 65451-50-5; 5α-**20**, 65423-60-1; 5β-**20**, 65451-51-6; **20** Me_3Si ether, 65423-61-2; (9*R*)-**21**, 65423-62-3; (9*S*)-**21**, 65451-52-7; (9*R*)-**22**, 65423-45-2; (9*S*)-**22**, 65451-47-0; **23**, 65423-46-3; **25**, 65451-48-1; **25** Me_3Si ester, 65423-47-4; *t*-$BuMe_2SiCl$, 18162-48-6; *m*-bromophenol, 591-20-8; acetic anhydride, 108-24-7; methyl bromoacetate, 96-32-2.

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Studies on the Solid-Phase Synthesis of Peptide Fragments of Apolipoproteins A-I and A-II

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We report the solid-phase synthesis of four peptides chosen from a region of human serum high-density apolipoprotein A-I, which appears to be composed of repeating structural units of 22 amino acids, further divided into two similar 11-residue units. These repeat units have sequences that are predicted to give rise to amphipathic helices separated by small sections of random or β-turn structure, usually including a proline residue. The sequences of the peptides we have prepared correspond to: I, residues 158–168 of A-I; II, an analogue of I with Arg substituted for Asp_{160}; III, residues 147–168 of A-I; and IV, residues 114–133 of A-I. Additionally, a peptide (V) corresponding to residues 22–31 of A-II has been synthesized. The circular dichroism (CD) spectra of peptides I and V between 250 and 200 nm suggest that these peptides have predominantly random structures. While the longer peptides III and IV seem to have mostly random structure in the range pH 4–9, upon addition of trifluoroethanol the CD spectra undergo marked changes. In 50% trifluoroethanol, peptide III is calculated to have a 40% α-helical structure while peptide IV has a 33% helical structure. The lipid binding and surface properties of the synthetic peptides are now under examination.

The apoproteins of serum lipoproteins exhibit a number of unusual properties.[1] The manner in which these proteins bind to lipids is of particular interest. At the present time, the three-dimensional structures of the lipoproteins have not been unequivocally defined, and no x-ray crystallographic data for any apoprotein have been obtained. Amino acid sequences of several of the human apoproteins have been determined,[2-6] however, and estimates of their secondary structure can be made on the basis of circular dichroism (CD) measurements and predictions by the method of Chou and Fasman.[7] (See for example the structural predictions in ref 1.) As judged from CD measurements, the major protein components of high-density lipoproteins, A-I and A-II, have α-helix contents of approximately 55 and 35%, respectively; these values increase by 25–30% upon relipidation.[8] Examination of models of sections of these proteins in a helical conformation reveals that they have a polar surface containing pairs of acidic and basic amino acids and a nonpolar surface made up of hydrophobic residues. The C proteins, found mainly in very low density lipoproteins, also contain regions of potential helices of similar structure. It has been proposed that these two-sided or "amphipathic" helices are responsible for the lipid binding properties of the apolipoprotein.[9] We are currently engaged in a program to determine what structural features of the apolipoproteins are responsible for their physical properties and interactions with lipids.

One approach to assessing the functional importance of various regions of the apolipoproteins is to study the chemical and physical properties of synthetic peptides corresponding to various segments of the proteins. One such study of peptide fragments of the C-III protein has been reported.[10] The advantages of using synthetic peptides rather than chemically or enzymatically produced fragments derived from natural protein for studies of structure–activity relationships are that relatively large amounts of material can be obtained, the size and sequence of the fragments can be readily selected, and peptides with structural replacements or modifications can be prepared. In the investigation described in this report, the focus of our research was on the synthesis of peptides corresponding to segments of apolipoproteins which should have a high potential for forming amphipathic helices. Our attention was centered on the portion of human apolipoprotein A-I including residues 80–222, due to the observation made by Fitch[11] and, independently, McLachlan[12] that this region is composed of repeating structural units of 22 amino acids which are further divided into two similar 11-residue units. Interestingly, these repeat units correspond to sequences that are predicted to be amphipathic helices. The helices are separated by small sections of random or β-turn structure, usually including a proline residue. The presumption that these units of repeating structures arose from duplication of an ancestral gene suggests the possibility that one of the units alone could exhibit many of the properties of the complete protein. In this report the solid-phase synthesis of several of these repeating units of A-I apolipoprotein to be used in investigating their contributions to the properties of the protein is described. The results of work initiated on the synthesis of peptide fragments of human A-II lipoprotein are briefly summarized.

Results and Discussion

The following peptides have been synthesized: I, corresponding to residues 158–168 of A-I; II, an analogue of I with Arg substituted for Asp_{160}; III, corresponding to residues 147–168 of A-I; IV, corresponding to residues 114–133 of A-I; and V, corresponding to residues 22–31 of A-II (see Figure 1). Peptides I and III are representative 11 and 22 amino acid repeat units. Peptide IV contains segments of two predicted amphipathic helices separated by a bend or kink introduced by Pro_{124}. In the native lipoprotein complex the phospholipids could conceivably be bound within the loop formed by such structures. Peptide IV was acetylated at the N-terminal to give a structure more similar to that of the native protein. To investigate whether the correct amino acid sequence of the peptide, in particular, the location of the charged residues in the structure as described by Segrest et al.,[9] is necessary for imparting any special properties to these peptides, peptide II in which Asp is replaced by an Arg residue was synthesized. In addition to these peptide fragments of apolipoprotein A-I, a portion of A-II, peptide V, was synthesized. This peptide includes the single methionine residue of the apo A-II monomer. The lipid binding properties of the cyanogen bromide fragments of apo A-II have been studied by Assman and Brewer.[13] The fact that the Met residue is in the middle of a predicted amphipathic helix may explain why the lipid-binding capacity of the fragments was much less than that of the intact protein. For this reason we chose to make peptide V which includes the methionine residue as a starting point for our work on A-II synthetic fragments.

The peptides were synthesized by variations of the solid-phase method developed by Merrifield.[14,15] The benzyl ester linkage of the growing peptide chain to the polymer support was employed. Low substitution levels of peptide and 1% cross-linked resin were used to aid in attaining rapid, complete reactions and to minimize termination of the growing peptide

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His-Val-Asp-Ala-Leu-Arg-Thr-His-Leu-Ala-Pro
I

His-Val-Arg-Ala-Leu-Arg-Thr-His-Leu-Ala-Pro
II

Leu-Gly-Glu-Glu-Met-Arg-Asp-Arg-Ala-Arg-Ala-
His-Val-Asp-Ala-Leu-Arg-Thr-His-Leu-Ala-Pro
III

CH_3C-Glu-Met-Glu-Leu-Tyr-Arg-Gln-Lys-Val-Glu-
Pro-Leu-Arg-Ala-Glu-Leu-Gln-Glu-Gly-Ala
IV

Gly-Lys-Asp-Leu-Met-Glu-Lys-Val-Lys-Ser
V

Figure 1. Sequences of synthetic peptides prepared in this work.

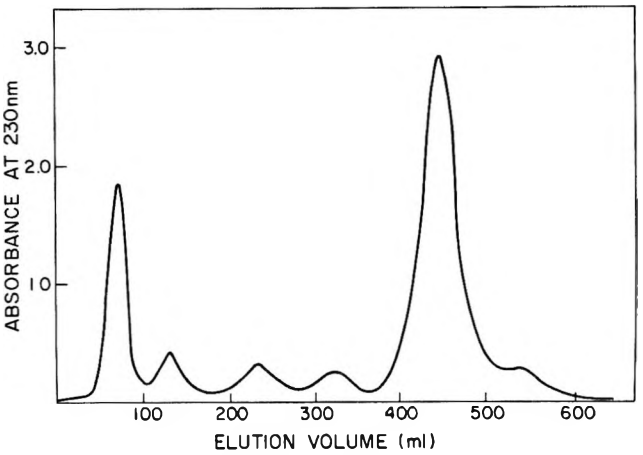

Figure 2. Ion-exchange chromatography of peptide I; 1.8 × 32 cm CM-Sephadex C-25 column employed using 0.02 M phosphate at pH 6.4 with 0–0.25 M NaCl gradient.

chain. Amino acid side chain protecting groups that are stable under the synthesis conditions were chosen to minimize chain branching. All of the protecting groups are known to be removable by HF treatment.[15] The completeness of the coupling reaction was monitored by the sensitive ninhydrin test described by Kaiser et al.[16] When a positive test was observed, the amino acid derivative was recoupled. Recoupling was found to be necessary in the case of the Val residue of peptide I, the second His residue of peptide II, the first Lys residue of peptide V, and the Gly moiety of peptide IV. Under the reaction conditions used, only the sterically hindered His-Val-Asp sequence and the first coupling step presented difficulty in achieving complete reaction.

In the synthesis of peptide III the symmetric anhydride method of coupling was employed.[17,18] It is claimed that using the preformed symmetric anhydride leads to a reduction in the formation of termination peptides.[19] We found that this method gave complete coupling in much shorter reaction times (45–75 min) than the DCC method.

The glutamine residues of peptide IV were introduced by coupling using the *p*-nitrophenyl ester. An equivalent of 1-hydroxybenzotriazole, which has been shown to catalyze the coupling reaction and also to minimize racemization,[20a,b,21] was added to the reaction mixture. After the incorporation of methionine into peptides III, IV, and V, anisole was added to the trifluoroacetic acid deprotection reagent to help prevent alkylation of the sulfur.

The amounts of the Boc-amino acid resins that were used in the syntheses and their substitution levels were: I, 4.87 g, 0.21 mmol Pro/g; II, 1.65 g, 0.24 mmol Pro/g; III, 5.00 g, 0.13 mmol Pro/g; IV, 5.5 g, 0.15 mmol Ala/g; V, 5.25 g, 0.05 mmol Ser/g. The analysis value for Ser may be low due to decomposition under the hydrolysis conditions employed. Yields of protected peptides calculated from the weight gain of the resins ranged from about 65% for peptide III and IV to 85% for peptide II, which indicates an average yield of about 98% for each amino acid incorporated. Some of the losses were due to the removal of samples for the ninhydrin test after each coupling step and amino acid analysis at several points in the synthesis. Another likely major loss of peptide resulted from diketopiperazine formation, particularly in the cases of those peptides which had proline at their C termini.[22,23] In the course of the synthesis of peptide III, an amino acid analysis on a hydrolyzate produced after incorporation of the fourth residue, threonine, on the polymer indicated that losses due to diketopiperazine formation had occurred. The substitution level of Pro at that point was calculated as being 0.102 mmol/g of polymer backbone which is a reduction of 0.029 mmol/g from the value at the start of the synthesis. At the end of the synthesis only a slight further decrease of the substitution level of Pro was noted.

The peptides were cleaved from the solid support by treatment with hydrofluoric acid under conditions that were designed to remove all of the protecting groups, yet cause minimal side reactions. The crude peptide mixtures were extracted from the resin with 10% acetic acid. Lyophilization yielded the deprotected peptides in 70–82% yield for this step.

Purification of the Peptides. Because of incomplete reactions, loss of side-chain protecting groups, deprotection of side chains leading to chain branching, and various side reactions,[15] careful purification of peptides synthesized by the solid-phase method is an essential part of the synthetic procedure. The crude peptides from the HF cleavage process were gel filtered to remove small termination peptides, as well as side products resulting from the HF cleavage reaction. The peptides were purified further by ion-exchange chromatography.

Peptide I was chromatographed on a CM-Sephadex cation exchange resin with a sodium chloride gradient. One major peak and several smaller peaks were observed in the elution profile (Figure 2). After desalting, isolation of the major product gave an amount of peptide that corresponded to 35% of the material that had been loaded on to the column. Therefore, the overall yield based on the starting substitution level of the solid support was 18%. The purity of the product from the ion-exchange chromatography step was assessed by thin-layer chromatography. A good separation of the components of the starting peptide mixture was found using cellulose TLC plates developed with 1:1:1 *n*-butyl alcohol–pyridine–water. The purified peptide gave a single spot, R_f 0.45. Amino acid analysis of peptide I showed the expected ratios of amino acids (Table I). Sequencing of peptide I by the automated Edman degradation method established that the sequence was the desired one and confirmed the purity of the material (Table II).

Gel filtration of peptide II resulted in a 76% recovery of high molecular weight peptide. Cation exchange chromatography of this material with a sodium chloride gradient gave the major product in 21% yield after desalting. N-terminal analysis of this product by the Edman degradation method showed that it contained an impurity that had valine rather than histidine at the N-terminus. A problem in achieving complete coupling of the final histidine in the synthesis of peptide II had been indicated by the application of the ninhydrin test. Thus, peptide II was purified further by cation exchange chromatography with a pH step gradient of increasing pH. One minor and another very minor component eluted from the column before the major product. A center cut of the major component peak yielded 25 mg of purified peptide, 62% of the amount

Table I. Amino Acid Analyses of Synthetic Peptides

Amino acid	I	II	III	IV	V
Lys				1.19	3.16
His	2.09	2.01	2.16		
Arg	0.96	1.95	4.03	1.85	
Asp	1.09		2.04		1.02
Thr	0.94	0.96	0.98		
Ser					0.93
Glx			1.85	7.02	1.00
Pro	1.11	1.00	1.00	1.01	
Gly			0 87	1.29	1.08
Ala	2.20	2.10	4 02	2.34	
Val	0.93	0.72	0 97	0.73	0.91
Met			0.92	0.78	0.94
Leu	2.05	2.08	3.12	3.02	1.00
Tyr				0.70	

placed on the column. End-group analysis of this product by the dansylation method demonstrated that the only free amino group present was that due to histidine. Amino acid analysis of the purified peptide agreed with the theoretical values (Table I). On TLC peptide II had R_f values of 0.76 with 1:1:1 *n*-butyl alcohol–pyridine–water on cellulose and 0.66 with 50:30:15 pyridine–acetic acid–water on silica gel, and on paper electrophoresis it displayed a single spot, R_f 0.93, relative to lysine (3000 V for 45 min, pH 3.5).

In the case of peptide III, amino acid analysis of the peptide bound to the resin at the completion of the synthesis gave values of 0.10 mmol/g resin backbone for Pro, 0.082 mmol/g for Ala, and 0.057 mmol/g for Glu. Since proline is found only at the C-terminus, alanine throughout the peptide, and glutamic acid only near the N-terminal region of the peptide, considerable chain termination had occurred. Before gel filtering the crude peptide, it was dissolved in a solution of dithiothreitol to reduce any methionine sulfoxide back to methionine.[24] 2-Mercaptoethanol was added to the eluents in the chromatographic purification to prevent oxidation. Part of the product from the gel filtration step in the purification of the crude peptide was purified further by anion exchange chromatography, first with a concentration gradient of ammonium bicarbonate, then with a pH gradient of Tris buffer. A number of peaks were observed in the first ion-exchange column (Figure 3), but there was one major component. The material isolated from this peak was 35% of the total. Amino acid analysis of this product indicated that it was the desired peptide. Further purification of the peptide on the pH gradient column gave a 55% yield of peptide III. The purified peptide contained a single component as evidenced by TLC in the following systems: 15:10:3:12 *n*-butyl alcohol–pyridine–acetic acid–water on cellulose, R_f 0.68; 4:1:1 *n*-butyl alcohol–acetic acid–water on cellulose, R_f 0.39; 50:30:15 pyridine–acetic acid–water on silica, R_f 0.35. A single band was observed on high voltage paper electrophoresis of the product (2500 V for 1 h at pH 6.4, migration was toward the cathode; R_f 0.49 relative to arginine). Amino acid analysis of the final product agreed very well with the values expected for peptide III (Table I). Edman degradation of the purified peptide was fully consistent with the amino acid sequence (Table II).

Crude peptide IV was obtained in 77% yield from the HF cleavage reaction. Gel chromatography of this material on Sephadex G-10 resulted in the separation of three low molecular weight components; one of these components had an absorbance at 280 nm and the other two only at 230 nm. The product obtained from the void volume peak was 85% of the total. Ion-exchange chromatography of this material with an ammonium bicarbonate gradient resulted in an elution profile showing two major peaks which were unsymmetrical and not

Table II. Edman Degradation Results[a]

Cycle	Amino acids detected	Amount
	Peptide I	
1	His	Spot test
2	Val	900 nmol
3	Asp	800 nmol
4	Ala	750 nmol
5	Leu	700 nmol
6	Arg	Spot test
7	Thr	500 nmol
8	His	Spot test
9	Leu	350 nmol
10	Ala	50 nmol
11	Pro	Small amount
	Peptide III	
1	Leu	1950 nmol
2	Gly	1600 nmol
3	Glu	1890 nmol
4	Glu	1800 nmol
5	Met	1800 nmol
6	Arg	Spot test
7	Asp	1720 nmol
8	Arg	Spot test
9	Ala	1600 nmol
10	Arg	Spot test
11	Ala	1300 nmol
12	His	Spot test
13	Val	825 nmol
14	Asp	810 nmol
15	Ala	800 nmol
16	Leu	820 nmol
17	Arg	Spot test
18	Thr	350 nmol
19	His	Spot test
20	Leu	300 nmol
21	Ala	200 nmol
22	Pro	50 nmol
	Cyanogen Bromide Fragment of Peptide IVa	
1	Glu	500 nmol
2	Leu	500 nmol
3	Tyr	475 nmol
4	Arg	Spot test
5	Gln,Glu	200, 100 nmol
6	Lys	300 nmol
7	Val	350 nmol
8	Glu	310 nmol
9	Pro	300 nmol
10	Leu	300 nmol
11	Arg	Spot test
12	Ala	250 nmol
13	Glu	250 nmol
14	Leu	260 nmol
15	Gln,Glu	120, 70 nmol
16	Glu	100 nmol
17	Gly	70 nmol
18	Ala	40 nmol
	Peptide V	
1	Gly	2.25 μmol
2	Lys	1.75 μmol
3	Asp	2.00 μmol
4	Leu	1.75 μmol
5	Met	1.50 μmol
6	Glu	1.10 μmol
7	Lys	1.20 μmol
8	Val	1.20 μmol
9	Lys	0.85 μmol
10	Ser	0.20 μmol

[a] Degradation experiments carried out by P. Keim and R. Heinrikson.

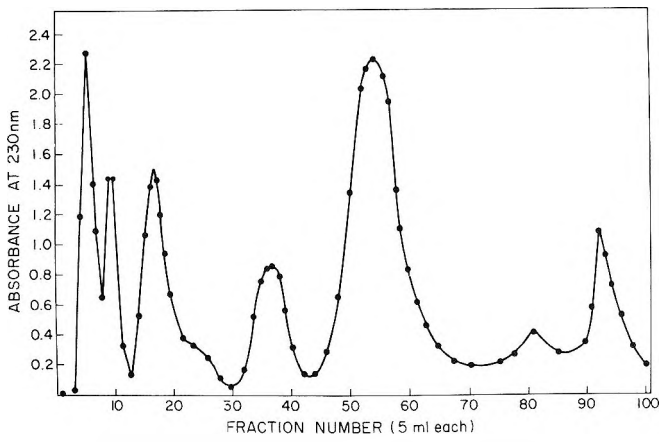

Figure 3. Ion-exchange chromatography of peptide III; DEAE Sephadex A-25 column, using 0.01 M–0.40 M $NH_4^+HCO_3^-$.

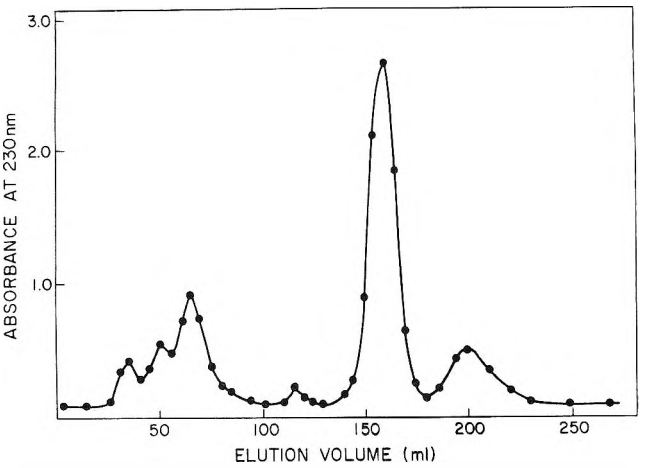

Figure 4. Ion-exchange chromatography of peptide V; 1.8 × 32 cm CM-Sephadex C-25 column employed, using 0.02 M phosphate at pH 7.0 with 0–0.4 M NaCl gradient.

well separated. The products isolated from these two fractions had essentially the same amino acid analysis. Analysis after basic hydrolysis established that neither product contained methionine sulfoxide, a possible side product of the synthesis. The component eluting from the column first (IVa) was found to be appreciably more soluble in dilute acetic acid than the other product (IVb), accounting for the partial solubility that was observed in the gel chromatography of the crude peptide. Peptide IVa was further purified by partition chromatography on Sephadex LH-20. The major peptide fraction (86%) eluted near the void volume and was followed by several smaller peaks. Edman sequence analysis indicated that this product was not homogeneous (previews began appearing at cycle 9), but most of it had the correct amino acid sequence. It should be noted that since the amino terminus of the peptide was acetylated, the reaction with phenyl isothiocyanate could not be performed directly on the peptide; instead, the peptide was cleaved at the methionine residue with cyanogen bromide and the 18-residue fragment was sequenced. A final purification of peptide IVa was effected with a sodium chloride gradient ion-exchange chromatography in which two minor impurities were separated from the main product. Peptide IVb separated into several components under the same column conditions implying that IVb is a mixture of side products. The purified peptide IVa exhibited a single band in high voltage paper electrophoresis (pH 6.4, 3000 V for 50 min) with an R_f of 0.14 relative to aspartic acid. On TLC on silica gel, the peptide showed one ninhydrin positive spot with R_f values of 0.41 in 15:10:3:12 *n*-butyl alcohol–pyridine–acetic acid–H_2O and 0.032 in 4:1:1 *n*-butyl alcohol–acetic acid–water. The Edman degradation analysis of the cyanogen bromide fragment of IVa (Table II) confirmed its purity and covalent structure. No previews were observed and the only extra amino acid detected was Glu at cycles 5 and 15 due to the decomposition of Gln under the reaction conditions. The amino acid analysis of peptide IVa is shown in Table I.

Peptide V was purified by gel filtration and ion-exchange chromatography. In preliminary pH step chromatography, the main component of the product isolated from the gel filtration step was found to be eluted at around pH 7.5. Based on this observation, a cation exchange column at pH 7.0 employing sodium chloride gradient elution was chosen to purify peptide V. The resulting elution profile is shown in Figure 4. The isolated yield of the main component was 42% of the amount of material which was applied to the chromatographic column. This product displayed a single spot on TLC with several solvent systems: 4:1:1 *n*-butyl alcohol–acetic acid–water on cellulose, R_f 0.11; 15:10:3:12 *n*-butyl alcohol–pyridine–acetic acid–water, R_f 0.35; and 50:30:15 pyridine–acetic acid–water on silica gel, R_f 0.69. Only two fluorescent spots, corresponding to the dansyl derivatives of Gly and ϵ-Lys, were observed in dansyl end group analysis of purified peptide V. The amino acid analysis of the product is shown in Table I. Finally, an Edman sequence determination established the structure and homogeneity of peptide V (Table II).

Circular Dichroism Studies. As mentioned in the introductory section, it has been proposed that amphipathic helices are responsible for the lipid binding properties of apolipoproteins. Peptides I–V were chosen for synthesis because of their correspondence to regions that were predicted to have this type of structure. Accordingly, it was desirable to determine if they existed in a helical conformation in solution. Greenfield and Fasman have shown that circular dichroism can be used to evaluate protein conformation.[25a,b] Using synthetic polypeptides, they observed that α-helical structures display characteristic negative extrema at 208 and 222 nm in their CD spectra and they developed a method for calculating an approximate α-helical content using the mean residue ellipticities at these two wavelengths. Although polypeptides may not provide the best models for analyzing the CD spectra of proteins,[26,27] due in part to the smaller length of helices in proteins, the chain length dependent factor discussed in ref 26 introduces only a small correction for helices of over 20 amino acids. The percentages of helical structure of the peptides described in the present report were estimated from their $[\theta]_{222nm}$ values using the equation: % α helix = $([\theta]_{222nm} + 3000)/(36000 + 3000)$.

The circular dichroism spectra of peptides I, III, IV, and V were measured in the pH range 4–9 and in the presence of organic solvents. Organic solvents such as chloroethanol and trifluoroethanol are known to induce α-helix conformation preferentially.[28a,b] The spectra of peptides I and V between 250 and 200 nm were typical of a peptide that had predominantly random structure. In the presence of a high concentration of chloroethanol they appeared to have only a slight amount of helical structure. Perhaps these two peptides are too small to attain a significantly ordered structure, particularly since they have free end groups, and solvation may interfere with α-helix formation. Peptides III and IV also display mostly random structure throughout the pH 4–9 range; however, a helical contribution of 10–15% was calculated from their CD spectra. Upon addition of trifluoroethanol the spectra changed dramatically (definite troughs at 208 and 222 appeared (Figure 5)). Calculation of the percentage of α helix of peptide IV in 50% trifluoroethanol gave a value of 33%. Peptide III contained 35% helical structure in 25% trifluoroethanol and 40% helical structure in 50% of this solvent. The

Table III

Step	Reagent	Applications	Time, min
1	CH_2Cl_2 wash	2 × 40 mL	1
2	1:1 TFA–CH_2Cl_2	1 × 25 mL	1
3	1:1 TFA–CH_2Cl_2	1 × 40 mL	30
4	CH_2Cl_2 wash	3 × 40 mL	1
5	2-Butanol wash	1 × 25 mL	1
6	CH_2Cl_2 wash	2 × 25 mL	1
7	10% TEA or DIEA in $CHCl_3$	1 × 40 mL	4
8	CH_2Cl_2 wash	4 × 25 mL	1
9	Boc-amino acid in CH_2Cl_2[a]		1
10	DCC in CH_2Cl_2[b]		120–360
11	CH_2Cl_2 wash	2 × 25 mL	1
12	DMF wash	1 × 25 mL	1
13	CH_2Cl_2 wash	3 × 25 mL	1

[a] A 2.5-fold molar excess of amino acid derivative in about 15 mL of CH_2Cl_2 was used. The derivatives of lysine and arginine were dissolved in a small amount of DMF and then diluted with CH_2Cl_2. [b] A 2.5-fold molar excess in 5 mL of CH_2Cl_2 was employed.

two longer peptides are capable of forming an α helix, and possibly, in the presence of lipids, an increase in the percent helicity will be observed as is seen for the whole protein.

Conclusion. This report has described the solid-phase synthesis and purification of five peptide fragments of apolipoproteins for use in studies to determine the structural characteristics which impart to these proteins their surface properties, as well as their ability to bind lipids. The synthetic methods employed produced crude peptides in good yields, but for the preparation of peptides containing about 20 amino acid residues, extensive purification was necessary to isolate products substantially free of impurities. In the synthesis of larger peptide segments of the apolipoproteins it may be advisable to use methods involving the condensation of purified peptide fragments to obtain products of sufficient purity for structure-activity investigations. Work is continuing in this laboratory on the preparation of other peptide fragments of apolipoproteins A-I and A-II and on defining the physical and chemical properties of the synthetic peptides.

Experimental Section

Materials and Methods. Dichloromethane and chloroform from Burdick and Jackson Laboratories were distilled from phosphorus pentoxide. Triethylamine (Eastman) and *N,N*-diisopropylethylamine (Aldrich) were distilled from ninhydrin and then redistilled from calcium hydride. Trifluoroacetic acid obtained from Aldrich was distilled within 4 days of being used. Dimethylformamide (DMF) (Fisher Scientific) was purified by codistillation with dry benzene,[29] followed by distillation from ninhydrin under reduced pressure. The purified DMF was stored under nitrogen at 4 °C over molecular sieves. *sec*-Butyl alcohol from Matheson, Coleman and Bell was fractionally distilled. Dicyclohexylcarbodiimide from Aldrich was vacuum distilled.

Chloromethylated styrene–divinylbenzene copolymer (1% cross-linked) was obtained from Pierce and Bachem. *tert*-Butoxycarbonyl-L-amino acid derivatives were purchased from Bachem. These derivatives were as follows: L-alanine, N^g-nitro or tosyl-L-arginine, L-aspartic acid β-benzyl ester, N^{im}-tosyl-L-histidine, *O*-benzyl-L-serine, *O*-benzyl-L-threonine, *O*-2,6-dichlorobenzyl-L-tyrosine, ϵ-2-chlorobenzyloxycarbonyl-L-lysine, L-glutamic acid γ-benzyl ester, L-glutamine *p*-nitrophenyl ester, glycine, L-leucine, L-methionine, L-proline, and L-valine.

Sephadex G-10, DEAE-Sephadex A-25, CM-Sephadex C-25, and Sephadex LH-20 were purchased from Pharmacia.

Ninhydrin, 1-hydroxybenzotriazole, cyanogen bromide, trifluoroethanol, and 2-mercaptoethanol were obtained from Aldrich. Dithiothreitol was purchased from Sigma. Solvents for the peptide synthesis were stored over Linde 4A molecular sieves (Union Carbide). Buffers were prepared from tris(hydroxymethyl)aminomethane (Eastman) and from sodium phosphate (Fisher Scientific). Boiled, deionized water was used to prepare buffer solutions.

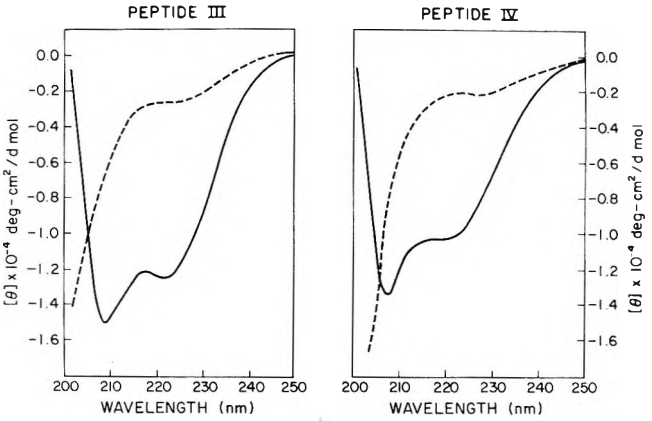

Figure 5. Circular dichroism spectra of peptides III and IV. Solid line represents spectra in 50% trifluoroethanol. For peptide III the dashed line shows the spectrum at pH 7.0 and for peptide IV it illustrates the spectrum at pH 7.5.

The optical densities of column fractions were measured with a Gilford Spectrophotometer. Circular dichroism spectra were recorded with a Cary 60 spectropolarimeter. Amino acid analyses were performed on a Beckman Spinco Model 121 amino acid analyzer. Measurements of pH were made with a Beckman Model 3500 digital pH meter.

The amino acid sequences of the peptides were determined by the method of Edman and Begg[30] using automatic techniques similar to those described by Niall[31] with a Beckman Model 890-C protein-peptide sequencer. The phenylthiohydantoins were identified and quantitated by gas chromatography. Peptide IV was reacted with a large excess of cyanogen bromide in 70% formic acid for 24 h prior to sequencing. At the end of this period the reaction mixture was added to a large volume of water and lyophilized, and the residue was gel filtered to obtain the cleaved peptide.

Amino end group analyses by dansylation were done using the procedures of Gray.[32] The dansyl derivative products were chromatographed on polyamide TLC sheets (Cheng Chin) developed with 100:1.5 water–formic acid in the first dimension, 9:1 benzene–acetic acid in the second dimension, and in the same direction with 20:1:1 ethyl acetate–acetic acid–methanol.

The purity of the peptides was also assessed by thin-layer chromatography using silica gel and cellulose TLC sheets obtained from Eastman Chemicals.

High-voltage paper electrophoresis experiments were carried out with a Savant Flat plate electrophoresis apparatus and 5000 V power supply. The buffers used were pyridine–acetic acid, pH 3.5 and 6.4. The samples were spotted on Whatman 3M chromatography paper along with standard amino acids.

The peptides described in this article were synthesized with the aid of a Beckman Model 990 automated peptide synthesizer. Chloromethylated styrene–divinylbenzene copolymer was esterified with the appropriate Boc-amino acid derivative by the method of Marglin.[33] Substitution levels were determined by amino acid analysis after hydrolysis with 1:1 12 N HCl–propionic acid[34] and were found to be in the range 0.05–0.23 mmol/g. The amino acid substituted resin was placed in the reaction vessel of the peptide synthesizer which executed the programmed sequence of reaction and washing steps shown in Table III. For active ester coupling, a fourfold molar excess of glutamine *p*-nitrophenyl ester and an equivalent of 1-hydroxybenzotriazole in DMF solution were added at the coupling step, the addition being preceded by washing the resin twice with DMF. Addition of DCC was omitted. In the symmetric anhydride coupling procedure, step 10 was also omitted and in step 9 a freshly prepared solution of Boc-amino acid anhydride (threefold excess, prepared as in ref 35) was added. The coupling was allowed to proceed for 45 min, then 1.5 equiv of DIEA was added and stirring was continued for another 15 min, followed by washing as usual. The completeness of the coupling reaction was determined by the use of the ninhydrin color test.[16] When a positive test was observed, the coupling reaction (step 9–13) was repeated. After completion of the synthesis, the peptide resin was washed with methanol and dichloromethane and finally vacuum dried.

The peptides were cleaved from the polymer support by reaction with hydrofluoric acid.[36] The apparatus and procedure for the cleavage have been described previously.[37] After washing the cleaved peptide and resin mixture with ethyl acetate to remove HF and ani-

sole, the peptide was extracted with about 50 mL of 10% acetic acid and the extracts were lyophilized to obtain the crude peptide.

Purification of Peptides. Peptide I. The crude peptide obtained from HF cleavage was gel filtered through a 2.0 × 41 cm Sephadex G-10 column, eluted with 0.2 M aqueous acetic acid. The fractions with a high-UV absorbance at 230 nm just following the void volume were pooled and lyophilized to give 616 mg of solid material. A portion of this product (138 mg) was loaded onto a 1.8 × 32 cm column of CM-Sephadex C-25 cation exchange resin equilibrated with 0.02 M phosphate buffer at pH 6.4. Elution was begun with this buffer at a rate of 50 mL/h; 5-mL fractions were collected. After 40 fractions had been collected, a sodium chloride gradient of 0–0.25 M over a volume of 400 mL was begun. The fractions were analyzed by their optical density at 230 nm. An elution profile is shown in Figure 2. Fractions 82–94 were combined, reduced in volume by rotary evaporation, and desalted on the Sephadex G-10 column. Lyophilization of the salt-free, peptide-containing fractions yielded 48 mg of fluffy white solid.

Peptide II. Lyophilization of the acetic acid extracts of the product of the HF cleavage reaction yielded 308 mg of solid. This material was passed through a 2.0 × 40 cm column of Sephadex G-10 with 0.2 N acetic acid. The fractions containing the major portion of the UV-absorbing material were lyophilized to give 234 mg of peptide. Part of this product (121 mg) was dissolved in a few milliliters of 0.02 M phosphate buffer, pH 7.5, and applied to a CM-Sephadex C-25 cation exchange resin column (1.8 × 32 cm), equilibrated with the same buffer. The column was eluted with 100 mL of the buffer. Then, a sodium chloride gradient solution was begun using a mixing chamber containing 300 mL of the 0.02 M phosphate buffer and a reservoir containing 300 mL of the same buffer but which was 0.25 M in NaCl. Fractions of 5 mL were collected and their absorbance at 230 nm was measured. The major component came off the column in fractions 120–143. The contents of the tubes containing these fractions were combined and reduced to about 6 mL in volume by rotary evaporation. This solution was desalted with a 2.5 × 42 cm column of Sephadex G-10. The lyophilized product which weighed 25 mg was combined with 15 mg of material obtained from another similar column chromatographic run, and the combined material was further purified by chromatography on a 1.8 × 32 cm column of CM-Sephadex C-25 with a pH step elution. After application of the peptide, the column was eluted with 100 mL each of 0.04 M sodium phosphate buffers at pH 6.5, 7.4, and 8.0, followed by elution with 0.10 M phosphate at pH 8.0. Five-milliliter fractions were collected. The contents of tubes 85–95 yielded 24.8 mg of peptide after desalting with a Sephadex G-10 column and lyophilization.

Peptide III. The amount of material obtained from the HF cleavage reaction was approximately 800 mg. The crude peptide was dissolved in 10 mL of water containing 0.12 g of dithiothreitol, and the solution was allowed to stand at 4 °C overnight. The solution then was applied to a 3.8 × 50 cm column of Sephadex G-10 and eluted with 0.2 M acetic acid containing 0.004 M 2-mercaptoethanol. The eluate with an optical density greater than 1.0 at 240 nm was lyophilized, yielding 747 mg of an off-white powder. Two portions of this material (282-mg total) were chromatographed on a 1.8 × 34 cm column of DEAE-Sephadex-A-25 anion exchange resin with an ammonium bicarbonate gradient of 0.01–0.40 M/600 mL. The slope of the gradient was increased after 400 mL of eluate had been collected. Those fractions of both column runs which contained the major peaks were combined, reduced in volume, and desalted on a Sephadex G-10 column. Lyophilization of the peptide fraction produced 97.4 mg of solid. This product (96.6 mg) was dissolved in a few milliliters of 0.05 M Tris buffer at pH 8.2 and added to a 1.8 × 33 cm DEAE-Sephadex A-25 column that had been equilibrated with the same buffer. A pH gradient elution was applied using a mixing chamber containing 250 mL of 0.05 M Tris buffer at pH 8.2 and a reservoir containing 250 mL of 0.05 M Tris buffer at pH 7.0. From a center cut of the main peak fraction, 53 mg of peptide was obtained after desalting.

Peptide IV. The crude, cleaved peptide (957 mg) was divided into two portions for gel chromatography. The crude material was found to be only partially soluble in dilute acetic acid, but it dissolved readily when the solvent was made slightly basic with ammonium hydroxide. The peptide was gel filtered through a 2.8 × 40 cm column of Sephadex G-10, eluting with this solvent and analyzing the fractions by their absorbances at 280 and 230 nm. Approximately 225 mg of the product of the gel-filtration step was chromatographed on a 1.8 × 42 cm column of DEAE-Sephadex A-25, using a gradient elution of 0.10–1.0 M ammonium bicarbonate. The fractions corresponding to the two largest peaks of the elution profile (A_{280}) were lyophilized. The peptide fraction from the earlier eluting material (73 mg) was subjected to partition chromatography on a 2.4 × 54 cm column of Sephadex LH-20 using 50% aqueous acetone containing 0.05 M pyridine as the eluent. Fractions of 4 mL were collected and analyzed for their peptide content by the ninhydrin reaction. Peptide IV was further purified by a sodium chloride gradient ion-exchange chromatography. A 1.8 × 31 cm column of DEAE-Sephadex A-25 was equilibrated with 0.05 M Tris at pH 8.4 and eluted using a mixing chamber containing 300 mL of the same buffer and a reservoir containing 300 mL of the buffer that was 0.60 M in sodium chloride. The fractions corresponding to the major peak of the elution profile were combined, reduced in volume, and desalted on a Sephadex G-10 column using 10% acetic acid as the eluent. Lyophilization of the peptide fractions yielded 48.8 mg of product.

Peptide V. Crude peptide V was gel filtered on a 2.5 × 42 cm column of Sephadex G-10 with 0.1 M acetic acid containing 4 mM 2-mercaptoethanol as the eluent. Several fractions eluting after the void volume were collected and lyophilized to obtain the peptide. Purification of a portion of this material (70.8 mg) was accomplished by chromatography on a 1.8 × 32 cm CM-Sephadex C-25 column eluted at pH 7.0 (0.02 M phosphate) with a sodium chloride gradient of 0–0.4 M over 300 mL. The fractions containing most of the main product were pooled, reduced in volume by rotary evaporation, and eluted through the Sephadex G-10 column. Lyophilization of the desalted peptide solution yielded 29.7 mg of white solid.

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Registry No.—I, 65452-43-9; II, 65392-53-2; III, 65392-52-1; IV, 65452-62-2; V, 65392-51-0.

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Examples of Amino Acid Transaminations with o-Formylbenzoic Acid

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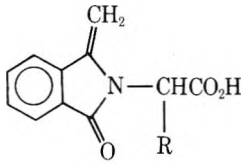
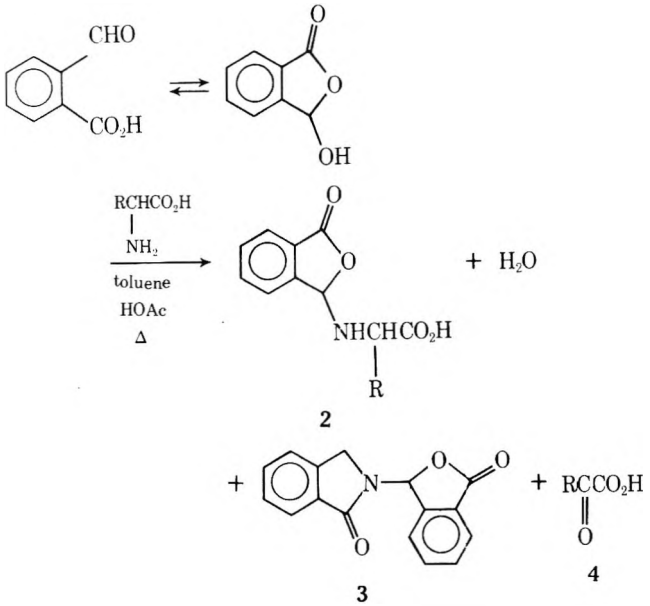
The present paper describes an unusual example of a nonenzymatic transamination of two amino acids by a nonpyridoxal-type carbonyl compound. During the course of some recent research on the interaction of certain o-carbonylbenzoic acids with amino acids, o-formylbenzoic acid was found to undergo transamination reactions with L-glutamic acid and L-alanine in the presence of acetic acid and toluene. The products of this novel reaction are an α-ketocarboxylic acid (**4**) and *N*-(3-phthalidyl)phthalimidine (**3**). Structural proof of the products was based on derivative formation, spectral and elemental analyses, and synthesis. α-Amino-o-toluic acid (**6**) was a probable intermediate in the transformation. Apparently, o-formylbenzoic acid condensed with **6** or with phthalimidine (**5**) to form product **3**. With L-glutamic acid, an additional product (the anhydride of **2**, where R = $CH_2CH_2CO_2H$) was obtained which resulted from a simple condensation of starting materials.

In a recent publication,[2] o-acetylbenzoic acid was reported to condense readily with various amino acids and produce 3-methylenephthalidylamino acids (**1**).



1

When o-formylbenzoic acid was treated with L-glutamic acid, the expected product, **2** (R = $CH_2CH_2CO_2H$), was formed, but only in 19% yield. However, other products were obtained which indicated that transamination had occurred: **3** in 19% yield and **4** (R = $CH_2CH_2CO_2H$) in 17% yield as the semicarbazone derivative. The yield of product **3** was increased to 46% when dioxane was used in place of toluene. Transamination was apparently the only reaction when L-alanine and L-phenylalanine were each treated with o-formylbenzoic acid. None of the condensation product, **2**, was obtained with these amino acids. In the reaction of L-alanine with o-formylbenzoic acid, product **3** was formed in 66% yield and a crystalline phenylhydrazone derivative of pyruvic acid (**4**, R = CH_3) was isolated in 19% yield.

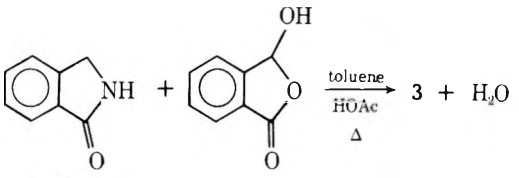


2

3

4

The structure of the base-insoluble product (**3**) was established by an unambiguous synthesis from phthalimidine[3] (**5**) and o-formylbenzoic acid under conditions identical to those used with the latter compound and an amino acid. The product from this experiment was isolated in 50% yield and was identical to that obtained from the transamination reaction with respect to the thin-layer chromatogram R_f value, infrared spectrum, and melting point. Similar reactions of amides with o-formylbenzoic acid are in the literature.[4]



5

The formation of α-amino-o-toluic acid (**6**) and the keto acid (**4**) may be rationalized by analogy with the well-established mechanism for the transamination with pyridoxal phosphate. Experiment has shown that no reaction occurs in the absence of acetic acid. In fact, a large excess of the reagent was found to afford optimum yields of products. Apparently, α-amino-o-toluic acid (**6**) reacts with o-formylbenzoic acid or its tautomer as soon as it is formed and two molecules of water are eliminated. Two equally plausible routes are possible for this transformation. In the first, **6** cyclizes to phthalimidine (**5**) which then condenses with o-formylbenzoic acid, a reaction which has already been demonstrated (see above). The

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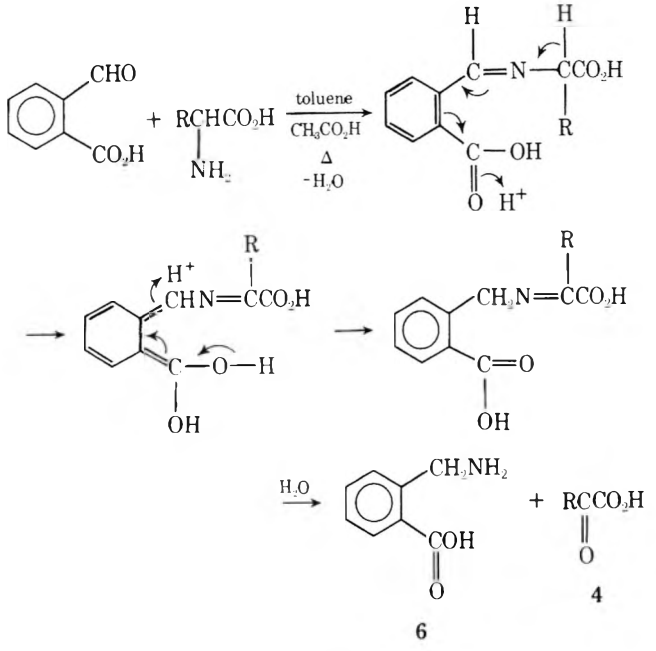
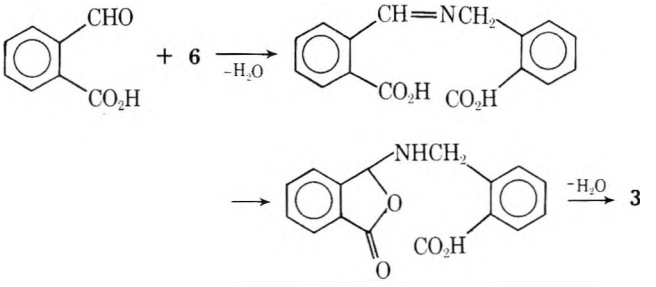
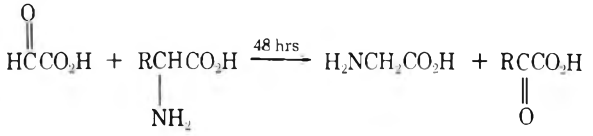


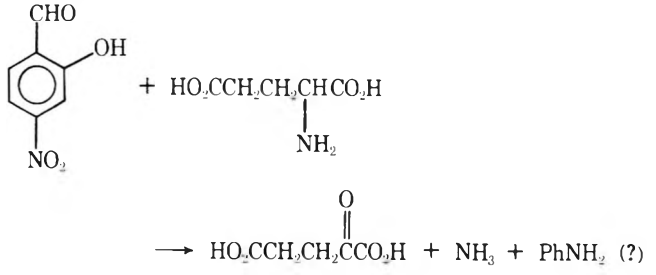
second alternative could produce **3** by the following transformation.



The chief difference between the transamination reaction reported herein and those catalyzed by pyridoxal phosphate is that the former shows no evidence for decarboxylation. The present reaction, then, is an unusual example of a nonenzymatic transamination of amino acids by a non-pyridoxal-type



carbonyl compound that is not accompanied by decarboxylation. As far as we are aware, only two analogous reactions have been reported. The first involved the reaction of glyoxylic acid with various amino acids under physiological conditions to produce glycine and an α-keto acid.[5] The second was the conversion of L-glutamic acid into α-ketoglutaric acid by 4-



or 6-nitrosalicylaldehydes.[6] The authors of that report described the latter reaction as an oxidative deamination rather than a transamination, since ammonia was produced and an "aromatic amine". Apparently, the nitro moiety was the oxidant. They suggested that pyridoxal-like activity in benzenoid compounds requires the presence of a phenolic hydroxyl group (since *p*-nitrobenzaldehyde failed to form significant amounts of keto acids) and the presence of a powerful electron-attracting group in the 4 or 6 position of salicylaldehyde (as shown by the failure of salicylaldehyde itself and 4-carboxysalicyaldehyde to bring about the reaction). Although the carboxyl group is meta directing, it was considered not to be a sufficiently powerful electron-attracting group to effect the deamination.

Experimental Section

IR spectra were recorded on a Perkin-Elmer Model 521 or a Beckman Acculab 3 spectrophotometer. Mass spectra were obtained using a duPont 21-472 instrument. ^{1}H-NMR spectra were run on a Perkin-Elmer R-24B instrument and ^{13}C-NMR spectra on a JEOL FX60Q. Melting points are corrected. Microanalyses were performed by the Analytical Department, Bristol Laboratories, Syracuse, N.Y.

The Transamination of L-Alanine. A mixutre of 3.0 g (20 mmol) of *o*-formylbenzoic acid, 0.89 g (10 mmol) of L-alanine, 3.66 mL (3.84 g, 64 mmol) of HOAc, and 30 mL of toluene was heated to the reflux temperature until no more water was collected in a Dean and Stark trap (about 16 h). The reaction mixture was allowed to cool to 25 °C and diluted with an equal volume of water; the pH was adjusted from 3.0 to 8.5 with aqueous NaOH. An insoluble white solid, *N*-(3-phthalidyl)phthalimidine (**3**), was collected by filtration and recrystallized from HOAc: wt 1.74 g (66%); mp 241.0–241.5 °C; IR (Nujol) 1765 (γ-lactone carbonyl), 1700 cm^{-1} (γ-lactam carbonyl), no absorption in the NH or OH region except for that of Nujol; ^{1}H NMR (Me_2SO-d_6) 7.5 (multiplet, ~8 aromatic H's), 7.05 (singlet, 1 benzyl H on phthalidyl ring), 3.95 and 3.75 (two singlets, 2 benzyl H's on phthalimidine ring); ^{13}C NMR ($CDCl_3/Me_4Si$ = 0, 20 MHz) 44.7 (1 C), 81.4 (1 C), 123.1–144.6 ppm (10 C); mass spectrum *m/e* 265 (100, M$^+$), 237 (30), 221 (55), 133 (33), 132 (20), 44 (15), 28 (15). Anal. Calcd for $C_{16}H_{11}NO_3$ (**3**): C, 72.45; H, 4.18; N, 5.28; mol wt, 265.27. Found: C, 72.19; H, 4.26; N, 5.20.

The pH 8.5 aqueous filtrate from above was adjusted to pH 2.0 with 6 N HCl and then extracted twice with *n*-BuOH. The organic extracts were washed with water and distilled under reduced pressure until all of the easily volatilized material was removed. The residual oil weighed 1.47 g and was dissolved in CH_2Cl_2. Petroleum ether (bp 30–60 °C) was added, and a small quantity of crystals (**3**) separated. The CH_2Cl_2–petroleum ether solvents were removed from the filtrate and replaced with EtOH. To this solution was added 1.1 g (10 mmol) of phenylhydrazine and two drops of HOAc. This mixture was diluted with approximately an equal volume of water, and the resultant solution was heated to the boiling point and then allowed to cool. Yellow crystals of pyruvic acid phenylhydrazone were collected and dried: wt 0.25 g; mp 191.5–194.0 °C dec with gas evolution (lit. mp 192 °C); IR (Nujol) 3280 (NH stretching), 2600–2800 (bonded carboxyl OH), 1675 (α,β-unsaturated carboxyl carbonyl), 1660 (imine), 1450 and 1250 (CO stretching), 700–750 cm^{-1} (aromatic CH stretching). A second fraction of crystals was obtained: wt 87 mg; mp 189.5–194.0 °C dec. Total yield of pyruvic acid phenylhydrazone was 19%.

The Transamination of L-Glutamic Acid. A similar mixture containing 1.47 g (10 mmol) of L-glutamic acid was heated to the reflux temperature for 20 h. About 0.45 mL (25 mmol) of water was collected in a Dean and Stark trap during this period. The reaction mixture was allowed to cool and 30 mL of water was added. The pH was adjusted from 3.0 to 8.7 with aqueous NaOH and the crystals (**3**) were collected by filtration and dried: wt 0.21 g; mp 229.5–234.5 °C. Another fraction of **3** was obtained by concentration of the toluene portion of the filtrate, wt 0.31 g. Both of these fractions were identical with authentic **3** by IR and TLC and the total yield of **3** was 19.4%. In another experiment run exactly as above, except that dioxane was used in place of toluene, the yield of **3** was 1.21 g (45.8%).

The pH 8.7 aqueous layer that remained after the separation of the *N*-(3-phthalidyl)phthalimidine (**3**) was acidified to pH 2.0 with 6 N HCl and then extracted twice with *n*-BuOH. The organic layer was washed with water and distilled under reduced pressure until all of the easily volatilized material was removed. The oily residue was triturated with 15 mL of acetone to afford a white crystalline solid (the anhydride of **2** where R = $CH_2CH_2CO_2H$) which was recrystallized from methanol: wt 0.49 g (18.6%); mp 225.5–228.0 °C dec with gas evolution; IR (Nujol) 1770 (γ-lactone carbonyl), 1790 and 1740 (cyclic anhydride), 1050 and 950 cm^{-1} (COC stretching); ^{1}H NMR (Me_2SO-d_6) 7.7 (multiplet, 4 aromatic H's), 7.05 (singlet, 1 benzyl H

on phthalidyl ring), 3.8 (multiplet, 1 methine H on glutaric anhydride ring), 2.2 ppm (multiplet, 4 methylene H's on glutaric anhydride ring). Anal. Calcd for $C_{13}H_{11}NO_5$ (the anhydride of **2**, where R = $CH_2CH_2CO_2H$): C, 59.77; H, 4.24; N, 5.36. Found: C, 59.68, 59.78; H, 4.58, 4.43; N, 5.34, 5.89.

After separation of the above product, the remaining base-soluble, BuOH-extracted, reaction mixture was chomatographed on a silica gel column with a mixture of C_6H_6 and EtOAc (70:30) in order to obtain a fraction that corresponded to 2-ketoglutaric acid (**4**, R = $CH_2CH_2CO_2H$), wt 1.54 g. This was treated with an equal weight of semicarbazide hydrochloride and 2.3 g of NaOAc in hot aqueous EtOH. Crystals of 2-ketoglutaric acid semicarbazone separated on cooling: wt 180 mg; mp 219.5–220.5 °C dec with gas evolution (lit. mp for 2-ketoglutaric acid semicarbazone is 220 °C); IR (Nujol) 3440 (NH stretching), 2500–2700 (bonded carboxyl OH), 1640–1700 (several bands for carboxyl carbonyl, imine, and urea moieties), 1440 and 1255 cm^{-1} (CO stretching). Another fraction of 2-ketoglutaric acid semicarbazone was obtained by treatment of the pH 2.0 BuOH-extracted aqueous solution with 1.0 g of semicarbazide hydrochloride and 1.5 g of NaOAc: wt 62.4 mg; mp 211.5–214.0 °C dec with gas evolution. The total yield of this product was 243 mg (16.6%).

***N*-(3-Phthalidyl)phthalimidine (3) from Phthalimidine and *o*-Formylbenzoic Acid.** A solution of 0.80 g (6 mmol) of phthalimidine,[3] 0.90 g (6 mmol) of o-formylbenzoic acid, 1.1 mL (1.15 g, 19.2 mmol) of HOAc, and 10 mL of toluene was heated to reflux for 6 h. A trap was used to collect the water of reaction. A white solid was separated by filtrating: wt approximately 2 g: mp 238.6–242.0 °C. This was suspended in MeOH for a few minutes and the insoluble fraction was collected and dried: wt of 3 was 0.79 g (49.7%); mp 241.5–242.5 °C; IR was identical to that of the product isolated from the transamination experiments.

Registry No.—**2** (R = $CH_2CH_2CO_2H$) anhydride, 65898-29-5; **3**, 65898-30-8; **4** (R = $CH_2CH_2CO_2H$), 328-50-7; **H** (R = $CH_2CH_2CO_2H$) semicarbazone, 2704-31-6; *o*-formylbenzoic acid, 119-67-5; L-alanine, 56-41-7; pyruvic acid phenylhydrazone, 5330-70-1; L-glutamic acid, 56-86-0; phthalimidine, 480-91-1.

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Iminium Salts from α-Amino Acid Decarbonylation. Application to the Synthesis of Berbines[1]

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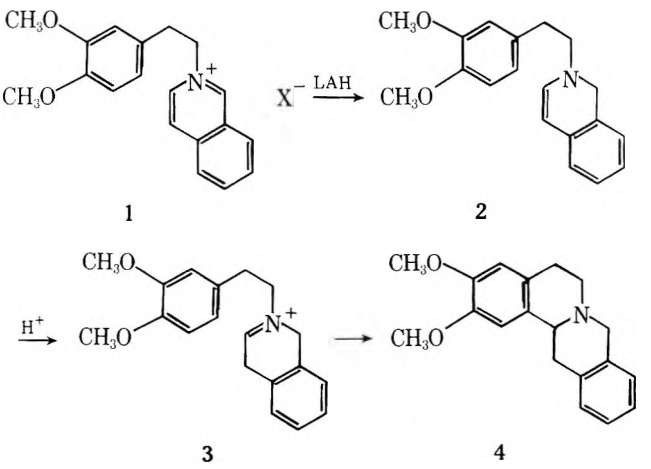
Berbines are synthesized from α-(tertiary amino) acids in high yields through decarbonylation to regiospecific iminium salts followed by an acid-catalyzed cyclization reaction. Syntheses of the α-(tertiary amino) acids from various phenylalanines which involve as the key step alkylation of a 1,2,3,4-tetrahydro-3-isoquinolinecarboxylic acid with a 2-phenylethyl bromide are described. The synthesis of isopropyl 1,2,3,4-tetrahydro-7,8-dimethoxy-3-isoquinolinecarboxylate (**15**), obligatory to the synthesis of 9,10-dimethoxyberbines by the above method, is described. It utilizes a metalation to align four contiguous substituents on the aromatic nucleus followed by a difficult selective reduction of an amide α to an ester.

A general, high-yield, regiospecific method for generating iminium salts should have broad applicability to the preparation of nitrogen-containing fused ring systems. One such system is the berbines, a class of naturally occurring and synthetic bases of the isoquinoline alkaloid group. Compounds of this type, such as 2,3-dimethoxyberbine (**4**),[2] have been synthesized via an iminium salt **3** derived from lithium aluminum hydride (LAH) reduction of an isoquinolinium salt **1**, followed by acid treatment of the dihydroisoquinoline **2** (Scheme I).

The overall yields of berbines reported for this process vary from low to moderate (18–66%).[2–4] Three factors may detract from the efficacy of generating the iminium salt by this reductive process. First, though reduction of the isoquinolinium salt with LAH produces the dihydroisoquinoline, this may be slowly reduced itself by LAH to the 1,2,3,4-tetrahydroisoquinoline.[5] Second, the resulting dihydroisoquinoline is subject to dimerization on acid treatment.[6,7] Third, dihydroisoquinolines are reported to disproportionate to a 1,2,3,4-tetrahydroisoquinoline and isoquinoline especially when a C-4 substituent is present.[8,9] In addition this classical process has significant limitations in potential substitution patterns.

We reported recently that iminium salts could be isolated from α-tertiaryamino acids by mild treatment (room temperature or warming in $POCl_3$) in high yields (>90%) and

Scheme I. Synthesis of Berbines via Partial Reduction of Isoquinolinium Salts



importantly regiospecifically by command of the position by the carboxyl substituent.[10] This decarbonylation of an α-tertiaryamino acid would avoid the pitfalls of the previous method. As a test of its effectiveness, we have applied our decarbonylative iminium salt procedure to the synthesis of a variety of berbines. Our process consists in every case of

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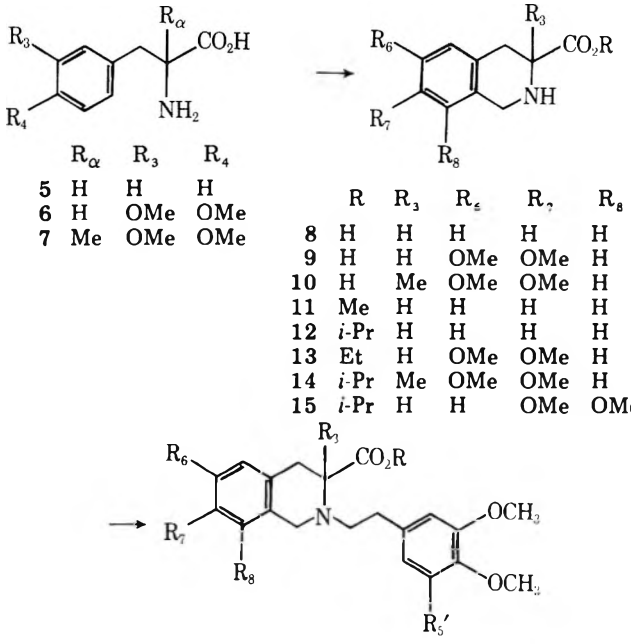
Scheme II. Phenylalanines, Tetrahydro-3-isoquinolinecarboxylates, and *N*-Phenylethylated-α-tertiaryamino Acids Required as Berbine Intermediates



	R_α	R_3	R_4
5	H	H	H
6	H	OMe	OMe
7	Me	OMe	OMe

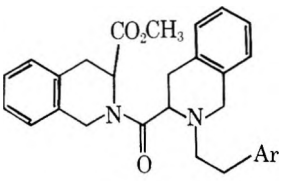
	R	R_3	R_6	R_7	R_8
8	H	H	H	H	H
9	H	H	OMe	OMe	H
10	H	Me	OMe	OMe	H
11	Me	H	H	H	H
12	*i*-Pr	H	H	H	H
13	Et	H	OMe	OMe	H
14	*i*-Pr	Me	OMe	OMe	H
15	*i*-Pr	H	H	OMe	OMe

	R	R_3	R_6	R_7	R_8	R_5'
16	*i*-Pr	H	H	H	H	H
17	Et	H	OMe	OMe	H	H
18	*i*-Pr	Me	OMe	OMe	H	H
19	Et	H	OMe	OMe	H	OMe
20	*i*-Pr	H	H	OMe	OMe	H
21	H	H	H	H	H	H
22	H	H	OMe	OMe	H	H
23	H	Me	OMe	OMe	H	H
24	H	H	OMe	OMe	H	OMe
25	H	H	H	OMe	OMe	H

essentially four steps: (1) preparation of a substituted phenylalanine, (2) ring closure to the tetrahydroisoquinoline, (3) *N*-alkylation with a 2-phenylethyl bromide, and (4) decarbonylation followed by cyclization. Steps 1 and 2 are well documented in the literature; however, new procedures have been developed for the high-yield *N*-phenylethylation, for the synthesis of 8-substituted 1,2,3,4-tetrahydroisoquinolines, and primarily for the formation of iminium salts by decarbonylation and subsequent cyclization by electrophilic aromatic substitution.

Synthesis of the α-Tertiaryamino Acids. For a direct evaluation of our method, we considered the synthesis of 2,3-dimethoxyberbine for which the required α-tertiaryamino acid is 2-[2-(3,4-dimethoxyphenyl)ethyl]-1,2,3,4-tetrahydro-3-isoquinolinecarboxylic acid (**21**). We envisioned this intermediate as being derived from phenylalanine (**5**), which when treated with formaldehyde and concentrated HCl gives 1,2,3,4-tetrahydro-3-isoquinolinecarboxylic acid (**8**) as the hydrochloride.[11] *N*-alkylation of the amino acid to produce the *N*-2-phenylethyl derivative completes the process which is summarized in Scheme II.

Alkylation of **8** was attempted reductively with phenylacetaldehyde but self-condensation products of the aldehyde necessitated chromatography to obtain a pure product. A cleaner route was sought through alkylation of the amino methyl ester **11**. Treatment of **11** with a 2-phenylethyl bromide derivative in DMF with potassium carbonate gave a low yield of the alkylated amino ester; however, **26** was a major side product. Its structure served to guide manipulation of factors necessary to avoid its formation. Increasing the steric hindrance at the carbonyl by using the isopropyl ester gave a marked improvement in the ratio of product to side product.



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Independent of the ester, adding benzene as a cosolvent favored product, indicating the transition state for acylation may be more polar than for alkylation. No reaction was observed in benzene alone, however. The bromide was found to give a better result than the *O*-tosylate, and the *O*-trichloro acetate was inert. Concentration of the reactants produced a surprising result. In experiments between 0.2 to 0.4 M in reactants in DMF/benzene, side product was suppressed enough so that even the ethyl ester could be used effectively. Thus it was found that optimum yields (75–88%) could be obtained by alkylating the ethyl or, better, isopropyl esters in DMF/benzene (1:1) at concentrations of 0.2 to 0.4 M using the 2-phenylethyl bromide.

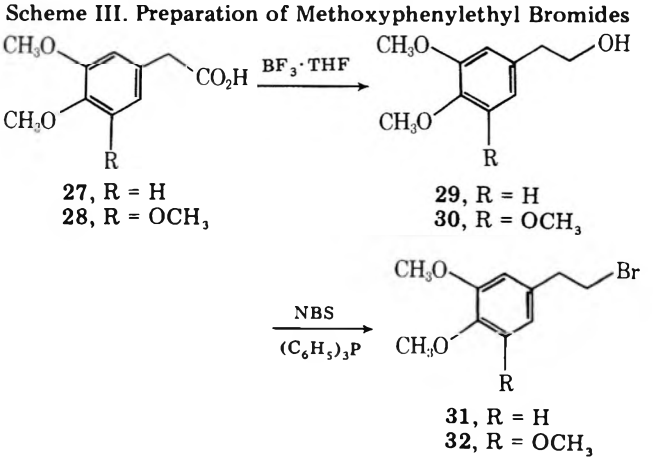
The 2-phenylethyl bromides were obtained from the readily available phenylacetic acids **27** and **28**. The acids were reduced with diborane/tetrahydrofuran to the alcohols **29** (98%) and **30** (94%), and the bromides **31** and **32** were prepared in 94% yield with the *N*-bromosuccinimide/triphenylphosphine reagent (Scheme III). The oxygenation pattern in the 2-phenylethyl bromides determined the substitution pattern in ring A of the berbines.

The isopropyl ester **12**, as well as other isopropyl esters, was prepared using 15% fuming sulfuric acid in *i*-PrOH; **12** was alkylated with 2-(3,4-dimethoxyphenyl)ethyl bromide (**31**) to give α-tertiary amino ester **16** which was hydrolyzed to *N*-phenylethylated isoquinoline carboxylic acid **21**. This process produced **21** in an overall yield of 63% from phenylalanine (**5**) and involves simple isolations.

We thought that this route to berbines could be demonstrated to be quite versatile and effective and accordingly set out to prepare five representative examples **4, 33, 34, 35,** and **36**. The versatility is derived from the ready availability of the required substituted phenylalanines. Thus **4** is derived from phenylalanine (**5**) itself as described, **33** (norcoralydine) requires 3,4-dimethoxyphenylalanine (**6**),[12] **34** requires α-methyl(3,4-dimethoxyphenyl)alanine (**7**),[13] and **35** is derived from **6** also using 2-(3,4,5-trimethoxyphenyl)ethyl bromide (**32**) to alkylate the nitrogen. The overall yields to the α-tertiaryamino acids **22** and **24** are 63 and 65%, respectively, as in the case of **21**. The yields from **14** are lower under the same conditions because hindrance of the α-methyl group retards the *N*-alkylation and subsequent ester hydrolysis; however, starting material is easily recovered.

9,10-Disubstituted Berbines. The Synthesis of Iso-

Scheme III. Preparation of Methoxyphenylethyl Bromides

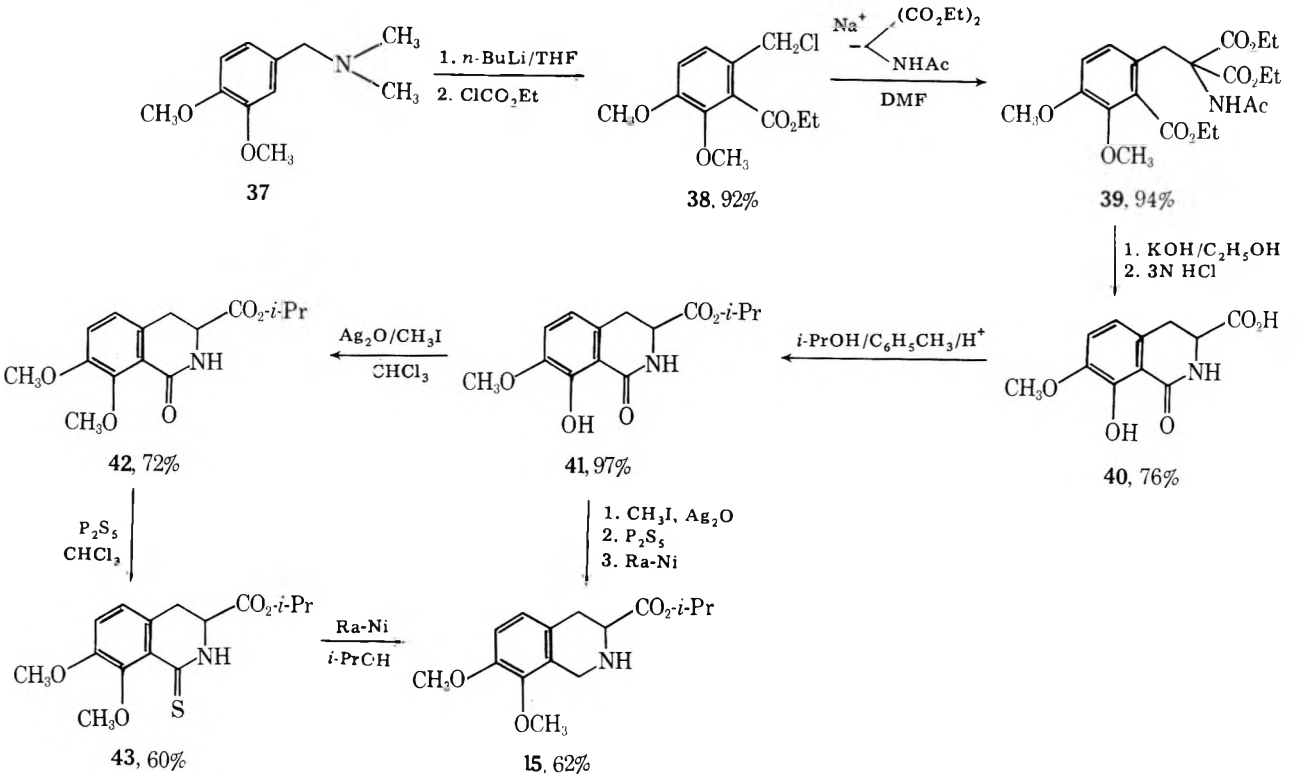


27, R = H
28, R = OCH_3

29, R = H
30, R = OCH_3

31, R = H
32, R = OCH_3

Scheme IV. Synthesis of 1,2,3,4-Tetrahydro-7,8-dimethoxy-3-isoquinolinecarboxylates



propyl 1,2,3,4-Tetrahydro-7,8-dimethoxy-3-isoquinolinecarboxylate (15). Tetrahydropalmatine (**36**) requires an unusual phenylalanine derivative since the natural tendency of the formaldehyde/H^+ type ring closure of (3,4-dimethoxyphenyl)alanine (**6**) is exclusively to the 6,7-substituted isoquinoline **9**. After investigating a number of routes to the 7,8-disubstituted 3-isoquinolinecarboxylate **15** a path was developed utilizing a metalation to align the four substituents on the aromatic ring. There is ample precedent for this procedure.[14] A number of substituents are now known which, when present on an aromatic ring, will direct the metal from an alkyllithium compound into the ortho position either preferentially or exclusively. The substituents giving the most impressive results, in terms of exclusive ortho metalation and high yield, include methyl ethers,[15] *N,N*-dimethylaminomethyls,[16] secondary and tertiary carboxamides,[17-19] secondary and tertiary sulfonamides,[20,21] fluorine,[22] secondary thioamides,[23] and oxazolines.[24] Trifluoromethyl[25] gives a fair yield of preferentially ortho metalation.

We began with the *N,N*-dimethylaminomethyl substituent because it appeared the easiest to subsequently displace after quaternization, and by necessity the other substituent would be a methyl ether. Thus with ortho directing substituents in the 1, 3, and 4 position we expected attack exclusively at C-2. There is good precedent for this also in di- and trisubstituted systems.[25,26] Once committed to this strategy the final ring would be elaborated by selective transformations at the two carbon-containing substituents. The substituent introduced via the lithium could then be a carbon in one of three oxidation states. We reasoned that the alkoxycarbonyl group was a good first choice, being chemically more stable to subsequently envisioned reactions than either a formyl or hydroxymethyl group. Final ring closure would involve a very favorable amide formation.

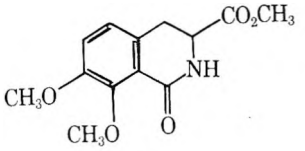
The process is shown in Scheme IV and began with metalation of (3,4-dimethoxyphenylmethyl)-*N,N*-dimethylamine (**37**). Addition of 150 mol % of ethyl chloroformate produced a 1:1 mixture of ethyl 6-(chloromethyl)-2,3-dimethoxybenzoate (**38**) and ethyl 6-(*N,N*-dimethylaminomethyl)-2,3-dimethoxybenzoate. The excess ethyl chloroformate had dealkylated the tertiary amine of the product to displace the benzyl group. This result was quite advantageous since nucleophilic displacement of a benzyl halide is more facile than that of a quaternary benzylamine. The reaction was repeated with 200 mol % of ethyl chloroformate to produce the desired benzyl chloride **38** in 92% yield, which was then treated with diethyl acetamidomalonate anion in DMF to give the substituted phenylalanine **39** in 94% yield.

Alkaline hydrolysis of one or more ester groups gave a more soluble product which was then heated with acid to effect complete amide and ester hydrolysis, decarboxylation, and ring closure to isoquinolone **40**. An *O*-methyl group was lost in the process and it was concluded that the phenolic group was at C-8 based on (1) precedent for the acid cleavage of the more hindered methyl ether;[27] (2) greater polarity on silica of the dimethoxy ester compared to the demethylated ester, suggesting hydrogen bonding of the 8-hydroxy with the 1-oxo substituent; (3) shift of the amide carbonyl from 1665 cm^{-1} in the dimethoxy case (**42**) to 1653 cm^{-1} in the hydroxy, methoxy compound **41**, strongly supporting the presence of a hydrogen bonded amine carbonyl.

Demethylation could be avoided by using only alkaline hydrolysis but yielded only 15% of the desired 1,2,3,4-tetrahydro-7,8-dimethoxy-1-oxo-3-isoquinolinecarboxylic acid (**48**). Under the alkaline conditions the *N*-acetyl was resistant to hydrolysis, possibly because of the sterically crowded environment at the adjacent tetrasubstituted carbon. However, the phenolic hydroxyl was easily and selectively methylated in the isopropyl ester with silver oxide and methyl iodide, yielding crystalline **42**. This methylation is a nearly quantitative reaction, and excess reagents or longer reaction times produced the imidate of **42** as a side product. At this point the remaining transformation for completion of the synthesis of **15** was the removal of the amide carbonyl at C-1.

The literature is surfeit with methods for the reduction of amides, a number purporting to be selective for this function

in the presence of an ester. However, with our amide **42** all methods reported to reduce the amide selectively, save one, produced either no reaction or an unsatisfactory mixture of products. The only method cleanly producing one basic product was conversion to the thioamide followed by Raney nickel desulfurization. Since these methods have broad potential applications, a brief description of our results follows. We attempted the reduction of **44** via the imidate–borohydride procedure.[28] Using trimethyloxonium tetrafluoroborate to prepare **45** followed by treatment with sodium borohydride in methanol, ethanol, or isopropyl alcohol gave only unreacted imidate **45.** Refluxing **45** in ethanol with sodium borohydride reduced the ester and not the imidate, and treatment with sodium cyanoborohydride at pH 4 gave no reaction. Amide **44** with phosphorus pentachloride/chloroform then sodium borohydride/ethanol gave no volatile products. Attempted catalytic hydrogenation of **45** in the presence of methanolic HCl and Pd/C gave no reaction. Treatment of **44** with phosphorus oxychloride followed by hydrogenation over Pd/C gave interestingly the isoquinoline **47** in low yield as the only basic product, whereas **44** with phosphorus oxychloride in the presence of hydrogen and Pd/C gave on isolation, with ethanol present, only imidate **46.** Treatment of the more hindered



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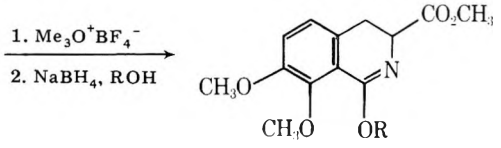
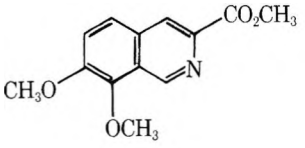


45, R = CH_3
46, R = C_2H_5



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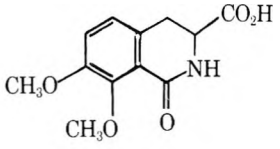

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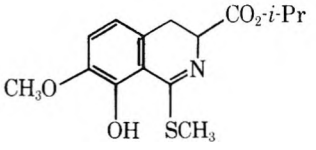

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ester **42** with (a) diborane gave a mixture of basic products, with (b) $POCl_3$, Pd/C, PtO_2, and hydrogen gave a mixture of three basic products in less than 30%, with (c) $NaBH_4$ and acetic acid[29] (1:1) in dioxane with heat gave a trace of material chromatographically similar to the desired product **15,** and (d) $NaBH_4$/acetic acid (1:1) in THF gave 20% of two basic products.

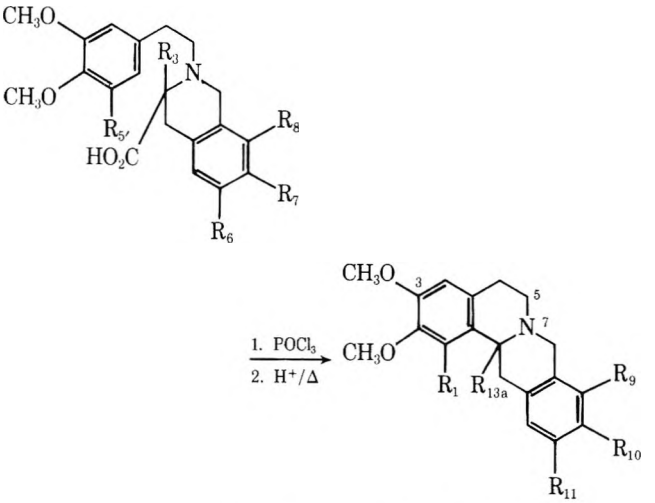
When acid **48** was treated with $NaBH_4$/acetic acid (1:1) in dioxane at reflux for 3 h, 83% of starting material was recovered, in *i*-PrOH at reflux for 3 h, 95% of starting material was recovered, and in Me_2SO at 100 °C for 5.25 h, 83% of starting material was recovered. Treatment of lactam acid **48** with trimethyloxonium tetrafluoroborate in methylene chloride followed by $NaBH_4$ in ethanol, conditions that have been reported to reduce pyroglutamic acid to glutamic acid,[30] gave a poor yield of a three-component mixture, whereas treating phenolic lactam acid **40** in the same manner gave no reaction and phenolic lactam ester **41** gave 38% of the imidate as the only basic product. Heating **48** in sodium cyanoborohydride and acetic acid gave no reaction. Finally, treating **48** with $NaBH_4/CF_3CO_2H$ (1:1) in Me_2SO at 100 °C gave a mixture of starting material and a reaction product which was not an amino acid.

The ability to reduce an amide to an amine in the presence of an ester is synthetically very useful. The problem has been addressed again recently[31] and an additional selective method is reported; however all these methods were ineffective with our substrates. As mentioned previously, we reduced this amide most productively by the classical procedure of converting first to the thioamide and then treating with Raney nickel. The thioamide was formed with P_2S_5 in $CHCl_3$ or THF. Prolonged reaction times or other solvents (dioxane) resulted in the thioamide **43** being converted to its phenolic methyl thioimidate **49,** presumably by methyl transfer from the 8-methoxyl group. Crystalline thioamide **43** could be obtained in 60% after chromatography and the desulfurization was carried out with an active Raney nickel[32,33] in a manner described[34] in 62% yield. Starting with phenolic amide **41** and proceeding through **42** and **43** to **15** without any isolations, the yield for the three transformations is 45%. The overall sequence is simple and produces pure product without complex isolations; it is delineated in Scheme IV. The subsequent alkylation of 15 and hydrolysis to the α-tertiaryamino acid **25** was carried out in the same manner as described above.

Cyclization to the Berbines. With the α-tertiaryamino acids at hand, we were ready to complete the final step of our synthesis of berbines. This consisted in the regiospecific formation of iminium salts by decarbonylation followed by electrophilic cyclization. It is presented in Scheme V for the five variations we synthesized.

Decarbonylation of the α-tertiaryamino acids **21, 22, 23, 24,** and **25** was effected by brief heating in $POCl_3$. Subsequent addition of water followed by warming cyclized the iminium salts to the berbines: **4** (79%), **33** (82%), **34** (65%), **35** (85%), and **36** (90%). Except for **34,** where the 65% yield probably reflects a steric effect, the yields were 79–90% with the overall yields of **4, 33,** and **35** from **5** and **6** greater than 50%. Cyclization of the iminium salt from **24** involved electrophilic attack ortho

Scheme V



	R_1	R_9	R_{10}	R_{11}	R_{13a}
21 → **4**	H	H	H	H	H
22 → **33**	H	H	OCH_3	OCH_3	H
23 → **34**	H	H	OCH_3	OCH_3	CH_3
24 → **35**	OCH_3	H	OCH_3	OCH_3	H
25 → **36**	H	OCH_3	OCH_3	H	H

to a methoxyl group. However, the rate of ring closure relative to that of the iminium salt derived from **22**, which does not have this methoxyl, is 4.6 times faster, indicating the steric effect of the additional methoxyl group is less important on the rate than the added electronic effect.

The cyclization yields, where direct comparison can be made to identical products, are significantly higher when the iminium salt is generated via the decarbonylation method than through the dihydroisoquinoline method. Also, the general availability of α-amino acids, the immediate precursors to the iminium salts, gives this method considerable scope. The fact that the carboxyl group is sacrificed to obtain the iminium salt allows synthetic manipulation with the carboxyl protected as the relatively inert ester function until iminium salt is needed. Also, this method potentially may yield stereospecifically synthesized berbines. Although the asymmetry at the α carbon is lost when iminium salt is formed, the tetrahydroisoquinoline intermediate may bear other chirality which in turn may exert steric influence on the iminium salt cyclization.

Experimental Section[35]

1,2,3,4-Tetrahydro-3-isoquinolinecarboxylic acid hydrochloride (8) was prepared as described[11] in 88% yield, mp 286–290 °C dec (lit.[11] mp 308–309 °C).

1,2,3,4-Tetrahydro-6,7-dimethoxy-3-isoquinolinecarboxylic Acid Hydrochloride (9). To (3,4-dimethoxyphenyl)alanine[6] (**6**, 10.41 g, 46.3 mmol) was added water (33 mL), concentrated HCl (42 mL) and 37% formaldehyde solution (42 mL, 558 mmol) and the mixture was heated at 97 °C for 20 min. The solvent was evaporated and the residue was dried in vacuo to give 12.52 g (45.7 mmol, 99%) of crude shown to be a single product by GC analysis [derivatization with *N,O*-bis(trimethylsilyl)acetamide]. A sample was recrystallized from ethanol mp 256–258 °C dec (lit.[36] mp 257 °C); however, all subsequent reactions were done using the crude product: IR 1750, 1618 cm^{-1}; NMR (CF_3CO_2H) δ 6.36 (2 H, s), 4.14–3.97 (1 H, c), 4.00–3.87 (6 H, m), 3.54–3.33 (2 H, c), 3.18–2.94 (2 H, c).

1,2,3,4-Tetrahydro-6,7-dimethoxy-3-methyl-3-isoquinolinecarboxylic Acid Hydrochloride (10). α-Methyl-(3,4-dimethoxyphenyl)alanine[13] (**7**, 12.00 g, 50.3 mmol), 37% formaldehyde solution (40 mL, 532 mmol) and 6 N HCl (95 mL) were heated at 100 °C for 35 min. The solvent was evaporated and the residue was dried in vacuo overnight to give 15.23 g; single spot by TLC and single peak by GC [derivatized by *N,O*-bis(trimethylsilyl)acetamide]. This material was used in the next step with no further purification. A sample was recrystallized from isopropyl alcohol: mp 231–233 °C dec; IR 3480, 3340, 2010, 1730, 1620, 1594 cm^{-1}; NMR (CF_3CO_2H) δ 6.93 (2 H, d), 4.87–4.51 (2 H, c), 4.04 (6 H, s), 3.57 (1 H, s), 3.45 (1 H, s), 1.99 (3 H, s). Anal. Calcd for $C_{13}H_{18}ClNO_4 \cdot H_2O$: C, 51.1; H, 6.6; N, 4.6. Found: C, 51.3; H, 6.3; N, 4.6.

Isopropyl 1,2,3,4-Tetrahydro-3-isoquinolinecarboxylate (12). To 1,2,3,4-tetrahydro-3-isoquinolinecarboxylic acid hydrochloride (**8**, 15.40 g, 71.6 mmol) in isopropyl alcohol (473 mL) was added 15% fuming sulfuric acid (40 mL, 161 mmol of SO_3) and the mixture was refluxed. After 90 min, benzene (600 mL) was added, and the solution was refluxed through 4A molecular sieves for 15 h. The solvent was evaporated and the residue was treated with 2 N NaOH (500 mL) and crushed ice and extracted with chloroform (200, 100, 50 mL). Drying, evaporating, and distilling to 125 °C (0.08 Torr) gave 14.02 g (64.0 mmol, 89%) of ester: IR 1737, 3350 cm^{-1}; NMR δ 6.94 (4, H, c), 5.02 (1 H, c), 3.94 (2 H, s), 3.65–3.35 (1 H, pr d), 2.95–2.71 (2 H, c), 2.13 (1 H, s), 1.22 (6 H, d).

Ethyl 1,2,3,4-Tetrahydro-6,7-dimethoxy-3-isoquinolinecarboxylate (13). To the crude amino acid **9** (7.12 g, 26.0 mmol) was added ethanol (125 mL), the mixture was heated to reflux, and thionyl chloride (4.0 mL, 55.7 mmol) was added dropwise. Reflux was continued for 5 h and the solvent was evaporated; to the residue was added water (150 mL) and 20% Na_2CO_3 solution (50 mL). The mixture was quickly extracted with CH_2Cl_2 (50, 35, 15 mL), the extracts were dried and evaporated, and the crystalline residue was distilled to 145 °C (0.3 Torr) to give 6.31 g (23.9 mmol, 92%) of the ethyl ester **13**: mp 81–84 °C; IR 3350, 1735, 1612 cm^{-1}; NMR δ 6.57 (2 H, d), 4.25 (2 H, q), 4.05 (2 H, d), 3.87 (6 H, s), 3.80–3.59 (1 H, c), 3.05–2.80 (2 H, c), 2.14 (1 H, s), 1.30 (3 H, t); MS *m/e* (rel intensity) 265 (12), 236 (9), 206 (5), 193 (13), 192 (100), 190 (30), 161 (27).

Isopropyl 1,2,3,4-Tetrahydro-6,7-dimethoxy-3-methyl-3-isoquinolinecarboxylate (14). Amino acid **10** (14.02 g, 46.4 mmol), isopropyl alcohol (675 mL), and *p*-toluenesulfonic acid (8.93 g, 47.0 mmol) were refluxed through 4A molecular sieves for 1 day, after which 15% fuming H_2SO_4 (4.5 mL, 16.0 mmol of SO_3) and toluene (50 mL) were added and refluxing continued until no starting acid remained (TLC, 20 days), replacing the sieves periodically. The solvent was evaporated, methylene chloride (100 mL) and saturated sodium carbonate solution (100 mL) were added to the residue, the organic layer was dried and evaporated, and the residue was distilled to 138 °C (0.08 Torr) to give 12.63 g (43.1 mmol, 93%) of the isopropyl ester **14**: mp 57–60 °C; IR 3315, 2845, 1720, 1610 cm^{-1}; NMR δ 6.56 (2 H, d), 5.0 (1 H, m), 4.03 (2 H, s, broad), 3.87 (6 H, d), 3.20 (1 H, d), 2.65 (1 H, d), 2.20 (1 H, s), 1.40 (3 H, s), 1.17 (6 H, t); MS *m/e* (rel intensity) 293 (3), 250 (4), 220 (2), 206 (100).

Isopropyl 1,2,3,4-Tetrahydro-7,8-dimethoxy-3-isoquinolinecarboxylate (15). A. From 41. To **41** (1.37 g, 4.90 mmol) was added $CHCl_3$ (20 mL), Ag_2O (1.35 g, 5.80 mmol), and CH_3I (0.82 mL, 13.6 mmol) and the mixture was shaken at room temperature for 39 h. The catalyst was removed and the solvent was evaporated to leave a residue of 1.44 g (4.90 mmol) to which was added $CHCl_3$ (58 mL) and P_2S_5 (1.44 g, 32.4 mmol of S) and this mixture was heated at reflux for 40 min. After addition of saturated Na_2CO_3 solution (200 mL) and water (50 mL) the $CHCl_3$ layer was separated and the aqueous phase was extracted further with $CHCl_3$ (2 × 20 mL) and then ether (20 mL). The combined organic extracts were washed with saturated NaCl solution (70 mL), dried, and evaporated. Isopropyl alcohol (100 mL) and Raney nickel (8.35 g, W-4) were added to the residue of 1.60 g and the mixture was heated at reflux for 20 min, the catalyst was removed and washed with boiling isopropyl alcohol (4 × 25 mL), the solvent was evaporated, and the residue was distilled to 130 °C (0.03 Torr) to give 614 mg (2.20 mmol, 45%) of isopropyl ester **15**: NMR δ 6.72 (2 H, s), 5.03 (1 H, m), 4.27 (1 H, d, J_{ab} = 16 Hz), 3.87 (1 H, d, J_{ab} = 16 Hz), 3.80 (6 H, d), 3.70–3.44 (1 H, c), 3.00–2.75 (2 H, c), 2.30 (1 H, s), 1.29 (6 H, d); IR 3340, 1739 cm^{-1}. $C_{15}H_{21}NO_4$ requires 279.1470; found 279.1459.

B. From 42. To **42** (2.84 g, 9.70 mmol) was added $CHCl_3$ (100 mL) and P_2S_5 (2.84 g, 64.1 mmol of sulfur), the mixture was heated at reflux for 40 min and then poured into saturated Na_2CO_3 solution (300 mL), and the aqueous phase was extracted with $CHCl_3$ (2 × 25 mL) and then with ether (50 mL). The combined organic extracts were dried and evaporated to give 2.80 g of residue which was dissolved in isopropyl alcohol (150 mL); Raney nickel (7.7 g, W-4) was added and the solution refluxed for 15 min. More Raney nickel (7.7 g, W-4) was added and refluxing was continued for 17 min. The catalyst was removed and washed with boiling isopropyl alcohol (2 × 25 mL), the solvent was evaporated, and the residue was distilled to 130 °C (0.01 Torr) to give 1.22 g (4.36 mmol, 45%) of isopropyl ester **15**.

C. From 43. To **43** (110 mg, 0.356 mmol) was added isopropyl alcohol (5 mL) then Raney nickel (1.1 g, W-4) and the mixture was refluxed for 20 min. The catalyst was removed and washed successfully with isopropyl alcohol (5 mL), $CHCl_3$ (5 mL), and acetone (5 mL), and the filtrates were combined and evaporated to give the isopropyl ester **15** (64 mg, 0.22 mmol, 62%).

Isopropyl 2-[2-(3,4-Dimethoxyphenyl)ethyl]-1,2,3,4-tetrahydro-3-isoquinolinecarboxylate (16). Amino ester **12** (8.054 g, 38.9 mmol) in benzene/DMF (100 ml, 1/1), potassium carbonate (13.8 g, 100 mmol), and 2-(3,4-dimethoxyphenyl)ethyl bromide (11.9 g, 48.6 mmol) were heated at reflux for 21.5 h, the mixture was cooled, and water (250 mL) and ether (150 mL) were added. After separation, the aqueous layer was re-extracted with ether (50 mL), the combined organic phase was washed with water (200 mL) and 0.1 N HCl (70 mL), and the product was then extracted quantitatively from the organic phase with 1 N HCl (3 × 100 mL). These extracts were basified (K_2CO_3) and extracted into ether (150, 50 mL), dried, and evaporated and the residue was distilled at 180 °C (0.06 Torr) to give 12.5 g (32.7 mmol, 84%) of amino ester **16**: IR 1725 cm^{-1}; NMR (CCl_4) δ 7.02 (4 H, s), 6.68 (3 H, s), 4.91 (1, H, c), 3.97 (2 H, c), 3.72 (6 H, s), 3.66 (1 H, s), 3.17–2.67 (6 H, c), 1.12 (3 H, d), 1.06 (3 H, d).

Ethyl 2-[2-(3,4-Dimethoxyphenyl)ethyl]-1,2,3,4-tetrahydro-6,7-dimethoxy-3-isoquinolinecarboxylate (17). This was prepared from amino ester **13** in the same manner as described for **16** and distilled to 215 °C (0.08 Torr) to give **17** in 88% yield: mp 100–102 °C; IR 1730, 1615, 1591 cm^{-1}; NMR δ 6.73 (3 H, s), 6.55 (2 H, d), 5.05 (1 H, m), 4.10–3.87 (2 H, c), 3.85 (12 H, s), 3.80–3.51 (1 H, m), 3.10–2.74 (4 H, c), 1.33–1.05 (6 H, c); MS *m/e* (rel intensity) 443 (0.4), 356 (12), 292 (24), 165 (19).

Isopropyl 2-[2-(3,4-Dimethoxyphenyl)ethyl]-1,2,3,4-tetrahydro-6,7-dimethoxy-3-methyl-3-isoquinolinecarboxylate (18). The amino ester **14** (5.86 g, 20 mmol) was alkylated with the ethyl bromide **31** as described for the preparation of **16** but heating for 91.5

h. Distillation to 150 °C (0.04 Torr) gave 2.6 g of recovered **14**; continued distillation to 190 °C (0.09 Torr) gave 4.67 g (10.2 mmol, 76%) of alkylated ester **18**: IR 2850, 1723, 1614, 1590 cm^{-1}; NMR δ 6.72 (3 H, s), 6.50 (2 H, s), 4.94 (1 H, m), 3.92 (2 H, s, broad), 3.80 (12 H, s), 3.05–2.50 (6 H, c), 1.30 (3 H, s), 1.14 (3 H, d), 1.09 (3 H, d); MS *m/e* (rel intensity) 455 (2), 370 (39), 306 (94), 165 (100).

Ethyl 2-[2-(3,4,5-trimethoxyphenyl)ethyl]-1,2,3,4-tetrahydro-6,7-dimethoxy-3-isoquinolinecarboxylate (19) was prepared in the manner described for **16** starting with amino ester **13** and the phenylethyl bromide **32**. Distillation at 140–200 °C (0.08 Torr) gave **19** in 80% yield: mp 92–94 °C; IR 2840, 1728, 1610, 1588 cm^{-1}; NMR δ 6.63–6.57 (4 H, c), 4.30–4.07 (3 H, c), 3.84 (15 H, s), 3.78–3.28 (2 H, c), 3.11–2.81 (6 H, c), 1.17 (3 H, t); MS *m/e* (rel intensity) 459 (3), 386 (15), 279 (17), 280 (100), 250 (17).

Isopropyl 2-[2-(3,4-dimethoxyphenyl)ethyl]-1,2,3,4-tetrahydro-7,8-dimethoxy-3-isoquinolinecarboxylate (20) was prepared from amino ester **15** in the manner described for the preparation of **16** and distilled collecting the fraction between 150 and 185 °C (0.05 Torr) to give 1.91 g (4.30 mmol, 75.9%) of **20**: NMR δ 6.72 (5 H, s), 4.94 (1 H, m), 3.99 (2 H, s), 3.81 (12 H, d), 3.71–3.51 (1 H, c), 3.07–2.84 (6 H, c), 1.15 (6 H, d); IR 1728, 1610, 1590 cm^{-1}; MS *m/e* (rel intensity) 443 (2), 292 (100).

2-[2-(3,4-Dimethoxyphenyl)ethyl]-1,2,3,4-tetrahydro-3-isoquinolinecarboxylic Acid (21). Amino ester **16** (12.16 g, 31.8 mmol), 95% ethanol (50 mL), and KOH (3.8 g, 60 mmol) were refluxed for 2 h (hydrolysis complete by GC) after which the solvent was evaporated. To the residue was added water (70 mL), the solution was filtered, and 1 N HCl was added until pH 9. After standing overnight, the solution was acidified with 1 N HCl to pH 4, giving 10.41 g (30.6 mmol, 96%) of acid **21**: mp 131–135 °C dec; mp 157 °C dec after recrystallization from methanol. Anal. Calcd for $C_{20}H_{23}NO_4$: C, 70.4; H, 6.8; N, 4.1. Found: C, 70.1; H, 6.8; N, 4.2.

2-[2-(3,4-Dimethoxyphenyl)ethyl]-1,2,3,4-tetrahydro-6,7-dimethoxy-3-isoquinolinecarboxylic acid (22) was prepared in 82% yield by hydrolysis of the corresponding ester **17** as described above. A sample was recrystallized from methanol: mp 179–182 °C dec; IR 3520, 1659, 1612 cm^{-1}; NMR (CF_3CO_2H) δ 8.22–7.58 (1 H, br), 6.92 (1 H, br), 4.92–4.36 (3 H, c), 3.95 (12 H, s), 3.86–3.00 (6 H, c). Anal. Calcd for $C_{22}H_{27}NO_6 \cdot {}^1/_4 H_2O$: C, 65.1; H, 6.8; N, 3.5. Found: C, 65.1; H, 6.8; N, 3.6.

2-[2-(3,4-Dimethoxyphenyl)ethyl]-1,2,3,4-tetrahydro-6,7-dimethoxy-3-methyl-3-isoquinolinecarboxylic Acid (23). To amino ester **18** (4.38 g, 9.6 mmol) was added 95% ethanol (50 mL) and KOH (600 mg, 10.8 mmol) and the mixture was refluxed for 72 h. More water (10 mL) and KOH (300 mg, 5.4 mmol) were added and reflux continued for 3 days. The solvent was evaporated, water (50 mL) and ether (50 mL) were added to the residue, and the ether layer was dried and evaporated to give 1.58 g, 3.46 mmol, of recovered starting material. The aqueous layer was adjusted to pH 6.0 with 6 N HCl, and after reducing the volume to 15 mL, it was extracted with chloroform (3 × 15 mL). Drying and evaporating the chloroform gave 2.47 g (5.90 mmol, 97% based on recovered **18**) of acid **23**: mp 189–192 °C dec; IR ($CDCl_3$) 2840, 2580, 2240, 1620, 1513 cm^{-1}; NMR δ 10.28 (1 H, s, br), 6.65 (5 H, s), 4.57 (2 H, s, br), 3.87 (6 H, s), 3.80 (3 H, s), 3.72 (3, H, s), 3.46–2.95 (6 H, c), 1.59 (3 H, s). Anal. Calcd for $C_{23}H_{29}NO_6$: C, 66.5; H, 7.0; N, 3.4. Found: C, 66.2; H, 7.0; N, 3.4.

1,2,3,4-Tetrahydro-6,7-dimethoxy-[2-(3,4,5-trimethoxyphenyl)ethyl]-3-isoquinolinecarboxylic acid (24) was prepared by hydrolysis of ester **19** in the manner described above to give crystalline amino acid **24** in 88% yield: mp 110–112 °C, resolidified at 142 °C, melts again 188–191 °C dec; IR 3430, 1654, 1626, 1587 cm^{-1}; NMR (CF_3CO_2H) δ 7.02–6.72 (4 H, c), 5.05–4.40 (3 H, c), 4.02 (15 H, s), 3.81–3.08 (6 H, c). Anal. Calcd for $C_{23}H_{29}NO_7$: C, 64.0; H, 6.8; N, 3.3. Found: C, 63.8; H, 6.8; N, 3.3.

2-[2-(3,4-Dimethoxyphenyl)ethyl]-1,2,3,4-tetrahydro-7,8-dimethoxy-3-isoquinolinecarboxylic acid (25) was prepared by hydrolysis of **20** and was isolated as described in the preparation of **21**. Crystals which formed slowly over a 16-h period were collected, washed with water (5 mL), and dried to give 1.38 g (3.45 mmol, 84%) of acid **25**: mp 162–164 °C dec; NMR δ 6.77–6.56 (6 H, m), 4.40–4.17 (2 H, d), 3.87–3.57 (1 H, c), 3.76 (12 H, s), 3.24–2.80 (6 H, c); IR 3570, 3450, 1655 cm^{-1}. Anal. Calcd for $C_{22}H_{27}O_6N$: C, 65.8; H, 6.8; N, 3.5. Found: C, 65.6; H, 6.7; N, 3.4.

2-(3,4-Dimethoxyphenyl)ethanol (29). To (3,4-dimethoxyphenyl)acetic acid in THF (30 mL) at 0 °C was added BH_3·THF (99 mL, 1 M in THF, 99 mmol) over 15 min. The mixture was stirred at room temperature for 2 days and then quenched by slowly adding THF/water (1/1, 30 mL) and potassium carbonate (excess, until H_2O layer saturated). The layers were separated, the aqueous layer was extracted with ether (3 × 50 mL), the combined organic extracts were dried and evaporated, and the residue was distilled at 110 °C (0.2 Torr) to give 13.38 g (73.5 mmol, 98%) of alcohol **29**: mp 44–45 °C (lit.[37] mp 44.5–45.0 °C).

2-(3,4,5-Trimethoxyphenyl)ethanol (30). To (3,4,5-trimethoxyphenyl)acetic acid (38.9 g, 0.172 mol) in THF (100 mL) was added BH_3·THF (200 mL, 1 M in THF, 200 mmol) while cooling in an ice bath, over 20 min. The mixture was allowed to stir overnight and excess hydride was destroyed by slowly adding H_2O/THF (100 mL, 1/1) then potassium hydroxide (ca. 25 g, 0.4 mol). Solvent was evaporated, the residue was extracted with ether (3 × 100 mL), and the ether was dried and evaporated. Distillation of the residue at 170 °C (0.25 Torr) gave 34.2 g (0.162 mol, 94%) of alcohol **30**: mp 39–40 °C (previously reported[38] as an oil); IR 3450 cm^{-1}; NMR δ 6.5 (2 H, s), 3.8 (9 H, s), 3.8 (2 H, t), 2.8 (2 H, t), 2.4 (1 H, s). Anal. Calcd for $C_{11}H_{16}O_4$: C, 62.2; H, 7.6. Found: C, 62.1; H, 7.6.

2-(3,4-Dimethoxyphenyl)ethyl Bromide (31). To 2-(3,4-dimethoxyphenyl)ethanol (13.12 g, 72 mmol) dissolved in benzene (70 mL) was added triphenylphosphine (26.3 g, 80 mmol). The mixture was cooled in an ice bath and NBS (13.3 g, 75.0 mmol) was added portionwise such that the internal temperature did not rise above 10 °C. After the addition the ice bath was removed, the mixture was allowed to stir for 1 h, 10% $Na_2S_2O_3$ solution (70 mL) was added, and the two phases were separated. The organic layer was extracted with 1 N NaOH (70 mL) and then water (70 mL), extracting each aqueous layer with ether (20 mL), and the combined organic layers were dried and evaporated. To the residual oil was added ether (125 mL) to precipitate triphenylphosphine oxide, the solution was filtered, and the filtrate was evaporated and distilled to 110 °C (0.1 Torr) to give 16.62 g (67.9 mmol, 94%) of bromide **31**, mp 51–52 °C, on crystallization from ethanol (lit.[39] mp 47–50 °C).

2-(3,4,5-Trimethoxyphenyl)ethyl Bromide (32). To 2-(3,4,5-trimethoxyphenyl)ethanol (**30**) (33.9 g, 160 mmol) in benzene (170 mL) was added triphenylphosphine (42.2 g, 160 mmol), the mixture was cooled to 0 °C, and NBS (28.8 g, 160 mmol) was added portionwise keeping the temperature below 10 °C. The mixture was then allowed to reach room temperature and stirred for 16 h after which it was filtered and washed with 5% $Na_2S_2O_3$ (150 mL), then 0.5 N NaOH (2 × 150 mL), and finally saturated NaCl (150 mL). The benzene was evaporated, ether (250 mL) was added, the precipitated triphenylphosphine oxide was removed after cooling, and the filtrate was passed through an alumina filter. The filtrate was evaporated and the residue distilled to 120 °C (0.2 Torr) (lit.[40] bp 92–96 °C (1 μm)) to give 41.3 g (150 mmol, 94%) of bromide **32**: mp 30–31 °C; MS *m/e* (rel intensity) 276 (61), 274 (61), 261 (24), 259 (25), 195 (31), 181 (100), 179 (28); IR 1587, 1507, 1457, 1418 cm^{-1}; NMR δ 6.4 (2 H, s), 3.9 (9 H, s), 3.7–3.4 (2 H, c), 3.3–2.9 (2 H, c). Anal. Calcd for $C_{11}H_{15}O_3Br$: C, 48.0; H, 5.5. Found: C, 48.2; H, 5.5.

5,8,13,13a-Tetrahydro-2,3-dimethoxy-6*H*-dibenzo[*a,g*]quinolizine; 2,3-Dimethoxyberbine (4). To amino acid **21** (341 mg, 1.0 mmol) was added phosphorus oxychloride (1.0 mL, 10.95 mmol) and the mixture was heated for 2.5 min in a 100 °C bath, with vigorous stirring, then cooled quickly in an ice bath. Through the condensor was added concentrated HCl (10 mL) with vigorous stirring, and the mixture was heated at 50–53 °C for 22 h. The contents of the flask were emptied into a separatory funnel, basified with excess K_2CO_3, and extracted with chloroform (2 × 50 mL). The aqueous layer was dried and evaporated and the dark red residue was dissolved in acetone (5 mL). To this was added concentrated HCl (1.0 mmol) and a white solid precipitated, which was collected, washed with acetone, and dried to give 263 mg (0.793 mmol, 79%) of berbine **4** hydrochloride, mp 236–239 °C dec and mp 238–241 °C after recrystallization from ethanol/ether (lit.[2a] mp 236–238 °C dec).

5,8,13,13a-Tetrahydro-2,3,10,11-tetramethoxy-6*H*-dibenzo[*a,g*]-quinolizine; Norcoralydine (33). A. Isolation as the Hydrochloride. To amino acid **22** (203 mg, 0.505 mmol) was added $POCl_3$ (1.0 mL), the mixture was immersed in a 70 °C bath and stirred vigorously for 9.0 min and then cooled in an ice bath and water (11 mL) added all at once with vigorous stirring. The mixture was then heated at 100 °C for 1 h, the volume was reduced to 2 mL, the mixture was cooled, and the crystals were collected by filtration, washed with ether (2 × 3 mL), and dried to yield 169 mg, mp 132–138 °C, which was a mixture of H_3PO_4 (48%) and HCl (52%) salts. The crystalline solid was sustended in water (50 mL), 6 N HCl (1.0 mL) was added, the mixture was extracted with chloroform (2 × 17 mL), NaCl solution (150 mL) was added, and again the mixture was extracted with chloroform (17 mL). The chloroform extracts were filtered, the filtrate was evaporated, and the residue was dried to give 154 mg (0.394 mmol, 78%) of pure hydrochloride: mp 220–222 °C (lit.[41] mp 220–221 °C); IR 3450, 2530, 1615 cm^{-1}; NMR (CF_3CO_2H) δ 6.97–6.70 (4 H, c), 4.65 (3 H, c, br), 3.98 (12 H, s), 3.81–2.91 (6 H, c).

A portion of the hydrochloride was added to water, basified with 20% Na_2CO_3, and extracted into chloroform. The residue on evaporation was recrystallized from ethanol/water (1:1): mp 146–147 °C (lit.[42] mp 146 °C, α form); NMR ($CDCl_3$) δ 7.26 (1 H, s), 6.76–6.53 (3 H, c), 3.90 (12 H, m), 3.80–2.35 (9 H, c); MS *m/e* (rel intensity) 355 (1).

B. Isolation as the Hydrofluoroborate. After reaction as described above, the water was evaporated and to the residue was added water (30 mL) and 48% hydrofluoroboric acid (0.6 mL), followed by ethanol (5 mL) addition at the boiling point to dissolve all solid. The solution was cooled and the resulting crystals, 185 mg, 0.42 mmol, 82%, melted at 235–238 °C dec after recrystallized from acetone. Anal. Calcd for $C_{21}H_{26}BF_4NO_4$: C, 56.9; H, 5.9; N, 3.2. Found: C, 56.9; H, 5.8; N, 3.2.

5,8,13,13a-Tetrahydro-2,3,10,11-tetramethoxy-13a-methyl-6*H*-dibenzo[*a,g*]quinolizine; 2,3,10,11-Tetramethoxyberbine (34). The amino acid **23** (215 mg, 0.51 mmol) and phosphorus oxychloride (1.0 mL, 10.95 mmol) were heated at 73 °C for 5 min then cooled in an ice bath and water was (11 mL) added. The solution was heated at 100 °C for 4 h, cooled, poured into 2 N NaOH (30 mL), and the precipitate collected after 16 h to give 122 mg (0.33 mmol, 65%) of **34**, mp 101–104 °C after recrystallized from acetone/water: IR 1614, 1591 cm^{-1}; NMR (CF_3CO_2H) δ 6.92–6.65 (4 H, c), 4.89 (2 H, s, br), 4.36 (2 H, t), 4.07 (2 H, s, br), 3.99 (6 H, s), 3.92 (3 H, s), 3.70 (3 H, s), 3.18 (2 H, t), 2.40 (3 H, s); MS *m/e* (rel intensity) 371 (4), 370 (27), 269 (100), 354 (13), 231 (22), 218 (96), 203 (23). Anal. Calcd for $C_{22}H_{27}NO_4$: C, 71.5; H, 7.4; N, 3.8. Found: C, 71.3; H, 7.3; N, 3.7.

5,8,13,13a-Tetrahydro-1,2,3,10,11-pentamethoxy-6*H*-dibenzo[*a,g*]quinolizine; 1,2,3,10,11-Pentamethoxyberbine (35). A. Isolation as Hydrofluoroborate Salt. To amino acid **24** as the half hydrate (230 mg, 0.522 mmol) was added phosphorus oxychloride (1.0 mL, 11 mmol) and the mixture was heated with vigorous stirring at 70 °C for 7.0 min and then cooled thoroughly in an ice bath before adding water (11 mL). The mixture was then heated at 100 °C for 45 min, diluted to 30 mL with water, and 48% HBF_4 (0.6 mL) was added. A light yellow precipitate formed which was removed and dried to give 46 mg (0.1 mmol) and a second crop of 150 mg (0.32 mmol, total 0.42 mmol, 79%) was obtained by reducing the volume of the mother liquor to 10 mL and cooling: mp 229–232 °C; IR 3180, 1612, 1600, 1588 cm^{-1}; NMR (CF_3CO_2H) δ 6.97 (1 H, s), 6.90 (1 H, s), 6.80 (1 H, s), 5.34–4.95 (1 H, c), 4.77–4.40 (2 H, c), 4.20 (3 H, s), 4.12 (3 H, s), 4.02 (9 H, s), 3.84–3.02 (6 H, c). Anal. Calcd for $C_{22}H_{28}BF_4NO_5$: C, 55.8; H, 6.0; N, 3.0. Found: C, 55.7; H, 6.0; N, 3.0.

B. Isolation as the Free Base. After reaction as above, the mixture was cooled, poured into 1 N NaOH (60 mL) and ice (40 mL), and the precipitate collected by filtration, washed thoroughly with water, and dried. Two additional crops were obtained from the mother liquor; total, 164 mg, 0.43 mmol, 84.5% of **35**: mp 151–152 °C (lit.[43] mp 154–155 °C); IR 3620, 2805, 2760, 1612, 1580 cm^{-1}; NMR δ 6.63 (2 H, d), 6.48 (1 H, s), 3.91 (15 H, m), 3.84–2.40 (9 H, c); MS *m/e* (rel intensity) 385 (6), 220 (18), 164 (100).

5,8,13,13a-Tetrahydro-2,3,9,10-tetramethoxy-6*H*-dibenzo-[*a,g*]quinolizine; Tetrahydropalmatine (36). A. Isolation as the Free Base. Amino acid **25** (203 mg, 0.51 mmol) and $POCl_3$ (1.0 mL, 11 mmol) were heated at 70 °C for 10 min and cooled in an ice bath, water (11 mL) was added, and the solution was heated at reflux for 1 h and then poured into 2 N NaOH (30 mL) and ice (30 mL) to give a total of 161 mg (0.45 mmol, 90%) of **36**: mp 145–146 °C from ethanol/H_2O (lit.[44] mp 147 °C); NMR δ 6.90 (2 H, slightly broadened singlet with a small peak downfield at 7.00, J_{ab} = 8 Hz), 6.77 (1 H, s), 6.65 (1 H, s), 3.95 (12 H, c), 3.74–2.52 (9 H, c); MS *m/e* (rel intensity) 356 (19), 355 (81), 354 (46), 353 (18), 324 (16).

B. Isolation as the Hydrochloride. The reaction was performed as described above, omitting the final NaOH and H_2O treatment. Cooling at room temperature for 16 h gave 154 mg (0.39 mmol, 78%) of **36** HCl: mp 227–228 °C dec (lit.[44] mp 215–216 °C) and 206–208 °C after recrystallization from CH_3OH/H_2O; NMR (CF_3CO_2H) δ 7.07 (2 H, s), 6.87 (1 H, s), 6.78 (1 H, s), 5.20–4.35 (3 H, s), 4.00 (12 H, c), 3.87–2.90 (6 H, c); IR 3570, 3450, 3380, 2600, 1612 cm^{-1}. Anal. Calcd for $C_{21}H_{26}ClNO_4$: C, 64.4; H, 6.7; N, 3.6. Found: C, 64.1; H, 6.9; N, 3.5.

Ethyl 6-Chloromethyl-2,3-dimethoxybenzoate (38). To [(3,4-dimethoxyphenyl)methyl]-*N,N*-dimethylamine (**37**)[43] (39 g) in THF (500 mL) cooled in an ice bath was added *n*-butyllithium (121 mL of 1.82 M in hexane, 220 mmol), the mixture was stirred at 0 °C for 1 h and then cooled to −78 °C, $ClCO_2Et$ (45.6 g, 420 mmol) was added all at once, and the mixture was then stirred at room temperature for 12 h. The solvent was evaporated and to the residue was added CH_2Cl_2 (150 mL) then water (100 mL). The aqueous layer was extracted again with CH_2Cl_2 (50 mL) and the combined organic extracts were dried and evaporated and the residue was distilled to 130 °C (0.04 Torr) to give 47.3 g (183 mmol, 92%) of **38**: NMR δ 7.08 (2 H, d, J_{ab} = 8 Hz), 6.85 (2 H, d, J_{ab} = 8 Hz), 4.60 (2 H, s), 4.43 (2 H, q), 3.87 (6 H, d), 1.40 (3 H, t); IR 1728, 1601, 1584 cm^{-1}; MS *m/e* (rel intensity) 260 (11), 259 (5), 258 (32), 212 (100).

Diethyl 1-Acetamido-2-(2-ethoxycarbonyl-3,4-dimethoxyphenyl)-1,1-ethanedicarboxylate (39). To NaH (2.16 g of a 50% dispersion in oil, 45 mmol) washed with hexane (3 × 10 mL) was added DMF (60 mL) followed by diethyl acetamidomalonate (9.76 g, 45 mmol) in portions with stirring. After being stirred for 2.5 h at room temperature the mixture was filtered into ethyl 6-chloromethyl-2,3-dimethoxybenzoate (**38**) (8.38 g, 32.4 mmol) and stirred at room temperature for 14 h, after which the dimethylformamide was evaporated and water (200 mL) was added. Extraction with benzene (100, 50, 50 mL), drying, and evaporating left a residue which was distilled, collecting the fraction between 155–190 °C (0.03 Torr) to give 13.4 g (30.5 mmol, 94%) of **39**: NMR δ 6.93–6.47 (3 H, c), 4.55–4.05 (6 H, c), 3.85 (6 H, s), 3.60 (2 H, s), 2.01 (3 H, s), 1.50–1.10 (9 H, c); IR 3420, 1738, 1672 cm^{-1}; MS *m/e* (rel intensity) 440 (3), 439 (12), 394 (3), 380 (27).

1,2,3,4-Tetrahydro-8-hydroxy-7-methoxy-1-oxo-3-isoquinolinecarboxylic Acid (40). To malonate **39** (2.49 g, 5.7 mmol) in ethanol/H_2O (36.4 mL/3.6 mL) was added KOH (1.3 g, 23 mmol) and the mixture was refluxed for 1.25 h, the solvent was evaporated, and 3 N HCl (140 mL) was added. This mixture was refluxed for 18 h, decolorizing carbon was added, and the solution was filtered hot and allowed to stand for two days to give 1.026 g (4.3 mmol, 76%) of **40**: mp 250–251 °C; NMR (Me_2SO-d_6) δ 8.53–8.40 (1 H, d, br), 6.98 (1 H, d, J_{ab} = 8 Hz), 6.58 (1 H, d, J_{ab} = 8 Hg), 4.37–4.10 (1 H, c), 3.77 (3 H, s), 3.25–3.02 (2 H, c); IR 3250, 1725, 1624 cm^{-1}. Anal. Calcd for $C_{11}H_{11}NO_5$: C, 55.7; H, 4.7; N, 5.9. Found: C, 55.6; H, 4.7; N, 5.9.

Isopropyl 1,2,3,4-Tetrahydro-8-hydroxy-7-methoxy-1-oxo-3-isoquinolinecarboxylate (41). Acid **40** (3.55 g, 15 mmol), isopropyl alcohol (75 mL), and 100% H_2SO_4 (10 drops) were refluxed for 2 h, then toluene was added and the solution was refluxed through 4A molecular sieves for 48 h, replacing the molecular sieves twice. The solvent was evaporated, the residue was dissolved in $CHCl_3$ (100 mL) and washed with 50% saturated $NaHCO_3$ (100 mL), the aqueous phase was backwashed with $CHCl_3$ (20 mL) and the combined organic layers were dried and evaporated to give 4.05 g (14.5 mmol, 97%) of **41**: mp 123–124 °C; NMR δ 12.38 (1 H, s), 6.86 (1 H, d, J_{ab} = 8 Hz), 6.53 (1 H, d, J_{ab} = 8 Hz), 6.50 (1 H, br), 5.07 (1 H, m), 4.47–4.14 (1 H, c), 3.90 (3 H, s), 3.23–3.01 (2 H, c), 1.29 (6 H, d); IR 3280, 1740, 1653 cm^{-1}; MS *m/e* (rel intensity) 280 (1), 279 (24), 192 (67).

Isopropyl 1,2,3,4-Tetrahydro-7,8-dimethoxy-1-oxo-3-isoquinolinecarboxylate (42). Phenolic acid **41** (8.97 g, 32.2 mmol), $CHCl_3$ (200 mL), CH_3I (14.5 g, 102 mmol), and Ag_2O (8.60 g, 37.2 mmol) were shaken at room temperature for 10 h. More CH_3I (7.25 g, 51 mmol) and Ag_2O (4.30 g, 18.6 mmol) were added and shaking was continued at room temperature an additional 17 h. The silver salts were removed, the solvent was evaporated, and the residue was recrystallized (*n*-propylacetate) to give **42** in two crops of 5.42 g (18.5 mmol, 58%), mp 116–117 °C. An additional 1.33 g (4.55 mmol, total yield 72%) was recovered from the mother liquor by column chromatography (silica, 60 g, Et_2O): NMR δ 6.88 (2 H, s), 6.37 (1 H, br), 5.02 (1 H, m), 4.35–3.99 (1 H, c), 3.93 (3 H, s), 3.85 (3 H, s), 3.16–2.91 (2 H, c), 1.22 (6 H, d); IR 3320, 1740, 1665 cm^{-1}; MS *m/e* (rel intensity) 294 (2), 293 (20), 250 (13), 206 (100). Anal. Calcd for $C_{15}H_{19}NO_5$: C, 61.4; H, 6.5; N, 4.8. Found: C, 61.6, H, 6.5; N, 4.7.

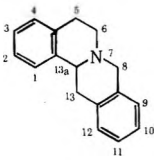
Isopropyl 1,2,3,4-Tetrahydro-7,8-dimethoxy-1-thio-3-isoquinolinecarboxylate (43). To **42** (200 mg, 0.68 mmol) was added THF (6 mL) then P_2S_5 (200 mg, 4.52 mmol sulfur) and the mixture was refluxed for 30 min after which the solvent was evaporated. To the residue was added $CHCl_3$ (20 mL) and 5% Na_2CO_3 solution (20 mL). The aqueous portion was extracted again with $CHCl_3$ (3 × 10 mL). The combined organic extracts were washed with saturated NaCl solution (60 mL), dried, and evaporated, and the residue was chromatographed (silica, 15 g, Et_2O) to give 127 mg (0.412 mmol, 60%) of thiolactam **43**, mp 88–90 °C after recrystallization from ethyl acetate/hexane: NMR δ 8.50 (1 H, br), 6.90 (2 H, s), 5.02 (1 H, m), 4.44–3.97 (1 H, c), 3.95 (3 H, s), 3.87 (3, H, s), 3.30–2.86 (2 H, c), 1.30 (6 H, d); IR 3360, 1737, 1500, 1435, 1247 cm^{-1}; MS *m/e* (rel intensity) 311 (7), 310 (20), 309 (99). Anal. Calcd for $C_{15}H_{27}NO_4S$: C, 58.3; H, 6.2; N, 4.5. Found: C, 58.3; H, 6.2; N, 4.5.

Registry No.—4 HCl, 3972-88-1; **6**, 55-59-4; **7**, 10128-06-0; **8** HCl, 41994-51-8; **9** HCl, 30740-95-5; **10** HCl, 65495-42-3; **12**, 61212-42-8; **13**, 50290-79-4; **14**, 65495-32-1; **15**, 65495-33-2; **16**, 61212-43-9; **17**, 65495-34-3; **18**, 65495-35-4; **19**, 65495-36-5; **20**, 65495-37-6; **21**, 61212-44-0; **22**, 65495-38-7; **23**, 65495-39-8; **24**, 65495-40-1; **25**,

65495-41-2; **27**, 93-40-3; **28**, 951-82-6; **29**, 7417-21-2; **30**, 37785-48-1; **31**, 40173-90-8; **32**, 65495-26-3; **33**, 4216-86-8; **33** H_3PO_4 salt, 65495-27-4; **33** HCl, 10301-89-0; **33** HBF_4 salt, 65495-28-5; **34**, 65495-29-6; **35**, 22048-26-6; **35** HBF_4 salt, 65495-30-9; **36**, 10097-84-4; **36** HCl, 2506-20-9; **37**, 65495-21-8; **38**, 65495-31-0; **39**, 65516-34-9; **40**, 65495-22-9; **41**, 65495-23-0; **42**, 65495-24-1; **43**, 65495-25-2.

References and Notes

(1) The systematic name for the fundamental nucleus i of this ring system is 5,8,13,13a-tetrahydro-6*H*-dibenzo[*a*,*g*]quinolizine or alternatively 5,6,13,13a-tetrahydro-8*H*-dibenzo[a,*g*]quinolizine. Recently, the much less cumbersome name berbine is being used to represent this nucleus,



and we find it preferable to the somewhat confused nomenclature implicit in the two other widely used terms, tetrahydroberberine and tetrahydroprotoberberine. For those compounds where a common name derived from its natural product origins is available, it has been used.

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Synthesis of 4-Methylnicotine and an Examination of Its Possible Biosynthesis from 4-Methylnicotinic Acid in *Nicotiana tabacum*[1]

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Condensation of ethyl 4-methylnicotinate with *N*-methyl-2-pyrrolidone in the presence of sodium hydride yielded the nicotinoyl derivative **6**, which on hydrolysis and reduction afforded 4-methylnicotine (**8**). This nicotine analogue was also obtained from 4-methylpyridine-3-carboxaldehyde by preparing the acyl carbanion equivalent **2**, which was added to acrylonitrile. Hydrolysis of the Michael addition product yielded the ketonitrile **3**, which was hydrogenated to give 4-methylnornicotine, which afforded **8** on methylation. A biomimetic synthesis of **8** involved reaction between 3-methylglutaraldehyde, ammonia, and *N*-methyl-Δ^1-pyrrolinium acetate in the presence of air. Optically active 4-methylnicotine was obtained as previously described by reaction of (−)-(2′*S*)-nicotine with methyllithium. The administration of 4-methyl[4-^{14}C]nicotinic acid (prepared from ethyl [3-^{14}C]acetoacetate) to *Nicotiana tabacum* plants did not result in the formation of radioactive 4-methylnicotine. 4-Methylnicotine showed no nicotine-like activity in pharmacological tests.

Nicotinic acid is the established precursor of the pyridine ring of the tobacco alkaloid nicotine.[4,5] We have previously shown[6] that 5-fluoronicotinic acid was utilized by *Nicotiana tabacum* to yield 5-fluoronicotine by what we term an "aberrant biosynthesis". The present article describes our attempts to produce 4-methylnicotine (**8**) by administering 4-methylnicotinic acid to the tobacco plant.

A reference specimen of 4-methylnicotine was required for comparison with any material which might be isolated from tobacco. 4-Methylnicotine has been previously described by

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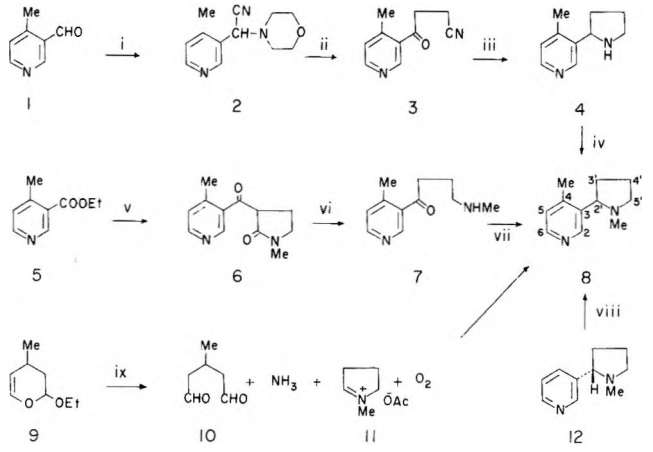
Scheme I. Syntheses of 4-Methylnicotine[a]

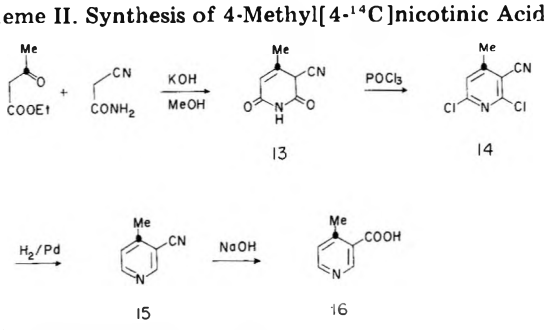


[a] i, Morpholine, $HClO_4$, KCN; ii, KO-*t*-Bu, CH_2=CHCN, HOAc; iii, H_2/Ni, $NaBH_4$; iv, HCHO, HCOOH; v, *N*-methyl-2-pyrrolidone, NaH; vi, 48% HBr; vii, $NaBH_4$; viii, MeLi; ix, HCl.

Haglid,[7] who obtained it in small yield, along with 6-methylnicotine, by the reaction of nicotine with methyllithium. We have repeated this reaction obtaining essentially the same results, except that our 4-methylnicotine derived from (−)-(2′*S*)-nicotine (the natural isomer) had a higher specific rotation ($[\alpha]^{23}_D$ −170°) than that reported by Haglid ($[\alpha]^{22}_D$ −103.5°). (*RS*)-4-Methylnicotine was prepared by three methods which are illustrated in Scheme I. The first is analogous to that used by Späth[8] for the synthesis of nicotine. In contrast to the experience of Haglid,[9] we were able to condense ethyl 4-methylnicotinate (**5**)[10] with *N*-methyl-2-pyrrolidone, in the presence of sodium hydride, to yield the nicotinoyl derivative **6**. The second synthesis started with 4-methylpyridine-3-carboxaldehyde (**1**)[10] using the procedure recently developed for the synthesis of myosmine and nornicotine[11]. The third method is analogous to the biomimetic synthesis of nicotine from glutaraldehyde, ammonia, and *N*-methyl-Δ^1-pyrrolinium acetate (**11**)[12] in the presence of air.[13] 3-Methylglutaraldehyde (**10**) was obtained by acid hydrolysis of the commercially available 2-ethoxy-4-methyl-2,3-dihydropyran (**9**). Reaction with ammonia and **11** in the presence of air gave a small yield of 4-methylnicotine and 4-methylpyridine.

4-Methyl[4-^{14}C]nicotinic acid (**16**) was made from ethyl [3-^{14}C]acetoacetate by the route illustrated in Scheme II, which is essentially that developed by Bobbit,[10] modified for synthesis on a small scale. The ^{14}C-labeled 4-methylnicotinic acid was fed to *N. tabacum* plants by the wick method, along with an equivalent amount of [2-^{3}H]nicotinic acid. The latter was fed at the same time so that the efficiency of "aberrant biosynthesis" could be compared with the normal biosynthesis of nicotine. A similar experimental procedure was used by Kirby[14] in a study of the biosynthesis of morphine and its analogues in *Papaver somniferum*. The crude alkaloids from tobacco contained both ^{14}C and tritium. A portion of the crude

Scheme II. Synthesis of 4-Methyl[4-^{14}C]nicotinic Acid[a]



[a] ^{14}C indicated with a heavy dot.

alkaloids was diluted with nonradioactive (*RS*)-4-methylnicotine. Nicotine and 4-methylnicotine were then separated by GLC. The resultant nicotine was labeled, as expected, with tritium (0.72% absolute incorporation); however, the recovered 4-methylnicotine was completely devoid of ^{14}C. Thus the enzymes responsible for nicotine biosynthesis from nicotinic acid are apparently incapable of utilizing an analogue which contains a methyl group in the 4 position. This result contrasts with the observations of Rueppel and Rapoport,[15] who found that methyl groups could be introduced into the *N*-methyl-Δ^1-pyrrolinium salt (even at C-2, the point of attachment to C-3 of nicotinic acid) to afford analogues of nicotine with extra methyl groups in the pyrrolidine ring. The utilization of other methyl derivatives of nicotinic acid, where the methyl groups are further removed from the site of condensation with **11**, is being examined.

Experimental Section[16]

4-Methylnicotine. (a) From Ethyl 4-Methylnicotinate by the Späth Method. Ethyl 4-methylnicotinate[10] (6.0 g, 36 mmol) and *N*-methyl-2-pyrrolidone (7.2 g, 72 mmol) were added slowly in a N_2 atmosphere to a magnetically stirred suspension of sodium hydride (3.5 g, 146 mmol) in benzene (25 mL), and the mixture was refluxed for 18 h. The cooled mixture was added to ice, neutralized with acetic acid, and extracted with benzene (4 × 50 mL). The combined organic extracts were washed with 10% $NaHCO_3$. Distillation (140 °C, 10^{-3} mm) of the residue obtained on evaporation of the dried ($MgSO_4$) benzene extract afforded a colorless solid (2.76 g) (**6**). This compound was refluxed with 48% HBr (10 mL) in a N_2 atmosphere for 18 h. The residue obtained on evaporation of this reaction mixture was dissolved in methanol (50 mL), the solution neutralized with KOH, and sodium borohydride (3 g) added. After standing 18 h the solution was acidified with HCl and evaporated to dryness. The residue was made basic with NaOH, extracted with chloroform, dried ($MgSO_4$), and evaporated to yield a brown oil. Distillation (110 °C, 10^{-3} mm) afforded (*RS*)-4-methylnicotine (1.66 g) as a colorless oil: IR (neat) 1600 cm^{-1} (C=N); ^{13}C NMR[18] ($CDCl_3$) ppm from Me_4Si, 151.1 (C-2), 150.0 (6), 147.4 (4), 139.3 (3), 127.1 (5), 67.1 (2′), 57.9 (5′), 41.2 (NMe), 34.1 (3′), 23.1 (4′), 19.0 (4-Me); mass spectrum, *m/e* 176 (M^+), 161 (M − Me), 147, 133; TLC on silica gel G (Merck), developing with a mixture of chloroform, methanol, and concentrated NH_3 (100:10:1), indicated that 4-methylnicotine had an R_f of 0.85 (nicotine 0.83). It was revealed as a purple spot (nicotine, orange-brown) on spraying with *p*-aminobenzoic acid and then exposing to CNBr. It afforded a dipicrate, mp 212–213 °C, yellow needles from ethanol.

Anal. Calcd for $C_{23}H_{22}N_8O_{14}$: C, 43.54; H, 3.50; N, 17.66. Found: C, 43.97; H, 3.29; N, 17.21.

It yielded a diperchlorate, colorless plates from ethanol–ethyl acetate, mp 276–277 °C dec.

Anal. Calcd for $C_{11}H_{16}N_2 \cdot 2HClO_4$: C, 35.03; H, 4.81; N, 7.43. Found: C, 35.03; H, 4.57; N, 7.55.

(b) From 4-Methylpyridine-3-carboxaldehyde. α-(4-Methyl-3-pyridyl)-α-morpholinoacetonitrile (2). 4-Methylpyridine-3-carboxaldehyde[10] (1.61 g) and morpholine perchlorate (2.8 g) were dissolved in morpholine (10 mL) and the solution was heated at 80 °C for 1 h under N_2. Potassium cyanide (1 g) dissolved in a minimum of water was added and the mixture heated at 100 °C for 2 h. The cooled mixture was added to 10% K_2CO_3 and extracted with chloroform. The dried ($MgSO_4$) extract was evaporated, and the residue sublimed (110 °C, 10^{-4} mm), affording **2**, which was crystallized from benzene–hexane to yield colorless plates (1.5 g), mp 127–128 °C.

Anal. Calcd for $C_{12}H_{15}N_3O$: C, 66.34; H, 6.96; N, 19.34. Found: C, 65.97; H, 6.97; N, 18.83.

3-Cyano-1-(4-methyl-3-pyridyl)propan-1-one (3). The nitrile (**2**) (0.94 g) was dissolved in *tert*-butyl alcohol (50 mL) containing 30% KOH in methanol (0.2 mL). Acrylonitrile (0.37 mL) in *tert*-butyl alcohol (15 mL) was added to the mixture which was then stirred at room temperature for 45 min. After dilution with an equal volume of water the mixture was extracted with chloroform, which was then back-washed with water and dried over $MgSO_4$. Evaporation yielded a viscous oil, having an absorption in the IR at 2250 cm^{-1} (C≡N) and a mass spectrum *m/e* 270 (M^+ for $C_{15}H_{18}N_4O$) and 244 (M − HCN). This crude γ-cyano-γ-morpholino-γ-(4-methyl-3-pyridyl)butyronitrile (0.75 g) was dissolved in a mixture of acetic acid (10 mL), water (5 mL), and tetrahydrofuran (1.5 mL) and heated at 53 °C for 24 h. The reaction mixture was added to K_2CO_3 and water and extracted

with chloroform. The solid residue obtained on evaporation of the dried ($MgSO_4$) pale purple extract was sublimed (70 °C, 10^{-4} mm) to afford **3**, which yielded colorless needles from ether (0.75 g): mp 83–84 °C; mass spectrum, *m/e* 174 (M^+), 144 ($M - CH_2CH_2CN$).

Anal. Calcd for $C_{10}H_{10}N_2O$: C, 68.95; H, 5.79; N, 16.08. Found: C, 68.70; H, 5.71; N, 15.85.

4-Methylnornicotine (4). The keto nitrile (**3**) (184 mg) dissolved in a mixture of ethanol (20 mL) and concentrated NH_3 (2 mL) was hydrogenated at 2 atm pressure in the presence of Raney nickel (½ teaspoon) for 18 h. TLC of the reaction mixture indicated the presence of mostly 4-methylnornicotine with some 4-methylmyosmine (4-methyl-1′,2′-dehydronornicotine). Sodium borohydride was added to the filtered mixture, and the solution refluxed for 1 h. The cooled solution was acidified with HCl and evaporated to dryness. The residue was made basic with NaOH and extracted with methylene chloride, dried ($MgSO_4$), evaporated, and distilled (140 °C, 10^{-2} mm) to afford 4-methylnornicotine as a colorless oil (140 mg), mass spectrum, *m/e* 162 (M^+), 147 (M − Me). It afforded a dipicrate, yellow needles from 95% ethanol, mp 230–231 °C.

Anal. Calcd for $C_{22}H_{20}N_8O_{14}$: C, 42.59; H, 3.25; N, 18.06. Found: C, 42.16; H, 3.11; N, 18.47.

4-Methylnicotine (8). 4-Methylnornicotine (100 mg), 90% formic acid (1 mL), and 40% formaldehyde (3 mL) were refluxed for 18 h. One drop of concentrated HCl was then added, and the refluxing continued for an additional hour. The residue obtained on evaporation was made basic with NaOH, extracted with chloroform, dried ($MgSO_4$), evaporated, and distilled to yield 4-methylnicotine (95 mg), identical (IR, TLC, mixed mp of dipicrate) with material obtained by method a.

(c) From 3-Methylglutaraldehyde and *N*-Methyl-Δ¹-pyrrolinium Acetate. *N*-Methyl-2-pyrrolidone (1.0 g) was added to a suspension of sodium aluminum hydride (170 mg) in ether (50 mL) and the mixture refluxed for 2 h. The cooled solution was added to ice and acetic acid (2 mL) and then lyophilized. The resultant residue was dissolved in water (50 mL) and filtered, and 3-methylglutaraldehyde[20] (1.14 g) and concentrated NH_3 (10 mL) were added. The solution (pH 10.5) was stirred in an open beaker at room temperature for 3 days. The mixture was then extracted with chloroform. This solution was then extracted with 2 N HCl (3 × 50 mL). The aqueous extract was made basic with NaOH and extracted with ether. The residue obtained on evaporation of the dried ($MgSO_4$) extract was distilled (140 °C, 10^{-3} mm), yielding a pale yellow oil which was subjected to preparative TLC in silica gel PF-254 (Merck), developing with a mixture of chloroform, benzene, ethanol, and concentrated NH_3 (125:75:20:1). The zone at R_f 0.4 corresponded to 4-methylnicotine. This was extracted with methanol and evaporated, and the residue distilled, affording 4-methylnicotine (75 mg) identical with material obtained by the previous methods. 4-Methylpyridine (R_f 0.6) was also obtained from the preparative TLC plates and was characterized as its picrate, mp 166–167 °C.

(d) From Nicotine and Methyllithium.[10] Methyl iodide (1.25 mL) was added to a suspension of lithium ribbon (0.28 g) in ether (30 mL), and the mixture stirred under N_2 until all the lithium had dissolved. (−)-(2′*S*)-Nicotine (1.62 g, 20 mmol) in toluene (50 mL) was added. Ether was distilled out of the reaction mixture and the residual solution was heated under reflux for 7 h with stirring. The dark brown reaction mixture was cooled and added to ice and 2 N HCl. The aqueous solution was extracted with ether which was discarded. The aqueous solution was made basic with NaOH, extracted with chloroform, dried ($MgSO_4$), evaporated, and distilled (140 °C, 10^{-3} mm). The pale yellow distillate (250 mg) was subjected to GLC (Varian Aerograph 90 AP) on an 8 ft × ⅜ in. column of 10% 20M Carbowax, 70/80 mesh, with an He flow rate of 60 mL/min at 180 °C. Under these conditions the retention times of nicotine, 6-methylnicotine, and 4-methylnicotine were 4.4, 4.8, and 6.5 min, respectively. 4-Methylnicotine was obtained as a colorless oil (52 mg, 3% yield from nicotine) having an IR spectrum identical with that of a previously prepared racemic material. Its specific rotation was $[\alpha]^{23}_D$ −170°, $[\alpha]^{23}_{365}$ −593° (c 1.8 in $CHCl_3$). Its picrate was obtained as fine yellow needles from 95% ethanol, mp 195–197 °C (lit.[7] 193–195 °C).

4-Methyl[4-^{14}C]nicotinic Acid (16). Potassium hydroxide (0.275 g) dissolved in methanol (5 mL) was added to a solution of 2-cyanoacetamide (0.336 g, 4 mmol) and ethyl [3-^{14}C]acetoacetate (0.52 g, 4 mmol, nominal activity 0.25 mCi, Amersham-Searle) in methanol (5 mL). After refluxing for 5 h, the mixture was cooled and the white potassium salt which separated was removed by filtration. This salt was dissolved in water, and the solution neutralized with HCl when 13 separated (0.37 g, 62%). This compound was heated in a sealed glass tube with $POCl_3$ (1 mL) for 5 h at 180 °C. The contents of the tube were added to ice when 2,6-dichloro-3-cyano-4-methylpyridine (**14**) (0.421 g, 91%) separated. This dichloro compound was dissolved in methanol (10 mL) containing sodium acetate (0.4 g) and palladium chloride (50 mg) and hydrogenated for 18 h at 3 atm pressure. The filtered mixture was evaporated, aqueous $NaHCO_3$ added to the residue, and the mixture extracted several times with ether. The dried ($MgSO_4$) extract was evaporated, affording 3-cyano-4-methylpyridine (**15**) (150 mg, 57%). This compound was heated with NaOH (0.2 g) in ethylene glycol (3 mL) at 175 °C in an N_2 atmosphere for 18 h. The cooled reaction mixture was diluted with water, adjusted to pH 4 with HCl, and extracted continuously with ether. The residue obtained on evaporation of the ether extract was sublimed (200 °C, 10^{-4} mm), affording 4-methyl[4-^{14}C]nicotinic acid (65 mg, 37%), mp 219–220 °C (lit.[10] 215–216 °C). Specific activity was 1.31×10^8 dpm/mmol (theoretical activity based on the nominal activity of the starting material: 1.37×10^8 dpm/mmol).

Feeding of 4-Methyl[4-^{14}C]nicotinic Acid and [2-^{3}H]Nicotinic Acid to *Nicotiana tabacum*, and Isolation of the Alkaloids. An aqueous solution (10 mL) of 4-methyl[4-^{14}C]nicotinic acid (15 mg, 0.11 mmol, 1.43×10^7 dpm) and [2-^{3}H]nicotinic acid[4] (13.3 mg, 0.11 mmol, 5.73×10^7 dpm), $^3H/^{14}C = 4.0$, was administered to four 3-month-old (12 in. high) *N. tabacum* plants growing in soil in a greenhouse, by the wick method. After 5 days the plants (fresh weight 550 g) were harvested and maserated with chloroform (2 L) and concentrated NH_3 (200 mL). Filtration yielded two layers. The aqueous layer had an activity (^{3}H) of 3.42×10^7 dpm and $^3H/^{14}C = 3.6$. The chloroform layer was evaporated in the presence of 2 N HCl. The filtered aqueous solution was made basic with NaOH and extracted with chloroform. Distillation (140 °C, 10^{-3} mm) of this dried ($MgSO_4$) extract afforded a pale yellow oil (146 mg) having an activity (^{3}H) of 1.87×10^6 dpm (3.3% of the amount of [^{3}H]nicotinic acid fed), $^3H/^{14}C = 5.0$. Some of this oil (50 mg) was mixed with (*RS*)-4-methylnicotine (50 mg) and the mixture subjected to GLC as previously described. The recovered nicotine, assayed as its dipicrate, had a specific activity (^{3}H) of 4.6×10^5 dpm/mmol and was devoid of ^{14}C. The recovered 4-methylnicotine, characterized and assayed as its dipicrate, was completely inactive (both ^{3}H and ^{14}C).

Pharmacology of (*RS*)-4-Methylnicotine. (The procedure was carried out by Herbert McKennis, Professor of Pharmacology, Medical College of Virginia, Richmond, Va.) The (*RS*)-4-methylnicotine diperchlorate (5×10^{-4} M) showed no nicotine-like activity when tested on isolated rabbit aortic strips. One easily sees a contractile response to nicotine at 1×10^{-4} M. The 4-methylnicotine (5×10^{-4} M) showed no antagonism to the stimulating effect of norepinephrine (5×10^{-8} M). These results are consistent with those of Haglid,[7] who reported very low pharmacological activity for 4-methylnicotine.

Registry No.—**1,** 51227-28-2; **2,** 65504-55-4; **3,** 65504-56-5; **4,** 65504-58-7; **4** picrate, 65504-59-8; **5,** 55314-29-9; **6,** 65504-63-4; **7,** 65504-64-5; **8,** 65556-02-7; 8 dipicrate, 65556-03-8; 8 diperchlorate, 65556-04-9; **10,** 6280-15-5; **11,** 65504-65-6; **12,** 54-11-5; **13,** 65504-60-1; **14,** 65504-61-2; **15,** 65504-66-7; **16,** 65504-62-3; 4-methylpyridine, 108-89-4; 4-methylpyridine picrate, 4810-81-5; 2-cyanoacetamide, 107-91-5; ethyl [3-^{14}C]acetoacetate, 39169-78-3; [2-^{3}H]nicotinic acid, 65878-88-8; γ-cyano-γ-morpholino-γ-(4-methyl-3-pyridyl)butyronitrile, 65504-57-6.

References and Notes

(1) Part 3 in the series "Aberrant Syntheses in Higher Plants". For Part 2 see ref 2. This investigation was supported by Research Grant GM-13246 from the National Institutes of Health, U.S. Public Health Service, and also by Grant 929 from the Council for Tobacco Research—U.S.A., Inc. Presented in part at the 31st Tobacco Chemists Research Conference, Oct 5–7, 1977, Greensboro, N.C.
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(16) Melting points are corrected. Elemental analyses were performed by Clark

Microanalytical Laboratories, Urbana, Ill. Mass spectra were determined by Dr. Roger Upham and his assistants at the University of Minnesota on an AEI-MS-30 instrument. Optical rotations were determined on a Perkin-Elmer 241 instrument. Radioactivity measurements were carried out on a Nuclear Chicago liquid scintillation Mark II counter, using as solvent dioxane–ethanol with the usual scintillators.[17]

(17) A. R. Friedman and E. Leete, *J. Am. Chem. Soc.*, **85**, 2141 (1963).

(18) The Fourier transform ^{13}C NMR spectra were determined by Dr. Robert M. Riddle at the University of Minnesota on a Varian XL-100 spectrometer (25.2 MHz). Assignments were made by comparison with the ^{13}C NMR spectrum of nicotine[19] and by continuous wave off-resonance decoupling.

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(20) Obtained by the acid hydrolysis of 2-ethoxy-4-methyl-2,3-dihydropyran (Aldrich Chemical Co.) and distilled (bp 80 °C, 100 mm) immediately before use. Its IR (neat) had absorptions at 2740 (CH stretch of CHO) and 1730 cm^{-1} (C=O): K. Adler, H. Betzing, R. Kuth, and H. A. Dortmann, *Justus Liebigs Ann. Chem.*, **620**, 73 (1959).

Synthesis of a "Bridged Nicotine": 1,2,3,5,6,10b-Hexahydropyrido[2,3-*g*]indolizine[1]

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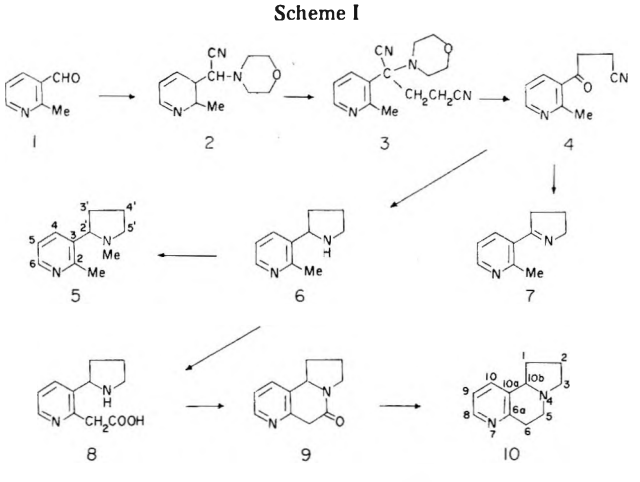
The bridged nicotine **10**, a pyridoindolizidine, has been prepared by reduction of the tricyclic lactam **9**, which was obtained by cyclization of the amino acid **8**. This compound was produced by carboxylation of the dilithium derivative of 2-methylnornicotine, which was synthesized by recently developed methods.

Many analogues of nicotine have been prepared, and their pharmacology has been studied in an effort to obtain structure–activity relationships.[3] Haglid has reviewed[4] this work and stated that it would be of great interest to examine the pharmacology of bridged nicotines, such as the pyridoindolizidine **10**, in which the configuration of the pyrrolidine ring would be fixed relative to the pyridine ring. This article describes the synthesis of compound **10** and also 2-methylnicotine (**5**) by the route illustrated in Scheme I.[5]

2-Methylpyridine-3-aldehyde (**1**) was converted to 2-methylnornicotine (**6**) by the procedure recently developed for the synthesis of myosmine and nornicotine.[7] Reaction of **1** with morpholine and sodium cyanide in the presence of perchloric acid yielded **2**. The anion generated by reaction of **2** with potassium *tert*-butoxide was added to acrylonitrile to yield the Michael addition product **3**. Acid hydrolysis of this compound afforded the keto nitrile **4**.[8] Hydrogenation of this compound in the presence of Raney nickel yielded a mixture of 2-methylmyosmine (**7**) and 2-methylnornicotine (**6**). The yield of the latter increased with the duration of the hydrogenation. Reaction of 2-methylnornicotine with 2 equiv[9] of butyllithium, followed by treatment with carbon dioxide, afforded the carboxylic acid **8**, which was cyclized to the lactam **9**. This reaction was achieved with the aid of 1-ethyl-3(3-dimethylaminopropyl)carbodiimide.[10] However, a better yield of the lactam was obtained by prolonged chloroform extraction of a solution of the amino acid **8** in dilute aqueous hydrochloric acid. Reduction of the lactam with borane in tetrahydrofuran produced the desired bridged nicotine **10** in excellent yield. Reduction of the lactam with lithium aluminum hydride gave only a 30% yield.

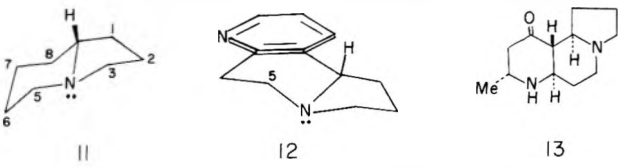
Scheme I



The indolizidine ring system can exist in two configurations, a conversion of the cis to the trans fused ring junction occurring by inversion of the lone electron pair. It is generally agreed that the trans configuration (**11**) is thermodynamically more stable.[11] The infrared spectrum of **10** has Bohlmann bands[12] at 2730, 2675, and 2630 cm^{-1} characteristic of an axial C–H group trans to the lone electron pair on nitrogen. We thus assign the trans configuration to the indolizidine ring system in the bridged nicotine **10**. The (*S*) enantiomer of **10** is illustrated in formula **12**. In nicotine an analogous configuration has been found,[13] i.e., the *N*-methyl group (equivalent to C-5 in the bridged nicotine) is trans to the pyridine ring.

No Bohlmann bands were found in the IR spectrum of the lactam **9**. It is, therefore, suggested that this compound has a *cis*-indolizidine ring junction. Indeed, inspection of a Dreiding model of the lactam indicates a preference for the cis isomer.

The heterocyclic system found in compounds **9** and **10** exists in elaeokanidine A (**13**), one of the alkaloids of *Elaeocarpus*



11 12 13

kaniensis.[14] The pharmacology of 2-methylnicotine and the bridged nicotine **10** is being examined and will be reported elsewhere.

Experimental Section[15]

α-(2-Methyl-3-pyridyl)-α-morpholinoacetonitrile (2). 2-Methylpyridine-3-aldehyde[16] (3.31 g, 27 mmol) was added to a solution of morpholine perchlorate (5.64 g, 30 mmol) in morpholine (35 mL), and the mixture was heated at 76 °C for 1 h under N_2. Sodium cyanide (1.32 g, 27 mmol) in water (2 mL) was added and the mixture was heated at 100 °C for 45 min. The cooled solution was poured into 10% sodium carbonate (100 mL) and extracted with chloroform. The residue obtained on evaporation of the dried (K_2CO_3) extract was triturated with ether to yield **2** (4.82 g, 82%). Crystallization from ether afforded colorless prisms: mp 112.5–113.5 °C; IR (Nujol) ν_{max} 1590, 1580, 1105 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.58 (t, 4 H, NCH_2), 2.65 (s, 3 H, $PyCH_3$), 3.69 (t, 4 H, OCH_2), 4.90 (s, 1 H, α-H), 7.17 (dd, 1 H, 5-PyH), 7.80 (dd, 1 H, 4-PyH), 8.54 (dd, 1 H, 6-PyH); *m/e* 217 (M^+). Anal.

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Calcd for $C_{12}H_{15}N_3O$: C, 66.34; H, 6.96; N, 19.34. Found: C, 66.60; H, 7.19; N, 19.53.

γ-Cyano-γ-(2-methyl-3-pyridyl)-γ-morpholinobutyronitrile (3). Methanolic potassium hydroxide (30%, 0.75 mL) was added dropwise during 5 min to a stirred solution of **2** (2.64 g, 12.2 mmol) in *tert*-butyl alcohol (60 mL) under N_2 at room temperature. After 30 min acrylonitrile (0.78 g, 14.6 mmol) in *tert*-butyl alcohol (30 mL) was added during 2.5 h. The mixture was stirred an additional 1.5 h and then water (90 mL) was added. A dried (K_2CO_3) chloroform extract, on evaporation, afforded a pale pink oil (3.3 g, 100%) which crystallized on standing. An analytical sample was obtained as colorless plates from ether: mp 99.5–100.5 °C; IR (KBr pellet) ν_{max} 2240 (C≡N), 1685, 1560 cm^{-1}; H^1 NMR ($CDCl_3$) δ 2.31 (m, 8 H), 2.82 (s, 3 H, $PyCH_3$), 3.78 (t, 4 H, OCH_2), 7.22 (dd, 1 H, 5-PyH), 7.94 (dd, 1 H, 4-PyH), 8.59 (dd, 1 H, 6-PyH); *m/e* no M^+, 243 (M − HCN), 228, 203, 118, 117, 86. Anal. Calcd for $C_{15}H_{18}N_4O$: C, 66.64; H, 6.71; N, 20.72. Found: C, 66.47 H, 6.84; N, 20.66.

3-Cyano-1-(2-methyl-3-pyridyl)propan-1-one (4). Compound **3** (1.81 g) was heated in 50% aqueous acetic acid (25 mL) at 60 °C for 18 h. The solution was then made basic with K_2CO_3 and extracted with chloroform. The residue obtained on evaporation of the dried (K_2CO_3) extract was crystallized from a mixture of ether and chloroform to afford colorless plates of the keto nitrile **4** (0.99 g, 85%): mp 81.5–83.5 °C; IR (Nujol) ν_{max} 2250 (C≡N), 1675 (C=O), 1565 (C=N) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.74 (s, 3 H, $PyCH_3$), 2.75 (t, 2 H, CH_2CN), 3.30 (t, 2 H, $COCH_2$), 7.23 (dd, 1 H, 5-PyH), 7.93 (dd, 1 H, 4-PyH), 8.52 (dd, 1 H, 6-PyH); *m/e* 174 (M^+). Anal. Calcd for $C_{10}H_{10}N_2O$: C, 68.95; H, 5.79; N, 16.08. Found: C, 69.13; H, 5.72; N, 16.31.

2-Methylnornicotine (6) and 2-Methylmyosmine (7). The keto nitrile (**4**) (1.07 g) dissolved in 95% ethanol (200 mL), previously saturated with ammonia, was hydrogenated in the presence of Raney nickel (about 5 g) for 6 h at 3 atm of pressure. Evaporation of the filtered reaction mixture afforded a pale yellow oil which was subjected to preparative TLC on silica gel PF-254 (Merck), developing with a mixture of chloroform, methanol, and concentrated ammonia (90:10:1). Extraction (methanol–chloroform) of the lower zone (R_f 0.25) followed by distillation (110 °C, 4×10^{-3} mm) of the residue obtained on evaporation afforded (*R,S*)-2-methylnornicotine (0.39 g, 39%) as a colorless oil: IR (neat) ν_{max} 3310 (NH), 1590 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.32–2.39 (m, 5 H, NH, 3′,4′-H), 2.54 (s, 3 H, $PyCH_3$), 2.58–3.29 (m, 2 H, 5′-H), 4.30 (t, 1 H, 2′-H), 7.03 (dd, 1 H, 5-PyH), 7.78 (dd, 1 H, 4-PyH), 8.27 (dd, 1 H, 6-PyH); *m/e* 162 (M^+), 161, 133, 119, 70. It yielded a dipicrate, mp 186.5–187 °C dec, from ethanol. Anal. Calcd for $C_{22}H_{20}N_8O_{14}$: C, 42.59; H, 3.25; N, 18.06. Found: C, 42.59; H, 3.25; N, 17.95. **6** has been prepared independently.[8]

The upper zone (R_f 0.66) on extraction yielded 2-methylmyosmine (0.61 g, 61%) as a colorless oil: IR (neat) ν_{max} 1620 (C=N), 1570 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.01 (m, 2 H, 4′-H), 2.73 (s, 3 H, $PyCH_3$), 2.92 (t, 2 H, 5′-H), 4.11 (t, 2 H, 3′-H), 7.11 (dd, 1 H, 5-PyH), 7.70 (dd, 1 H, 4-PyH), 8.51 (dd, 1 H, 6-PyH); *m/e* 160 (M^+), 159, 132, 131. Its dipicrate had mp 185.5–186 °C. Anal. Calcd for $C_{22}H_{18}N_8O_{14}$: C, 42.74; H, 2.93; N, 18.12. Found: C, 42.61; H, 3.05; N, 17.88.

By extending the hydrogenation time the amount of 2-methylnornicotine was increased at the expense of the 2-methylmyosmine. Thus hydrogenation of the keto nitrile **4** (4.5 g) for 17 h afforded 2-methylnornicotine (3.49 g, 83%). Reduction of 2-methylmyosmine with sodium borohydride in ethanol also yielded 2-methylnornicotine.

2-Methylnicotine (5). 2-Methylnornicotine (106 mg), 40% formaldehyde (3 mL), and 90% formic acid (3 mL) were heated at 100 °C for 24 h. The residue obtained on evaporation of the reaction mixture was made basic with K_2CO_3, extracted with chloroform, dried (K_2CO_3), and evaporated. The residue was subjected to preparative TLC on silica gel PF-254, developing with a mixture of chloroform, ethanol, and concentrated ammonia (100:20:1). The lower zone (R_f 0.31) afforded unreacted 2-methylnornicotine (11 mg, 11%). The upper zone (R_f 0.56) yielded (*R,S*)-2-methylnicotine, obtained as a colorless oil (81 mg, 70%) after distillation (110 °C, 4×10^{-3} mm): IR (neat) ν_{max} 1580, 1440 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.18 (s, 3 H, NCH_3), 2.55 (s, 3 H, $PyCH_3$), 7.30 (dd, 1 H, 5-PyH), 7.78 (dd, 1 H, 4-PyH), 8.29 (dd, 1 H, 6-PyH); *m/e* 176 (M^+), 175, 84. Its dipicrate was obtained as yellow prisms from ethanol, mp 224.5–225 °C. Anal. Calcd for $C_{23}H_{22}N_8O_{14}$: C, 43.54; H, 3.50; N, 17.66. Found: C, 43.29; H, 3.42; N, 17.87. **5** has been prepared independently.[8]

Its diperchlorate was obtained as colorless needles from a mixture of methanol and ether, mp 264–270 °C dec. Anal. Calcd for $C_{11}H_{16}N_2 \cdot 2HClO_4$: C, 35.03; H, 4.81; N, 7.43; Cl, 18.80. Found: C, 35.10; H, 4.90; N, 7.58; Cl, 18.93.

5-Oxo-1,2,3,5,6,10b-hexahydropyrido[2,3-*g*]indolizine (9). 2-Methylnornicotine (0.84 g, 5.2 mmol) dissolved in tetrahydrofuran (15 mL) was added to a solution of butyllithium (5.2 mL of a 2.2 M solution in hexane, 11.4 mmol) in tetrahydrofuran at −78 °C in a N_2 atmosphere. After stirring at this temperature for 2 h, carbon dioxide (liberated from $BaCO_3$ (2.06 g, 10.5 mmol) with concentrated sulfuric acid) was passed into the reaction mixture, which was then allowed to slowly warm to room temperature during 4 h. 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (3.72 g, 20.9 mmol) in water (20 mL) was added and the solution was stirred at room temperature for 6 h. The reaction mixture was made basic with ammonia and evaporated; the residue was extracted with methylene chloride. The dried (K_2CO_3) extract was evaporated and the residue was subjected to preparative TLC on silica gel PF-254, developing with a mixture of chloroform, ethanol, and concentrated ammonia (90:10:1). The main zone (R_f 0.45) was extracted with a mixture of chloroform and methanol (85:15) and evaporated; the residue was distilled (110 °C, 4×10^{-3} mm) to yield a pale yellow oil (0.4 g, 41%) which crystallized on standing: mp 91.5–92.5 °C; UV (95% ethanol) λ_{max} (log ε) 254 (sh, 3.66), 260 (3.75), 264 nm (sh, 3.70); IR (neat liquid) ν_{max} 1640 cm^{-1}; ^1H NMR ($CDCl_3$) complex overlapping signals including δ 3.70 (s, 2 H, CH_2CO), 7.20 (dd, 1 H, 9-PyH), 7.51 (d, 1 H, 10-PyH), 8.48 (d, 1 H, 8-PyH). Anal. Calcd for $C_{11}H_{12}N_2O$: C, 70.18; H, 6.43; N, 14.88. Found: C, 70.37; H, 6.20; N, 15.11.

A higher yield (78%) of the lactam **9** was obtained by the following procedure. The reaction mixture after carboxylation was added to 1 N HCl (25 mL) which was then extracted with ether (2 × 20 mL). The residual aqueous solution was then extracted in a continuous extractor with chloroform for 60 h. The aqueous solution was then adjusted to pH 9.5 with ammonia and extracted for an additional 18 h with chloroform. The combined, dried (K_2CO_3) chloroform extracts were evaporated to yield the lactam, purified by sublimation as before.

1,2,3,5,6,10b-Hexahydropyrido[2,3-*g*]indolizine (10). Borane in tetrahydrofuran (1 M, 10 mL, 12 mmol) was added rapidly at 0 °C to a solution of the lactam **9** (256 mg, 1.36 mmol) in tetrahydrofuran (12 mL) in a N_2 atmosphere. The solution was then refluxed for 1.5 h and cooled and water (5 mL) was carefully added. The residue obtained on evaporation was refluxed with 2 N HCl (25 mL) for 1.5 h. Evaporation and refluxing with HCl was repeated. The final residue was made basic with 20% KOH (20 mL) and extracted with chloroform. Evaporation of the dried (K_2CO_3) extract yielded a pale yellow oil which was distilled (100 °C, 10^{-3} mm) to afford **10** as a colorless oil (186 mg, 79%): UV (95% ethanol) λ_{max} (log ε) 255 (sh, 3.44), 263 (3.56), 268 (sh, 3.52), 276 nm (sh, 3.40); IR (neat) ν_{max} 2795, 1568, 1435 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.56–3.50 (complex multiplet, 11 H), 7.04 (dd, 1 H, 9-PyH), 7.34 (d, 1 H, 10-PyH), 8.36 (d, 1 H, 8-PyH); *m/e* 174 (M^+), 173, 118, 146. The dipicrate was obtained as yellow needles from ethanol, mp 224–224.5 °C. Anal. Calcd for $C_{23}H_{20}N_8O_{14}$: C, 43.68; H, 3.19; N, 17.72. Found: C, 43.96; H, 3.15; N, 17.46.

Registry No.—**1**, 60032-57-7; **2**, 65718-98-1; **3**, 65718-99-2; **4**, 60032-59-9; **5**, 64114-31-4; **5** dipicrate, 65719-00-8; **5** diperchlorate, 65719-01-9; **6**, 64114-19-8; **6** dipicrate, 65719-02-0; **7**, 65719-03-1; **7** dipicrate, 65719-04-2; **8**, 65719-05-3; **9**, 65719-06-4; **10**, 65719-07-5; **10** dipicrate, 65719-08-6; morphorine perchlorate, 35175-75-8; acrylonitrile, 107-13-1; methyl 2-methylnicotinate, 65719-09-7; 3-hydroxymethyl-2-methylpyridine, 56826-61-0; propynal, 74-99-7; methyl 3-aminocrotonate, 14205-39-1.

Supplementary Material Available: Proton noise decoupled ^{13}C-NMR spectra of compounds **5, 6, 7, 9,** and **10** (1 page). Ordering information is given on any current masthead page.

References and Notes

(1) This investigation was supported by Research Grant GM-13246 from the National Institutes of Health, U.S. Public Health Service, and also Grant 929 from the Council for Tobacco Research—U.S.A., Inc.
(2) Contribution No. 154 from this Laboratory.
(3) (a) J. H. Burckhalter and J. H. Short, *J. Org. Chem.*, **23,** 1281 (1958); (b) H. Erdtman, F. Haglid, I. Wellings, and U. S. von Euler, *Acta Chem. Scand.*, **17,** 1717 (1963); (c) F. Haglid and I. Wellings, *ibid.*, **17,** 1727, 1735, 1743 (1963); (d) I. Yamamoto, H. Kamimura, and R. Yamamoto, *Mem. Tokyo Univ. Agric.*, **7,** 67 (1963); (e) F. Haglid, *Acta Chem. Scand.*, **21,** 329 (1967); (f) F. Haglid and J. O. Norén, *Acta Chem. Scand.*, **21,** 335 (1967); (g) F. Haglid, *Ark. Kemi*, **26,** 489 (1967); (h) N. Castagnoli, A. P. Melikian, and V. Rosnati, *J. Pharm. Sci.*, **58,** 860 (1969); (i) W. Hawkins and A. Burger, *ibid.*, **59,** 342 (1970); (j) M. Cushman and N. Castagnoli, *J. Org. Chem.*, **37,** 1268 (1972).
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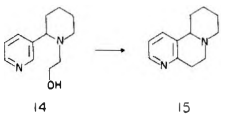

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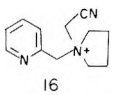

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(9) Two equivalents of butyllithium are required since one is consumed by reaction with the NH group of the pyrrolidine ring.
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(15) Melting points are uncorrected. Elemental analyses were determined by MHW Laboratories, Garden City, Mich. Mass Spectra were determined by Dr. Roger Upham and his assistants at the University of Minnesota on an AEI-MS-30 instrument. The Fourier transform ^{13}C-NMR spectra were determined by Dr. Robert M. Riddle at the University of Minnesota on a Varian XL-100 spectrometer (25.2 MHz). ^{1}H-NMR spectra were determined on a Varian HFT-80 spectrometer. Infrared spectra were recorded on a Perkin-Elmer Model 257 spectrometer. Ultraviolet spectra were determined on a Cary 11 spectrometer.
(16) The 2-methylpyridine-3-aldehyde was obtained from methyl 2-methylnicotinate[17] via 3-hydroxymethyl-2-methylpyridine, using the method whereby J. M. Bobbit and D. A. Scola, *J. Org. Chem.*, **25**, 560 (1960), obtained 4-methylpyridine-3-aldehyde from methyl 4-methylnicotinate.
(17) Prepared in 66% yield from propynal and methyl 3-aminocrotonate according to the method used by F. Bohlmann and D. Rahtz, *Chem. Ber.*, **90**, 2265 (1957), for the synthesis of the corresponding ethyl ester.

Cembranoid Diterpenes from a South Pacific Soft Coral

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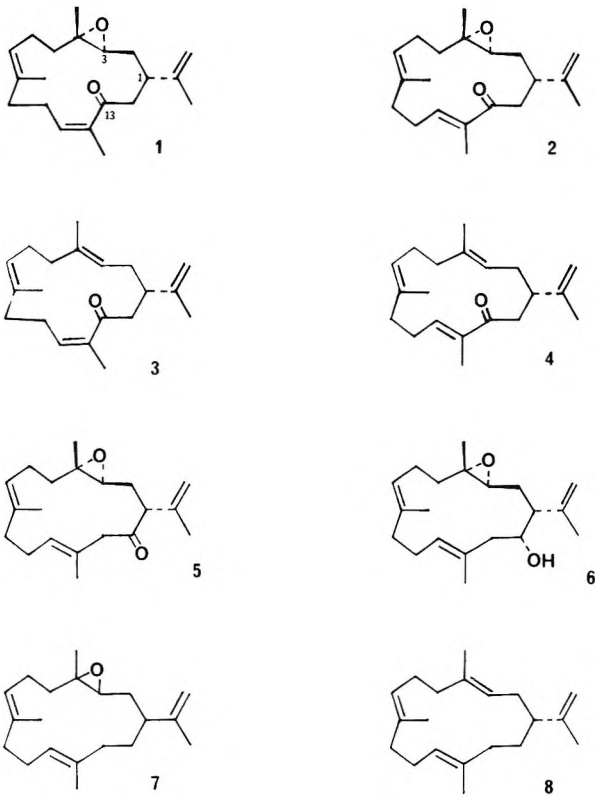
Eight cembranoid diterpenes have been isolated from an unidentified soft coral. The structures were elucidated from spectral data and chemical degradation sequences. The compounds were identified as (1*S**,3*S**,4*S**,7*E*,11*Z*)-3,4-epoxy-13-oxo-7,11,15-cembratriene, (1*S**,3*S**,4*S**,7*E*,11*E*)-3,4-epoxy-13-oxo-7,11,15-cembratriene, (3*E*,7*E*,11*Z*)-13-oxo-3,7,11,15-cembratetraene, (3*E*,7*E*,11*E*)-13-oxo-3,7,11,15-cembratetraene, (1*S**,3*S**,4*S**,7*E*,11*E*)-3,4-epoxy-14-oxo-7,11,15-cembratriene, (1*S**,3*S**,4*S**,14*R**,7*E*,11*E*)-3,4-epoxy-14-hydroxy-7,11,15-cembratriene, (7*E*,11*E*)-3,4-epoxy-7,11,15-cembratriene, and (−)-cembrene-A. The application of ^{13}C NMR spectroscopy to the determination of stereochemistry is discussed.

The soft corals or alcyonaceans are known to be a source of interesting marine natural products[1] which include sesquiterpenes,[2] cembranoid diterpenes,[3] polyhydroxylated sterols,[4] and pregnanes.[5] Some cembranoid diterpenes from soft corals are known to be toxic and have been cast in the role of deterrents to predation by reef fishes.[1] We wish to report the isolation and identification of eight cembranoid diterpenes from an unidentified soft coral[6] which was collected at Canton Island in the South Pacific.

Silica gel chromatography of the chloroform-soluble material from the combined acetone and 15% methanol in chloroform extracts of the soft coral gave a series of fractions from which the ketones **1** and **2** and the hydrocarbon **8** were obtained in high purity. Chromatography of one of the mixed fractions on silver nitrate impregnated silica gel gave two pure compounds, the ketones **3** and **5**, and a mixture of the ketone **4** and the epoxide **7** which could only be separated after reduction of the ketone **4**. The alcohol **6** was isolated from a mixture with the ketone **2** as the corresponding acetate. The molecular formulas, optical rotations, and yields of the compounds isolated are summarized in Table I.

The ketone **1** was shown to have the molecular formula $C_{20}H_{30}O_2$ by high-resolution mass measurement. The infrared band at 1690 cm^{-1} and the UV absorption at 236 nm (ϵ 3000) both suggested the presence of an α,β-unsaturated ketone. The ^{1}H NMR spectrum contained signals at δ 5.68 (1 H, t, J = 6.5 Hz) due to the β proton on an α,β-unsaturated ketone, 5.08 (1 H, t, J = 7 Hz) assigned to the vinyl proton on a trisubstituted olefinic bond, 4.85 (1 H, bs) and 4.74 (1 H, bs) for the terminal methylene protons and four methyl signals at 1.84, 1.80, 1.67, and 1.21 ppm. When recorded in $CDCl_3$ solution, the ^{1}H-NMR spectrum contained an unresolved proton multiplet at δ 2.84 and a signal at 2.64 (1 H, t, J = 6.5 Hz)



1 2 3 4 5 6 7 8

which could be assigned to an α-epoxy proton. When recorded in C_6D_6 solution, the ^{1}H-NMR spectrum of **1** contained three mutually coupled signals at δ 3.06 (1 H, m, J = 7 Hz, H_c), 2.77 (1 H, dd, J = 17, 7 Hz, H_a), and 2.58 (1 H, dd, J = 17, 7 Hz, H_b)

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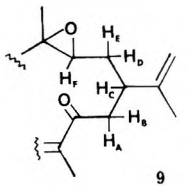
Table I. The Molecular Formulas, Percent Dry Weight, and Optical Rotations of Compounds 1–8

Compd No.	Molecular formula	% dry weight	$[\alpha]^{20}_D$, deg
1	$C_{20}H_{30}O_2$	0.76	+8.8
2	$C_{20}H_{30}O_2$	1.1	+12.8
3	$C_{20}H_{30}O$	0.09	−20.6
4	$C_{20}H_{30}O$	<0.01	
5	$C_{20}H_{30}O_2$	0.15	+38.7
6	$C_{20}H_{32}O_2$	0.51	
7	$C_{20}H_{32}O$	0.09	−19.3
8	$C_{20}H_{32}$	0.02	−3.5

and the α-epoxy proton signal at 2.64 (1 H, t, J = 6.5 Hz, H_f). Irradiation of a two-proton triplet at δ 1.67 (H_d, H_e) caused the α-epoxy proton signal to become a singlet and the signal at 3.06 (H_c) to become a triplet. Thus the ketone **1** must contain the partial structure **9**. Decoupling studies showed that the methyl signals at δ 1.84 and 1.61 were coupled to the vinyl protons at 5.68 and 5.08, respectively, while the methyl signal at 1.80 was coupled to the methylene protons at 4.85 and 4.75 ppm, forming an isopropenyl group. The ^{13}C-NMR spectrum contained signals for one carbonyl carbon, six olefinic carbons, the two carbons of the trisubstituted epoxide, and four methyl carbons. Since the ketone must be monocyclic, it was assigned the cembranoid structure **1**.[7]

The presence of the trisubstituted epoxide was confirmed by periodic acid oxidation of the ketone **1** to obtain a ketoaldehyde **10** in low yield. Ozonolysis of the ketone **1**, followed by oxidation and methylation, gave methyl levulinate, indicating the presence of a 1,5-diene system. Reduction of the



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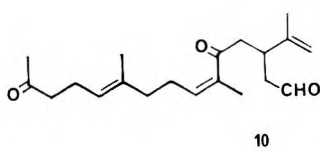

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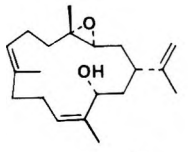

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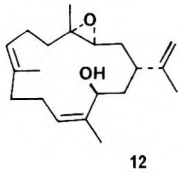

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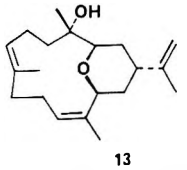

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ketone **1** with lithium aluminum hydride in refluxing ether resulted in the formation of two epimeric alcohols **11** and **12** in a ratio of 3:2.[8] The alcohols **11** and **12** were both treated with p-toluenesulfonic acid in refluxing chloroform. The alcohol **12** underwent a smooth isomerization to the ether **13**, while alcohol **11** gave a complex mixture of products. The ^{1}H-NMR spectrum of the cyclic ether **13** clearly indicated the regiochemical and stereochemical relationships between the epoxide, the isopropenyl side chain, and the allylic alcohol in **12**. The signals at δ 3.88 (1 H, dd, J = 12, 2 Hz, C-13) and δ 3.22 (1 H, dd, J = 12, 2 Hz, C-3) were assigned to axial protons on the α carbons in a six-membered cyclic ether, while the signal at 2.59 (1 H, bs, $w_{1/2}$ = 13 Hz, C-1) was due to an equatorial proton on the carbon bearing the isopropenyl group. Examination of molecular models revealed that the 13α-alcohol **11** could not attain a suitable conformation for ether formation.

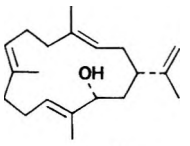
The stereochemistry of the Δ^{11} double bond was established by comparing spectral data with those of the isomeric ketone **2**. On catalytic hydrogenation over 10% palladium on charcoal, both ketones **1** and **2** gave the identical hexahydro derivative which could be purified by sublimation. This indicated that both molecules contained epoxide and ketone functionalities in the same positions on the same carbon skeleton. Since ozonolysis of **2** also gave methyl levulinate, the positions of the olefinic bonds must be the same. Thus the ketones **1** and **2** must be geometrical isomers.

The major differences in spectral data for the ketones **1** and **2** were all associated with the α,β-unsaturated ketone system. Whereas the ketone **2** was rapidly reduced with lithium tri-*tert*-butoxyaluminum hydride in ether at room temperature, the ketone **1** did not undergo a similar reduction. In the ^{1}H-NMR spectra, the signal for the proton at C-11 appeared at 5.68 ppm in ketone **1** and 6.64 ppm in ketone **2**, suggesting that the C-11 proton was trans to the carbonyl group in **1** and cis in **2**. The ^{13}C-NMR spectra also supported this assignment, with signals at δ 20.5 (C-20) and 134.5 (C-11) obtained from ketone **1** and δ 11.4 (C-20) and 143.4 (C-11) from ketone **2**. In addition, the extinction coefficients in the UV spectra can be correlated with cisoid and transoid enone systems.[9] Ketone **1**, λ_{max} 236 (ϵ 3000), has a cisoid configuration, while ketone **2**, λ_{max} 234 (ϵ 9500), has a transoid configuration. The stereochemistry about all remaining trisubstituted olefinic bonds and epoxide rings is E (see discussion on ^{13}C-NMR correlations).

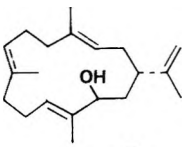
Among the minor metabolites of the soft coral, there were two α,β-unsaturated ketones **3** and **4** which lacked an epoxide functionality. The ketone **4** was obtained from an inseparable mixture with the epoxide **7** by reduction of the mixture with lithium aluminum hydride in dry ether to obtain a mixture of two alcohols **14** and **15**, which were separated from the unreacted epoxide **7**. The alcohol mixture was reoxidized with Jones' reagent to obtain the ketone **4** in low yield. Although there was insufficient material to perform chemical transformations on either compound, the spectral data indicated that the ketones **3** and **4** were 3,4-deoxy derivatives of ketones **1** and **2**, respectively. In particular, each compound had the molecular formulation $C_{20}H_{30}O$ and contained two E-trisubstituted olefinic groups and an isopropenyl group. We propose that the ketone **3**, UV 234 nm (ϵ 3200), ^{1}H NMR δ 5.61 (1 H, t, J = 7 Hz, C-11), has the 11Z stereochemistry, while ketone **4**, UV 231 (ϵ 8100), ^{1}H NMR δ 6.62 (1 H, t, J = 7 Hz, C-11), is the 11E geometrical isomer.

The ketone **5** had the molecular formula $C_{20}H_{30}O_2$ and was therefore an isomer of ketones **1** and **2**. The infrared band at 1705 cm^{-1} indicated an unconjugated carbonyl group, while the UV absorption at 217 nm (ϵ 1070) suggested that **5** was a β,γ-unsaturated ketone. On equilibration with deuterium oxide, three protons were exchanged to obtain a trideuterio derivative **16**. The ^{1}H-NMR spectrum of **16** lacked the three-proton multiplet at δ 2.61. Since the spectral data of ketone **5** indicated the presence of two trisubstituted olefinic bonds, an isopropenyl group, and a trisubstituted epoxide ring, and ozonolysis of **5** gave methyl levulinate, the carbonyl group must be at C-14 in a cembrane containing a 3,4-epoxide.

Reduction of ketone **5** with sodium borohydride gave a 3:1 mixture of two alcohols, both of which still contained the epoxide ring. The major alcohol was shown to be identical to the



14



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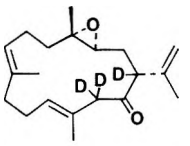

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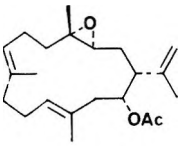
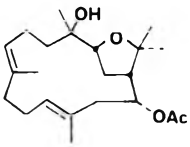


17



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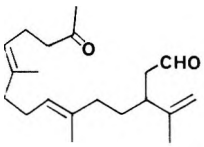

19

alcohol **6**, which had been isolated from the soft coral as the acetate **17**. The acetate **17** was converted into the alcohol **6** by treatment with lithium aluminum hydride in ether. Moffatt oxidation of the alcohol **6** gave the ketone **5**. Examination of a molecular model of the ketone **5** suggested that the hydride attack occurred from the face of the ring opposite the isopropenyl ring to give the stereochemistry shown for the alcohol **6**. The relative stereochemistry of the isopropenyl group and the epoxide was determined when it was found that treatment of the acetate **17** with *p*-toluenesulfonic acid in benzene caused formation of an ether **18** which could not be acetylated. The most likely mechanism for this reaction required formation of a carbonium ion at C-15, which rearranged, with participation of the epoxide oxygen, to an ether with a new carbonium ion at C-4, which was subsequently hydrated. Since this reaction did not occur in simpler systems, it is possible that the carbonium ion was stabilized by transannular interaction with the acetate carbonyl. If this mechanism is correct, the epoxide oxygen and the isopropenyl group must be on the same face of the large ring. The geometry of the trisubstituted olefinic bonds was again deduced from ^{13}C-NMR spectra.

The two remaining minor metabolites were identified as (−)-cembrene-A (**8**)[10] and a monoepoxide **7** related to cembrene-A. Since the monoepoxide **7** gave methyl levulinate on ozonolysis and contained an isopropenyl group, the epoxide ring must be at C-3 or C-11. Oxidation of the epoxide **7** with periodic acid in ether gave a ketoaldehyde **19**. The ^{1}H-NMR spectrum of the ketoaldehyde **19** contained an aldehyde signal at δ 9.75 (t, 1 H, J = 2 Hz) which was coupled to a two-proton signal at 2.50 (dd, 2 H, J = 7.5, 2 Hz) which was in turn coupled to part of a three-proton multiplet at 2.34, which was assigned to protons on the carbon bearing the isopropenyl group and the methylene group adjacent to the ketone group. The epoxide must therefore be situated at C-3. We were unable to define the relative stereochemistry of the epoxide and isopropenyl groups.

The ^{13}C-NMR spectra have been particularly helpful in the assignment of the stereochemistry about the trisubstituted olefinic bonds. It appears that the 14-membered ring of the cembrane skeleton is large enough that transannular effects are small and that the chemical shift criteria for establishing the stereochemistry of trisubstituted double bonds in acyclic polyisoprenoids can be applied to cembranolides. In acyclic polyisoprenoids, the chemical shift of a methyl carbon on an *E*-trisubstituted olefinic bond is 15–16 ppm, while that of methyl on a *Z*-trisubstituted olefin is 23–24 ppm.[11] The methyl of the isopropenyl group should give rise to a signal at 19–21 ppm. The methyl signal in an *E*-trisubstituted epoxide should be at ~17 ppm and that in a *Z*-trisubstituted epoxide at ~25 ppm. The differences between methyl signals in *E*- and *Z*-trisubstituted olefins are more easily observed in ^{13}C-NMR spectra than in the corresponding ^{1}H-NMR spectra.[12] On the basis of these correlations, we have assigned the *E* stereochemistry for all trisubstituted olefins and epoxides, with the exception of the C-11 olefinic bonds in **1** and **3**. The *Z*-trisubstituted olefinic bonds in ketones **1** and **3** are unique among cembranes from marine organisms.

Experimental Section

Infrared spectra were recorded on a Perkin-Elmer Model 137 spectrophotometer. Ultraviolet spectra were recorded on a Perkin-Elmer Model 124 double beam spectrophotometer. Optical rotations were measured on a Perkin-Elmer Model 141 polarimeter, using a 10-cm microcell. ^{1}H-NMR spectra were recorded on a Varian HR-220 NMR spectrometer, and ^{13}C spectra were recorded on a Varian CFT-20 NMR spectrometer; all chemical shifts are reported with respect to Me_4Si (δ 0). Low-resolution mass spectra were recorded on a Hewlett-Packard 5930A mass spectrometer. High-resolution mass spectra were recorded on a Varian MAT 311 spectrometer and were also supplied by the Analytical Facility at California Institute of Technology. Melting points were determined on a Fisher-Johns apparatus and are reported uncorrected. All solvents used were either spectral grade or distilled from glass prior to use.

Collection and Extraction of Soft Coral. The unidentified soft coral was collected by hand, using scuba at a depth of 15 m on the leeward side of Canton Island (2°50′S, 171°42′W) in October 1976. The soft coral was stored and shipped in acetone. The soft coral (195 g dry weight) was homogenized in acetone and filtered and the solid material was extracted with 15% methanol in chloroform in a Soxhlet extractor for 48 h. Evaporation of the combined extracts gave a brown gum (21 g, 10.8% dry weight).

Isolation of Cembranes 1–8. The crude extract (20 g) was applied to a column (100 × 5 cm diameter) of silica gel (50–200 mesh) and material was eluted with solvents of gradually increasing polarity from hexane through ether. Fraction 1, eluted with hexane, contained (−)-cembrene-A (**8**) (40 mg, 0.02% dry weight). Fraction 2, eluted with 10% ether in hexane, contained a mixture of compounds **3**, **4**, **5**, and **7**. Fraction 2 was rechromatographed on silica gel impregnated with 10% silver nitrate using 5% ether in hexane as eluant to obtain the ketone **3** (175 mg, 0.09% dry weight), the ketone **5** (275 mg, 0.15% dry weight), and a mixture of ketone **4** and epoxide **7**. Fraction 3, eluted with 25% ether in hexane, contained the ketone **1** (1.65 g, 0.89% dry weight). Fraction 4, eluted with 50% ether in hexane, contained the ketone **2** (1.55 g, 0.76% dry weight). Fraction 5, eluted with ether, contained a mixture of the ketone **2** and the alcohol **6**.

(1*S,3*S**,4*S**,7*E*,11*Z*)-3,4-Epoxy-13-oxo-7,11,15-cembratriene (1):** $[\alpha]^{20}_D$ +8.8° (*c* 1.6, $CHCl_3$); UV (hexane) 236 nm (ϵ 3000); IR ($CHCl_3$) 1690, 1642, 918 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.68 (1 H, t, J = 6.5 Hz), 5.08 (1 H, t, J = 7 Hz), 4.85 (1 H, s), 4.74 (1 H, s), 2.84 (3 H, m), 2.64 (1 H, t, J = 6.5 Hz), 1.84 (3 H, s), 1.80 (3 H, s), 1.61 (3 H, s), 1.21 (3 H, s); ^{13}C NMR ($CDCl_3$) δ 186.66 (s), 147.25 (s), 137.30 (s), 135.40 (s), 134.46 (d), 124.06 (d), 110.49 (t), 60.36 (d), 59.49 (s), 44.89 (t), 38.99 (t), 38.19 (d), 31.09 (t), 29.24 (t), 23.54 (t), 21.72 (q), 20.54 (q), 16.71 (q), 16.71 (q); high resolution mass measurement 302.2245, $C_{20}H_{30}O_2$ requires 302.2245.

(1*S,3*S**,4*S**,7*E*,11*E*)-3,4-Epoxy-13-oxo-7,11,15-cembratriene (2):** $[\alpha]^{20}_D$ +12.78° (*c* 1.65, $CHCl_3$); UV (hexane) 234 nm (ϵ 9000); IR ($CHCl_3$) 1690, 1650, 910 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.64 (1 H, t, J = 7 Hz), 5.18 (1 H, t, J = 7 Hz), 4.74 (1 H, s), 4.64 (1 H, s), 3.09 (1 H, dd, J = 7, 14 Hz), 2.76 (1 H, dd, J = 5, 7 Hz), 2.64 (1 H, broad q), 1.75 (3 H, s), 1.73 (3 H, s), 1.64 (3 H, s), 1.22 (3 H, s); ^{13}C NMR ($CDCl_3$) δ 189.01 (s), 147.36 (s), 143.39 (d), 137.25 (s), 134.18 (s), 125.46 (d), 110.78 (t), 61.74 (d), 59.85 (s), 43.68 (d), 40.88 (t), 38.61 (t), 38.22 (t), 32.49 (t), 25.46 (t), 24.06 (t), 19.41 (q), 16.58 (q), 15.69 (q), 11.41 (q); high resolution mass measurement 302.2286, $C_{20}H_{30}O_2$ requires 302.2245.

(3*E*,7*E*,11*Z*)-13-Oxo-3,7,11,15-cembratetraene (3): $[\alpha]^{20}_D$ −20.56° (*c* 5.3, CCl_4); IR ($CHCl_3$) 1692, 1650, 921 cm^{-1}; UV (hexane)

234 nm (ε 3200); ^{1}H NMR ($CDCl_3$) δ 5.61 (1 H, t, J = 5 Hz), 5.02 (2 H, m), 4.71 (1 H, s), 4.69 (1 H, s), 2.71 (3 H, m), 1.83 (3 H, s), 1.78 (3 H, s), 1.62 (3 H, s), 1.55 (3 H, s); ^{13}C NMR ($CDCl_3$) δ 181.5 (s), 148.2 (s), 136.4 (s), 135.39 (s), 134.52 (d), 134.38 (s), 124.30 (d), 123.19 (d), 109.13 (t), 45.27 (t), 40.48 (d), 38.96 (t), 38.71 (t), 32.17 (t), 29.17 (t), 23.98 (t), 21.00 (q), 20.11 (q), 16.73 (q), 15.13 (q); high resolution mass measurement 286.2295, $C_{20}H_{30}O$ requires 286.2296.

(1*S,3*S**,4*S**,7*E*,11*E*)-3,4-Epoxy-14-oxo-7,11,15-cembratriene (5):** mp 66 °C (ether); $[\alpha]^{20}_D$ +38.65° (*c* 4.16, $CHCl_3$); UV (hexane) 217 nm (ε 1070); IR ($CHCl_3$) 1706, 1650, 915 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.02 (1 H, t, J = 7 Hz), 4.88 (1 H, t, J = 7 Hz), 4.73 (1 H, s), 4.66 (1 H, s), 2.86 (1 H, t, J = 6.5 Hz), 2.61 (3 H, m), 1.71 (3 H, s), 1.60 (3 H, s), 1.40 (3 H, s), 1.35 (3 H, s); ^{13}C NMR ($CDCl_3$) δ 209.56 (s), 148.36 (s), 136.21 (s), 132.13 (s), 127.74 (d), 122.29 (d), 110.20 (t), 63.57 (s), 58.50 (d), 39.43 (t), 38.99 (d), 37.04 (t), 36.61 (t), 30.71 (t), 25.37 (t), 24.68 (t), 21.69 (q), 15.45 (q), 14.98 (q), 12.37 (q); high resolution mass measurement 302.2244, $C_{20}H_{30}O_2$ requires 302.2245.

(−)-Cembrene-A (8) $[\alpha]^{20}_D$ −3.5° (*c* 3, $CHCl_3$); IR ($CHCl_3$) 1640, 1462, 1441, 1393, 1382, 904 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.19 (1 H, t, J = 7 Hz), 5.07 (1 H, t, J = 7 Hz), 4.98 (1 H, t, J = 7 Hz), 4.72 (1 H, s), 4.66 (1 H, s), 1.66 (3 H, s), 1.59 (3 H, s), 1.55 (6 H, s); ^{13}C NMR ($CDCl_3$) δ 149.16 (s), 134.65 (s), 133.8 (s), 133.2 (s), 125.81 (d), 124.01 (d), 121.84 (d), 110.0 (t), 45.94 (d), 39.33 (t), 38.89 (t), 33.93 (t), 32.36 (t), 28.21 (t), 24.81 (t), 23.69 (t), 19.20 (q), 17.88 (q), 15.40 (q), 15.21 (q); mass spectrum *m/e* 272 ($M^{+\cdot}$).

Separation of Ketone 4 from Epoxide 7. Lithium aluminum hydride (~50 mg) was added to a solution of the mixture (175 mg) in dry ether (10 mL), and the reaction mixture was stirred at room temperature for 30 min. Ethyl acetate was added dropwise to destroy excess reagent, and the product was partitioned between ether and 3 N hydrochloric acid. The ether extracts were dried over anhydrous sodium sulfate and filtered and the solvent was evaporated to yield an oil. The oil was chromatographed on silica gel to obtain the epoxide **7** (140 mg, equivalent to 0.09% dry weight) and a mixture of alcohols **14** and **15** (18 mg combined).

Jones' reagent (3 drops) was added to a solution of the alcohol mixture (18 mg) in acetone (5 mL), and the reaction mixture was stirred at room temperature for 10 min. Excess reagent was destroyed by addition of isopropyl alcohol. The reaction mixture was filtered and the filtrate was evaporated. The residue was purified by preparative TLC in silica gel to obtain the ketone **4** (1.7 mg).

(7*E*,11*E*)-3,4-Epoxy-7,11,15-cembratriene (7): $[\alpha]^{20}_D$ −19.3° (*c* 3.9, CCl_4); IR ($CHCl_3$) 932 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.07 (2 H, m), 4.77 (1 H, s), 4.64 (1 H, s), 2.64 (1 H, dd, J = 5, 7 Hz), 1.71 (3 H, s), 1.64 (3 H, s), 1.53 (3 H, s), 1.21 (3 H, s); ^{13}C NMR ($CDCl_3$) δ 147.55 (s), 135.00 (s), 132.56 (s), 126.22 (d), 124.44 (d), 110.00 (t), 61.03 (s), 61.03 (d), 45.03 (d), 38.72 (t), 36.30 (t), 32.61 (t), 29.84 (t), 24.72 (t), 24.44 (t), 24.24 (t), 21.04 (q), 17.25 (q), 14.94 (q), 14.94 (q); high resolution mass measurement 288.2450, $C_{20}H_{32}O$ requires 288.2453.

(3*E*,7*E*,11*E*)-13-Oxo-3,7,11,15-cembratetraene (4): UV (hexane) 231 nm (ε 8100); ^{1}H NMR ($CDCl_3$) δ 6.62 (1 H, t, J = 7 Hz), 5.16 (2 H, m), 4.73 (1 H, s), 4.68 (1 H, s), 3.29 (1 H, dd, J = 15, 5 Hz), 2.82 (1 H, m), 1.71 (3 H, s), 1.66 (3 H, s), 1.61 (3 H, s). 1.56 (3 H, s); ^{13}C NMR ($CDCl_3$) δ 191.1 (s), 148.0 (s), 141.25 (d), 135.9 (s), 134.5 (s), 132.5 (s), 126.5 (d), 122.0 (d), 110.0 (t), 45.6, 37.5, 34.5, 31.7, 28.0, 26.0, 22.25 (q), 18.85 (q), 15.75 (q), 10.75 (q); mass spectrum, *m/e* 286 ($M^{+\cdot}$).

Separation of Alcohol 6 from a Mixture with Ketone 2. Acetic anhydride (1 mL) and pyridine (1 mL) were added to a solution of a mixture of alcohol **6** and ketone **2** (1.7 g) in benzene (5 mL), and the reaction mixture was stirred at room temperature overnight. The solvent and reagents were removed in vacuo. The residue was chromatographed on silica gel to obtain the ketone **2** (0.5 g) and the acetate **17** (1.2 g). Lithium aluminum hydride (~100 mg) was added to a solution of the acetate **17** (500 mg) in dry ether (25 mL), and the reaction mixture was stirred for 1 h at room temperature. Ethyl acetate was added dropwise to destroy excess reagent, and the product was partitioned between ether and 3N hydrochloric acid. The ether extracts were dried over anhydrous sodium sulfate and the ether was evaporated to yield an oil which was chromatographed on silica gel to obtain the alcohol **6** (397 mg).

(1*R,3*S**,4*S**,14*R**,7*E*,11*E*)-3,4-Epoxy-14-hydroxy-7,11,15-cembratriene (6):** IR ($CHCl_3$) 3200, 1642, 910 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.14 (1 H, t, J = 8 Hz), 5.08 (1 H, t, J = 7 Hz), 4.82 (1 H, bs), 4.77 (1 H, bs), 3.58 (1 H, bs), 2.98 (1 H, t, J = 7 Hz), 1.74 (3 H, s), 1.63 (3 H, s), 1.55 (3 H, s), 1.30 (3 H, s); ^{13}C NMR ($CDCl_3$) δ 148.3 (s), 135.9 (s), 133.0 (s), 126.3 (d), 123.6 (d), 110.9 (t), 70.6 (d), 60.8 (s), 59.5 (d), 45.4 (d), 38.7 (t), 36.5 (t), 36.1 (t), 33.8 (t), 33.2 (t), 24.8 (t), 24.8 (q), 19.4 (q), 16.6 (q), 15.8 (q).

Periodic Acid Oxidation of Ketone 1. A saturated solution of periodic acid in anhydrous ether (2 mL) was added to a solution of ketone **1** (30 mg, 0.1 mmol) in dry ether (10 mL). The mixture was stirred at room temperature for 1 h and washed with water. The ether layer was dried over anhydrous sodium sulfate and the solvent was evaporated to yield an oil, which was chromatographed on a silica gel plate to obtain starting material (12 mg) and a ketoaldehyde **10** (1 mg, 6% theoretical): ^{1}H NMR ($CDCl_3$) δ 9.69 (1 H, t, J = 6.5 Hz), 5.67 (1 H, t, J = 7 Hz), 5.10 (1 H, t, J = 6.5 Hz), 4.82 (2 H, bs), 2.13 (3 H, s), 1.91 (3 H, s), 1.73 (3 H, s).

Ozonolysis of Ketone 1 (and Other Cembranes). Ozone in oxygen was bubbled through a solution of the ketone **1** (10 mg) in ethyl acetate (10 mL) which had been cooled to −78 °C. After 5 min, the excess reagent was removed by flushing with dry nitrogen. The solvent was evaporated and the residue was dissolved in acetone (2 mL) and titrated with Jones' reagent (4 drops). After 30 min, the reaction mixture was filtered. The filtrate was evaporated to dryness and a solution of diazomethane in ether was added until a slight excess of reagent caused a yellow solution. Analysis of the product by GC–MS indicated the presence of methyl levulinate, identical with an authentic sample.

Reduction of Ketone 1 with Lithium Aluminum Hydride. Lithium aluminum hydride (~25 mg) was added to a solution of the ketone **1** (90 mg, 0.3 mmol) in dry ether (15 mL), and the reaction mixture was boiled under reflux for 2 h. Excess reagent was destroyed by addition of ethyl acetate and then water; the solution was filtered to remove salts. The ether solution was dried over anhydrous sodium sulfate and the solvent was evaporated to yield an oil. Chromatography of the product on a preparative TLC plate (silica gel, 1:1 cyclohexane/ether) gave alcohol **11** (32 mg, 35% theoretical) as an oil and alcohol **12** (22 mg, 24% theoretical) as a crystalline solid from hexane.

Alcohol 11: IR ($CHCl_3$) 3367, 1634, 911 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.17 (1 H, t, J = 7.5 Hz), 5.06 (1 H, t, J = 7.5 Hz), 4.81 (1 H, s), 4.76 (1 H, s), 4.53 (1 H, broad m), 2.93 (1 H, dd, J = 3, 10 Hz), 1.78 (3 H, s), 1.71 (3 H, s), 1.62 (3 H, s), 1.24 (3 H, s); ^{13}C NMR ($CDCl_3$) δ 148.57 (s), 136.91 (s), 135.75 (s), 127.64 (d), 124.79 (d), 110.89 (t), 69.49 (d), 61.69 (d), 60.93 (s); 39.72, 38.82, 38.27, 37.79, 33.84, 26.91, 23.36, 20.80, 19.29, 17.86, 17.36; high resolution mass measurement 304.2391, $C_{20}H_{32}O_2$ requires 304.2402.

Alcohol 12: mp 111 °C; IR ($CHCl_3$) 3355, 1636, 908 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.06 (1 H, t, J = 7 Hz), 4.91 (1 H, t, J = 7.5 Hz), 4.70 (1 H, s), 4.60 (1 H, s), 4.45 (1 H, dd, J = 5, 7 Hz), 2.73 (1 H, t, J = 5 Hz), 2.41 (1 H, q, J = 7 Hz), 1.79 (3 H, s), 1.73 (3 H, s), 1.59 (3 H, s), 1.25 (3 H, s); high resolution mass measurement 304.2401, $C_{20}H_{32}O_2$ requires 304.2402.

Transannular Cyclization of Alcohol 12. The alcohol **12** (4 mg) and *p*-toluenesulfonic acid (1 mg) were dissolved in chloroform (5 mL), and the stirred solution was boiled under reflux for 1 h. The reaction mixture was partitioned between chloroform and 5% aqueous sodium bicarbonate solution, and the chloroform extract was dried over anhydrous sodium sulfate. The product was chromatographed on a silica gel plate to obtain the ether **13** (3.5 mg, 82% theoretical): ^{1}H NMR ($CDCl_3$) δ 5.26 (1 H, t, J = 8 Hz), 5.03 (1 H, bs), 4.91 (1 H, m), 4.87 (1 H, s), 3.88 (1 H, dd, J = 12, 2 Hz), 3.22 (1 H, dd, J = 12, 2 Hz), 2.59 (1 H, broad), 1.79 (3 H, s), 1.66 (3 H, s), 1.65 (3 H, s), 1.12 (3 H, s); mass spectrum 304 ($M^{+\cdot}$). The ether **13** did not form an acetate.

Hydrogenation of Ketones 1 and 2. A solution of ketone **1** or ketone **2** (80 mg) in anhydrous ether (25 mL) was hydrogenated over 10% palladium on charcoal catalyst for 18 h. The solution was filtered and the solvent was evaporated. The residue was chromatographed on a preparative TLC plate (silica gel, 10% ether in hexane) to obtain, among other products, a solid hexahydro derivative which sublimed at 96 °C. The same product was obtained from both ketones (25 mg, 31% theoretical from **1**; 6 mg, 7% theoretical from **2**): ^{1}H NMR ($CDCl_3$) δ 1.30 (3 H, s), 1.04 (3 H, d, J = 7 Hz), 0.89 (3 H, d, J = 7 Hz), 0.87 (3 H, d, J = 7 Hz), 0.85 (3 H, d, J = 7 Hz); mass spectrum, *m/e* 308 ($M^{+\cdot}$).

Reduction of Ketone 2 with Lithium Tri-*tert*-butoxyaluminum Hydride. Lithium tri-*tert*-butoxyaluminum hydride (25 mg) was added to a solution of ketone **2** (25 mg, 0.08 mmol) in 1:1 ether–tetrahydrofuran (10 mL), and the solution was stirred at room temperature for 100 min. Excess reagent was destroyed with water and the precipitate was removed by filtration. Evaporation of the solvent gave an inseparable mixture of alcohols. The corresponding acetates could be separated by preparative TLC on silica gel.

Equilibration of Ketone 5 with Deuterium Oxide. Potassium *tert*-butoxide (15 mg) was added to a solution of the ketone **5** (10 mg) in dry ether (2 mL). The reaction mixture was stirred for 1 h and deuterium oxide (100 μL) was added. After 15 min, the solution was neutralized with CO_2 and dried over anhydrous sodium sulfate. The

solvent was evaporated, the residue was taken up in hexane, and the solution was filtered. Evaporation of the solvent gave the trideuterio derivative **16**, in which three hydrogens had exchanged with deuterium. The ^{1}H-NMR spectrum of **16** did not contain the usual signals at 2.61 ppm but did contain a broad signal thought to be a contaminant (<1 H). The mass spectrum of **16** contained a group of four peaks at *m/e* 305 (M + 3), 304 (M + 2), 303 (M + 1), and 302 ($M^{+\cdot}$), indicating that three protons had been replaced by deuterium.

Reduction of Ketone 5 with Sodium Borohydride. Sodium brohydride (50 mg) was added to a solution of the ketone **5** (20 mg, 0.66 mmol) in methanol (10 mL) and the solution was stirred at room temperature for 3 h. The solvent was evaporated and the residue was partitioned between water (10 mL) and dichloromethane (3 × 10 mL). The dichloromethane extract was dried over anhydrous sodium sulfate and the solvent was evaporated to obtain a 3:1 mixture of two alcohols. The mixture was chromatographed on a preparative silica gel plate using ether as eluant to obtain the major alcohol, which was shown to be identical in all respects to a sample of the alcohol **6**.

Treatment of Acetate 17 with *p*-Toluenesulfonic Acid. A solution of the acetate **17** (46 mg, 0.13 mmol) and *p*-toluenesulfonic acid (2 mg) in benzene (10 mL) was boiled under reflux for 10 min. The cooled benzene solution was washed with aqueous sodium bicarbonate solution and dried over anhydrous sodium sulfate. The solvent was evaporated and the residue was chromatographed on silica gel to yield the ether **18** (22 mg, 45% theoretical) as the major product: IR (CCl_4) 3270, 1728 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.23 (1 H, t, J = 7 Hz), 5.05 (1 H, bs), 4.76 (1 H, t, J = 6.5 Hz), 3.86 (1 H, dd, J = 11, 5 Hz), 2.11 (3 H, s), 1.61 (3 H, s), 1.55 (3 H, s), 1.28 (3 H, s), 1.11 (3 H, s), 1.06 (3 H, s); ^{13}C NMR (CCl_4) δ 169.2, 135.3, 134.8, 125.7, 124.4, 81.3, 81.0, 75.2, 74.4, 48.8, 39.1, 34.8, 32.8, 29.5, 27.3, 27.2, 25.2, 24.1, 20.6, 20.4, 16.5, 15.6; mass spectrum *m/e* 364 (M^+). The ether **18** did not form an acetate when treated with acetic anhydride in pyridine.

Moffatt Oxidation of the Alcohol 6. Dicyclohexylcarbodiimide (23 mg, 0.11 mmol), 100% phosphoric acid (1 drop), and dimethyl sulfoxide (1 mL) were added to a solution of the alcohol **6** (11 mg, 0.36 mmol) in benzene (10 mL). The reaction mixture was stirred overnight and then washed with water. The benzene solution was dried over sodium sulfate and the solvent evaporated to obtain a semisolid residue. The residue was purified to HPLC using a μ-porasil column and 5% ether in hexane as eluant to obtain the ketone **5** (3 mg, 27% theoretical), mp 65–66 °C.

Oxidation of Epoxide 7 with Periodic Acid. A saturated solution of periodic acid in dry ether (2 mL) was added to a solution of the epoxide **7** (20 mg, 0.07 mmol) in dry ether (5 mL) and the reaction mixture was stirred at room temperature for 30 min. The reaction mixture was washed with water and the ether layer was dried over anhydrous sodium sulfate. The product was purified by HPLC on μ-porasil using 20% ether in hexane to obtain the ketoaldehyde **19** (17 mg, 80% theoretical): IR (CCl_4) 2720, 1720, 1642 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 9.74 (1 H, t, J = 2 Hz), 5.13 (1 H, m), 5.04 (1 H, m), 4.77 (1 H, bs), 4.67 (1 H, bs), 2.50 (2 H, dd, J = 7.5, 2 Hz), 2.34 (3 H, m), 2.11 (3 H, s), 1.62 (3 H, s), 1.59 (6 H, s); mass spectrum, *m/e* 304 (M^+).

Acknowledgments. This research was supported by grants from the National Institutes of Health (AI-11969) and the Office of Sea Grant, Department of Commerce (04-6-158-44110). The UCSD NMR Facility was supported by a grant from the National Institutes of Health (RR-00708).

Registry No.—**1**, 65622-45-9; **1** hexahydro derivative, 65622-46-0; **2**, 65634-83-5; **3**, 65622-47-1; **4**, 65622-49-3; **5**, 65622-48-2; **6**, 65622-50-6; **7**, 65622-51-7; **8**, 31570-39-5; **10**, 65622-52-8; **11**, 65622-53-9; **12**, 65634-84-6; **13**, 65622-54-0; **17**, 65622-55-1; **18**, 65622-56-2; **19**, 65622-57-3.

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(6) The soft coral was tentatively assigned to the genus *Sarcophytum*. A voucher sample (76-265) is available.
(7) The presence of the cembranoid skeleton can be rigorously established through a series of arguments which have been omitted for the sake of clarity and brevity. In essence, there is only one way in which fragment 9 can be joined to a five-carbon fragment in order that levulinic acid can be produced by ozonolysis of two trisubstituted olefinic bonds. The remaining three carbon atoms must be in the ring in order to obtain the observed multiplicities in the ^{13}C-NMR spectrum.
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Dimethyl Selenoxide Oxidation of Trivalent Phosphorus Compounds, Thio- and Selenophosphoryl Compounds, and Thiocarbonyl Compounds. Stereochemical Studies and Selective Modification of the Thiocarbonyl-Containing Nucleic Acid Components[1]

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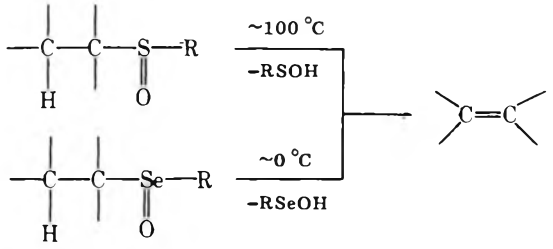
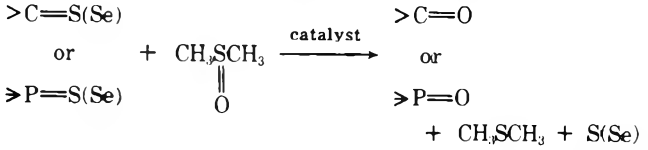
Dimethyl selenoxide was found to be an excellent oxidizing agent which converts P^{III} compounds, thio- and selenophosphoryl compounds, and thiocarbonyl compounds into their phosphoryl or carbonyl analogues under very mild conditions in the absence of catalysts. For this reason it is a reagent of choice for selective modification of the thiocarbonyl-containing minor components of transfer ribonucleic acids such as thiouracils and the corresponding thionucleosides and thionucleotides. The oxidation of cyclic six-membered phosphites and thio(seleno)phosphates with dimethyl selenoxide is accompanied by retention of configuration at phosphorus. In contrast, the oxidation of chiral acyclic P^{III} compounds as well as the conversion of chiral phosphine sulfides and selenides into phosphoryl derivatives proceed with inversion of configuration around the phosphorus atom. The mechanism of the dimethyl selenoxide oxidations is discussed.

The application of organic selenium reagents in organic synthesis has attracted increasing interest in recent years.[2] In comparison with sulfur reagents, the corresponding selenium analogues are usually more reactive, which allows the performance of desired reactions under milder conditions. The best illustration is the synthesis of olefins from sulfoxides and selenoxides involving the syn elimination of sulfenic and selenenic acid, respectively. It has been found that, in contrast to thermal decomposition of sulfoxides to olefins taking place under forced conditions,[3] the elimination of selenoxides occurs spontaneously at room temperature or below. This difference in behavior of sulfoxides and selenoxides is most probably a



consequence of the greater basicity of the selenynyl oxygen atom. It was expected, therefore, that the increased reactivity of selenoxides vs. sulfoxides may be also observed in other reactions.

Recently, we reported[4] a convenient method of oxidation of carbon and phosphorus compounds containing the thiono(seleno) groups >C=S(Se) and >P=S(Se) by dimethyl

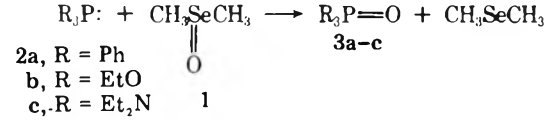


sulfoxide. This reaction is, however, catalyzed by strong acids or iodine and in the majority of cases it takes place at elevated temperatures. For this reason the above oxidation method cannot be applied to oxidation of the acid and thermally labile compounds. Moreover, its application as a method for selective modification of the thiocarbonyl-containing minor components in transfer ribonucleic acids[5] is, for the same reasons, of limited value.

This fact prompted us to investigate the reaction of dimethyl selenoxide (Me_2SeO, 1) with trivalent phosphorus compounds, thio- and selenophosphoryl compounds, and thiocarbonyl compounds hoping to effect their oxidation under milder conditions and in the absence of an electrophilic catalyst. This was found to be the case and the results of this study are reported here.

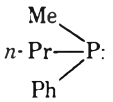
Results and Discussion

Oxidation of Trivalent Phosphorus Compounds by Dimethyl Selenoxide (1). It was found that treatment of P^{III} compounds (2) with dimethyl selenoxide (1) at room tem-



perature yielded the corresponding phosphoryl derivatives (3) and dimethyl selenide as the reduction product. The reaction is quantitative and practically complete after 1 h as evidenced by TLC. It should be pointed out that oxidation of triphenylphosphine (2a) by 1 was achieved under these mild conditions, whereas the analogous oxidation by dimethyl sulfoxide[6] requires higher temperature and acid catalysis.

If the reactions of P^{III} compounds with dimethyl selenoxide (1) are stereospecific it would be the preferred reagent for oxidation of chiral phosphines. With this in mind we have examined oxidation of optically active methyl-*n*-propylphenylphosphine (4)[7] by 1 and found that it resulted in the



(*S*)-4, $[\alpha]_{589}$ +15.21° (78% o.p.)
(*R*)-4, $[\alpha]_{589}$ −4.6° (23% o.p.)
(*S*)-4, $[\alpha]_{589}$ +9.36° (48% o.p.)

(*S*)-5, $[\alpha]_{589}$ −14.80° (74% o.p.)
(*R*)-5, $[\alpha]_{589}$ +4.31° (21.5% o.p.)
(*S*)-5, $[\alpha]_{589}$ −9.25° (46% o.p.)

formation of optically active phosphine oxide (5)[8] with nearly full *inversion of configuration at phosphorus*.

We used also in the present study optically active *O*-methyl ethylphenylphosphinite (6) and *S*-ethyl ethylphenylthiophosphinite (7) as model compounds. Asymmetric synthesis

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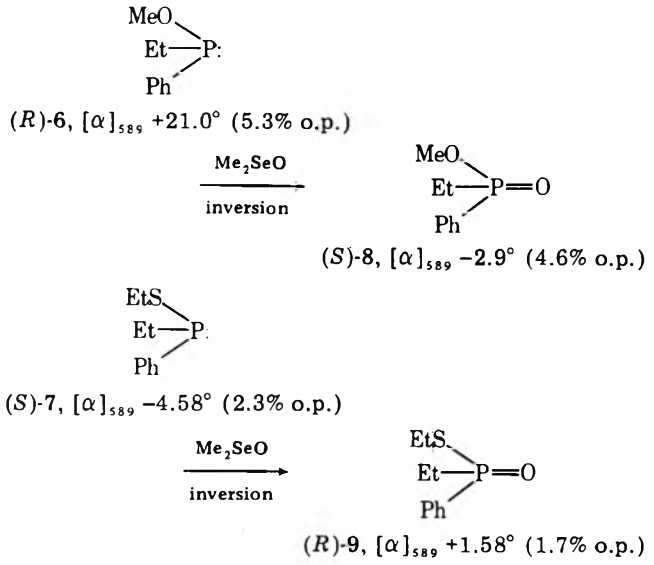


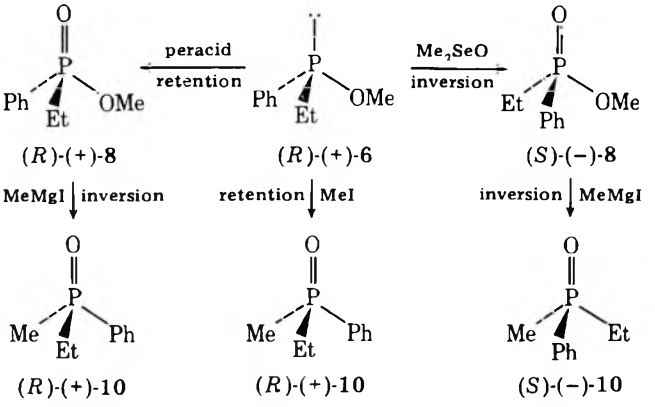
and stereochemistry of these P^{III} esters has recently been reported from this laboratory.[9] The results concerning oxidation of **6** and **7** by **1** are shown below.

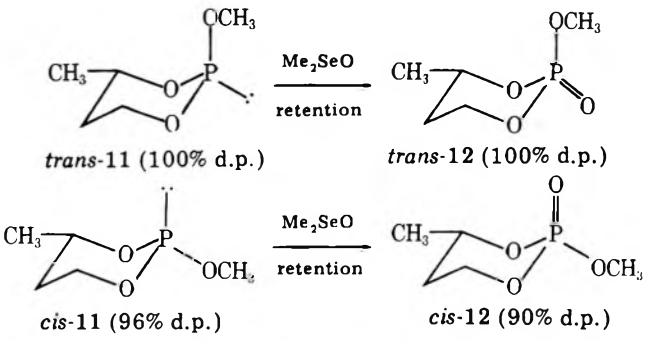
When (*R*)-(+)-**6**, $[\alpha]_{589}$ + 21.0°, was treated with **1**, (−)-*O*-methyl ethylphenylphosphinate (**8**), $[\alpha]_{589}$ −2.9°, was obtained. In order to establish the optical purity as well as the chirality at phosphorus of (−)-**8** it was further treated with methylmagnesium iodide to give (*S*)-(−)-methylethylphenylphosphine oxide (**10**), $[\alpha]_{589}$ −0.99° (4.3% optical purity). Since the latter reaction is known to proceed with inversion of configuration around phosphorus,[10] it follows that oxidation of the ester **6** by dimethyl selenoxide (**1**) is accompanied by inversion of configuration at the chiral phosphorus atom and the ester (−)-**8** should have the *S* configuration. In accord with this finding oxidation of (*R*)-(+)-**6**, $[\alpha]_{589}$ + 15.0°, by means of *m*-chloroperbenzoic acid gave (*R*)-(+)-**8**, $[\alpha]_{589}$ +1.4°, with retention of configuration at phosphorus.

The results discussed above together with the direct conversion of (*R*)-(+)-**6** into (*R*)-(+)-**10** in the Arbuzov reaction[9a] enabled us to construct a new diligostatic, three-reaction cycle involving one ligand metathesis[11] (see Scheme I).

In the series of experiments with optically active acyclic P^{III} compounds we have demonstrated that Me_2SeO oxidation proceeds with inversion of configuration at phosphorus. However, when diastereomeric 2-methoxy-4-methyl-1,3,2-dioxaphosphorinanes (**11**)[12a] were used as model compounds net *retention of configuration at phosphorus* was observed. Thus, treatment of the diastereomerically pure *trans*-**11** with **1** at room temperature gave pure *trans*-phosphate **12**. Oxidation of *cis*-**11** containing 4% of the trans isomer with **1** at −10 °C yielded *cis*-phosphate **12**[12b] having a diastereomeric purity of 90%.

Scheme I





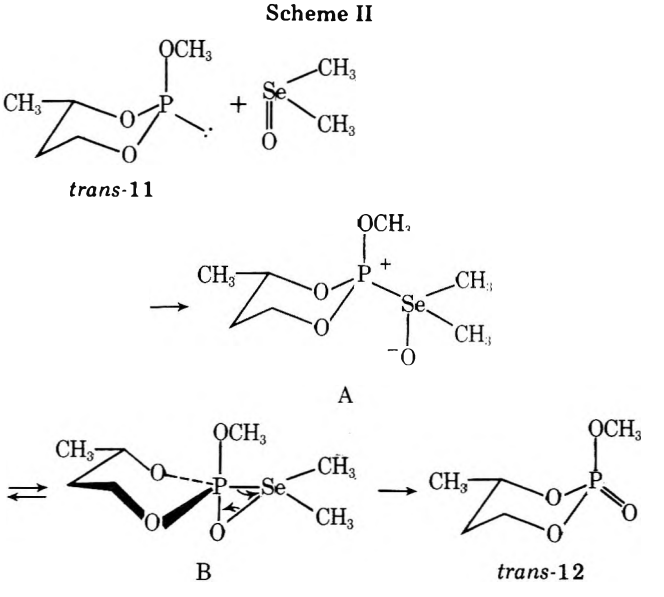
Retention at phosphorus observed in the oxidation of cyclic phosphites by Me_2SeO may be easily explained by the mechanistic sequence proposed in Scheme II.

It is reasonable to assume that the first step in the reaction between cyclic phosphites and **1** is the nucleophilic attack of phosphorus on the selenium atom of **1**, resulting in the formation of the "zwitterion" A. It may undergo then internal cyclization to give the intermediate phosphorane B, in which the six-membered ring spans two equatorial positions, the methoxy group and the three-membered ring oxygen atom occupy apical positions, and selenium occupies an equatorial position. This situation seems to us to be most convenient from the point of view of apicophilicity of substituents at phosphorus in trigonal-bypiramidal species.[13] Decomposition of the five-coordinate phosphorus intermediate B gives the phosphoryl compound with retention of configuration at phosphorus.

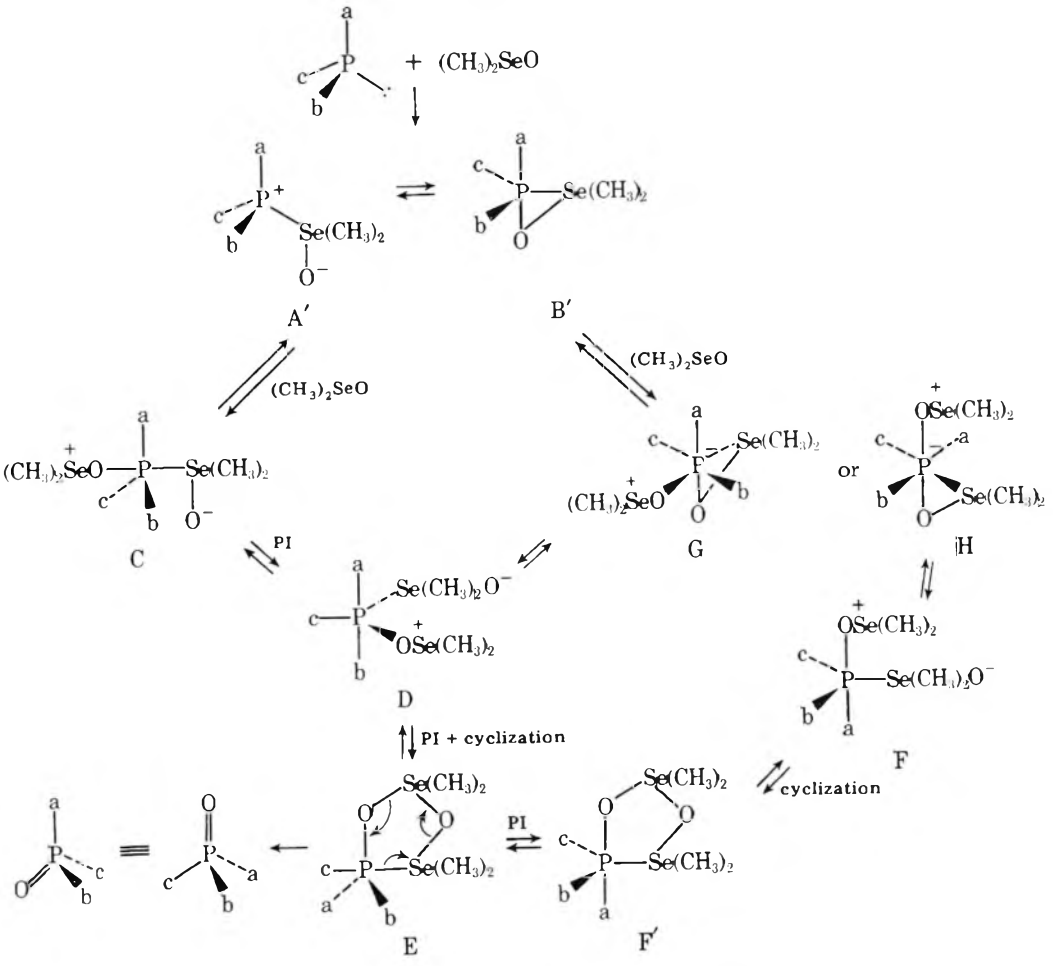
Since optically active acyclic trivalent phosphorus compounds were found to be oxidized by **1** with inversion of configuration at phosphorus, a different course of events should be considered (see Scheme III).

One can also assume that the phosphonium salt A′ and the pentacovalent phosphorus intermediate B′ are formed from **1** and acyclic P^{III} compounds.[14] However, the next step cannot be decomposition because it should give phosphoryl derivatives with retained configuration at phosphorus. We believe, therefore, that the second molecule of **1** attacks intermediate species A′ and B′ by means of the nucleophilic oxygen atom. The reaction of **1** with A′ should produce the phosphorane C, which after two permutational isomerizations (PI) and internal cyclization[15] should give the phosphorane E. Decomposition of E as depicted in Scheme III yields phosphoryl compound, dimethyl selenoxide, and dimethyl selenide. The overall stereochemistry of this cycle is inversion of configuration at phosphorus. If the phosphorane B′ is subjected to

Scheme II



Scheme III



nucleophilic attack by 1 the formation of two pentacoordinate phosphorus species D and F may be expected. The latter, after internal cyclization and one permutational isomerization, should also give the final pentacovalent phosphorus intermediate E, collapsing to the reaction products.

The transient formation of the hexacoordinate phosphorus anions G and H during the nucleophilic attack of 1 on B′ is an attractive hypothesis.[16]

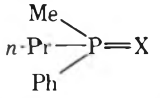
According to the mechanistic consideration presented above the opposite steric courses of the Me_2SeO oxidation of cyclic and acyclic systems may be attributed to the well-known difference in the sensitivity of cyclic and acyclic phosphorus compounds toward nucleophiles.[17]

Oxidation of Thio- and Selenophosphoryl Compounds by Dimethyl Selenoxide (1). As expected, dimethyl selenoxide (1) also reacts rapidly with thio- and selenophosphoryl compounds (13) at room temperature to give phosphoryl compounds (3), dimethyl selenide, and sulfur or selenium. The reaction is practically quantitative and the yields of the isolated phosphoryl derivatives 3 exceed 90%. Some representative examples are shown below.

$$R_3P{=}X + 1 \longrightarrow R_3P{=}O + CH_3SeCH_3 + X$$

13a, R = Ph; X = Se — 3a,b,d
b, R = EtO; X = Se
c, R = *n*-Bu; X = S

Since the stereochemistry and mechanism of the conversion of thio- and selenophosphoryl compounds into oxygen analogues have recently attracted attention in many laboratories[18] as well as in connection with our studies on the stereochemistry of this conversion by means of dimethyl sulfoxide,[4b,c] we have investigated the stereochemistry of the reaction now reported. It was found that oxidation of the optically active (*S*)-(−)-methylphenyl-*n*-propylphosphine sulfide



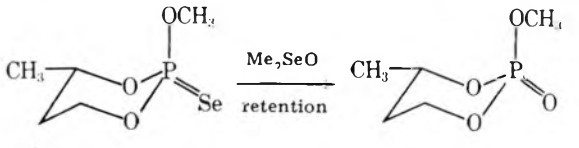
(*S*)-14, X = S, $[\alpha]_{589}$ −18.73° (84.2% o.p.)
(*S*)-15, X = Se, $[\alpha]_{589}$ −19.48° (100% o.p.)

(*R*)-5, $[\alpha]_{589}$ +14.4° (72% o.p.)
(*R*)-5, $[\alpha]_{589}$ +20.0° (100% o.p.)

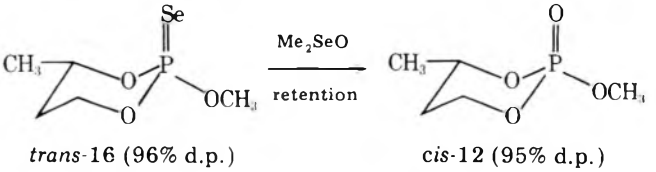
(14)[19] and (*S*)-(−)-methylphenyl-*n*-propylphosphine selenide (15)[20] by 1 leads to (*R*)-(+)-phosphine oxide (5)[8] and is accompanied *by inversion of configuration at phosphorus.*

Conversely, oxidation of cyclic *cis*- and *trans*-2-methoxy-2-seleno-4-methyl-1,3,2-dioxaphosphorinane (16)[18] by 1 was found to take place with full *retention at phosphorus* to give *trans*- and *cis*-phosphate 12, respectively.

The results described above show that the steric course of oxidation of cyclic and acyclic thio- and selenophosphoryl



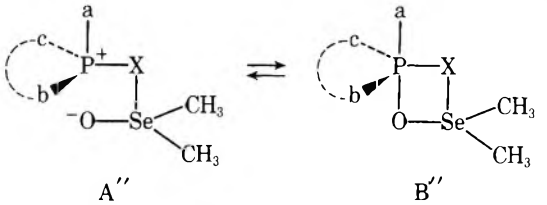
cis-16 (100% d.p.) — *trans*-12 (100% d.p.)



trans-16 (96% d.p.) — *cis*-12 (95% d.p.)

compounds by dimethyl selenoxide and by dimethyl sulfoxide[4b,c] is the same.

As in the case of the oxidation of cyclic 1,3,2-dioxaphosphorinanes and acyclic P^{III} compounds by Me_2SeO, the different stereochemistry of the oxidation of cyclic and acyclic thio(seleno)phosphoryl systems may be rationalized by assuming the formation of the intermediate adduct A″ or phosphorane B″, the mode of decomposition of which is dependent on the nature of substituents connected with the phosphorus atom.



A″ B″

X = S, Se

In the case of cyclic six-membered systems, which are less susceptible to nucleophilic attack at phosphorus, the intramolecular decomposition of these intermediates should be favored and would involve retention at phosphorus. On the other hand, nucleophilic attack of the second molecule of Me_2SeO on A″ or B″ containing acyclic substituents, followed by loss of dimethyl selenide and sulfur or selenium, would provide an alternative route to phosphoryl compounds accompanied by inversion at phosphorus.

Oxidation of Thiocarbonyl Compounds by Dimethyl Selenoxide (1). Selective Modification of 4-Thiouracil Nucleosides and Nucleotides. The present study on application of dimethyl selenoxide (1) as oxidizing agent was extended to thiocarbonyl compounds. In contrast to the electrophile-catalyzed Me_2SO oxidation,[4a,c] treatment of simple thioureas (17) with Me_2SeO itself at room temperature results in a clean conversion to the corresponding ureas (18).

$$(RNH)_2C{=}S + 1 \longrightarrow (RNH)_2C{=}O + CH_3SeCH_3 + S$$

17a–e 18a–e

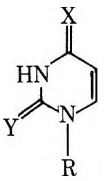
17a, R = H
b, R = *i*-Pr
c, R = *t*-Bu
d, R = c-Hex
e, R + R = $-CH_2CH_2-$

This new and extremely mild oxidation procedure of the thiocarbonyl group is of great importance from the point of view of chemical modification of nucleic acids. Following the discovery of 4-thiouridine in tRNA of *E. coli*,[21] many methods have been developed for the chemical transformation of the thio base[22] in order to elucidate the biochemical role of this minor component of tRNA. In the course of our studies we have used Me_2SO in the presence of acids or catalytic amounts of iodine.[5] However, as it has been mentioned above, there are some limitations connected with this method. This prompted an investigation of the Me_2SeO oxidation of thiouracils and higher nucleic acid components containing a thiocarbonyl group.

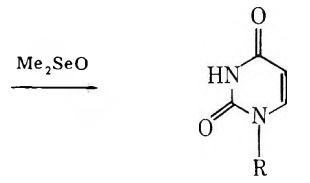
The reaction between thiouracils **19a–d** and **1** was carried out in methanol or methanol–chloroform mixture at 40 °C for ~6 h and it has been shown by TLC to give uracil **20a** isolated in 80–90% yields. Oxidation of 4-thiouridine (**19d**) by Me_2SeO in ethanol at room temperature afforded uridine (**20b**) in 82% yield.

Finally, oxidation of uridylyl-(3′-5′)-4-thiouridine (**21**) by Me_2SeO was investigated in order to show that the internucleotidic bond is stable under the reaction conditions. Also in this case quantitative conversion of the unprotected **21** into **22** was achieved at room temperature in ethanol solution.

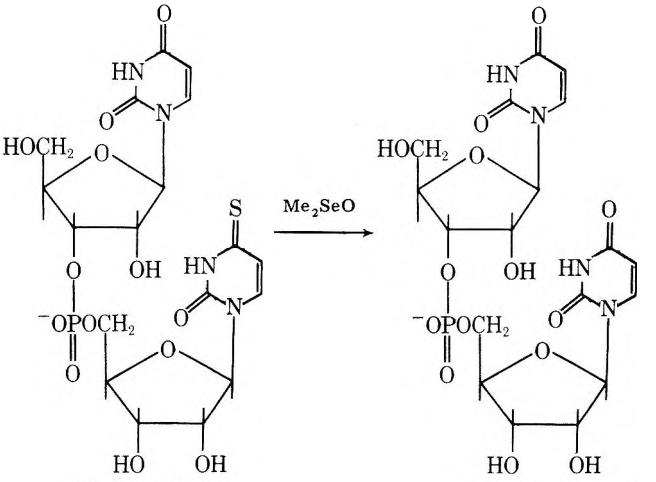
It should be pointed out that the ease with which thiouracils, 4-thiouridine, and thionucleotide **21**, are oxidized by



19a, Y = S; X = O; R = H
b, Y = O; X = S; R = H
c, Y = S; X = S; R = H
d, Y = O; X = S; R = ribofuranosyl



20a, R = H
b, R = ribofuranosyl



21, UpUs[4] 22, UpU

Me_2SeO as well as the fact that no degradation of the sugar moiety and no breaking of the internucleotide bond was observed under the experimental conditions employed could permit selective modification of the 4-thiouracil residues in tRNA. Studies in this direction are in progress in our Laboratory.

Experimental Section

General. Melting points and boiling points are uncorrected. ^1H NMR spectra were recorded on a R12B Perkin-Elmer spectrometer (Me_4Si as internal standard). ^{31}P NMR spectra were obtained on a Jeol JNM-C-60 H1 spectrometer (85% H_3PO_4 as external standard). In this paper the new convention of positive ^{31}P signals to low field from H_3PO_4 is used. IR spectra were recorded on a Spektromom 2000 spectrophotometer. Thin-layer chromatograms for analytical purposes were run on glass plates (5 × 20 cm) coated with a 2-mm layer of silica gel GF_{254} (Merck). Column chromatography was done on silica gel (Merck, 100–200 mesh) using the Laboratory Data Control set containing dual wavelength UV absorbance detector (254 and 280 nm), constametric IIG, and recorder 3402 units. GLC analysis was carried out with Varian Aerograph Model 1520 flame ionization gas chromatograph. Optical activity measurements were made with a Perkin-Elmer 241 MC photopolarimeter; concentrations of the solutions were about 2 g/100 mL.

Dimethyl selenoxide (1) was prepared according to Poetzold et al.[23] from dimethyl selenide via the dibromo derivative.[24]

Oxidation of Triphenylphosphine (2a) by Dimethyl Selenoxide (1). To a solution of triphenylphosphine (**2a**) (1.3 g, 0.005 mol) in chloroform (5 mL) an excess of **1** (0.75 g, 0.006 mol) in chloroform (5 mL) was added at room temperature. The reaction progress was controlled by TLC (R_f 0.88 and 0.12 for **2a** and **3a**, respectively). After 1 h dimethyl selenide was distilled off and trapped by an ethanol solution of mercury(II) chloride [0.5 g of $(CH_3)_2Se{\cdot}HgCl_2$, yield 91%, mp 150–152 °C (lit.[25] 151–153 °C)]. After cooling, chloroform (5 mL) was added and the organic layer was washed with water (3 × 3 mL), dried,

Table I. Oxidation of Trivalent Phosphorus, Thio(seleno)phosphoryl and Thio(seleno)carbonyl Compounds by Dimethyl Selenoxide 1

Substrate	Registry no.	Product	Registry no.	Yield, %	Physical data (lit. data)
2a, Ph_3P	603-35-0	**3a**, Ph_3PO	791-28-6	100	mp 156–158 °C (mp 154–157 °C[26])
2b, $(EtO)_3P$	122-52-1	**3b**, $(EtO)_3PO$	78-40-0	83	bp 90 °C (8 mmHg), n^{23}_D 1.4058, δ_{31P} − 1.0
2c, $(Me_2N)_3P$	1608-26-0	**3c**, $(Me_2N)_3PO$	680-31-9	84	bp 100 °C (0.2 mmHg)
13a, Ph_3PSe	3878-44-2	**3a**, Ph_3PO		100	mp 155–158 °C
13b, $(EtO)_3PSe$	2651-89-0	**3b**, $(EtO)_3PO$		92	bp 80 °C (15 mmHg), n^{20}_D 1.4062
13c, *n*-Bu_3PS	3084-50-2	**3d**, *n*-Bu_3PO	814-29-9	76	bp 90 °C (0.9 mmHg), δ_{31P} +43.7 (δ_{31P} +43.2[27])
17a, $(H_2N)_2CS$	62-56-6	**18a**, $(H_2N)_2CO$	631-62-9	81	mp 148–151 °C (mp 140–151 °C[28])[a]
17b, $(i\text{-PrNH})_2CS$	2986-17-6	**18b**, $(i\text{-PrNH})_2CO$	4128-37-4	84	mp 188–192 °C (mp 192 °C[29])
17c, $(t\text{-BuNH})_2CS$	4041-95-6	**18c**, $(t\text{-BuNH})_2CO$	5336-24-3	86	mp 239–242 °C (mp 242 °C[30])
17d, $(c\text{-}C_6H_{11}NH)_2CS$	1212-29-9	**18d**, $(c\text{-}C_6H_{11}NH)_2CO$	2387-23-7	93	mp 225–228 °C (mp 229–230 °C[31])
17e, c-$NHCH_2$-$CH_2NHC(=S)$	96-45-7	**18e**, c-$NHCH_2$-$CH_2NHC(=O)$	120-93-4	77	mp 130–135 °C (mp 131°C[32])

[a] Mp refers to the complex of urea with oxalic acid, $2Co(NH_2)_2{\cdot}H_2C_2O_4$.

and evaporated to give triphenylphosphine oxide (**3a**) (1.35 g, 100%, mp 154–157 °C). Recrystallization from benzene–petroleum ether afforded analytically pure phosphine oxide 3a [1.2 g, mp 156–158 °C (lit.[26] mp 154–157 °C)].

The experimental results concerning oxidation of triethyl phosphite (**2b**) and hexaethyl phosphorotriamidite (**2c**) are given in Table I.

Conversion of (*R*)-(−)-Methylphenyl-*n*-propylphosphine (4) to Phosphine Oxide (*R*)-(+)-5 by Means of Dimethyl Selenoxide (1). To a solution of 4 (0.24 g, 0.0014 mol), $[\alpha]_{589}$ −4.6° (toluene), in chloroform (5 mL) a small molar excess of 1 in chloroform was added. After 15 min, chloroform and dimethyl selenide were removed and water (5 mL) was added to the residue. The aqueous layer was extracted with chloroform (3 × 5 mL) and the organic layer was dried over $MgSO_4$ and evaporated. The residue was distilled to give (*R*)-(+)-methylphenyl-*n*-propylphosphine oxide (**5**), 0.16 (64%), $[\alpha]_{589}$ +4.31° (methanol), δ_{31P} +42.46 ppm.

Under the same conditions phosphine (*S*)-(+)-**4**, $[\alpha]_{589}$ +15.21° (toluene) and $[\alpha]_{589}$ +9.36° (toluene), was converted into phosphine oxide (*S*)-(−)-**5**, having $[\alpha]_{589}$ −14.80° (methanol) and $[\alpha]_{589}$ −9.25° (methanol), respectively.

Reaction of (*R*)-(+)-*O*-Methyl Ethylphenylphosphinite (6) with Dimethyl Selenoxide (1). To a stirred solution of 6 (0.6 g, 0.0035 mol), $[\alpha]_{589}$ +21.0° (benzene), in chloroform (5 mL) **1** (0.5 g, 0.004 mol) in methanol or chloroform (5 mL) was added at −20 °C. After stirring at room temperature for 10 min the reaction mixture was treated with water (10 mL) and the reaction product was extracted with chloroform (3 × 10 mL). The chloroform layer was dried over anhydrous $MgSO_4$ and evaporated to afford (*S*)-(−)-*O*-methyl ethylphenylphosphinate (**8**) purified by distillation: 0.55 g (84%); bp 95–98 °C (0.5 mmHg); n^{22}_D 1.5213; $[\alpha]_{589}$ −2.9° (methanol); δ_{31P} +49.95 ppm.

Oxidation of (*R*)-(+)-*O*-Methyl Ethylphenylphosphinite (6) by *m*-Chloroperbenzoic Acid. To a solution of 6 (0.5 g, 0.003 mol), $[\alpha]_{589}$ +15.0° (benzene), in ether (5 mL) a solution of *m*-chloroperbenzoic acid (0.75 g, 0.0043 mol) in ether (15 mL) and benzene (1 mL) was added at room temperature. After the usual workup and distillation at 0.2 mmHg, phosphinate (*R*)-(+)-**8** was obtained, $[\alpha]_{589}$ +1.4° (c 4.5, methanol). The ester was identical in all respects with that prepared as described above.

Reaction of (*S*)-(−)-*S*-Ethyl Ethylphenylthiophosphinite (7) with Dimethyl Selenoxide (1). A solution of 0.6 g (0.003 mol) of **7**, $[\alpha]_{589}$ −4.58° (neat), in chloroform (10 mL) was treated with an equimolar amount of 1 (0.375 g) in chloroform (5 mL) at −10 °C. After stirring for 10 min at room temperature water (20 mL) was added to the reaction mixture. The aqueous layer was extracted with chloroform (3 × 10 mL). The combined chloroform extracts were dried and evaporated to give the crude (*R*)-(+)-*S*-ethyl ethylphenylthiophosphinate (**9**) purified by distillation: 0.5 g (78%); n^{21}_D 1.5298; $[\alpha]_{589}$ +1.58° (benzene); δ_{31P} +53.3 ppm.

Conversion of (*S*)-(−)-*O*-Methyl Ethylphenylphosphinate (8) to (*S*)-(−)-Methylethylphenylphosphine Oxide (10). A solution of methylmagnesium iodide prepared from methyl iodide (0.55 g) and magnesium (0.08 g) in ether (20 mL) was treated with **8**, $[\alpha]_{589}$ − 2.9° (0.55 g, 0.003 mol) in ether (5 mL). The reaction was then quenched with saturated aqueous ammonium chloride (10 mL). The layers were separated and the aqueous layer was extracted with chloroform (3 × 10 mL). The organic layers were combined, dried, and evaporated. After distillation at 0.4 mmHg (*S*)-(−)-methylethylphenylphosphine oxide (**10**) was obtained: 0.3 g (60%); $[\alpha]_{589}$ −0.99° (methanol); δ_{31P} +44.55 ppm. The material was identical by TLC with **10** prepared by us in another study.[9]

Oxidation of *trans*-2-Methoxy-4-methyl-1,3,2-dioxaphosphorinane (11) by Dimethyl Selenoxide (1). A solution of *trans*-**11** (1.5 g, 0.01 mol) in benzene (10 mL) was treated with **1** (1.375 g, 0.011 mol) in benzene (5 mL) at room temperature. After a few minutes benzene and dimethyl selenide were removed and chloroform (20 mL) was added. The organic layer was washed with water, dried, and evaporated to give *trans*-2-methoxy-2-oxo-4-methyl-1,3,2-dioxaphosphorinane (**12**) isolated by distillation: 0.72 g (85%); bp 95 °C (0.1 mmHg). The product was diastereomerically pure by GLC.

Oxidation of *cis*-11 by 1. To a solution of **11** (1.5 g, 0.01 mol) consisting of *cis*-**11** (96%) and *trans*-**11** (4%) in benzene–chloroform (15 mL–5 mL) a solution of **1** (1.375 g, 0.011 mol) in chloroform (5 mL) was added at −10 °C. The workup as described above gave *cis*-2-methoxy-2-oxo-4-methyl-1,3,2-dioxaphosphorinane (**12**) as a 90% diastereomerically pure sample (GLC assay); 1.38 g (82%); bp 92 °C (0.1 mmHg).

Reaction of Triphenylphosphine Selenide (13a) with Dimethyl Selenoxide (1). A solution of triphenylphosphine selenide (**13a**) (0.345 g, 0.001 mol) in chloroform (10 mL) was treated with **1** (0.13 g, 0.00104 mol) in chloroform (2 mL). After 15 min dimethyl selenide was distilled off and trapped by an ethanol solution of mercury(II) chloride (0.103 g of $(CH_3)_2Se{\cdot}HgCl_2$, yield 94%). To a residual solution, after cooling, chloroform (10 mL) was added and selenium (0.079 g, 100%) was filtered off. The chloroform solution was washed with water, dried, and evaporated to give triphenylphosphine oxide (**3a**); 0.278 g (100%); mp 155–158 °C; R_f 0.20 for **3a**, R_f 0.78 for **13a** (benzene–ethyl acetate, 1:1).

The experimental results concerning oxidation of triethyl selenophosphate (**13b**) and tri-*n*-butylphosphine sulfide (**13c**) are given in Table I.

Conversion of (*S*)-(−)-Methylphenyl-*n*-propylphosphine Sulfide (14) to (*R*)-(+)-Methylphenyl-*n*-propylphosphine Oxide (5) by Means of Dimethyl Selenoxide (1). To a solution of **14** (0.215 g, 0.001 mol), $[\alpha]_{589}$ −18.73° (methanol), in chloroform (5 mL) was added a solution of **1** (0.1375 g, 0.0011 mol) in chloroform (2 mL). After few minutes methanol (5 mL) was added to the reaction mixture and sulfur (0.029 g, 90%) was filtered off. The filtrate was evaporated and water (10 mL) was added to the residue. The aqueous layer was extracted with ether (3 mL) and then with chloroform (3 × 3 mL). The combined organic extracts were dried and evaporated. The residue was distilled to give 0.137 g (76%) of (*R*)-(+)-methylphenyl-*n*-propylphosphine oxide (**5**), $[\alpha]_{589}$ +14.4° (methanol).

Conversion of (*S*)-(−)-Methylphenyl-*n*-propylphosphine Selenide (15) to (*R*)-(+)-Methylphenyl-*n*-propylphosphine Oxide (5) by Means of Dimethyl Selenoxide (1). A solution of **15** (54 mg, 0.00022 mol), $[\alpha]_{578}$ −19.48° (methanol), in benzene (5 mL) was treated with **1** used in small molar excess. Selenium (17.2 mg, 100%) was filtered off and the filtrate evaporated. The residue was treated with water (3 mL) and the aqueous phase was extracted with chloroform (3 × 3 mL). The organic layer was dried and evaporated to give **5** isolated by distillation: 32 mg (80%); $[\alpha]_{589}$ +20.0 (methanol); δ_{31P} +42.4 ppm.

Oxidation of *cis*-2-Methoxy-2-seleno-4-methyl-1,3,2-dioxaphosphorinane (16) by Dimethyl Selenoxide (1). To a solution of *cis*-**16** (1.15 g, 0.005 mol) in chloroform (10 mL) an equimolar amount

of **1** in chloroform was added. After a few minutes dimethyl selenide formed and was distilled off and trapped by an ethanol solution of mercury(II) chloride [0.47 g of $(CH_3)_2Se{\cdot}HgCl_2$, 93%]. The reaction mixture was then treated with chloroform (5 mL), cooled, and filtered in order to remove selenium (0.39 g, 100%). The chloroform solution was washed with water, dried, and evaporated to afford *trans*-**12** purified by distillation: 0.7 g (83%); bp 94 °C (0.2 mm). The product was identical (^{31}P NMR and GLC assay) with an authentic sample.[12b]

Oxidation of *trans*-16 by 1. Oxidation of *trans*-**16** (1.15 g, 0.005 mol) as a 96% diastereomerically pure sample according to the procedure described above gave selenium (0.39 g, 100%) and *cis*-**12** (0.74 g, 88%) having a diastereomeric purity 95% (GLC assay).

Oxidation of Thiourea (17a) by Dimethyl Selenoxide (1). To a solution of **17a** (0.76 g, 0.01 mol) in a mixture of chloroform and ethanol (5 mL, 1:1) a solution of **1** (1.375 g, 0.011 mol) in chloroform (5 mL) was added at room temperature. After 1 h sulfur (0.28 g, 87%) was filtered off. The filtrate was concentrated and treated with an acetone solution of oxalic acid. After 12 h the complex of urea (**18a**) with oxalic acid, $2CO(NH_2)_2{\cdot}H_2C_2O_4$, that crystallized was collected: 1.7 g (81%); mp 148–151 °C (lit.[28] mp 140–151 °C).

Oxidation of Diisopropylthiourea (17b) by 1. 17b (0.8 g, 0.005 mol) was dissolved in a mixture of chloroform and methanol (5 mL, 1:1) and treated with an equimolar amount of **1** in chloroform. After 1.5 h methanol (15 mL) was added to the reaction mixture and sulfur (0.13 g, 81%) filtered off. The filtrate was evaporated and the residue was crystallized from ethanol to give diisopropylurea (**18b**): 0.61 g (84%); mp 188–192 °C (lit.[29] mp 192 °C).

Oxidation of other thioureas (**17c**, **17d**, and **17e**) was carried out according to the procedure described above. The results are summarized in Table I.

Oxidation of Thiouracils 19 by Dimethyl Selenoxide (1). General Procedure. Thiouracil **19** (0.005 mol) dissolved in a mixture of methanol (2.5 mL) and chloroform (2.5 mL) was treated with **1** (0.0055 mol). The reaction mixture was heated at 40 °C for 6 h. Dimethyl selenide which distilled off during the reaction was trapped by an ethanol solution of mercury(II) chloride. After cooling and addition of methanol, sulfur was filtered off. Then, the solution was evaporated and the crude product, **20**, was isolated by column chromatography on silica gel (GF_{254}).

The purity of uracil **20** was controlled by TLC using isopropyl alcohol–ammonia–water (7:1:2) as developing system; in the case of uridine (**20b**) butanol–water (86:14) was used: R_f 0.78 for **19a**, 0.80 for **19b**, 0.89 for **19c**, 0.40 for **19d**, 0.72 for **20a**, and 0.18 for **20b**.

From **19a**, **19b**, and **19c** uracil **20a** was obtained in 90, 85, and 79% yield, respectively. Oxidation of 4-thiouridine (**19d**) afforded uridine **20b** in 82% yield.

Synthesis of Uridylyl-(3′-5′)-4-thiouridine (21). To a solution of the calcium salt of 2′-*O*-tetrahydropyranyl-5′-*O*-acetyluridine 3′-phosphate[33] (100 mg, 2×10^{-4} mol) Dowex 50X(H^+) was added. After few minutes the ion exchanger was filtered off and the filtrate was concentrated at 10 °C. The residue was coevaporated with three portions of pyridine and dissolved in anhydrous pyridine (3 mL). To this solution 2′-3′-isopropylidene-4-thiouridine[34] (300 mg) in pyridine (10 mL) was added and then dicyclohexylcarbodiimide (0.5 g). The reaction mixture was left to stand for 72 h at room temperature and then treated with water (12 mL) and pyridine (10 mL). After 8 h the reaction solution was extracted with petroleum ether in order to remove unreacted carbodiimide, filtered, and evaporated. The residue was kept with a dioxane–ammonia (1:1, 10 mL) mixture for 12 h at room temperature. After evaporation of solvents the concentrate was dissolved in ethanol and acetic acid and refluxed for 20 min. Then the solution was concentrated at 0.2 mmHg and coevaporated with methanol. The residue was dissolved in pyridine and chromatographed on a paper Whatman 3MM using isopropyl alcohol–ammonia–water (7:1:3) as solvent system. The fraction containing the title compound **21**, R_f 0.20, was extracted with water. Evaporation of the water solution afforded **21**;[35] 35 mg (30%).

Compound **21** (3 mg) was dissolved in water (0.1 mL) and treated with aqueous ammonia (pH 8) and then with the pancreatic ribonuclease solution. After the incubation for 5 h the mixture was chromatographed on a glass plate covered with cellulose using isopropyl alcohol–ammonia–water (7:1:2) as developing system. Two spots, R_f 0.13 and 0.38, were observed which correspond to uridine 3′-phosphate and 4-thiouridine, respectively.

Conversion of 21 to 22 by Means of Dimethyl Selenoxide (1). A sample of 13 mg (2×10^{-5} mol) of **21** was dissolved in ethanol and treated with **1** in methanol. After 24 h the solvents were evaporated and the product, **22**, was isolated by preparative TLC using butanol–water (86:14) as developing system: R_f 0.52.

In order to confirm the structure it was dissolved in aqueous pyridine solution and treated with the pancreatic ribonuclease solution for 48 h at room temperature. The solution was concentrated and subjected to paper electrophoresis on Whatman No 1 paper. Two spots, R_f 1.00 and 0.17, were observed which correspond to uridine 3′-phosphate and uridine, respectively.

Acknowledgment. We thank Dr. J. Omelańczuk for providing us with the results of oxidation of optically active phosphinite **8** with *m*-chloroperbenzoic acid.

Registry No.—**1**, 4371-90-8; (*R*)-**4**, 13153-89-4; (*S*)-**4**, 701-03-1; (*R*)-**5**, 17170-48-8; (*S*)-**5**, 1515-99-7; (*R*)-**6**, 57322-07-3; (*S*)-**7**, 62621-07-2; (*S*)-**8**, 65665-33-0; (*R*)-**9**, 65665-34-1; (*S*)-**10**, 26515-05-9; *trans*-**11**, 7735-81-1; *cis*-**11**, 7735-85-5; *trans*-**12**, 33996-03-1; *cis*-**12**, 33996-04-2; (*S*)-**14**, 13153-91-8; (*S*)-**15**, 34641-79-7; *cis*-**16**, 33996-02-0; *trans*-**16**, 33996-01-9; **19a**, 141-90-2; **19b**, 591-28-6; **19c**, 2001-93-6; **19d**, 13957-31-8; **20a**, 66-22-8; **20b**, 58-96-8; **21**, 22249-22-5; **22**, 2415-43-2; 2′-*O*-tetrahydropyranyl-5′-*O*-acetyluridine 3′-phosphate calcium salt, 65665-35-2; 2′,3′-isopropylidene-4-thiouridine, 14795-36-9.

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(15) We assumed that the formation of the five-membered ring is more probable in apical and equatorial positions.
(16) Discussion on the participation of a hexacoordinate phosphorus species during phosphorylation may be found in recent papers by Ramirez and his co-workers: F. Ramirez, J. F. Marecek, H. Tsuboi, H. Okazaki, and M. Nowakowski, *Phosphorus*, **6**, 215 (1976); F. Ramirez and J. F. Marecek, *Tetrahedron Lett.*, 3791 (1976); F. Ramirez, M. Nowakowski, and J. F. Marecek, *J. Am. Chem. Soc.*, **98**, 4330 (1976); F. Ramirez, J. F. Marecek and H. Okazaki, *ibid.*, **98**, 5310 (1976); F. Ramirez and J. F. Marecek, *Tetrahedron Lett.*, 967 (1977); F. Ramirez, J. F. Marecek, H. Tsuboi, and H. Okazaki, *J. Org. Chem.*, **42**, 771 (1977).
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On the other hand, inversion at phosphorus observed in the case of oxidation of acyclic trivalent phosphorus compounds may be a consequence of a nucleophilic attack of A′ by means of the negatively charged oxygen atom on the second Me_2SeO molecule and the decomposition of this intermediate via the cyclic phosphorane in which the selenium and oxygen atoms of two Me_2SeO molecules forming the five-membered ring occupy two equatorial positions. These mechanistic possibilities are currently being investigated.
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Heavy-Atom Effect in Photoisomerization of 4-Pyrones and 4-Pyridones

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Internal and external heavy-atom effects were applied to determine the excited state involved in photoisomerization of 2,6-dimethyl-3,5-bis(para-substituted phenyl)-4-pyrones to 3,6-bis(para-substituted phenyl)-4,5-dimethyl-2-pyrones. A similar method was used in the photorearrangement of 1,2,6-trimethyl-3,5-bis(para-substituted phenyl)-4-pyridones to 1,4,6-trimethyl-3,5-bis(para-substituted phenyl)-2-pyridones. Both 4-pyrones and 4-pyridones phosphoresce at 77 K from the π,π^* triplet state and show a shorter phosphorescence lifetime with increasing atomic number of the halogen substituents. Quantum yields of both the photoisomerization and intersystem crossing of these 4-pyrones and 4-pyridones are not internally dependent on the atomic number of the substituent. Addition of the heavy-atom solvent (*n*-butyl bromide) decreases quantum yield of photoisomerization and increases intersystem crossing efficiency from the singlet to triplet excited states. This photoisomerization was not quenched by dienes, indicating that the photoisomerization of both 4-pyrones and 4-pyridones proceeds via their π,π^* singlet.

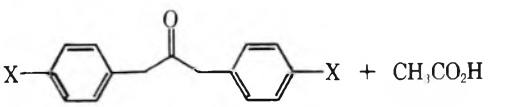
Although internal and external heavy-atom effects on photophysical processes have been extensively investigated using the spectroscopic and theoretical methods,[2-5] studies on a heavy-atom effect on a photochemical reaction have been relatively few until the discovery by Cowan and Drisco[6] that the photodimerization of acenaphthylene was beneficially perturbed when a heavy-atom solvent was present. Somewhat later, a heavy-atom effect was widely utilized in the photochemical cycloaddition of acenaphthylene to acrylonitrile,[7] pentadiene,[8] cyclopentadiene,[9] and maleic anhydride.[10] The effect was also observed in the photochemical isomerization of bicyclo[4.2.1]nona-2,4-dienes[11] and bromostilbenes[12] and in the photoabstraction–cyclization of methyl *o*-benzyloxyphenylglyoxylate.[13]

We recently reported the photoisomerization of 4-pyrones to 2-pyrones[14] and of 4-pyridones to 2-pyridones.[15] Evidence was given to support the idea that the photorearrangement of the 4-pyridone[15] occurred in the excited singlet state, although the photoexcited state responsible for the photoisomerization of 4-pyrones[14] was not determined and further study has remained.

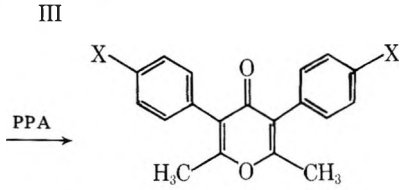
We now wish to report a study illustrating an application of a heavy-atom effect in determining the excited state involved in the photoisomerization of 4-pyrones. Emission spectra of 2,6-dimethyl-3,5-bis(para-substituted phenyl)-4-pyrones (I) were measured and the quantum yield in the photoisomerization of I, perturbed internally or externally by a heavy atom, was also determined. A similar study was extended to the photorearrangement of 1,2,6-trimethyl-3,5-bis(para-substituted phenyl)-4-pyridones (II). Comparison of the internal and external heavy-atom effects in the photoisomerization of I with those in the photorearrangement of II was anticipated to determine the nature of the excited state involved in the photoreaction of I, since the excited state responsible for the photoreaction of II was firmly established.[15]

Results and Discussion

2,6-Dimethyl-3,5-bis(para-substituted phenyl)-4-pyrones (I) were prepared by condensation of para,para'-disubstituted bibenzyl ketone (III) with acetic acid in the presence of polyphosphoric acid (PPA) as employed for the synthesis of Ia.[16,17] These 4-pyrones were condensed with methylamine in a sealed tube to form the corresponding 4-pyridones (II).[15b,18] The structures assigned to I and II rest on the



III



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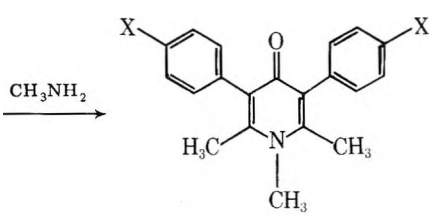

II

a, X = H; b, X = CH_3; c, X = F; d, X = Cl; e, X = Br

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Table I. Spectral Data of Absorption and Phosphorescence of 4-Pyrones and 4-Pyridones in Ethanol

Substrate	Registry no.	λ_{max}, nm (Absorption, ϵ)	λ_{max}, nm Phosphorescence	E_T,[b] kcal/mol	τ, s
Ia[a]	33731-54-3	221 (22600), 258 (12200)	454	62	0.29
Ib	65622-25-5	221 (22000), 261 (10600), 297 (860)	459	62	0.30
Ic	65622-26-6	255 (10100), 299 (320)	465	61.5	0.35
Id	65622-27-7	225 (30600), 256 (13800)	490	58	0.012
Ie	65622-28-8	229 (41900), 261 (sh, 21000)	492	58	0.0011
IIa[a]	42215-29-2	236 (19600), 275 (13500)	430	66.5	1.30
IIb	65622-29-9	236 (sh, 22000), 276 (13900)	430	66.5	1.40
IIc	65622-30-2	227 (24100), 274 (15200)	430	66.5	1.50
IId	65622-31-3	225 (26700), 275 (13200)	435	66	0.33
IIe	65622-32-4	228 (14600), 275 (14600)	435	66	0.045

[a] Reference 19. [b] Band maxima were taken as the triplet energy.

Table II. Quantum Yield and Intersystem Crossing Efficiency of 2,6-Dimethyl-3,5-bis(*p*-substituted phenyl)-4-pyrones and 1,2,6-Trimethyl-3,5-bis(para-substituted phenyl)-4-pyridones at Ambient Temperature

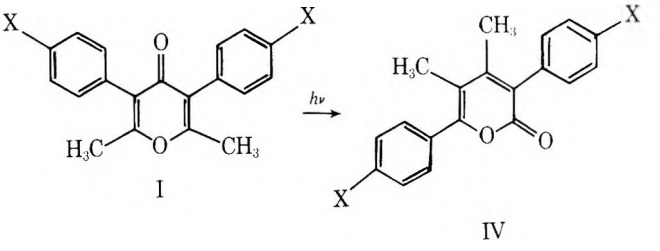
Substrate[a]	Quantum yield Φ	Φ_{rel}[b]	Intersystem crossing efficiency, ϕ_{isc}	$\phi_{rel\ isc}$[c]
Ia	0.40	(1)	0.36	(1)
Ib	0.48	1.2	0.25	0.69
Ic	0.44	1.1	0.27	0.75
Id	0.35	0.87	0.38	1.05
Ie	0.20[d]	0.5	0.38	1.05
IIa	0.21	(1)	0.074	(1)
IIb	0.18	0.84	0.080	1.1
IIc	0.22	1.0	0.065	0.87
IId	0.23	1.1	0.097	1.3
IIe	0.23[d]	1.1	0.10	1.35

[a] Solvents were dioxane for I and methanol for II. [b] Quantum yield relative to Ia for I and IIa for II. [c] Intersystem crossing efficiency relative to Ia for I and to IIa for II. [d] Because of the fast formation of by-products, quantum yield could not be determined as accurately as that of other compounds.

spectral (IR, NMR, and mass) and elemental analysis data which are detailed in the Experimental Section.

Electronic absorption spectra of 4-pyrones (Ib–e) and 4-pyridones (IIb–e) were measured in ethanol, and their band maxima and molar extinction coefficients are given in Table I together with those of each parent compound, Ia and IIa.[19] The 4-pyrones except Ic exhibit two intense π,π^* absorption bands at 220–230 and 255–261 nm. In addition to the strong π,π^* absorptions two 4-pyrones, Ib and Ic, show a weak n,π^* absorption band at 297–299 nm. This spectral pattern is similar to the spectrum of Ia.[19] 4-Pyridones (IIb–e) also show two intense π,π^* bands at 225–236 and 274–276 nm but no n,π^* band is observed, the pattern being similar to the spectrum of IIa.[19] Both 4-pyrones and 4-pyridones show no fluorescence at room temperature and 77 K. All 4-pyrones and 4-pyridones studied phosphoresce in rigid media at 77 K, and their triplet energies, band maxima, and phosphorescence lifetimes are listed in Table I. A similar pattern is observed in phosphorescence spectra of the substituted heteroaromatics (Ib–e and IIb–e) and the parent compounds (Ia and IIa), suggesting that the lowest triplet state of these compounds is mainly of π,π^* character.[19] The substituent effect (halogen atoms and the methyl group) on the excitation energy is not apparently observed in the absorption and phosphorescence spectra. On the other hand, the phosphorescence lifetime of 4-pyrones and 4-pyridones decreases with increasing atomic number of a halogen atom (Table I). This is in line with expectation based on the internal heavy-atom effect upon the phosphorescence rate from the π,π^* triplet,[2b,20] although this internal heavy-atom effect on the intersystem crossing efficiency from singlet to triplet states is not observed at room temperature. (See Table II and the following discussion.)

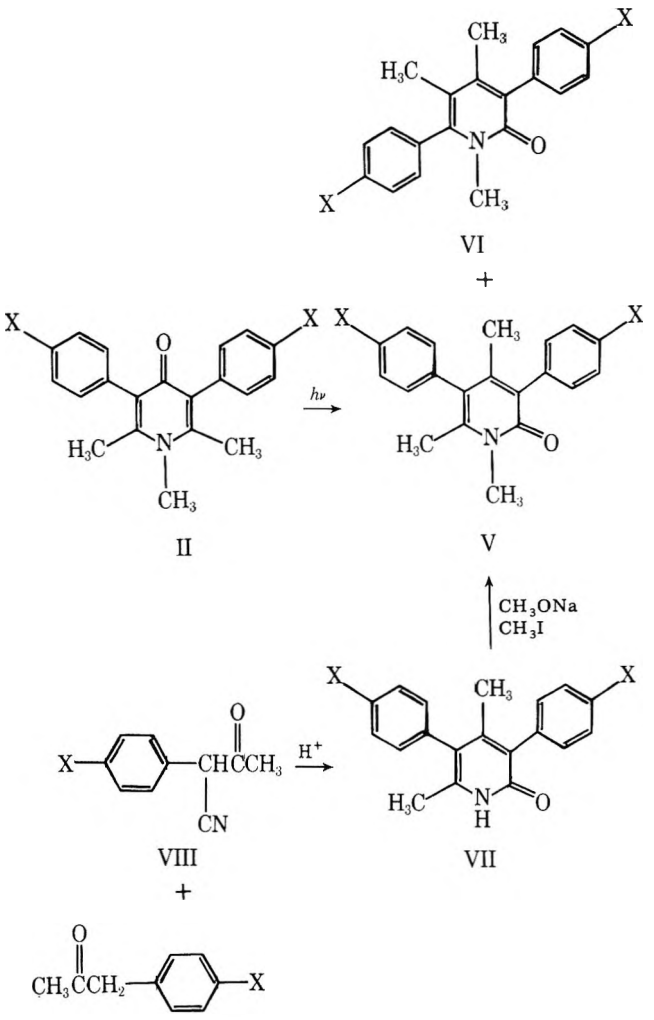
Preparative photochemical reaction was carried out with a medium-pressure mercury lamp in an immersion apparatus using a Vycor filter. Irradiation of 4-pyrones (Ib–e) in acetonitrile gave 2-pyrones (IVb–e) and the structural assignment was based on the spectral data. (Firm structural evidence was obtained in the parent compound IVa.[14b]) Photolysis of 4-pyridones (IIb–e) in methanol afforded 2-pyridones (Vb–e and VIb–e[21]). The structure of V was confirmed by no depression of melting point in a mixture of the photoproduct with an authentic sample and by agreement of NMR in IR spectra of the photoproduct with those of the authentic sample. Each authentic sample was independently prepared by *N*-methylation of 4,6-dimethyl-3,5-bis(para-substituted phenyl)-2-pyridones (Vb-e), which were synthesized from the reaction of α-acetyl para-substituted benzylcyanides (VIIb–e) with para-substituted phenylacetones (IXb–e). (For X = H the preparative procedure was reported.)[15b,22]



I IV

Quantum yield for appearance of IV from I or of V from II was determined in order to study the internal heavy-atom effect. Degassed and sealed quartz tubes containing a solution of I or II and an aqueous solution of potassium ferrioxalate for actinometry[23] were irradiated with 253.7-nm light in a rotating photochemical assembly. Reaction was controlled at low conversion to prevent appreciable light absorption by a photoproduct. Yield of the product was determined by an UV method. The results are given in Table II.

Table II also shows intersystem crossing efficiencies of I and II, which were measured by comparing the cis–trans conversion of *cis*-piperylene in the sensitized reaction by I or II with



that of the bezophenone-sensitized reaction.[24] Degassed and sealed quartz tubes containing the solutions of benzophenone and *cis*-piperylene were irradiated with 253.7-nm light for actinometry. The intersystem crossing efficiency for benzophenone at 253.7 nm was determined as 1.02 using potassium ferrioxalate actinometry.[23] The intersystem crossing efficiency was determined by extrapolating to infinite concentration of *cis*-piperylene. The results in Table II show that the presence of heavier atoms tends to slightly decrease quantum yield of the photoisomerization of I and II with slight increase of the intersystem crossing efficiency, although the internal heavy-atom effect is clearly observed in the phosphorecence lifetime at 77 K as shown in Table I. On the other hand, the external heavy-atom effect evidently increases intersystem crossing efficiencies of Ia, Id, IIa, and IId at room temperature and, then, decreases quantum yield of the photorearrangement (Table III). The intersystem crossing efficiency increases with higher concentration of *n*-butyl bromide as observed in the photodimerization of acenaphthylene.[6d] We cannot explain at the present time why the external heavy-atom effect on ϕ_{isc} and Φ is more effective than the internal one.[25]

Both *cis*- and *trans*-piperylene did not quench the photoisomerization of 4-pyrones (Ia and Id) to 2-pyrones.[26] Similarly the photoreaction of 4-pyridones (IIa and IId) was not quenched by *cis*- and *trans*-piperylene (Table IV). This quenching experiment suggests that the singlet state is responsible for the photoisomerization of both I and II. It was previously established that the photorearrangement of 4-pyridones to 2-pyridones proceeded via the π,π^* singlet.[15]

As shown in Table III for IIa and IId, use of high concentration of the heavy-atom solvent increases ϕ_{isc} for the S_1–T_1 process and, then, decreases quantum yield of the photoisomerization of II. A similar trend is observed in the external heavy-atom effect on the photorearrangement of Ia and Id (Table III).

Table III. External Heavy-Atom Effect on Intersystem Crossing Efficiency and Quantum Yields of Ia, Id, IIa, and IId at Ambient Temperature

Substrate[a]	*n*-Butyl bromide, %	Quantum yield Φ	Intersystem crossing efficiency, ϕ_{isc}
Ia	0	0.40	0.36
	10	0.33	
	50	0.27	0.47
	90	0.11	0.62
	100	0.095	0.68
Id	0	0.35	0.38
	10	0.25	
	50	0.23	0.40
	100	0.097	
IIa	0	0.21	0.074
	10	0.21	
	50	0.11	0.15
	90[b]	0.030	0.29
IId	0	0.23	0.097
	10	0.20	
	50	0.046	0.24
	90[b]	0.023	0.44

[a] Dioxane for Ia and Id. Methanol for IIa and IId. [b] Both IIa and IId are not soluble in neat *n*-butyl bromide.

Table IV. Quantum Yields for Formation of 2-Pyrones and 2-Pyridones

4-Pyrones or 4-pyridones[a]	Additive	Quantum yield, Φ
Ia	None	0.40
	trans-Piperylene (0.15 M)	0.38
	cis-Piperylene (0.15 M)	0.37
Id	None	0.35
	trans-Piperylene (0.2 M)	0.35
	cis-Piperylene (0.2 M)	0.33
IIa	None	0.21
	trans-Piperylene (0.15 M)	0.21
	cis-Piperylene (0.15 M)	0.19
IId	None	0.23
	trans-Piperylene (0.2 M)	0.21
	cis-Piperylene (0.2 M)	0.20

[a] The concentration was $1–3 \times 10^{-3}$ M for I and $3–7 \times 10^{-3}$ M for II. Solvents were dioxane for I and methanol for II.

Ineffectiveness of quenching by dienes and decrease of quantum yield in the heavy-atom solvent indicate that the photoisomerization proceeds via π,π^* singlet state,[27] since the n,π^* excited state is expected to be relatively insensitive to the heavy-atom perturbation[2,28] and since the n,π^* excitation of Ia did not produce IIa.[14b] These results suggest that the formation of IV involves the singlet excited states of both I and a 4,5-epoxycyclopent-2-en-1-one intermediate, because the photochemical rearrangement of the 4-pyrone to the latter intermediate and, then, to the 2-pyrone was recently established in UV irradiation of 3,5-dimethyl-4-pyrone in trifluoroethanol.[29]

This work illustrates an application of the heavy-atom effect in elucidating the nature of the excited state of the photoisomerization, in which care must be taken with evaluation of both internal and external heavy-atom effects.

Experimental Section

Microanalyses were conducted by Microanalytical Laboratories, Kyoto University. Infrared spectra were measured on a Jasco DS-

Table V. Preparation of 2,6-Dimethyl-3,5-bis(para-substituted phenyl)-4-pyrones

Substituent	Bibenzyl ketone, wt in g	Product, wt in g (%)	Mp, °C	% Calcd, Found C	H	Cl	Br
CH_3	IIIb,[a] 0.3	Ib, 0.23 (77)	162–163	82.86	6.62		
				82.71	6.56		
Cl	IIId,[b] 5	Id, 1.0 (20)	197–198.5	66.10	4.09	20.54	
				66.33	4.09	20.26	
Br	IIIe,[c] 0.3	Ie, 0.028 (10)	210–212	52.57	3.25		36.81
				52.75	3.44		36.95

[a] S. B. Cowan, D. E. Trucker, and E. I. Becker, *J. Am. Chem. Soc.*, **77**, 60 (1955). [b] F. J. Thaller, D. E. Trucker, and E. I. Becker, *ibid.*, **73**, 228 (1951). [c] E. J. Corey and M. F. Semmelhack, *ibid.*, **89**, 2755 (1967); E. Yoshisato and S. Tsutsumi, *J. Org. Chem.*, **33**, 869 (1968).

Table VI. Preparation of 1,2,6-Trimethyl-3,5-bis(para-substituted phenyl)-4-pyridones

Substituent	4-Pyrones, wt in g	4-Pyridones, wt in g (%)	Mp, °C	% Calcd, Found C	H	N	Cl	Br
CH_3	Ib, 0.4	IIb, 0.2 (50)	>300	83.24	7.30	4.41		
				83.18	7.15	4.37		
Cl	Id, 2.0	IId, 1.25 (63)	296–298	67.05	4.78	3.91	19.79	
				67.26	4.90	3.61	19.89	
Br	Ie, 1.5	IIe, 1.0 (66)	275–276	53.72	3.82	3.13		35.74
				53.54	3.84	3.11		35.82

402G grating spectrophotometer. Ultraviolet absorption spectra were obtained on a Hitachi 323 spectrophotometer. Phosphorescence excitation and emission spectra were measured on a Hitachi MPF-4 spectrofluorometer equipped with a Hitachi phosphoroscope attachment. Phosphorescence spectra (uncorrected) were measured by photographing the decay of emmission signals (displayed on an oscilloscope screen), following excitation of the exciting light. Lifetimes were calculated from the exponential decay curves obtained. NMR spectra were obtained at 60 MHz (Varian T-60A) or 100 MHz (Joel PS-100) using tetramethylsilane as internal standard. Chemical shifts were reported in parts per million (δ) from Me_4Si. Mass spectra were obtained by direct insertion on a Hitachi RMU-6L spectrometer. Melting points were uncorrected.

Preparation of 2,6-Dimethyl-2,5-bis(para-substituted phenyl)-4-pyrones. In general procedure 5 g of 4,4′-diflurobibenzyl ketone was added to a mixture of 31.5 g of acetic acid and 50 g of polyphosphoric acid at 70 °C. The mixture was stirred at 110–130 °C for 3 h and poured into 1000 mL of ice-cooled water. The reaction mixture was extracted with 200 mL of ether five times. The combined extracts were neutralized with aqueous sodium bicarbonate, washed thoroughly with water, and dried over anhydrous sodium sulfate. After removal of the solvent in vacuo the residual solid was chromatographed on silica gel with chloroform as eluent. Recrystallization of crude crystals from methanol gave 3.5 g (70%) of 2,6-dimethyl-3,5-bis(*p*-fluorophenyl)-4-pyrone (Ic): mp 212.0–214.0 °C; IR (KBr) 1640, 1600, 1500, 1430, 1415. 1400, 1325, 1295, 1220, 1155, 1145, 1095, 990, 840, 820 cm^{-1}; NMR ($CDCl_3$) δ 2.23 (s, 6 H), 6.80–7.40 (m, 8 H); mass spectrum (*m/e*) 313 (17), 312 (M^+, 87), 311 (100), 136 (15), 134 (21), 133 (40), 43 (71). Anal. Calcd for $C_{19}H_{14}O_2F_2$: C, 73.07; H, 4.52; F, 12.17. Found: C, 73.15; H, 4.28; F, 12.25.

The preparative condition and analytical results for other 4-pyrones are given in Table V. The spectral data for these compounds are as follows.

2,6-Dimethyl-3,5-bis(*p*-tolyl)-4-pyrone (Ib): IR (KBr) 1630, 1600, 1500, 1400, 1325, 1230, 1100, 1020, 980, 910, 800, 745 cm^{-1}; NMR ($CDCl_3$) δ 2.26 (s, 6 H), 2.40 (s, 6 H), 7.20 (s, 8 H); mass spectrum (*m/e*) 305 (15), 304 (M^+, 80), 303 (100), 151 (7), 132 (7), 130 (7), 129 (9), 128 (6), 115 (11), 43 (13).

2,6-Dimethyl-3,5-bis(*p*-chlorophenyl)-4-pyrone (Id): IR (KBr) 1645, 1620, 1590, 1490, 1410, 1390, 1330, 1295, 1230, 1090, 990, 845, 825, 790 cm^{-1}; NMR ($CDCl_3$) δ 2.22 (s, 6 H), 7.30 (q, J = 8.0 Hz, 8 H); mass spectrum (*m/e*) 347 (6), 346 (8), 345 (8), 344 (M^+, 10), 121 (7), 120 (6), 107 (7), 106 (30), 90 (27), 89 (21), 78 (27).

2,6-Dimethyl-3,5-bis(*p*-bromophenyl)-4-pyrone (Ie): IR (KBr) 1645, 1610, 1580, 1490, 1385, 1225, 1065, 1010, 985, 810, 780 cm^{-1}; NMR ($CDCl_3$) δ 2.22 (s, 6 H), 7.33 (q, J = 8.0 Hz, 8 H); mass spectrum (*m/e*) 437 (9), 436 (43), 435 (57), 434 (M^+, 100), 433 (93), 432 (52), 431 (43), 355 (11), 354 (21), 353 (11), 352 (20), 202 (18), 198 (13), 196 (25), 194 (14), 149 (71), 137 (21), 105 (86), 89 (16), 57 (61), 43 (43).

Preparation of 1,2,6-Trimethyl-3,5-bis(para-substituted phenyl)-4-pyridones. A typical procedure follows with the results for the remaining cases tabulated in Table VI. A mixture containing 1 g of 2,6-dimethyl-3,5-bis(*p*-fluorophenyl)-4-pyridone and 30 g of 40% aqueous methylamine in 100 mL of ethanol was heated in a stainless steel pressured bottle at 90 °C for 30 h. After evaporation of the solvent and excess methylamine under reduced pressure, the residual solid was recrystallized from benzene to yield 0.8 g (80%) of 1,2,6-trimethyl-3,5,-bis(*p*-fluorophenyl)-4-pyridone (IIc): mp 292.5–293.5 °C; IR (KBr) 1610, 1555, 1510, 1395, 1300, 1225, 1160, 1100, 830 cm^{-1}; NMR (CCl_4) δ 2.23 (s, 6 H), 3.55 (s, 3 H), 6.8–7.4 (m, 8 H); mass spectrum (*m/e*) 326 (8), 325 (M^+, 45), 324 (100), 312 (6), 311 (7), 297 (6), 296 (8), 162 (7), 133 (9), 78 (11), 56 (19). Anal. Calcd for $C_{20}H_{17}NOF_2$: C, 73.82; H, 5.27; N, 4.31, F, 11.68. Found: C, 73.55; H, 5.14; N, 4.49; F, 11.52.

Spectral Data. 1,2,6-Trimethyl-3,5-bis(*p*-tolyl)-4-pyridone (IIb): IR (KBr) 1610, 1545, 1490, 1300, 1175, 1150, 1105, 990, 960, 800, 750 cm^{-1}; NMR (CCl_4) δ 2.26 (s, 6 H), 2.35 (s, 6 H), 3.60 (s, 3 H), 7.0–7.4 (m, 8 H); mass spectrum (*m/e*) 318 (9), 317 (M^+, 46), 316 (100), 301 (5), 300 (4(= 2—9 (4), 158 (7), 157 (14), 56 (16).

1,2,6-Trimethyl-3,5-bis(*p*-chlorophenyl)-4-pyridone (IId): IR (KBr) 1615, 1595, 1495, 1390, 1300, 1155, 1095, 990, 960, 940, 850, 815, 790 cm^{-1}; NMR (CCl_4) δ 2.29 (s, 6 H), 3.60 (s, 3 H), 7.0–7.6 (m, 8 H); mass spectrum (*m/e*) 361 (6), 360 (15), 359 (29), 358 (M^+, 70), 357 (45), 356 (100), 321 (12), 143 (9), 141 (12), 56 (23).

1,2,6-Trimethyl-3,5-bis(*p*-bromophenyl)-4-pyridone (IIe): IR (KBr) 1615, 1595, 1485, 1390, 1300, 1070, 1010, 990, 960, 810, 785, 690 cm^{-1}; NMR (CCl_4) δ 2.23 (s, 6 H), 3.57 (s, 3 H), 7.0–7.6 (m, 8 H); mass spectrum (*m/e*) 449 (23), 448 (55), 447 (M^+, 48), 446 (100), 445 (27), 444 (51), 434 (6), 433 (6), 419 (4), 418 (4), 367 (12), 366 (9), 365 (10), 184 (10), 183 (12), 143 (27), 136 (14), 115 (19), 78 (64), 56 (40).

Irradiation of 2,6-Dimethyl-3,5-bis(para-substituted phenyl)-4-pyrones. A typical preparative photoirradiation of 2,6-dimethyl-3,5-bis(para-substituted phenyl)-4-pyrones follows with the results for the remaining cases summarized in Table VII.

A solution containing 0.2 g of 1,2,6-trimethyl-3,5-bis(*p*-fluorophenyl)-4-pyrone in 250 mL of acetonitrile was irradiated under nitrogen for 3 h using a 500-W Taika medium-pressure mercury lamp equipped with a Vycor filter. Removal of the solvent in vacuo left a pale yellow solid, which was chromatographed on silica gel with chloroform as eluent. The 1000-mL collection afforded colorless crystals, which, after recrystallization from cyclohexane–chloroform, gave 0.092 g (46%) of 3,6-bis(*p*-fluorophenyl)-4,5-dimethyl-2-pyrone (IVc): mp 161.0–162.5 °C; UV (CH_3CN) λ_{max} 233 (ϵ 9300), 325 nm (10400); IR (KBr) 1685, 1625, 1600, 1545, 1500, 1380, 1340, 1215, 1160, 1090, 1025, 1010, 955, 945, 840, 825 cm^{-1}; NMR ($CDCl_3$) δ 2.03 (s, 3 H), 2.06 (s, 3 H), 7.0–7.8 (m, 8 H); mass spectrum (*m/e*) 313 (7), 312 (M^+, 36), 285 (15), 284 (100), 161 (86), 123 (33), 95 (31). Anal. Calcd for $C_{19}H_{14}O_2F_2$: C, 73.07; H, 4.52; F, 12.17. Found: C, 73.26; H, 4.62; F, 12.34.

Spectral Data. 3,6-Bis(*p*-tolyl)-4,5-dimethyl-2-pyrone (IVb): UV (CH_3CN) λ_{max} 242 (ϵ 13500), 325 nm (16700); IR (KBr) 1700, 1630, 1540, 1500, 1445, 1380, 1335, 1185, 1080, 1030, 1010, 950, 935, 815, 715

Table VII. Irradiation of 2,6-Dimethyl-3,5-bis(para-substituted phenyl)-4-pyrones

Substituent	4-Pyrone, wt in g	Solvent mL	Irradiation time, h	2-Pyrone, wt in g (%)	Mp, °C	% Calcd, Found C	H	Cl	Br
CH_3	Ib, 0.3	CH_3CN 250	1.5	IVb, 0.23 (77)	148–149	82.86 82.67	6.62 6.47		
Cl	Id, 0.9	CH_3CN 900	5	IVd, 0.19 (21)	156–157	66.10 65.82	4.09 3.88	20.54 20.26	
Br	Ie, 0.3	CH_3CN 250	0.5	IVe, 0.03[a] (10)	193–194	52.57 52.50	3.25 3.08		36.81 36.95

[a] Prolonged irradiation produced tarry materials and reduced yield of IVe further.

Table VIII. Irradiation of 1,2,6-Trimethyl-3,5-bis(para-substituted phenyl)-4-pyridones

Substituent	4-Pyridones, wt in g	Solvent mL	Irradiation time, h	2-Pyridones, wt in g (%)	Mp, °C	% Calcd, Found C	H	N	Cl	Br
CH_3	IIb, 0.2	CH_3CN 250	2	Vb, 0.038 (19)	207–209	83.25 83.27	7.30 7.18	4.41 4.50		
				VIb, 0.006 (3)	160–162	83.25 83.08	7.30 7.20	4.41 4.31		
Cl	IId, 0.6	CH_3OH 600	7	Vd, 0.073 (14)[a]	166–168	67.05 67.21	4.78 5.06	3.91 3.78	19.79 19.66	
Br	IIe, 0.5	CH_3CN 250	0.5[b]	Ve, 0.049 (5)[b]	189–191	53.72 53.73	3.83 3.69	3.13 3.27		35.74 35.48

[a] An isomer of Vd appeared to be formed on the basis of TLC as in the case of IIb, but an amount of isolated product could not permit its identification. [b] Prolonged irradiation produced tarry materials and reduced yield of Ve further.

cm^{-1}; NMR ($CDCl_3$) δ 2.02 (s, 3 H), 2.06 (s, 3 H), 2.35 (s, 6 H), 7.0–7.5 (m, 8 H); mass spectrum (*m/e*) 305 (7), 304 (M^+, 26), 277 (24), 276 (100), 157 (48), 141 (14), 119 (21), 115 (13), 91 (27), 65 (16).

3,6-Bis(*p*-chlorphenyl)-4,5-dimethyl-2-pyrone (IVd): UV (CH_3CN) λ_{max} 242 (ϵ 12700), 325 nm (16700); IR (KBr) 1700, 1630, 1585, 1530, 1445, 1390, 1375, 1330, 1180, 1080, 1000, 945, 930, 870, 835, 825 cm^{-1}; NMR ($CDCl_3$) δ 2.05 (s, 3 H), 2.10 (s, 3 H), 7.0–7.6 (m, 8 H); mass spectrum (*m/e*) 348 (5), 347 (6), 346 (28), 345 (9), 344 (M^+, 48), 320 (12), 319 (13), 318 (65), 317 (20), 316 (100), 179 (13), 177 (40), 159 (8), 158 (12), 141 (25), 139 (25), 115 (9), 111 (15).

3,6-Bis(*p*-bromophenyl)-4,5-dimethyl-2-pyrone (IVe): UV (CH_3CN) λ_{max} 248 (ϵ 7500), 325 nm (15900); IR (KBr) 1705, 1625, 1585, 1535, 1485, 1380, 1340, 1185, 1085, 1070, 1005, 950, 935, 840, 830, 810 cm^{-1}; NMR ($CDCl_3$) δ 2.07 (s, 3 H), 2.12 (s, 3 H), 7.1–7.7 (m, 8 H); mass spectrum (*m/e*) 436 (18), 434 (M^+, 39), 432 (18), 408 (47), 407 (18), 406 (100), 404 (51), 223 (33), 221 (35), 203 (16), 185 (23), 183 (26), 155 (15), 141 (30), 115 (10), 77 (6).

Irradiation of 1,2,6-Trimethyl-3,5-bis(para-substituted phenyl)-4-pyridones. A typical procedure for the preparative irradiation of 1,2,6-trimethyl-3,5-bis(para-substituted phenyl)-4-pyridones is as follows. The irradiation conditions and results for the remaining compounds are summarized in Table VIII.

A solution of 0.3 g of 1,2,6-trimethyl-3,5-bis(*p*-fluorophenyl)-4-pyridone in 250 mL of acetonitrile was irradiated under nitrogen with a 500-W medium-pressure mercury lamp using Vycor filter at 29 °C for 2 h. The solvent was removed under reduced pressure and the residual solid was chromatographed on silica gel with chloroform–ether (8:2) as eluent. The first 600-mL collection afforded colorless crystals, which, after recrystallization from benzene–ligroin, gave 0.009 g (3.5%) of 1,4,5-trimethyl-3,6-bis(*p*-fluorophenyl)-2-pyridone (VIc): mp 215–217 °C; IR (KBr) 1630, 1605, 1580, 1540, 1505, 1420, 1390, 1280, 1220, 1210, 1155, 1090, 1010, 910, 880, 845, 825 cm^{-1}; NMR ($CDCl_3$) δ 1.80 (s, 3 H), 2.03 (s, 3 H), 3.23 (s, 3 H), 7.0–7.5 (m, 8 H); mass spectrum (*m/e*) 326 (18), 325 (M^+, 86), 324 (100), 298 (5), 297 (23), 296 (24), 162 (8), 136 (13), 133 (9), 95 (12). Anal. Calcd for $C_{20}H_{17}NOF_2$: C, 73.83; H, 5.27; N, 4.31; F, 11.68. Found: C, 73.55; H, 5.24; N, 4.29; F, 11.62.

The next 500-mL fraction furnished a solid, which, after recrystallization from benzene–ligroin, gave 0.10 g (36%) of 1,4,6-trimethyl-3,5-bis(*p*-fluorophenyl)-2-pyridone (Vc): mp 128–129 °C; UV (MeOH) λ_{max} 240 (ϵ 8700), 317 nm (9800); IR (KBr) 1625, 1600, 1585, 1525, 1500, 1420, 1300, 1215, 1150, 1085, 1010, 950, 865, 820, 785 cm^{-1}; NMR (CCl_4) δ 1.62 (s, 3 H), 2.05 (s, 3 H), 3.52 (s, 3 H), 6.8–7.4 (m, 8 H); mass spectrum (*m/e*) 326 (23), 325 (M^+, 99), 324 (100), 298 (7), 297 (33), 296 (33), 162 (11), 78 (20), 57 (23), 56 (52). Anal. Calcd for $C_{20}H_{17}NOF_2$: C, 73.83; H, 5.27; N, 4.31; F, 11.68. Found: C, 73.60; H, 5.42; N, 4.12, F, 11.41.

Spectral Data. 1,4,6-Trimethyl-3,5-bis(*p*-tolyl)-2-pyridone (Vb): UV (MeOH) λ_{max} 240 (ϵ 13000), 315 nm (11700); IR (KBr) 1625, 1580, 1530, 1510, 1420, 1370, 1355, 1300, 1235, 1200, 1175, 1105, 1095, 1015, 950, 865, 805, 780, 735 cm^{-1}; NMR (CCl_4) δ 1.60 (s, 3 H), 2.03 (s, 3 H), 2.33 (s, 6 H), 3.50 (s, 3 H), 6.8–7.2 (m, 8 H); mass spectrum (*m/e*) 318 (25), 317 (M^+, 100), 316 (96), 290 (8), 289 (34), 288 (22), 158 (11), 157 (18), 149 (16), 91 (14), 56 (17).

1,4,5-Trimethyl-3,6-bis(*p*-tolyl)-2-pyridone (VIb): IR (KBr) 1625, 1585, 1545, 1510, 1440, 1420, 1280, 1175, 1105, 1090, 1010, 905, 880, 805, 735, 715 cm^{-1}; NMR (CCl_4) δ 1.78 (s, 3 H), 2.03 (s, 3 H), 2.40 (s, 3 H), 2.45 (s, 3 H), 3.22 (s, 3 H), 7.0–7.4 (m, 8 H); mass spectrum (*m/e*) 318 (21), 317 (M^+, 87), 316 (100), 290 (7), 289 (74), 288 (17), 136 (7), 132 (9), 119 (14), 115 (8), 105 (6), 91 (19), 78 (28), 77 (10), 57 (14), 56 (11).

1,4,6-Trimethyl-3,5-bis(*p*-chlorophenyl)-2-pyridone (Vd): UV (MeOH) λ_{max} 246 (ϵ 6400), 318 nm (6700); IR (KBr) 1615, 1550, 1490, 1390, 1300, 1105, 1085, 1015, 990, 960, 850, 815, 790, 695 cm^{-1}; NMR ($CDCl_3$) δ 1.66 (s, 3 H), 2.10 (s, 3 H), 3.60 (s, 3 H), 7.0–7.4 (m, 8 H); mass spectrum (*m/e*) 361 (12), 360 (22), 359 (63), 358 (M^+, 81), 357 (100), 356 (95), 331 (19), 330 (22), 329 (28), 328 (22), 324 (14), 323 (22), 322 (26), 295 (10), 278 (10), 202 (11), 115 (11), 101 (11), 56 (40).

1,4,6-Trimethyl-3,5-bis(*p*-bromophenyl)-2-pyridone (Ve): UV (MeOH) λ_{max} 255 (ϵ 10200), 318 nm (10400); NMR (CCl_4) δ 1.67 (s, 3 H), 2.12 (s, 3 H), 3.60 (s, 3 H), 7.0–7.6 (m, 8 H); mass spectrum (*m/e*) 449 (47), 448 (52), 447 (M^+, 100), 446 (80), 445 (62), 444 (36), 419 (16), 418 (13), 369 (39), 368 (42), 367 (46), 366 (37), 339 (10), 202 (15), 144 (54), 143 (60), 137 (16), 135 (21), 122 (10), 105 (14), 56 (8).

Preparation of 1,4,6-Trimethyl-3,5-bis(para-substituted phenyl)-2-pyridones. 1,4,6-Trimethyl-3,5-bis(para-substituted phenyl)-2-pyridones were prepared by condensation of α-acetyl para-substituted benzylcyanides with para-substituted arylacetones to 4,6-dimethyl-3,5-bis(para-substituted phenyl)-2-pyridones[15b,22] followed by *N*-methylation.

A mixture of 2 mmol of α-acetyl *p*-fluorobenzylcyanide and 4 mmol of *p*-fluorophenyl acetone in 6 mL of glacial acetic acid and 2 mL of concentrated sulfuric acid was heated until evolution of carbon dioxide began. If the reaction tended to become vigorous, the mixture was cooled with water. After about 1 h, the mixture was gently heated again until evolution of carbon dioxide ceased. After cooling, the mixture was poured into water and neutralized with a sodium carbonate solution. The precipitate obtained was filtered off and washed with water and acetone. This crude product, after drying, was dissolved into a solution of a slight excess of sodium methylate in methanol. Methyl iodide was added dropwise to this solution at 5 °C. The reaction mixture was extracted with ether, washed with water, and dried over anhydrous sodium sulfate. After evaporation of the solvent, column chromatography of the residual solid on silica gel with

chloroform–ether (5:1) gave a solid, which, after recrystallization from a ligroin–benzene mixture, afforded 1,4,6-trimethyl-3,5-bis(*p*-fluorophenyl)-2-pyridone. No depression of melting point in admixture of this product with the photoproduct, Vc, was observed. Its IR and NMR spectra were identical with those of Vc.

Quantum Yield Determination. Dilute solutions of I ($2–5 \times 10^{-3}$ M) in dioxane and of II ($1–3 \times 10^{-3}$ M) in methanol in quartz test tubes were irradiated in a merry-go-round apparatus with four Taika 15W low-pressure mercury lamps. The samples in photolysis tubes were degassed using three freeze–pump (to about 10^{-2} Torr)–thaw cycles and then sealed under vacuum. These samples were irradiated to less than 3% conversion. Potassium ferrioxalate actinometer[23] provided light intensities in the order of 6.0×10^{-3} mEinstein/min (10 cm^3). After irradiation, the concentration of the photoproduct was determined by quantitative ultraviolet spectroscopy. Absorption due to the starting material was corrected to determine the degree of reaction.

The quantum yield of photoreaction of I or II in a heavy-atom solvent (*n*-butyl bromide) was determined similarly.[27]

Determination of Intersystem Crossing Efficiency. *cis*- and *trans*-piperylenes (99.5%) were obtained from the Chemical Sample Co. and used as received. Dohjin Chemical Spectrograde solvents (methanol, dioxane, and *tert*-butyl alcohol) were used without further purification. Benzophenone was purified by recrystallization. The cis–trans isomers ratio was determined by vapor-phase chromatography using a Yanagimoto GCG-500T equipped with a hydrogen-flame ionization detector on a 20×0.125 in. column packed with 15% 1,2-bis(cyanoethoxy)ethane on Chromosorb P (40–60 mesh) at room temperature. Irradiation with 253.7-nm light was carried out in a merry-go-round apparatus similar to the case of the quantum yield determination mentioned above. The method developed by Lamola and Hammond[24] was employed for determining the intersystem crossing efficiency. Potassium ferrioxalate actinometry[23] was used in the determination of ϕ_{isc} for benzophenone. For actinometry at 253.7 nm the benzophenone ($\phi_{isc} = 1.02$) sensitized isomerization of *cis*-piperylene was employed. At the photostationary state $[cis]_s/[trans]_s = 0.82$ (lit. value 0.81[24]). Each sensitizer ($1–4 \times 10^{-3}$ M for I and II) was run at least twice in the presence of *cis*-piperylene at different concentrations (0.01–0.1 M). The value of ϕ_{isc} was obtained by extrapolating to infinite concentration of *cis*-piperylene.

The value of ϕ_{isc} of I and II in the heavy-atom solvent (*n*-butyl bromide) was similarly determined.

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Substituent Effect on Selectivity in Photoisomerization of 4-Pyrones and 4-Pyridones

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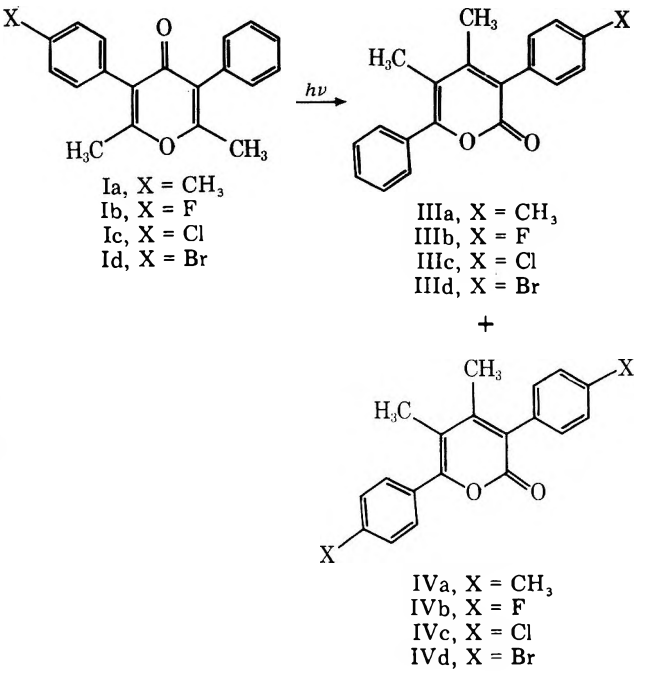
Ultraviolet irradiation of 2,6-dimethyl-3-phenyl-5-(*p*-X-phenyl)-4-pyrones (X = Me, F, Cl, and Br) gave both 3-phenyl-6-(*p*-X-phenyl)-4,5-dimethyl-2-pyrones and 3-(*p*-X-phenyl)-6-phenyl-4,5-dimethyl-2-pyrones. Similarly 1,2,6-trimethyl-3-phenyl-5-(*p*-X-phenyl)-4-pyridones (X = Me, F, Cl, and Br) were photoisomerized to both 1,4,6-trimethyl-3-phenyl-5-(*p*-X-phenyl)-2-pyridones and 1,4,6-trimethyl-3-(*p*-X-phenyl)-5-phenyl-2-pyridones. Effect of para substituents on selectivity in this photoisomerization was discussed.

In the past the study of the substituent effect on the photochemical reaction of ketones has provided much information concerning the electronic nature of species undergoing rearrangement.[3] Such an approach was found to be useful in interpreting photochemistry of the di-π-methane[4] and sigmatropic rearrangements[5] and of lactones.[6] In a hope that such a study would prove to be similarly informative in understanding the photorearrangement of 4-pyrones[7] and 4-pyridones,[8] we have examined the effect of para substituents on selectivity in the photoisomerization of 2,6-dimethyl-3-phenyl-5-(para-substituted phenyl)-4-pyrones and 1,2,6-trimethyl-3-phenyl-5-(para-substituted phenyl)-4-pyridones to the 2-pyrones and 2-pyridones, respectively. In the preceding paper[9] the quenching effect by dienes and the external heavy-atom effect on quantum yield indicated that the π,π^* singlet state was responsible for the photorearrangement of 4-pyrones to 2-pyrones and that of 4-pyridones to 2-pyridones. Involvement of the π,π^* singlet state can be reflected in selectivity in the formation of 2-pyrones and 2-pyridones. Recently, Pavlik et al.[10] suggested the formation of two isomeric 2-hydroxypyrylium cations in the photolysis of 2,6-dimethyl-3-phenyl-4-hydroxypyrylium cation but could not isolate their isomeric 2-pyrones.



Results and Discussion

2,6-Dimethyl-3-phenyl-5-(para-substituted phenyl)-4-pyrones (I) were synthesized from 1-(para-substituted phenyl)-3-phenylacetones by polyphosphoric acid-catalyzed condensation with acetic acid. The corresponding 4-pyridones (II) were obtained by the condensation of 4-pyrones with methylamine in a sealed tube as described in the preceding paper.[9,11] The structures assigned to I and II are based on their spectral (IR, NMR, and mass) data and elemental analyses which were described in the Experimental Section.

Preparative scale photolysis of I was carried out on solutions of 4-pyrones in acetonitrile using Vycor-filter light from a Taika 300-W medium-pressure mercury arc. Irradiation of I gave two isomeric 2-pyrones, III and IV, which were separated by careful column or thick-layer chromatography. The structure assignment to 2-pyrones rests on the spectral data. Three strong absorptions characteristic of the 2-pyrone are observed at 1700, 1630, and 1550 cm^{-1} in the infrared spectra and two nonequivalent methyl protons are detected at δ 2.00–2.08 and 2.05–2.12 in the NMR spectra, the pattern being similar to that of the parent 2-pyrone, 3,6-diphenyl-4,5-dimethyl-2-pyrone.[7]

Mass spectra of the photoproduct obtained at low voltage bombardment were particularly relevant to determine which substituent (either the phenyl or para-substituted phenyl group) is located on C-6 of the 2-pyrone ring, because the favorable fragmentation of 2-pyrones involves loss of the substituent at C-6 of the 2-pyrone ring as acyl radical from the fragment ion $[M - CO]^+$.[12,13] Their mass spectra are summarized in Table I. At the low bombarding electron energies (15–30 eV) the presence of the fragment ion corresponding to $[M - CO - Ph]^+$ indicates the presence of the phenyl group at C-6, whereas the formation of fragment ion corresponding

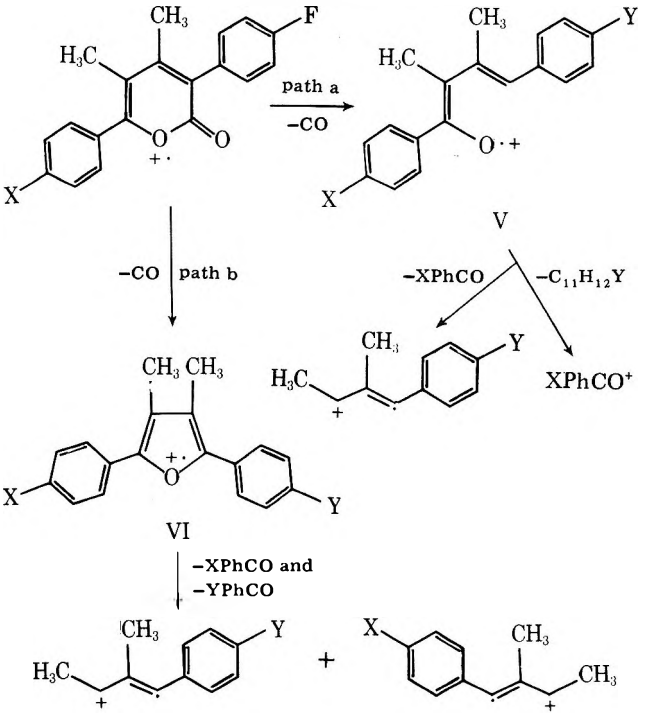


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Table I. Mass Spectral Fragmentation of 2-Pyrones

2-Pyrone[a]	Registry no.	Bombardment voltage, eV	Fragment *m/e* (rel intensity)
IIIa	65636-01-3	25	291 (6), 290 (M^+, 36), 263 (21), 262 (100), 157 (25), 143 (3), 105 (8)
IIIb	65636-02-4	30	295 (5), 294 (M^+, 29), 267 (15), 266 (100), 258 (9), 161 (13), 143 (5), 105 (21)
IVb	65636-03-5	30	295 (4), 294 (M^+, 26), 267 (16), 266 (100), 161 (3), 143 (19), 105 (5)
IIIc	65636-04-6	24	312 (16), 311 (9), 310 (M^+, 46), 285 (7), 284 (33), 283 (21), 282 (100), 179 (4), 177 (13), 143 (2), 105 (21)
IVc	65636-05-7	24	312 (10), 311 (5.5), 310 (M^+, 30), 285 (4), 284 (33), 283 (20), 282 (100), 177 (4), 143 (22), 139 (9)
IIId	65636-06-8	22.5	357 (3), 356 (22), 355 (5), 354 (M^+, 24), 329 (17), 328 (98), 327 (21), 326 (100), 223 (10), 221 (11), 143 (9), 105 (41)
IVd	65636-07-9	15	357 (20), 356 (100), 355 (23), 354 (M^+, 97), 329 (20), 328 (87), 327 (20), 326 (80), 185 (10), 183 (10), 143 (15)

[a] Pure IVa could not be isolated by column or thick-layer chromatography.

Table II. Selectivity in Photorearrangement of 2,6-Dimethyl-3-phenyl-5-(para-substituted phenyl)-4-pyrones and 1,2,6-Trimethyl-3-phenyl-5-(para-substituted phenyl)-4-pyridones

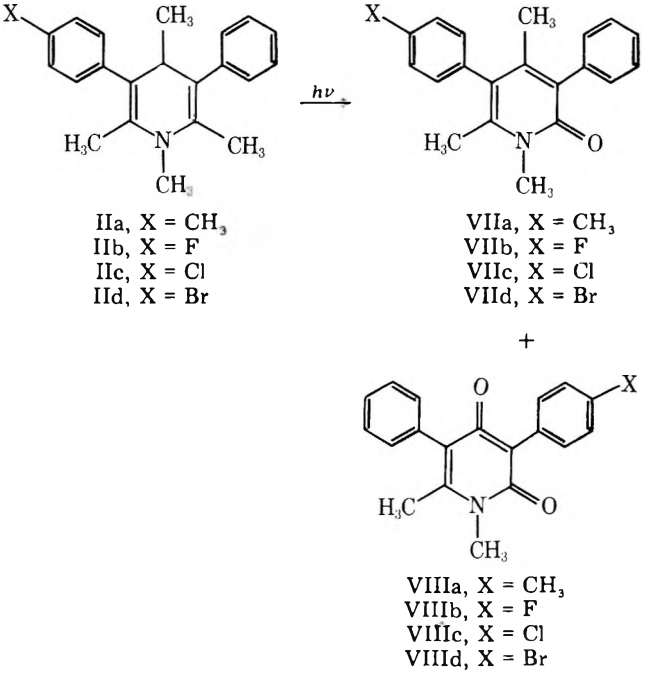
Substrate	Registry no.	Substituent	Yield, %	Ratio[b]
Ia	65636-08-0	CH_3	61	IIIa/IVa = 0.62[c]
Ib	65636-09-1	F	83	IIIb/IVb = 1.8
Ic	65636-10-4	Cl	76	IIIc/IVc = 2.2
Id	65636-11-5	Br	51[a]	IIId/IVd = 2.5
IIa	65636-12-6	CH_3	64	VIIIa/VIIa = 0.43
IIb	65636-13-7	F	64	VIIIb/VIIb = 1.9
IIc	65636-14-8	Cl	68	VIIIc/VIIc = 3.0
IId	65636-15-9	Br	32[a]	VIIId/VIId = 3.0

[a] The prolonged irradiation decreased yield because of formation of a tarry material. [b] Estimated maximum analytical error was within 5% except for that in Ib and IIb ranging ±9%. [c] Although pure IVa was not isolated, the 220 MHz NMR spectra of the isomeric mixture showed the different chemical shift for the methyl protons and the integration then gave the relative ratio of the isomers.

to $[M - CO - XPhCO]^+$ indicates the presence of the para-substituted phenyl group at C-6. The 2-pyrone, III, possessing the phenyl group instead of the para-substituted phenyl group at C-6 shows no or a very weak fragment corresponding to the para-substituted benzoyl cation but exhibits a strong peak of the benzoyl cation. On the other hand, the isomer of 2-pyrone, IV, produces a much more intense fragment of the para-substituted benzoyl cation relative to a fragment of the benzoyl cation. These results together with the fragmentation pathway of the substituent at C-6 of the 2-pyrone support our structural assignment of the photoproduct. As shown in Table I the elimination of the substituent at C-6 in 2-pyrones predominates over that at C-3 as the most favorable fragmentation pathway from the fragment ion $[M - CO]^+$, suggesting that the elimination of carbon monoxide gives the intermediate V (path a)[13] rather than VI (path b),[12] the latter being anticipated to eliminate both benzoyl and para-substituted benzoyl groups from $[M - CO]^+$.

Preparative photolysis of II was performed on a methanol solution of II under nitrogen using a Taika 300-W medium-pressure mercury lamp fitted with a Vycor filter. Two major products[14] were carefully separated by column chromatography on silica gel. Their structures were assigned as 1,4,6-trimethyl-3-phenyl-5-(para-substituted phenyl)-2-pyridones, VII, and 1,4,6-trimethyl-3-(para-substituted phenyl)-5-phenyl-2-pyridones, VIII, respectively. These assignments were established by comparison of their spectral (IR, NMR, and mass) data with those of authentic samples independently prepared from *N*-methylation of the corresponding 2-pyridones, which were synthesized by condensation–cyclization of either para-substituted phenylacetones with α-acetyl benzylcyanide or phenylacetone with α-acetyl para-substituted benzylcyanide.

After irradiation of I in acetonitrile and II in methanol for the same period of time and after drying of the reaction mixture under vacuum, the products were analyzed by a 100 or



IIa, X = CH_3
IIb, X = F
IIc, X = Cl
IId, X = Br

VIIa, X = CH_3
VIIb, X = F
VIIc, X = Cl
VIId, X = Br

+

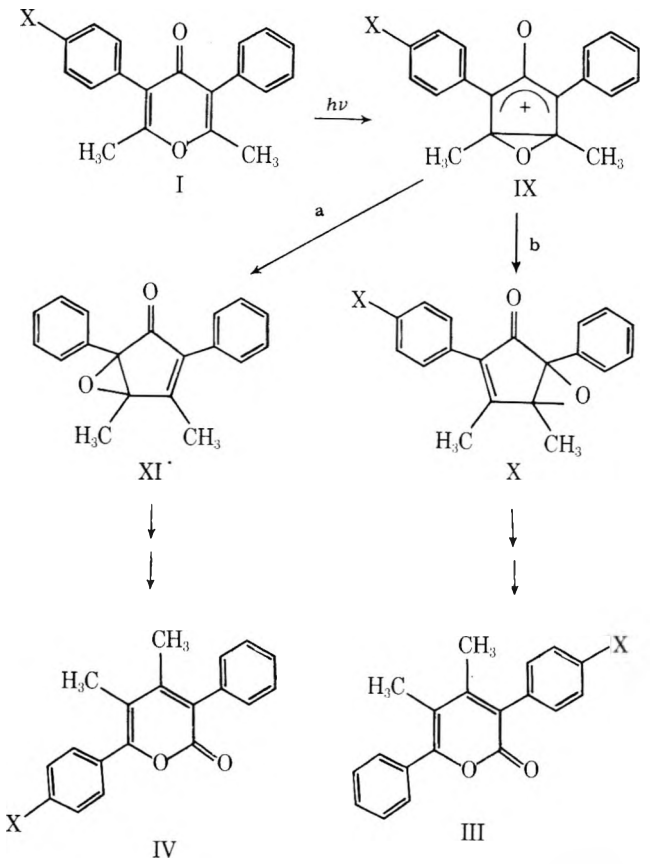
VIIIa, X = CH_3
VIIIb, X = F
VIIIc, X = Cl
VIIId, X = Br

220 MHz NMR spectrometer in which the integration gave the ratio of the isomers. The results are given in Table II.

It is immediately clear that the polar substituents exert an evident effect on selectivity in the formation of both 2-pyrones and 2-pyridones. The presence of the electron-withdrawing group in 4-pyrones enhances the preferable formation of III over IV and conversely increasing the electron density at C-5 (Ia) favors the formation of IV over III. The mechanism consistent with the rearrangement of 4-pyrones is shown in Scheme I.

Assuming conjugation of the phenyl group with the heterocyclic ring to some extent, the electron-withdrawing sub-

Scheme I



stituent decreases the electron density at the 1-phenylpropenyl terminus (C-3 in IX) so that the nucleophilic oxygen attacks preferably at C-3 (path b). Involvement of this zwitterionic 2,6-bonded intermediate in 4-pyrone photochemistry was recently established.[15] The 4,5-epoxycyclopent-2-en-1-one intermediate, X, formed further rearranges to III.[16] The pattern of the substituent effect observed in the photorearrangement of I[17] appears to be analogous to that predicted for ground-state rearrangement of the epoxy oxygen atom where the rearrangement is predicted to become less favorable at the rearrangement terminus going from cationic to radical-like to anionic.

In the photorearrangement of 4-pyridones, II, to 2-pyridones the electron-withdrawing group (IIb–d) increases the formation of VIII relative to VII and conversely the electron-donating group (IIa) favors the formation of VII over VIII. Assuming that this selectivity is determined by the formation of either the C_3–C_6 or C_2–C_5 bond in the mechanism proposed previously,[8] the electron-withdrawing group decreases the electron density at C-6 of II, resulting in favorable bonding between C-3 and C-6. On the other hand, the electron-donating substituent increases the charge density at C-6 of II, leading to the preferential formation of IX, although the ring-closured intermediate has to isomerize further to 2-pyridones.[17]

Experimental Section

Microanalyses were conducted by Microanalytical Laboratories, Kyoto University, Kyoto, Japan. Infrared spectra were recorded on a Jasco DS-402G spectrophotometer. Ultraviolet absorption spectra were obtained on a Hitachi 323 spectrophotometer. NMR spectra were measured at 60 MHz (Varian T-60A) or 100 MHz (Varian HA-100) or 220 MHz (Varian HR-220) using tetramethylsilane as internal standard. Chemical shifts were reported in parts per million (δ) from Me_4Si. Mass spectra were obtained by direct insertion on a Hitachi RMU-6L spectrometer at 70 eV unless otherwise cited. Melting points were uncorrected.

Preparation of 2,6-Dimethyl-3-phenyl-5-(para-substituted phenyl)-4-pyrones. In the general procedure 5 g of 1-phenyl-3-(*p*-fluorophenyl)-2-propanone was added to a mixture of 32 g of acetic acid and 51 g of polyphosphoric acid at room temperature. The mixture was stirred at 120–130 °C for 2 h and poured into 1000 mL of ice-cooled water. The reaction mixture was extracted with 200 mL of ether five times. The combined extracts were neutralized with aqueous sodium bicarbonate, washed thoroughly with water, and dried over anhydrous sodium sulfate. After removal of the solvent in vacuo the residual solid was chromatographed on silica gel with chloroform as eluent. Recrystallization of the crude crystals from methanol gave 3.5 g (70%) of 2,6-dimethyl-3-phenyl-5-(*p*-fluorophenyl)-4-pyrone (Ib): mp 196–198 °C; IR (KBr) 1640, 1600, 1500, 1430, 1410, 1365, 1320, 1310, 1295, 1275, 1220, 1175, 1150, 1090, 1070, 1020, 985, 910, 845, 815, 800, 780, 750, 700 cm^{-1}; NMR ($CDCl_3$) δ 2.23 (s, 6 H), 6.9–7.5 (m, 9 H); mass spectrum (*m/e*) 295 (14), 294 (M^+, 80), 293 (100), 276 (12), 275 (17), 251 (13), 233 (10), 223 (16), 149 (22), 147 (28), 136 (25), 134 (27), 133 (52), 118 (38), 116 (31), 115 (52), 108 (13), 90 (17), 89 (14), 43 (52). Anal. Calcd for $C_{19}H_{15}O_2F$: C, 77.54; H, 5.14; F, 6.46. Found: C, 77.24; H. 5.29; F, 6.30.

Preparative conditions and analytical results for other 4-pyrones are summarized in Table III. All values for the elemental analyses (C, H, and halogen) were within 0.3% of those calculated.

Spectral data for these compounds are as follows.

2,6-Dimethyl-3-phenyl-5-(*p*-tolyl)-4-pyrone (Ia): IR (KBr) 1645, 1620, 1600, 1500, 1440, 1415, 1370, 1310, 1235, 990, 920, 800, 750, 700 cm^{-1}; NMR ($CDCl_3$) δ 2.225 (s, 6 H), 2.35 (s, 3 H), 7.16 (s, 5 H), 5.30 (d, J = 8.2 Hz, 4 H); mass spectrum (*m/e*) 291 (8), 290 (M^+, 55), 289 (42), 288 (57), 275 (6), 246 (11), 219 (9), 204 (7), 203 (11), 202 (11), 145 (20), 144 (35), 132 (25), 130 (30), 129 (28), 128 (19), 127 (11), 116 (11), 115 (67), 104 (14), 103 (12), 90 (10), 83 (28), 77 (17), 56 (39), 55 (19), 43 (100), 42 (24).

2,6-Dimethyl-3-phenyl-5-(*p*-chlorophenyl)-4-pyrone (Ic): IR (KBr) 1640, 1620, 1585, 1560, 1490, 1435, 1410, 1395, 1370, 1330, 1315, 1230, 1150, 1085, 985, 920, 855, 830, 795, 755, 700 cm^{-1}; NMR ($CDCl_3$) δ 2.23 (s, 6 H), 7.1–7.4 (m, 9 H); mass spectrum (*m/e*) 312 (34), 311 (57), 310 (M^+, 93), 309 (100), 275 (12), 274 (16), 267 (14), 249 (11), 232 (14), 204 (16), 203 (24), 155 (24), 152 (34), 150 (22), 149 (14), 137 (17), 124 (14), 119 (14), 118 (45), 116 (46), 115 (71), 90 (24), 89 (31), 63 (27), 43 (71).

2,6-Dimethyl-3-phenyl-5-(*p*-bromophenyl)-4-pyrone (Id): IR (KBr) 1640, 1610, 1480, 1415, 1390, 1325, 1230, 1145, 1090, 1055, 1035, 1005, 985, 915, 840, 830, 800, 790, 745, 700 cm^{-1}; NMR ($CDCl_3$) δ 2.60 (s, 6 H), 7.1–7.7 (m, 9 H); mass spectrum (*m/e*) 357 (14), 256 (72), 355 (100), 354 (72), 353 (89), 275 (8), 274 (17), 203 (8), 202 (8), 196 (8), 118 (8), 117 (9), 116 (18), 115 (58), 90 (8), 89 (18), 43 (89).

Preparation of 1,2,6-Trimethyl-3-phenyl-5-(para-substituted phenyl)-4-pyridones. A typical procedure follows with the result for the remaining cases tabulated in Table III. All C, H, N, and halogen (Cl and Br) were within 0.2% of calculated.

A mixture containing 1.5 g of 2,6-dimethyl-3-phenyl-5-(*p*-fluorophenyl)-4-pyrone and 30 g of 40% methylamine in 100 mL of ethanol was heated in a stainless steel bomb at 90 °C for 48 h. After removal of the solvent and methylamine under reduced pressure, the residual solid was recrystallized from benzene to yield 0.9 g (60%) of 1,2,6-trimethyl-3-phenyl-5-(*p*-fluorophenyl)-4-pyridone (IIb): mp 276–278 °C; IR (KBr) 1615, 1565, 1555, 1440, 1390, 1305, 1225, 1100, 995, 960, 850, 815, 805, 755, 710 cm^{-1}; NMR ($CDCl_3$) δ 2.21 (s, 6 H), 3.53 (s, 3 H), 6.9–7.4 (m, 9 H); mass spectrum (*m/e*) 308 (8), 307 (M^+, 41), 306 (100), 277 (7), 56 (9). Anal. Calcd for $C_{20}H_{18}NOF$: C, 78.15; H, 5.90; N, 4.56; F, 6.18. Found: C, 77.91; H, 5.82; N, 4.73; F, 6.05.

Table III. Preparation of 2,6-Dimethyl-3-phenyl-5-(para-substituted phenyl)-4-pyrones and 1,2,6-Trimethyl-3-phenyl-5-(para-substituted phenyl)-4-pyridones

Substituent	4-Pyrones[a] or 4-Pyridones, wt in g (%)	Mp, °C
CH_3	Ia, 0.92 (18)	121–122.5
Cl	Ic, 1.35 (27)	167.5–168
Br	Id, 1.85 (37)	169–170.5
CH_3	IIa (52)	267–269
Cl	IIc (63)	262–263
Br	IId (66)	228–230

[a] Five grams of 1-aryl-3-phenyl-2-propanones was used. These ketones were prepared according to the following literature: S. B. Coan and E. I. Becker, *J. Am. Chem. Soc.*, **76**, 501 (1954); R. C. Elderfield and K. L. Burgess, *ibid.*, **82**, 1975 (1960).

Table IV. Irradiation of 2,6-Dimethyl-3-phenyl-5-(para-substituted phenyl)-4-pyrones and 1,2,6-Trimethyl-3-phenyl-5-(para-substituted phenyl)-4-pyridones

Substituent	4-Pyrones or 4-Pyridones, wt in g	Solvent (mL)	Irradiation time, h	2-Pyrones or 2-pyridones, wt in g (%)[a]	Mp, °C
CH_3	Ia, 0.45	CH_3CN (400)	20	IIIa, 0.030 (7)	158–160
F	Ib, 0.5	CH_3CN (600)	13	IIIb, 0.025 (5)	186–188
				IVb, 0.008 (1.7)	126–128
Br	Id, 0.5	CH_3CN (600)	5	IIId, 0.089 (10)	204–206
				IVd, 0.018 (2)	148–150
CH_3	IIa, 0.7	CH_3CN (400)	5	VIIIa[b]	164–166
				VIIa[b]	153–155
F	IIb, 0.5	CH_3OH (400)	3	VIIIb, 0.01 (8)	143–146
				VIIb, 0.003 (2.8)	130–131
Br	IId, 0.5	CH_3OH (400)	0.5	VIIId, 0.007 (5)	174–176
				VIId, 0.003 (1.2)	139–141

[a] Yield was based on an isolated amount of pure product. [b] Reference 19.

Table V. Synthesis of 2-Pyridones

Substituent	Phenylacetones,[a] wt in g	α-Acetyl benzylcyanides,[a] wt in g	2-Pyridones, wt in g (%)	Registry no.
CH_3	p-CH_3, 2.2	H, 2.5	VIIa, 0.95 (25)	65636-17-1
	H, 2.5	p-CH_3, 2.2	VIIIa, 0.75 (46)	65636-18-2
F	p-F, 5	H, 5	VIIb, 4.5 (50)	65636-19-3
	H, 5	p-F, 5	VIIIb, 2.0 (20)	65636-20-6
Cl	p-Cl, 5.4	H, 4.8	VIIc, 2.3 (26)	65636-21-7
	H, 5	p-Cl, 5	VIIIc, 3.5 (44)	65636-22-8
Br	p-Br, 5	H, 5	VIId, 5.0 (56)	65636-23-9
	H, 5	p-Br, 5	VIIId, 2.0 (20)	65636-24-0

[a] p-X = a substituent X on the para position of the benzene ring.

Spectral Data. 1,2,6-Trimethyl-3-phenyl-5-(p-tolyl)-4-pyridone (IIa): IR (KBr) 1610, 1550, 1490, 1440, 1385, 1300, 1150, 1105, 985, 955, 795, 740, 700 cm^{-1}; NMR ($CDCl_3$) δ 2.20 (s, 6 H), 2.35 (s, 3 H), 3.50 (s, 3 H), 6.9–7.3 (m, 9 H); mass spectrum (*m/e*) 304 (9), 303 (M^+, 47), 302 (100), 274 (5), 129 (4), 115 (5), 105 (7), 91 (8), 78 (22), 77 (7), 56 (17).

1,2,6-Trimethyl-3-phenyl-5-(p-chlorphenyl)-4-pyridone (IIc): IR (KBr) 1615, 1545, 1490, 1440, 1430, 1390, 1300, 1155, 1105, 1085, 1070, 1010, 980, 960, 850, 825, 795, 755, 705 cm^{-1}; NMR ($CDCl_3$) δ 2.23 (s, 6 H), 3.60 (s, 3 H), 7.20–7.30 (m, 9 H); mass spectrum (*m/e*) 325 (15), 324 (41), 323 (M^+, 44), 322 (100), 294 (5), 287 (7), 150 (5), 136 (5), 125 (5), 119 (5), 115 (7), 91 (8), 81 (6), 77 (3), 69 (11), 56 (17).

1,2,6-Trimethyl-3-phenyl-5-(p-bromophenyl)-4-pyridone (IId): IR (KBr) 1615, 1560, 1545, 1490, 1440, 1390, 1300, 1150, 1100, 1070, 1005, 985, 955, 845, 820, 790, 750, 700 cm^{-1}; NMR (CCl_4) δ 2.33 (s, 6 H), 3.75 (s, 3 H), 7.0–7.6 (m, 9 H); mass spectrum (*m/e*) 369 (44), 368 (98), 367 (M^+, 45), 366 (100), 287 (14), 144 (15), 115 (13), 56 (36).

Irradiation of 2,6-Dimethyl-3-phenyl-5-(para-substituted phenyl)-4-pyrones. A typical procedure for UV irradiation of 2,6-dimethyl-3-phenyl-5-(para-substituted phenyl)-4-pyrones is as follows. The irradiation condition and the results for the remaining 4-pyrones are given in Table IV. All elemental analyses for C, H, and halogen (F and Br) gave the values within 0.25% of calculated.

A solution of 0.7 g of 2,6-dimethyl-3-phenyl-5-(*p*-chlorophenyl)-4-pyrone in 800 mL of acetonitrile was irradiated under nitrogen with a 500-W medium-pressure mercury lamp using a Vycor filter at ambient temperature for 6 h. The solvent was removed under vacuum and the residual solid was chromatographed on silica gel with chloroform–benzene (5:5) as eluent. Every 5-mL fraction was collected and the solvent was removed under vacuum. The residual solid melted within a short range of temperature was collected and recrystallized from methanol to give 0.142 g (20%) of 3-(*p*-chlorophenyl)-6-phenyl-4,5-dimethyl-2-pyrone (IIIc): mp 215–217 °C; IR (KBr) 1700, 1625, 1545, 1495, 1450, 1385, 1345, 1190, 1085, 1015, 960, 945, 830, 770, 700 cm^{-1}: NMR ($CDCl_3$) δ 2.05 (s, 3 H), 2.10 (s, 3 H), 7.0–7.6 (m, 9 H). Anal. Calcd for $C_{19}H_{15}O_2Cl$: C, 73.43; H, 4.87; Cl, 11.41. Found: C, 73.07; H, 4.83; Cl, 11.34.

Further collection of solids from every 5-mL fraction gave 0.17 g of colorless crystals which melted at 110–170 °C, indicating a mixture of IIIc and IVc.

The next fraction, after recrystallization from methanol, gave 0.065 g (9%) of 3-phenyl-6-(*p*-chlorophenyl)-4,5-dimethyl-2-pyrone (IVc): mp 126.5–128 °C; IR (KBr) 1710, 1690, 1625, 1605, 1545, 1490, 1385, 1340, 1190, 1095, 1010, 950, 850, 790, 770, 710, cm^{-1}; NMR ($CDCl_3$) δ 2.05 (s, 3 H), 2.10 (s, 3 H), 7.1–7.6 (m, 9 H). Anal. Calcd for $C_{19}H_{15}O_2Cl$: C, 73.43; H, 4.87; Cl, 11.41. Found: C, 72.99; H, 4.79; Cl, 11.30.

Finally 0.275 g of the starting material was recovered.

Spectral Data. 3-(p-Tolyl)-6-phenyl-4,5-dimethyl-2-pyrone (IIIa): NMR ($CDCl_3$) δ 2.08 (s, 3 H), 2.12 (s, 3 H), 2.38 (s, 3 H), 7.1–7.6 (m, 9 H).

3-Phenyl-6-(p-tolyl)-4,5-dimethyl-2-pyrone[18] (IVa): NMR ($CDCl_3$) δ 2.09 (s, 3 H), 2.12 (s, 3 H), 2.37 (s, 3 H), 7.1–7.6 (m, 9 H).

3-(p-Fluorophenyl)-6-phenyl-4,5-dimethyl-2-pyrone (IIIb): NMR ($CDCl_3$) δ 2.06 (s, 3 H), 2.10 (s, 3 H), 7.0–7.7 (m, 9 H).

3-Phenyl-6-(p-fluorophenyl)-4,5-dimethyl-2-pyrone (IVb): NMR ($CDCl_3$) δ 2.06 (s, 3 H), 2.10 (s, 3 H), 7.0–7.7 (m, 9 H).

3-(p-Bromophenyl)-6-phenyl-4,5-dimethyl-2-pyrone (IIId): IR (KBr) 1700, 1625, 1540, 1475, 1445, 1380, 1335, 1185, 1090, 1070, 1005, 950, 940, 920, 825, 715, 700 cm^{-1}; NMR ($CDCl_3$) δ 2.06 (s, 3 H), 2.11 (s, 3 H), 7.1–7.6 (m, 9 H).

3-Phenyl-6-(p-bromophenyl)-4,5-dimethyl-2-pyrone (IVd): NMR ($CDCl_3$) δ 2.00 (s, 3 H), 2.05 (s, 3 H), 7.2–7.7 (m, 9 H).

Irradiation of 1,2,6-Trimethyl-3-phenyl-5-(para-substituted phenyl)-4-pyridone. Typical photolysis of 1,2,6-trimethyl-3-phenyl-5-(para-substituted phenyl)-4-pyridones is described as follows with the remaining cases which are summarized in Table IV. All C, H, N, and halogen (F and Br) were within 0.3% of calculated values.

A solution containing 0.6 g of 1,2,6-trimethyl-3-phenyl-5-(*p*-chlorophenyl)-4-pyridone in 950 mL of methanol was irradiated under nitrogen for 6 h using a 500-W Taika medium-pressure mercury lamp equipped with a Vycor filter. Removal of the solvent in vacuo left solid which was chromatographed on silica gel with chloroform–ether (4:1) as eluent. Every 10-mL fraction was evaporated to remove the solvent and the residual solids which showed a similar range of the melting point were combined together. Recrystallization from benzene gave 0.109 g (31%) of 1,4,6-trimethyl-3-(*p*-chlorophenyl)-5-phenyl-2-pyridone (VIIIc): mp 166–167 °C; IR (KBr) 1625, 1580, 1525, 1485, 1435, 1425, 1300, 1235, 1095, 1080, 1010, 945, 815, 810, 765, 700 cm^{-1}; NMR (CCl_4) δ 1.80 (s, 3 H), 2.25 (s, 3 H), 3.75 (s, 3 H), 7.0–7.5 (m, 9

H); mass spectrum (*m/e*) 325 (30), 324 (50), 323 (M^+, 95), 322 (100), 297 (10), 296 (14), 295 (31), 294 (26), 244 (11), 202 (10), 115 (19), 77 (11), 56 (90). Anal. Calcd for $C_{20}H_{18}NOCl$: C, 74.18; H, 5.60; N, 4.33; Cl, 10.95. Found: C, 74.08; H, 5.29; N, 4.03; Cl, 10.66.

Further collection of crystals from every 10-mL fraction yielded, after recrystallization from benzene, 0.15 g of colorless crystals which melted at 138–160 °C, indicating a mixture of VIIc and VIIIc.

Further careful column chromatography gave, after recrystallization from benzene, 0.036 g (10%) of 1,4,6-trimethyl-3-phenyl-5-(*p*-chlorophenyl)-2-pyridone (VIIc): mp 150–152 °C; IR (KBr) 1630, 1600, 1540, 1490, 1440, 1420, 1300, 1240, 1094, 1085, 1015, 955, 830, 820, 760, 705, 700 cm^{-1}; NMR (CCl_4) δ 1.66 (s, 3 H), 2.06 (s, 3 H), 3.56 (s, 3 H), 7.0–7.5 (m, 9 H); mass spectrum (*m/e*) 325 (32), 324 (49), 323 (M^+, 89), 322 (100), 296 (13), 295 (24), 223 (14), 205 (16), 167 (14), 150 (34), 149 (44), 122 (14), 121 (10), 115 (10), 105 (25), 99 (26), 92 (20), 91 (38), 83 (16), 81 (20), 77 (19), 71 (23), 70 (20), 69 (42), 57 (99), 56 (43), 43 (40), 41 (53). Anal. Calcd for $C_{20}H_{18}NOCl$: C, 74.18; H, 5.60; N, 4.33; Cl, 10.95. Found: C, 74.17; H, 5.72; N, 4.28; Cl, 10.73.

Finally 0.25 g of the starting material was recovered by further elution.

Spectral Data. 1,4,6-Trimethyl-3-(*p*-tolyl)-5-phenyl-2-pyridone[19] (VIIIa): IR (KBr) 1570, 1545, 1515, 1450, 1415, 1390, 1375, 1335, 1285, 1235, 1220, 1170, 1090, 1025, 995, 810, 740, 725 cm^{-1}; NMR (CCl_4) δ 1.60 (s, 3 H), 2.08 (s, 3 H), 2.39 (s, 3 H), 3.55 (s, 3 H), 6.9–7.4 (m, 9 H); mass spectrum (*m/e*) 304 (23), 303 (M^+, 100), 302 (97), 289 (23), 288 (25), 275 (29), 274 (22), 56 (48).

1,4,6-Trimethyl-3-phenyl-5-(*p*-tolyl)-2-pyridone[18] VIIa: IR (KBr) 1620, 1580, 1530, 1495, 1445, 1425, 1375, 1360, 1300, 1100, 950, 810, 770, 710 cm^{-1}; NMR (CCl_4) δ 1.63 (s, 3 H), 2.07 (s, 3 H), 2.39 (s, 3 H), 3.55 (s, 3 H), 6.8–7.4 (m, 9 H); mass spectrum (*m/e*) 304 (22), 303 (M^+, 100), 302 (98), 275 (31), 274 (25), 56 (36).

1,4,6-Trimethyl-3-(*p*-fluorophenyl)-5-phenyl-2-pyridone (VIIIb): IR (KBr) 1620, 1600, 1580, 1525, 1500, 1425, 1375, 1300, 1215, 1155, 1085, 950, 865, 825, 810, 770, 700 cm^{-1}; NMR (CCl_4) δ 1.63 (s, 3 H), 2.12 (s, 3 H), 3.68 (s, 3 H), 6.9–7.4 (m, 9 H); mass spectrum (*m/e*) 308 (20), 307 (M^+, 99), 306 (100), 279 (28), 278 (29), 56 (46), 41 (12).

1,4,6-Trimethyl-3-phenyl-5-(*p*-fluorophenyl)-2-pyridone (VIIb): IR (KBr) 1625, 1600, 1585, 1525, 1505, 1420, 1355, 1300, 1215, 1155, 1090, 950, 835, 815, 785, 765, 750, 700 cm^{-1}; NMR (CCl_4) δ 1.67 (s, 3 H), 2.11 (s, 3 H), 3.63 (s, 3 H), 7.0–7.4 (m, 9 H); mass spectrum (*m/e*) 308 (16), 307 (M^+, 83), 306 (81), 289 (18), 288 (34), 279 (36), 278 (41), 260 (14), 92 (47), 91 (78), 83 (16), 78 (13), 77 (16), 71 (28), 70 (22), 65 (19), 63 (16), 57 (44), 56 (94), 55 (38), 50 (13), 43 (100), 42 (38), 41 (81).

1,4,6-Trimethyl-3-(*p*-bromophenyl)-5-phenyl-2-pyridone (VIIId): IR (KBr) 1625, 1580, 1530, 1485, 1440, 1420, 1380, 1300, 1240, 1100, 1070, 1010, 950, 865, 815, 770, 705 cm^{-1}; NMR (CCl_4) δ 1.63 (s, 3 H), 2.03 (s, 3 H), 3.47 (s, 3 H), 7.0–7.6 (m, 9 H); mass spectrum (*m/e*) 370 (21), 369 (98), 368 (91), 367 (M^+, 100), 366 (76), 341 (26), 340 (26), 339 (27), 338 (23), 288 (12), 244 (11), 203 (12), 202 (14), 144 (38), 136 (21), 135 (10), 115 (17), 101 (14), 89 (11), 77 (10), 56 (88), 41 (10).

1,4,6-Trimethyl-3-phenyl-5-(*p*-bromophenyl)-2-pyridone (VIId): IR (KBr) 1630, 1595, 1530, 1485, 1440, 1420, 1200, 1100, 1070, 1010, 950, 820, 790, 755, 700 cm^{-1}; NMR (CCl_4) δ 1.64 (s, 3 H), 2.07 (s, 3 H), 3.55 (s, 3 H), 7.0–7.5 (m, 9 H); mass spectrum (*m/e*) 370 (14), 369 (66), 368 (74), 367 (M^+, 63), 366 (56), 341 (18), 340 (16), 339 (18), 338 (13), 323 (10), 322 (11), 289 (47), 288 (50), 261 (14), 260 (14), 244 (13), 78 (62), 77 (19), 56 (43), 52 (14), 51 (16).

NMR Determination of the Relative Ratio of Isomeric Photoproduct. A solution of 4-pyridone (0.05–0.1 g) in methanol (100 mL) was irradiated under nitrogen with a 100-W medium-pressure mercury lamp equipped with a Vycor filter. After irradiation for 2–3 h, the solvent was removed under vacuum and the residual solid was quickly passed through a short column packed with dry silica gel to eliminate a polymeric compound. After drying either $CDCl_3$ or CCl_4 containing 1% tetramethylsilane was added to the mixture and a NMR spectrum was recorded. The relative ratio of the photoproduct and the percent reactivity were determined by monitoring change of the methyl proton integration. Two or three runs were carried out for each sample. The average results were given in Table II.

Independent Synthesis of 1,4,6-Trimethyl-3-phenyl-5-(para-substituted phenyl)-2-pyridones and 1,4,6-Trimethyl-3-(para-substituted phenyl)-5-phenyl-2-pyridones. 1,4,6-Trimethyl-3-(para-substituted phenyl)-5-phenyl-2-pyridones were prepared by condensation of α-acetyl-para-substituted benzylcyanides with phenylacetone to 4,6-dimethyl-3-(para-substituted phenyl)-5-phenyl-2-pyridones, followed by *N*-methylation. 1,4,6-Trimethyl-3-phenyl-5-(para-substituted phenyl)-2-pyridones were also synthesized by a similar method using α-acetyl benzylcyanide and para-substituted phenylacetones. The preparative condition was similar to that described in the preceding report.[9] The results are summarized in Table V.

Registry No.—IVa, 65636-24-0; 1-phenyl-3-(*p*-fluorophenyl)-2-propanone, 330-97-2; 1-phenyl-3-(*p*-tolyl)-2-propanone, 35730-02-0; 1-phenyl-3-(*p*-chlorophenyl)-2-propanone, 35730-03-1; 1-phenyl-3-(*p*-bromophenyl)-2-propanone, 65636-25-1.

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(15) J. A. Barltrop, A. C. Day, and C. J. Samuel, *J. Chem. Soc., Chem. Commun.*, 822 (1976).
(16) Indirect evidence for involvement of 4,5-epoxycyclopent-2-en-1-one was given previously in the photorearrangement of 2,3,5,6-tetraphenyl-4-pyrone.[7] We assumed that the rearrangement of IX to either X or XI is important in determining the product selectivity relative to the rearrangement of 4,5-epoxycyclopent-2-en-1-one to the 2-pyrone. Recently photochemical conversion of the epoxide to the 2-pyrone was demonstrated by J. A. Barltrop, A. C. Day, and C. J. Samuel, *J. Chem. Soc., Chem. Commun.*, 598 (1977).
(17) A referee pointed out the possibility that the substituent effect observed was a heavy atom rather than inductive and/or resonance effect. Lack of quenching data cannot exclude this possibility, but yield of the photoproduct in Table II does not correlate well with the atomic number of the substituent. The preceding paper also shows no internal heavy-atom effect in the photorearrangement. These results strongly suggest that an electronic rather than heavy-atom effect plays a major role in determining selectivity.
(18) A pure compound was not isolated. The 220 MHz NMR spectra of the isomeric mixture gave the different chemical shifts for the C-methyl proton.
(19) Conventional column or thick-layer chromatography could not separate the mixture. Spectral data were given for the authentic sample prepared by the chemical method.

Reactions of an α-Phosphono-γ-butyrolactone Carbanion with Acid Anhydrides, Epoxides, Carbonates, and a Lactone

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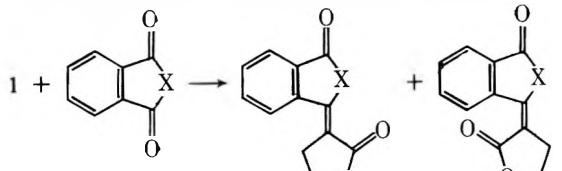
Reactions of an α-phosphono-γ-butyrolactone carbanion (**1**) with various acid anhydrides, epoxides, carbonates, and a lactone were investigated. Phthalic (**2**) and thiophthalic anhydrides (**3**) gave 3-(2-oxotetrahydrofuran-3-ylidene)phthalide (**4**) and -thiophthalide (**5**) in quantitative yields, while homophthalic (**6**) and isatoic anhydrides (**8**) produced 3-(2-oxotetrahydrofuran-3-yl)isocoumarin (**7**) and 4*H*-2-(2-oxotetrahydrofuran-3-yl)benz[*d*][1,3]oxazin-4-one (**9**) in good yields. The reaction products between **1** and *N*-methylisatoic anhydride (**11**) were solvent dependent. The reaction in benzene gave mainly 2*H*,4*H*-1-methyl-(*E*)-4-(2-oxotetrahydrofuran-3-ylidene)benz[*d*][1,3]-oxazin-2-one (**12a**) and in DMF provided only 2*H*,3*H*,4*H*-9-methylfuro[2,3-*b*]quinolin-4-one (**13**) in high yield. Epoxides **14** led to isomeric spirolactones **15** and **16**. Epoxy ketones **18**, 1,2-carbonyldioxybenzene (**20**), and γ-butyrolactone **21** gave the corresponding α-ylidene-γ-butyrolactones **19**, **22**, and **23**, respectively.

The development of facile methods for introduction of the γ-butyrolactone moiety to organic molecules has become one of the targets of organic chemists because of the occurrence in nature of many compounds of this class having significant biological activity. [1]

We have previously reported the synthesis of various α-ylidene-γ-butyrolactones from an α-(*O*,*O*-diethylphosphono)-γ-butyrolactone carbanion (**1**) and simple carbonyl reagents such as aldehydes and ketones.[2] In an attempt to explore further synthetic utility of the phosphonate carbanion **1**, we have investigated the reaction titled above.

Results and Discussion

Acid Anhydrides. The phosphonate carbanion **1** easily reacted with phthalic (**2**) and thiophthalic anhydrides (**3**) in refluxing benzene for 3 h to give a mixture of (*Z*)-3- (**4a**, 58%) and (*E*)-3-(2-oxotetrahydrofuran-3-ylidene)phthalide (**4b**, 42%) and (*Z*)-3-(2-oxotetrahydrofuran-3-ylidene)thiophthalide (**5**), respectively, in quantitative yields.

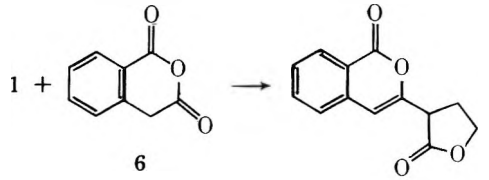


2, X = O
3, X = S

4a, X = O
5, X = S

4b, X = O

Although the reaction with homophthalic anhydride (**6**) required relatively vigorous conditions (at 140 °C for 4 h in a sealed tube), 3-(2-oxotetrahydrofuran-3-yl)isocoumarin (**7**)



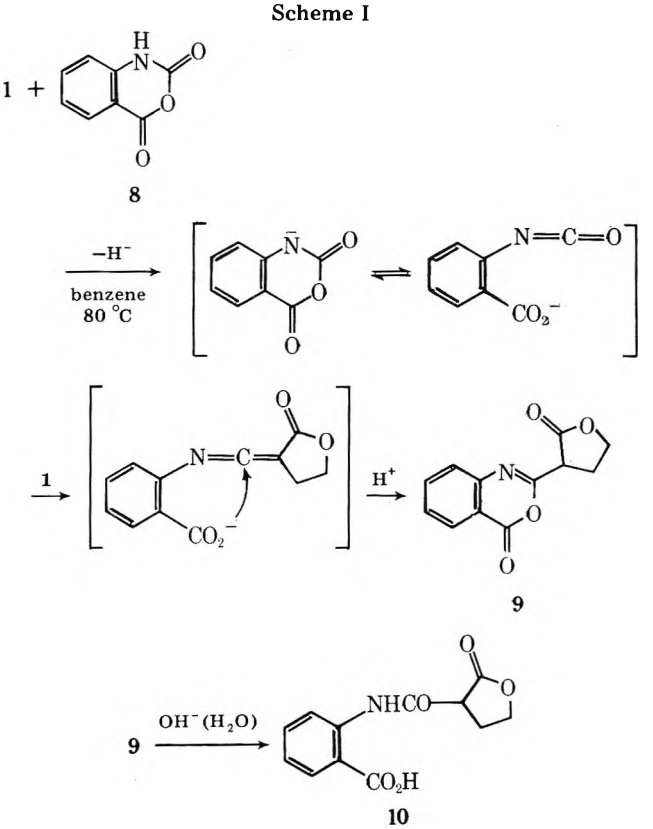
6 **7**

was obtained in good yield. However, treatment of maleic and succinic anhydrides with **1** under similar conditions gave no corresponding product. This result suggests that the carbonyl group of the acylated phosphonates derived from attack of **1** on these acid anhydrides could not have an appropriate configuration for being subsequently attacked by the generated carboxylate anion due to easy rotation of the anionic moiety.

On the other hand, the reaction products of isatoic **8** and *N*-methylisatoic anhydrides **11** with **1** were drastically solvent dependent. The reaction of **8** in refluxing benzene for 3 h led to 4*H*-2-(2-oxotetrahydrofuran-3-yl)benz[*d*][1,3]oxazin-4-one (**9**, 91%) corresponding to **7**, but the reaction in *N*,*N*-dimethylformamide (DMF) at 110 °C gave only *N*-ethylisatoic anhydride in 79% yield. The structural assignment of product **9** was made by spectral data and elemental analysis and by alkaline hydrolysis of the product **9** yielding 2-*N*-(2-oxotetrahydrofuran-3-carboxyamido)benzoic acid (**10**) (Scheme I). Whereas the reaction of **11** in benzene solvent at 140 °C for 7 h in a sealed tube gave 2*H*,4*H*-1-methyl-(*E*)-4-(2-oxotetrahydrofuran-3-ylidene)benz[*d*][1,3]oxazin-2-one (**12a**, 43%) along with 2*H*,3*H*,4*H*-9-methylfuro[2,3-*b*]quinolin-4-one (**13**, 5%), the reaction in DMF at 110 °C for 4 h produced only **13** in high yield with the accompanying evolution of carbon dioxide gas. Heat of the separated (*E*) isomer **12a** in refluxing ethanol containing NaOH for confirmation of its stereochemistry led to the corresponding (*Z*) isomer **12b**.

Thus, the phosphonate anion **1** was observed to react with isatoic anhydride **8** with the less reactive carbonyl group at

Scheme I



8 **9** **10**

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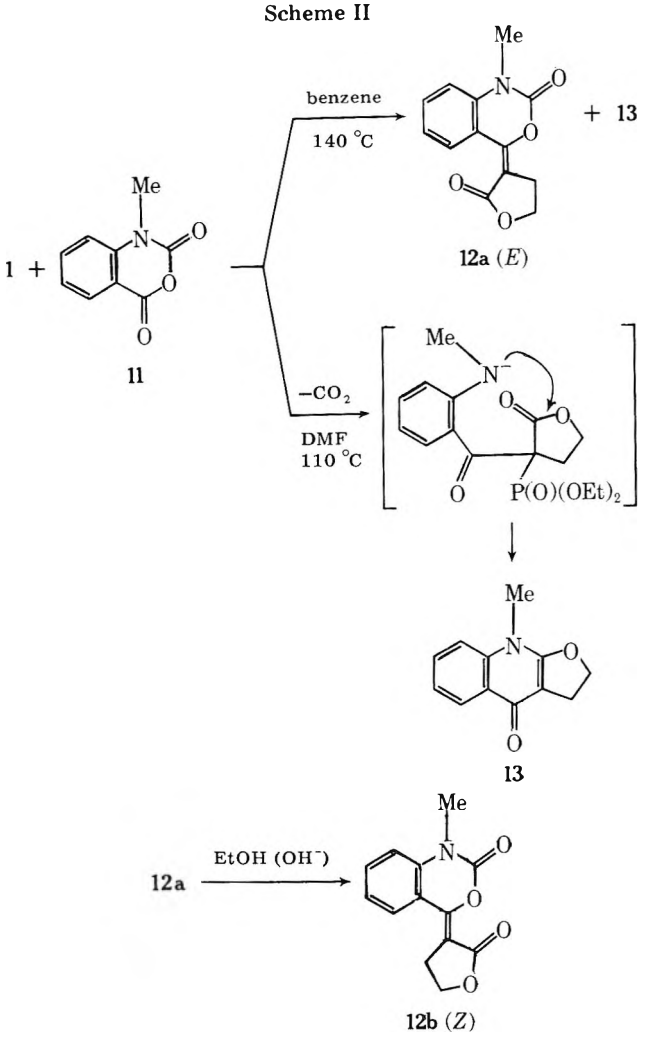
Table I. Reaction of the Phosphonate Anion 1 with Epoxides 14

Epoxides 14	R^1	R^2	Registry no.	Reaction conditions[a] Temp, °C	Time, h	Products,[e] 15 + 16 Yield,[b] %	Ratio[c] of 15:16	bp °C (1 mmHg)	Empirical formula	Anal., % Calcd C	Calcd H	Found C	Found H
14a	Ph	H	96-09-3	150	3	44	1:1	105–109	$C_{12}H_{12}O_2$	76.57	6.43	76.71	6.56
14b	Me	H	75-56-9	160	2	61	2:1	44–45	$C_7H_{10}O_2$	66.64	7.99	66.29	8.04
14c	Me	Me	558-30-5	180	5	60	1:3	44–46	$C_8H_{12}O_2$	68.54	8.63	68.21	8.90
14d	$-(CH_2)_5-$		185-70-6	180	5	60	1:2	100–105	$C_{11}H_{16}O_2$	73.30	8.95	73.11	9.10
14e[d]	H	H	75-21-8	180	5	55		40–41	$C_6H_8O_2$	64.27	7.19	63.78	7.86

[a] The reactions were carried out in a benzene solution in a sealed tube. [b] All yields are for distilled products. [c] Based on VPC and NMR. [d] Ethylene carbonate was used. [e] Registry No.—**15a**, 65652-07-5; **15b**, 65652-08-6; **15c**, 65652-09-7; **15d**, 65652-10-0; **15e**, 65652-11-1; **16a**, 65652-12-2; **16b**, 65652-13-3; **16c**, 65652-10-0; **16d**, 65652-14-4.

Scheme II

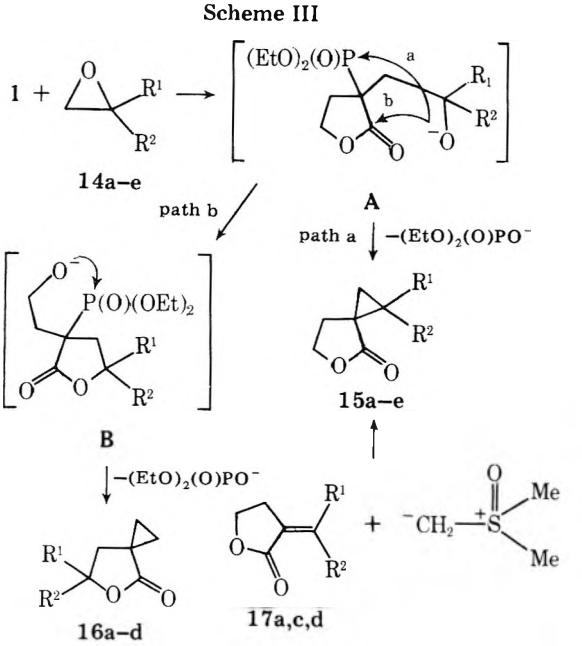


the 2 position to yield **9** and with *N*-methylisatoic anhydride **11** with the relatively reactive carbonyl group at the 4 position to afford **12a** and **13**. To the phosphonate anion **1**, **8** is more reactive than **11** as shown in the reactions using benzene as solvent. The difference in reactivities between **8** and **11** could be due to the presence of a labile hydrogen at the 1 position of **8**. That is, hydrogen abstraction of the 1 position of **8** by the phosphonate anion **1** would cause cleavage of the anhydride ring to produce a reactive intermediate isocyanate[3] in benzene solvent, which could easily react with **1** to yield a ketenimine[2] followed by cyclization to the product **9** (Scheme I). On the other hand, the formation of *N*-ethylisatoic anhydride in DMF could be similarly explained by *N*-ethylation of the solvent stabilized intermediate isatoic anhydride anion with **1** and/or α-diethylphosphono-γ-butyrolactone, as *N*-alkylation of nitrogen heterocycles with alkyl esters of phosphorus oxy acids has been already reported.[4] In contrast, the reaction between **1** and **11** in DMF would be reasonably explained by a sequence of the nucleophilic attack of **1** on the 4-position carbon atom of the anhydride ring, successive elimination of CO_2, and the nucleophilic attack of the resulting nitrogen anion on the carbonyl group of the lactone ring, followed by elimination of sodium diethylphosphate to the product **13**, as shown in Scheme II.

Such one step synthesis of the furoquinoline **13** suggests applicability to total synthesis of natural furoquinoline alkaloids such as lunacrine and balfourodine.[5]

Epoxides, Carbonates, a Lactone. Interestingly, treatment of epoxides **14a–d** in benzene solution with **1** gave a mixture of two isomers, spirolactones **15a–d** and **16a–d** in 40–60% yields, although the reaction required heating in a sealed tube at 150–180 °C for 2–5 h (Table I). In the example using propylene oxide (**14b**), separation of individual pure samples, **15b** and **16b**, was carried out by a gas chromatographic technique. The structures of **15b** and **16b** were assigned to be 1-methyl-4-oxo-5-oxaspiro[2,4]heptane and 6-methyl-4-oxo-5-oxaspiro[2,4]heptane, respectively, by elemental analysis and spectral data (see Experimental Section). The structures of the products **15a,c,d**, one of the isomers, were identified as 1-substituted 4-oxo-5-oxaspiro[2,4]heptane derivatives by comparison of their spectral data with authentic samples alternatively prepared from corresponding α-yli-

Scheme III



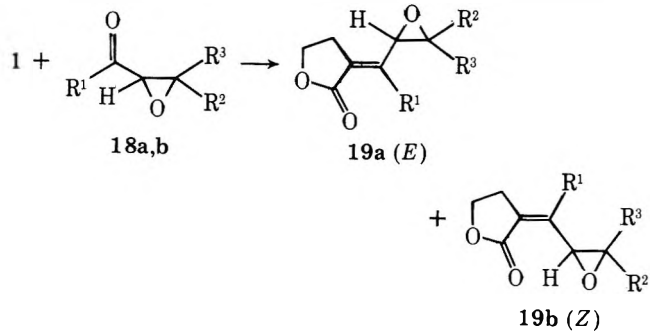
14a, 15a, 16a, 17a, R^1 = Ph; R^2 = H
14b, 15b, 16b, R^1 = Me; R^2 = H
14c, 15c, 16c, 17c, R^1 = R^2 = Me
14d, 15d, 16d, 17d, R^1, R^2 = $-(CH_2)_5-$
14e, 15e, R^1 = R^2 = H

dene-γ-butyrolactones[2,15] and dimethyloxosulfonium methylide. The structural assignments of the other isomers **16a,c,d** were similarly made by elemental analyses and spectral data of the mixtures.

In the case where ethylene carbonate as a precursor of ethylene oxide was used under similar conditions, an anticipated single product, 4-oxo-5-oxaspiro[2,4]heptane (**15e**), was obtained in 55% yield.

Based on these results, it is reasonable to consider that the initial intermediate oxy anions A generated by nucleophilic attack of **1** on the unsubstituted carbon of epoxides **14a–d** would competitively attack the phosphonate moiety to give one of the isomers **15a–d** (path a) and the carbonyl group of the lactone ring following by the formation of the other intermediate B to yield the other isomers **16a–d** (path b) (Scheme III).

On the other hand, similar treatment of epoxy ketones **18** containing two reactive sites under mild conditions (80 °C, 1 h) selectively led to products **19**, which were derived from

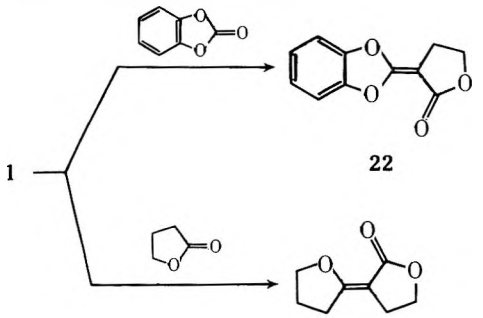


18a,b **19a** (*E*) **19b** (*Z*)

18a, **19a**, $R^1 = R^2 = R^3 = Me$
18b, **19b**, $R^1 = R^2 = Ph$; $R^3 = H$

the reactions in only the carbonyl site of **18**, in good yields. Thus, to the phosphonate anion **1**, the carbonyl group was observed to be more reactive than the epoxy group.

Furthermore, we found that less reactive carbonyl compounds such as 1,2-carbonyldioxybenzene (**20**) and γ-butyrolactone (**21**) likewise reacted with the phosphonate anion **1** to produce the corresponding α-ylidene-γ-butyrolactones **22** and **23** in 56 and 31% yields, respectively.



22 **23** (*Z*)

In conclusion, the α-phosphono-γ-butylrolactone anion can serve as a versatile reagent not only for the introduction of the γ-butyrolactone ring, but for syntheses of furoquinoline alkaloids and of related compounds consisting of furan ring systems.

Experimental Section

General. All melting points of products were determined with a Yanagimoto micromelting apparatus and are uncorrected. The NMR spectra were recorded with a JEOL JNM-PS-100 or JNM-PMX-60 spectrometer with tetramethylsilane as an internal standard. The IR spectra were obtained with a Jasco IRA-1 spectrometer. The mass spectra were taken with a Hitachi RMU-6E spectrometer.

Materials. α-(*O,O*-Diethylphosphone)-γ-butyrolactone,[2,6] thiophthalic[7] (**3**), homophthalic[8] (**6**), and *N*-methylisatoic anhydrides[9] (**11**), isobutylene[10] (**14c**) and methylenecyclohexane oxides[10] (**14d**), 3,4-epoxy-4-methyl-2-pentanone[11] (**18a**), chalconepoxide[11] (**18b**), and 1,2-carbonyldioxybenzene[12] (**20**) were prepared according to the established procedures.

3-(2-Oxotetrahydrofuran-3-ylidene)phthalide (4a and 4b). To a solution of an α-phosphono-γ-butyrolactone carbanion[2] (**1**) (0.02 mol) in 100 mL of dry benzene was added phthalic anhydride (**2**) (2.96 g, 0.02 mol) in 30 mL of THF with stirring and then the reaction mixture was refluxed for 3 h. The resulting solid was filtered and washed with water, and the residual solid (2.51 g, 58%) was recrystallized from a large amount of ethanol–benzene to give pure (*Z*)-3-**(2-oxotetrahydrofuran-3-ylidene)phthalide (4a)**: mp 255–260 °C dec; IR (Nujol) 1775 and 1745 (C=O) and 1670 cm^{-1} (C=C); NMR (Me_2SO-d_6) δ 3.44 (t, J = 7.5 Hz, 2 H, methylene protons), 4.52 (t, J = 7.5 Hz, 2 H, OCH_2), and 7.80–8.20 (m, 4 H, aromatic protons); mass spectrum (70 eV) *m/e* 216 (M^+). Anal. Calcd for $C_{12}H_8O_4$: C, 66.67; H, 3.73. Found: C, 66.55; H, 3.37.

The filtrate was concentrated and the resulting solid (1.81 g, 42%) was recrystallized from benzene–hexane to yield pure (*E*)-3-**(2-oxotetrahydrofuran-3-ylidene)phthalide (4b)**: mp 222 °C; IR (Nujol) 1775 and 1735 (C=O) and 1660 cm^{-1} (C=C); NMR (Me_2SO-d_6) δ 3.36 (t, J = 7.5 Hz, 2 H, methylene protons), 4.60 (t, J = 7.5 Hz, 2 H, OCH_2), 7.80–8.20 (m, 3 H, aromatic protons), and 9.15 (d, J = 7.5 Hz, 1 H, aromatic proton); mass spectrum (70 eV) *m/e* 216 (M^+). Anal. Calcd for $C_{12}H_8O_4$: C, 66.67; H, 3.73. Found: C, 66.42; H, 3.42.

(*Z*)-3-(2-Oxotetrahydrofuran-3-ylidene)thiophthalide (5). This derivative was similarly obtained from **1** and thiophthalic anhydride (**3**). After similar treatment, crude **5** was isolated in quantitative yield. Recrystallization of crude **5** from benzene–hexane gave the pure sample: mp 230–232 °C; IR (Nujol) 1720 and 1680 (C=O) and 1605 cm^{-1} (C=C); NMR (Me_2SO-d_6) δ 3.65 (t, J = 7.5 Hz, 2 H, methylene protons), 4.65 (t, J = 7.5 Hz, 2 H, OCH_2), and 7.85–8.30 (m, 4 H, aromatic protons); mass spectrum (70 eV) *m/e* 232 (M^+). Anal. Calcd for $C_{12}H_8O_3S$: C, 62.07; H, 3.47. Found: C, 61.93; H, 3.59.

3-(2-Oxotetrahydrofuran-3-yl)isocoumarin (7). The reaction of **1** with homophthalic anhydride (**6**) was carried out in a sealed tube at 140 °C for 4 h. After removal of sodium diethyl phosphate by filtration, the filtrate was concentrated under reduced pressure. The residue was chromatographed on silica gel to give 3.40 g (74%) of **7**: mp 174–175 °C (from acetonitrile); IR (Nujol) 1760 and 1715 (C=O) and 1650 cm^{-1} (C=C); NMR (CD_3CN) δ 2.64 (m, 2 H, methylene protons), 3.84 (t, J = 9 Hz, 1 H, methine proton), 4.42 (m, 2 H, OCH_2), 6.65 (s, 1 H, vinylic proton), 7.30–7.90 (m, 3 H, aromatic protons), and 8.24 (d, J = 8 Hz, 1 H, aromatic proton); mass spectrum (70 eV) *m/e* 230 (M^+). Anal. Calcd for $C_{13}H_{10}O_4$: C, 67.82; H, 4.38. Found: C, 67.55; H, 4.25.

Reaction of 1 with Isatoic Anhydride (8). A. A mixture of **1** (0.02 mol) and **8** (3.26 g, 0.02 mol) in benzene (50 mL) was heated at 80 °C for 3 h. The organic layer was concentrated to give 4.20 g (91%) of crude **4*H*-2-(2-oxotetrahydrofuran-3-yl)benz[*d*][1,3]oxazin-4-one (9)**, which was recrystallized from benzene–hexane to provide the pure sample: mp 176–177 °C; IR (Nujol) 1765 and 1705 (C=O) and 1660 cm^{-1} (C=N): NMR ($CDCl_3$) δ 2.83 (m, 2 H, methylene protons), 4.00 (t, J = 9 Hz, 1 H, methine proton), 4.30–4.66 (m, 2 H, OCH_2), and 7.50–8.30 (m, 4 H, aromatic protons); mass spectrum (70 eV) *m/e* 231 (M^+). Anal. Calcd for $C_{12}H_9NO_4$: C, 62.34; H, 3.92; N, 6.06. Found: C, 62.16; H, 3.65; N, 6.12.

B. In a similar reaction (0.02 mol scale) at 110 °C for 3 h, using DMF (50 mL) as solvent, *N*-ethylisatoic anhydride was obtained in a yield of 3.02 g (79%) together with recovered **8** (0.60 g, 18%). *N*-Ethylisatoic anhydride had mp 124–125 °C (lit.[13] mp 123–124 °C): IR (Nujol) 1760 (C=O) and 1715 cm^{-1} (C=O); NMR ($CDCl_3$) δ 1.51 (t, 3 H, methyl protons), 4.15 (q, 2 H, methylene protons), 7.18–7.39 (m, 2 H, phenyl protons), 7.66–7.90 (m, 1 H, phenyl proton), and 8.09 (d, 1 H, phenyl proton).

Alkaline Hydrolysis of 9. A solution of **9** (2.31 g, 0.01 mol) in ethanol (50 mL) was stirred with NaOH (0.88 g, 0.022 mol) in water (20 mL) at room temperature for 5 h. After the reaction mixture was neutralized with hydrochloric acid (5%) and extracted with ether, the ether extract was distilled to remove solvents. The residue was chromatographed on silica gel using benzene–ethanol (95:5) as eluent to give 2.0 g (80%) of **2-*N*-(2-oxotetrahydrofuran-3-carboxyamido)benzoic acid (10)**, which was recrystallized from acetonitrile to provide a pure sample: mp 181–183 °C; IR (Nujol) 3160 (NH), 2500 (broad, OH), 1770 (lactone C=O), 1680 (C=O), and 1660 cm^{-1} (amide C=O); NMR (Me_2SO-d_6) δ 2.40–2.80 (m, 2 H, methylene protons), 3.96 (t, J = 8.0 Hz, 1 H, methine proton), 4.22–4.52 (m, 2 H, OCH_2), 7.06–8.52 [m, 5 H, aromatic protons (4 H) and NH], and 11.56

(s, 1 H, COOH). Anal. Calcd for $C_{12}H_{11}NO_5$: C, 57.83; H, 4.54; N, 5.62. Found: C, 58.04; H, 4.29; N, 5.60.

Reaction of 1 with *N*-Methylisatoic Anhydride (11). A. A mixture of **1** (0.03 mol) and **11** (5.31 g, 0.03 mol) in benzene (200 mL) was heated at 140 °C in a sealed tube for 7 h. The organic layer was separated and concentrated to give **2*H*,4*H*-1-methyl-(*E*)-4-(2-oxotetrahydrofuran-3-ylidene)benz[*d*][1,3]oxazin-2-one (12a)** (2.70 g). The filtrate was chromatographed on silica gel using benzene–hexane and benzene as eluent to give **12a** (0.50 g) and **2*H*,3*H*,4*H*-9-methylfuro[2,3-*b*]quinolin-4-one (13)** (0.32 g, 5%). The combined yield of **12a** was 3.20 g (43%). The crude product **12a** was recrystallized from benzene–hexane, giving a pure sample: mp 182–183 °C; IR (Nujol) 1760 and 1710 (C=O) and 1640 cm^{-1} (C=C); NMR (Me_2SO-d_6) δ 3.12 (t, 2 H, methylene protons), 3.36 (s, 3 H, NMe), 4.36 (t, 2 H, OCH_2), 7.13–7.68 (m, 3 H, aromatic protons), and 8.72 (d, J = 8 Hz, 1 H, aromatic proton); mass spectrum (70 eV) m/e 245 (M^+). Anal. Calcd for $C_{13}H_{11}NO_4$: C, 63.67; H, 4.52; N, 5.71. Found: C, 63.83; H, 4.43; N, 5.51.

A pure sample of **13**, which was obtained by recrystallization of the crude **13** from benzene–hexane, had mp 141–142 °C: IR (Nujol) 1660 (C=O) and 1620 cm^{-1} (C=C); NMR ($CDCl_3$) δ 3.17 (t, J = 9.0 Hz, 2 H, methylene protons), 3.63 (s, 3 H, NMe), 4.77 (t, J = 9.0 Hz, 2 H, OCH_2), and 7.03–7.80 (m, 4 H, aromatic protons); mass spectrum (70 eV) m/e 201 (M^+), 172 ($M^+ - C_2H_4 - H$), 134 ($M^+ - C_4H_4O + H$), and 132 ($M^+ - C_4H_4O - H$). Anal. Calcd for $C_{12}H_{11}NO_2$: C, 71.62; H, 5.51; N, 6.90. Found: C, 71.62; H, 5.54; N, 6.86.

B. In a similar reaction (0.02 mol scale) at 110 °C for 4 h, using DMF (90 mL) as solvent, **13** was obtained in a yield of 3.35 g (83%) along with *N*-methylanthranilic acid (0.50 g).

Base-Catalyzed Isomerization of 12a to 2*H*,4*H*-1-methyl-(*Z*)-4-(2-oxotetrahydrofuran-3-ylidene)benz[*d*][1,3]oxazin-2-one (12b). A solution containing **12a** (1.0 g, 4.0 mmol) and NaOH (0.32 g, 8.0 mmol) in 100 mL of ethanol was refluxed for 4 h. The solution was concentrated to give 0.51 g of recovered starting material **12a** (from acetonitrile). The filtrate was neutralized with hydrochloric acid and extracted with ether. The ether extract gave 0.40 g (40%) of **12b**, which was recrystallized from benzene–hexane to afford a pure sample: mp 123–125 °C; IR (Nujol) 1760 and 1695 (C=O) and 1650 cm^{-1} (C=C); NMR ($CDCl_3$) δ 3.07 (t, 2 H, methylene protons), 3.50 (s, 3 H, NMe), 4.60 (t, 2 H, OCH_2), and 7.03–8.10 (m, 4 H, aromatic protons); mass spectrum (70 eV) m/e 245 (M^+). Anal. Calcd for $C_{13}H_{11}NO_4$: C, 63.67; H, 4.52; N, 5.71. Found: C, 63.58; H, 4.73; N, 5.35.

Reaction of 1 with Propylene Oxide (14b). The reaction of **1** (0.03 mol) with propylene oxide (**14b**) (3.48 g, 0.06 mol) in benzene (60 mL) was heated at 160 °C in a sealed tube for 2 h. After removal of the resulting salt by filtration, the organic layer was concentrated and distilled to give 2.31 g (61%) of a 2:1 mixture of **15b** and **16b**. Analytically pure samples of each were obtained by preparative VPC. The product **15b** had the following properties: IR (neat) 1755 cm^{-1} (C=O); NMR ($CDCl_3$) δ 0.55–0.64 (dd, J = 5.4 Hz, 2.2 Hz, 1 H, cyclopropyl CH), 1.10 (d, J = 5.4 Hz, 3 H, cyclopropyl CMe), 1.35–1.60 (m, 2 H, cyclopropyl CH), 1.98–2.44 (m, 2 H, lactone CH_2), and 4.36 (t, 2 H, OCH_2).

The product **16b** had the following properties: IR (neat) 1755 cm^{-1} (C=O); NMR ($CDCl_3$) δ 0.90–1.04 (m, 2 H, cyclopropyl CH), 1.10–1.34 (m, 2 H, cyclopropyl CH), 1.46 (d, J = 6.2 Hz, 3 H, OCHMe), 1.88–2.08 (dd, 1 H, one proton of lactone CH_2), 2.24–2.44 (dd, 1 H, other proton of lactone CH_2), and 4.52–4.88 (m, 1 H, methine proton). Anal. Calcd for $C_7H_{10}O_2$: C, 66.64; H, 7.99. Found for a mixture of **15b** and **16b**: C, 66.29; H, 8.04.

Reactions of 1 with Epoxides 14a,c,d and Ethylene Carbonate. The reactions were carried out in a similar manner. After similar treatments, mixtures of **15a,c,d** and **16a,c,d** and **15e** were obtained by distillation. The results are summarized in Table I. The mixtures of **15a,c,d** and **16a,c,d** and **15e** had the following properties.

1-Phenyl-4-oxo-5-oxaspiro[2,4]heptane (15a) and 6-phenyl-4-oxo-5-oxaspiro[2,4]heptane (16a): IR (neat) 1755 cm^{-1} (C=O); NMR ($CDCl_3$) δ 0.94 (t, J = 3.0 Hz, 1 H), 1.16 (t, J = 3.0 Hz, 1 H), 1.20–2.75 (m, 4.5 H), 4.00–4.35 (m, 1 H, OCH_2), 5.45 (t, J = 7.8 Hz, 0.5 H, OCHPh), and 6.90–7.40 (m, 5 H, phenyl protons).

1,1-Dimethyl-4-oxo-5-oxaspiro[2,4]heptane (15c) and **6,6-dimethyl-4-oxo-5-oxaspiro[2,4]heptane (16c):** IR (neat) 1753 cm^{-1} (C=O); NMR spectrum ($CDCl_3$) δ 0.80–1.00 (m, 7/4 H, cyclopropyl CH), 1.20–1.36 (m, 13/4 H, cyclopropyl CH and Me), 1.50 (s, 9/2 H, $-CMe_2-$), 2.00–2.40 (m, 2 H, lactone CH_2), and 4.00–4.40 (m, 1/2 H, $-OCH_2-$).

1-Oxo-2-oxadispiro[4,0,5,1]dodecane (15d) and **4-oxo-5-oxadispiro[2,2,5,1]dodecane (16d):** IR (neat) 1750 cm^{-1} (C=O); NMR ($CDCl_3$) δ 0.77–1.05 (m, 5/3 H, cyclopropyl CH), 1.15–2.05 (m, 34/3 H, cyclopropyl and cyclohexyl protons), 2.10 (s, 4/3 H, lactone CH_2 of **16d**), 2.30 (t, J = 7.2 Hz, 2/3 H, lactone CH_2 of **15d**), and 4.00–4.50 (m, 2/3 H, OCH_2).

4-Oxo-5-oxaspiro[2,4]heptane (15e): IR (neat) 1755 cm^{-1} (C=O); NMR ($CDCl_3$) δ 0.90–1.10 (m, 2 H, cylopropyl CH), 1.10–1.30 (m, 2 H, cyclopropyl CH), 2.32 (t, J = 7.4 Hz, 2 H, lactone CH_2), and 4.36 (t, J = 7.4 Hz, 2 H, OCH_2).

Preparation of Authentic Spirolactones 15a,c,d. To a dimethylsulfoxide solution containing dimethyloxosulfonium methylide (0.04 mol) prepared according to the established procedure[14] was added α-benzylidene-γ-butyrolactone[2,15] (**17a**) (6.96 g, 0.04 mol) and the mixture was stirred at room temperature for 12 h; then the reaction was poured into water and extracted with ether. The ether extract was concentrated and chromatographed on silica gel using benzene and benzene–alcohol as eluent to give **15a** (2.0 g, 27%) and 1.10 g (16%) of a dimeric product of starting **17a** whose structure was tentatively assigned as 6,12-diphenyl-1,8-dioxo-2,9-dioxadispiro[4,1,4,1]dodecane on the basis of spectral data shown below. Distillation of crude **15a** gave the pure sample: bp 106–109 °C (1 mm); IR (neat) 1755 cm^{-1} (C=O); NMR ($CDCl_3$) δ 1.25–2.20 [m, 4 H, cyclopropyl CH (2 H) and lactone CH_2 (2 H)], 2.65 [dd, J = 9.0, 7.5 Hz, 1 H, cyclopropyl C(Ph)H], 4.05–4.40 (m, 2 H, OCH_2), and 6.90–7.45 (m, 5 H, phenyl protons). The dimeric product had mp 195–197 °C (from benzene–alcohol): IR (Nujol) 1740 cm^{-1} (C=O); NMR (Me_2SO-d_6) δ 2.0–3.0 (m, 4 H, methylene protons), 3.65–4.25 (m, 4 H, OCH_2), 4.40 (s, 2 H, –CHPh–), and 7.15–7.40 (m, 10 H, phenyl protons); mass spectrum (70 eV) m/e 348 (M^+) and 174 ($M^+ - C_{11}H_{10}O_2$). Anal. Calcd for $C_{22}H_{10}O_4$: C, 75.84; H, 5.79. Found: C, 75.53; H, 5.66.

Other authentic samples of **15c** and **15d** were prepared in the same way as **15a**, from α-isopropylidene-[2] (**17c**) and α-cyclohexylidene-γ-butyrolactone[2,15] (**17d**). The yields of authentic **15c** and **15d** were obtained in 50 and 74% yields.

15c had bp 54–56 °C (1 mm): IR (neat) 1750 cm^{-1} (C=O); NMR ($CDCl_3$) δ 0.84 (d, 1 H, cyclopropyl CH), 1.20 (s, 3 H, methyl protons), 1.30 (d, 1 H, cyclopropyl CH), 1.35 (s, 3 H, methyl protons), 2.08–2.45 (m, 2 H, lactone CH_2), and 4.15–4.50 (m, 2 H, OCH_2); mass spectrum (70 eV) m/e 140 (M^+). Anal. Calcd for $C_8H_{12}O_2$: C, 68.54; H, 8.63. Found: C, 68.36; H, 8.91.

15d had mp 51–52 °C (from benzene–hexane): IR (Nujol) 1750 cm^{-1} (C=O); NMR ($CDCl_3$) δ 0.79 (d, J = 3.6 Hz, 1 H, cyclopropyl CH), 1.29 (d, J = 3.6 Hz, 1 H, cyclopropyl CH), 1.30–2.20 (m, 10 H, cyclohexyl CH_2), 2.28 (dd, J = 6.1, 9.1 Hz, 2 H, lactone CH_2), and 4.04–4.50 (m, 2 H, OCH_2); mass spectrum (70 eV) m/e 180 (M^+). Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C, 73.35; H, 8.79.

α-(1,3-Dimethyl-(*E*)-2,3-epoxybutylidene)-γ-butyrolactone (19a). The reaction was carried out at 80 °C for 1 h with **1** (0.03 mol) and 3,4-epoxy-4-methyl-2-pentanone (**18a**) (3.42 g, 0.03 mol) in benzene (60 mL). After similar treatment, distillation of the residue gave 4.20 g (77%) of **19a**: bp 88–90 °C (1 mm); IR (neat) 1740 (C=O) and 1650 cm^{-1} (C=C); NMR ($CDCl_3$) δ 1.18 (s, 3 H, epoxy Me), 1.44 (s, 3 H, epoxy Me), 2.05–2.30 [m, 3 H, cis Me of –(CO)C=C(Me)–], 2.70–3.20 (m, 2 H, lactone CH_2), 3.20–3.40 (m, 1 H, epoxy methine proton), and 4.25 (t, 2 H, OCH_2). Anal. Calcd for $C_{10}H_{14}O_3$: C, 65.91; H, 7.74. Found: C, 65.74; H, 7.98.

Since the (*Z*)- and (*E*)-methyl protons of **17c** were observed at δ 2.15–2.30 and 1.80–1.92 in the NMR spectrum ($CDCl_3$), the assignment of the stereochemistry of **19a** could be clearly decided as above.

α-(1,3-Diphenyl-(*Z*)-2,3-epoxypropylidene)-γ-butyrolactone (19b). This derivative was similarly obtained in a 7.55-g (86%) yield by using **1** (0.03 mol) and *trans*-chalconepoxide (**18b**) (6.72 g, 0.03 mol). Recrystallization of crude **19b** from benzene–hexane gave the pure sample: mp 118–119 °C; IR (Nujol) 1731 (C=O) and 1636 cm^{-1} (C=C); NMR ($CDCl_3$) δ 2.50–2.95 (m, 2 H, lactone CH_2), 3.43 (d, J = 2.2 Hz, 1 H, epoxy methine proton), 4.22 (t, 2 H, OCH_2), 5.20 (d, J = 2.2 Hz, 1 H, epoxy methine proton), and 7.10–7.45 (m, 10 H, phenyl protons); NMR (C_6D_6) δ 1.70–2.15 (m, 2 H, lactone CH_2), 3.25–3.60 [m, 3 H, OCH_2 (2 H) and epoxy methine proton (1 H)], 5.17 (d, J = 2.2 Hz, 1 H, epoxy methine proton), and 6.90–7.35 (m, 10 H, phenyl protons). Anal. Calcd for $C_{19}H_{16}O_3$: C, 78.06; H, 5.52. Found: C, 78.13; H, 5.45.

2*H*-2-(2-Oxotetrahydrofuran-3-ylidene)benz[*d*][1,3]dioxole (22). The reaction of **1** (0.03 mol) with 1,2-carbonyldioxybenzene (**20**) (4.10 g, 0.03 mol) in benzene (80 mL) was carried out at 170 °C for 12 h in a sealed tube. After similar treatment, **22** was obtained in a 3.41-g (56%) yield along with unreacted **20** (1.20 g, 29%). **22** had mp 208–209 °C (from benzene–hexane): IR (Nujol) 1740 and 1690 (C=O) and 1620 cm^{-1} (C=C); NMR ($CDCl_3$) δ 3.05 (t, J = 7.5 Hz, 2 H, lactone CH_2), 4.40 (t, J = 7.5 Hz, 2 H, OCH_2), and 7.20 (broad s, 4 H, phenyl protons); mass spectrum (70 eV) m/e 204 (M^+). Anal. Calcd for $C_{11}H_8O_4$:

C, 64.70; H, 3.95. Found: C, 64.35; H, 3.80.

α-(Z)-(Tetrahydrofuran-2-ylidene)-γ-butyrolactone (23). The reaction of **1** (0.03 mol) and γ-butyrolactone (**21**) (2.58 g, 0.03 mol) in 50 mL of benzene at 150 °C for 8 h in a sealed tube gave 1.42 g (31%) of **23**: mp 81–82 °C (from benzene–hexane) (lit.[16] mp 86.5 °C); IR (Nujol) 1740 (C=O) and 1650 cm^{-1} (C=C); NMR ($CDCl_3$) δ 1.85–2.39 (m, 2 H, methylene protons), 2.70–3.30 [m, 4 H, C=C(-O-)CH_2 + C=C(CO)CH_2], and 4.30 (t, 4 H, OCH_2); NMR (C_6D_6) δ 1.05–1.62 (m, 2 H, methylene protons), 2.25–2.66 [m, 2 H, C=C(-O-)CH_2], 2.70–3.05 [m, 2 H, C=C(CO)CH_2], and 3.40–3.80 (m, 4 H, OCH_2); mass spectrum (70 eV) *m/e* 154 (M^+). Anal. Calcd for $C_8H_{10}O_3$: C, 62.32; H, 6.54. Found: C, 61.98; H, 6.29.

The stereochemistry of **23** was determined on the basis of upfield shifts of all protons by a change of solvent from $CDCl_3$ to benzene-d_6 in the NMR spectrum.[2]

Registry No.—**1**, 52217-10-4; **2**, 85-44-9; **3**, 5698-59-9; **4a**, 65652-15-5; **4b**, 65652-16-6; **5**, 65652-17-7; **6**, 703-59-3; **7**, 65652-18-8; **8**, 118-48-9; **9**, 65652-19-9; **10**, 65701-66-8; **11**, 10328-92-4; **12a**, 65701-67-9; **12b**, 65632-25-9; **13**, 65652-20-2; **17a**, 6285-99-0; **17c**, 24186-31-0; **17d**, 21681-63-0; **18a**, 4478-63-1; **18b**, 7570-86-7; **19a**, 65652-21-3; **19b**, 65652-22-4; **20**, 2171-74-6; **21**, 96-48-0; **22**, 65652-23-5; **23**, 65652-24-6; *N*-ethylisatoic anhydride, 50332-68-8; 6,12-diphenyl-1,8-dioxo-2,9-dioxadespiro[4.1.4.1]dodecane, 65652-25-7.

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Chemistry of Carbanions. 32. Formation of the Perhydroazulene System by Intramolecular Alkylation[1]

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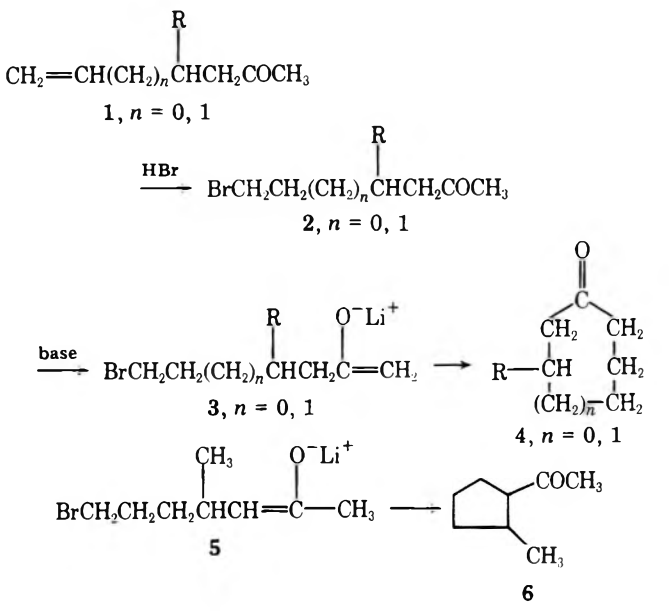
A synthetic route (Schemes II and III) for the formation of the perhydroazulene derivative **10** has been developed based upon the intramolecular cyclization of the bromo enolate **8** formed by the kinetic deprotonation of the bromo ketone **7**. Reaction of this bromo ketone with base under equilibrating conditions (KOBu-*t* in *t*-BuOH) yields the alternative cyclization product **19**. In seeking efficient synthetic routes to the intermediate unsaturated ketone **14**, we attempted to prepare the reagent $Br(CH_2)_3Li$; although this reagent could apparently be generated even at −110 °C in Et_2O–hexane solution, the material decomposed too rapidly to be useful.

In previous papers,[2,3] we have described general procedures for the formation of unsaturated ketones **1** (Scheme I) and the conversion of these intermediates **1**, via the bromo ketones **2** and the enolates **3**, to six- and seven-membered cyclic ketones **4**. In this earlier study, the cyclization of the bromo ketone **2** (R = CH_3, *n* = 1) to the seven-membered ketone **4** was complicated by the competing formation of the cyclopentyl ketone **6** (40% of the monomeric product). This competing cyclization **2** → **6** was attributed to a combination of three factors: (1) kinetically controlled deprotonation of methyl *n*-alkyl ketones with the hindered base *i*-Pr_2NLi typically forms 80–85% of the terminal enolate (e.g., **3**) accompanied by 15–20% of the internal enolate (e.g., **5**);[4] (2) the reaction of internal enolates (e.g., **5**) with alkyl halides is usually more rapid than the corresponding reaction with terminal enolates (e.g., **3**) that are presumably more highly aggregated;[4,5] (3) intramolecular alkylation to form five-membered rings is more rapid than the analogous reaction to form seven-membered rings.[6] This latter unfavorable rate factor is further enhanced in the present case because the cyclization **3** → **4** (*n* = 1) requires the additional strain of incorporating a planar enolate system into the cyclic transition state[3] while the cyclization **5** → **6** does not have this unfavorable requirement. The relatively slow rate of cyclization **3** → **4** (*n* = 1) allowed sufficient time for competing enolate equilbration **3** ⇌ **5** so that a significant amount of the unwanted cyclopentane by-product **6** was produced.

Scheme I



It was apparent that certain of the aforementioned difficulties associated with an intramolecular cyclization to form a cycloheptanone derivative could be mitigated by cyclization of a bromo ketone of the type **7** (Scheme II). In such cases,

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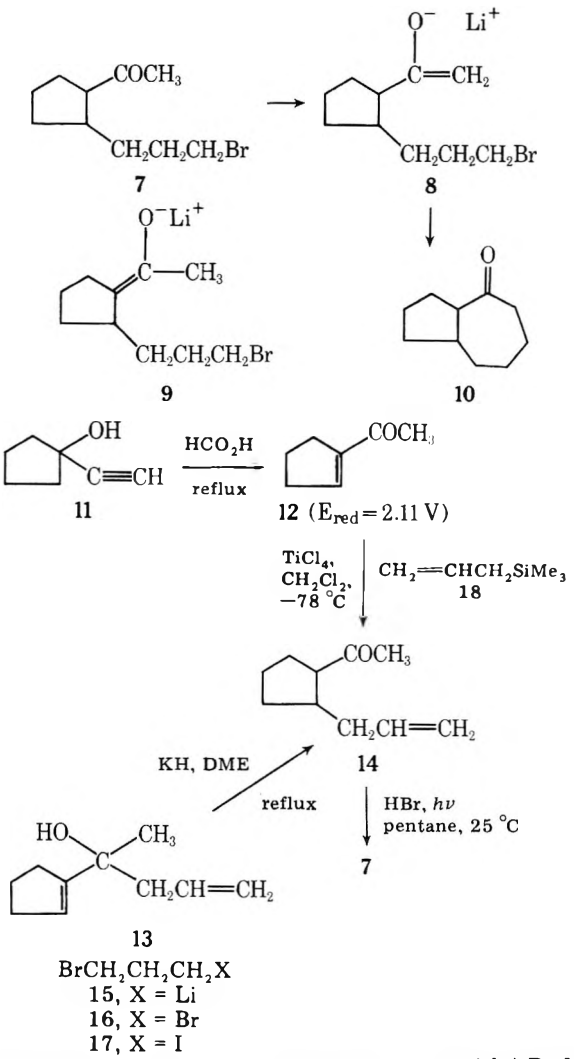
Scheme II



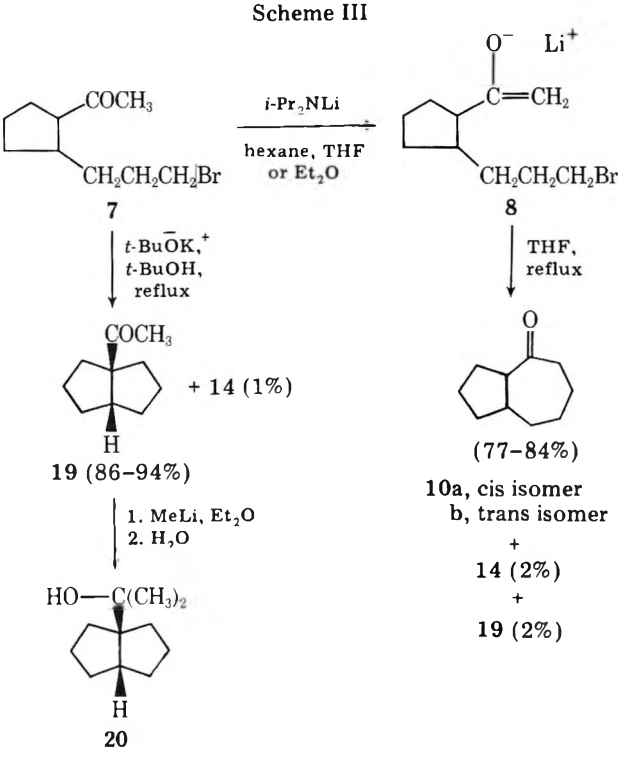
$BrCH_2CH_2CH_2X$
15, X = Li
16, X = Br
17, X = I

kinetically controlled reaction of the ketone **7** with *i*-Pr_2NLi to form a terminal enolate **8** rather than a fully substituted internal enolate **9** is more regiospecific (typically forming >95% of the terminal enolate).[4] Also, attachment of the two reacting functionalities to a preformed ring favors the proximity of the two reacting centers and can be expected[3] to increase the rate of cyclization.

To obtain the desired bromo ketone **7**, the acetylenic carbinol **11** was isomerized with boiling HCO_2H[7] to form the enone **12**. From consideration of the reduction potential (−2.11V vs. SCE in DMF solution) of the enone **12**, conjugate addition of $(allyl)_2CuLi$ to this substrate **12** to form the olefinic ketone **14** would be expected to be only marginally satisfactory.[8] In fact, reaction of $(allyl)_2CuLi$ with this enone **12** produced a mixture of the ketone **14** (29%), the enone **12** (11–24%, from enolate formation), and the alcohol **13** (31%). A more satisfactory synthetic route involved conversion of the enone **12** to the alcohol **13** (83% yield) with the allyl Grignard reagent followed by a base-catalyzed[9] oxy-Cope rearrangement of the alcohol **13** to form the ketone **14** in 78% yield. A still more efficient synthetic route involved direct reaction of the enone **12** with $CH_2=CHCH_2SiMe_3$ (**18**) and $TiCl_4$[10] to form the ketone **14** in 83–94% yield. The usual[2] light-induced free-radical addition of HBr to the olefinic ketone **14** (a mixture of stereoisomers) in pentane solution formed the bromo ketone **7** (a mixture of stereoisomers) in 88% yield.

We also examined one other possible procedure for the direct conversion of the enone **12** to the bromo ketone **7**. The reduction potential of the enone **12** is sufficiently positive that the conjugate addition of organocuprates derived from *n*-alkyllithium reagents would be a satisfactory synthetic procedure.[8] (For example, Me_2CuLi readily gives a conjugate addition product with the enone **12**.[3]) Consequently, if the cuprate reagent $(BrCH_2CH_2CH_2)_2CuLi$[11] could be prepared, such a reagent would offer a direct method for the conversion of the enone **12** to the bromo **7**. To explore the possibility of forming the lithium reagent **15**, we examined the behavior of mixtures of *n*-BuLi and the dihalides **16** and **17** in Et_2O–hexane mixtures at low temperatures.[12] Although, as would be expected from earlier work,[13] little if any metal–halogen exchange was observed with the dibromide **16** and *n*-BuLi at −78 °C, the corresponding exchange with *n*-BuLi and the bromoiodide **17** was relatively rapid both at −78 and at −110 °C. Unfortunately, even at −110 °C the decomposition of the lithium reagent **15** (presumably to form cyclopropane) was also rapid. Thus, protonation of the reaction mixtures at −110 °C led to the recovery of *n*-BuI (from lithium–iodine exchange) and a small amount of unchanged dihalide **17** but no *n*-PrBr (the product expected from protonation of **15**).

Scheme III



Conversion of the bromo ketone **7** to its enolate under equilibrating conditions (*t*-BuOK in *t*-BuOH) resulted in a relatively rapid conversion to the methyl ketone **19** (86–94%, Scheme III) with none of the seven-membered cyclic product **10** being detected. This result is, of course, compatible with the idea that the intramolecular reaction **9** → **19** to form a five-membered ring is faster than cyclization **8** → **10** to form a seven-membered ring. The structure and stereochemistry of methyl ketone **19** were confirmed by its conversion to the known alcohol **20**.[14] As we had hoped, kinetic deprotonation of the bromo ketone **7** with *i*-Pr_2NLi exhibited high regiospecificity to form the terminal enolate **8** and, after cyclization, the ketone **10**. Under the best conditions we found (refluxing THF) for cyclization of the enolate, the yields were 77–84% of the desired ketone **10** (a mixture of cis and trans isomers), 2% of the isomeric ketone **19**, and 2% of the dehydrobromination product **14**. When the previously described[3] cyclization conditions (Et_2O–hexane + 4 molar equiv of HMP at 25 °C) were used, the yields of monomeric products were lower (67% **10**, 6% **14**, and 3% **19**) and more high molecular weight by-products (presumably from competing intermolecular alkylation)[3] were formed. When the reaction solvent was either boiling THF or boiling DME, the addition of 4 molar equiv of HMP to coordinate with the Li^+ cation was unnecessary.

In summary, we may conclude that the synthetic route **12** → **14** → **7** → **10** constitutes an efficient and useful route to perhydroazulene derivatives.[15] Furthermore, the high yield obtained in the final intramolecular alkylation step **7** → **10** indicates that, with appropriate substitution to disfavor formation of the isomeric five-membered ring product (e.g., **7** → **19**), this intramolecular alkylation reaction can be a useful method for the formation of cycloheptanone derivatives.

Experimental Section[16]

Preparation of the Enone 12. Our previously described[3] procedure for the HCO_2H-catalyzed isomerization of the acetylenic carbinol **11** to the enone **12** was improved by adding 15.88 g (0.14 mol) of the carbinol **11**, dropwise and with stirring during 50 min, to 150 mL of refluxing 92% HCO_2H. After the addition was complete, the purple reaction mixture was refluxed for an additional 10 min and then partitioned between pentane and aqueous $NaHCO_3$ containing excess solid $NaHCO_3$ to neutralize the HCO_2H. The organic layer was dried, concentrated, and distilled to separate 9.51 g (60%) of the enone **12**, bp 70 °C (18 mm), n^{25}_D 1.4771–1.4781 [lit.[7] bp 67° (16 mm), n^{23}_D 1.4776] with IR absorption corresponding to that previously described.[3] Solutions in anhydrous DMF containing 0.5 M n-Bu_4NBF_4 and 1.2×10^{-3} M enone **12** exhibited a polarographic $E_{1/2}$ value[17] of −2.11 V vs. SCE (n = 1.0, i_d = 51 μA).

Preparation of the Alcohol 13. To a cold (4 °C) solution containing 88.5 mmol of CH_2=$CHCH_2MgBr$ in 200 mL of Et_2O was added, dropwise with stirring and cooling during 30 min, a solution of 8.12 g (73.8 mmol) of the enone **12** in 40 mL of Et_2O. After the addition was complete, the cooling bath was removed and the reaction solution was stirred for 2 h and then poured into an ice–H_2O mixture and extracted with Et_2O. After the ethereal solution had been washed with aqueous $NaHCO_3$, dried, and concentrated, distillation separated 9.29 g (83%) of the alcohol **13** as a colorless liquid: bp 76–78 °C (4.8 mm); n^{25}_D 1.4825–1.4837; IR (CCl_4) 3600, 3570 (OH), 1640 (C=C), and 922 cm^{-1} (CH=CH_2); UV (95% EtOH) end absorption with ε 102 at 210 nm; NMR (CCl_4) δ 4.7–6.0 (4 H, m, vinyl CH), 1.4–2.5 (9 H, m, CH_2 and OH), and 1.25 (3 H, s, CH_3); mass spectrum, m/e (rel intensity) 134 (2), 119 (3), 111 (40), 43 (100), 41 (13), and 39 (10). Anal. Calcd for $C_{10}H_{16}O$: C, 78.89; H, 10.59. Found: C, 78.83; H, 10.62.

Preparation of the Olefinic Ketone 14. A. From the Alcohol 13. Following a previously described[9] general procedure, a mixture of 9.00 g (230 mmol) of KH (prewashed with pentane) and 290 mL of DME was treated, dropwise and with stirring during 20 min, with a solution of 11.44 g (75 mmol) of the alcohol **13** in 30 mL of DME. After the resulting mixture had been stirred at 25 °C for 2 h (most of the KH had reacted) it was refluxed for 2.5 h at which time TLC and GLC analysis of an aliquot indicated that the rearrangement was complete. After the reaction mixture had been cautiously siphoned into aqueous NH_4Cl, the combined organic layer and Et_2O extract of the aqueous phase were washed successively with aqueous $NaHCO_3$ and with aqueous NaCl and then dried and concentrated. The residual crude liquid product (11.30 g) was fractionally distilled to separate 508-mg of fractions, bp 80–91 °C (14 mm), n^{25}_D 1.4540–1.4601, containing the ketone **14** and lower boiling impurities. Later distillation fractions contained (GPC) 8.90 g (78%) of the ketone **14** (a mixture of stereoisomers): bp 91–93 °C (14 mm); n^{25}_D 1.4605; IR (CCl_4) 1712 (C=O), 1641 (C=C), and 922 cm^{-1} (CH=CH_2); UV_{max} (95% EtOH) 281 nm (ε 24); NMR (CCl_4) δ 4.7–6.1 (3 H, m, vinyl CH), and 1.0–3.2 (13 H, m, aliphatic CH including a CH_3CO singlet at 2.06); mass spectrum, m/e (rel intensity) 152 (M^+, 1), 137 (3), 109 (17), 94 (12), 79 (14), 71 (19), 67 (29), 43 (100), 41 (18), and 39 (12). The ketone **14** exhibited GPC peaks (UCON 50HB280X on Chromosorb P) for the two stereoisomers at 14.9 and 15.9 min; the corresponding retention time for the enone **12** (a by-product in the rearrangement) was 7.7 min. Anal. Calcd for $C_{10}H_{16}O$: C, 78.89; H, 10.59. Found: C, 78.90; H, 10.61.

B. From the Enone 12. Following a literature procedure,[18a] a solution of 73.8 g (0.61 mol) of CH_2=$CHCH_2Br$ and 66.3 g (0.61 mol) of Me_3SiCl in 200 mL of Et_2O was added to 38.61 g (1.59 g-atom) of Mg in 400 mL of refluxing Et_2O during 4 h and the resulting mixture was refluxed for an additional 1 h and then allowed to stand overnight. After the mixture had been filtered and then partitioned between pentane and aqueous NH_4Cl, the organic solution was washed with H_2O, dried, and concentrated. Distillation separated 57.0 g (82%) of the silane **18** as a colorless liquid: bp 85–86 °C; n^{25}_D 1.4052 [lit. bp 86 °C,[18a] n^{20}_D 1.4074[18b]]; IR (CCl_4) 1632 (C=C) and 902 cm^{-1} (CH=CH_2); NMR (CCl_4) δ 4.5–6.1 (3 H, m, vinyl CH), 1.44 (2 H, d, J = 8 Hz, CH_2), and 0.00 (9 H, s, MeSi); mass spectrum, m/e (rel intensity) 114 (M^+, 4), 99 (10), 73 (100), 59 (16), 45 (18), and 43 (10).

Following a previously described[10] procedure, a cold (−78 °C) solution of 4.95 g (45 mmol) of the enone **12** in 100 mL of anhydrous CH_2Cl_2 was treated, dropwise and with stirring, with 8.54 g (45 mmol) of $TiCl_4$. The resulting slurry of a yellow solid was stirred at −78 °C for 5 min and then a solution of 6.3 g (55 mmol) of the silane **18** in 70 mL of CH_2Cl_2 was added, dropwise and with stirring during 30 min at −78 °C. The resulting purple solution was stirred at −78 °C for an additional 30 min and then 50 mL of H_2O was added, dropwise and with stirring, to the cold solution. After the resulting colorless mixture had warmed to 25 °C, the organic layer was separated, combined with the Et_2O extract of the aqueous phase, dried, and concentrated. After an aliquot of the crude yellow liquid product (11.55 g) had been mixed with an internal standard (1,3,5-triisopropylbenzene), GLC analysis (silicone XE-60 on Chromosorb P, apparatus calibrated with known mixtures) indicated the presence of 1,3,5-triisopropylbenzene (retention time 9.8 min) and the olefinic ketone **14** (13.2 min, 94% yield). The remaining crude product was chromatographed on silica gel with an Et_2O–pentane elutent (1:4 v/v) and the eluted ketone **14** fractions (5.85 g) were distilled to separate 5.65 g (83%) of the olefinic ketone **14**, bp 84.5–85 °C (10 mm), n^{25}_D 1.4609.

Several comparable small-scale experiments were performed at different reaction temperatures and the yield of ketone **14** was determined by GPC analysis. When the reactants were mixed and stirred for 30 min at −78 °C and then allowed to warm to 25 °C and stir overnight, the initial purple solution changed to a deep red colored solution and the yield (GLC) of ketone **14** was 61%. When the reactants were mixed at 25 °C and then stirred for 5 min a deep red solution was obtained immediately and the yield (GLC) of ketone **14** was only 48%.

C. From the Enone 12 and Lithium Diallylcuprate. To a cold (−72 °C) partial solution of 3.94 g (19.1 mmol) of freshly recrystallized[8] Me_2SCuBr in 57 mL of Et_2O and 57 mL of Me_2S was added, dropwise and with stirring at −70 to −72 °C during 20 min, 60 mL of ethereal solution containing 38.4 mmol of CH_2=$CHCH_2Li$ (from CH_2=$CHCH_2OPh$[8]). During this addition the reaction mixture was deep red in color during the first part of the addition and became a pale orange *solution* as the second equivalent of the lithium reagent was added. A solution of 1.057 g (9.6 mmol) of the enone **12** in 20 mL of Et_2O was added, dropwise and with stirring during 20 min, to the cold (−70 to −73 °C) reaction solution with the accompanying reappearance of the red color in the reaction mixture. After the red reaction solution had been warmed to −50 °C during 30 min and then stirred at −40 to −50 °C for 75 min, the mixture was hydrolyzed at −40 °C by the dropwise addition of a solution of 10 mL of HOAc in 100 mL of Et_2O. The resulting mixture was washed successively with an aqueous solution (pH 8) of NH_3 and NH_4Cl, with aqueous 10% NaOH, and with aqueous NaCl and then dried and concentrated. A 223-mg aliquot of the crude liquid product (3.16 g) was mixed with n-$C_{15}H_{32}$ (an internal standard) for GLC analyses [FFAP (Regis Chemical Co.) on Chromosorb P, apparatus calibrated with known mixtures]. The product contained (GLC) the enone **12** (retention time 9.2 min, 24% yield), the cis and trans isomers of ketone **14** (15.1 and 16.3 min, total yield 24%), a peak corresponding to the alcohol **13** (or its dehydration product, 22.2 min), and n-$C_{15}H_{32}$ (27.7 min). Collected (GLC) samples of ketones **12** and **14** were identified with authentic samples by comparison of IR and NMR spectra. The remaining crude product was chromatographed on silica gel with Et_2O–hexane mixtures as the eluent to separate, in order of elution, 390 mg (29%) of the ketone **14**, n^{25}_D 1.4616, 142 mg (11%) of the enone **12**, n^{25}_D 1.4793, and 421 mg (31%) of the alcohol **13**, n^{25}_D 1.4823 (identified with the previous sample by comparison of IR and NMR spectra).

Preparation of the Bromo Ketone 7. A solution of 1.00 g (6.6 mmol) of the olefinic ketone **14** in 300 mL of anhydrous, olefin-free pentane was irradiated with the light from a Hanovia 450-W medium-pressure Hg lamp for 6.5 min while a stream of anhydrous HBr gas was passed through the reaction solution. The resulting pentane solution was washed successively with aqueous $Na_2S_2O_3$, with aqueous $NaHCO_3$, and with aqueous NaCl and then dried and concentrated. Distillation afforded 1.37 g of crude product as a brown liquid, bp 82–86 °C (0.05 mm). Redistillation separated 1.34 g (88%) of the pure bromo ketone **7** (presumably a mixture of stereoisomers) as a colorless liquid: bp 76 °C (0.02 nm); n^{25}_D 1.4926–1.4928; IR (CCl_4) 1711 cm^{-1} (C=O); NMR (CCl_4) δ 3.34 (2 H, t, J = 6 Hz, CH_2Br), and 1.0–2.6 (15 H, m, aliphatic CH including a CH_3CO singlet at 2.09); mass spectrum, m/e (rel intensity) 234 (M^+, 0.3), 232 (M^+, 0.3), 153 (9), 111 (33), 109 (20), 71 (30), 67 (28), 43 (100), and 41 (20). Anal. Calcd for $C_{10}H_{17}BrO$: C, 51.52; H, 7.35; Br, 34.27. Found: C, 51.52; H, 7.39; Br, 34.18.

Cyclization of the Bromo Ketone 7. A With KOBu-*t*. To a solution of KOBu-*t*, from 0.78 g (20 mg-atom) of K and 40 mL of *t*-BuOH, was added, dropwise and with stirring during 10 min, a solution of 4.66 g (20 mmol) of the bromo ketone **7** in 40 mL of pentane.

The resulting mixture was stirred at 25 °C for 30 min and at reflux for an addition 60 min to complete the reaction. After the reaction mixture had been partitioned between Et_2O and H_2O, the organic layer was dried and concentrated. A 50.2-mg aliquot of the crude liquid product (17.75 g) was mixed with 35.0 mg of 1-phenyloctane for GLC analysis (silicone XE-60 on Chromosorb P, apparatus calibrated with known mixtures). The crude product contained low-boiling materials, the unsaturated ketone **14** (1% yield, retention time 9.0 min), the ketone **19** (94% yield, 12.0 min), and 1-phenyloctane (17.4 min) but lacked GLC peaks corresponding to the trans ketone **10b** (24.1 min) and the cis ketone **10a** (21.7 min). The remaining crude product was distilled to separate *t*-BuOH and then chromatographed on silica gel with an Et_2O–pentane eluent (1:19 v/v). The colorless fractions (2.62 g) containing the ketone **19** were combined and distilled to separate 2.60 g (86%) of the ketone **19** as a colorless liquid: bp 89–89.5 °C (10 mm); $n^{25}D$ 1.4762; IR (CCl_4) 1699 cm^{-1} (C=O); NMR (CCl_4) δ 2.5–3.0 (1 H, m, CH) and 1.1–2.3 (15 H, m, aliphatic CH including a CH_3CO singlet at 2.07); mass spectrum, *m/e* (rel intensity) 152 (M^+, 3), 137 (35), 111 (25), 109 (100), 67 (90), 55 (24), 43 (46), 41 (23), and 39 (23). Anal. Calcd for $C_{10}H_{16}O$: C, 78.89; H, 10.59. Found: C, 78.87; H, 10.62.

To confirm the structure and stereochemistry of the ketonic product, a solution of 1.52 g (10 mmol) of the ketone **19** in 10 mL of Et_2O was added, dropwise and with stirring during 30 min, to a cold (−78 °C) solution of 10 mmol of MeLi in 17 mL of Et_2O. The resulting solution was allowed to warm to 25 °C with stirring during 30 min and then stirred at 25 °C for 20 min and added to aqueous $NaHCO_3$. After the mixture had been extracted with Et_2O, the ethereal extract was dried and concentrated to leave 1.52 g of crude liquid product that contained (GLC, XE-60 on Chromosorb P) the starting ketone **19** (retention time 13.8 min, ca. 15%) and the alcohol **20** (16.8 min, ca. 85%). Collected (GLC) samples of both products were identified with authentic samples by comparison of IR and mass spectra and GLC retention times. Chromatography of the crude product on silica gel with an Et_2O–hexane eluent (1:9 v/v) separated 0.24 g (14%) of early fractions containing the ketone **19** and 1.22 g (73%) of later fractions containing the alcohol **20**. Distillation afforded 1.19 g (71%) of the pure alcohol **20** as a colorless liquid: bp 90–90.5 °C (4.5 mm); $n^{25}D$ 1.4873; IR (CCl_4) 3610 and 3490 cm^{-1} (OH); NMR (CCl_4) δ 2.1–2.4 (1 H, m, CH) and 1.0–2.1 [19 H, m, OH and aliphatic CH including a $(CH_3)_2C$ singlet at 1.15]; mass spectrum, *m/e* (rel intensity) 153 (2), 135 (17), 108 (31), 82 (26), 79 (27), 67 (46), 59 (100), 58 (28), 43 (42), 41 (44), and 39 (23). Anal. Calcd for $C_{11}H_{20}O$: C, 78.51; H, 11.98. Found: C, 78.53; H, 12.02.

Our product was identified with a previously reported[14] sample of the alcohol **20** by comparison of IR and NMR spectra.

B. With *i*-Pr_2NLi. To a cold (−72 °C) solution, prepared by adding a solution[3] of 33.3 mmol of *i*-Pr_2NLi in 62 mL of hexane to 350 mL of cold THF, was added, dropwise with stirring and cooling during 20 min, a solution of 6.43 g (27.7 mmol) of the bromo ketone **7** in 50 mL of THF. The resulting solution was warmed to boiling during 15 min and then refluxed for 2 h. After the solution had been cooled, it was siphoned into aqueous NH_4Cl and then extracted with Et_2O. The ethereal extract was washed successively with aqueous $NaHCO_3$ and with aqueous NaCl and then dried and concentrated. An aliquot of the residual liquid (7.08 g) was mixed with a known weight of 1-methylnaphthalene (an internal standard) for GLC analysis [FFAP (Regis Chemical Co.) on Chromosorb P, apparatus calibrated with known mixtures]. The crude product contained (GLC) the unsaturated ketone **14** (retention time 6.8 min, 2% yield), the ketone **19** (9.0 min, 1% yield), a mixture of the stereoisomeric ketones **10** (19.6 min for cis isomer **10a** and 22.0 min for trans isomer **10b**, 84% yield), 1-methylnaphthalene (31.8 min), and a series of minor (<2%) unidentified components (3.7, 5.4, 14.1, and 15.9 min). Distillation separated 3.73 g of distillate, bp 100–103 °C (8 mm), containing (GLC) 92% of the ketone **10** (corresponds to an 84% yield) from 0.42 g of higher molecular weight residue (presumably from competing intermolecular alkylation[3]). The distillate was subjected to low-pressure liquid chromatography on silica gel with Et_2O–hexane mixtures as the eluent. Early fractions (278 mg) contained (GLC) mixtures of ketones **14**, **19**, and other minor unidentified impurities. Samples of ketones **14** and **19** collected (GLC) from these fractions were identified with authentic samples by comparison of GLC retention times and IR, NMR, and mass spectra. Subsequent chromatographic fractions contained (GLC) 191 mg of a mixture of the cis ketone **10a** and several more rapidly eluted components, 1.94 g of a mixture of cis and trans ketones **10** and 1.32 g of the trans ketone **10b**. The intermediate fractions were rechromatographed twice on silica gel to separate an additional 1.12 g (total yield 2.44 g) of pure trans ketone **10b** and 762 mg of pure cis ketone **10a** as well as fractions containing mixtures of both stereoisomers.

Table I. Cyclization of the Lithium Enolate 8

Solvents	Temp, °C	Time, min	Product yields, % 10	14	19
Hexane, Et_2O, HMP	25	90	67	6	3
Hexane, DME, HMP	84	60	67	4	1
Hexane, DME	84	60	68	4	<1
Hexane, THF, HMP	65	50	79	2	2
Hexane, THF	65	120	77–84	2	1–2

Distillation of the fractions containing the cis isomer afforded 597 mg (14%) of the pure cis ketone **10a** as a colorless liquid: bp 92–97 °C; (6.5 mm); $n^{25}D$ 1.4878–1.4883; IR (CCl_4) 1702 cm^{-1} (C=O); UV_{max} (95% EtOH) 283 nm (ε 18); mass spectrum, *m/e* (rel intensity) 152 (M^+, 33), 111 (93), 108 (21), 95 (68), 81 (22), 67 (100), 55 (25), 41 (44), and 39 (25); ^1H NMR (CCl_4) δ 2.8–3.2 (1 H, m, CHCO) and 0.7–2.8 (15 H, m, aliphatic CH); ^{13}C NMR ($CDCl_3$, multiplicity in off-resonance decoupling) 212.8 (s), 54.5 (d), 43.1 (d), 40.3 (t), 35.1 (t), 32.4 (t), 27.7 (t), 26.2 (t), 25.4 (t), and 24.5 (t). Reaction of 0.20 g of the cis ketone **10a** with H_2NOH in boiling H_2O–EtOH for 10 min yielded 0.18 g of the cis oxime as white needles, mp 117–118 °C. Recrystallization from EtOH–H_2O raised the melting point of the cis oxime to 118–119 °C (lit.[19] mp 119 °C); IR (CCl_4) 3580 and 3250 cm^{-1} (OH) with no C=O absorption. Reaction of 31.8 mg of the ketone **10a** with 44.6 mg of 2,4-$(O_2N)_2C_6H_3NHNH_2$ in 5 mL of boiling EtOH containing ca. 0.2 mL of aqueous 12 M (HCl (the minimum required for reaction) for 15 min resulted in extensive epimerization of the cis ketone **10a** so that the major product was 48 mg of the crude 2,4-DNP of the trans ketone **10b**, mp 203–209 °C. Fractional crystallization from EtOH of the more soluble material in the mother liquor separated 2.6 mg of the 2,4-DNP of the cis ketone **10a** as yellow needles: mp 162–163 °C (lit.[20] mp 162–163 °C); UV_{max} (95% EtOH) 234 nm (ε 10 000) and 369 nm (ε 13 000).

Distillation of the chromatographic fractions containing the trans ketone separated 1.98 g (48%) of the pure trans ketone **10b** as a colorless liquid: bp 96–100 °C (7 mm); $n^{25}D$ 1.4867–1.4872; IR (CCl_4) 1701 cm^{-1} (C=O); UV_{max} (95% EtOH) 285 nm (ε 29); mass spectrum, *m/e* (rel intensity) 152 (M^+, 19), 111 (23), 95 (100), 67 (65), 55 (22), 41 (33), and 39 (20); ^1H NMR (CCl_4) δ 0.8–3.1 (m, aliphatic CH); ^{13}C NMR ($CDCl_3$, multiplicity in off-resonance decoupling) 212.6 (s), 56.8 (d), 45.3 (d), 43.7 (t), 36.7 (t), 35.7 (t), 29.1 (t), 26.1 (t), 24.1 (t), and 23.5 (t). Reaction of 170 mg of the trans ketone **10b** with NH_2OH in boiling H_2O–EtOH for 10 min yielded 142 mg of the oxime as white needles from EtOH–H_2O: mp 138.5–140 °C (lit.[19] mp 140 °C); IR (CCl_4) 3580 and 3250 cm^{-1} (OH) with no C=O absorption. Reaction of 153 mg of the trans ketone **10b** with 2,4-$(O_2N)_2C_6H_3NHNH_2$ in 27 mL of boiling EtOH containing 0.5 mL of aqueous 12 M HCl for 15 min yielded 252 mg of the 2,4-DNP of the trans ketone **10b**, mp 215–218 °C. Two recrystallizations from EtOH afforded the 2,4-DNP as red-orange needles: mp 219–220 °C (lit.[20] mp 220°); UV_{max} (95% EtOH), 232 nm (ε 11 700) and 369 nm (ε 14 500). Previous physical constants reported for the ketone **10** (a mixture of stereoisomers) included: bp 92–93 °C (4.5 mm);[21] $n^{25}D$ 1.4862,[20] 1.4870,[21] and 1.4872;[22] IR 1702 cm^{-1};[21] UV_{max} (EtOH) 288 nm (ε 27);[21] and mass spectrum, 152 (M^+), 111 (56), 95 (100), and 67 (90).[23] The equilibrium composition of the ketone **10** stereoisomers is reported[24] to be 20% cis ketone **10a** and 80% trans ketone **10b**.

To determine the best conditions for the cyclization **8** → **10**, a series of small scale experiments were performed in which solutions of the enolate **8** were generated by adding the bromo ketone **7** to cold (−70 to −72 °C) solutions containing 1.2 equiv of *i*-Pr_2NLi in a mixture of hexane and Et_2O, THF, or DME. In certain cases, 4 molar equiv of $(Me_2N)_3PO$(HMP) per mol of enolate **8** was then added. The solutions were then stirred for the times and at the temperatures indicated in Table I and then subjected to the previously described isolation procedure. The crude neutral products were mixed with 1-methylnaphthalene (an internal standard) for GLC analysis. The yields of ketones **10**, **14**, and **19** are summarized in Table I; the bulk of the remaining material in each reaction was higher molecular weight material (presumably from intermolecular alkylation reactions).

Preparation of the Dihalide 17. To a solution of 20.2 g (100 mmol) of the dibromide **16** in 100 mL of anhydrous acetone was added, dropwise and with stirring during 12 h, a solution of 15.0 g (100 mmol) of NaI in 100 mL of anhydrous acetone. The resulting yellow solution, containing a white precipitate (LiBr), was filtered, concentrated,

washed successively with aqueous $Na_2S_2O_3$ and with H_2O, and dried. Fractional distillation separated 8.6 g of liquid, bp 29–42 °C (1.1 mm) containing (NMR analysis) mainly the dihalide **16**, 14.2 g of liquid, bp 42–50 °C (1.1 mm), containing (NMR) mainly dihalide **17**, and 6.4 g of liquid, bp 55–63 °C (1.1 mm), containing (NMR) mainly 1,3-diiodopropane. Redistillation of the center fraction through a 60-cm Vigreux column separated 12.6 g (51%) of the dihalide **17** as a colorless liquid: bp 46–47 °C (1.1 mm); n^{25}_D 1.5820 [lit.[25] bp 88 °C (17.5 mm); n^{25}_D 1.5810]; NMR (CCl_4 δ 3.1–3.7 [4, m. overlapping triplets, J = 6 Hz, for CH_2I and CH_2Br] and 2.30 (2 H, quintuplet, J = 6 Hz, CH_2); mass spectrum, m/e (rel intensity) 250 (M^+, 100), 248 (M^+, 98), 204 (24), 202 (43), 200 (26), 169 (53), 155 (34), 141 (51), 128 (38), 127 (80), 124 (23), 123 (99), 122 (23), 121 (94), 95 (36), 93 (33), 42 (33), 41 (78), and 39 (49).

Reaction of *n*-BuLi with the Dihalide 17. Following a general halogen–lithium exchange procedure described previously,[13] a cold solution (−110 °C)[26] of 1.25 g (5.0 mmol) of the dihalide **17** in 25 mL of Et_2O was treated, dropwise and with stirring during 1 min, with 3.3 mL of a hexane solution containing 5.0 mmol of *n*-BuLi. The resulting solution was stirred at −110 °C for 2 h and then siphoned into a cold (−110 °C), rapidly stirred solution of 10 mmol of HOAc in 20 mL of Et_2O. The resulting solution was warmed to 0 °C and partitioned between Et_2O and aqueous $NaHCO_3$. After the organic solution had been dried and concentrated, an aliquot of the crude liquid product (3.17 g) was mixed with *n*-$C_{11}H_{24}$ for GLC analysis (silicone XE-60 on Chromosorb P, apparatus calibrated with known mixtures). The crude product contained *n*-BuI (retention time 13.4 min, 82% yield) and *n*-$C_{11}H_{24}$ (22.6 min) but no GLC peak was detected corresponding to *n*-PrBr (5.2 min). Analysis on the same GLC column at higher temperature with *n*-$C_8H_{17}Ph$ as the internal standard indicated the presence of the starting dihalide **17** (retention time 6.2 min, 3% recovery) and *n*-$C_8H_{17}Ph$ (21.0 min). Thus, we conclude that the dihalide **17** and *n*-BuLi underwent lithium–iodine exchange but that the organolithium reagent **15** was not stable at −110 °C in Et_2O. From a comparable experiment with *n*-BuLi and the dihalide **17** in Et_2O at −78 °C, the yields were 78% of *n*-BuI and 4% of the dihalide **17** and no GLC peak corresponding to *n*-PrBr was detected. A collected sample of *n*-BuI from this reaction were identified with an authentic sample by comparison of mass spectra. In a similar experiment employing an Et_2O solution of *n*-BuLi and the dibromide **16** at −78 °C, the bulk of the unchanged dibromide **16** was recovered. This result would be expected based on the earlier observation[13] that *n*-BuLi underwent rapid metal–halogen exchange with alkyl iodides but not with alkyl bromides.

Registry No.—*cis*-**7**, 65682-05-5; *trans*-**7**, 65682-06-6; **8**, 65682-07-7; **10a**, 5365-37-7; **10a** oxime, 5365-39-9; **10a** 2,4-DNP, 65682-00-0; **10b**, 5365-38-8; **10b** 2,4-DNP, 65682-01-1; **10b** oxime, 5365-40-2; **11**, 17356-19-3; **12**, 16112-10-0; **13**, 65682-08-8; *cis*-**14**, 65682-09-9; *trans*-**14**, 65682-10-2; **16**, 109-64-8; **17**, 22306-36-1; 18, 762-72-1; **19**, 65682-11-3; **20**, 62726-63-0; CH_2=$CHCH_2Br$, 106-95-6; 1,3-diiodopropane, 627-31-6.

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Synthesis of Macrocyclic Fulvalene Derivatives[1]

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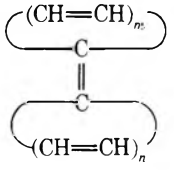
Reactions of the bis(cyclohexene)-annelated bisdehydro[13]annulenone **5** are described, which led to the pentatridecafulvalene **7**, the tridecatridecafulvalene **12**, and the vinylogous pentatridecafulvalene **19**. The attempted electrocyclization of **19** to **22** did not succeed.

Bicyclic polyenes containing a cyclic cross-conjugated π-electron system of the fulvalene type (**1**) have been extensively investigated.[2] More recently, a number of vinylogous fulvalenes (compounds of type **2**) have been studied.[3] Nearly all of these compounds contained three-, five-, or seven-membered rings, the only macrocyclic fulvalene derivatives prepared previously being the pentatridecafulvalene **3**[4] and the tridecatridecafulvalene **4**[5] containing a cumulated triene



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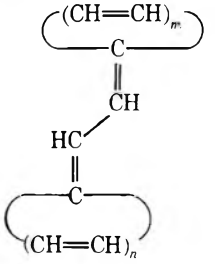

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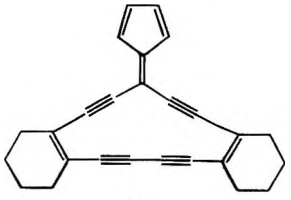

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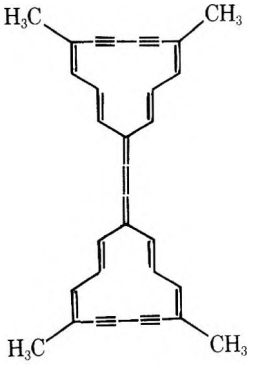

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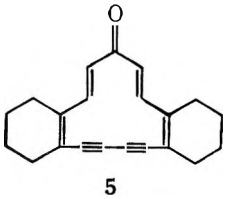
between the two macrocyclic rings.[6] The convenient syntheses of the bisdehydro[13]annulenones **5**[7] and **6**[1] in satisfactory yield made it desirable to utilize these compounds for the syntheses of other fulvalene derivatives of type **1** and **2**, in which one or both rings are 13 membered. We now describe this objective, the derivatives prepared being the pentatridecafulvalene **7**, the tridecatridecafulvalene **12**, and the vinylogous pentatridecafulvalene **19**.



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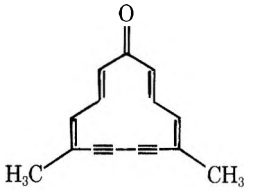

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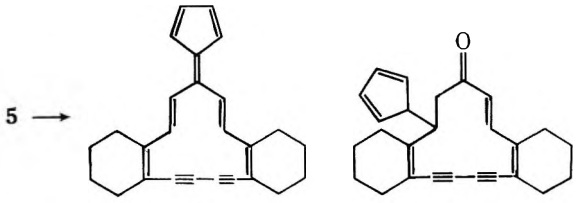
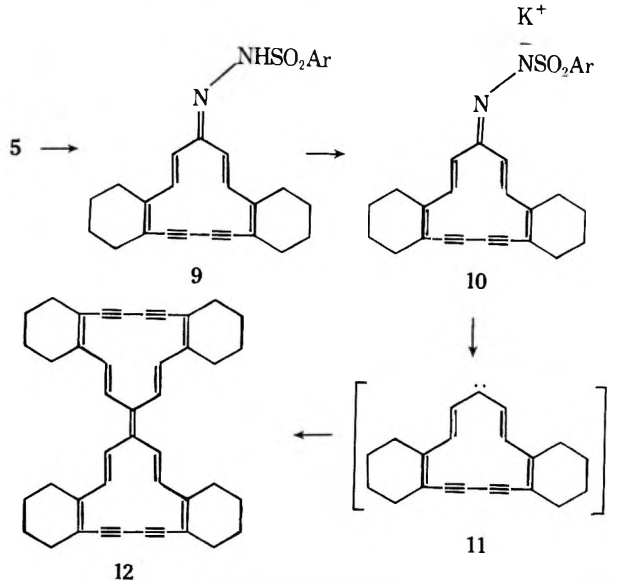
The Pentatridecafulvalene 7. The pentatridecafulvalene **7** was prepared as red crystals in 16% yield by treatment of the bisdehydro[13]annulenone **5** with a large excess of sodium cyclopentadienide (prepared from cyclopentadiene and sodium methoxide). The structure[8] of **7** was established by spectral means. As in other cases,[4,9] the cyclopentadiene olefinic resonances in the ^{1}H-NMR spectrum of the fulvalene **7** resonated as a singlet (τ 3.40), and there was no evidence for a ring current. Comparison of the electronic spectrum of the fulvalene **7** [main λ_{max} 390 nm (ϵ 16400)] with that of the tetradehydro derivative **3**[4] [main λ_{max} 401 nm (ϵ 43500)] indicates that the conjugated 13-membered ring system in **7** is less planar than that in **3**.



7 **8**

A yellow oily by-product was obtained in the synthesis of the pentatridecafulvalene **7**, and this was the main product when a smaller excess of sodium cyclopentadienide was used in the reaction with **5**. The spectral properties of this material are consistent with a structure such as **8**, arising from conjugate addition.

The Tridecatridecafulvalene 12. After several routes designed to convert the bisdehydro[13]annulenone **5** to the tridecatridecafulvalene **12** failed, the following sequence led to success. Substance **5** was first converted to the *p*-toluenesulfonylhydrazone **9** (92% yield), which was then transformed to the potassium salt **10** by means of potassium *tert*-butoxide. This type of species has been shown to be convertible to products derived from the corresponding carbene (type **11**,



9 **10** **11** **12**

formed via the diazo compound), either by pyrolysis[6b,10] or photolysis.[11]

In practice, pyrolysis of **10** under various conditions led to no new conjugated macrocyclic products. On the other hand, irradiation of **10** at 0°C with a Hanovia high-pressure lamp gave the required tridecatridecafulvalene **12** relatively rapidly,

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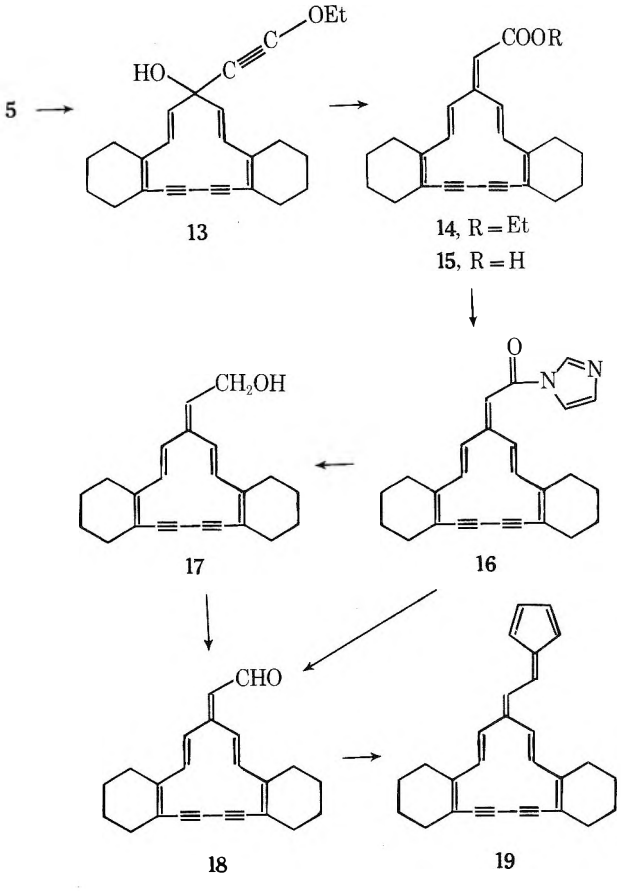
although only in poor yield (1.3%). The deep red fulvalene **12** proved to be rather unstable and underwent considerable decomposition on evaporation to dryness. Its structure was confirmed by the ^{1}H-NMR and electronic spectra given in the Experimental Section. As expected, the ^{1}H-NMR spectrum showed the compound to possess no appreciable ring current. It is of interest that both types of olefinic protons in the ^{1}H-NMR spectrum of **12** appear as a singlet (τ 2.87) and no separation could be observed by changing solvent. In the electronic spectrum of **12**, the main maximum occurred at 446 nm, the expansion of the 5-membered ring in **7** to a 13-membered ring in **12** resulting in a bathochromic shift of 56 nm.

The molecular weight of the fulvalene **12** could not be determined by the mass spectrum, in view of its involatility and relative instability. It was therefore hydrogenated in acetic acid over a platinum catalyst to the corresponding perhydro derivative, the mass spectrum of which showed it to possess the expected molecular formula.

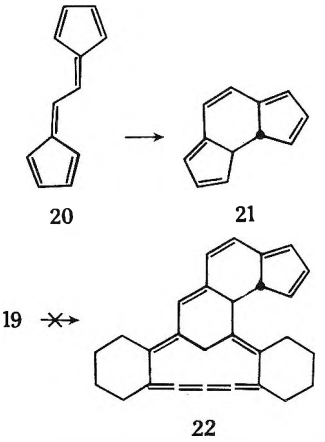
The Vinylogous Pentatridecafulvalene 19. A suitable intermediate in the conversion of the bisdehydro[13]annulenone **5** to the vinylogous pentatridecafulvalene **19** appeared to be the α,β-unsaturated aldehyde **18**. The transformation of **5** to **18** at first presented some difficulty (e.g., **5** did not undergo the normal Wittig reaction with carbethoxymethylenetriphenylphosphorane[12] to give the ester **14**). After some experimentation, the following route to **18** proved to be successful.

Treatment of the bisdehydro[13]annulenone **5** with excess lithium ethoxyacetylide led to the ethoxyacetylenic carbinol **13**, which on direct rearrangement with aqueous sulfuric acid[13] yielded 75% (based on **5**) of the α,β-unsaturated ester **14**, mp 137–138 °C. Saponification of **14** with potassium carbonate gave the corresponding acid **15**, which was converted to the imidazolide **16** with excess *N,N'*-carbonyldiimidazole in boiling tetrahydrofuran. Reduction of **16** with excess lithium tri-*tert*-butoxyaluminum hydride[14] led to a mixture of the alcohol **17** and the aldehyde **18**, which was then treated with activated manganese dioxide[15] in order to convert **17** to **18**. This procedure resulted in the aldehyde **18**, mp ~135 °C, in 48% yield (based on the ester **14**). Finally, reaction of **18** with an excess of sodium cyclopentadienide (prepared from cyclopentadiene and sodium methoxide) gave 19% of the desired vinylogous pentatridecafulvalene **19** as dark red crystals, which decomposed on attempted melting point determination.



The structure of **19** follows from the mass, ^{1}H-NMR, and electronic spectra, given in the Experimental Section. In the ^{1}H-NMR spectrum the olefinic protons resonated in the region τ 2.15–4.05, showing the absence of a ring current. In the electronic spectrum, the main maximum was at 416 nm; the bathochromic shift of 26 nm compared with the main maximum of the pentatridecafulvalene **7** (390 nm) is due to the extra double bond.

It has been shown by Sauter, Gallenkamp, and Prinzbach[3] that the vinylogous pentapentafulvalene **20** readily undergoes conrotatory electrocyclization to the trans dihydro-*as*-indacene **21** at room temperature. By contrast, the vinylogous pentatridecafulvalene **19** was stable in organic solvents at room temperature. On boiling in solvents such as benzene or



ethyl acetate, **19** gradually formed an insoluble polymer. It is possible that this is derived from the cumulene **22** (the conrotatory electrocyclization product of **19**), but all attempts to isolate this compound failed.

Experimental Section

General Procedures. Melting points were determined on a Kofler hot-stage apparatus and are uncorrected. Infrared spectra were measured on a Unicam SP 200 spectrophotometer (s = strong, m = medium, w = weak); only significant maximum are reported. Electronic spectra were determined on a Unicam SP 800 spectrophotometer (sh = shoulder). ^{1}H-NMR spectra were recorded on a Varian T-60 spectrometer, tetramethylsilane being used as internal standard. Mass spectra were determined on an AEI MS-902 spectrometer operating at 70 eV. All reactions were carried out under prepurified nitrogen.

The Pentatridecafulvalene 7. Freshly distilled cyclopentadiene (150 mL) was added during 10 min to an ice-cooled solution of sodium methoxide [from sodium (4.0 g)] in methanol (250 mL) under nitrogen, and the solution was stirred at 0 °C for a further 10 min. A solution of the [13]annulenone **5**[7] (480 mg) in dry ether (150 mL) was then added at 0 °C during 10 min, and the mixture was stirred at this temperature for a further 3 h. Water (500 mL) was added, and the organic layer was separated. The aqueous layer was washed with ether (2 × 500 mL) and the combined organic extracts were washed with brine and dried over magnesium sulfate. The solvent was evaporated and the residue was chromatographed on silica gel. Elution with petroleum ether (49:1) and crystallization from ether gave the fulvalene **7** (90 mg, 16%) as red crystals, which decomposed at ~150 °C on attempted melting point determination: MS *m/e* 336.1871 (M^+, calcd 336.1877); UV (Et_2O) λ_{max} 260 nm (ϵ 14700), 274 (13800), 318 (14900), 390 (16400); IR (KBr) 2170 w (C≡C), 970 cm^{-1} m (*trans*-HC=CH); ^{1}H NMR (60 MHz, $CDCl_3$) τ 2.08 (d, J = 16 Hz, 2 H, olefinic H), 3.15 (d, J = 16 Hz, 2 H, olefinic H), 3.40 (s, 4 H, cyclopentadiene H), 7.4–8.0 (m, 8 H, allylic CH_2), 8.05–8.55 (m, 8 H, nonallylic CH_2).

Further elution with ether gave a yellow oily material: MS *m/e* 354; UV (Et_2O) main λ_{max} 269, 281 nm; IR (CCl_4) 1670 cm^{-1} (s, C=C-C=O); ^1H NMR (60 MHz, CCl_4, olefinic:aliphatic H = 6:20). This material, which may have structure **8**, was the main product when a much smaller excess of sodium cyclopentadienide was used in the reaction with **5**.

The Tridecatridecafulvalene 12. A solution of the [13]annulenone **5** (500 mg, 1.74 mmoles) in benzene (100 mL) and ethanol (100 mL) was treated with *p*-toluenesulfonylhydrazide (330 mg, 1.77 mmol) and then with 5 drops of concentrated hydrochloric acid at room temperature. The resulting insoluble *p*-toluenesulfonylhydrazone **9** (733 mg, 92%) formed orange crystals, mp >230 °C dec: UV λ_{max} ($CHCl_3$, qualitative) ~270 (sh), 295, ~350 nm (sh); IR (KBr) 2170 (w, C≡C), 1345 (m), 1165 cm^{-1} (s, SO_2). Substance **9** was too insoluble in the usual solvents for a ^1H-NMR spectrum to be obtained. The yield of **9** was only 64% when the reaction was carried out in boiling ethanol for 3 h.

A solution of potassium *tert*-butoxide (300 mg, 2.68 mmol) in tetrahydrofuran (150 mL) was added during 10 min to the *p*-toluenesulfonylhydrazone **9** (1.00 g, 2.19 mmol) in tetrahydrofuran (400 mL) at 0 °C under nitrogen. The resulting potassium salt **10** (deep red solution) was then irradiated at 0 °C under N_2 with a Hanovia high-pressure lamp. Aliquots were removed at intervals and analyzed by TLC (silica plates). The reaction was found to be complete after 30 min, and irradiation was terminated (irradiation for 90–120 min was found to result in a reduced yield of **12**). The photolysate was poured into ice (~500 g), and benzene (500 mL) was added. The organic layer was separated, and the aqueous layer was extracted with ether (2 × 500 mL). The combined organic extracts were dried over magnesium sulfate.

One-half of the extract was concentrated to ~5 mL (external temperature not greater than 40 °C), carbon tetrachloride (250 mL) was added, and the solution was again concentrated to ~5 mL. The concentrate was chromatographed on silicic acid (50 g, Mallinckrodt), with carbon tetrachloride as eluent. The same procedure was employed with the other half of the extract, giving a total of 8 mg (1.3%) of the fulvalene **12** as a deep red solution, which underwent substantial decomposition on evaporation to dryness: UV λ_{max} (Et_2O) 253 (ε 36600),[16] ~265 (sh, ε 32800), ~295 (sh, ε 25700), ~340 (sh, ε 13600), 446 nm (11300); IR (CCl_4) 2180 (w, C≡C), 975 cm^{-1} (m, *trans*-HC=CH); ^1H NMR (60 MHz, CCl_4) τ 2.87 (s, 8 H, olefinic H), 7.5–8.0 (m, 16 H, allylic CH_2), 8.1–8.5 (m, 16 H, nonallylic CH_2); the olefinic protons remained as a singlet in acetone-d_6 or in benzene-d_6. No mass spectrum could be obtained at probe temperatures up to 215 °C, presumably due to the involatility and relative instability of **12**.

Catalytic Hydrogenation of the Tridecatridecafulvalene 12 to the Perhydro Derivative. The fulvalene **12** (~4 mg) in glacial acetic acid (5 mL) was stirred under hydrogen in the presence of a prereduced platinum catalyst (from ~10 mg of PtO_2) until uptake of hydrogen had ceased. The mixture was diluted with ether (100 mL), filtered, and washed well with sodium bicarbonate solution. The ether solution was dried over magnesium sulfate and evaporated to give the perhydro derivative of **12** as a colorless oil. The mass spectrum showed a base peak at 578.5771 (M^+, calcd 578.5787).

The α,β-Unsaturated Ester 14. A solution of methyllithium (2.2 mmol) in ether was added to a stirred solution of ethoxyacetylene (250 mg, 3.5 mmol) in ether (20 mL) at −78 °C under nitrogen. The mixture was stirred at this temperature for 10 min, and a solution of the [13]annulenone **5** (100 mg, 0.35 mmol) in ether (25 mL) was then added. The cooling bath was removed, and the mixture was stirred for a further 15 min. Saturated aqueous sodium chloride was then added; the organic layer was washed with water and was dried over magnesium sulfate. Removal of solvent yielded the crude alcohol **13**, which was used directly for the next step.

The crude alcohol **13** was dissolved in ether (25 mL) and ethanol (3 mL) and shaken vigorously with 10% aqueous sulfuric acid (25 mL) at room temperature for 10 h. The organic layer became deep orange during this time. The organic layer was washed with water, dried over magnesium sulfate, and evaporated. Chromatography on silica gel and elution with pentane–ether (19:1) yielded the α,β-unsaturated ester **14** (60 mg, 48% based on **5**) as orange crystals: mp 137–138 °C; MS *m/e* 358.1924 (M^+, calcd 358.1933); UV (Et_2O) λ_{max} 255 (ε 15200), 268 (sh, ε 18000), 297 (27800), 343 nm (sh, ε 14800); IR (KBr) 2190 (w, C≡C), 1705 (s, ester), 975 cm^{-1} (s, *trans*-HC=CH); ^1H NMR (60 MHz, $CDCl_3$) τ 1.78 (d, J = 16 Hz, 1 H, ring olefinic H), 2.18 (d, J = 16 Hz, 1 H, ring olefinic H), 2.53 (d, J = 16 Hz, 1 H, ring olefinic H), 3.73 (d, J = 16 Hz, 1 H, ring olefinic H), 4.12 (s, 1 H, α-olefinic H), 5.81 (q, J = 7 Hz, 2 H, CH_2CH_3), 7.4–8.05 (m, 8 H, allylic CH_2), 8.1–8.55 (m, 8 H, nonallylic CH_2), 8.73 (t, J = 7 Hz, 3 H, CH_2CH_3).

Subsequently it was found that the yield of **14** from **5** could be improved to 75%, and the transformation of **13** to **14** could be completed in 2–3 h, by increasing the amount of ethanol used for the conversion of **13** to **14**.

The α,β-Unsaturated Acid 15. The ester **14** (75 mg) in methanol (50 mL) was saponified by being boiled under reflux with a solution of potassium carbonate (2 g) in water (10 mL) and methanol (50 mL) for 4 h. The solution was cooled, acidified with 10% sulfuric acid, and thoroughly extracted with ether. The organic extracts were washed with brine, dried over magnesium sulfate, and evaporated. Purification of the residue by preparative LC on silica gave the acid **15** (60 mg, 87%) as an orange solid: mp >300 °C: MS *m/e* 330.1612 (M^+, calcd 330.1620); UV (Et_2O, qualitative) λ_{max} 255 (sh), 268 (sh), 296, ~340 nm (sh); IR (KBr) 3400–2400 (b, COOH), 2190 (w, C≡C), 1665 (s, COOH), 975 cm^{-1} (s, *trans*-HC=CH); ^1H NMR (60 MHz, THF) 1.85 (d, J = 17 Hz, 1 H, ring olefinic H), 2.20 (d, J = 16 Hz, 1 H, ring olefinic H), 2.41 (d, J = 17 Hz, 1 H, ring olefinic H), 3.67 (d, J = 16 Hz, 1 H, ring olefinic H), 4.06 (s, 1 H, α-olefinic H).

The α,β-Unsaturated Aldehyde 18. A solution of the acid **15** (60 mg, 0.19 mmol) in dry tetrahydrofuran (10 mL) was treated with a solution of *N,N'*-carbonyldiimidazole (200 mg, 1.23 mmol) in tetrahydrofuran (100 mL), and the solution was boiled under reflux for 4 h, moisture being excluded. The solvent was evaporated; the residue was dissolved in the minimum amount of chloroform and chromatographed on silica gel. Elution with chloroform yielded the imidazolide **16** (65 mg, 91%) as a red solid, which was used directly in the next step.

A slurry of lithium tri-*tert*-butoxyaluminum hydride (prepared by the addition of 3 molar equiv of *tert*-butyl alcohol to lithium aluminum hydride in ether) in ether was added in small portions to a stirred solution of the imidazolide **16** (65 mg) in tetrahydrofuran (10 mL) at room temperature, until no **16** could be detected by TLC. Water and ether were added; the organic layer was washed with water, dried over magnesium sulfate, and evaporated. TLC examination of the residue indicated it to consist of the alcohol **17** and the aldehyde **18**. The residue in ether (10 mL) was therefore shaken with activated manganese dioxide[15] (1 g) for 10 min, when oxidation of **17** to **18** appeared to be complete (TLC). The solid was removed by filtration and washed well with ether, and the combined filtrates were evaporated. Preparative LC of the residue on silica (elution with 50% ether–pentane) yielded the α,β-unsaturated aldehyde **18** (35 mg, 61%) as a red solid, mp 135 °C dec (rapid heating): MS *m/e* 314.1665 (M^+, calcd 314.1671); UV (Et_2O) λ_{max} 263 (ε 16300), ~ 280 (sh, 18000), 302 (ε 21300), ~345 nm (sh, ε11800); IR (KBr) 2180 (w, C≡C), 1660 (s, unsaturated CHO), 965 cm^{-1} (s, *trans*-HC=CH); ^1H NMR (60 MHz, $CDCl_3$) τ 0.03 (d, J = 7.5 Hz, 1 H, CHO), 2.05 (d, J = 16 Hz, 1 H, ring olefinic H), 2.57 (d, J = 16 Hz, 1 H, ring olefinic H), 3.20 (d, J = 16 Hz, 1 H, ring olefinic H), 3.65 (d, J = 16 Hz, 1 H, ring olefinic H), 3.98 (d, J = 7.5 Hz, 1 H, α-olefinic H), 7.5–8.0 (m, 8 H, allylic CH_2), 8.1–8.5 (m, 8 H, nonallylic CH_2).

The Vinylogous Pentatridecafulvalene 19. Freshly distilled cyclopentadiene (10 g) was added during 5 min to an ice-cooled solution of sodium methoxide [from sodium (0.23 g)] in methanol (50 mL) under nitrogen, and the solution was stirred at 0 °C for a further 10 min. A solution of the aldehyde **18** (50 mg) in dry ether (50 mL) was added, and the resulting deep orange mixture was stirred at 0 °C under N_2 for 15 min (TLC examination at this stage showed the reaction to be terminated). Water (100 mL) was added, and the organic layer was separated. The aqueous layer was washed with ether (2 × 100 mL); the combined organic extracts were washed with brine and dried over magnesium sulfate. The solvent was evaporated and the residue was subjected to preparative LC on silica. Elution with 5% ether–pentane yielded the vinylogous fulvalene **19** (11 mg, 19%) as dark red crystals, which decomposed on attempted melting point determination: MS *m/e* 362.2025 (M^+, calcd 362.2034); UV λ_{max} 274 (ε 26100), 334 (ε 24600), 416 (ε 47800), ~435 nm (sh, ε 42700); IR (KBr) 2180 (m, C≡C), 975 cm^{-1} (s, *trans*-HC=CH); ^1H NMR (60 MHz, CCl_4) τ 2.15–4.05 (m, 10 H, olefinic H), 7.4–8.0 (m, 8 H, allylic CH_2), 8.1–8.5 (m, 8 H, nonallylic CH_2).

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Registry No.—**5**, 39694,95-6; **7**, 65682-12-4; **8**, 65682-13-5; **9**, 65682-14-6; **10**, 65682-15-7; **12**, 65682-16-8; **12** perhydro derivative, 65682-17-9; **13**, 65682-18-0; **14**, 65682-19-1; **15**, 65682-20-4; **16**, 65682-21-5; **17**, 65682-22-6; **18**, 65682-23-7; **19**, 65682-24-8; sodium cyclopentadienide, 4984-82-1; ethoxyacetylene, 927-80-0; *N,N*-carbonyldiimidazole, 530-62-1.

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Rate Acceleration of the Intramolecular Ene Reactions of 1,6- and 1,7-Enynes by Electron-Withdrawing Substituents

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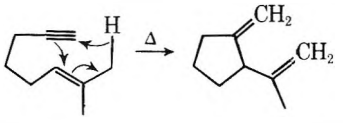
The intramolecular ene reactions of 1,6- and 1,7-enynes containing a hydrogen, methyl, or carbomethoxy substituent of the acetylene have been investigated. Since the acetylene is acting as the enophile, the methyl substituent retards the reaction while the carbomethoxy group significantly accelerates it. A terminal 1,6-enyne, **1**, cyclizes at 210 °C while the carbomethoxy enyne **2** cyclizes at 135 °C. The cyclization of 1,7-enynes has been shown to be slow, typically requiring temperatures 100 °C higher than the corresponding 1,6-enyne. The acetylene **10** activated by both ketone and a carbomethoxy group cyclizes cleanly at 90 °C.

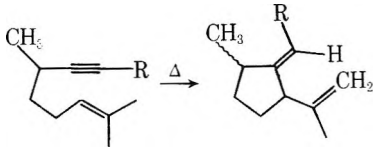
The intramolecular ene reaction of 1,6-enynes (eq 1) has recently been shown to be a useful method for the synthesis of complex molecules,[1] including chiral acetic acid[1h] and prostaglandins.[1i] For terminal acetylenes this reaction typically takes place in 1–5 h at 220 °C. In this intramolecular ene reaction the triple bond is functioning as the enophile so that electron-withdrawing substituents on the acetylene should



(1)

accelerate the rate of the ene reaction while electron-donating or bulky substituents on the acetylene should retard the reaction. We were interested in examining the magnitude of these effects and the extension of this ene reaction to 1,7- and 1,8-enynes. We report here that the addition of electron-withdrawing substituents to 1,6- and 1,7-enynes drastically lowers the temperature required for the intramolecular ene reaction and makes it a mild, general route for the formation of both five- and six-membered rings.

Enynes **1–3** were chosen for initial study because of their accessibility from the noraldehyde using the procedure of



1, R = H
2, R = CO_2CH_3
3, R = CH_3

4, R = H
5, R = CO_2CH_3
6, R = CH_3

Corey and Fuchs.[2] Reaction of 2,6-dimethyl-5-heptenal[3] with dibromomethylenetriphenylphosphorane affords 1,1-dibromo-3,7-dimethyl-1,6-octadiene. Treatment of this dibromide with 2 equiv of butyllithium yields the lithium salt of 3,7-dimethyl-6-octen-1-yne.[2] Addition of water, methyl chloroformate, or methyl iodide yields **1**,[4] **2**, or **3**, respectively. Pyrolysis of **1** in toluene for 62 h at 210 °C gives the ene adduct **4** in greater than 95% yield as a ca. 1:1 mixture of diastereomers. These conditions are similar to those reported for similar systems.[1] Adduct **4** contains the skeleton of the iridoid monoterpenes with appropriate functionality for conversion to a variety of iridodiols.[5] Enyne **3**, a methyl acetylene, cyclizes more slowly than **1**. Pyrolysis of **3** for 48 h at 225 °C gives 15% conversion to **6**. At higher temperatures or longer reaction times a variety of unidentified products are formed. A previous study has shown that *trans*-6-octen-1-yne (**7**) cyclizes 5.7 times faster than the homologous methylacetylene, *trans*-7-nonen-2-yne (**8**), at 382 °C in the vapor phase.[1b,1c] While these results are not strictly comparable to our solution studies, they are consistent with our results. Huntsman found that the terminal acetylene **7** cyclizes cleanly to the expected ene adduct, while the methyl acetylene **8** gives two products. The expected ene adduct is obtained in 80% yield and 2-ethyl-1-vinylidenecyclopentane (**9**) is formed in 10% yield. The allene **9** is derived from the double bond functioning as the enophile. *cis*-7-Nonen-2-yne gives only **9** and recovered starting material.[1b,cc]

Substitution of the terminal hydrogen of **1** with a carbomethoxy group was expected to lower the temperature required for the ene reaction. Pyrolysis of the alkenynoate **2** for 24 h at 135 °C results in conversion to the ene adduct **5** in

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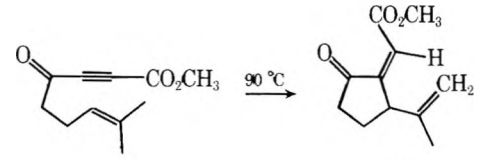
greater than 95% yield. Spectroscopic and gas chromatographic analysis indicate that **5** is a mixture of diastereomers but that only one double bond isomer is formed. The mild conditions required and stereospecific formation of the α,β-unsaturated ester make this a useful synthetic procedure. We have recently found that with aluminum chloride catalysis the ene reaction of methyl propiolate and a variety of alkenes occurs at 25 °C. However, treatment of **2** with aluminum chloride in benzene at 25 °C gives only recovered starting material.

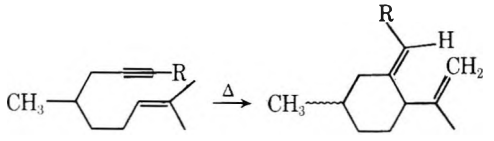
To investigate the effect of additional electron-withdrawing groups on the rate of the ene reaction, the ene reaction of keto ester **10** was studied. Treatment of 5-methyl-4-hexenoyl chloride with the silver salt of methyl propiolate in methylene chloride affords **10** in good yield.[6] Heating **10** in benzene for



10 **11**

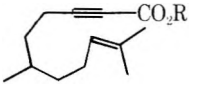
12 h at 90 °C gives complete conversion to the ene adduct **11** as a single isomer. At higher temperatures partial isomerization about the conjugated double bond occurs. This cyclopentanone synthesis is clearly applicable to the synthesis of prostaglandins.

To the best of our knowledge, ene reactions of 1,7 enynes have not been reported previously.[7] In order to determine the usefulness of this reaction for the synthesis of six-membered rings we have examined the cyclization of **12** and **13**, the homologues of **1** and **2**. These compounds were prepared from citronellal using the previously described procedures.[2] Pyrolysis of **12** in toluene for 48 h at 255 °C gives 17% conversion to the ene adduct **14**. At higher temperatures extensive de-



12, R = H
13, R = CO_2CH_3

14, R = H
15, R = CO_2CH_3



16, R = CH_3
17, R = H

composition occurs. On the other hand, pyrolysis of the ester **13** for 62 h at 225 °C gives ene adduct **15** in 85% yield.

The 1,8-alkynoate **16** was investigated to determine the ability of the intramolecular ene reaction to form cycloheptanes. Treatment of citronellyl bromide with dilithium propiolate[8] gives **17** in 18% yield. Esterification with methanol and sulfuric acid gives **16** in 50% yield. Pyrolysis of **16** in toluene at 270 °C gives slow decomposition to several unidentified products. No ene adduct could be isolated. This observation is consistent with the slow rates of other intramolecular reactions which form seven-membered rings.

Our results indicate that the electron-withdrawing carbomethoxy group vastly increases the rate of these intramolecular ene reactions. This allows formation of cyclopentanes under mild conditions and allows the extension of this reaction to the synthesis of cyclohexanes. In a previous study of related intramolecular ene reactions, Huntsman has shown that methyl 5,9-dimethyl-2,8-decadienoate cyclizes in a flow system at 400 °C while the hydrocarbon 8-methyl-1,7-nonadiene cyclizes at 490 °C in a flow system.[9,10]

Our studies have shown that while intramolecular ene reactions are facile for 1,6-enynes to give cyclopentanes, they proceed efficiently only for activated 1,7-enynes to give cyclohexanes and they cannot be used to produce cycloheptanes. Conia, in studies of ene reactions of the enols of unsaturated ketones, found little preference for the formation of five- rather than six-membered rings.[11] Huntsman, in studies of intramolecular ene reactions of 1,6- and 1,7-dienes, found that 7-methyl-1,6-octadiene cyclizes in a flow system at 450 °C,[12] while 8-methyl-1,7-octadiene requires 490 °C for a similar reaction.[9] This rate difference is in the same direction though much less pronounced than the difference between **2** and **13**.

The intramolecular ene reactions of alkenynoates provide efficient routes to both five- and six-membered rings. We are currently exploring applications of these reactions to total synthesis of natural products.

Experimental Section

All boiling points are uncorrected. Infrared spectra were determined with a Perkin-Elmer 283 infrared spectrometer. NMR spectra were determined on a Varian A-60 spectrometer. The mass spectra were obtained with an AEI MS9 mass spectrometer. GC analyses were performed on a Perkin-Elmer 3920 gas chromatograph. THF was purified by distillation from sodium benzophenone ketyl.

1,1-Dibromo-3,7-dimethyl-1,6-octadiene.[2] To 500 mL of CH_2Cl_2 containing 26.2 g (0.1 mol) of triphenylphosphine, 33.2 g (0.1 mol) of carbon tetrabromide, and 6.54 g (0.1 mol) of zinc powder was added 7.01 g (0.05 mol) of freshly distilled 2,6-dimethyl-5-heptenal. The reaction mixture was stirred at room temperature overnight. Workup, consisting of diluting the reaction mixture to 2.5 L with pentane, filtering the precipitate, dissolving the precipitate in 200 mL of fresh CH_2Cl_2, reprecipitating the precipitate with 1.5 L of pentane, refiltering the precipitate, and evaporating the combined pentane fractions, afforded 13.9 g of crude product. Distillation yielded 4.78 g (0.0162 mol, 32% yield) of pure dibromide: bp 73–85 °C (0.05 mm); NMR ($CDCl_3$) δ 6.16 (d, 1, J = 9 Hz, $CH{=}CBr_2$), 5.08 (bd t, 1, J = 7 Hz, $CH{=}C(CH_3)_2$), 2.9 to 1.15 (m, 11), and 0.98 (d, 3, J = 6 Hz, $CHCH_3$); IR (neat) 2964, 2926, 2868, 2851, 1616, 1451, 1375, 1260, 846, and 779 cm^{-1}.

1,1-Dibromo-4,8-dimethyl-1,7-nonadiene.[2] The previous procedure was used to treat 66.4 g (0.2 mol) of carbon tetrabromide, 52.4 g (0.2 mol) of triphenylphosphine, and 13 g (0.2 mol) of zinc powder with 15.2 g (0.098 mol) of freshly distilled citronellal in 500 mL of CH_2Cl_2 yielding 16.94 g of crude product. Distillation afforded 9.05 g (0.0292 mol, 30% yield) of pure dibromide: bp 90–110 °C (0.10–0.15 mm); NMR ($CDCl_3$) δ 6.43 (t, 1, J = 7 Hz, $CH{=}CBr_2$), 5.12 (bd t, 1, J = 7 Hz, $CH{=}C(CH_3)_2$), 2.3–1.0 (m, 13), and 0.9 (d, 3, J = 6 Hz, $CHCH_3$); IR (neat) 2962, 2915, 2852, 2726, 1618, 1453, 1378, 1347, 1117, 891, 863, 827, and 779 cm^{-1}.

Lithium Salt of 3,7-Dimethyl-6-octen-1-yne.[2] n-Butyllithium in hexane (6.2 mL, 2.3 M, 14.3 mmol) was added to a solution containing 1.77 g (5.97 mmol) of 1,1-dibromo-3,7-dimethyl-1,6-octadiene in 20 mL of anhydrous THF at −78 °C. The reaction mixture was stirred for 1 h at −78 °C and then 1 h at room temperature. This solution of lithium acetylide was immediately used in the following reactions.

Lithium Salt of 4,8-Dimethyl-7-nonen-1-yne.[2] In a manner similar to the above, 6 mL of 2.1 M n-butyllithium in hexane (12.6 mmol) was added to 1.78 g (6 mmol) of 1,1-dibromo-4,8-dimethyl-1,7-nonadiene and this solution was immediately used in the following reactions.

3,7-Dimethyl-6-octen-1-yne (1). To the above solution of the lithium salt of 3,7-dimethyl-6-octen-1-yne in 20 mL of THF at 0 °C was added 5.0 mL of water. Warming to room temperature, followed by extraction with 3 × 10 mL of pentane, drying of the extracts ($MgSO_4$), and evaporation of solvent afforded 0.9365 g of product contaminated with octane. Preparative GC on a 6 ft × 0.25 in. 5% DEGS column at 80 °C (T_r = 9 min) afforded pure 3,7-dimethyl-6-octen-1-yne: NMR ($CDCl_3$) δ 5.1 (t, 1, J = 7 Hz, $CH{=}C(CH_3)_2$), 2.0 (d, 1, J = 2 Hz, C≡CH), 2.7–1.25 (m, 11), and 1.15 (d, 3, J = 7 Hz, $CHCH_3$); IR (neat) 3310, 2970, 2925, 2875, 2855, 2105 (w), 1450, and 1375 cm^{-1}.

Methyl 4,8-Dimethyl-7-nonen-2-ynoate (2). To a solution containing 0.852 g (6 mmol) of the lithium salt of 3,7-dimethyl-6-octen-1-yne in 20 mL of THF at −30 °C was added 0.683 g (7 mmol) of methyl chloroformate. The reaction mixture was stirred at room temperature for 1 h, diluted to 75 mL with pentane, washed with 3

× 50 mL of H_2O, dried ($MgSO_4$), and evaporated. The crude product (0.973 g, 84% yield) was purified by preparative gas chromatography on a 4 ft × 0.25 in. 20% DEGS column at 160 °C (T_r = 8.5 min): NMR $CDCl_3$) δ 5.12 (t, 1, J = 7 Hz, C**H**=C(CH_3)$_2$), 3.75 (s, 3, OCH_3), 2.61 (m, 1), 2.4–1.4 (m, 10, CH_2 and C=C(CH_3)$_2$), and 1.23 (d, 3, J = 7 Hz, CHC**H**$_3$); IR (neat) 2968, 2950, 2928, 2871, 2855, 2232 (s), 1719, 1434, 1376, 1258, 1204, 1128, 1075, 1032, and 751 cm^{-1}.

4,8-Dimethyl-7-nonen-2-yne (3). To a THF solution of the lithium salt derived from 2.37 g (8 mmol) of 1,1-dibromo-3,7-dimethyl-1,6-octadiene at −78 °C was added 1.35 g (9.5 mmol) of methyl iodide. The reaction mixture was stirred at room temperature overnight and then diluted to 50 mL with pentane, washed with 3 × 25 mL of H_2O, dried ($MgSO_4$), and evaporated giving 1.44 g of crude product. Preparative gas chromatography on 4 ft × 0.25 in. 20% DEGS column at 80 °C afforded pure **3** (T_r = 6.8 min): NMR ($CDCl_3$) δ 5.10 (bd t, 1, J = 7 Hz, C**H**=C(CH_3)$_2$), 2.4–1.2 (m with d at 1.71, J = 2 Hz, 14, CH_2, CH, C≡CCH_3), and 1.05 (d, 3, J = 7 Hz, CHC**H**$_3$); IR (neat) 2955, 2926, 2859, 1456, 1377, 1261, 1108, and 737 cm^{-1}.

4,8-Dimethyl-7-nonen-1-yne (12). 1,1-Dibromo-4,8-dimethyl-1,7-nonadiene (1.24 g, 4 mmol) was converted to **12** as previously described giving 0.975 g of crude product which was purified by GC on a 4 ft × 0.25 in. 20% DEGS column at 70 °C (T_r = 9 min): NMR ($CDCl_3$) δ 5.11 (bd t, 1, J = 7 Hz, C**H**=C(CH_3)$_2$), 2.3–1.2 (m with d at 1.96, J = 2 Hz, 14. C≡CH), and 1.01 (d, 3, J = 7 Hz, CHC**H**$_3$); IR (neat) 3313, 2966, 2921, 2856, 2117 (w), 1454, 1378, and 1112 cm^{-1}.

Methyl 5,9-Dimethyl-8-decen-2-ynoate (13). 1,1-Dibromo-4,8-dimethyl-1,7-nonadiene (1.68 g, 5.4 mmol) was converted to **13** as described for **2** yielding 0.9876 g of crude product. Column chromatography on 50 g of silica gel using 15% ether in pentane as eluant yielded 0.3153 g (1.52 mmol, 28% yield) of pure **13**: NMR ($CDCl_3$) δ 5.08 (bd t, 1, J = 7 Hz, C**H**=C(CH_3)$_2$), 3.72 (s, 3, OCH_3), 2.5–1.15 (m, 13), and 1.00 (d, 3, J = 6 Hz, $CHCH_3$); IR (neat) 2960, 2920, 2875, 2855, 2235 (s), 1718, 1450, 1432, 1380, 1255, 1075, 818, 751, and 735 cm^{-1}.

Methyl 6,10-Dimethyl-9-undecen-2-ynoate (16). The dilithium salt of propiolic acid (1.57 g, 22.5 mmol) was prepared by the method of Carlson and Oyler[12] and treated with 4.93 g (22.5 mmol) of 1-bromo-3,7-dimethyl-6-octene in 24 mL of 1:1 THF–HMPA at −45 °C. The slurry was stirred at −10 °C for 2 h and then at room temperature for 72 h. Workup, consisting of diluting the reaction mixture to 100 mL with Et_2O, washing with 3 × 30 mL of saturated $NaHCO_3$, acidifying the basic layer (5% HCl) and extracting it with 3 × 20 mL of Et_2O, drying the Et_2O extracts ($MgSO_4$), and evaporating the solvent afforded 0.7735 g of acid **17** (4 mmol, 18% yield).

To 0.54 g of acid **17** in 25 mL of methanol was added 45 μL of concentrated H_2SO_4 and the solution was stirred at room temperature overnight. Workup, consisting of diluting the reaction mixture to 75 mL with Et_2O, washing the mixture with 3 × 100 mL of saturated $NaHCO_3$ and 3 × 70 mL of H_2O, drying the mixture ($MgSO_4$), and evaporating the solvent afforded 0.270 g of crude ester. Chromatography on 10 g of silica gel using 10% ether in benzene as eluant yielded 0.089 g of pure **16**: NMR ($CDCl_3$) δ 5.10 (bd t, 1, J = 7 Hz, CH=C(CH_3)$_2$), 3.72 (s, 3, OCH_3), 2.5–1.05 (m, 15), and 0.9 (distorted d, 3, J = 6 Hz, $CHCH_3$); IR (neat) 2960, 2925, 2875, 2860, 2243, 1720, 1450, 1436, 1380, 1257, 1075, 752, and 735 cm^{-1}.

Methyl 8-Methyl-4-oxo-7-nonen-2-ynoate (10). To a 20-mL THF suspension of 0.557 g of NaH (50% dispersion, 12 mmol) was added 1.42 g (11 mmol) of 5-methyl-4-hexenoic acid followed by 1.68 g (13.2 mmol) of oxalyl chloride and the reaction mixture was stirred overnight. The acid chloride solution was filtered through celite and evaporated yielding 1.06 g of acid chloride which was used immediately in the following reaction. The acid chloride was added to a 20-mL CH_2Cl_2 suspension of methyl propiolate silver salt[6] and stirred in the dark for 4 days. Filtration through celite and evaporation of solvent afforded 1.11 g of crude keto ester, contaminated with anhydride. Chromatography of 0.577 g of crude product on 30 g of silica gel using 8% ether in pentane as eluant yielded 0.372 g (65% yield) of pure **10**: NMR ($CDCl_3$) δ 5.08 (bd t, 1, J = 6 Hz, CH=C(CH_3)$_2$), 3.83 (s, 3, OCH_3), 2.85–2.10 (m, 4, CH_2), and 1.67 (m, 6, C=C(CH_3)$_2$); IR (neat) 2961, 2921, 1727, 1691, 1436, 1257, 1122, 986, and 748 cm^{-1}.

Thermal Reactions of Enynes. General Procedure. A pyridine washed NMR or resealable tube was charged with between 0.5 and 1.5 mL of toluene containing 0.9 to 1.5 mmol of enyne. The tube was then flushed with N_2, cooled to −78 °C, evacuated to 0.1 mm Hg, and sealed. The sealed tubes were immersed to ~⅔ their length and heated in a thermostatically controlled oil bath (DC-710H fluid). Upon completion of reaction (which was monitored by NMR) the tubes were opened and the products were separated by preparative gas chromatography.

Ene Reaction of 3,7-Dimethyl-6-octen-1-yne (1). A solution of 0.098 g of **1** in 0.5 mL of toluene in a sealed NMR tube was heated to 205–215 °C for 62 h. Preparative gas chromatography on a 6 ft × 0.25 in. SE-30 column at 80 °C (T_r = 14 min) afforded **4** as an isomeric mixture: NMR ($CDCl_3$) δ 4.75 (m, 4, C=CH_2), 3.18 (m, 1, C=C-CHC=C), 2.85–1.2 (m, 8), 1.08 and 1.05 (2 doublets, 3, J = 6 Hz, isomeric $CHCH_3$); IR ($CHCl_3$) 3073, 2954, 2914, 2866, 1643, 1441, 1380, 1372, and 889 cm^{-1}; mass spectrum m/e 136 (M^+), 121, 95, and 93.

Ene Reaction of Methyl 4,8-Dimethyl-7-nonen-2-ynoate (2). Heating 0.054 g of ester **2** in 0.5 mL of toluene at 130–140 °C for 24 h as described above followed by preparative gas chromatography on a 4 ft × 0.25 in. 20% DEGS column at 160 °C (T_r = 19.2 min) gave **5** as an isomeric mixture: NMR ($CDCl_3$) δ 5.61 (m, 1, C=C**H**CO_2Me), 4.85 (m, 2, C=CH_2), 3.70 (s, 3, OCH_3), 3.38 (m, 1, C=CCHC=C), 2.2–1.3 (m, 8), 1.13 and 1.10 (2 doublets, 3, J = 7 Hz, isomeric $CHCH_3$); IR ($CHCl_3$) 3080, 2958, 2875, 1721, 1651, 1465, 1452, 1436, 1375, 1355, 1302, 1206, 1176, 1134, 1030, 898, and 876 cm^{-1}; mass spectrum m/e 194 (M^+), 179, 163, 135, 119, and 93.

Ene Reaction of 4,8-Dimethyl-7-nonen-2-yne (3). Heating a 0.8-mL toluene solution containing 0.060 g of **3** at 220–230 °C for 48 h followed by preparative gas chromatography on a 5 ft × 0.25 in. 5% DEGS column at 80 °C yielded a complex mixture containing 15% of **6** (T_r = 2 min): NMR ($CDCl_3$) δ 4.69 (m, 3, C=CH_2, CH=C), 2.67 (m, 1, C=CCHC=C), 2.45–0.75 (m, 14); IR ($CHCl_3$) 3075, 2962, 2930, 2873, 1642, 1460, 1375, and 892 cm^{-1}; mass spectrum m/e 150 (M^+), 135, 121, 109, 107, 95, 93, and 91.

Ene Reaction of 4,8-Dimethyl-7-nonen-1-yne (12). A solution containing 0.15 g of **12** in 1.5 mL of toluene was heated to 250–260 °C for 48 h. Preparative gas chromatography on an 8 ft × 0.25 in 5% DEGS column at 80 °C gave **14** as an isomeric mixture in 17% yield (T_r = 14.8 min): NMR ($CDCl_3$) δ 4.65 (m, 4, C=CH_2), 2.8–1.0 (m, 11), and 0.9 (m, 3, C**H**CH_3); IR ($CHCl_3$) 3078, 2948, 2929, 2869, 1644, 1454, 1374, and 891 cm^{-1}; mass spectrum m/e 150 (M^+), 135, 121, 107, 95, and 93.

Ene Reaction of Methyl 5,9-Dimethyl-8-decen-2-ynoate (13). A solution of 0.8 mL of toluene containing 0.13 g of ester **13** was heated to 215–230 °C for 62 h. Preparative gas chromatography on a 4 ft × 0.25 in. 20% DEGS column at 160 °C gave **15** as an isomeric mixture in 85% yield (T_r = 8.1 min): NMR ($CDCl_3$) δ 5.7 and 5.53 (m, 1, C=C**H**CO_2Me), 5.0 and 4.8 (m, 2, isomeric C=CH_2), 4.0–1.1 with singlet at 3.66 (m, 13), and 1.0 and 0.95 (2 doublets, 3, J = 5 Hz, isomeric $CHCH_3$); IR ($CHCl_3$) 3085, 2945, 2922, 2865, 1718, 1642, 1455, 1445, 1432, 1375, 1258, 1205, 1156, 892, and 871 cm^{-1}; mass spectrum m/e 208 (M^+), 193, 177, and 149.

Ene Reaction of Methyl 8-Methyl-4-oxo-7-nonen-2-ynoate (10). A solution containing 0.081 g of keto ester **10** in 0.5 mL of toluene was heated to 87–95 °C for 20 h in a sealed tube and then cooled and evaporated to yield 0.080 g of pure **11**: NMR ($CDCl_3$) δ 5.93 (d, 1, J = 3 Hz, C=C**H**CO_2Me), 4.96 (m, 2, C=CH_2), 3.82 (s, 3, OCH_3), 3.8–3.4 (m, 1), and 2.6–1.5 (m, 7); IR ($CHCl_3$) 3080, 2955, 2920, 1730, 1645, 1600, 1435, 1340, 1160, 1025, and 897 cm^{-1}; mass spectrum m/e 194 (M^+), 166, 163, 162, 147, 134, and 119.

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Registry No.—**1**, 18791-15-6; **1** Li salt, 65890-28-0; **2**, 65890-29-1; **3**, 65890-30-4; *cis*-**4**, 65890-31-5; *trans*-**4**, 65890-32-6; *cis*-**5**, 65890-33-7; *trans*-**5**, 65890-34-8; **6**, 65890-35-9; **10**, 65915-86-8; **11**, 65890-36-0; **12**, 65890-37-1; **13**, 65890-38-2; *cis*-**14**, 65890-39-3; *trans*-**14**, 65890-40-6; *cis*-**15**, 65890-41-7; *trans*-**15**, 65890-42-8; **16**, 65890-43-9; **17**, 65890-44-0; 1,1-dibromo-3,7-dimethyl-1,6-octadiene, 65890-45-1; 2,6-dimethyl-5-heptenal, 106-72-9; 1,1-dibromo-4,8-dimethyl-1,7-nonadiene, 65890-46-2; citronellal, 106-23-0; 4,8-dimethyl-7-nonen-1-yne lithium salt, 65890-47-3; propiolic acid dilithium salt, 65890-27-9; 1-bromo-3,7-dimethyl-6-octene, 4895-14-1; 5-methyl-4-hexenoic acid, 5636-65-7; 5-methyl-4-hexenoyl chloride, 65890-48-4; methyl propiolate silver salt, 57031-37-5.

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trans-1-*N*-Acylamino-1,3-dienes: Preparation from Dienoic Acids

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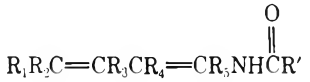
The convenient preparation of *trans* 1-*N*-acylamino-1,3-dienes from conjugated dienoic acids by a modified Curtius procedure is reported. This procedure is specifically illustrated by the preparation of the 1,3-butadiene and 1,3-pentadiene carbamates, thiocarbamates, and ureas (**4–13**) in yields of 44–80%. The ^{13}C NMR spectra of these acylamino-1,3-dienes have been determined, and the shift assignments are discussed.

Dienamides are extremely useful components for Diels–Alder synthesis.[2] The application of *N*-acyl-*N*-alkyl-1-amino-1,3-butadienes for the intramolecular Diels–Alder elaboration of natural products has been impressively demonstrated by Oppolzer and co-workers,[3] while recent reports from our laboratory have clearly demonstrated the utility of *N*-acyl-1-amino-1,3-dienes, and intermolecular Diels–Alder strategies, for solving stereochemical problems in the area of alkaloid total synthesis.[4]

A recent report from our laboratory described a versatile synthetic route to both *N*-trichloroacetyl-1-amino-1,3-dienes (**1**, R′ = CCl_3) and *N*-trichloroacetyl-2-amino-1,3-dienes.[5]

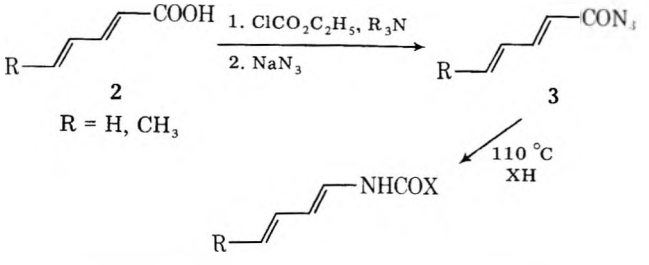


1

Synthetic applications of these dienes were limited to a certain extent, however, by their moderate Diels–Alder reactivity, a property attributed to the electron-withdrawing nature of the trichloroacetyl substituent. In this paper we report[6] that a variety of *trans*-1-*N*-acylamino-1,3-dienes can be conveniently prepared, on large scales, from dienoic acids using a modified Curtius sequence.[7] This route provides a general entry to the more reactive dienamides **1**[8] which have heteroatom acyl substituents (R′ = OR, SR, NR_2).

Results

Preparation. Dienoic acids **2** were converted, via their mixed anhydrides, into the azide derivatives **3**. The acyl azides were not isolated but instead extracted into toluene and added directly to a refluxing toluene solution containing the free-radical inhibitor 4-*tert*-butylcatechol. The diene isocyanate thus produced was either trapped as it was formed (procedure A) or cooled to room temperature before the trapping agent was added (procedure B). Concentration of the toluene solution and filtration through silica gel afforded the pure crystalline *trans*-1-*N*-acylamino-1,3-dienes **4–13** in overall yields of 44–80%. It is critical that the crude dienamides be purified immediately, as yields were dramatically reduced if the concentrated toluene solution was stored for several days before purification. Results are summarized in Table I.



2
R = H, CH_3

3

4, R = H; X = $OCH_2C_6H_5$
5, R = H; X = $OC(CH_3)_3$
6, R = H; X = OC_2H_5
7, R = H; X = OC_6H_5
8, R = H; X = SC_6H_5
9, R = H; X = $N(CH_2)_4$
10, R = CH_3; X = OC_2H_5
11, R = CH_3; X = OC_6H_5
12, R = CH_3; X = SC_6H_5
13, R = CH_3; X = $N(CH_2)_4$

The in situ trapping procedure (procedure A) is preferred for the preparation of diene carbamates, but it was markedly inferior for the preparation of diene ureas. The latter result is likely due to decomposition of the more reactive diene ureas in refluxing toluene. The amount of trapping reagent used was dictated by its ease of removal from the product dienamide. When a trapping reagent was employed which was not significantly more reactive than ethanol (e.g., *tert*-butyl alcohol or benzyl alcohol), the ethanol produced from the mixed anhydride condensation had to be removed in order to avoid the formation of contaminating amounts of the ethyl carbamate **6**. This is most easily done by concentrating the acyl azide solution to one-half its volume on a rotary evaporator, with ethanol being removed as a toluene azeotrope. In our early experiments we experienced significant problems with reproducibility. After convincing ourselves that this did not derive from the source or purity of the sodium azide employed,[9] we looked in greater detail at the mixed anhydride formation step. In our hands the reaction of *trans*-2,4-pentadienoic acid and ethyl chloroformate was not reproducible using standard conditions.[7] However, this reaction was totally reliable when *N*,*N*-diisopropylethylamine was substituted for triethylamine as the acid scavenger.

Properties. Dienamides **4–13** are reasonably stable crystalline solids which, when pure, can be stored in a freezer (but not at room temperature) for several months with little decomposition. The only exceptions are the phenyl thiocarbamates **8** and **12**, which decompose in a freezer within days with the loss of thiophenol.

The ^{13}C NMR spectra for the acylamino-1,3-dienes prepared in this study, and for *trans*-1-trichloroacetamido-1,3-butadiene (**14**),[5] are summarized in Table II.[10] For the butadienes the assignment for the terminal methylene carbon

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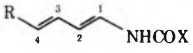
Table I. Preparation of *trans*-1-*N*-Acylamino-1,3-dienes

Dienamide	R	X	Procedure[a] (equiv of HX)	Mp, °C	Isolated yield, %
4	H	$OCH_2C_6H_5$	A (0.8)	74–75	53[b]
			B (0.8)		35[c]
5	H	$OC(CH_3)_3$	A (3)	67–68	59
			B (3)		44
10	CH_3	OCH_2CH_3	A (5)	91–92	80
6	H	OCH_2CH_3	A (5)	44–45	71[b]
11	CH_3	OC_6H_5	A (5)	118–120	72
7	H	OC_6H_5	B (1)[d]	118–119	66
			A (1)		45
13	CH_3	$N(CH_2)_4$	B (1)	164–165	77
			A (1)		10[c]
9	H	$N(CH_2)_4$	B (1)	163–164	44
12	CH_3	SC_6H_5	B (1)	116–118	78
8	H	SC_6H_5	B (1)	92–93	47

[a] Isocyanate was trapped as formed at 110 °C (procedure A), or isocyanate was preformed at 110 °C and trapped at 25 °C (procedure B). The amount of trapping reagent employed is shown in parentheses. [b] Mean yield of four to six preparations. All other table entries are nonoptimized yields of a single experiment. [c] Yield estimated by ^1H NMR spectroscopy. [d] A few drops of triethylamine were added.

Table II. ^{13}C NMR Spectra and Assignments for *trans*-1-*N*-Acylamino-1,3-dienes



Diene	Registry no.	R	X	Chemical shift[a] C_1	C_2	C_3	C_4	Other
4	65899-49-2	H	$OCH_2C_6H_5$	127.2	112.5	134.6	113.5	128.3 (p-C_6H_5), 128.4 and 128.7 (o and m-C_6H_5), 136.0 (ipso C_6H_5), 153.7 (C=O), 67.5 (CH_2)
5	65899-50-5	H	$OC(CH_3)_3$	127.8	111.3	134.9	112.7	28.3 (CH_3), 80.9 ($C(CH_3)_3$), 152.9 (C=O)
6	61759-61-3	H	OC_2H_5	127.6	112.1	134.8	113.2	14.5 (CH_3), 61.7 (CH_2), 154.1 (C=O)
7	61759-55-5	H	OC_6H_5	126.7	113.5	134.3	114.1	121.6 (o-C_6H_5), 125.8 (p-C_6H_5), 129.5 (m-C_6H_5), 150.8 (ipso C_6H_5),*[5] 151.9 (C=O)*
8	61759-58-8	H	SC_6H_5	125.7	114.3	134.2	115.0	127.5 (ipso C_6H_5), 129.5 (m-C_6H_5), 130.0 (p-C_6H_5), 135.5 (o-C_6H_5), 164.6 (C=O)
9	61759-62-4	H	$N(CH_2)_4$	128.8	110.0	135.5	111.6	25.5 (CH_2CH_2N), 45.8 (CH_2N), 153.4 (C=O)
14	59403-10-9	H	CCl_3	124.4	118.6	133.4	117.3	92.0 (CCl_3), 159.1 (C=O)
10	61759-53-3	CH_3	OCH_2CH_3	124.8*	111.9	128.9	125.4*	14.5 (CH_3), 18.0 (=CCH_3), 61.6 (CH_2), 154.0 (C=O)
11	61759-54-4	CH_3	OC_6H_5	123.9	113.3	128.5	126.4	18.1 (CH_3), 121.6 (o-C_6H_5), 125.7 (p-C_6H_5), 129.4 (m-C_6H_5), 150.7 (ipso C_6H_5),* 152.1 (C=O)*
12	61759-57-7	CH_3	SC_6H_5	123.1	114.2	128.5	127.2	18.2 (CH_3), 127.6 (ipso C_6H_5), 129.4 (m-C_6H_5), 129.7 (p-C_6H_5), 135.4 (o-C_6H_5), 164.3 (C=O)
13	61759-56-6	CH_3	$N(CH_2)_4$	126.0	109.7	129.5	123.6	18.1 (CH_3), 25.4 (CH_2CH_2N), 45.7 (CH_2N), 153.3 (C=O)

[a] In $CDCl_3$; chemical shifts are given in ppm from internal Me_4Si; assignments with an asterisk may be reversed.

can be uniquely made on the basis of off-resonance decoupled spectra. The vinylic carbon resonance at 134.2–135.5 ppm, which is similar to the central carbon of 1,3-butadiene (136.9 ppm), is easily assigned to C_3 since this carbon, like a meta carbon of a substituted benzene, should be only slightly affected by a trans substituent at carbon 1. The observation of this resonance at ca. 135 ppm also confirms the expected trans stereochemistry since C_3 would be shifted noticeably upfield if the substituent at carbon 1 were cis oriented. The carbon absorptions at 124.4–128.8 ppm are assigned to C_1 on the basis of chemical shift additivity relationships using the 11.1-ppm downfield shift (relative to benzene) for the ipso carbon of acetanilide[11] as a model for the butadiene series. The assignments for the acylaminobutadiene vinylic carbons are internally consistent and show the expected effects of changes in the electron-donating ability of the acylamino substituent. Thus, carbons 2 and 4 are observed at progressively higher field for the series **14** (X = CCl_3), **6** (X = OC_2H_5), and **9** (X = $N(CH_2)_4$). This trend of increasing electron density in the butadiene π system is of course also observed in the butadiene vertical ionization potentials (ψ_2) measured by photoelectron spectroscopy: **14**, 8.66 eV; **6**, 8.21 eV; and **9**, 7.90 eV.[8] The ^{13}C shift assignments for the acylaminopentadienes are easily made from a consideration of the expected chemical shift effects of a terminal trans methyl substituent.[12]

Discussion

Only a few examples previously existed of the conversion of a dienoic acid to a 1-*N*-acylamino-1,3-diene. Sorbic acid (*trans,trans*-2,4-hexadienoic acid) was reported to be converted in low yield to a pentadiene urea by a Curtius sequence,[13] and sorbic amide and 4-phenyl-2,4-pentadienamide were reported to be converted under Hoffman conditions to the corresponding methyl carbamates in good yield.[14] The modified Curtius procedure detailed here makes 1,3-diene carbamates, thiocarbamates, and ureas generally available,

on large scales, from dienoic acid precursors. It is particularly noteworthy that this procedure succeeds in the labile butadiene series, and one would expect yields to be even higher in more substituted cases. Since a variety of conjugated dienoic acids are readily accessible from Knoevenagel, Wittig, and related reactions,[15] 1-*N*-acylamino-1,3-dienes with both a diversity of carbon skeletons and acyl substituents should be conveniently available by this method. Diene carbamates promise to be extremely useful components for Diels–Alder synthesis,[4] and it is particularly significant that their preparation from dienoic acids allows one to specifically tailor the acyloxy function (amino-protecting group) for later synthetic manipulation. A recent study of the Diels–Alder reaction of acylaminobutadienes **4–9** has confirmed the expectation of an increase in reactivity with increasing electron-donating ability of the acyl substituent, although the effects observed were not large.[8] With a diversity of 1-*N*-acylamino-1,3-dienes readily available, a variety of synthetic applications await exploration.

Experimental Section[16]

***trans*-2,4-Pentadienoic acid** was prepared by a modification of the original procedure of Doebner.[17] We have found this procedure to give higher yields and to be more convenient than other commonly used procedures for preparing this material.[18] A 1-L three-neck flask was equipped with a mechanical stirrer, an ice water chilled condenser topped with a calcium chloride drying tube, and a dropping funnel. The flask was charged with 210 mL (2.6 mol) of pyridine, vigorous stirring was begun, and 208 g (2.0 mol) of powdered malonic acid was added portionwise. Acrolein (150 mL, 2.2 mol) was then added dropwise over 30 min to the resulting vigorously stirred suspension. An exothermic reaction began immediately with vigorous carbon dioxide evolution and gentle reflux ensued. The reaction was allowed to continue for 1 h, at which time carbon dioxide evolution had nearly ceased. The reaction mixture was then poured into 1 L of ice and carefully acidified with 130 mL of concentrated sulfuric acid. The aqueous mixture was extracted with four 250-mL portions of dichloromethane, and the organic extracts were dried ($MgSO_4$) for about 10 min and filtered. The dichloromethane solution was concentrated to about 300 mL on a rotary evaporator and allowed to crystallize in a refrigerator (−10 °C) for several hours. Filtration afforded a first crop of 40–50 g. Three additional crops were taken after successive concentrations to 150, 70, and 30 mL. After vacuum drying (over P_2O_5), the combined four crops yielded 86–100 g (44–51%) of off-white crystals, mp 69–71 °C. This material appears free of polymer and is satisfactory for the next step. Material of this purity may be stored in a freezer for several months without significant decomposition. Pure *trans*-2,4-pentadienoic acid melts at 72 °C.[17,18]

Modified Curtius Rearrangement: Procedure A (In Situ Trapping). Benzyl *trans*-1,3-Butadiene-1-carbamate (4). A 1-L three-neck flask was fitted with a stirring bar, a thermometer, and a dropping funnel. The flask was flushed with nitrogen and charged with 49 g (0.50 mol) of *trans*-2,4-pentadienoic acid, 80 g (0.62 mol) of *N,N*-diisopropylethylamine, and 300 mL of acetone, and the resulting solution was cooled to 0 °C. A solution of 55 g (0.50 mol) of ethyl chloroformate and 150 mL of acetone was added over 30 min while maintaining the temperature below 0 °C. After stirring for an additional 30 min at 0 °C, a chilled solution of 65 g (1.0 mol) of sodium azide and 150 mL of water was added. The mixture was stirred for an additional 15 min at 0 °C and poured into 500 mL of ice water. The acyl azide was isolated by extraction with six 250-mL portions of toluene, dried over $MgSO_4$ for about 20 min, and filtered, and residual ethanol was removed by concentration to a volume of about 300 mL on a rotary evaporator. The acyl azide solution was then added over 30 min to a vigorously stirred solution of 43 g (0.40 mol) of benzyl alcohol, 250 mg of 4-*tert*-butylcatechol, and 200 mL of dry toluene while rapid reflux was maintained. Reflux was continued for 10–30 min by which time the acyl azide (2130 cm^{-1}) and isocyanate (2270 cm^{-1}) IR bands had disappeared. The reaction mixture was rapidly cooled to room temperature and concentrated to afford a yellow semisolid residue which was purified immediately. Crystallization of this residue from 95% ethanol (50 mL; −25 °C) yielded 39–46 g of pale yellow crystalline product, mp 69–72 °C. Column chromatography (silica gel; 9:1 hexane–ethyl acetate) of the oily residue afforded a second batch of crystalline product, bringing the yield to 50–57 g (49–56%) of nearly pure **4**, mp 70–73 °C. An analytical sample was prepared by recrystallization from hexane–ethyl acetate: mp 74–75 °C; IR ν_{max} (Nujol) 3300, 1692, 1625, 1515, 1230, 690 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.32 (s, C_6H_5), 6.71 (broadened d, J = 9 Hz, =CHNH), 6.26 (apparent dt, J = 10, 17 Hz, CH=CH_2), 5.4–5.8 (m, CH=CHNH and NH), 5.15 (s, $CH_2C_6H_5$), 4.8–5.2 (m, =CH_2); mass spectrum, *m/e* 203.093 (25) ($C_{12}H_{13}NO_2$ requires *m/e* 203.095), 144 (12), 92 (14), 91 (100).

***tert*-Butyl *trans*-1,3-Butadiene-1-carbamate (5).** In a similar reaction which employed *tert*-butyl alcohol (3 equiv) as the trapping agent, 33.3 g (0.34 mol) of *trans*-2,4-pentadienoic acid afforded, after one recrystallization from ethanol–water, 34.1 g (59%) of nearly pure **5**, mp 61–63 °C. An analytical sample was prepared by two recrystallizations from ethanol–water: mp 67–68 °C; IR ν_{max} (Nujol) 3300, 1690, 1620, 1500 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.1–7.3 (m, vinylic and NH), 4.5–5.0 (m, =CH_2), 1.47 (s, $C(CH_3)_3$); mass spectrum, *m/e* 169.110 (10) ($C_9H_{15}NO_2$ requires *m/e* 169.110).

In our early experiments the mixed anhydride was prepared using triethylamine (1.1 equiv) as the base and excess ethyl chloroformate (1.3 equiv). (This procedure is *not* recommended.) The toluene solution of the acyl azide was also not concentrated (to remove ethanol), and 1–5 equiv of the trapping reagent was employed. Using these modifications of the procedure described for the preparation of **4**, the following dienes were prepared on a 80–100-mmol scale. In all cases the crude product was purified by chromatography on silica gel (hexane–ether). Yields refer to chromatographically homogeneous crystalline samples.

Ethyl *trans*-1,3-butadiene-1-carbamate (6) was prepared in 60–91% yield (six preparations). Recrystallization from hexane–ether afforded an analytical sample: mp 44–45 °C; IR ν_{max} (Nujol) 3360, 1695, 1665, 1530 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.7 (broadened d, NH), 5.3–6.9 (m, vinylic), 4.5–5.1 (m, =CH_2), 4.13 (q, J = 7 Hz, OCH_2), 1.26 (t, J = 7 Hz, CH_3); mass spectrum, *m/e* 141.079 (34) ($C_7H_{11}NO_2$ requires *m/e* 141.079), 69 (49), 44 (100), 43 (47).

Phenyl *trans*-1,3-butadiene-1-carbamate (7) was prepared in 45% yield when a few drops of triethylamine were added to catalyze phenol addition to the isocyanate. Recrystallization from hexane–ether afforded an analytical sample: mp 118–119 °C; IR ν_{max} (Nujol) 3310, 1715, 1660, 1530 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.2–7.7 (m, C_6H_5, vinylic, and NH), 4.5–5.2 (m, =CH_2); mass spectrum, *m/e* 189.079 (12) ($C_{11}H_{11}NO_2$ requires *m/e* 189.079), 95 (7), 94 (100), 67 (8).

Diene **7** was also obtained in 66% yield when the isocyanate was preformed (procedure B).

Ethyl *trans,trans*-1,3-pentadiene-1-carbamate (10) was prepared from sorbic acid in 80% yield. Recrystallization from dichloromethane afforded an analytical sample: mp 91–92 °C; IR ν_{max} (Nujol) 3300, 1705, 1670, 1640, 1520 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.0–7.0 (m, vinylic), 4.15 (q, J = 7 Hz, CH_2O), 1.67 (d, J = 6 Hz, =CCH_3), 1.23 (t, J = 7 Hz, CH_2CH_3); mass spectrum, *m/e* 155 (26), 82 (100), 67 (32), 55 (37). Anal. ($C_8H_{13}NO_2$): C, H, N.

Phenyl *trans,trans*-1,3-pentadiene-1-carbamate (11) was prepared from sorbic acid in 72% yield: mp 118–120 °C; IR ν_{max} (Nujol) 3260, 1735, 1705, 1660, 1640, 1520 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.0–7.7 (m, C_6H_5, vinylic, and NH), 1.68 (d, J = 6 Hz, =CCH_3); mass spectrum, *m/e* 203.095 (6) ($C_{12}H_{13}NO_2$ requires *m/e* 203.095), 112 (12), 97 (12), 94 (100).

Procedure B (Preformed Isocyanate). *N*-(*trans,trans*-1,3-Pentadien-1-yl)-1-pyrrolidinecarboxamide (13). A solution of 11.9 g (0.11 mol) of ethyl chloroformate and 40 mL of acetone was added dropwise to a stirred solution of 9.52 g (85 mmol) of sorbic acid (*trans,trans*-2,4-hexadienoic acid), 10.2 g (0.10 mol) of triethylamine, and 50 mL of acetone at 0 °C. (This procedure for making the mixed anhydride is *not* recommended.) After 30 min a solution of 8.45 g (0.13 mol) of sodium azide and 30 mL of water was added dropwise while maintaining the temperature below 10 °C. After 1 h the reaction mixture was poured into 200 mL of ice water and extracted with three 60 mL-portions of toluene, and the toluene solution was dried over $MgSO_4$ for 30 min. The acyl azide solution was then added dropwise over 1 h to 100 mL of refluxing toluene which contained ca. 50 mg of 4-*tert*-butylcatechol. Reflux was continued for 30–60 min, by which time the acyl azide IR band (2130 cm^{-1}) had disappeared, and the reaction mixture was rapidly cooled to room temperature by placing it in an ice–water bath. A solution of 7.1 mL (85 mmol) of freshly distilled pyrrolidine and 30 mL of xylene was added over 30 min, by which time IR analysis indicated that the isocyanate band (2270 cm^{-1}) had disappeared. The reaction mixture was concentrated to afford a brown solid, which was purified by column chromatography (silica gel, ethyl acetate) to afford 11.8 g (77%) of **13** as a white solid, mp 163–164 °C. Recrystallization from hexane–ethyl acetate afforded an analytical sample: mp 164–165 °C; IR ν_{max} (Nujol) 3310, 1658, 1650, 1630, 1520 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.0–7.4 (m, vinylic and NH), 3.1–3.5 (m, NCH_2), 1.7–2.1 (m, NCH_2CH_2), 1.70 (d, J = 6 Hz,

$=CCH_3$); mass spectrum, *m/e* 180.129 (57) ($C_{10}H_{16}N_2O$ requires *m/e* 180.126), 114 (26), 98 (100), 55 (57).

***N*-(*trans*-1,3-Butadien-1-yl)-1-pyrrolidinecarboxamide (9)** was prepared in a similar fashion in 44% yield. Recrystallization from hexane–ethyl acetate afforded an analytical sample: mp 163–164 °C; IR ν_{max} (Nujol) 3250, 1671, 1630, 1600, 1510 cm^{-1}; ^1H NMR ($CDCl_3$), δ 5.2–7.5 (m, vinylic and NH), 4.5–4.9 (m, $=CH_2$), 3.0–3.5 (m, NCH_2), 1.5–1.9 (m, NCH_2CH_2); mass spectrum, *m/e* 166.109 (30) ($C_9H_{14}N_2O$ requires *m/e* 166.111), 98 (100), 55 (85).

Phenyl *trans,trans*-1,3-pentadiene-1-thiocarbamate (12) was prepared in a similar fashion in 78% yield. This diene was labile and showed considerable decomposition, with the formation of thiophenol, when stored for 1 week at −20 °C. Recrystallization from ether–hexane afforded an analytical sample: mp 116–118 °C; IR ν_{max} (Nujol) 3220, 1660, 1630, 1520 cm^{-1}; ^1H NMR ($CDCl_3$) δ (5.0–7.8 (m, C_6H_5, vinylic, and NH), 1.64 (d, J = 6 Hz, $=CCH_3$); mass spectrum, *m/e* 219.070 (17) ($C_{12}H_{13}NOS$ required *m/e* 219.072), 110 (100) (C_6H_5SH probably formed from decomposition), 109 (56), 81(20), 80 (19).

Phenyl *trans*-1,3-butadiene-1-thiocarbamate (8) was prepared in a similar fashion in 47% yield. This diene was labile and showed considerable decomposition, with the formation of thiophenol, when stored for 1 week at −20 °C. Recrystallization from ether–hexane afforded an analytical sample: mp 92–93 °C; IR ν_{max} (Nujol) 3240, 1645, 1610, 1535 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.2–8.0 (m, C_6H_5, vinylic, and NH), 4.5–5.1 (m, $=CH_2$); mass spectrum, *m/e* 205.056 (15) ($C_{11}H_{11}NOS$ requires *m/e* 205.056), 110 (100) (C_6H_5SH probably formed from decomposition), 109 (44), 95 (32).

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Registry No.—2 (R = H), 21651-12-7; 2 (R = Me), 110-44-1; 3 (R = H), 65899-51-6; 3 (R = Me), 65899-52-7; malonic acid, 141-82-2; *trans*-1-isocyanatobuta-1,3-diene, 65899-53-8; *trans,trans*-1-isocyanatopenta-1,3-diene, 65899-54-9.

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Chloromethylation of Ortho-Disubstituted Benzenes. A Simple Preparation of Some Useful α Isomers of Indan, Tetralin, and Benzosuberane

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Functionalization of ortho-disubstituted benzenes by the chloromethylation procedure has been shown to yield more of the so-called "α isomer" than previously anticipated. The chloromethyl functionality is readily modified to the corresponding alcohol or aldehyde. The aldehyde can be oxidized to the carboxylic acid or reacted with malonic acid (Doebner) to give acrylic acid derivatives. These high-yield manipulations, combined with key purification techniques, have permitted the synthesis of some novel "α-substituted" derivatives of indan, tetralin, and benzosuberane.

We required preparative amounts of indan, tetralin, and benzosuberane derivatives which were substituted on the benzene ring next to the carbocyclic ring, i.e., **1**, **3**, or **5**, the so-called α isomers, and which were capable of being elaborated to derivatives containing functionalized alkyl chains of varying length. However, in contrast to reasonably facile preparations of **2**,[2] **4**,[3] or **6**,[4] i.e., the β isomers, no direct or general methods have been reported for obtaining preparatively useful quantities of isomerically pure α isomers.[5] In general most aromatic substitution reactions of ortho-disubstituted benzenes give a preponderance of the β isomer although some specific conditions of nitration or halogenation have been reported to give mixtures rich in the α isomer.[6]

Thus, the tetralin derivative **3e** has been prepared by a long sequence beginning with the corresponding nitro derivative obtained by fractional distillation[7] or from partially hydro-

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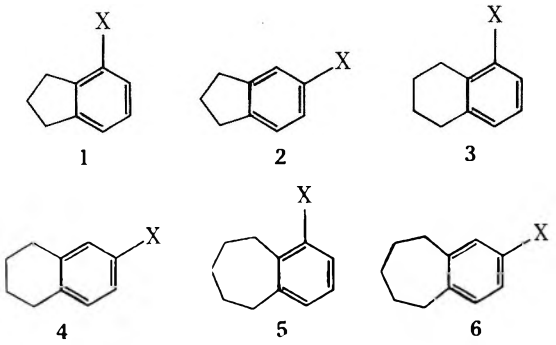

1 2 3

4 5 6

a, X = CH_2Cl d, X = CHO
b, X = CH_2OAc e, X = COOH
c, X = CH_2OH f, X = CH=CHCOOH

genated mixtures of naphthalene derivatives.[8] The indan and benzosuberane acids **1e** and **5e** have been obtained by grignard reactions on the halo derivatives themselves formed by ring closure sequences of the appropriate halo-substituted benzenes.[7,9] Partial separation of the mixed carboxylic acids obtained from chloromethylation of the hydrocarbon has also been reported.[9,10]

The chloromethylation of ortho-disubstituted benzenes[11] was eventually recognized to produce two isomers and estimations of isomer ratios have either been unsubstantiated[5] or ingenious but indirect.[9,12] However, they have been uniformly discouraging for preparative purposes in ascribing low percentages (5–25%) to the α isomer. In this paper we wish to describe methods which permit: (i) direct analysis of the ratio of mixtures of the monochloromethylation isomers of indan, tetralin, and benzosuberane that indicate larger amounts of the α isomer than previously reported, and (ii) short, high-yield modifications and enrichment procedures which permit isolation of preparatively useful quantities of some new α-substituted derivatives of these hydrocarbons.

The Synthetic Sequence. Chloromethylation of the hydrocarbons under standard conditions[5,9] produced a mixture of the monochloromethylated isomers **1a–6a**. Displacement by acetate yielded **1b–6b**, subsequent hydrolysis to the alcohols produced **1c–6c**, and oxidation produced the aldehydes **1d–6d**. All were high-yield steps necessitating no intermediate purification. Substantial amounts of **2c** and **6c** could be directly crystallized leaving mixtures predominating in the corresponding α isomer.

The aldehyde functionality permitted separation of all isomer mixtures by thin layer, gas liquid, or column chromatography. The aldehydes could be oxidized to the carboxylic acids **1e–6e** or transformed into mixtures of the acrylic acids **1f–6f** from which further separations were possible.[16]

Isomer Ratios and Structure Proof. In the ^1H NMR spectra of the α aldehydes, **1d, 3d**, and **5d**, the benzylic hydrogens "peri" to the formyl group experienced a downfield shift that allows them to be easily distinguished from the other benzylic hydrogens. This is presumably due to an anisotropic effect of the carbonyl group since it does not occur in the β isomers, **2d, 4d**, and **6d**. The phenomenon occurs also to some extent with the carboxylic acids **1e–6e**. This constitutes the first unambiguous structure proof reported for any of these compounds and underlines the general lack of characterization even for those compounds previously reported. Chemical shift differences in the ^1H NMR spectra also seem more useful for rapid differentiation of α and β isomers in the aldehydes (CHO) and acrylic acids (CH=CH—COOH) than minor differences in the IR or UV spectra.[17]

The ratio of isomers could most accurately and generally be measured on mixtures functionalized to the aldehydes.[18] Thus we have determined that the chloromethylation reaction yields the following isomer ratios (α:β), indan (30:70), tetralin (42:58), benzosuberane (22:78), and o-xylene (32:68), which are substantially more favorable for the α isomers than previously estimated, e.g., ref 9 and 10 report indan (19:81), tetralin (24:76), benzosuberane (5:95), and o-xylene (19:82). The simple enrichment procedures permit the following mixtures of alcohols to be obtained: indan (72α:28β) and benzosuberane (55α:45β). Consequently, as demonstrated, the sequences here described become preparatively useful for obtaining a variety of α-substituted derivatives of ortho-disubstituted benzenes.

The formation of the carcinogen bis(chloromethyl) ether makes the chloromethylation reaction potentially hazardous.[19] Therefore we are investigating some recent aromatic functionalization methods to ascertain their degree of α substitution.[20a–c]

Experimental Section

Melting points were obtained on a Buchi SMP-20 melting range apparatus. IR spectra (ν_{max} in cm^{-1}) were recorded on a Perkin-Elmer 237B spectrophotometer. UV spectra [λ_{max} in nm (ϵ)] were obtained in 95% EtOH on a Perkin-Elmer Coleman-124 spectrophotometer. Proton magnetic resonance (^1H NMR) spectra were recorded on Varian T-60 (60 MHz) or Varian HA-100 (100 MHz) instruments; all values are recorded in ppm (δ) with reference to Me_4Si. All ^1H NMR were taken in $CDCl_3$ with 1% Me_4Si. Band shape is indicated by s (singlet), d (doublet), t (triplet), m (multiplet), and b (broad). TLC was performed using silica gel G (0.25-mm layers) on glass plates (Merck). Refractive indices were taken on an Officine Galileo Di Milano (Jo. 50532) refractometer. Analytical GLC data were obtained on: (i) a Hewlett Packard F&M 402 instrument using 0.25 in. × 6 ft column packed with 3% OV-210 on Chromosorb W, an oven temperature of 130 °C, and flow rate of nitrogen at 70 mL/min or (ii) a Perkin-Elmer 990 using a 1/8 in. × 12 ft column packed with 3% OV-17, on Chromosorb W, temperature 150 °C, and nitrogen flow rate 25 mL/min. Petroleum ether with boiling range 30–60 °C was used exclusively. Microanalyses were obtained from Spang Microanalytical Laboratory, Ann Arbor, Mich.

Chloromethylation. Preparation of 1a–6a. Chloromethylation was accomplished by heating at 60 °C a mixture of hydrocarbon, aqueous formaldehyde, hydrochloric acid, and sulfuric acid according to Arnold and Barnes.[5] The mixture of monochloromethyl isomers was purified by distillation to obtain: **1a/2a**, 61% from indan; bp 80–90 °C (0.3 mm), n^{25}_D 1.5615 (lit.[21] bp 111 °C (4 mm), n^{21}_D 1.5625); ^1H NMR 7.28–7.05 (3 H, m, aromatic H), 4.56 (1 H, s, CH_2Cl), 3.10–2.68 (4 H, m, benzylic H), 2.40–1.70 (2 H, m). **3a/4a**: 59% from tetralin; bp 90–100 °C (0.3 mm); n^{19}_D 1.5705 (lit.[5] bp 110–114 °C (0.3 mm)); ^1H NMR, 7.28–6.95 (3 H, m, aromatic H), 4.59 and 4.51 (total 2 H, 2 s, ratio 54:46, CH_2Cl of α and β isomer, respectively), 3.00–2.61 (4 H, m, benzylic H), 2.08–1.65 (4 H, m). **5a/6a**: 40% from benzosuberane (45% recovered benzosuberane); bp 105–115 °C (0.5 mm); n^{26}_D 1.5610 (lit.[22] bp 140 °C (9 mm), n^{23}_D 1.5672); ^1H NMR 7.13–6.85 (3 H, m, aromatic H), 4.53, 4.44 (total 2 H, 2 s, ratio 22:78, CH_2Cl of α and β isomer, respectively), 2.98–2.64 (4 H, m, benzylic H), 2.03–1.48 (6 H, m). Similarly o-xylene yielded a mixture of monochloromethylated isomers[10] in 60% yield: bp 110–120 °C (14 mm); n^{19}_D 1.1542; ^1H NMR 7.26–7.00 (3 H, m, aromatic H), 4.60, 4.52 (total 2 H, 2 s, ratio 32.68, CH_2Cl of α and β isomer, respectively), 1.50–1.20 (6 H, m).

Preparation of Alcohols 1c–6c via Acetates 1b–6b. (i) As similarly described[13] the monochloromethylated hydrocarbons **1a–6a** (*X* g) were converted to the corresponding acetates, **1b–6b**, by anhydrous sodium acetate (*X* g) in glacial acetic acid (2–3*X* mL) after refluxing for 10 h. Yields of crude products were ≥95% and essentially pure by spectroscopy. Thus were obtained **1b/2b**: IR 1735 (OAc); ^1H NMR 7.38–7.12 (3 H, m, aromatic H), 5.08, 5.05 (2 H, d, CH_2OAc of both isomers), 3.18–2.68 (4 H, m, benzylic H), 2.08 (3 H, s, $OCOCH_3$), 2.44–1.75 (2 H, m). **3b/4b**: IR 1735 (OAc); ^1H NMR 7.23–6.84 (3 H, m, aromatic H), 5.08, 5.00 (total 2 H, 2 s, ratio 42:58, CH_2OAc of α and β isomer, respectively), 2.96–2.51 (4 H, m, benzylic H), 2.08 (3 H, s, $OCOCH_3$), 2.00–1.57 (4 H, m). **5b/6b**: IR 1735 (OAc); ^1H NMR 7.08 (3 H, s, aromatic H), 5.13, 5.03 (total 2 H, 2 s, ratio 27:73, CH_2OAc of α and β isomers, respectively), 2.05–2.65 (4 H, m, benzylic H), 2.09 (3 H, s, $OCOCH_3$), 2.00–1.45 (6 H, m).

(ii) The acetate mixtures were hydrolyzed in methanol and aqueous sodium hydroxide after heating and stirring for 30 min at 50 °C.[14] Yields of crude alcohol were ≥90% and quite pure as judged by ^1H NMR. Dissolution of **1c/2c** in petroleum ether and cooling yielded two crops of pure **2c** (~65%) so that the mother liquors contained a

mixture enriched in **1c**. Similar treatment yielded pure **6c** (57%) plus an enriched (in **5c**) mixture of **5c/6c**. The remaining alcohols **1c**, **3c**, **4c**, and **5c** were obtained in pure form by reduction of the corresponding aldehydes (vide infra).

Preparation of Aldehydes 1d–6d.[29] The benzylic alcohols, **1c–6c**, were readily oxidized by Corey's pyridinium chlorochromate reagent[15] after stirring for 2 h at room temperature in CH_2Cl_2. The crude product was filtered through a short column of silica gel (or Florisil) with benzene to produce the corresponding aldehyde **1d–6d**, as a yellowish oil in 90% yield. Purity of this material was excellent as judged by ^1H NMR and TLC (benzene–petroleum ether, 1:1). A mixture of α and β isomers could be resolved by GLC or separated on a preparative scale (10–20 g) by the short, wide column technique[23] using silica gel H (Merck, particle size 10–40 × 10^{-6} m) and benzene–petroleum ether (1:1) as eluent. The aldehydes were susceptible to air oxidation but nicely characterized by spectroscopy (as well as conversion to the corresponding alcohols, carboxylic acids, or acrylic acids) as follows (bp are from bulb-to-bulb distillations and approximate only). **1d:** bp 80 °C (0.2 mm), 2,4-DNP, mp 231–232 °C; n^{22}_D 1.5707; IR 1683 (ArCHO); UV 252 (10 970); ^1H NMR 10.18 (1 H, s, CHO), 7.72–7.08 (3 H, m, aromatic H), 3.53–3.12 (2 H, t, benzylic H "peri" to CHO), 3.10–2.71 (2 H, t, other benzylic H), 2.40–1.91 (2 H, m).

2d: bp 79 °C (0.2 mm) (lit.[21] bp 136 °C (23 mm)); 2,4-DNP, mp 242–244 °C; n^{22}_D 1.5719; IR 1683 (ArCHO); UV 243 (12 540); ^1H NMR 9.95 (1 H, s, CHO), 7.75–7.10 (3 H, m, aromatic H), 3.13–2.60 (4 H, m, benzylic H), 2.34–1.82 (2 H, m).

3d: bp 85 °C (0.3 mm); 2,4-DNP, mp 230 °C; n^{22}_D 1.5769; IR 1685 (ArCHO); UV 254 (10 810); ^1H NMR 10.43 (1 H, s, CHO), 7.86–7.18 (3 H, m, aromatic H), 3.38–3.05 (2 H, m, benzylic H "peri" to CHO), 3.03–2.60 (2 H, m, other benzylic H), 2.04–1.58 (4 H, m).

4d: bp 79 °C (0.3 mm) (lit.[24] bp 116–119 °C (3 mm)); 2,4-DNP, mp 216–218 °C; n^{20}_D 1.5740; IR 1688 (ArCHO); UV 266 (13 710); ^1H NMR 10.29 (1 H, s, CHO), 7.94–7.25 (3 H, m, aromatic H), 3.11–2.60 (4 H, m, benzylic H), 2.14–1.60 (4 H, m).

5d: bp 78 °C (0.2 mm); 2,4-DNP, mp 176–177 °C; n^{20}_D 1.5671; IR 1681 (ArCHO); UV 254 (8620); ^1H NMR 10.38 (1 H, s, CHO), 7.78–7.04 (3 H, m, aromatic H), 3.46–3.18 (2 H, m, benzylic H "peri" to CHO), 3.04–2.70 (2 H, m, other benzylic H), 2.00–1.43 (6 H, m).

6d: bp 79 °C (0.20 mm); 2,4-DNP, mp 222–223 °C; n^{20}_D 1.5716; IR 1681 (ArCHO); UV 260 (15 350); ^1H NMR 9.93 (1 H, s, CHO), 7.75–7.05 (3 H, m, aromatic H), 3.01–2.65 (4 H, m, benzylic H), 2.05–1.38 (6 H, m).

In the ^1H NMR spectra the distinctive chemical shifts of aldehydic protons for each isomer allowed easy analysis of isomer ratios. The following data were obtained by oxidizing mixtures of the corresponding alcohols (values from integration of GLC separations in brackets): from "normal" mixture of **1c/2c**, ratio of **1d/2d** = 30:70 (31:69), from "enriched" mixture of **1c/2c**, ratio of **1d/2d** = 72:28 (70:30); normal mixture of **3c/4c** gave **3d/4d** = 42:58 (41:59); a "normal" mixture of **5c/6c** gave **5d/6d** = 22:78 (24:76); the "enriched" mixture of **5c/6c** gave **5d/6d** = 55:45 (53:47).

Preparation of the Alcohols 1c–6c: Chromatographically pure samples of the various aldehydes, **1c**, **3c**, **4c**, **5c** (0.5 g), were reduced by $NaBH_4$ (100 mg) in ethanol (30 mL) at room temperature. Workup after 30 min produced the corresponding alcohols in >85% yield. Analytical samples were obtained by bulb-to-bulb distillation. Alcohols **2c** and **6c** were crystalline (vide supra) and sublimed for analysis.

1c: bp 101 °C (0.5 mm); IR 3610 (OH), 790; ^1H NMR 7.11 (3 H, s, aromatic H), 4.52 (1 H, 6 s, CH_2OH), 3.10–2.50 (4 H, m, benzylic H), 2.75 (1 H, s, disappears with D_2O, CH_2OH), 2.32–1.78 (2 H, m). Anal. Calcd for $C_{10}H_{12}O$: C, 81.04; H, 8.16. Found: C, 81.19; H, 8.10.

2c: mp 73–75 °C (lit.[12] mp 74 °C); IR 3600 (OH), 826; ^1H NMR 7.18 (3 H, s, aromatic H), 4.58 (2 H, s, CH_2OH), 2.90 (4 H, t, benzylic H), 2.14 (1 H, 6 s, disappears with D_2O, CH_2OH), 2.32–1.78 (2 H, m). Anal. Calcd for $C_{10}H_{12}O$: C, 81.04; H, 8.16. Found: C, 80.69; H, 8.18.

3c: bp 104 °C (0.5 mm) (lit.[8] bp 106 °C (0.5 mm)); IR, 3590 (OH), 780; ^1H NMR 7.15 (3 H, s, aromatic H), 4.60 (2 H, s, CH_2OH), 2.80 (1 H, 6 s, disappears with D_2O, CH_2OH), 2.97–2.58 (4 H, m, benzylic H), 2.05–1.81 (4 H, m). Anal. Calcd for $C_{11}H_{14}O$: C, 81.44; H, 8.70. Found: C, 81.30; H, 8.70.

4c: bp 103 °C (0.5 mm) (lit.[24] bp 133 °C (4 mm)); IR 3590 (OH), 830, 815; ^1H NMR 7.00 (3 H, s, aromatic H), 4.53 (2 H, s, CH_2OH), 2.64 (1 H, bs, disappears with D_2O, CH_2OH), 2.92–2.54 (4 H, m, benzylic H), 1.98–1.60 (4 H, m). Anal. Calcd for $C_{11}H_{14}O$: C, 81.44; H, 8.70. Found C, 81.47; H, 8.83.

5c: bp 109 °C (0.5 mm); IR 3600 (OH), 800, 790; ^1H NMR 7.02 (3 H, s, aromatic H), 4.62 (2 H, s, CH_2OH), 2.75 (1 H, bs, disappears with D_2O, CH_2OH), 3.00–2.60 (4 H, m, benzylic H), 1.98–1.40 (6 H, m). Anal. Calcd for $C_{12}H_{16}O$: C, 81.77; H, 9.15. Found: C, 81.58; H, 9.20.

6c: mp 64–65 °C (lit.[25] mp 65 °C); IR 3600 (OH), 828; ^1H NMR 7.02 (3 H, s, aromatic H), 4.53 (2 H, s, CH_2OH), 2.70 (1 H, bs, disappears with D_2O, CH_2OH), 2.94–2.58 (4 H, m, benzylic H), 1.98–1.38 (6 H, m). Anal. Calcd for $C_{12}H_{16}O$: C, 81.77; H, 9.15. Found: C, 81.79; H, 9.13.

Preparation of the Carboxylic Acids 1e–6e.[29] The acids could be obtained after oxidation of the corresponding aldehydes **1d–6d** by prolonged exposure to air, $CoCl_2/NaOCl$,[26] Ag_2O,[9] or Jones conditions. Only the indan mixture, **1e/2e**, could be resolved by TLC (ether–benzene, 1:9). Partial separation of isomers can evidently be achieved by fractional crystallization of the barium salts.[9,10] The free acids were nicely crystallized from ether–petroleum ether and sublimed for analysis.

1e: mp 151–154 °C (lit.[27] mp 153 °C); ^1H NMR 10.88 (1 H, bs, disappears with D_2O, COOH), 8.04–7.01 (3 H, m, aromatic H), 3.45 (2 H, t, benzylic H "peri" to COOH), 2.97 (2 H, t, other benzylic H), 2.07 (2 H, m).

2e: mp 182–184 °C (lit.[21] mp 177, 183 °C[12]); ^1H NMR 11.83 (1 H, bs, disappears with D_2O, COOH), 8.05–7.16 (3 H, m, aromatic H), 2.98 (4 H, t, benzylic H), 2.09 (2 H, m). Anal. Calcd for $C_{10}H_{10}O_2$: C, 74.06; H, 6.21. Found: C, 73.83; H, 6.19.

3e: mp 148–150 °C (lit.[7] mp 151 °C); ^1H NMR, 11.20 (1 H, bs, disappears with D_2O, COOH), 8.15–7.10 (3 H, m, aromatic H), 3.22 (2 H, m, benzylic H "peri" to COOH), 2.90 (2 H, m, other benzylic H), 1.81 (4 H, m). Anal. Calcd for $C_{11}H_{12}O_2$: C, 74.98; H, 6.86. Found: C, 74.94; H, 6.79.

4e: mp 156–158 °C (lit.[24] mp 154–155 °C); ^1H NMR 11.93 (1 H, bs, disappears with D_2O, COOH), 8.20–7.14 (3 H, m, aromatic H), 2.90 (4 H, m, benzylic H), 1.85 (4 H, m). Anal. Calcd for $C_{11}H_{12}O_2$: C, 74.98; H, 6.86. Found: C, 74.65; H, 6.86.

5e: mp 105–107 °C (lit.[9] mp 107 °C); ^1H NMR 11.05 (1 H, bs, disappears with D_2O, COOH), 8.18–7.11 (3 H, m, aromatic H), 3.25 (2 H, m, benzylic H "peri" to COOH), 2.91 (2 H, m, other benzylic H), 1.82 (6 H, m). Anal. Calcd for $C_{12}H_{14}O_2$: C, 75.76; H, 7.42. Found: C, 75.32; H, 7.40.

6e: mp 178–179 °C (lit.[9] mp 178 °C); ^1H NMR 11.87 (1 H, bs, disappears with D_2O, COOH), 8.21–7.14 (3 H, m, aromatic H), 2.91 (4 H, m, benzylic H), 1.87 (6 H, m). Anal. Calcd for $C_{12}H_{14}O_2$: C, 75.76; H, 7.42. Found: C, 75.58; H, 7.27.

Preparation of Acrylic Acids 1f–6f.[29] As described by Standridge et al.[28] the aldehyde(s) **1d–6d**, malonic acid, and a catalytic amount of piperidine were heated in dry pyridine for 2.5 h and worked up to give the acrylic acid(s), **1f–6f**, in >90% yields and essentially pure by ^1H NMR. The "enriched" mixture of **1f/2f** when crystallized from CH_2Cl_2 yielded directly pure **1f** in 50–60% yield. When the resulting mother liquors were dissolved in acetone and the solvent was allowed to evaporate slowly **1f** and **2f** were deposited as distinct crystal forms which could be mechanically separated. The mixture of **3f/4f** also yielded some pure **3f** (~20%) on fractional crystallization from chloroform or benzene.[16] These derivatives could be crystallized from acetone, ether, or dichloromethane and sublimed for analysis.

1f: mp 174–176 °C; ^1H NMR 9.82 (1 H, bs, disappears with D_2O, COOH), 8.10, 7.85 (1 H, d, CH=CHCOOH, J = 16 Hz), 7.58–7.15 (3 H, m aromatic H), 6.58, 6.30 (1 H, d, CH=CHCOOH, J = 16 Hz), 3.29–2.78 (4 H, m, benzylic H), 2.43–1.81 (2 H, m). Anal. Calcd for $C_{12}H_{12}O_2$: C, 76.57; H, 6.43. Found: C, 76.24; H, 6.27.

2f: mp 164–166 °C (lit.[21] mp 161 °C); ^1H NMR 10.17 (1 H, bs, disappears with D_2O, COOH), 8.00, 7.75 (1 H, d, CH=CHCOOH, J = 16 Hz), 7.56–7.15 (3 H, m, aromatic H), 6.60, 6.35 (1 H, d, CH=CHCOOH, J = 16 Hz), 3.25–2.58 (4 H, m, benzylic H), 2.40–1.81 (2 H, m).

3f: mp 211–213 °C; ^1H NMR 9.25 (1 H, bs, disappears with D_2O, COOH), 8.28, 8.01 (1 H, d, CH=CHCOOH, J = 16 Hz), 7.58–7.02 (3 H, m, aromatic H), 6.50, 6.22 (1 H, d, CH=CHCOOH, J = 16 Hz), 3.04–2.57 (4 H, m, benzylic H), 2.18–1.65 (4 H, m). Anal. Calcd for $C_{13}H_{14}O_2$: C, 77.20; H, 6.98. Found: C, 76.84; H, 6.96.

4f: mp 173–175 °C (lit.[24] 171–172 °C); ^1H NMR 9.22 (1 H, bs, disappears with D_2O, COOH), 7.91, 7.66 (1 H, d, CH=CHCOOH, J = 16 Hz), 7.48–6.97 (3 H, m, aromatic H), 6.57, 6.31 (1 H, d, CH=CHCOOH), J = 16 Hz), 3.04–2.55 (4 H, m, benzylic H), 2.09–1.58 (4 H, m). Anal. Calcd for $C_{13}H_{14}O_2$: C, 77.20; H, 6.98. Found: C, 77.44; H, 6,87.

5f: mp 163–165 °C; ^1H NMR 10.63 (1 H, bs, disappears with D_2O-COOH), 8.41, 8.16 (1 H, d, CH=CHCOOH, J = 15 Hz), 7.58–7.08 (3 H, m, aromatic H), 6.46, 6.21 (1 H, d, CH=CHCOOH, J = 15 Hz), 3.20–2.64 (4 H, m, benzylic H), 2.68–1.40 (6 H, m). Anal. Calcd for $C_{14}H_{16}O_2$: C, 77.75; H, 7.46. Found: C, 77.37; H, 7.60.

6f: mp 161–163 °C; ^1H NMR 9.40 (1 H, bs, disappears with D_2O,

COOH), 7.97, 7.71 (1 H, d, CH=CHCOOH, J = 16 Hz), 7.51–7.10 (3 H, m, aromatic H), 6.59, 6.34 (1 H, d, CH=CHCOOH, J = 16 Hz), 3.08–2.64 (4 H, m, benzylic H), 2.15–1.45 (6 H, m). Anal. Calcd for $C_{14}H_{16}O_2$: C, 77.75; H, 7.46. Found: C, 77.48; H, 7.49.

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Registry No.—**1a,** 65898-31-9; **1b,** 65898-32-0; **1c,** 65898-33-1; **1d,** 51932-70-8; **1d** DNP, 65898-34-2; **1e,** 4044-54-6; **1f,** 65898-35-3; **2a,** 18775-42-3; **2b,** 65898-36-4; **2c,** 51632-06-5; **2d,** 30084-91-4; **2d** DNP, 65898-37-5; **2e,** 65898-38-6; **2f,** 56635-88-2; **3a,** 17450-62-3; **3b,** 65898-39-7; **3c,** 41790-30-1; **3d,** 41828-13-1; **3d** DNP, 65898-40-0; **3e,** 4242-18-6; **3f,** 65898-41-1; **4a,** 17450-63-4; **4b,** 65898-42-2; **4c,** 6883-81-4; **4d,** 51529-97-6; **4d** DNP, 65898-43-3; **4e,** 1131-63-1; **4f,** 7498-69-3; **5a,** 65898-44-4; **5b,** 65898-45-5; **5c,** 65898-46-6; **5d,** 65898-47-7; **5d** DNP, 65898-48-8; **5e,** 4087-43-8; **5f,** 65898-49-9; **6a,** 41635-37-4; **6b,** 55037-99-5; **6c,** 65898-50-2; **6d,** 65898-51-3; **6d** DNP, 65898-27-3; **6e,** 41068-24-0; **6f,** 65898-28-4; indan, 496-11-7; tetralin, 119-64-2; benzosuberane, 1075-16-7; *o*-xylene, 95-47-6; 3-(chloromethyl)-*o*-xylene, 13651-55-3; 4-(chloromethyl)-*o*-xylene, 102-46-5.

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Metalation of Ethylbenzene with *n*-Pentylsodium in the Presence of *N,N,N′,N′*-Tetramethylethylenediamine

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Ethylbenzene was metalated with *n*-pentylsodium activated by *N,N,N′,N′*-tetramethylethylenediamine (TMEDA) to give exclusively α-methylbenzylsodium (**1**) after 1 h in yields in excess of 95%. An examination of the reaction at shorter reaction times (5, 15, and 30 min) revealed that metalation occurred initially in a kinetically controlled process giving, in addition to **1**, *o*-, *m*-, and *p*-ethylphenylsodium (**2a, 2b,** and **2c**) and a disodio compound identified as α,α-disodioethylbenzene (**3**). With time, the ring and disodio compounds isomerized to the α isomer **1** in a thermodynamically controlled sequence.

Relatively few reports appear in the literature regarding the activation of organosodium reagents such as *n*-pentylsodium with *N,N,N′,N′*-tetramethylethylenediamine (TMEDA) even though this effect is well documented for the corresponding organolithium reagents.[2] Trimitsis and coworkers[3] found that *n*-pentylsodium in the presence of TMEDA promoted the quantitative dimetalation of 1,3-dimethylnaphthalene and *m*-xylene on the benzylic carbons. In the absence of TMEDA, monometalation occurred in low yield. Recently, this laboratory[4] reported that cumene was metalated with *n*-pentylsodium activated with TMEDA to give α-cumylsodium in good yields and high isomeric purity. When TMEDA was omitted from the reaction, metalation occurred on the ring giving *m*- and *p*-isopropylphenylsodium.

In view of the rather profound effect which TMEDA had on the above reactions, we were prompted to investigate the metalation of ethylbenzene by *n*-pentylsodium in the presence of TMEDA. Previously, Benkeser and co-workers[5] reported that ethylbenzene was metalated by *n*-pentylsodium (no TMEDA) giving 68% α-methylbenzylsodium (**1**) along with 19% *m*- and 13% *p*-ethylphenylsodium (**2b** and **2c**) in an

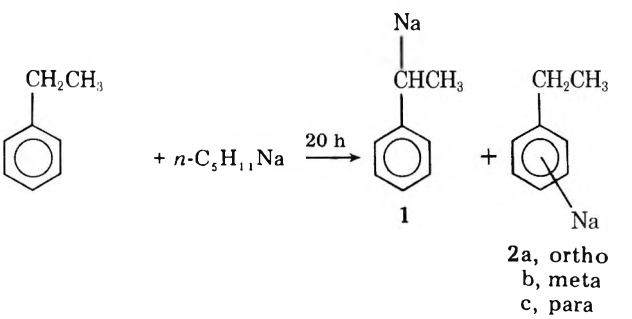

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Table I. Metalation of Ethylbenzene with *n*-Pentylsodium in the Presence of TMEDA as a Function of Time[a]

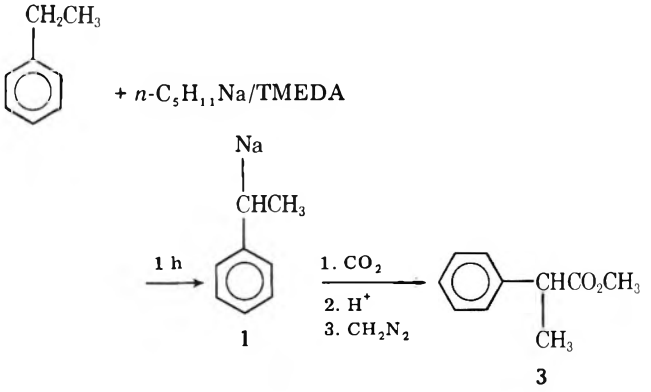
Time, min	Product distribution, %[b]				
	α	Ortho	Meta	Para	Di
5	12 (13)[c]	2 (2)	55 (57)	28 (25)	3 (3)
15	27 (31)	2 (2)	41 (38)	24 (21)	6 (8)
30	77 (87)	0 (0)	14 (7)	9 (6)	0 (0)
60	100 (100)	0 (0)	0 (0)	0 (0)	0 (0)

[a] The values reported in this table were obtained by removing and carbonating aliquots at 5-, 15-, and 30-min increments and carbonating the reaction after 60 min. [b] The yield of the combined crude esters was in excess of 95% for both sets of data. [c] Values in parentheses represent the results of a duplicate experiment.

overall yield of 46% after 20 h. At shorter reaction times, metalation occurred in a kinetically controlled process preferentially on the ring followed by a slow ring to side-chain isomerization.

Results and Discussion

The metalation of ethylbenzene with *n*-pentylsodium in the presence of TMEDA for 1 h gave *exclusively α-methylbenzylsodium* (**1**) *in a near quantitative yield*[6] based on the isolation of methyl 2-phenylpropanoate (**3**) upon carbonation



1 3

and esterification of the reaction. The identity of **3** was established by comparing its IR and NMR spectra and VPC retention time with an authentic sample of this compound. Practically all of the *n*-pentylsodium was consumed as adjudged by the trace quantity of methyl hexanoate observed in the gas chromatogram.[7] In the absence of TMEDA, metalation of ethylbenzene gave in our hands 41% of the meta isomer **2b**, 33% of the para isomer **2c**, and 26% of the α isomer **1** in an overall yield of 55% after 24 h.

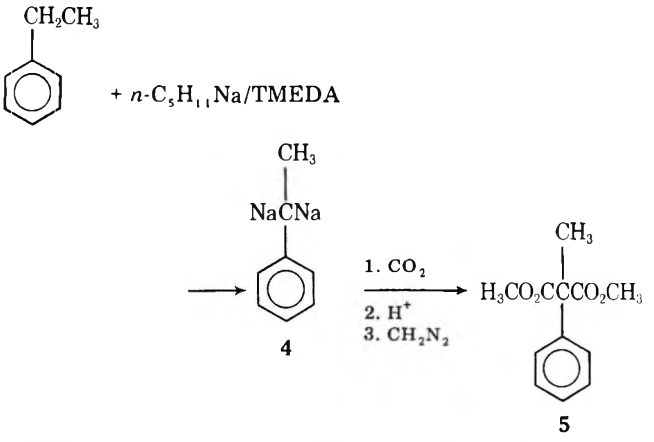
The metalation of ethylbenzene was also studied as a function of time by removing aliquots from the reaction. Table I shows that ethylbenzene was metalated with the *n*-pentylsodium/TMEDA reagent at short reaction times in a kinetically controlled fashion giving rise to ring and side-chain compounds (**1** and **2**) and a disodio compound. With time the ring compounds and the disodio compound rapidly equilibrated to α-methylbenzylsodium (**1**) in a thermodynamically controlled process. Presumably, the driving force for the equilibration was the stability derived from benzylic resonance. Previous work[5] has demonstrated that this equilibration is a transmetalation sequence occurring in the presence of excess ethylbenzene. It is important to note that the α isomer did not arise by the metalation of ethylbenzene with *n*-pentylsodium over the 1 h reaction period since the *n*-pentylsodium was practically all consumed in the first 5 min of reaction. This observation is based on the small quantity of methyl hexanoate found in the gas chromatogram of the 5-min sample using our usual method of analysis.

The disodio compound which formed at short reaction times was shown to be α,α-disodioethylbenzene (**4**) based on

Table II. Isomerization of *p*-Ethylphenylsodium[a] in the Presence of TMEDA[b]

Time, min	Product distribution, %[c]				
	α	Ortho	Meta	Para	Di
0[d]	0	0	0	100	0
5	4.5	trace	24.5	71	trace
15	21	2	39	38	0
30	61	2	20	13	4
60	100	0	0	0	0

[a] Prepared from *p*-bromoethylbenzene and sodium. [b] The values reported in this table were obtained by removing and carbonating aliquots at 0-, 5-, 15-, and 30-min increments and carbonating the reaction after 60 min. [c] The yield of the combined crude esters was 70% based on the starting *p*-bromoethylbenzene. [d] The data obtained at 0 min represent the isomer distribution prior to the addition of ethylbenzene and TMEDA.



4 5

the isolation of dimethyl methylphenylmalonate (**5**) after carbonation, esterification, and vacuum distillation of the reaction. The identity of **5** was established by comparing its IR and NMR spectra and VPC retention time with an authentic sample synthesized from dimethyl phenylmalonate via a malonic ester synthesis. Admittedly, we were surprised to find that dimetalation yielded a product in which both sodiums were on the benzylic carbon. One would have predicted that such a compound would be so reactive that it would isomerize to a monosodio compound before its isolation as the dimethyl ester. Presumably, the short term stability of **4** could be due to its insolubility in the reaction mixture, thus slowing its conversion to the isomer **1**. It is of interest to point out that compounds in which two metal atoms are on the same carbon are not without precedence in the literature. West and Jones[8] reported that lithiation of toluene employing *n*-butyllithium in the presence of TMEDA gave α,α,*p*-trilithiotoluene in addition to the mono- and dilithiotoluenes.

In a related experiment, a sample of pure *p*-ethylphenylsodium prepared from *p*-bromoethylbenzene and sodium was permitted to equilibrate in the presence of ethylbenzene and TMEDA. Table II shows that initially the *p*-ethylphenylsodium reverted to the α, ortho, and meta isomers in addition to the di compound. After 1 h these compounds equilibrated to the more thermodynamically stable α isomer **1**. These findings corroborate the data presented in Table I and attest once again to the rapid formation of the α isomer in the presence of TMEDA. In sharp contrast, Benkeser and coworkers[5] reported that the isomerization of either *o*-, *m*-, or *p*-ethylphenylsodium in the presence of ethylbenzene (no TMEDA) gave only a 62% to 88% conversion to the α isomer even after 20 h.

An interesting comparison can be made between our findings and the corresponding lithium system. Broaddus[9] reported that ethylbenzene was metalated by *n*-butyllithium

Table III

Ester	Synthetic mixture, mol %	VPC analysis, %
α	31	31
Ortho	8	8
Meta	24	24
Para	29	28
Di	9	9

activated with TMEDA to give 38% α-methylbenzyllithium and 9% o-, 36% m-, and 17% p-ethylphenyllithium after 0.5 h. However, after 6.5 h, the isomer distribution remained unchanged demonstrating that no ring to side-chain conversions were occurring. Thus, in the sodium system the reaction is initially kinetically controlled followed by a rapid isomerization of the ring isomers **2** to the thermodynamically more stable α isomer **1**. In contrast, in the lithium system, metalation occurs either in a strictly kinetically controlled sequence on the ring or isomerization of the kinetic products to the thermodynamically favored α isomer is too slow to be observed in the 6.5 h reaction period.

In summary, the rapid ring to side-chain isomerization giving rise to α-methylbenzylsodium, the high yield of metalation products, and the formation of α,α-disodioethylbenzene once again attests to the profound activating influence which TMEDA has on these reactions. Presumably, the organosodium reagents complex with the TMEDA producing very reactive metalating agents. With n-pentylsodium, this effect accounts for the high yield of metalation products and, possibly, the formation of α,α-disodioethylbenzene. Similarly, under the influence of TMEDA, the ring sodio compounds are activated as metalating agents, thus promoting the rapid ring to side-chain transmetalation sequence. The exclusive formation of α-methylbenzylsodium can be explained by complex formation between the benzylic sodium and the TMEDA producing a resonance or peptizing effect as discussed in our previous paper.[4]

Experimental Section

Organosodium reactions were run in a Morton flask fitted with a Stir-O-Vac (La Pine Scientific Co.) high-speed stirring apparatus under a positive nitrogen pressure. All glassware employed in these reactions was dried in an oven at 110 °C and flushed with nitrogen before use. n-Octane, 1-chloropentane, and ethylbenzene were purified by standard techniques. TMEDA was distilled from CaH_2 immediately before use. NMR spectra were obtained on a Hitachi Perkin-Elmer R20A spectrometer and IR spectra on a Perkin-Elmer 457 spectrometer.

Reference Compounds. Methyl 2-phenylpropanoate and methyl o-, m-, and p-ethylbenzoate were prepared by esterifying the corresponding carboxylic acids with diazomethane. 2-Phenylpropanoic acid was purchased from Aldrich Chemical Co. and o- and p-ethylbenzoic acids were prepared by reacting o- and p-bromoethylbenzene (Aldrich Chemical Co.) with magnesium followed by carbonation. m-Ethylbenzoic acid was synthesized from m-ethylaniline (Aldrich Chemical Co.) by an adaptation of a standard literature method.[10]

Dimethyl methylphenylmalonate was prepared by treating phenylmalonic acid (Aldrich Chemical Co.) with excess diazomethane followed by the reaction of the resulting dimethyl ester with sodium methoxide prepared from 1.7 g (0.074 mol) of sodium in 40 mL of anhydrous methanol. To the resulting solution was added 10.65 g (0.075 mol) of methyl iodide using an adaptation of a literature procedure.[11] The dimethyl methylphenylmalonate boiled at 98 °C (0.6 mm) [lit.[12] 144–147 °C (9 mm)] and gave the expected IR and NMR spectra.

Analytical Method. Metalation reactions were analyzed by carbonating the reaction mixtures and esterifying the resulting carboxylic acids with diazomethane. The resulting methyl esters were analyzed on a Perkin-Elmer Model 3920 gas chromatograph equipped with a thermal conductivity detector using a 12 ft × ⅛ in. Apiezon L column (15% on Chromosorb W) at a column temperature of 200 °C with a helium flow of ca. 50 cm^3/min. Analysis of an authentic mixture of methyl esters demonstrated the validity of the analytical technique as listed in Table III.

***n*-Pentylsodium.** To a vigorously stirred 9.2 g (0.4 mol) sodium dispersion in 125 mL of octane maintained at −10 to −20 °C was added 16.0 g (0.15 mol) of 1-chloropentane in 25 mL of octane over 1.5 h. The resulting n-pentylsodium was stirred for an additional 0.5 h at −10 to −20 °C to ensure complete reaction.

Metalation of Ethylbenzene with *n*-Pentylsodium in the Presence of TMEDA. To a n-pentylsodium sample in 150 mL of octane was added 31.8 g (0.3 mol) of ethylbenzene and 23.2 g (0.2 mol) of TMEDA. After the mixture stirred for 1 h at room temperature, carbonation was effected by pouring the reaction onto a dry ice–ether slurry. The resulting mixture was hydrolyzed followed by workup and esterification with diazomethane employing a previously described method.[4] VPC analysis of the crude product revealed that it was composed exclusively of methyl 2-phenylpropanoate. Distillation of this product gave 15.9 g (97% yield) of pure methyl 2-phenylpropanoate, bp 91 °C (6.5 mm) [lit.[13] 119 °C (22 (mm))], whose IR and NMR spectra were superimposable with a reference sample.

Metalation of Ethylbenzene with *n*-Pentylsodium in the Absence of TMEDA. Ethylbenzene was metalated with n-pentylsodium for 24 h in the absence of TMEDA at room temperature using the above procedure. A 55% yield of crude ethylbenzene methyl esters was realized consisting of 26% α, 41% meta, and 33% para isomers.

Metalation of Ethylbenzene with *n*-Pentylsodium in the Presence of TMEDA as a Function of Time. To a n-pentylsodium sample in 150 mL of octane was added 31.8 g (0.30 mol) of ethylbenzene and 23.2 g (0.2 mol) of TMEDA. Aliquots (20 mL) were removed and carbonated at 5-, 15-, and 30-min increments followed by carbonation of the reaction at 60 min. The results obtained upon workup, esterification, and VPC analysis of the samples appear in Table I. Additionally, the 5-min sample contained only trace quantities of n-pentylsodium based on the low concentration of methyl hexanoate in the gas chromatogram of this sample.

Isomerization of *p*-Ethylphenylsodium in the Presence of TMEDA. p-Ethylphenylsodium was prepared by the addition of 18.5 g (0.1 mol) of p-bromoethylbenzene to a 6.9 g (0.3 mol) sodium dispersion over 1.5 h. Initially the p-ethylbromobenzene solution was added to the sodium dispersion at room temperature until the reaction commenced as adjudged by the darkening of the mixture. At this point the flask was cooled to −10 to −20 °C. After the p-bromoethylbenzene was added, the mixture was stirred for an additional 0.5 h at −10 to −20 °C before a 20-mL aliquot was removed and carbonated prior to the addition of ethylbenzene and TMEDA to identify the isomer distribution at zero time. Ethylbenzene (26.6 g, 0.25 mol) and TMEDA (17.4 g, 0.15 mol) were then added to the flask. Aliquots (20 mL) were removed and carbonated at 5-, 15-, and 30-min increments followed by carbonation of the reaction at 60 min. The samples were worked up, esterified with diazomethane, and analyzed in the usual manner giving the results appearing in Table II.

Registry No.—1, 29706-16-9; **2a**, 65749-01-1; **2b**, 65749-02-2; **2c**, 65749-03-3; **3**, 31508-44-8; **4**, 65749-04-4; **5**, 65749-05-5; TMEDA, 110-18-9; ethylbenzene, 100-41-4; n-pentylsodium, 1822-71-5; p-bromoethylbenzene, 1585-07-5; methyl o-ethylbenzoate, 50604-01-8; methyl m-ethylbenzoate, 50604-00-7; methyl p-ethylbenzoate, 7364-20-7; 1-chloropentane, 543-59-9.

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Reactions of Methyl-Substituted Cyclopentanones with Lithium Aluminum Hydride and Methyllithium. Structural Determinations and Proton Nuclear Magnetic Resonance Study of the Reaction Products

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Four methyl-substituted cyclopentanones were reacted with lithium aluminum hydride in tetrahydrofuran and with methyllithium in ether at 0 °C. In general, secondary trans alcohols were formed preferentially with lithium aluminum hydride, while tertiary cis alcohols were obtained as the major product with methyllithium. In 2,5-dimethyl- and 2,2,5-trimethylcyclopentanones, the original preference of the cis alcohols was reversed when methyllithium was replaced with methylmagnesium iodide. The structures of the reaction products were determined by comparison with an authentic trans alcohol which was prepared from the hydroboration–oxidation of the corresponding olefin. ^{1}H NMR studies of the resultant alcohols are presented. The chemical shift of 1-H or 1-Me decreases as the number of methyl substituents increases; these chemical shifts are smaller in the trans alcohol series than those in the cis alcohols. An enormously large decrease in chemical shift, 1.25 ppm, was observed when 1-H was shielded by two *cis*-methyl groups at C-2 and C-5. The same phenomenon was observed for the 1-Me group. The vicinal coupling constants of 1-H were found to be 4.5 Hz for the cis alcohols and 8.0 Hz for the trans alcohols in the 2,5-dimethyl- and 2,2,5-trimethylcyclopentanol systems.

Enormous amounts of studies have been conducted on the stereochemical and conformational problems in the cyclohexyl[2] and norbornyl[3] systems. In the simple cyclopentyl system, only relatively few studies have been reported. Conformational analysis of cyclopentyl derivatives was reviewed in brief.[4] Solvolyses of secondary methyl-substituted cyclopentyl tosylates were reported.[5,6] Due to the similarity in bond strain in the cyclopentyl and norbornyl derivatives, Brown and co-workers have used the cyclopentyl derivatives as the model compounds for the norbornyl derivatives in the solvolyses reactions.[7] However, the basic informations of these cyclopentanols, such as the stereochemistry[8,9] of their formation from the corresponding ketones and the structural determination of these reaction products, were only studied briefly.[10] To bridge this gap, the stereochemical course of the addition of methyllithium and of lithium aluminum hydride to four methyl-substituted cyclopentanones and the structural determinations of the resultant alcohols are reported in this paper. The stereochemical courses of these reactions are analyzed and explained with an empirical equation and are to be reported later.[11] In that equation, the energy difference responsible for the stereochemical course of the lithium aluminum hydride reduction of a ketone is expressed in terms of steric strain and product stability controls. In the case of the methyllithium addition reaction, only the steric strain control is responsible for the stereochemistry.

Experimental Section

Materials. All the ketones used in this study were specially purchased from Chemical Sample Co. (Columbus, Ohio 43220) by Professor H. C. Brown and made available to the author (Table I). The purity of these ketones was better than 99%, and no further purification was attempted. Ethyl ether and tetrahydrofuran (THF) were reagent grade, dried with calcium hydride, and stored under positive nitrogen pressure before use. An ethereal solution of methyllithium (1.67 M) was obtained from Foote Mineral Co. (Exton, Pa. 19341).

General Procedure for the Addition of Methyllithium (MeLi). In a nitrogen-flushed and flame-dried flask, an ethereal MeLi solution (10 mmol) was cooled to 0 °C in an ice bath and was added to an ethereal solution of ketone (1 M, 10 mmol). After 3 h, the reaction was terminated by the addition of a saturated ammonium chloride solution (1 mL). The organic layer was decanted from the fine inorganic salt, dried over anhydrous magnesium sulfate or potassium bicarbonate, and analyzed directly by GLC[12] without further purification. For product isolation, a larger scale reaction (50 or 100 mmol) was conducted at room temperature and the products were isolated by preparative GLC.

1,2,4,4-Tetramethylcyclopentene. 1,2,4,4-Tetramethylcyclopentanols (79 g, 50 mmol) which were prepared from the reaction of 2,4,4-trimethylcyclopentanone with methylmagnesium iodide (MeMgI) were refluxed with iodine (20 mg) for 2 h. After separation by a preparative GLC, two olefins were obtained in a ratio of 18 to 82 with n^{20}D 1.4285 and 1.4354, respectively. Having a single vinyl proton in its ^{1}H NMR spectrum, the minor component was assigned to 1,3,3,5-tetramethylcyclopentene. The major one was 1,2,4,4-tetramethylcyclopentene according to its ^{1}H NMR spectrum (Table II). Anal. Calcd for C_9H_{16}: C, 87.02; H, 12.98. Found: C, 86.69; H, 12.98. Other olefins prepared by this method were 1,2,3-trimethylcyclopentene and 1,2,3,3-tetramethylcyclopentene. Anal. Calcd for C_8H_{14}: C, 87.19; H, 12.81. Found: C, 87.25; H, 12.77. Anal. Calcd for C_9H_{16}: C, 87.02; H, 12.98. Found: C, 87.02; H, 13.00.

Hydroboration–Oxidation of 1,2,3,3-Tetramethylcyclopentene. The olefin (2 mmol) was hydroborated and oxidized according to a literature method.[13] Two alcohols in a ratio of 16 to 84 were obtained after the reaction products were worked up. By comparing GLC retention times of the two alcohols which were obtained from the reaction of MeLi and the corresponding ketone, the minor alcohol from the hydroboration–oxidation of the olefin was found to be 1,2,2,*trans*-5-tetramethylcyclopentan-*r*-1-ol.[29] Other trans alcohols prepared by this method were *trans*-2-methylcyclopentan-1-ol, *trans,trans*-2,5-dimethylcyclopentan-*r*-1-ol, *cis,trans*-2,5-dimethylcyclopentan-*r*-1-ol, 1,*trans,trans*-2,5-trimethylcyclopentan-*r*-1-ol, 1,*cis,trans*-2,5-trimethylcyclopentan-*r*-1-ol, 2,2,*trans*-5-trimethylcyclopentan-*r*-1-ol, and 1,*trans*-2,4,4-tetramethylcyclopentan-*r*-1-ol (see Table III for ^{1}H NMR data).

2,5-Dimethylcyclopentyl Tosylhydrazone. This compound was prepared according to the method of Acharya and Brown.[14] The commercial 2,5-dimethylcyclopentanone (6 g, 53.5 mmol) in methanol (30 mL) was treated with *p*-toluenesulfonyl hydrazide (9.3 g, 50 mmol) in THF (50 mL) for 14 h at room temperature. The hydrazone crystal (12 g) gave mp 124–125 °C dec after recrystallization (methanol–hexane). Anal. Calcd for $C_{14}H_{20}N_2O_2S$: C, 59.97; H, 7.19; N, 9.99; S, 11.43. Found: C, 59.67; H, 7.19; N, 9.68; S, 11.45.

1,3-Dimethylcyclopentene. The hydrazone (11.43 g, 41 mmol) obtained above was treated with MeLi (82 mmol) in ether (40 mL) for 3 h at room temperature.[15] After hydrolysis, 1,3-dimethylcyclopentene (1.6 g) was obtained. Anal. Calcd for C_7H_{12}: C, 87.42; H, 12.50. Found: C, 87.67; H, 12.70. Also prepared by this method was 1,3,3-trimethylcyclopentene. Anal. Calcd for C_8H_{14}: C, 87.19; H, 12.80. Found: C, 87.25; H, 12.86.

Results and Discussions

Four methyl-substituted cyclopentanones were treated with MeLi[16] in ether and $LiAlH_4$ in THF at 0 °C. In all the reactions studied, the alcohols were produced in yields greater than 80% and were not isomerized, which are in agreement with the results reported in the literature. Dehydration of the

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Table I. ^{1}H NMR Spectroscopic Data of the Methyl-Substituted Cyclopentanones

Methyl-substituted cyclopentanones	Registry no.	n^{20}D	δ, ppm (J, Hz) 2-Me	3- or 4-Me	5-Me
2-Methyl	1120-72-5	1.4354	1.05 (d, 6)		
cis-2,5-Dimethyl	6672-39-5	1.3415	1.05 (d, 6)		
trans-2,5-Dimethyl	32476-60-1		1.10 (d, 6)		
2,2,5-Trimethyl	4573-09-5	1.4288[a]			
		1.4289	0.94, 1.03		1.08 (d, 6.5)
2,2,4-Trimethyl	4694-12-6	1.4300	0.97, 1.02	1.12 (d, 6)	
2,4,4-Trimethyl		1.4320	1.03 (d, 6.5)	1.07, 1.15	
2,2,4,4-Tetramethyl	4694-11-5	1.4305	1.05	1.12	
2,2,5,5-Tetramethyl	4541-35-9	1.4288[b]	1.00		1.00
		1.4278			

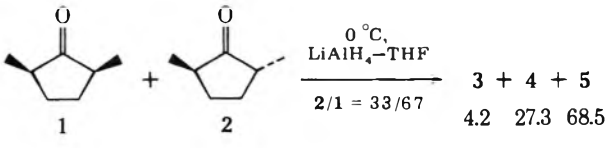
[a] Dr. K. W. Greenlee of Chemical Sample Co. made this value available to the author through Professor H. C. Brown. [b] A. Haller and R. Cornabert, *Bull Soc. Chim. Fr.*, **33**, 1724 (1926).

Table II. ^{1}H NMR Spectroscopic Data of the Methyl-Substituted Cyclopentenes

Methyl-substituted cyclopentene[a]	Registry no.	n^{20}D	1-Me	δ, ppm (J, Hz) 2-H	2-Me	3-H	3-Me	4- or 5-Me
1-Methyl	693-89-0	1.4335	1.72	5.23 ($W_{1/2}$ = 6)				
1,3-Dimethyl	62184-82-1	1.4298	1.67	5.13		2.68	0.95 (d, 6)	
1,2,3-Trimethyl	473-91-6	1.4323[b]	1.57		1.57		0.97 (d, 6)	
1,3,3-Trimethyl	57497-14-0		1.65	5.06			1.00	
1,2,3,3-Tetramethyl	65378-75-8	1.4426	1.57		1.48		0.95	
1,2,4,4-Tetramethyl	65378-76-9	1.4354	1.53		1.53	2.05		1.03
1,3,3,5-Tetramethyl	65378-77-0	1.4285	1.61	4.98			1.03, 0.96	1.00

[a] All the new olefins give satisfactory elemental analyses and are reported in the text. [b] At 25 °C.

Scheme I



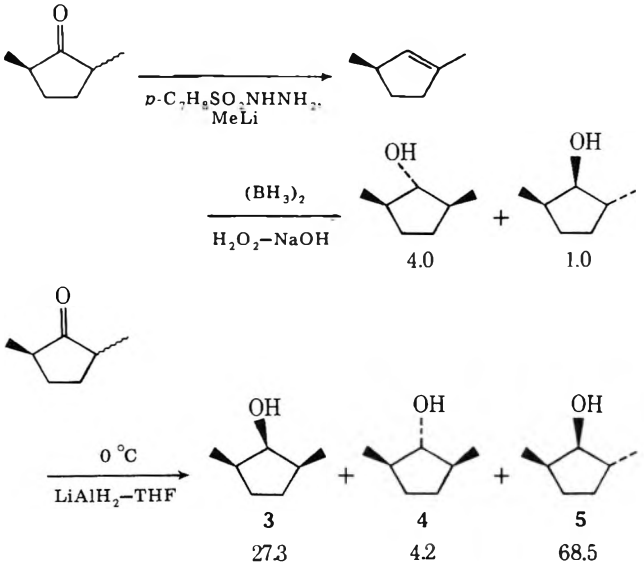
tertiary alcohol during GLC analysis was not observed, as judged from the absence of unknown or olefinic compounds in the chromatogram. The epimeric pair of alcohols was assumed to have equal area response in the GLC analysis.[17]

To determine the structure of these reaction products, an authentic trans alcohol was prepared from the hydroboration–oxidation of the corresponding olefin. In general, the more stable trans alcohols were the preferred reaction products when $LiAlH_4$ was reacted with the ketones. With methyllithium, these cyclopentanones yielded predominantly the cis alcohols with the two methyl groups in a trans relationship.

2-Methylcyclopentyl System. Both secondary[18] and tertiary[19] trans alcohols from 2-methylcyclopentanone have been reported in the literature. Hence structures of the reaction products were determined by comparing their retention times in GLC analysis with the corresponding authentic samples. Using methylmagnesium chloride, Hennion and O'Shea[8] reported 70% of 1,*trans*-2-dimethylcyclopentan-*r*-1-ol from 2-methylcyclopentanone in ether. In our hands, we obtained 67% of the trans alcohol at 0 °C. With methylmagnesium iodide, however, the ketone yielded 52% of the trans alcohol.[16]

2,5-Dimethylcyclopentyl System. The commercial ketones were a mixture of *cis*- and *trans*-dimethylcyclopentanones in a ratio of 33 to 67 according to GLC analysis. Separation of these two ketones by distillation or preparative GLC was unsuccessful. Hence, all the studies in this system were carried out with the isomeric ketone mixture. ^{1}H NMR spectroscopic analysis of the mixture indicated that the two methyl groups of the major component 1 had chemical shift

Scheme II



at a lower field than those of the minor component **2**, 1.10 vs. 1.05 ppm (J = 6 Hz, d). Since the two *cis*-dimethyl groups were expected to be more shielded owing to the bond anisotropy of the C–CH_3 bond,[20] the minor component was believed to be *cis*-2,5-dimethylcyclopentanone. This assignment was further supported by the product distribution of the following reactions. With $LiAlH_4$, the *trans*-dimethyl ketone is expected to yield only one alcohol, **5**, whereas the *cis*-dimethyl ketone would form two isomeric alcohols, **3** and **4**. The ratio of these alcohols, **5**/(**3** + **4**), would correspond to the ratio of the two starting ketones, **1**/**2**, or 67/33 (Scheme I).

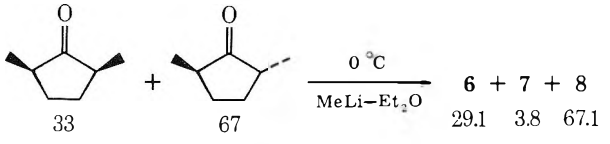
In the actual experiments, three alcohols, **3**–**5**, were obtained from the two starting ketones in 4.2, 27.3, and 68.5% yields, respectively (Scheme I). Unreacted ketones recovered from the reaction showed the same ratio as that of the two starting ketones, **1**/**2** = 67/33, indicating no isomerization.

Table III. Physical Properties and ^{1}H NMR Data of Methyl-Substituted Cyclopentanols

Substituted cyclopentanol	Registry no.	δ, ppm (J, Hz) 1-H	1-Me	2-Me	4-Me	5-Me	n^{20}D	Mp of OPNB, °C[d]
1-H	96-41-3	4.20, 4.18[e]						
cis-2-Methyl	25144-05-2	3.99 (m, $W_{1/2}$ = 4)		0.97 (d, 7)				
trans-2-Methyl	25144-04-1	3.63 (m, $W_{1/2}$ = 9)		0.93 (d, 7)				
cis,cis-2,5-Dimethyl[a]	65404-79-7	3.65 (t, 4.5)		1.00 (d, 7)		1.00 (d, 7)		
cis,trans-2,5-Dimethyl[a]	65378-78-1	3.53 (t, 5.0)		0.95 (d, 7)		0.98 (d, 7)		
trans,trans-2,5-Dimethyl[a]	63057-29-4	2.97 (t, 8.0)		0.92 (d, 7)		0.92 (d, 7)		
2,2,*cis*-5-Trimethyl[b]	65378-79-2	3.34 (d, 4.5)		0.97, 1.00		0.96 (d, 7)		
12,2,*trans*-5-Trimethyl[b]	65378-80-5	3.03 (d, 8.0)		0.97, 1.00		0.90 (d, 7)		
cis-2,4,4-Trimethyl[c]	57905-84-7	4.02[f]		0.95 (d, 7)	0.97, 1.11			
trans-2,4,4-Trimethyl[c]	57905-83-6	3.60[g]		1.02 (d, 7)	1.00, 1.07			
1-Methyl	1462-03-9		1.30					82–83
1,*cis*-2-Dimethyl	16467-13-3		1.21	0.91 (d, 6)			1.4505 1.4506[h]	99.5–100.5
1,*trans*-2-Dimethyl	16467-04-2		1.10	0.86 (d, 6)			1.4538 1.4541[h]	116.5–117
1,*cis,cis*-2,5-Trimethyl	65378-81-6		1.06	0.87 (d, 6)		0.92 (d, 6)	1.4463	113–114
1,*cis,trans*-2,5-Trimethyl	65378-82-7		1.06	0.87 (d, 6)		0.90 (d, 6)	1.4543	104–105
1,*trans,trans*-2,5-Trimethyl	65378-83-8		0.80	0.89 (d, 6)		0.89 (d, 6)	1.4557	116–117
1,2,2,*cis*-5-Tetramethyl	65378-84-9		0.99	0.86, 0.99		0.91 (d, 6)	1.4511	121.5–123.5
1,2,2,*trans*-5-Tetramethyl	65378-85-0		0.87	0.93, 0.93		0.92 (d, 6)	1.4603	108–109
1,*cis*-2,4,4-Tetramethyl	58493-56-4		1.20	0.93 (d, 6)	0.98, 1.11		1.4370	106–107
1,*trans*-2,4,4-Tetramethyl	58493-55-3		1.09	0.92 (d, 6)	1.00, 1.09		1.4453	109–110

[a] Calculated from the cis and trans alcohol mixture. Anal. Calcd for $C_7H_{14}O$: C, 73.63; H, 12.36. Found: C, 73.67; H, 12.28. [b] Calculated from the cis and trans alcohol mixture. Anal. Calcd for $C_8H_{16}O$: C, 74.13; H, 12.99. Found: C, 73.95; H, 12.92. [c] Calculated from the cis and trans alcohol mixture. Anal. Calcd for $C_8H_{16}O$: C, 74.13; H, 12.99. Found: C, 73.99; H, 13.02. [d] For solvolysis purpose, *p*-nitrobenzoates (OPNB) of all these tertiary alcohols were prepared, and their elemental analyses were found to be satisfactory according to Professor H. C. Brown and Dr. F. J. Chloupek of Purdue University, 1963. [e] H. Booth and J. H. Little, unpublished observation quoted by H. Booth in ref 19. [f] Appears as a quartet with spacing of 4.5 Hz. [g] Appears as a quartet with spacing of 8.0 Hz. [h] Reference 8.

Scheme III



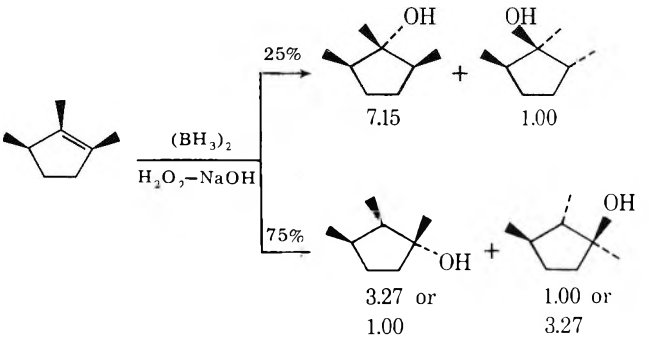
Hence, appropriate grouping of the observed products' distribution should yield a ratio of about 67/33. The only way to group the experimental result is to have **3** and **4** from the same starting ketone and **5** from the other, **5**/(**3** + **4**) = 68.5/31.5. Consequently, one can readily conclude that **5** was from the ketone **1** and had two methyl groups in a trans relationship. The alcohols **3** and **4** are from the ketone **2** and these two compounds had the two methyl groups in a cis relationship.

Having identified compound **5** as *cis,trans*-2,5-dimethylcyclopentan-*r*-1-ol, compound **4** was identified as *trans,trans*-2,5-dimethylcyclopentan-*r*-1-ol by the use of hydroboration–oxidation of 1,3-dimethylcyclopentene which gave both **4** and **5** (Scheme II). Hence compound **3** was *cis,cis*-2,5-dimethylcyclopentan-*r*-1-ol.

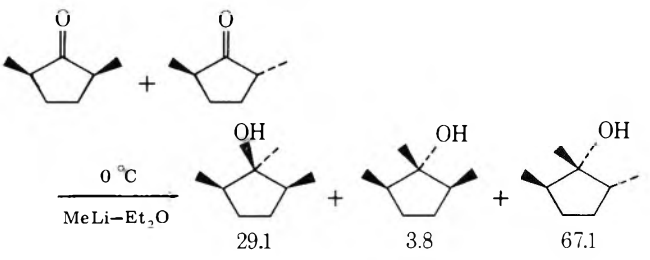
Addition of methyllithium to the *cis*- and *trans*-2,5-dimethylcyclopentanone mixture yielded three alcohols, **6–8**, in a ratio of 29.1, 3.8, and 67.1%, respectively (Scheme III).

As explained earlier, 67% of the starting ketones was 2,5-*trans*-dimethylcyclopentanone; alcohol **8** was readily concluded to be 1,*cis,trans*-2,5-trimethylcyclopentan-*r*-1-ol. From the hydroboration–oxidation raction of 1,2,3-trimethylcyclopentene, four compounds were obtained (Scheme IV). Two of them in a ratio of 7.15 to 1.0 had the same retention times as those of **7** and **8**, respectively. The other two in a ratio of 3.27 to 1.0 were not identified. Consequently, alcohol **7** was identified as 1,*trans,trans*-2,5-trimethylcyclopentan-*r*-1-ol

Scheme IV



Scheme V



and compound **6** as 1,*cis,cis*-2,5-trimethylcyclopentan-*r*-1-ol.

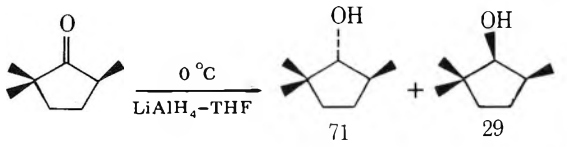
Thus, the structures of the three alcohols from the reaction of methyllithium and 2,5-dimethylcyclopentanone become clear and are summarized in Scheme V.

As shown in Scheme VI, as the number of methyl substituents increases, both configurational (trans/cis) and positional

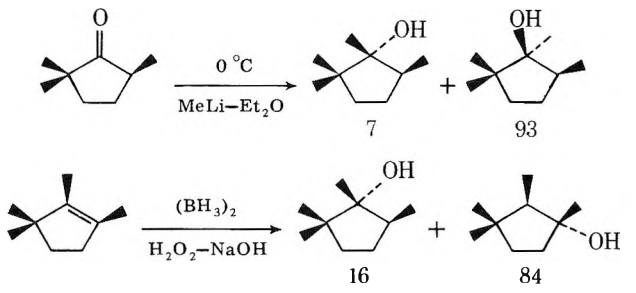
Scheme VI

	C-2 trans/cis	C-1 trans/cis	C-1/C-2
$R_1 = R_2 = H$	2.24	1.26	1.1
$R_1 = CH_3$; $R_2 = H$	4.00		0
$R_1 = R_2 = CH_3$	7.15	3.27 or 1/3.27	3.0

Scheme VII



Scheme VIII



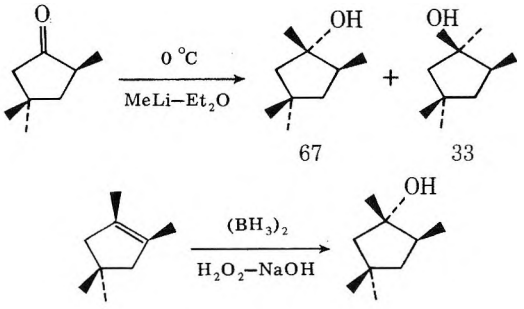
(C-1/C-2) selectivity increase in the hydroboration–oxidation of 3-methylcyclopentene[21] derivatives. Apparently, the methyl substituent in the olefinic bond makes the 3-methyl group exert greater influence on the steric selectivity of the reaction.

Grignard reactions of the 2,5-dimethylcyclopentanones are interesting yet puzzling;[16] the observed results are not understood at the present time. While MeMgCl reacted with the ketones to give a comparable result—**6** (27%), **7** (6%), and **8** (67%) to methyllithium—MeMgI, however, resulted in a different result—**6** (7%), **7** (26%), and **8** (67%). The *cis*-dimethyl ketone forms **7** as the major product with MeLi and MeMgCl, whereas with MeMgI, **6** is the preferred one.

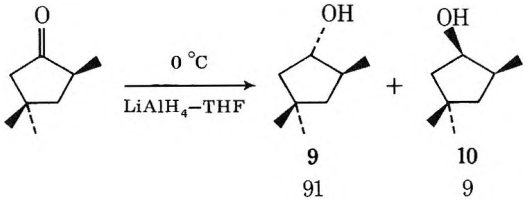
2,2,5-Trimethylcyclopentyl System. $LiAlH_4$ reduction of 2,2,5-trimethylcyclopentanone yielded two alcohols in a 71 to 29 ratio (Scheme VII). The major reaction product was found to be 2,2,*trans*-5-trimethylcyclopentan-*r*-1-ol, after comparing its retention time in the GLC analysis with that of an authentic trans alcohol. The trans alcohol was prepared by the hydroboration–oxidation of 1,3,3-trimethylcyclopentene. The olefin was prepared by the elimination of the tosylhydrazone of the starting ketone.

Addition of methyllithium to the ketone yielded merely 7% of 1,2,2,*trans*-5-tetramethylcyclopentan-*r*-1-ol, in addition to 93% of the cis alcohol (Scheme VIII). The trans alcohol was the minor one of the two reaction products of the hydroboration–oxidation reaction of 1,2,3,3-tetramethylcyclopentene. The olefin was obtained from pyrolytic dehydration of 1,2,2,5-tetramethylcyclopentanols. As in the preceding system, methylmagnesium iodide reacted with the ketone to form 1,2,2,*trans*-5-tetramethylcyclopentan-*r*-1-ol preferentially (72%). Again we do not fully understand the cause of this reversal in the stereochemistry of the reactions when methyllithium is replaced with MeMgI.[16]

Scheme IX



Scheme X



2,4,4-Trimethylcyclopentyl System. At first glance this system could be treated as a 2-methylcyclopentyl system; however, this was found to be oversimplified. The 2,4,4-trimethylcyclopentyl system was found to be the most complex of the four systems studied.

Addition of methyllithium to the ketone gave trans alcohol as the major component (Scheme IX). The trans alcohol was identified by comparison with an authentic sample of 1,*trans*-2,4,4-tetramethylcyclopentan-*r*-1-ol, which was obtained from the hydroboration–oxidation of 1,2,4,4-tetramethylcyclopentene.

The fact that a trans alcohol was the major reaction product of methyllithium with 2,4,4-trimethylcyclopentanone deserves further comment. With this ketone, methylmagnesium iodide also yielded trans alcohol as the major product (78%). Unlike the preceding three systems in which the stereochemistry of the reaction was controlled by the methyl group at the neighboring β position, the stereochemistry of the reaction in the present system is apparently governed by one of the methyl groups at C-4. Conceivably, the methyl group which is trans to the methyl group at C-2 is forced to take a quasi-axial conformation in order to minimize 1,3 interaction between the two *cis*-methyl groups at C-2 and C-4. One sees a similarity in 3,3,5-trimethylcyclohexanone in which the axial methyl group at C-3, but not the sole methyl group at C-5, plays the key role in the determination of conformational energy[2] and the stereochemistry of the reaction.[22]

Lithium aluminum hydride reduction of 2,4,4-trimethylcyclopentanone was highly selective; 91% of *trans*-2,4,4-trimethylcyclopentanol (**9**) was obtained in this reaction (Scheme X). The high stereoselectivity could be attributed to the confluence of both steric strain control and product stability control.[11]

Structural proofs of the reaction products by the methods used in the preceding three systems were unsuccessful. All attempts to prepare and isolate 1,4,4-trimethylcyclopentene by the elimination of 2,4,4-trimethylcyclopentyl tosylates (1) with sodium methoxide in methanol or Me_2SO, (2) with potassium *tert*-butoxide in *tert*-butyl alcohol or Me_2SO, or (3) by refluxing the alcohols with potassium bisulfate resulted in the formation of two olefins; they were assigned as 1,4,4- and 3,3,5-trimethylcyclopentenes in a ratio of 45 to 55, respectively, according to ^1H NMR and GLC analyses. Separation of the two olefins by preparative GLC, unfortunately, was unsuccessful. Due to the expected steric effect of the methyl

group at C-2, elimination of 2,4,4-trimethylcyclopentyl tosylhydrazone was not tried.

cis- and *trans*-2,4,4-trimethylcyclopentan-*r*-1-ols were separated and collected by analytical GLC. Structural determination of these two alcohols was finally accomplished by comparing the chemical shift of 1-H with those of the alcohols mentioned earlier and the europium shift parameter S[23] (or equimolar paramagnetic shift value) of 2-H and 2-Me (Table IV). In Table III, ^{1}H NMR data of all these alcohols are compiled.

As shown in Table III the chemical shifts of 1-H in the secondary alcohols bear a sensitive relationship to the change in the surrounding environment much more so than those of the 2-methyl group. The chemical shifts of 1-H of the cis alcohols are invariably more deshielded by 0.3–0.4 ppm. This could be attributed to the diamagnetic shift of the neighboring 2-methyl group.[20]

The chemical shift of 1-H in compound **9** is 3.60 ppm, whereas that in compound **10** is 4.02 ppm. This agrees well with the general pattern of the cyclopentyl system described below. Chemical shifts of 2-H's of this system merge with other ring protons and were not determined. However, addition of europium shift reagent (Table IV) reveals that the S value of 2-H in compound **9**, 16 ppm, is larger than that in compound **10**, 12.5 ppm. This points out that 2-H in compound **9** is cis to the OH group and that in compound **10** is trans to the OH group.

The 2-methyl group in compound **9**, although less shielded than **10**, 1.02 vs. 0.95 ppm, is expected to be less sensitive to the addition of shift reagent; the S value of the 2-methyl group in compound **9** is 9.6 ppm, whereas that in compound **10** is 15.5 ppm. The S value of 2-H is larger than that of 2-Me in the compound **9**, whereas in compound **10** 2-Me has a larger S value than has 2-H. This means that in compound **9** 2-H is nearer to the OH group than is 2-Me, whereas in compound **10** 2-Me is closer than is 2-H to the hydroxyl group. All these evidences indicate that 2-Me in compound **9** is trans to the OH group and that compound **10** has a cis relationship between the OH group and 2-Me group.

^{1}H NMR Spectroscopy of Methyl-Substituted Cyclopentanols. From Table III one sees a gradual decrease of the chemical shift of 1-H or that of the 1-Me group as the number of methyl substituents at C-2 or C-5 increases, irrespective of its stereochemistry. The larger decrease in the chemical shift of 1-H or 1-Me in the trans alcohol series is caused apparently by the combined effects of the electron-releasing effect of methyl substituents and of the diamagnetic effect of the C–CH_3 bond.

As one would expect, the chemical shifts of 1-H of the secondary trans alcohols are smaller than those of the cis alcohols due to the diamagnetic effect of the neighboring methyl group in the trans series. The differences in the chemical shift between cis and trans alcohols are in the order of 0.3 ppm. Likewise, upfield shifts are also observed for the 1-Me group of the tertiary trans alcohol. However, the differences in the chemical shift of the cis and trans tertiary alcohols are below 0.1 ppm.

In those cases where there are two methyl substituents, one at C-2 and one at C-5, the chemical shift of 1-H is reduced by 0.55 ppm in the *cis,cis*-dimethyl alcohol and 1.23 ppm in the *trans,trans*-dimethyl alcohol, compared to that of the parent unsubstituted cyclopentanol. Such an enormous upfield shift by the double shielding of the neighboring *cis*-dimethyl groups in the *trans,trans*-alcohol is larger than that observed in the cyclohexyl system.[24,25]

In the tertiary system, the double shielding of the 1-Me group by the neighboring *cis*-dimethyl groups causes a 0.5-ppm upfield shift, compared to that of the parent 1-methylcyclopentanol.

Table IV. Paramagnetic Shift (S) of Compounds 9 and 10

Compd	S, ppm 2-H	2-CH_3	4-CH_3
9	16.0	9.6	6.0, 3.8
10	12.5	15.5	7.1, 5.1

The chemical shift of the 2-methyl group is less sensitive to the stereochemistry of the neighboring hydroxyl group at C-1. In general, the chemical shift of the 2-methyl group in the cis alcohol is only about 0.05 ppm less shielded than that of the trans alcohol. The smaller difference in the chemical shift between cis and trans alcohols is, however, unexpected. In the 2,4,4-trimethyl- and 1,2,4,4-tetramethylcyclopentyl systems, the difference in the chemical shift of the 2-methyl group between the cis and trans alcohols is reversed in the former or negligible in the latter. This abnormality could be attributed to a conformational change.

Coupling constants of vicinal protons in the cyclohexyl system have been well studied and successfully applied to evaluate ring torsional angles[26] and conformation.[20] In the cyclopentanol system, a systematic evaluation of the coupling constant remains highly desirable. Furthermore, "... there is hardly an example, involving a simple saturated five-membered ring, in which the shape of the molecule can be said to have been proved satisfactorily by the use of NMR spectra".[20] So often, assignments of J_{trans} and J_{cis} are done in order to make the corresponding dihedral angles (calculated according to the Karplus equation) agreeable with a model of the relatively flattened ring conformation.[27,28]

In this study, structural determinations of the cyclopentanol derivatives were made by an independent approach with one exception being the 2,4,4-cyclopentanols, which were characterized by the use of ^{1}H NMR spectroscopy. Therefore, assignments of J_{cis} and J_{trans} are based on proven structures without the use of ^{1}H NMR data.

In *cis,cis*-2,5-dimethyl- and *trans,trans*-2,5-dimethylcyclopentan-*r*-1-ols, the 1-H couples to two symmetrical protons at C-2 and C-5 with coupling constants of 4.5 and 8.0 Hz, respectively. In 2,2,*cis*- and *trans*-5-trimethylcyclopentan-*r*-1-ols, J_{cis} and J_{trans} are again 4.5 and 8.0 Hz, respectively.

In the cases where 1,3 interaction is not severe, one would expect a gradual flattening of the ring and decrease of J_{cis} and J_{trans}. In *cis,trans*-2,5-dimethylcyclopentan-*r*-1-ol, only one coupling constant of 5 Hz was obtained at room temperature. In the less crowded 2-methylcyclopentanol system, the rings are expected to flatten further. In this system the 1-H appeared as a multiple signal and the coupling constants could not be evaluated. The observed $W_{1/2}$ (4 Hz) indicates a smaller J_{cis}.

In the 2,4,4-trimethylcyclopentanol system, the 1-proton couples to three different protons at C-2 and C-5, and an AMXX′ spectrum would be expected. In reality, the spectra in both the cis and trans alcohols appear as quartets with spacing of 4.5 and 7.5 Hz, respectively. Furthermore, in this system, there are two types of 1,3 interaction, 4-Me with 2-Me and 4-Me with 1-OH. Hence, the molecule in the cis or trans alcohol is expected to be more mobile than in the 2,5-dimethyl- or 2,2,5-trimethylcyclopentanol systems. The observed quartet spectra may be brought about by the averaging of dihedral angles. Detailed study of this system has been undertaken and will be published later.

Acknowledgment. First the author is particularly grateful to Professor H. C. Brown of Purdue University for his kind encouragement and generous supply of these cyclopentanones; without these this work would not have been possible. Next the author is indebted to Dr. Kazuo Tori of Shionogi Research

Lab., Shionogi & Co., Japan, for his suggestions and help in identifying the *cis*- and *trans*-2,4,4-trimethylcyclopentanols.

Registry No.—2,5-Dimethylcyclopentyl tosylhydrazone, 65378-86-1; 2,2,5-trimethylcyclopentyl tosylhydrazone, 65378-87-2; lithium aluminum hydride, 16853-85-3; methyllithium, 917-54-4.

References and Notes

(1) Address correspondence to the National Science Council.
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New Mass Spectrometric Rearrangements Involving Silicon. A Study of Trimethylsilylated Di- and Polyamines and Their Isotopically Labeled Analogues

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The electron-impact spectra of six trimethylsilylated di- and polyamines and 12 deuterium labeled analogues have been examined. Structures of several ions in the spectra of the unlabeled compounds, unexplained by simple fragmentations, have been assigned consistent with the observed changes in *m/e* values of the corresponding labeled ions. The composition of these ions suggests molecular decomposition processes not previously reported for trimethylsilylated compounds. These include a McLafferty rearrangement involving hydrogen migration to an even-electron siliconium center and a 1,5-alkyl migration of a methyl group initially bonded to silicon. The primary impetus for these rearrangements is the high reactivity of the silicon center; however, in addition, the proximities of the various amine centers affect the fragmentation processes.

Trimethylsilyl (TMS) groups are widely utilized for protection of polar functions during synthetic and chromatographic (including coupled gas chromatography–mass spectrometry) procedures, and the mass spectra of a large number of trimethylsilylated compounds have been recorded. In many instances, primarily involving *O*-trimethylsilyl compounds, electron-impact induced rearrangements have been described which involve interaction between a TMS group and a second functional group.[1] Such interactions between functional groups are also observed in mass spectra of alkanes possessing multiple polar substituents,[2] e.g., the di- and polyamines[3] and their N-substituted derivatives.[4]

In view of our interest in the analysis of physiological polyamines using GC–MS techniques[5] and the impressive detection sensitivity reported for trimethylsilyldiamines,[6] we have investigated extensively the electron-impact mass spectrometry of TMS derivatives of selected di- and polyamines. Mass spectrometric data for the compounds studied (1–18, Chart I), which include a variety of specifically deuterated analogues, are recorded in Tables I–VI.

The novel rearrangements described in this study are excellent examples of the versatility of silicon-containing compounds upon activation by electron impact and provide some interesting insights into the *N*-trimethylsilyl group.[7] The migration of a TMS methyl group to a γ-methylene carbon represents one of a limited number of authenticated 1,5-alkyl rearrangements.[9-11] Another decomposition process is a McLafferty rearrangement, different in that a hydrogen migrates to a dimethylsiliconium center.

Results and Discussion

Isotopic Analyses. The per cent deuterium incorporation into the di- (**7** and **10**) and polyamines (**13**, **16**, and **17**) was determined from the intensities of ions in the $[M - CF_3\cdot]^+$ ion

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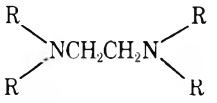
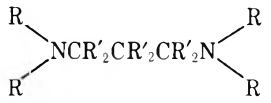
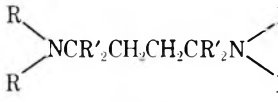
Chart I



1, R = TMS
2, R = TMS-d_9

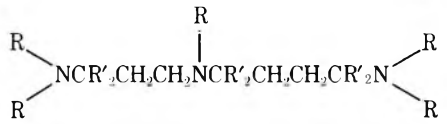


3, R = TMS; R′ = H
4, R = TMS; R′ = ^{2}H
5, R = TMS-d_9; R′ = H

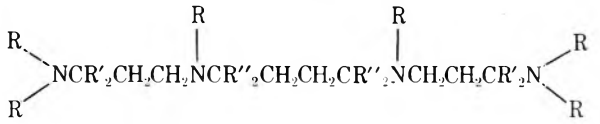


6, R = TMS; R′ = H
7, R = TMS; R′ = ^{2}H
8, R = TMS-d_9; R′ = H

9, R = TMS; R′ = H
10, R = TMS; R′ = ^{2}H
11, R = TMS-d_9; R′ = H

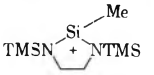


12, R = TMS; R′ = H
13, R = TMS; R′ = ^{2}H
14, R = TMS-d_9; R′ = H



15, R = TMS; R′ = R″ = H
16, R = TMS; R′ = ^{2}H; R″ = H
17, R = TMS; R′ = R″ = ^{2}H
18, R = TMS-d_9; R′ = R″ = H

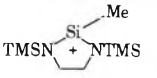
Table I. Principal Ions Observed in Mass Spectra of Tetra(trimethylsilyl)-1,2-diaminoethanes 1 and 2

Ion, *m/e*		Relative intensity,[a] %	Structure assignment
1	2 (d_{36})		
348	384	0.1	$M^+\cdot$
333	377	2	$[M-Me]^+$
259	283	4	$(TMS)_2NCH_2CH_2{=}N{-}Si^+Me_2$
245	266	6	
174	192	100[b]	$CH_2{=}N(TMS)_2$
100	109	6	$HC{\equiv}N^+TMS$
86	92	13	$CH_2{=}NSi^+Me_2$

[a] Relative intensities are for ions in the spectrum of the nondeuterated analogue 1. [b] Σ_{80} = 53%.

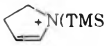
isotope cluster in spectra of the respective trifluoroacetylated derivatives.[5] This particular ion cluster appeared, in all instances, to be observable free from interference by ions resulting from other competing processes. The calculated per cent deuterium content (following a correction for natural abundance ^{13}C) at the designated sites was 96–97% for each of the di- and polyamines. This high level of isotopic enrichment greatly facilitated analysis of the mass spectra since essentially all of the ion intensity was expressed in the $^2H_{max}$ and $^2H_{max-1}$ ions. For example, for compound **17** (97% $^2H_8$) the intensities of ions in $^2H_{max}$ ion clusters are $^2H_8$, 77%, and $^2H_7$, 20%; for compounds **7, 10, 13,** and **16,** which possess equally high isotopic enrichments and fewer enriched sites, $^2H_{max}$ ions account for more than 80% of the total intensities of ion isotope clusters. As a result, the isotopic contents of ions in the various mass spectra can be determined qualitatively by inspection. The fact that the calculated isotopic enrichment levels of certain ions produced by simple fragmentation processes appear to be slightly lower than those calculated using the $^2H_{max}$ ions noted suggests that hydrogen scrambling may be occurring to a limited extent; it does not interfere with the analyses presented.

Table II. Principal Ions Observed in Mass Spectra of Tetra(trimethylsilyl)-1,3-diaminopropanes 3–5

Ion, *m/e*			Relative intensity,[a] %	Structure assignment
3	4 (d_6)	5 (d_{36})		
362	368	398	0.8	$M^+\cdot$
347	353	380	0.6	$[M-Me]^+$
273	278	297	0.2	$(TMS)_2NCH_2CH_2{-}CH{=}NSi^+Me_2$
259	265	297	1	
201	206	219	65	$\cdot CH_2CH_2CH{=}N(TMS)_2$
174	176	192	100[b]	$CH_2{=}N^+(TMS)_2$
172	175	187	26	$CH_2{=}CHN(TMS){-}Si^+Me_2$
160	163	175	48	$CH_2{=}N^+(TMS)Si{-}Me_2H$
130	130	142	5	$[(Me_2Si)_2N]^+$
100	101	109	6	$HC{\equiv}N^+TMS$
86	88	92	14	$CH_2{=}NSi^+Me_2$

[a] Relative intensities are for ions in the spectrum of the nondeuterated analogue 3. [b] Σ_{80} = 27%.

Table III. Principal Ions Observed in Mass Spectra of Tetra(trimethylsilyl)-1,4-diaminobutanes 6–8

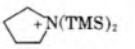
Ions, *m/e*			Relative intensity,[a] %	Structure assignment
6	7 (d_4)	8 (d_{36})		
376	380	412	2	$M^+\cdot$
361	365	394	5	$[M-Me]^+$
214	217	232	14	
200	204	215	8	$CH_2{=}CHCH_2CH_2N{-}(TMS)Si^+Me_2$
187	188	205	2.3	$CH_2{=}CHN^+(TMS)_2$
174	176	192	100[b]	$CH_2{=}N^+(TMS)_2$
130	130	142	4.7	$[(Me_2Si)_2N]^+$
100	101		4.5	$HC{\equiv}N^+TMS$
86	88	92	9	$CH_2{=}NSi^+Me_2$

[a] Relative intensities are for ions in the spectrum of the nondeuterated analogue 6. [b] Σ_{80} = 39%.

Rearrangements. A variety of electron-impact induced rearrangements are known which involve trimethylsilyl groups. These rearrangements often involve migration of groups containing a heteroatom to the charged silicon center generated by the loss of a TMS methyl radical.[1] Phenyl groups have also been shown to migrate to the silicon center under electron impact.[1a,12] Groups have been shown to migrate from both near and remote positions, relative to the TMS group, showing little sensitivity to ring size for the transition state.

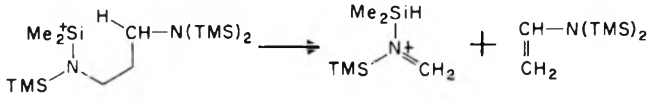
McLafferty-Type Rearrangements. McLafferty rearrangements have been extensively reviewed;[13] the reported participation of TMS groups in McLafferty rearrangements has been limited to that of a migration species. Migrations of a TMS group to carbonyl oxygen and sp^2 carbon have been reported.[14] The mass spectrum of trimethylsilylated 1,3-diaminopropane **3** exhibits a relatively intense ion (b, 48% of the base ion) at *m/e* 160, which is due to a quite different McLafferty-type rearrangement of an even-electron ion (a, *m/e* 347) involving hydrogen migration to silicon (Scheme I).

Table IV. Principal Ions Observed in Mass Spectra of Tetra(trimethylsilyl)-1,5-diaminopentanes 9–11

Ion, m/e			Relative intensity,[a] %	Structure assignment
9	10 (d_4)	11 (d_{36})		
390	394	426	1.2	$M^+\cdot$
375	399	408	16	$[M-Me]^+$
229	232	247	1.1	$\cdot CH_2CH_2CH_2CH_2$-$CH{=}N^+(TMS)_2$
216	218	234		
200	201	218	2	$CH_2{=}CH{-}CH{=}N^+$-$(TMS)_2$
174	176	192	100[b]	$CH_2{=}N^+(TMS)_2$
130	130	142	4	$[(Me_2Si)_2N]^+$
100	101	109	4	$HC{\equiv}N^+TMS$
86	88	92	5	$CH_2{=}NSi^+Me_2$

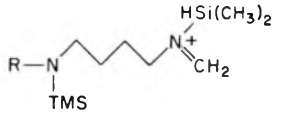
[a] Relative intensities are for ions in the spectrum of the nondeuterated analogue **9**. [b] $\Sigma_{80} = 45\%$.

Scheme I



a, m/e 347 b, m/e 160

Ions derived from similar rearrangements are observed in spectra of the 1,8-diamino-4-azaoctane (spermidine) and 1,12-diamino-4,9-diazadodecane (spermine)[15] derivatives (**12–14** and **15–18**, respectively) which possess trimethylsilylated 1,3-diaminopropane moieties. Because these derivatives (**12–18**) are unsymmetrical about the 1,3-diaminopropane molecular segment, the rearrangement in each case gives rise to two ions. In addition to ion b (*m/e* 160), ions c (*m/e* 303) and d (*m/e* 432) are observed in the spectra of TMS derivatives



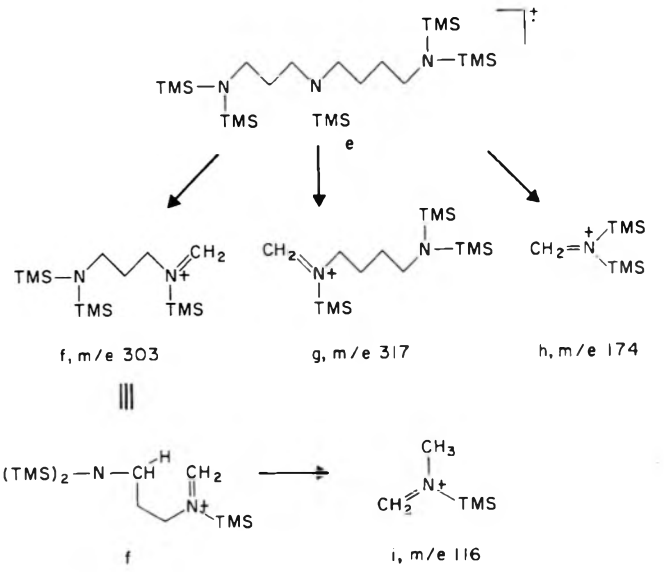
c, R = TMS; m/e 303
d, R = $(CH_2)_3N(TMS)_2$; m/e 432

of 1,8-diamino-4-azaoctane (spermidine, **12**) and 1,12-diamino-4,9-diazadodecane (spermine, **15**), respectively. That the rearrangement involves, at least primarily,[16] migration of a hydrogen α to the adjacent uncharged amine center is demonstrated by changes in *m/e* values for the corresponding ions observed in the spectra of analogues **13**, **16**, and **17** (Tables V and VI) in which specific α hydrogens have been replaced by deuterium.

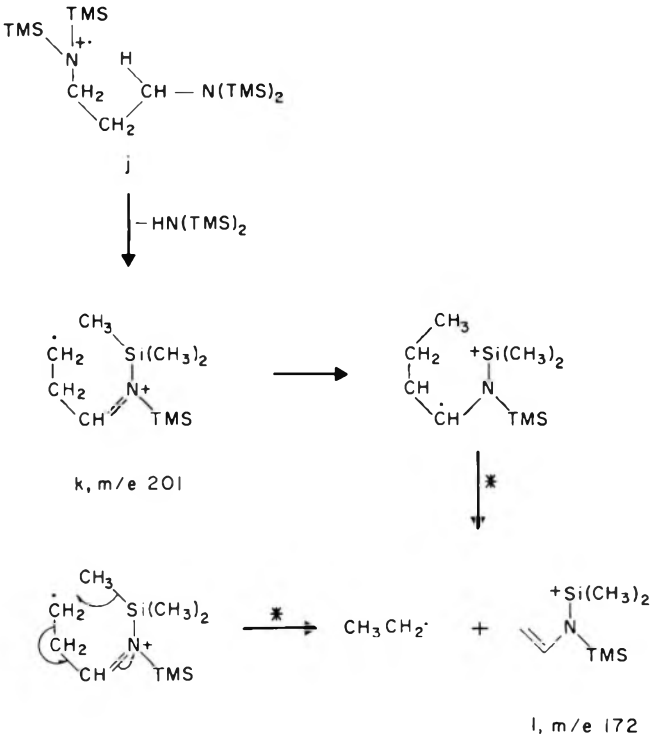
Rearrangements of hydrogen to silicon previously have been reported in the elimination of an olefin from a siliconium ion.[17] The migrating hydrogen in these rearrangements has been shown to originate from the β-carbon.[18]

Ion i (*m/e* 116), observed in the spectra of penta(trimethylsilyl)-1,8-diamino-4-azaoctane **12** and hexa(trimethylsilyl)-1,12-diamino-4,9-diazadodecane **15**, results from McLafferty-like rearrangement of another even-electron ion (f, *m/e* 303). This rearrangement, shown in Scheme II, involves 1,5 migration of a γ hydrogen as shown by deuterium labeling (Tables V and VI).[16] Previous reports have described McLafferty rearrangements involving even-electron immonium ions which were not specific for the β hydrogen;[19] the selectivity of hydrogen transfer in the present case[16] is presumably due to stabilization of the resulting carbon radical by the adjacent amine center.

Scheme II

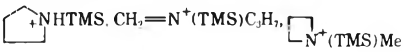


Scheme III



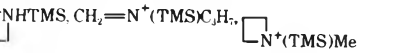
1,5-Methyl Migration. Ion k (65% of the base ion intensity) at *m/e* 201 in the spectrum of the 1,3-diaminopropane TMS derivative **3** appears to be derived from the molecular ion by abstraction of a hydrogen α to one nitrogen by the other nitrogen followed by loss of disilazane (Scheme III). Ion k further decomposes to an ion l at *m/e* 172 (26% of the base ion) as established by the appearance of a metastable ion centered at *m/e* 147. This process can be explained by a 1,5-methyl rearrangement followed by the loss of an ethyl radical to yield the resonance-stabilized ion l. As shown in Scheme III, the formation of ion l may be either a synchronous process or a two-step sequence. Ions k (*m/e* 201) and l (m/e 172) are also present in the spectra of the polyamine TMS derivatives **12** and **15**, which also possess the trimethylsilylated 1,3-diaminopropane moiety. The change in *m/e* value for ion k in the spectra of the isotopically labeled analogues of these polyamine derivatives (Tables V and VI). again indicates the primary origin of the hydrogen abstracted.[16] The polyamine derivatives **12** and **15**, which are unsymmetrical about the

Table V. Principal Ions Observed in Mass Spectra of Penta(trimethylsilyl)-1,8-diamino-4-azaoctanes (Spermidines) 12–14

Ions, m/e			Relative	Structure
12	13 (d_6)	14 (d_{45})	intensity,[a] %	assignment
505	511	550	0.5	$M^+\cdot$
490	496	532	6	$[M-Me]^+$
344	350	371	6	$\cdot CH_2CH_2CH{=}N^+(TMS)(CH_2)_4N(TMS)_2$
317	321	344	6	$CH_2{=}N^+(TMS)(CH_2)_4N(TMS)_2$
303-A	308	327	3.5[b]	$CH_2{=}N^+(SiMe_2H)(CH_2)_4N(TMS)_2$
303-B	307	330	3.5[b]	$CH_2{=}N^+(TMS)(CH_2)_3N(TMS)_2$
214	217	232	12	
201	202	219	22	$\cdot CH_2CH_2CH{=}N^+(TMS)_2$
174	176	192	97	$CH_2{=}N^+(TMS)_2$
172	173	187	29	$CH_2{=}CHN(TMS)Si^+Me_2$
160	162	175	36	$CH_2{=}N^+(TMS)SiMe_2H$
156	160	165	39	$CH_2{=}CHCH_2CH_2N^+(TMS){=}CH_2$
144	149	153	100[c]	
116	119	125	63	$CH_2{=}N^+(TMS)Me$
86	88	92	36	$CH_2{=}NSi^+Me_2$

[a] Relative intensities are for ions in the spectrum of the nondeuterated analogue **12**. [b] This intensity represents the sum of the *m/e* 303-A and *m/e* 303-B ions, which are present in a 2:1 ratio as determined from the spectra of **13** and **14**. [c] $\Sigma_{80} = 12\%$.

Table VI. Principal Ions Observed in Mass Spectra of Hexa(trimethylsilyl)-1,12-diamino-4,9-diazadodecanes (Spermines) 15–18

Ions, m/e				Relative	Structure
15	16 (d_4)	17 (d_8)	18 (d_{54})	intensity,[a] %	assignment
634	638	642	688	0.2	$M^+\cdot$
619	623	617	670	2.0	$[M-Me]^+$
446	448	452	482	1.5	$CH_2{=}N^+(TMS)(CH_2)_4N(TMS)(CH_2)_3N(TMS)_2$
432	435	439	465	0.6	$CH_2{=}N^+(SiMe_2H)(CH_2)_4N(TMS)(CH_2)_3N(TMS)_2$
329	331	332	356	14	$CH_2{=}CHCH{=}N^+(TMS)(CH_2)_3N(TMS)_2$
303	305	307	330	3	$CH_2{=}N^+(TMS)(CH_2)_3N(TMS)_2$
201	202	202	219	44	$\cdot CH_2CH_2CH{=}N^+(TMS)_2$
174	176	176	192	94	$CH_2{=}N^+(TMS)_2$
172	173	173	187	32	$CH_2{=}CHN(TMS)Si^+Me_2$
160	162	162	175	73	$CH_2{=}N^+(TMS)SiMe_2H$
156	156	160	165	38	$CH_2{=}N^+(TMS)(CH_2)_2CH{=}CH_2$
144	146	149	153	100[b]	
116	117	119	125	89	$CH_2{=}N^+(TMS)Me$
86	88	88	92	44	$CH_2{=}N(TMS)Si^+Me_2$

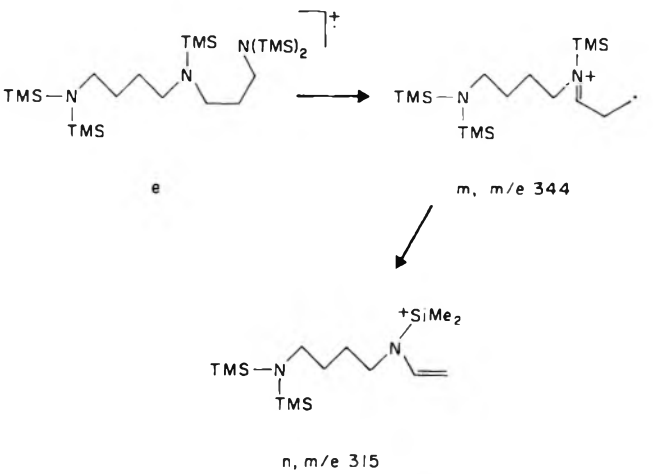
[a] Relative intensities are for ions in the spectrum of the nondeuterated analogue **15**. [b] $\Sigma_{80} = 8.7\%$.

1,3-diaminopropane unit, show the same process at the carbon-substituted ends, giving rise to ions at higher *m/e* values (see, e.g., Scheme IV). These higher mass ions, however, are of much lower abundance, and no corresponding metastable ions are observed.

These processes appear to be among the few authenticated cases of a 1,5-alkyl rearrangement occurring in a mass spectrometer. Goldsmith et al. have reported a 1,5-methyl migration in a McLafferty-type rearrangement in the spectrum of dipropyl ketoxime.[9] A possible 1,5-methyl rearrangement ion in the mass spectrum of acetophenone azine can also be accounted for by a 1,3 migration,[10] a process encountered more frequently in mass spectrometry. Also, a 1,5-phenyl rearrangement has been reported in the mass spectral decomposition of 3-(β-hydroxy-β-phenylethyl)-2-iminothiazolidine.[17]

Polyamine Base Ion. In the mass spectra of both penta(trimethylsilyl)-1,8-diamino-4-azaoctane **12** and hexa(trimethylsilyl)-1,12-diamino-4,9-diazadodecane **15** the base ion appears at *m/e* 144. In the spectra of the deuterated analogues **13** and **17** the mass of this ion is shifted to *m/e* 149, while that of the deuterated analogue **16** shifts to *m/e* 146.[16] Derivatization with deuterated TMS reagents shifts the base ion to *m/e* 153 (**14** and **18**), indicating the presence of three TMS derived methyl groups.[16] Keeping the number of bonds to be broken and formed to a minimum, these data suggest the

Scheme IV



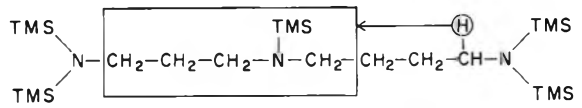
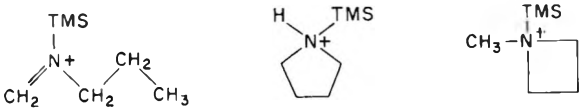


Figure 1. Composition of ion at *m/e* 144 for derivative **12**.

composition of the ion at *m/e* 144 to be that shown in Figure 1.

The data require that a α hydrogen at one end of the butylene group be abstracted by another atom at or near the other end of this alkyl chain as shown in Figure 1. Structure o for this ion at *m/e* 144 can be formed from four bond breaking and formation steps; two other possible structures for this ion (p and q) each require five steps.



o p q

Sterically Induced Rearrangements. The longer chain trimethylsilylated diamine homologues exhibit the simplest mass spectra. The base ion h (*m/e* 174) in the mass spectra of all of the diamine derivatives arises by cleavage between the α and β-carbons, giving the stabilized immonium structure. In the mass spectrum of the TMS derivative of 1,5-diaminopentane (Table IV), this ion constitutes 45% of the total ionization (Σ_{80}). In the shorter chain homologues, the proximity of the amine centers gives rise to a wider variety of ions.

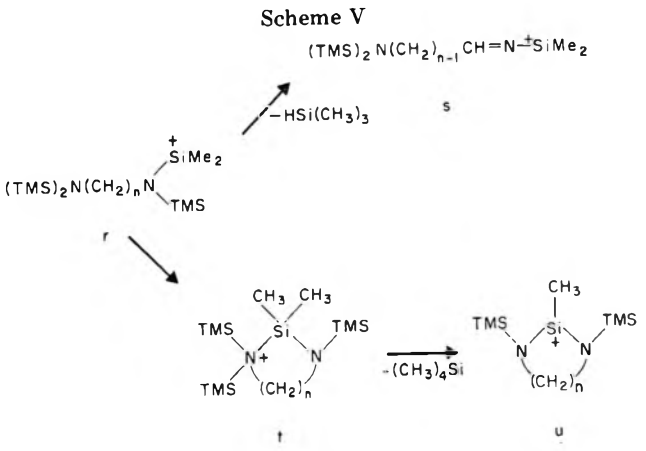
The spectra of the shorter chain diamine TMS derivatives exhibit ions at M − 89 and M − 103, i.e., *m/e* 259 and 245 for **1**, *m/e* 273 and 259 for **3**, and *m/e* 287 and 273 for **6**. The intensities of these two ions are 4 and 6%, respectively, for the diaminoethane derivative **1** and decrease with increasing chain length to 0.04 and 0.1% for the diaminobutane derivative **6**. Neither process is observed in the spectra of higher homologues. The proposed pathways (Scheme V) leading to these ions, assigned structures s and u, respectively, are consistent with the mass changes exhibited by the various deuterium labeled analogues.[16] The trend for these ions to become more intense with shorter methylene chain length suggests that these processes occur to relieve the steric strain between the four TMS groups. The process producing ion s has, however, been shown to occur as a decomposition pathway of *N*-ethyldisilazane, in which case the hydrogen migration is specifically from the α-carbon.[8a] Ion u arises from cyclization of ion r followed by expulsion of tetramethylsilane. Bond formation between a positively charged silicon atom and an atom bearing either nonbonding or π electrons is a process frequently invoked to explain rearrangements of trimethylsilyl compounds in which a neutral fragment is lost.[1] Although this process should be favored by the formation of five- and six-membered rings, similar intramolecular ring formation has been observed in longer chain aliphatic systems.[1d,e]

An ion of significant abundance (14% of the base ion) in the spectrum of the 1,4-diaminobutane TMS derivative **6** appears at *m/e* 214. The probable structure of this ion (w) and a plausible mode for its formation are shown in Scheme VI. This process parallels that outlined by Mayerl and Hesse[3c] for a similar decomposition of underivatized 1,4-diaminobutane (putrescine).

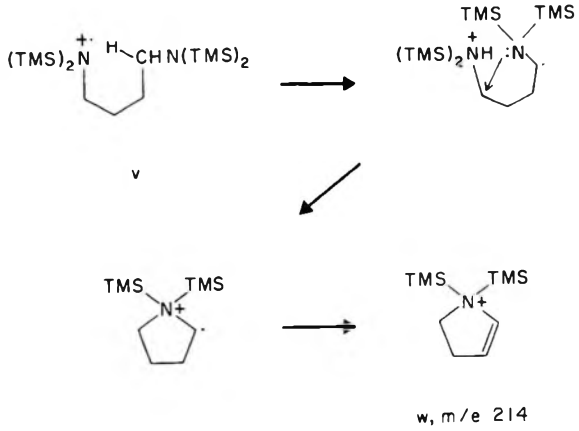
Experimental Section

Instrumental. Mass spectra were obtained using a DuPont 21-491B mass spectrometer interfaced with a Varian 2700 gas chromatograph and were recorded on oscillographic recording paper. The

Scheme V



Scheme VI



w, *m/e* 214

ionizing voltage was 70 eV, and the source temperature was 270 °C. The gas chromatograph was equipped with a 1.2 m × 2 mm glass column packed with 1.5% OV-101 coated 100–120 mesh Gas Chrom Q.

Materials. The nondeuterated amines 1,3-diaminopropane, 1,2-diaminoethane, 1,4-diaminobutane dihydrochloride, 1,5-diaminopentane dihydrochloride, 1,8-diamino-4-azaoctane trihydrochloride, and 1,12-diamino-4,9-diazadodecane tetrahydrochloride were obtained commercially. Standard 1.0 mM solutions of each amine were prepared in 1.0 N aqueous hydrochloric acid.

1,3-Diaminopropane-*1,1,2,2,3,3-d*$_6$ Dihydrochloride. Malononitrile (100 mg, 1.52 mmol) was dissolved in 10 mL of *O*-deuterioethanol (95% in deuterium oxide, 99% *d*), 1.0 mL of deuterium chloride (37% in deuterium oxide) and 100 mg of platinum oxide were added, and the mixture was shaken under 30 psi of deuterium gas (99.5% *d*) until gas uptake ceased. The mixture was filtered to remove the platinum, and the solvents were removed under reduced pressure to give an off-white solid. Recrystallization of the product from 100% ethanol yielded 104 mg of 1,3-diaminopropane-*1,1,2,2,3,3-d*$_6$ dihydrochloride, mp 248–250 °C (lit. mp 243 °C[20] for unlabeled 1,3-diaminopropane dihydrochloride).

1,4-Diaminobutane-*1,1,4,4-d*$_4$ Dihydrochloride. Preparation of this diamine, similar to that described for deuterated 1,3-diaminopropane, utilized 0.80 g (10 mmol) of succinonitrile, 20 mL of *O*-deuterioethanol, 3 mL of deuterium chloride solution, and 100 mg of platinum oxide. Recrystallization of the isolated product from 100% ethanol gave 0.66 g of 1,4-diaminobutane-*1,1,4,4-d*$_4$ dihydrochloride, mp >310 °C (lit. mp 290[21] and 315 °C[22] for unlabeled 1,4-diaminobutane dihydrochloride).

1,5-Diaminopentane-*1,1,5,5-d*$_4$ Dihydrochloride. Preparation of this diamine, similar to that described for deuterated 1,3-diaminopropane, utilized 0.94 g (10 mmol) of glutaronitrile in 20 mL of *O*-deuterioethanol and 3 mL of deuterium chloride solution and 100 mg of platinum oxide. Recrystallization of the isolated product from 100% ethanol gave 0.96 g of 1,5-diaminopentane-*1,1,5,5-d*$_4$ dihydrochloride, mp 258–260 °C (lit. mp 255[23] and 275 °C[22] for unlabeled 1,5-diaminopentane dihydrochloride).

1,12-Diamino-4,9-diazadodecane-*1,1,12,12-d*$_4$ Tetrahydrochloride. This compound was prepared by the addition of 2 equiv of acrylonitrile to 1,4-diaminobutane (as described by Tabor et al.[24]) followed by catalytic deuteration of the nitrile groups as described

above for deuterated 1,3-diaminopropane. The product, 1.8 g, was recrystallized by dissolving it in 13 mL of 12% aqueous HCl and adding this solution to 130 mL of hot 100% ethanol.[25] Upon cooling, 1.1 g was obtained of crystalline 1,12-diamino-4,9-diazadodecane-*1,1,12,12-d*$_4$ tetrahydrochloride, mp 299–308 °C (lit. mp 310–311 °C[25] for the unlabeled tetrahydrochloride salt).

1,8-Diamino-4-azaoctane-*1,1,5,5,8,8-d*$_6$ Trihydrochloride and 1,12-Diamino-4,9-diazadodecane-*1,1,5,5,8,8,12,12-d*$_8$ Tetrahydrochloride. To a suspension of 0.16 g (1.0 mmol) of 1,4-diaminobutane-*1,1,4,4-d*$_4$ dihydrochloride in 20 mL of ethanol was added 0.2 mL of 3.8 N aqueous NaOH, and the mixture was stirred for 10 min. Acrylonitrile (60 μL, 0.9 mmol) was added slowly, and the mixture was stirred for 24 h. The reaction was quenched with 2.0 mL of 6 N HCl, and the solvents were completely removed under reduced pressure. The residue was dissolved in 15 mL of deuterium oxide followed by the addition of 1.0 mL of 37% deuterium chloride and 50 mg of platinum oxide. This mixture was shaken under 30 psi of deuterium for 36 h. The platinum was removed by filtration, and the solvent was removed to dryness. The solid residue was dissolved and diluted to 50 mL using 1.0 N HCl. The concentrations of the various components of this solution were determined by selected ion monitoring analysis of an equal volume mixture of this solution and a solution 1.0 mM in each of the nondeuterated di- and polyamines. The concentrations were 5.2, 7.3, and 2.5 mM for 1,4-diaminobutane-*1,1,4,4-d*$_4$, 1,8-diamino-4-azaoctane-*1,1,5,5,8,8-d*$_6$, and 1,12-diamino-4,9-diazadodecane-*1,1,5,5,8,8,12,12-d*$_8$, respectively.

Per Cent Deuterium Incorporation. The di- (**7** and **10**) and polyamines (**13**, **16**, and **17**) were trifluoroacetylated[5] and their mass spectra determined. The intensities of ions in the $[M - CF_3\cdot]^+$ ion isotope cluster were measured, and, following a correction for natural abundance ^{13}C, the per cent deuterium was calculated; in each compound the enrichment was 96–97% of the indicated level.

Trimethylsilylation. Aliquots taken from aqueous solutions of the various di- and polyamine hydrochlorides were evaporated to dryness under a stream of nitrogen. The residue was treated with a 2:2:1 mixture of pyridine, *N,O*-bis(trimethylsilyl)acetamide, and trimethylchlorosilane and placed either in a sonic bath or a steam bath for 15 min. Upon cooling, the samples were examined by GC–MS, and the derivatizations were shown to be essentially complete to replace every N hydrogen with a trimethylsilyl group. Perdeuteriotrimethylsilylation was achieved in the same manner using a 2:2:1 mixture of pyridine, *N,O*-bis(tri(methyl-*d*$_3$)silyl)acetamide, and tri(methyl-*d*$_3$)chlorosilane.

Acknowledgment. This work was supported by a grant from the M. J. Murdock Charitable Trust, for which the authors express their appreciation.

Registry No.—**1**, 5577-69-5; **2**, 65898-72-8; **3**, 39772-64-0; **4**, 65898-73-9; **5**, 65898-74-0; **6**, 39772-63-9; **7**, 65372-71-6; **8**, 65898-75-1; **9**, 65898-76-2; **10**, 65898-77-3; **11**, 65898-78-4; **12**, 65898-79-5; **13**, 65898-80-8; **14**, 65898-81-9; **15**, 65898-82-0; **16**, 65898-83-1; **17**, 65898-84-2; **18**, 65898-85-3; malononitrile, 109-77-3; 1,3-diaminopropano-*1,1,2,2,3,3-d*$_6$ 2HCl, 65898-86-4; succinonitrile, 110-61-2; 1,4-diaminobutane-*1,1,4,4-d*$_4$ 2HCl, 65372-65-8; glutaronitrile, 544-13-8; 1,5-diaminopentane-*1,1,5,5-d*$_4$ 2HCl, 65372-66-9; acrylonitrile, 107-13-1; 1,4-diaminobutane, 110-60-1; 1,12-diamino-4,9-diazadodecane-*1,1,12,12-d*$_4$ 4HCl, 65898-87-5; 1,8-diamino-4-azaoctane-*1,1,5,5,8,8-d*$_6$ 3HCl, 65372-67-0; 1,12-diamino-4,9-diazadodecane-*1,1,5,5,8,8,12,12-d*$_8$ 4HCl, 65372-68-1; 1,4-diaminobutane 2HCl, 333-93-7; 1,5-diaminopentane 2HCl, 1476-39-7; 1,8-diamino-4-azaoctane 3HCL= 334-5]-9: [=[2-DIAMINO-4=9-DIAZADODECANE 4HCl, 306-67-2.

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Simple Cracking and Hydrogen Rearrangement–Cleavage for Oxetanes under Electron Impact. Substituent Effects and Energetics[1]

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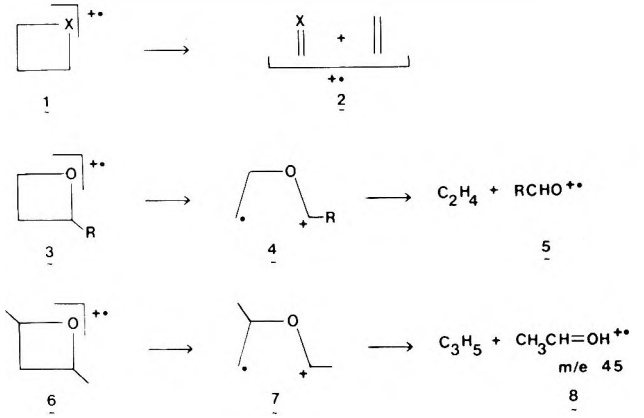
Mass spectral fragmentation of oxetanes substituted with aryl and other groups (**9**–**16**) gives simple patterns of product ions associated with carbonyl and olefin cycloelimination fragments. For oxetanes substituted with aryl groups in the 2 position, ions resulting from cleavage plus hydrogen rearrangement ($ArRC{=}OH^+$) are also prominent. The direction of two-bond cleavage without rearrangement does not correlate well with electron affinities of fragment ions alone. There is general agreement, however, between regioselectivity and overall stability of ions and neutrals, assessed from heats of formation of product pairs. The regiochemistry of fragmentation for 2-aryloxetanes is also correctly predicted by assessment of the relative stabilities of ring-opened valence isomers of the oxetane molecular ions. The competition between cleavage with and without hydrogen migration for 2-aryloxetanes is dependent on ionizing energy, with the former relatively more important at low voltages. A sizable β-secondary deuterium isotope effect on simple cleavage for **16** is also observed (k_H/k_D = 1.08–1.02, per deuterium, at 10–70 eV). A similarity in regioselectivity for mass spectral and thermal cracking for 2-aryloxetanes is noted.

Mass spectral decomposition of **1**, where X = C, N, O, and C=O, has been the subject of a number of investigations. Results for variously substituted cyclobutanes,[3] azetidines,[4] oxetanes,[5] and cyclobutanones[6] have been reported. For this family of small rings, ring cleavage under electron impact is extremely efficient, presumably due to the release of ring strain (generally >25 kcal/mol) and the stability of molecular products. Molecular ion intensities are low, and large fractions of the total ion current at low ionizing energies can be assigned to cleavage fragments **2**. Where substitution patterns in **1** are



unsymmetrical, cracking is regioselective, providing insight into the effect of substituents on the energetics of bond breaking and charge partitioning. Unlike most mass spectral fragmentations, cycloelimination of **1** may be thermoneutral or even exoergic with relatively large kinetic energy release[4a] as expected for 1,2 eliminations.[7]

A mechanism for mass spectral decomposition of 2-substituted oxetanes (**3** → **5**, R = Me, Et, and Ph) involving initial C–C cleavage to a ring-opened, valence isomeric molecular ion has been proposed,[5b] based on the regioselectivity of fragmentation. The decomposition of other cyclic ethers[8] appears also not controlled by initial C–O cleavage. An isolated case of hydrogen rearrangement for an oxetane (**6** → **8**) has been reported.[5a] This fragmentation which competes with simple cleavage may also involve a ring-opened ion precursor (**7**).

We have extended the survey of oxetane fragmentation in the mass spectrometer, exploring the factors which control the direction of ring cleavage and with pyrolysis chemistry data available for comparison.[9] We note the special importance of hydrogen rearrangement (analogous to **6** → **8**) for aryloxetanes and its requirements of structure for reactivity in competition with simple ring cleavage. The dependence of rearrangement and simple cleavage on ionizing energy and a β-secondary deuterium isotope effect on the direction of cracking are also reported.

Results and Discussion

Generation of oxetane molecular ions from **9** to **16** in the mass spectrometer resulted in virtually complete decomposition over a range of ionizing energies (10–70 eV, source temperature 50–70 °C, direct inlet procedure). Product ions which accounted for greater than 90% of the ion current at 10 eV were assigned (1) carbonyl compound and olefin structures expected to result from formal two-bond ring cleavage and (2) protonated carbonyl structures (e.g., $Ph_2C{=}OH^+$ from **11**) resulting from formal rearrangement of hydrogen to oxetane oxygen (with cleavage).[10] Fragmentation patterns, including metastable transitions obtained independently for olefins and carbonyl compounds, accounted for secondary fragmentation of the oxetanes. Metastables were not generally observed for primary oxetane molecular ion decomposition under a limited range of conditions. The exception is the hydrogen rearrangement of **14**, the details for which are shown in Table I along with metastable ion data for the fragmentation of oxetane cleavage products.

The relative abundances of product ions as a function of ionizing energy are shown in Table II. The cleavage modes and resultant ions are identified with reference to the oxetane structures depicted in Table II and the reference formulas **17** and **18**, which illustrate the direction of formal ring cleavage (with [RA, RB] and without [A, B] hydrogen rearrangement) and the residence of charge in product fragments (e.g., B2 for

Table I. Metastable Ions Observed in Oxetane Mass Spectra[a]

Oxetane	Metastable Ion	Transformation	Assignment
9	113.7	118 → 116	$(PhCH{=}CHMe)^{+\cdot} - H_2$
10	113.7	118 → 116	$(PhCH{=}CHMe)^{+\cdot} - H_2$
11	56.7	84 → 69	$(Me_2C{=}CMe_2)^{+\cdot} - Me$
12	56.7	84 → 69	$(Me_2C{=}CMe_2)^{+\cdot} - Me$
	184.0	242 → 211	$(An_2C{=}O)^{+\cdot} - OMe$
13	113.0	117 → 115	$(PhCH{=}CHCH_2)^+ - H_2$
14	121.1	276 → 183	$(M)^{+\cdot} - (Ph_2C{=}OH)^+$
15	82.0	110 → 95	$(MeC{=}CHCH{=}CMe_2)^{+\cdot} - Me$

[a] Also observed in the spectra of the appropriate carbonyl compound or olefin.

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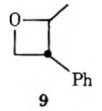
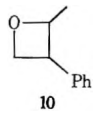
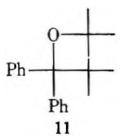
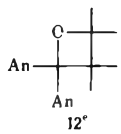
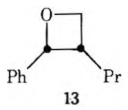
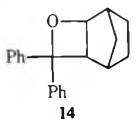
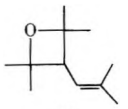
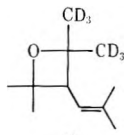
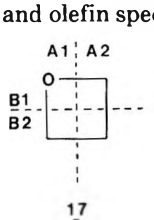
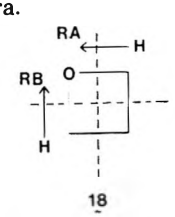
Table II. Mass Spectral Fragmentation of Substituted Oxetanes[a]

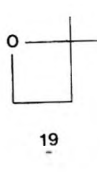
Oxetane	Registry no.	Fragmentation	m/e[b]	10 eV	15 eV	20 eV	50 eV	70 eV
 9	53699-68-6	A1	30					
		A2	118 (117)	31	29	22	25	23
		B1	44					
		B2	104	69	71	78	75	77
		RA	31					
		RB	45					
 10	53774-25-7	A1	30					
		A2	118 (117)	19	14	13	17	15
		B1	44					
		B2	104	81	86	84	83	85
		RA	31					
		RB	45					
 11	42245-06-7	A1	84 (69)	45	60	62	67	67
		A2	182 (105)	1	3	6	9	9
		B1	58 (43)	3	3	2	5	6
		B2	208 (193)	8	11	12	6	6
		RA	183	43	23	18	13	12
		RB	59					
 12[e]	56440-24-5	A1	242 (135)	12	22	20	34	33
		A2	84 (69)		2	17	25	24
		B1	58 (43)					
		B2	268 (253)	15	18	12	7	9
		RA	243	73	58	41	25	24
		RB	59					
 13	54541-25-2	A1	106 (105)	17	18	21	23	10
		A2	70	7	5	5	5	5
		B1	30	3	2	3	2	3
		B2	146 (117,115)	23	21	19	24	27
		RA	107	50	54	52	46	46
		RB	31					
 14	42245-07-8	A1	182 (105)	7	10	12	16	17
		A2	94 (79,66)	31	37	41	40	40
		B1	276[c] (248,207,191, 168,167)	29	21	18	18	16
		B2						
		RA	183	33	32	29	26	27
		RB	276[d]					
 15	31058-34-1	A1 = B1	58 (43)	11	13	13	17	14
		A2 = B2	110 (95)	81	77	78	75	81
		RA = RB	59	8	10	9	8	5
 16	65516-98-5	A1	58		9	13	16	18
		A2	116 (101,98)	39	34	29	27	26
		B1	64 (46)		4	6	8	9
		B2	110 (95)	61	48	44	40	39
		RA	59			3	3	2
		RB	64		5	6	6	6

[a] Ion intensities from two or more spectra corrected for secondary fragmentation and isotope contribution presented as percent total fragmentation (abundances <5% of base peak not generally included) according to modes indicated by reference structures **17** and **18**. [b] Numbers in parentheses indicate secondary fragment ion for which primary ion abundance was corrected. [c] Charge partitioning for cleavage B cannot be discerned. [d] RB is equivalent to the molecular ion. [e] An = *p*-$CH_3OC_6H_4$–.

10 = styrene molecular ion; RA for **11** = $Ph_2C{=}OH^+$). The percentages were calculated after correction was made for secondary fragmentation as determined from carbonyl compound and olefin spectra.


17


18


19

Relative abundances of product ions were dependent on sample inlet and temperature. For example, introduction of **11** to the ion chamber via the GC inlet virtually eliminated the rearrangement mode RA (*m/e* 183) so that the cracking mode B2 (*m/e* 208) predominated. This change almost certainly results from thermal, surface catalyzed[9b] decomposition of the oxetane in the heated inlet before entering the ion chamber. The preference for fragmentation modes in oxetanes **9–16** at 10 eV, under conditions where the survival of oxetane during the introduction of sample was assured, is presented in simplified fashion in Table III, where values for A, B, and

Table III. Preferred Fragmentation Modes for Oxetanes 9–16 at 10 eV[a]

Oxetane	Fragmentation mode A	B	RA
9	31	69	
10	19	81	
11	46	11	43
12	¶2	15	73
13	24	26	50
14	38	29	33
15[b]	92		8
16	39	61	

[a] Entries are sums of percentages of principal fragmentations from Table II. [b] Mode A = mode B.

RA represent sums from Table II.

Patterns of structure and reactivity noted for oxetane decomposition especially at, but not confined to, low ionizing energy are as follows. (1) Hydrogen rearrangement is a principal mode of decomposition for oxetanes which are 2-aryl substituted, whereas for 3-phenyl (**9, 10**) and 3-isobutenyl (**15, 16**) substituted oxetanes simple cleavage predominates. (2) Where hydrogen rearrangement occurs readily (**11–14**), the protonated carbonyl fragment (e.g., $Ph_2C{=}OH^+$) is aryl substituted (RA ≫ RB). (3) The pattern of alkyl substitution in **11–14** does not significantly control the competition between hydrogen rearrangement and simple cleavage; the data allow that transfer of hydrogen to oxetane oxygen may occur either from a 2-alkyl or a 3-alkyl or other substituent. Since 2-phenyloxetane does not give protonated benzaldehyde appreciably,[5] transfer of the oxetane ring hydrogen in the formation of protonated carbonyls (for **13** and **14**) appears unfavorable. (4) Since the 2,4-dimethyloxetanes (**6**) but not 2,3,4,-trimethyloxetane undergo hydrogen rearrangement,[5a] a subtle stereoelectronic requirement for hydrogen transfer might have been predicted. This orientation feature for transfer hydrogen may be responsible for the diminution in RA for **14**, but the effect is small. (5) A modest cis–trans effect is observed for **9** and **10**. This influence, in which cis more than trans substituents direct the cleavage which separates them, has been noted for azetidines[4b] and lactams.[6b] (6) For **16**, a β-secondary deuterium isotope effect is observed for simple cleavage (B ≫ A). (7) Cracking of the oxetanes is regioselective, but the preferences for mode A vs. mode B and the distribution of charge within developing fragments do not fit a simple pattern.

A mechanism for oxetane decomposition involving direct generation of carbonyl and olefin fragments might include regiochemical control by substituent effects on product ion stability, as illustrated by the preferences of 2-methylcyclobutanone and 3,3-dimethylcyclobutanone for fragmentation to $(methylketene)^{+\cdot}$ and $(isobutylene)^{+\cdot}$, respectively.[6a] This control of regiochemistry and charge development is understood in terms of the relative ionization potentials[11] for ketene (9.6 eV), ethylene (10.5 eV), and isobutylene (9.2 eV) (i.e., a preference for formation of ionic fragment of lowest electron affinity).[6a] This simple analysis is not consistent for the oxetanes. Tetramethylethylene (IP = 8.3 eV) radical ion is an expected and observed major cracking fragment from **11** (A2 cleavage), and cleavage of **12** to ions of dianisyl ketone and 1,1-dianisyl-2-methylpropene (A1 and B2) is favorable, perhaps reflecting the relatively low ionization potentials for the corresponding molecules (IP's for anisole and 4-methoxybenzophenone are 8.2 and 8.8 eV, respectively). However there are anomalies in other cases. The cracking fragments of lowest electron affinity from **9** (**10**) and **13** would be the ions of substituted styrenes (a model olefin is α-methylstyrene, IP = 8.4 eV), yet the ion of styrene (IP = 8.5 eV) is favored for **9** (**10**) (B2 cleavage) and the ions of 1-phenyl-1-pentene and benzaldehyde (IP = 9.5 eV) are formed in about equal amounts from **13** (A1 and B2 cleavage). Additionally, 2,2-dimethyloxetane (**19**) gives primarily the radical ion of acetone[5b] (IP = 9.7 eV) without deference to the ionization potential of isobutylene, and 2-phenyloxetane favors benzaldehyde ion over styrene ion.[5b]

Another quantitative approach to the evaluation of substituent effects involves the assessment of the relative stability of ionic *and* neutral product pairs. Calculations have been carried out for some of the oxetanes shown in Table II, 2,2-dimethyloxetane (**19**), and unsubstituted oxetane (**20**). The data in Table IV include heats of formation which are

Table IV. Heats of Formation (kcal/mol) of Potential Products[a] and Predicted and Observed Modes of Oxetane Decomposition

Registry no.	Oxetane (H_f, M^+)		Fragmentation mode A1	A2	B1	B2	Predicted	Observed[b]
	9 (200)**	C–O	223	−28	196	−40		
		C–C	28*	221**	35	232	B2 > A2	B2 > A2
		Sum	251	193	231	192		
	11 (198)**	C–O	229	13	171	−52		
		C–C	−16	175	44*	229**	B2 > A2	A2 > B2
		Sum	213	188	215	177		
	15 (140)**	C–O	171	−52				
		C–C	−4*	187**	[c]		A2 > A1	A2 > A1
		Sum	167	135				
6245-99-4	**19** (189)**	C–O	233	−28	171	−52		
		C–C	−4	209	12	253	A2 > B1	B1 > A2[d]
		Sum	229	181	183	201		
503-30-0	**20** (208)**	C–O	223	−28	[c]			
		C–C	13	253			A2 > A1	A2 > A1[e]
		Sum	236	225				

[a] Obtained from the sum of heats of formation (25 °C) of carbonyl containing and olefinic ions and neutrals as indicated with reference to general structures **17** and **18** and the orientation of oxetane formulas in Table III and structure **19** (e.g., A1 = vertical cleavage, oxygen containing ion). Calculated heats of formation are starred (* using known group values, or ** using known group equivalents to estimate ΔH_f for neutrals along with ionization potentials: see Supplementary Material). [b] From data at 10 eV, Table II and III, except where noted. [c] Mode A = mode B. [d] Reference 5b. [e] Reference 4c.

Table V. Isotope Effects on the Direction of Cracking and Development of Charge in Product Ions for Decomposition of 16

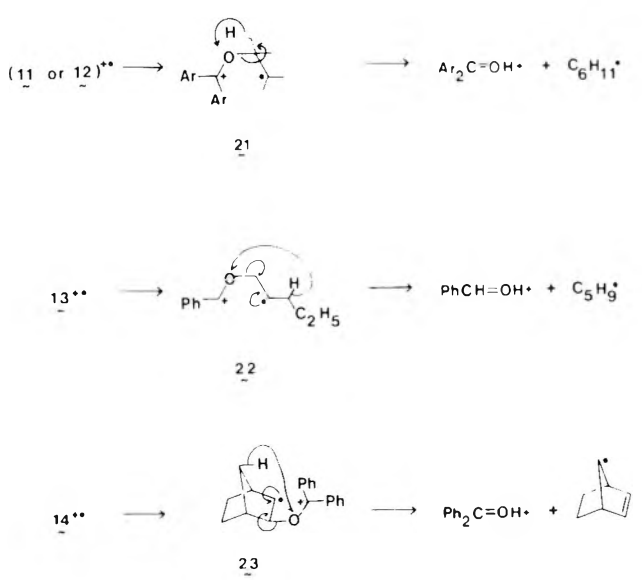
Ionizing energy, eV	10	15	20	50	70
$(k_H/k_D)_{tot}$	1.58	1.22	1.22	1.13	1.10
$(k_H/k_D)_{tot}^{1/6}$	1.08	1.03	1.03	1.02	1.02
F_1	1.00	0.79	0.70	0.62	0.59
F_2	1.00	0.92	0.89	0.83	0.82

[a] Directions for cleavage and charge location are identified in structure **24**.

known,[11] or which have been calculated by the addition of known thermodynamic groups.[12] Other entries (radical ions) derive from thermodynamic group values for the corresponding molecules along with ionization potential data.[11] Heats of formation of oxetane molecular ions (ring-closed, vide infra), also included in Table IV, derive from group additivity values for oxetane molecules and the ionization potentials of model compounds (see Supplementary Material).

Predicted modes of decomposition are those yielding the product fragments calculated to have the highest stability. Agreement with experiment is good for **15** and **20** (and in general for selecting two favorable paths). The prediction is acceptable for **9** and **19** (considering probable errors in experimentally derived[11,13] and calculated[14] heats of formation) but in error for **11**. Other calculations suggest a driving force for hydrogen rearrangement–cleavage. Thus, the products of RA cleavage for **11** ($Ph_2C{=}OH^+$, ΔH_f = 160; $CH_2CMeC{\cdot}Me_2$, ΔH_f = 11; sum = 171 kcal/mol) are exceptionally stable. On the other hand, where rearrangement–cleavage is not competitive, special stability is not indicated for product pairs; for **9**, CH_2OH^+, ΔH_f = 171[11] and $CH_2CHCH{\cdot}Ph$, ΔH_f = 62 kcal/mol (sum = 233 kcal/mol); for **19**, CH_2OH^+, ΔH_f = 171[11] and $CH_2{=}CMeCH_2{\cdot}$, ΔH_f = 30 kcal/mol (sum = 201 kcal/mol). The stability of aryl-substituted protonated carbonyls ($ArRC{=}OH^+$) which appears to control the preference for and direction of hydrogen transfer would be expected to promote rearrangement for any 2-aryloxetane in which the aryl group is not electron deficient due to further substitution. It is interesting that hydrogen rearrangement with two-bond cleavage is prevalent in aliphatic acyclic ethers[16] and is not general for oxetanes substituted only with alkyl groups,[5] but returns to a competitive position in the 2-aryloxetane series.[17]

The oxetane cycloreversions are not highly endoergic (Table IV) unlike most molecular ion fragmentations (but like most



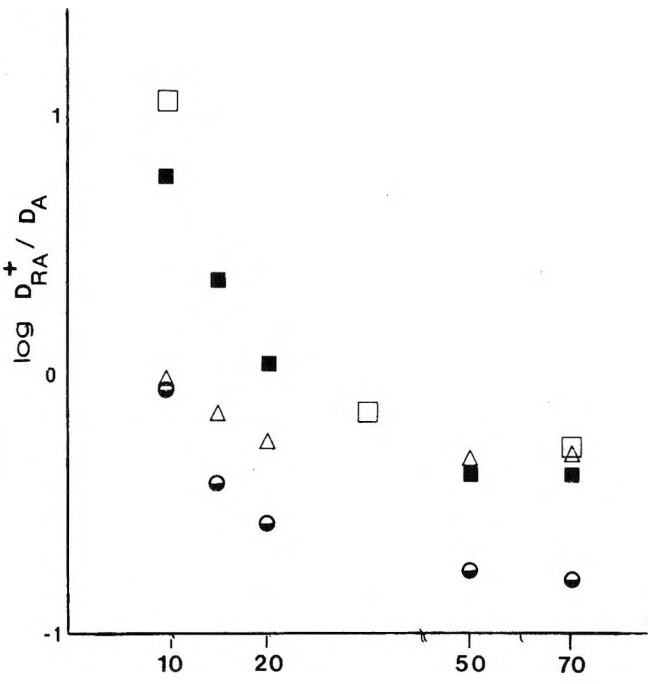


Figure 1. Competing rearrangement and simple cleavage for oxetane molecular ions **6** (□) (data from ref 5a), **11** (◒), **12** (■), and **14** (△) as a function of ionizing energy.

1,2-elimination reactions[7]). The suitability of decomposition paths need not be influenced by the relative energies of product fragments. An attractive alternative to concerted ring fragmentation is stepwise ring opening[5b] controlled by a preference in formation of valence isomeric ions. A very large fraction of the total decomposition of **11–14** (direct cleavage and cleavage–rearrangement) can be accommodated by the two-step mechanism and a preference for breaking the weaker C–C bond. Possible paths for hydrogen transfer in appropriate intermediates are illustrated in **21–23**.[20,21]

An important aspect of the competition of simple ring cleavage and hydrogen rearrangement–cleavage for **11–14** is the dependence on ionizing energy. The rise in daughter ion relative abundance for simple cleavage is shown in Figure 1 for several of the oxetanes. This familiar pattern[22] is anticipated for competing reactions in which theoretical curves depicting the dependence of reaction rate constant on ion internal energy cross. The physical picture in which the most energetic molecular ions preferably undergo simple cleavage, whereas ions of low internal energy favor rearrangement, has been commonly associated with a low activation energy and a low frequency factor for rearrangement and relatively high activation parameters for simple cleavage.[22a] The inference in the present case is that rearrangement proceeds through a tighter activated complex than simple cracking; i.e., that hydrogen transfer is an integral part of the product-determining step which gives $(carbonyl + 1)^+$ ions. Since the dependence of daughter ion ratios on beam energy is found for oxetanes of varying structure, the effect is indeed more likely a potential surface phenomenon than an artifact of internal energy distribution.

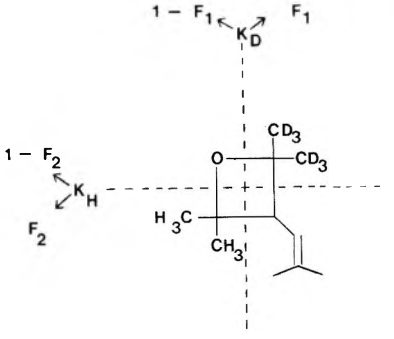
Exploiting the symmetry of **15** and the availability of specifically labeled **16**, we have measured a β-secondary deuterium isotope effect on oxetane cleavage. Data from Table II may be used to calculate a total isotope effect on the direction of cleavage according to eq 1. Scrambling of the deuterium

$$\left(\frac{k_H}{k_D}\right)_{tot} = \frac{(\text{diene-}d_0)^{+\cdot} + (\text{acetone-}d_6)^{+\cdot}}{(\text{diene-}d_6)^{+\cdot} + (\text{acetone-}d_0)^{+\cdot}} = \frac{B1 + B2}{A1 + A2} \quad (1)$$

Table VI. Mass Spectra (20 eV) of Ketones and Olefins Important in the Mass Spectral Fragmentation of Substituted Oxetanes

Registry no.	Compd	M+	m/e (% base)
100-42-5	$PhCH{=}CH_2$	104	104 (100), 103 (10), 78 (15)
873-66-5	PhCH=CHMe (trans)	118	119 (12), 118 (100), 117 (61)
766-90-5	PhCH=CHMe (cis)	118	119 (10), 118 (100), 117 (75)
563-79-1	$Me_2C{=}CMe_2$	84	84 (100), 69 (66), 56 (7), 55 (7)
781-33-9	$Ph_2C{=}CMe_2$	208	209 (19), 208 (100), 207 (7), 193 (19), 179 (8), 130 (9), 115 (7)
67-64-1	$Me_2C{=}O$	58	58 (33), 43 (100)
119-61-9	$Ph_2C{=}O$	182	183 (24), 182 (100), 105 (67)
666-52-4	$(CD_3)_2C{=}O$	64	64 (45), 46 (100)
498-66-8	Norbornene	94	95 (9), 49 (19), 82 (16), 79 (21), 57 (33), 66 (100)
764-13-6	2,5-Dimethyl-2,4-hexadiene	110	111 (15), 110 (95), 95 (100), 67 (40)
65516-99-6	*cis*-3-(2,2-Diphenylethenyl)cyclopentanecarboxaldehyde	276	277 (14), 276 (47), 258 (12), 248 (30), 207 (100), 191 (40), 180 (92), 168 (90), 167 (81), 166 (20), 165 (63), 152 (23), 129 (28), 128 (58), 115 (43), 91 (81), 85 (41), 83 (55), 81 (19), 77 (27), 59 (38)

label was not apparent, since acetone and diene product ions with intermediate deuteration were not observed. The distribution of label in product ions results from a selection of fragmentation mode and a residence of charge as shown with dissected structure **24**, where k_H and k_D refer to cleavage



24

modes and F_1 and F_2 refer to the fractional distribution of charge for formation of diene-d_6 and diene-d_0, respectively. Using the (B1 + B2)/(A1 + A2) ratios and the individual ion ratios, F_1 and F_2 are calculated using eq 2 and 3. The results

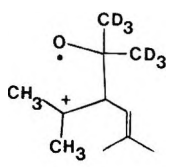
$$\frac{(\text{diene-}d_0)^{+\cdot}}{(\text{diene-}d_6)^{+\cdot}} = \left(\frac{k_H}{k_D}\right)_{tot}\left(\frac{F_2}{F_1}\right) \quad (2)$$

$$\frac{(\text{acetone-}d_0)^{+\cdot}}{(\text{acetone-}d_6)^{+\cdot}} = \left(\frac{k_D}{k_H}\right)_{tot}\left(\frac{1-F_1}{1-F_2}\right) \quad (3)$$

including the values of the isotope effect per deuterium are shown in Table V.

The isotope effect, which represents a ratio of rates for cleavage averaged over the distribution of internal energies of ions undergoing decomposition, is at a maximum at low ionizing energy, paralleling the behavior (temperature dependence) for most isotope effects in molecular thermal chemistry[23] and that of a primary deuterium isotope effect observed for mass spectral decomposition.[24] If ratios of daughter ion abundances at low voltage reflect ratios of rate constants for decomposition of **16**, the isotope effect (1.08 at 10 eV) may be nominally compared with k_H/k_D values (per deuterium) for nucleophilic substitution of labeled secondary and tertiary substrates in solution (limiting solvolyses, k_H/k_D = 1.09–1.10).[25] Another reference point is the negligible β-secondary effect (k_H/k_D = 1.00) observed[26] for a thermal retrograde Diels–Alder reaction in which rate-determining homolytic C–C cleavage is presumably important.

A mechanistic problem remains in that the isotope effect in **16** is more consistent with a two-step path involving initial C–O cleavage than one in which preliminary C–C cleavage is important (as proposed above for aryl-substituted systems). If ring opening of the molecular ion is akin to heterolysis in solvolysis chemistry and $k_H/k_D > 1.0$,[25] ions **25** and **26** would



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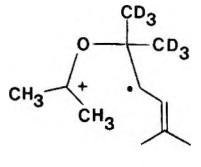

26

be favored for C–O and C–C cleavages, respectively. Only **25** leads to the preferred distribution of product ions so that either an "inverse" isotope effect on C–C cleavage is important, C–O cleavage leads the decomposition of **16** (**15**), or another mechanism such as concerted (two-bond) fragmentation prevails. In the transition state for concerted cracking, charge would be partially developed in one or the other of the nascent fragments. The preference for charge residence (F_1 and F_2 values) and the effects of ionizing energy and isotopic substitution thereon are not surprising (ionization potentials for acetone and 2,5-dimethyl-2,4-hexadiene are 9.7 and 7.9[27] eV, respectively). A direct cleavage mechanism with a normal isotope effect influencing the stability of developing charge would rationalize the data.[28]

Although a unified mechanism for oxetane cleavages does not emerge from our study in combination with earlier work,[5] it remains the case that for oxetanes substituted with aryl groups a mechanism involving cleavage of the "weaker" C–C bond followed by the partitioning of tautomeric molecular ions to cleavage products with and without hydrogen rearrangement is consistent with the observed directional selectivity and thermochemistry. A comparison with pyrolysis data is instructive. The effects of substituents on regio- and stereochemistry and on rates of cracking **9**–**11**[9b] are consistent with the intervention of diradicals which result from selective C–C cleavage (analogues of **21** and **22**). Whether these species are bona fide intermediates or descriptions of transitions states is unclear, but the evidence clearly supports a discontinuity between bond breaking and bond making for the reaction profile. The correspondence in the direction of cleavage for pyrolytic and mass spectral decompositions may be fortuitous or may depend on prevailing forces of orbital topology and

symmetry. There have been recent references to orbital symmetry imposed barriers to "four-electron" fragmentation[29] and rearrangement[30] under electron impact. The issue, as applied to oxetane cleavage, involves the potential electronic destabilization predicted for a geometrically favorable (roughly C_{2v}) transition state for concerted decomposition. Molecules could avoid barriers imposed by such unfavorable electronics through discontinuous or stepwise cracking (thermal or under electron impact). Similar mass spectral and thermal regiochemistries then result from a coincidence of substituent influences on the stability of diradicals and tautomeric radical ions.[31]

Experimental Section

Synthesis of the oxetanes,[33] *cis*- and *trans*-2-methyl-3-phenyloxetane (**9** and **10**),[34] 2,2-diphenyl-3,3,4,4-tetramethyloxetane (**11**),[35] 2,2-bis(*p*-methoxyphenyl)-3,3,4,4-tetramethyloxetane (**12**),[35] 2-phenyl-3-propyloxetane (**13**),[36] 4,4-diphenyl-3-oxatricyclo[4.2.1.0^{2,5}]-nonane (**14**),[37] and 2,2,4,4-tetramethyl-3-(2,2-dimethylethenyl)oxetane (**15**),[38] followed literature procedures. 2,2-Bis(trideuteriomethyl)-3-(2,2-dimethylethenyl)-4,4-dimethyloxetane (**16**)[39] was prepared using acetone-d_6 (99.5%, Stohler Isotope Chemicals) following the procedure for **15**. NMR analysis indicated that deuterium label was not scrambled during the photochemical cycloaddition procedure; i.e., **16** was >97% 2,2-dimethyl-d_6. Most of the reference carbonyl compounds and olefins were commercially available. The 1,1-diaryl-2-methylpropenes[40] and *cis*-3-(2,2-diphenylethenyl)cyclopentanecarboxaldehyde[37] were prepared following literature procedures.

Mass Spectra. Spectra were recorded on a Hitachi Perkin-Elmer RMU-6L instrument (chamber temperature 50–70 °C) using a direct sample insertion procedure and base-washed sample holders. Product ions were identified with reference to the spectra of proposed ketone and olefin cracking fragments obtained independently (Table VI) or assigned on the basis of literature data.[41]

Ion intensities were averaged from duplicate runs (average deviation generally 1.0%), primary ion abundances were corrected for secondary fragmentation (along with isotope corrections where necessary), and relative final intensities computed as percent abundance to produce the data in Table II.

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Supplementary Material Available: relative abundances of ions in oxetane mass spectra (Table VII) and details of calculations of heats of formation for radical ions (19 pages). Ordering information is given on any current masthead page.

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Studies in Nonpyridinoid Azaaromatic Systems. 7. Synthesis and Tautomeric Character of Cyclopenta[*c*]quinoline (Benzo[*c*][2]pyrindine)[1]

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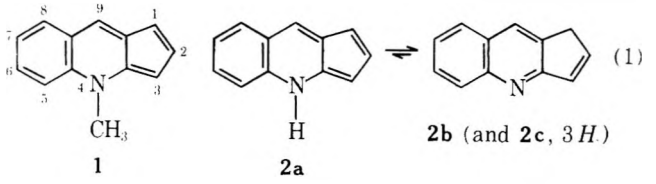
The further study of azaaromatic heterocycles isoelectronic with azulenes (the azalenes) has led to the syntheses of the tautomeric cyclopenta[c]quinolines (**12**) and the fully conjugated member, 5-methyl-5*H*-cyclopenta[c]quinoline (**14**). Compound **12** was synthesized from 4-oxo-2,3,4,5-tetrahydro-1*H*-cyclopenta[c]quinoline (**4**) by the following sequence: (1) reduction to 2,3-dihydro-1*H*-cyclopenta[c]quinoline (**5**); (2) N-oxidation of **5** to **5** *N*-oxide (**9**); (3) acetoxylation of **9** to 1-acetoxy-2,3-dihydro-1*H*-cyclopenta[c]quinoline (**10**); and (4) dehydroacetoxylation of **10** with sulfuric acid. Compound **12** was converted into **14** by a sequence of quaternization with methyl sulfate and dehydroacetoxylation with sulfuric acid. Spectral studies have demonstrated that **12** is a mixture of the 1*H*, 3*H*, and 5*H* tautomers, whose properties vary with physical state and the nature of solvent. In contrast to the cyclopenta[b]quinoline system (**1**), whose N-substituted derivatives have azulene-like visible spectra, the N–H tautomer of **12** and compound **14** do not. A resonance explanation is offered to account for the spectral differences between **1** and **14** and for the varying chromoisomerism of the cyclopentaquinolines themselves.

Heterocyclic systems formally derived from azulene by replacing CH=CH units by oxygen, sulfur, or nitrogen atoms have posed interesting challenges for both experimental and theoretical chemists.[2-6] The known number of such nitrogen analogues of azulene (azalenes) is limited,[7,8] and only recently have the unsubstituted cyclopentapyridines[9,10] and -quinolines[11-15] been reported. The properties of the most extensively studied azalene, 4-methyl-4*H*-cyclopenta[*b*]quinoline (**1**), accord well with its azulenoid character: a long wavelength maximum at 525 nm, nucleophilic attack at C_9, electrophilic attack at C_1 and C_3, and a general deshielding of the ring protons.[12-14] Hückel MO calculations on **1** and related azulene analogues give results in good agreement with the observed chemical properties, but they predict absorptions not at all in agreement with the observed visible spectra.[16,17]

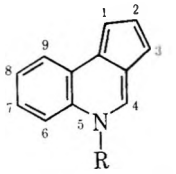
A further interesting aspect of the cyclopenta[*b*]quinoline itself (**2**) is its striking chromoisomerism: depending upon physical state, temperature, and solvent, the colorless 1*H*- and 3*H*-cyclopenta[*b*]quinolines exist in equilibrium with varying small amounts of the intensely purple **2a**. Such systems thus



1 **2a**

offer the opportunity for assessing the relative stability of the aromatic azalene delocalization through a study of the tautomeric equilibria.

To learn how the properties of cyclopentaquinolines change with the location of nitrogen, we have undertaken the synthesis and spectral examination of cyclopenta[*c*]quinolines (benzo[c][2]pyrindine) (**3**). We now wish to report that under certain conditions **3** shows a pronounced preference to exist as the NH tautomer (**3a**) and that its 5-methyl derivative (**3b**), in sharp contrast to **1**, shows no resemblance whatsoever in its visible spectrum to its azulene analogue, 4,5-benzazulene.

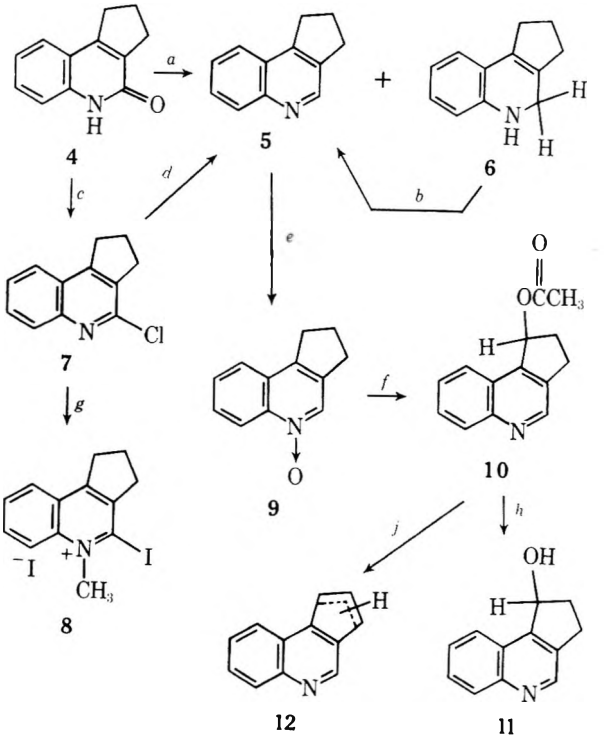


3a, R = H
b, R = CH_3

Results

Synthesis of 1*H*- (3*H*- and 5*H*-) Cyclopenta[*c*]quinoline (12). The basic heterocyclic skeleton required was obtained by the thermal condensation of ethyl cyclopentanone-2-carboxylate with aniline at 95 °C to yield the cyclic amide **4**[19] (Scheme I). This amide could be reduced to 2,3-dihydro-1*H*-cyclopenta[*c*]quinoline (**5**) in a number of reasonably efficient procedures: (1) **4** could be converted into a mixture of **5** and its 4,5-dihydro derivative **6** by means of $LiAlH_4$ in refluxing tetrahydrofuran, and then the overreduced component **6** could be reoxidized to **5** with 30% H_2O_2; (2) **4** could be treated with PCl_5 and $POCl_3$ to yield the 4-chloro derivative of **5** and the chloro derivative **4** then reduced with Raney nickel and sodium methoxide in methanol to yield **5** and some **6**; the **6** was then oxidized with picric acid to yield

Scheme I



4 **5** **6** **7** **8** **9** **10** **12** **11**

[a] $LiAlH_4$ in THF. [b] H_2O_2 or picric acid, followed by base. [c] PCl_5 and $POCl_3$. [d] Raney Ni and CH_3ONa, or Sn, $POCl_3$, and H_2O. [e] *m*-$C_6H_4ClCO_3H$. [f] $(CH_3C])_2Q$ in HOAc. [g] Excess CH_3I. [h] NaOH in CH_3OH. [j] Concentrated H_2SO_4 at 130 °C.

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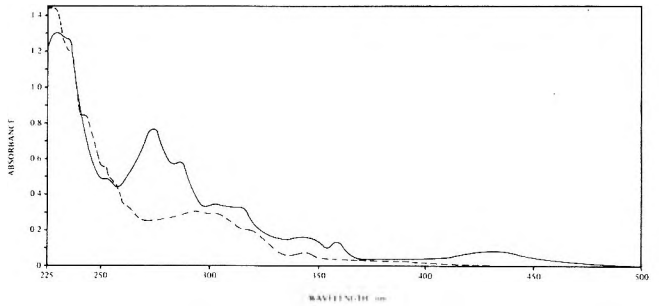


Figure 1. Ultraviolet and visible spectra of 5.3×10^{-5} M solutions of cyclopenta[*c*]quinoline (**12**): A (----) in cyclohexane and B (—) in diethyl ether.

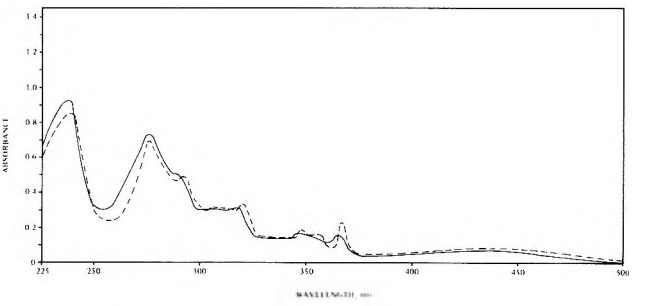


Figure 2. Ultraviolet and visible spectra of 5.0×10^{-5} M solutions of 5-methyl-5*H*-cyclopenta[c]quinoline (**14**): A (----) in cyclohexane and B (—) in diethyl ether.

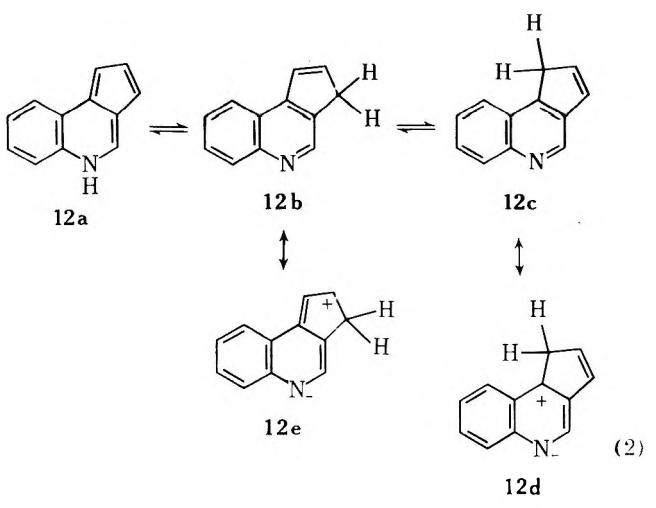
5 picrate; or (3) the chloro derivative could be reduced solely to **5** by means of tin, $POCl_3$, and water.[20]

The resulting 2,3-dihydro-1*H*-cyclopenta[c]quinoline (**5**) displayed the expected deshielded protons at C_4 and C_6 in its NMR spectrum and the three ultraviolet maxima characteristic of substituted quinolines.[21] Compound **5** underwent smooth quaternization with methyl iodide and almost quantitative *N*-oxide formation (**9**) with *m*-chloroperbenzoic acid in methylene chloride. It might be noted that even the chloro derivative **4** underwent quaternization with methyl iodide, albeit slowly, but the product was the 4-iodo methiodide (**8**).[22]

The acetoxylation of **9** with acetic anhydride in glacial acetic acid solution gave a moderate yield of the 1-acetoxy derivative (**10**), whose structure is assigned based upon the characteristic tendency of acetoxylation to occur on methylene groups α or γ to nitrogen in pyridine derivatives.[23-26] Saponification of **10** with methanolic sodium hydroxide yielded the 1-hydroxy derivative **11** whose NMR spectrum displayed a two-proton multiplet at 2.20–2.75 ppm, comparable to the H_2 protons in **5** (2.11), and another two-proton multiplet at 2.78–3.25 ppm, comparable to the H_3 protons in **5** (3.05). Such similarities offer direct support for assigning **10** and **11** the 1-substituted structures.

Either **10** or **11** could be subjected to an elimination reaction by means of concentrated sulfuric acid; the reaction was conducted at 130 °C for short contact times and then quenched with ice and sodium hydroxide solution at or below 0 °C. The mixture of 1*H*-, 3*H*-, and 5*H*-cyclopenta[*c*]quinolines (**12**) was isolated as an orange crystalline solid, which was quite stable if stored under nitrogen at 0 °C.

Spectral Properties of the Cyclopenta[*c*]quinolines (12). The infrared spectra of **12** in a neat condition (evaporation of solutions) or in mineral oil suspension showed intense NH bands in the 3300 cm^{-1} region, but these disappeared in solutions of **12** in $CHCl_3$ or CCl_4. The NMR spectrum in $CDCl_3$ exhibited two sharp absorptions at 8.97 and 8.99 ppm in an intensity ratio of 2:1, corresponding to the different C_4 protons in the 3*H*- and 1*H*-cyclopenta[c]quinolines (**12b** and **12c**). Likewise, two multiplets appeared at 3.64 and 3.75 ppm, also in a ratio of 2:1, and these could be assigned to the methylene absorptions of **12b** and **12c**, respectively. The greater magnetic deshielding of the methylene protons in **12c** can be ascribed to polar resonance contributions, such as **12d**. An analogous polar contributor to **12b**, namely **12e**, would be less important, since it involves greater charge separation. Therefore, from the infrared and NMR spectra alone, it is clear that significant proportions of all three tautomers can be present at equilibrium (eq 2).



(2)

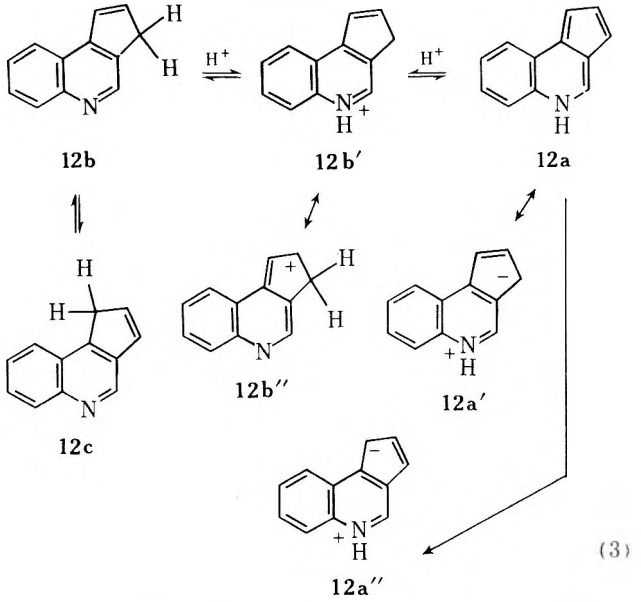
Examination of the ultraviolet and visible spectra of **12** as well as its NMR spectrum in concentrated sulfuric acid further revealed that pronounced variations in the proportions of **12a**, **12b**, and **12c** could occur. As the subsequent synthesis of 5-methyl-5*H*-cyclopenta[*c*]quinoline (**14**) has established (cf. infra), the orange color of **12** is properly attributed to the chromophoric system in **12a**. The presence of the NH infrared bands in very concentrated samples of **12** and their absence in more dilute solutions show how sensitive the proportion of **12a** is to the nature of the medium. The visible spectrum of **12** in different solvents was even more indicative of drastic variations in the ratio of the tautomers: not only did **12** dissolve slowly in cyclohexane, but an almost colorless solution resulted. Its molecular spectrum (Figure 1A) shows little resemblance to the spectra of either **12** in diethyl ether (Figure 1B) or **14** in cyclohexane (Figure 2A). Although the concentration of **12** in both solvents is the same (5.3×10^{-5} mol/L), the ethereal solution is distinctly yellow. From these spectra one can conclude that very little **12a** is present at equilibrium, since almost no absorption is observable in the 410–450-nm region. The spectrum of **12** in cyclohexane is similar to that of **5**, with the kinds of bathochromic shifts to be expected from vinylquinolines, such as **12b** and **12c**.[11]

On the other hand, the almost superimposable spectra of **12** and **14** in diethyl ether solution (both 5×10^{-5} mol/L, Figure 1B) lead to the conclusion that in this solvent **12** exists almost entirely in the form of **12a**. Ethanolic solutions also favor the preponderance of **12a**.

The dissolution of orange **12** in concentrated sulfuric acid produced a light-amber colored solution, whose NMR spectrum now showed only a broad singlet at 4.35 ppm, corresponding to one methylene group. In accordance with this view, only one C_4 proton was displayed downfield, at 9.20 ppm, although it was split by the adjacent NH^+ group. Verification that this was indeed splitting, rather than two signals, was secured by observing only a singlet at 9.20 ppm, when the spectrum of **12** was recorded in D_2SO_4.

The absence of any significant color and the presence of only one methylene group rule out the formation of any N-

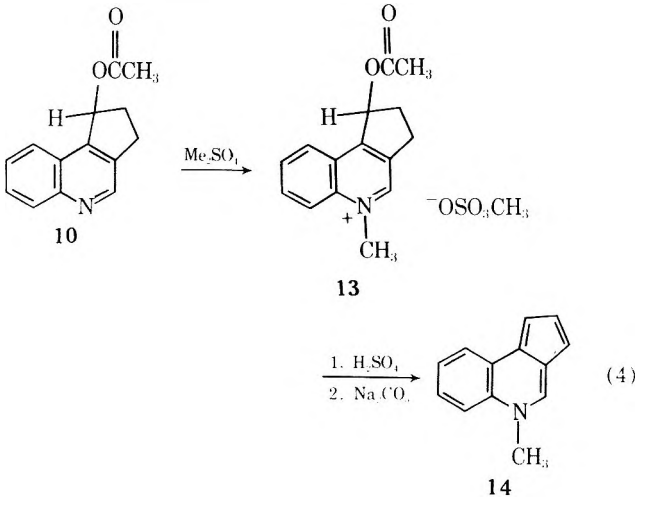
Scheme II



(3)

protonated cation of **12a**. The generation of one methylene group supports the preferential protonation of **12b** or **12c**. Because its cation (**12b′**) has the more advantageous delocalization of charge, **12b** would seem to be more basic than **12c** and thus undergo preferential protonation (Scheme II). Any component **12a** present in the initial tautomeric mixture could also lead to cation **12b′** by undergoing protonation exclusively at C_3. Consideration of the polar resonance structures **12a′** and **12a″** suggests that **12a′** would contribute more to the ground state stabilization of **12a** because of: (1) smaller charge separation and (2) superior conjugation of the exocyclic vinyl group when γ rather than β substituted on the pyridinoid nucleus.[27]

5-Methyl-5*H*-cyclopenta[c]quinoline (14). In order to determine the spectral properties of the azalene nucleus present in tautomer **12a** (or **3a**), the *N*-methyl derivative (**14**) was synthesized from the 1-acetoxy derivative **10.** This transformation was readily achieved by quaternizing **10** to **13** with methyl sulfate, dehydroacetoxylating **13** in hot, concentrated sulfuric acid, and neutralizing the reaction mixture to release **14** (eq 4).



(4)

The resulting orange product **14** lacked any infrared absorption in the NH region. Its electronic spectrum in either cyclohexane or diethyl ether closely resembled the spectrum of **12** in diethyl ether or ethanol. The spectrum of **12** in cyclohexane, however, was quite different from that of **14** in the same solvent (cf. Figure 1). This finding supports the above-mentioned conclusion that in cyclohexane **12** exists largely in the form of tautomers **12b** and **12c,** but that in ether or ethanol **12** exists chiefly as **12a.**

The spectrum of **14** in diethyl ether was identical with that in methanol, but the addition of one drop of 0.1 N hydrochloric acid to the latter solution caused pronounced spectral changes. No absorption occurred over 380 nm and spectral peaks were now at 322, 275, 244, 239, and 204. In general features, this latter spectrum resembles the spectra of other protonated vinylquinolines.[11]

Finally, the NMR spectrum of **14** displays all its nuclear protons between 6.95 and 8.24 ppm, an observation more consistent with aromatic deshielding of protons by ring current than with the shielding to be expected of C–H protons vinylogously β to an enamine nitrogen (i.e., those at C_1, C_2, or C_3).[28]

Discussion

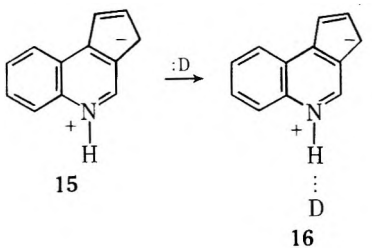
The properties of the cyclopenta[*b*]quinoline (**2**) and the cyclopenta[c]quinoline (**3**) nuclei provide a striking and instructive contrast. Although the N-substituted derivatives are isoelectronic with the 5,6-benzazulene (long wavelength λ_{max} 557 nm) and the 4,5-benzazulene (λ_{max} 575 nm) systems, respectively, only **1** and **2a** show a close similarity to their azulene counterpart in their visible spectra. Their purple color (λ_{max} at ca. 510 nm) contrasts sharply with the yellow-orange of **3a** and **3b** (λ_{max} at ca. 430 nm).

Even the tautomeric equilibria existing among the cyclopenta[*c*]quinolines (**12a–c,** eq 2) offer some unusual aspects when compared with similar equilibria established among the cyclopenta[*b*]quinolines (**2a–c,** eq 1). It is true that with both systems the ratio of the two C–H tautomers (C_1:C_3 in **2** and C_3:C_1 in **12**) is 2:1 in $CDCl_3$ or CCl_4 solution. The relative amounts of the N–H tautomers, (**2a** and **12a**), however, are clearly different. Although liquid samples of **2** are purple, solidified **2** is essentially colorless. Solutions of **2,** 2 M in benzene, are estimated to contain ca. 5% of tautomer **2a,** but dilute solutions in 95% ethanol or cyclohexane are colorless and do not absorb above 350 nm. On the other hand, samples of **12** in the solid state and in ethanolic or ethereal solution are distinctly yellow or orange; in fact, the visible spectra of **12** and **14** in diethyl ether are superimposable. These observations support the conclusion that **12** exists largely or exclusively as tautomer **12a** under these conditions. It is readily apparent that the NH tautomer is much more stable (relative to its C–H tautomers) in the cyclopenta[*c*]quinoline system than in the cyclopenta[*b*]quinoline system.

Yet with both heterocycles, the solvent employed can reduce the content of the N–H tautomer to a negligible amount. Already in dilute solutions the percentage of **2a** in **2** has fallen under 1%. More remarkable, however, is the dramatic change in the electronic spectrum of **12** when recorded in cyclohexane. The content of **12a** is now 1% or less. The spectral behavior of **12** (and less so, **2**) in various solvents seems to be another vivid example of how solvents can influence tautomeric equilibria.[29] As explicated by Hammett, a solvent in which one tautomer is relatively more soluble than the other tautomer(s) will favor that tautomer at equilibrium. Such changes in the K_{eq} are due to variations in the activity coefficient of the tautomer as the solvent is varied.[30] The observed spectral changes of **12** in ether and in cyclohexane can be interpreted to mean, therefore, that **12a** is more soluble than **12b** and **12c** in ether (and in ethanol), while **12b** and **12c** are more soluble than **12a** in cyclohexane. The slow dissolution of the orange solid **12** in cyclohexane thus seems to be due to the necessity of the dominant isomer **12a** to rearrange slowly to the more soluble isomers **12b** and **12c.**

Since tautomer **12a** is more soluble in polar solvents than **12b** and **12c,** it appears reasonable to ascribe its heightened

solubility to its greater dipolar character (**15**) and its ability to form hydrogen-bonded solvates (**16**) (eq 5). The behavior



(5)

of **12** in strong acids is, in part, also related to the polar character of **12a** (**15**), whereby C_3 protonation should yield the more stable cation (cf. supra).

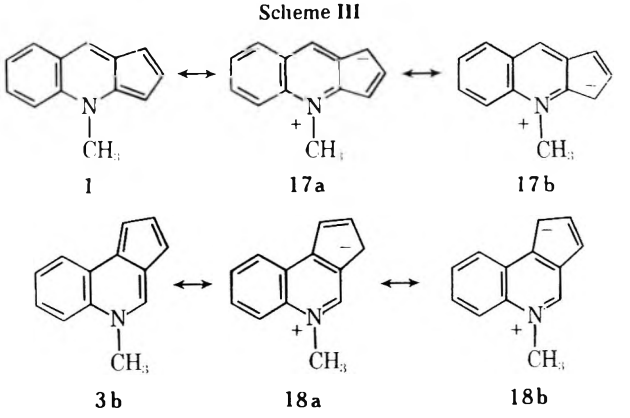
Some attempt should now be made to understand both the visible spectra of the methyl derivatives, **1** and **3b**, as well as the relative stability of the N–H tautomers, **2a** and **12a**. A common explanation underlies, we believe, both phenomena. In the introduction we have already mentioned how inadequate Hückel MO treatments are in reproducing the spectra of these azalenes. Hence, we shall attempt a qualitative analysis in the terms of resonance theory.

The long wavelength absorptions of **1** and **3b** can be viewed as the lowest π–π^* transitions of these systems.[31] The energy of this transition is clearly lower for **1** (510 nm) than for **3b** (430 nm). The difference could be ascribed to a greater stabilization of one of the ground states, of one of the two first excited states, or some combination of the two energy perturbations. Without claiming to have made a definitive choice, we believe that relative ground-state stabilization can be invoked to explain both the spectra and the N–H tautomer stability.

Evidence has been offered above on the polar character of the azalene ring (**15**) in the ground state. If those polar resonance structures are now considered for **1** and **3b** that do not disrupt the quinoline 10π-electron set, then it is apparent that **18a** and **18b** retain aromatic sextets in all rings, while **17a** and **17b** do not (Scheme III). Therefore, either by the intuitive Fries rule or more rational MO–structure enumeration techniques[32] canonical structures **18a** and **18b** should be of lower energy than **17a** and **17b** and thus should stabilize the ground state of **3b**, more than **17a** and **17b** should stabilize that of **1**.[33a] Furthermore, the more energy-rich structures **17a** and **17b** should contribute more to stabilizing the first excited state of **1** than **18a** and **18b** do to the excited state of **3b** (because of the lower energy of the latter contributors) (Figure 3). Hence, the hypsochromic shift in the π–π^* transition of **3b** is accounted for satisfactorily.

Clearly it remains highly desirable to seek a theoretical interpretation of these unusual spectral changes in the language of molecular orbital theory. Although large molecules (>15–20 atoms) of low symmetry lie at the border of quantitative MO calculations (cf. Bock's discussion[33b]), approximations may provide insights. Thus, the ω technique of HMO theory has been used to rationalize the spectral differences between 1- and 2-pyrindines.[33c]

Scheme III



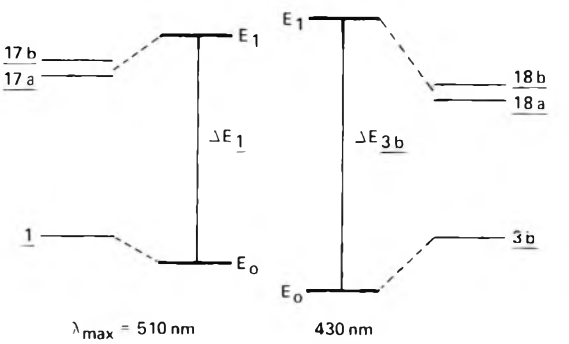


Figure 3. Relative contributions of resonance canonical structures, **1**, **17a**, and **17b** for 4-methyl-4*H*-cyclopenta[*b*]quinoline and **3b**, **18a**, and **18b** for 5-methyl-5*H*-cyclopenta[*c*]quinoline, to the ground-state (E_0) and first excited-state (E_1) energies of these heterocylces. The energies ΔE_1 and ΔE_{3b} represent those of the longest wavelength π-π^* absorptions of the cyclopenta[*b*]quinoline and the cyclopenta[*c*]-quinoline, respectively.

This suggested stabilization of **3b** over **1** should also be reflected in the tautomeric equilibria of **12** (eq 2) and of **2** (eq 1). Thus, it is expected that, in competition with various C–H tautomers of similar energy (N.B., ratio of CH tautomers, 2:1 in both cases), the greater azalene stabilization of **12a** over **2a** should shift the equilibrium in eq 2 farther to the left than that in eq 1.

By such resonance considerations, a consistent interpretation of the properties of these tautomeric cyclopentaquinolines can be formulated. It is clear, however, that chromoisomerism in heterocyclic compounds is a complex and significant phenomenon, deserving of further study.

Experimental Section

Melting points were determined with a Thomas-Hoover "Unimelt" apparatus and are uncorrected. Infrared spectra of samples were recorded on Perkin-Elmer spectrophotometer, Model 457, as solutions in pure solvents (spectral grade) or as mineral oil suspensions. Proton magnetic resonance spectra were measured with Varian spectrometers, Model A-60 (60 MHZ) or V-3521A (100 MHZ), on samples dissolved in pure solvents containing tetramethylsilane as an internal standard. Signals 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. Ultraviolet and visible spectral data were obtained with a Perkin-Elmer spectrophotometer, Model 202, on samples in solvents of spectral grade purity. Mass spectra of samples were recorded at Baker Laboratories, Cornell University, Ithaca, N.Y., either on Associated Electrical Industries, Model AEI MS902, or Perkin-Elmer, Model 270, mass spectometer. TLC was run on a plate made up of silica gel with 10% calcium sulfate as binder. Iodine was used as a spot developer. Silica gel, supplied by Baker Chemicals, was used for all column chromatography. Elemental analyses were carried out by the Spang Microanalytical Laboratory, Ann Arbor, Mich.

All preparations and reactions involving sensitive, reactive heterocyclic intermediates were conducted under an atmosphere of dry, oxygen-free nitrogen. Appropriate techniques for such manipulations, including the necessary purification of solvents, have already been described.[20]

4-Oxo-2,3,4,5-tetrahydro-1*H*-cyclopenta[*c*]quinoline (4). The preparation of **4** was carried out by a slightly modified procedure of Blount et al.[19] In a 250-mL, three-neck, round-bottom flask, fitted with a thermometer and a Dean-Stark trap, were placed ethyl cyclopentanone-2-carboxylate (39.0 g, 250.0 mmol) and freshly distilled (over zinc dust) aniline (23.25 g, 250.0 mmol). The mixture was heated to reflux (~95 °C) with magnetic stirring. With the distillation of ethanol the temperature of the reaction mixture rose slowly at first and sharply at the end. By the time ca. 11 mL of distillate was collected, the temperature reached 170 °C. The heating was discontinued and the reaction mixture was allowed to stand at room temperature for 18 h. The resulting light-brown oil was slowly added to 75 mL of

36 N H_2SO_4 with cooling. The reddish-brown syrup was heated on a steam bath (80–90 °C) for 15 min. The dark-red liquid was poured into 1 L of ice-chilled water. The light-yellow solid that separated was filtered and thoroughly washed (neutral to litmus) with water. The crude product (mp >250 °C) was recrystallized from boiling ethanol to yield[34] 16.3 g (35%) of the pure crystalline product: mp 262–264 °C dec (with previous blackening) (lit.[19] 256 °C, 259–61 °C); IR (Nujol) 1660 (vs, C=O), 1622 (vw), 1612 (vw), 1568 (m), 1510 (m), 1480 (w), 1441 (s), 1438 (s), 1408 (w), 1402 (w), 1350 (w), 1308 (vw), 1288 (vw), 1280 (vw), 1270 (w), 1258 (w), 1165 (m), 1155 (w), 1122 (w), 1030 (vw), 940 (m), 960 (sh), 950 (m), 852 (vw), 765 (vw), 760 (s), 755 (s), 642 cm^{-1} (m).

2,3-Dihydro-1*H*-cyclopenta[c]quinoline (5). Method A. Step 1. Lithium Aluminum Hydride Reduction of 4-Oxo-2,3,4,5-tetrahydro-1*H*-cyclopenta[c]quinoline (4). To a magnetically stirred solution of lithium aluminum hydride[35] under a nitrogen atmosphere (4.45 g, 117.0 mmol) in 800 mL of absolute tetrahydrofuran was added carefully, in small portions (frothing, H_2 evolution), powdered **4** (21.40 g, 116.0 mmol). As the reaction mixture was heated at gentle reflux, the color of the reaction mixture gradually changed from gray to green (18 h) and finally to pale green (40 h). After 6 days of reflux (color change pale green to green at 18 h to pale green at 40 h), 4.5 mL of H_2O and then 4.5 mL of NaOH and 13.5 mL of H_2O were added. Upon further stirring, the hydrolyzed mixture formed a white granular precipitate which was filtered off. The precipitate was thoroughly washed with methylene chloride. The filtrate was dried ($MgSO_4$), and the solvent was evaporated under reduced pressure to yield 17.7 g of a brownish solid (crude yield ca. 90%). The NMR of the crude product showed it to be a mixture of **5** and 2,3,4,5-tetrahydro-1*H*-cyclopenta[*c*]quinoline (**6**).

The crude product from the reduction of **4** gave, after six recrystallizations from ethanol, a fairly pure sample of 2,3,4,5-tetrahydro-1*H*-cyclopenta[*c*]quinoline (**6**): mp 89–92 °C; NMR ($CHCl_3$) δ 6.42–7.08 (complex m, 4, H_6, H_7, H_8, and H_9), 4.25 (br s, 2, H_4), 3.30 (br s, 1, NH, chemical shift varied with concentration and signal disappeared upon shaking with D_2O), 1.67–2.83 (complex m, 6, H_1, H_2, and H_3); picrate, mp 196–197 °C dec (orange, from ethanol).

Step 2. Hydrogen Peroxide Oxidation of 6 to 5. Usually after the workup of lithium aluminum hydride reduction, the aluminum hydroxide precipitate was filtered off and the tetrahydrofuran solution was treated directly with 1 equiv of 30% hydrogen peroxide[37] (13.3 mL, 116 mmol), whereupon a mild exotherm occurred. Since the reaction mixture yielded a positive KI starch test, it was heated at gentle reflux for 6 h. The completion of the reaction could be easily followed with NMR by observing the disappearance of the complex multiplet at 7.08–6.42 ppm and the increase in integrated intensity of H_4 singlet absorption at 8.73.

Most of the solvent was evaporated under reduced pressure and at low temperature (~40 °C). The residual orange thick oil was taken upon methylene chloride and washed twice with saturated sodium bicarbonate solution, then with water, and finally by sodium sulfite solution and water. After the organic layer was dried ($MgSO_4$) and the solvent removed in vacuo, the remaining thick brownish oil was vacuum distilled [113–115 °C (0.1 mm)] to give 14.2 g of **5** (yield 72% based on starting compound **4**), mp 55–56 °C. The distillate yielded a white solid upon recrystallization from ether–petroleum ether, tiny sugar-like cubes: mp 58–59 °C; IR (CCl_4) 3061 (m), 3030 (2), 3000 (w), 2955 (vbr vs), 2864 (vw), 2950 (s), 1616 (w), 1600 (m), 1582 (s), 1561 (s), 1500 (vs), 1456 (s), 1432 (s), 1428 (sh), 1415 (sh), 1382 (vs), 1366 (w), 1354 (m), 1306 (vs), 1298 (s), 1290 (sh), 1275 (vw), 1254 (m), 1200 (w), 1178 (vw), 1152 (vs), 1031 (m), 1020 (s), 1000 (vw), 955 (s), 927 (s), 902 (w), 885 (w), 852 (m), 680 (w), 632 cm^{-1} (m); UV (cyclohexane) λ_{max} (log ε) 233 (3.35), 277 (3.28), 308 (3.22), 310, 317 (3.25). These absorptions are close to those of other cycloalkenoquinolines reported earlier[11] and can be compared with quinoline values:[21] λ_{max} (ϵ_{max}) 228 (40 000), 270 (3162), 315 (2500) in cyclohexane; NMR ($CDCl_3$) 8.73 (s, 1, H_4), 8.17 (m of d, 1, H_6), 7.73–7.17 (complex m, 3, H_7, H_8, and H_9), 3.05 (q, 4, H_1 and H_3), 2.11 (m resembling a quintet, 2, H_2); mass spectrum (70 eV) *m/e* (rel intensity) 169 (M^+, 100).

Anal. Calcd for $C_{12}H_{11}N$: C, 85.21; H, 6.51; N, 8.29. Found: C, 85.26; H, 6.46; N, 8.22. Picrate: a yellow crystalline powder (EtOH), mp 205 °C dec (with previous blackening) (lit. 216–217 °C dec, 212–215 °C dec).

Anal. Calcd for $C_{18}H_{14}N_4O_7$: C, 54.27; H, 3.54. Found: C, 54.26; H, 3.77.

Method B. Step 1. 4-Chloro-2,3-dihydro-1*H*-cyclopenta[c]quinoline (7). A mixture of 2.0 g (10.8 mmol) of **4**, 3.0 g of phosphorus pentachloride, and 30 mL of phosphorus oxychloride was heated at reflux for 30 min, the excess phosphorus oxychloride was distilled off, and the residue was poured into ice–water. The colorless solid product was filtered off and recrystallized from methanol, 70%: mp 120–120.5 °C (lit.[38] 118–120 °C); IR (mineral oil) absence of C=O; NMR δ 2.1–2.4 (m, 2, CH_2), 3.0–3.5 (m, 4, C_1 and C_3), and 7.5–8.0 (m, 4). Heating **7** with an excess of methyl iodide in benzene solution slowly (>24 h) led to the deposition of a yellow solid, mp 220–222 °C dec, that by mass spectrometry proved to be the methiode of 4-iodo-2,3-dihydro-1*H*-cyclopenta[c]quinoline (**8**): mass spectrum (70 eV) *m/e* (rel intensity) 310 ($C_{13}H_{13}IN^+$, 46), 309 (37), 295 ($M^+ - CH_3$, 37), and 168 (100).

Step. 2. Raney Nickel Reduction of 7. In a hydrogenation pressure bottle was placed a mixture of 5.5 g (27 mmol) of **7**, 5.4 g of fresh Raney nickel catalyst, and a solution of sodium methoxide in methanol (prepared from 3.2 g of sodium metal and 50 mL of methanol). After the mixture was shaken at room temperature and pressure for 48 h, the catalyst was filtered off and the filtrate freed of solvent. The residue was dissolved in ethyl ether, and the extracts were washed with water, dried, and then evaporated. Distillation of the residue yielded a mixture of **5** and **6**, bp 95–100 °C (0.65 mm). The distillate was treated directly with an excess of ethanolic picric acid to yield the picrate of **5**, mp 212–215 °C dec, after recrystallization from acetone (lit.[39] 216–217 °C dec). Treatment of an aqueous suspension of the picrate with a 20% NaOH solution yielded **5**, which formed colorless platelets from petroleum ether (bp 30–60 °C), mp 36.5–37.5 °C, but mp 58–59 °C from ether–petroleum ether pair, in an overall 55% yield.

Anal. Calcd for $C_{12}H_{11}N$: C, 85.21; H, 6.51; N, 8.29. Found: C, 85.26; H, 6.46; N, 8.29.

Warming **5** (850 mg) and 3 mL of methyl iodide in 25 mL of 95% ethanol for 30 min on a steam bath and cooling deposited 800 mg of the dull-green methiodide, mp 225–228 °C dec, from ethanol. Heating **5** methiodide with ethanolic picric acid and cooling yielded thick yellow needles of the methopicrate, mp 171–172 °C dec, from ethanol.

2,3-Dihydro-1*H*-cyclopenta[c]quinoline *N*-Oxide (9). To an ice-cooled solution of **5** (8.79 g, 52.0 mmol) in 200 mL of methylene chloride was added, in small portions, 10.5 g (52.2 mmol) of 85% *m*-chloroperbenzoic acid with cooling and stirring. An exothermic reaction occurred as the solution became yellow.[41] An excess of the peracid was confirmed by starch–iodide test paper. The reaction mixture was heated at reflux for 6 h under a nitrogen atmosphere. Completion of reaction was monitored by starch–iodide test paper and by NMR (upfield shift of H_4 absorption from 8.73 ppm in **5** to 8.47). The reaction mixture was chilled in ice and then excess peracid was destroyed by the addition of 10% aqueous sodium sulfite solution until a test with starch–iodide paper was negative. The layers of the reaction mixture were then separated, and the organic layer was vigorously shaken with 1.5 equiv of 2 N sodium hydroxide solution (ca. 39 mL) to extract the *m*-chlorobenzoic acid. The organic layer was washed with water and finally with saturated sodium chloride solution. The clear organic layer was dried ($MgSO_4$) and stripped of solvent to yield 9.15 g of a light-brown solid (yield ca. 95%): mp 148–50 °C dec. An analytical sample was prepared by recrystallization with ethanol–ether–pentane to yield a light-brownish crystalline material: mp 150–151.5 °C dec (previously black); IR (mineral oil) 1568 (m), 1512 (w), 1428 (2), 1420 (vw), 1402 (s), 1398 (m), 1365 (w), 1325 (m), 1295 (m), 1260 (w), 1222 (w), 1203 (w), 1188 (vw), 1160 (w), 1148 (m), 1141 (m), 1082 (s), 1018 (w), 1004 (vw), 962 (m), 872 (m), 865 (m), 782 (m), 775 (s), 760 cm^{-1} (w); NMR ($CDCl_3$) δ 8.88–8.57 (m of d, 1, H_6), 8.47 (S, 1, H_4), 7.87–7.33 (m, 3, H_7, H_8 and H_9), 3.10 (q, 4, H_1 and H_3, J = 7.0 Hz), 2.25 (q, 2, H_2, J = 7.0 Hz); mass spectrum (70 eV) *m/e* (rel intensity) 185 (M^+, 100), 184 (30), 169 (M − O, 14), 168 (M − OH, 31), 167 (M − H_2O, 35), 156 (M − C_2H_5, 37), 130 (30), 129 (45).

Anal. Calcd for $C_{12}H_{11}NO$: C, 77.81; H, 5.99; N, 7.56. Found: C, 77.75; H, 5.94; N, 7.59. Picrate: mp 160–162 °C dec (pale green, from EtOH).

Anal. Calcd for $C_{18}H_{14}N_4O_8$: C, 52.18; H, 3.40; N, 13.52. Found: C, 52.31; H, 3.53; N, 13.41.

1-Acetoxy-2,3-dihydro-1*H*-cyclopenta[c]quinoline (10). Under a nitrogen atmosphere a stirred portion of acetic anhydride (3.70 mL, 4.00 g, 39.25 mmol) was treated dropwise with a solution of *N*-oxide **9** (7.23 g, 39.1 mmol) in 75 mL of glacial acetic acid over a period of 1.5 h. The brown solution was heated on a steam bath for 2 h[42] with stirring. After a few minutes of heating, the reaction mixture became deep blood-red. After heating, the deep-red reaction mixture was allowed to stand at room temperature overnight and then stripped of most of the acetic acid under reduced pressure. The remaining reddish-brown, sticky material was dissolved in ether, and the etheral layer was washed with saturated sodium bicarbonate solution and then water. The ethereal layer was dried ($MgSO_4$) and the solvent removed to yield 5.76 g of a dark reddish-brown viscous product.

The acetoxy derivative **10** was separated by chromatography on a 210-g silica gel column (95 × 3.5 cm) prepared with petroleum ether. The eluting solvent was varied from petroleum ether through mixtures with ether (mainly 1:1), as fifty 50 mL fractions were collected. The fractions were analyzed by weight curve determination and by NMR spectroscopy. Fractions 1–15, weighing together 290 mg, were discarded since they contained unidentifiable oil products. Fractions 16–25 contained a colorless crystalline solid, whereas fractions 26–34 contained crystalline product ranging from light pink to red. However, all these fractions (16–34) contained **10**, by NMR, and were combined to give 4.23 g of the product. The remaining fractions contained some polymeric material (mp 143–152 °C dec) which gave an intense bright-red solution in organic solvents, showed very broad NMR absorptions, and hence were discarded.

The product **10** was recrystallized with hexane to give 3.90 g (44%)[43] of colorless, compact crystals, mp 96–97 °C. An analytical sample was prepared by two more recrystallizations from ether–petroleum ether: mp 97–98 °C; TLC (1:1.5 mixture of petroleum ether–ether) showed a single spot with R_f 0.5; IR ($CHCl_3$) 3050 (sh), 3030 (sh), 2950 (br m), 2856 (vw), 1730 (br vs), 1592 (w), 1570 (w), 1509 (m), 1468 (w), 1450 (vw), 1430 (vw), 1372 (s), 1320 (w), 1300 (w), 1225 (vbr vs), 1158 (m), 1132 (vw), 1080 (w), 1022 (s), 978 (w), 948 (m), 922 (m), 890 (w), 864 cm^{-1} (w); NMR ($CDCl_3$) δ 8.72 (S, 1, H_2), 8.08 (m of d, 1, H_6), 7.88–7.28 (m 3, H_7, H_8, and H_9), 6.56 (q, 1, H_1), 3.38–1.90 (complex m, 4, H_2 and H_3), 2.02 (S, 3, $OCOCH_3$). Irradiation of H_1 affects the upfield part of multiplet (i.e., 2.76–1.90) which is the absorption due to $2H_2$: mass spectrum (70 eV) *m/e* (rel intensity) 227 (M^+, 1), 184 (M − CH_3CO, 6), 168 (M −CH_3CO_2, 38), and 167 (M − CH_3CO_2H, 100). For comparison, it should be noted that 3-acetoxy-2,3-dihydro-1*H*-cyclopenta[*b*]quinoline displays a similar cracking pattern: 227 (17), 184 (56), 158 (31), and 167 (100).

Anal. Calcd for $C_{14}H_{13}NO_2$: C, 73.99; H, 5.76; N, 6.16. Found: C, 74.09; H, 5.86; N, 6.35.

1-Hydroxy-2,3-dihydro-1*H*-cyclopenta[*c*]quinoline (11). The 1-acetoxy derivative **10** was saponified to yield the corresponding hydroxy derivative **11** by heating a solution of **10** (3.42 g, 15.1 mmol) in 75 mL of methanol with 16 mL of 1 N NaOH on a steam bath for 30 min and then allowing the mixture to stand at room temperature overnight. A crystalline solid thus formed was filtered and thoroughly washed with water, ether, and a small amount of methanol. The product weighed 2.20 g, mp 185–86 °C. The mother liquor was stripped of solvent, and the residue was taken up in water and extracted with four 50-mL portions of methylene chloride. The combined organic extracts were dried ($MgSO_4$), and the solvent was removed to give a grayish solid that was recrystallized with methanol–ether to yield 600 mg of the product (combined yield, quantitative). An analytical sample was prepared by two recrystallizations from methanol–ether: mp 187–188 °C; IR (mineral oil) 3120 (br m, OH), 1570 (w), 1505 (m), 1320 (sh), 1309 (m), 1270 (m), 1230 (w), 1155 (w), 1145 (w), 1078 (w), 1052 (w), 772 cm^{-1} (s); NMR (Me_2SO-d_6) δ 8.85 (s, 1, H_4), 8.45–7.43 (m, 4, H_6, H_7, H_8, and H_9), 5.73–5.40 (m, 2, H_1 and OH), 3.25–2.78 (m, 2, H_3), 2.75–2.20 (m, 2, H_2); NMR (CF_3CO_2H) δ 8.34 (br s, 1, H_4; it resembled doublet, possibly because of N-protonation: it became a doublet in concentrated H_2SO_4), 7.96 (m, 1, H_6), 7.80–6.95 (m, 3, H_7, H_8, and H_9), 5.80–5.33 (m, 1, H_1), 2.93–1.43 (m, 4, H_2 and H_3); mass spectrum (70 eV) *m/e* (rel intensity) 185 (M, 100), 184 (72), 168 (M − OH, 21), 167 (M − H_2O, 17), 156 (20), 143 (22), and 142 (22).

Anal. Calcd for $C_{12}H_{11}NO$: C, 77.81; H, 5.99; N, 7.56. Found: C, 77.69; H, 5.90; N, 7.64.

The 1-hydroxy derivative **11** can be reacetylated by the standard reaction with acetic anhydride and pyridine, but an attempted acetylation using acetic anhydride and glacial acetic acid was unsuccessful.

1*H*- (3*H*- and 5*H*-) Cyclopenta[*c*]quinoline (Benzo[*c*][*2*]pyridine) (12). To the powdered 1-hydroxy derivative **11** (3.0 g, 16.2 mmol), or an equivalent amount of 1-acetoxy compound **10**, was added dropwise 15 mL of cooled 36 N sulfuric acid (540 mmol). The magnetically stirred, partially dissolved mixture was heated in an oil bath at 130 °C for 5 min (10–12 min in the case of **10**), and the resulting light-brown solution was immediately poured over ice (~500 g), upon which the diluted mixture displayed faint purple coloration. Then the mixture was neutralized with saturated sodium carbonate solution and the temperature of the reaction mixture was kept below 0 °C. Interestingly, neutralization occurred like a titration and was visually observable (color change from faint purple to bright lemon-yellow). The reaction mixture was thoroughly extracted with four parts of 250 mL of ether. The bright-yellow etheral extracts were combined and dried (K_2CO_3) with ice bath cooling.[44] The solvent was removed at or below room temperature under reduced pressure to yield a yellow-orange solid (~1.65 g, 61% yield) which was triturated with methanol to give an orange crystalline powder, mp 109–111 °C dec (with previous darkening; shrinks from 105 °C).

Anal. Calcd for $C_{12}H_9N$: C, 86.20; H, 5.43; N, 8.38. Found: samples sent for analysis gave a low total for C, H, N, indicating uptake of oxygen but yielded the right ratio, $C_{12}H_9N$. Cf. mass spectrum (20 eV) *m/e* (rel intensity), source at 80 °C and probe at 50 °C; 168 (M + 1, 17.3), 167 (m, 100), 166 (18.2), 149 (27.3), 139 (15.5), 128 (20), 105 (18.2), and 88 (19.6) with no sign of peaks due to dimers (334) or higher oligomers; source at 80 °C and probe at 150 °C, 167 (100), with weak peak at 334, but no peaks for trimers (501) or tetramers (668); NMR ($CDCl_3$) 8.99 and 8.97 (two s, 1, for the H_4 of the isomeric 3*H*- and 1*H*-cyclopenta[c]quinolines in a ratio of 67:33), 7.53–8.23 (m, 4, H_6, H_7, H_8, and H_9), 6.59–7.06 (m, 2, vinylic H_1, H_2, and H_3), 3.75 and 3.64 (two t, 2, for the isomeric 1-CH_2 and 3-CH_2, respectively, in a ratio of 32:68); IR (neat) 3370 (br m), 3280 (br, m), 1625 (m), 1595 (m), 1570 (w), 1533 (w), 1500 (w), 1468 (w), 1443 (m), 1418 (w), 1358 (m), 1335 (m), 1325 (vw), 1288 (m), 1238 (vw), 1192 (w), 1160 (w), 1152 (w), 1093 (m), 1055 (vw), 1035 (w), 1018 (w), 975 (m), 940 (w), 920 (w), 870 (m), 862 (vw), 850 (w), 800 (br m), 760 (s), 756 (s), 732 (m), 685 cm^{-1} (w); IR (Mineral oil) 3370 (s, NH), 3286 (s, NH), 1630 (vs), 1625 (sh), 1598 (s), 1572 (m), 1546 (m), 1502 (w), 1445 (s), 1418 (w), 1410 (vw), 1361 (vs), 1338 (m), 1298 (w), 1288 (m), 1282 (w), 1258 (w), 1238 (w), 1192 (s), 1160 (w), 1152 (m), 1093 (vs), 1052 (w), 1034 (w), 1018 (m), 976 (s), 939 (w), 920 (w), 890 (vw), 870 (m), 864 (vw), 850 (w), 795 (m), 762 (sh), 758 (vs), 732 (s), 682 cm^{-1} (m). Although both these concentrated spectral samples showed absorptions in the NH regions, samples of **12** in either $CHCl_3$ of CCl_4 did not display such NH absorptions.

Ultraviolet Absorption Study of the 1*H*-, 3*H*-, and 5*H*-Cyclopenta[*c*]quinolines (12). Since **12** tended to discolor upon standing, a sample was prepared from **10** just prior to spectral measurements. To 1.5 mL of 36 N H_2SO_4 chilled in an ice bath was added 0.300 g of **10**, and the mixture was heated for 20 min in an oil bath held at 130 °C. Immediate cooling, followed by addition of 100 g of ice and slow neutralization with saturated $NaHCO_3$ solution, led to a bright-yellow suspension. The yellow product was taken up in ether, the solution dried over K_2CO_3, and the solvent removed. Redissolution in anhydrous ether gave an estimated concentration of **12:** 2.6×10^{-3} M (by UV absorption at 230 nm). Aliquots were introduced into volumetric flasks, and, where a different solvent was used, the ether was removed under reduced pressure. Of the solvents employed, the sample of **12** dissolved quickly in anhydrous ethyl ether or 95% ethanol but only slowly in cyclohexane. Dissolution of **12** from 1.0 mL of the 2.6×10^{-3} M ethereal stock solution in 50.0 mL of cyclohexane gave almost a colorless solution; in 50.0 mL of ethyl ether, the solution was light yellow; and in 95% ethanol, the solution was definitely yellow: UV (diethyl ether) λ_{max} 210 sh (21 500), 230 (33 000), 274 (19 500), 287 sh (14 500), 295–315 br sh (8500), 330–350 br sh (3800), and 430 (br, 410–450 nm, ϵ ca 1000); UV (95% EtOH) 210 sh (22 000), 230 (33 000), 274 (13 500), 287 sh (11 000), 292–312 sh (9000), 330–350 br sh (3100), and 430 (br 410–450 nm); UV (cyclohexane) 228 (33 000), 236 sh (27 000), 243 sh (19 000), 290–305 (6300), 315 (sh, 5000), 325 (sh, 3700), without any absorption over 400 nm.

NMR Spectral Study of the Dehydration of 1-Hydroxy-2,3-dihydro-1*H*-cyclopenta[*c*]quinoline (11) and of the Protonation of the Cyclopenta[*c*]quinolines (12). The NMR samples were prepared by treating **11** with 36 N H_2SO_4 for 0.5 h at 25 °C, 5 min at 125 °C and 24 h at 25 °C, The dehydration proceeded cleanly, for no extraneous peaks were observed: NMR (external Me_4Si) 9.20 (d, 1, H_4 split by NH^+, *J* 7.0 hz), 7.97–8.85 (m, 8, H_1, H_2, NH^+, H_6, H_7, H_8, H_9, and HSO_4^-), and 4.35 (br s, 2).

An analogous heating of a sample of **11** with 36 N D_2SO_4 gave a spectrum similar to that recorded above, except that the peak at 9.20 ppm was now a sharp singlet and the integration of the multiplet between 7.97 and 8.85 varied, with time, from 7 to almost 8. The increase in proton count may be due to the water that was lost from **11** exchanging with the DSO_4^-.

5-Methyl-5*H*-cyclopenta[*c*]quinoline (5-Methyl-5*H*-benzo[c][*2*]pyridine (14). A solution of 894 mg (3.94 mol) of acetate **10** (mp 96–97 °C) in 20 mL of dry benzene was allowed to stand under nitrogen with 2 mL of freshly distilled dimethyl sulfate for 12 h at 25 °C. Evaporation of volatiles in vacuo left the colorless crystalline methosulfate (**13**).

The product **13** was immediately treated with 4.4 mL of 36 N H_2SO_4 and heated for 15 min in an oil bath preheated to 130 °C (actually, however, the product **14** seemed more stable toward H_2SO_4 than **12**). The brown reaction mixture was poured over ice (no purple color as with **12**). Neutralization with saturated sodium carbonate solution, extraction with ether, and drying of the extracts over K_2CO_3 gave a bright yellow-orange ether solution, which appeared to be stable at

0 °C under nitrogen. Removal of solvent yielded a dark-orange solid, which was accompanied by varying amounts of dark-brown, insoluble, apparently polymeric material.

Noteworthy is that the orange product **14** is much more readily soluble in cyclohexane than is **12.** Purification of **14** was effected by solution in cyclohexane, filtration, and removal of the solvent from the filtrate all under nitrogen. The orange solid was sensitive to both heat and oxygen; it turns bluish green when treated with dilute HCl; as did **12, 14** formed bluish-green solutions with $CHCl_3$ or CCl_4; in CS_2 **14** formed a deep-red solution: IR (neat) 2964 (m), 1620 (m), 1592 (m), 1550 (w), 1490 (w), 1460 (w), 1440 (vw), 1390 (vw), 1378 (vw), 1350 (m), 1289 (m), 1260 (s), 1225 (w), 1100 (br s), 1030 (br s), 980 (vw), 800 (br s), 750 (m), 680 (m), 662 cm^{-1} (w); IR (mineral oil) 1620 (m), 1590 (m), 1550 (w), 1490 (w), 1365 (vw), 1350 (m), 1290 (m), 1287 (sh), 1280 (sh), 1260 (m), 1222 (m), 1110 (m), 1095 (sh), 1060 (vw), 1040 (w), 1020 (w), 982 (w), 800 (br m), 758 (m), 750 (m), 680 (m), 662 cm^{-1} (w); IR ($CHCl_3$) 3060 (vw), 2993 (m), 2955 (sh), 1628 (s), 1600 (m), 1550 (w), 1491 (m), 1465 (m), 1460 (sh), 1440 (vw), 1422 (vw), 1392 (w), 1378 (w), 1365 (sh), 1355 (s), 1328 (vw), 1290 (s), 1258 (s), 1214 (br m), 1110 (s), 1060 (w), 1040 (w), 1018 (w), 992 (m), 905 (w), 892 cm^{-1} (vw) (in all cases, the NH absorption, noticeable at 3280–3370 in **12,** was absent); NMR ($CDCl_3$) δ 8.10–8.24 (d of m, H_6), 7.78 (br s, H_4, J = 1.5 Hz), 7.22–7.31 (m, 3 H), 7.10–7.22 (d of d, H_2, J = 3 and 4 Hz), 6.95–7.02 (q, H_3), 6.74 (d of d, H_1, J = 1 and 4 Hz), and 3.84 ($N-CH_3$); mass spectrum (70 eV) *m/e* (rel intensity) 182 (7.0), 181 (M, 19.9), 168 (22.3), 167 (M − CH_3, 100), 166 (32.4), 155 (10.5), 154 (30.3), 153 (13.2), 152 (13.2), 139 (M − CH_3 and HCN), and 113 (M − CH_3 and HCN and HC≡CH); UV (cyclohexane) 238 (16 000), 276 (13 200), 292 (9300), 320 (6300), 325–358 (peak at 348) (3000), 367 (4400), and 430 (br 410–450 nm, ϵ ca. 1700); UV (diethyl ether) similar spectrum, except for peak at 212 (13 000); UV (max) (MeOH) 210, 238, 276, 296–312 (sh), 335–365 (br sh), and 410–450 (br); UV (max) (MeOH + HCl) 205, 238, 244, 270–280 (br) 320 (br) (nothing over 370 nm).

For comparison with the NMR of **14,** it should be noted that 4-methyl-4*H*-cyclopenta[*b*]quinoline displays the following NMR absorptions: 8.1 (br s, H_9), 7.84 (br d, H_5), 7.5 (m, 2*H*), 7.3 (d of d, H_2, J_{23} = 3 Hz, J_{12} = 4 Hz), 7.0–7.2 (m, H_6), 6.4 (d of d, H_3, J_{13} = 1.2 Hz, J_{12} = 4.0 Hz), 5.83 (br m, H_1), and 3.97 (s, $N-CH_3$). Previous NMR data reported for this compound inadvertently assigned the peak at 8.1 to H_5.

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Registry No.—**1,** 13038-93-2; **3a,** 35731-21-6; **3b,** 65733-50-8; **4,** 4514-03-8; **5,** 65733-51-9; **5** picrate, 65733-52-0; **5** methiodide, 65733-53-1; **5** methopicrate, 65776-59-2; **6,** 65733-54-2; 6 picrate, 65733-55-3; **7,** 15944-16-8; **8,** 65733-56-4; **9,** 65733-57-5; **9** picrate, 65733-58-6; **10,** 65733-59-7; **11,** 65733-60-0; **12b,** 19557-49-4; **12c,** 232-62-2; **13,** 65733-62-2; ethyl cyclopenlanone-2-carboxylate, 611-10-9; aniline, 62-53-3; 3-acetoxy-2,3-dihydro-1*H*-cyclopenta[*b*]-quinoline, 29411-26-5.

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(27) Cf. ref 11 for the similar shifting of the tautomeric equilibria of **2a, 2b,** and **2c** in trifluoroacetic acid.
(28) For comparison, the 1,2-dihydro derivative of **1** displays a typical shielded enamine signal at C_3 (4.15) and vinylogous β enamine signal at C_9 (5.85 ppm).
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(33) (a) Noteworthy is the observation that, for both 4,5-benzazulene and 5,6-benzazulene, polar structures can be written that maintain an aromatic sextet in each ring. Thus, in contrast to **1** and **3b,** neither benzazulene ground state has any significantly different stabilization on these grounds. In describing the excited states of **1** and **3b** in resonance terms, obviously many other ionic structures must also be considered. Here we limit ourselves just to the polar forms, **17a, 17b, 18a** and **18b,** which are also important in describing the ground state. The underlying principle in describing any state by resonance is that structures contribute more significantly the closer they are in energy. (b) H. Bock, *Angew. Chem.*, **89,** 631 (1977). (c) E. M. Evleth, Jr., J. A. Berson, and S. L. Manatt, *J. Am. Chem. Soc.*, **87,** 2908 (1965).
(34) The yield varies from 13–37% with an average yield of 23% from eight reactions. For a longer, but higher-yielding procedure, *cf.* W. Ried and W. Käppeler, *Justus Liebigs Ann. Chem., 688,* 177 (1965).
(35) Instead of lithium aluminum hydride, a mixture of $LiAlH_4$-$AlCl_3$ leads to similar result. However, reduction could not be achieved with amine-stabilized aluminum hydride solution (1.06 M 1:1 AlH_3:NEt_3 in benzene; Lithium Corp.).
(36) In a separate experiment, reaction was followed by NMR and IR spectroscopy, namely by working up portions of the reaction mixture at different intervals. Initially only **5** was observed besides unreacted **4.** However, after 11 h of reaction **6** was formed and its amount increased with time. It appears that **5,** being completely soluble in tetrahydrofuran, undergoes further reduction faster with $LiAlH_4$ than the sparingly soluble **4** to form a Lansbury type of complex. This reduces the reactivity of the hydride and, therefore, a longer reaction period is required for the completion of the reduction.
(37) In initial attempts, peracids were successfully employed for dehydrogenation of **6.** Peracetic acid oxidation of **6** yielded only **5,** but trifluoroperacetic gave, besides **5,** a trace amount (<1%) of the corresponding *N*-oxide; *m*-chloroperbenzoic acid can cause complete *N*-oxide formation (cf. infra).
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(40) Perphthalic and peracetic (CH_3CO_2H–H_2O_2) acids were tried unsuccessfully. Trifluoroacetic acid (CF_3CO_2H–H_2O; 4 h reflux), however, gave a very low yield of *N*-oxide **9** as its trifluoroacetate salt.
(41) Presence of impurities can cause the color to be brown or dark brown.
(42) The reaction was observed to occur only slowly at room temperature (followed by NMR). After 70 h of reaction period 20–25% *N*-oxide **9** remained. However, the reaction was complete after 2 h on a steam bath. Also, a slight decarboxylation was observed during the heating when the nitrogen from the reaction vessel was bubbled through barium hydroxide solution.
(43) In attempts to improve the yield of the acetoxy derivative **10,** by employing different reaction conditions, the following observations were made: (a) The use of 2 equiv of acetic anhydride to *N*-oxide **9** (instead of 1:1) did not affect the yield of **10** significantly. (b) When the amount of *N*-oxide **9** in glacial acid exceeded more than 20% (w/v) a significant drop (10%) in the yield of **10** was observed. However, use of lower concentration (5%) did not affect the yield. (c) A very poor yield (9.5%) was obtained when an acetic acid solution of **9** was added to already heated acetic anhydride on a steam bath instead of at room temperature. (d) Also, a poor yield (9.2%) of **10** was obtained when the reaction was run according to a published procedure for 3-acetoxy-2,3-dihydro-1*H*-cyclopenta[*b*]quinoline. (e) A poor yield of **10** resulted when no acetic acid was used.
(44) The product **12** is quite stable if kept as a solution at a low temperature 0 °C or below.

Preparation and Tautomeric Structures of Some Potential 2,5-Dihydroxythieno[3,2-*b*]thiophenes

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Some potential alkyl- and aryl-substituted 2,5-dihydroxythieno[3,2-*b*]thiophenes have been prepared and their structures determined by NMR spectroscopy. In no case could evidence be found for the presence of the hydroxy forms of these compounds which instead exist as dithiolactones. The preferred structure is in every case that of thieno[3,2-*b*]thiophen-2,5(6*H*,7*H*)-diones (b). Only in the unsubstituted compound could the thieno[3,2-*b*]thiophen-2,5(3*H*,6*H*)-dione form (a) be obtained; this, however, rapidly transforms into b. In the case of the 6-substituted compounds, two stereoisomers of form b were obtained having opposite configuration at C-6. The effect of the nature and the position of substituents on the stability of the tautomeric forms is examined and discussed.

In recent papers we described the synthesis, the tautomeric properties,[1] and the chemical behavior[2] of several alkyl- and aryl-substituted potential 2-hydroxythieno[3,2-*b*]thiophenes and 2-hydroxythieno[2,3-*b*]thiophenes. It was found that these compounds do not exist in the hydroxy form but have the structures of thiolactones. In the case of the thieno[2,3-*b*]thiophen system all of the compounds examined have the structure of thieno[2,3-*b*]thiophen-2(3*H*)-ones, while in the case of the [3,2-*b*] system a tautomeric equilibrium exists between the thieno[3,2-*b*]thiophen-2(3*H*)-ones and the thieno[3,2-*b*]thiophen-2(5*H*)-ones. The effects of the nature and the position of the substituents on the tautomeric equilibria have been explored.[1]

We report now the result of an investigation carried out on the potential 2,5-dihydroxythieno[3,2-*b*]thiophenes, **1–6**,[3] which present interesting tautomeric properties; these compounds also represented the starting materials for the synthesis of the corresponding thieno[3,2-*b*]thiophen-2,5-diones (8) which have been used as very suitable models for an ESR investigation of the intramolecular cation exchange in paramagnetic ion pairs.[4]

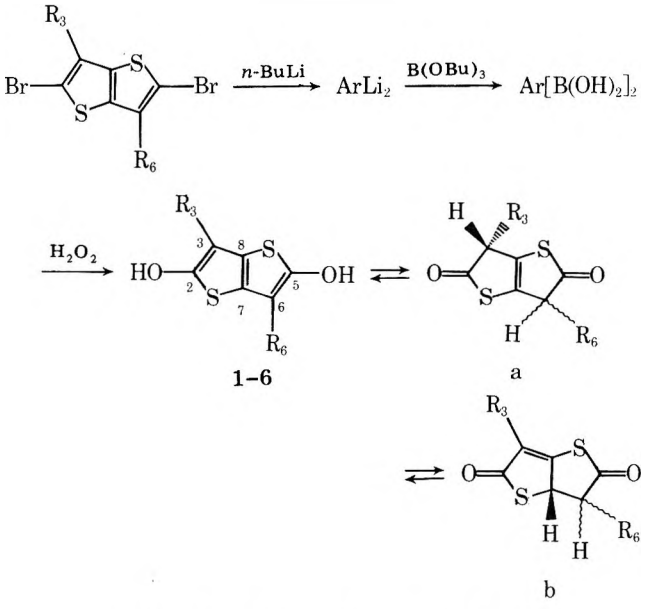
The products described in this paper were obtained through the hydrogen peroxide oxidation of the diboronic acids of thienothiophenes, as indicated in Scheme I. This synthetic method was introduced for the preparation of hydroxythiophenes[5] and also employed in the case of the monohydroxythienothiophenes[1] with very good results.

For these compounds, besides the hydroxy form, two other tautomeric structures can be written, the thieno[3,2-*b*]thiophen-2,5(3*H*,6*H*)-diones (a) and the thieno[3,2-*b*]thiophen-2,5(6*H*,7*H*)-diones (b). Moreover, depending on the nature of the substituents R_3 and R_6, other stereoisomers are possible for tautomers a and b according to the configuration of C-6. The structures of the possible isomers can be confidently assigned by NMR spectroscopy.

In no case was evidence obtained for the existence of the hydroxy forms, all the compounds investigated being a mixture of the dithiolactones a and/or b. Compounds **1–6** were always accompanied by small amounts of the monohydroxy derivatives,[1] in the tautomeric forms **7a** or/and **7b**, whose formation was very probably due to incomplete transformation of the dilithium compounds into the boronic acids. A second by-product was the thieno[3,2-*b*]thiophen-2,5-dione (8), which very easily forms[4] through the oxidation of **1–6** (Scheme II).

From the oxidation of the 2,5-thieno[3,2-*b*]thienyl diboronic

Scheme I



1, $R_3 = R_6 = H$ 4, $R_3 = CMe_3$; $R_6 = H$
2, $R_3 = R_6 = Me$ 5, $R_3 = Me$; $R_6 = H$
3, $R_3 = R_6 = Ph$ 6, $R_3 = Ph$; $R_6 = H$

Scheme II

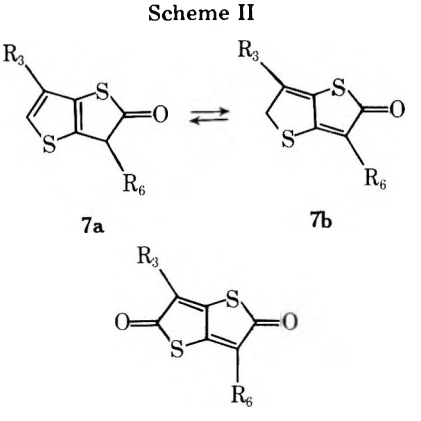


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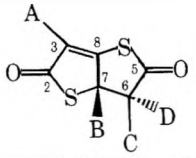
Table I.[a] **Physical and NMR (in CS_2) Data of the Thieno[3,2-*b*]thiophen-2,5(6*H*,7*H*)-diones**



Compound	Mp, °C	Chemical shifts				Coupling constants, Hz				
		A	B	C	D	J_{AB}	J_{BC}	J_{BD}	J_{CD}	J_{AC}
1b (R_3 = R_6 = H)	115–116	6.25	4.88	3.28	2.75	2.1	7.8	12	16.2	0.8
2b (R_3 = R_6 = Me)	130–132	1.9[b]	4.38	1.41[b]	2.7	2.0[f]		12	6.7[c]	
2b′ (R_3 = R_6 = Me)	*d*	1.9[b]	4.82	3.1	1.1[b]	2.0[f]	7.2		7.5[c]	
4b (R_3 = CMe_3; R_6 = H)	108–110	1.3[e]	4.67	3.21	2.73		7.5	12.3	15.9	
4b′ (R_3 = H; R_6 = CMe_3)	*d*	6.22	4.82	1.11[e]	2.78	2.1		11.1		
5b (R_3 = Me; R_6 = H)	110–111	1.9[b]	4.72	3.25	2.66	2.0[f]	7.8	11.8	15.9	
6b (R_3 = Ph; R_6 = H)	145–147	7.35[g]	4.82	3.24	2.69		7.7	12	16.2	

[a] Satisfactory analytical data were reported for all the compounds listed in the table. [b] Methyl group. [c] $J_{H_6\text{-}CH_3}$. [d] Not isolated (the NMR data were obtained from the spectrum of the mixture with the b isomer). [e] *tert*-Butyl group. [f] $J_{CH_3\text{-}H_7}$. [g] Phenyl group.

acid a single crystalline product was obtained in good yields, whose NMR spectrum was constituted by a singlet at δ 3.62; this compound presented the characteristic carbonyl stretching vibration in the infrared spectrum. On the basis of these spectroscopic results and of its analytical data, the structure of thieno[3,2-*b*]thiophen-2,5(3*H*,6*H*)-dione (**1a**) has been assigned to this compound. Product **1a**, however, is not very stable and on standing or on attempted column chromatography is completely and irreversibly transformed into a new crystalline compound, which in the light of its NMR spectrum was assigned the structure of the thieno[3,2-*b*]-thiophene-2,5(6*H*,7*H*)-dione (**1b**) (Scheme III). Treatment of a solution of **1a** with HCl gas results in instantaneous transformation into **1b**.

The NMR data of **1b** are reported in Scheme III; the portion of the spectrum due to the protons H_B, H_C, and H_D was analyzed as an ABX system, with coupling with H_A considered as first-order perturbations, which was justified by the $\Delta\delta/J$ ratios involved. Assignment of H_A and H_B can be confidently made on the basis of their chemical shifts and also in the light of the spectra of substituted products which will be discussed later (see Table I). Difficulties are instead encountered in the relative assignment of the two geminal protons H_C and H_D. The assignments indicated in Scheme III are based on the values of the vicinal coupling constants, J_{BC} and J_{BD}, under the assumption that the Karplus equation also holds for the systems under investigation. Thus, the larger J_{vic} (12 Hz) is assigned to the protons H_B and H_D which, as can be seen in the Newman projection along the C_6–C_7 bond reported in Scheme III, are in anti, and the smaller J_{vic} (7.8 Hz) to the protons H_B and H_C which are in a gauche position. This assignment is also confirmed by the long-range coupling (0.8 Hz) observed between H_A and one of the two geminal protons; this proton is H_C, because, as showed by molecular models, H_A and H_C are separated by an almost planar zig-zag pathway, while the C_6–H_D bond lies almost perpendicular to that plane. These assignments are of particular interest because they allow stereochemical assignments in the substituted compounds.

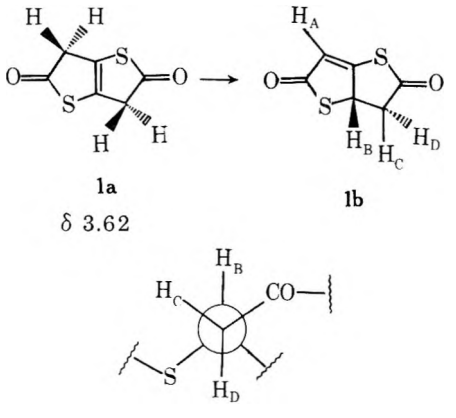
The easy isomerization of **1a** to **1b** is understandable in view of the greater thermodynamic stability of the latter compound where the carbonyl group is conjugated with the carbon–carbon double bond.

The reaction mixture of **2** showed the presence of two isomers in almost equimolecular amounts. Their NMR data are collected in Table I and clearly indicate that in this case we are dealing with two isomeric 3,6-dimethylthieno[3,2-*b*]-thiophen-2,5(6*H*,7*H*)-diones, which differ in the configuration at C-6. With respect to proton H_B, the hydrogen atom in C-6 in one case, **2b** (H_D), is anti and in the other, **2b′** (H_C), is gauche (Scheme IV).

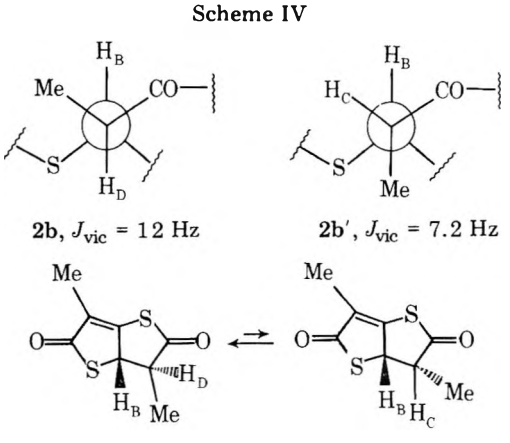
On the basis of the assignments reported above for the parent compound, the isomer presenting the larger J_{vic} was assigned the structure **2b.** This tautomer is also the thermodynamically more stable, since on treating the mixture of the two isomers with acids, or on standing, an equilibrium composition was reached in which the **2b**/**2b′** ratio has the value of 85:15. Pure **2b** could be obtained by crystallization and, after treatment with HCl gas, the same equilibrium mixture of **2b** and **2b′** was obtained.

An X-ray crystal structure determination of **2b** has been carried out[6] and this demonstrated that the two hydrogens

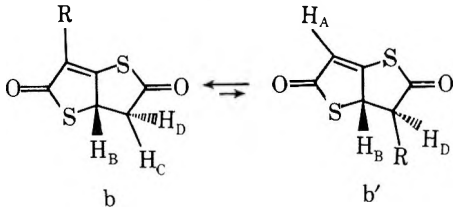
Scheme III



Scheme IV



Scheme V



b b′

4, R = CMe_3
5, R = Me
6, R = Ph

bonded at C-6 and C-7 are in the anti position, the torsional angle H_6–C_6–C_7–H_7 being 174°. This result unambiguously confirms the proposed structures and at the same time demonstrates the exact interpretation of the NMR spectra of **1b** and of the other compounds described below.

From the reaction of the diphenyl derivative (**3**), the desired products were not formed at all, the only compound obtained being the 3,6-diphenylthieno[3,2-*b*]thiophen-2,5-dione (**8**) (R_3 = R_6 = Ph). In the case of the 3-methyl-(**5**) and 3-phenyl-(**6**) derivatives only the isomers b were observed (Scheme V).

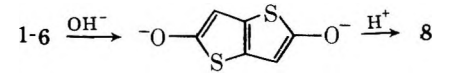
This is not unexpected since in these isomers the substituents can hyperconjugate or conjugate with the double bond thus achieving maximum stability. In fact when the substituent is a *tert*-butyl group, compound (**4**), a mixture of two isomeric 2,5(6*H*,7*H*)-diones in almost equimolecular amounts was obtained. The NMR of one of the two tautomers presented the usual ABX system leaving no doubts that it possesses the **4b** structure. The NMR spectrum of the other isomers (see Table I) clearly indicated that the *tert*-butyl group is bonded to C-6. Moreover, long-range coupling between H_A and the proton in C-6 was not observed and the J_{vic} has the value of 11.3 Hz. These observations indicate that the two vicinal protons are anti as indicated in structure **4b′** in Scheme V. The other possible stereoisomer with the two vicinal protons in gauche was not observed. Equilibration of the mixture of the two isomers gave a **4b/4b′** ratio of 90:10.

All of the results described above indicate that the preferred tautomeric form of these potential dihydroxythienothiophenes is in every case that of the thieno[3,2-*b*]thiophen-2,5(6*H*,7*H*)-dione (b). Whenever a substituent is present which can conjugate or hyperconjugate with the carbon–carbon double bond this is the only form which is obtained; the thieno[3,2-*b*]thiophen-2,5(3*H*,6*H*)-dione (a) is in fact observed only in the case of the unsubstituted compound (**1**).

Moreover, substituents bonded at C-6 of the 2,5(6*H*,7*H*)-diones (b) preferentially assume a gauche position with respect to the bridgehead proton, H_B. This isomer is dominant in the case of a methyl group (compound **2b**) and becomes the only one present in the case of the *tert*-butyl group (compound **4b′**), clearly indicating that the observed difference in stability is governed by steric effects.

In the case of hydroxythiophenes,[7] 2-hydroxythieno[3,2-*b*]thiophenes,[1] and 2,5-dihydroxythieno[2,3-*b*]thiophenes,[8] the base extraction method can be used to regenerate the thermodynamically less stable tautomeric forms. Application of this procedure to the products of the present investigation failed to give the expected results; in every case acidification of the alkaline solution of **1–6** afforded only the oxidation products, thieno[3,2-*b*]thiophenes-2,5-diones (**8**) (Scheme VI). This method was utilized for the synthesis of the dithiolactones **8** necessary for an ESR investigation of their radical anions.[4]

Scheme VI



Experimental Section[9]

(A). Thieno[3,2-*b*]thiophenes. With the exception of the 3-*tert*-butyl derivative, all the other thieno[3,2-*b*]thiophenes necessary for the present work were already described in the literature.

3-*tert*-Butylthieno[3,2-*b*]thiophene (9). A solution of 3-mercaptothiophene[10] in methanol (40 mL) containing sodium methoxide (from 2.3 g of Na) was added dropwise, at 0 °C, to a solution of bromopinacolone[11] (20 g) in methanol (60 mL) and the mixture was stirred overnight at room temperature. The solvent was evaporated and the residue dissolved in water and ether. The organic layer was washed, dried, and evaporated and the residue distilled to afford 3-thienylthiopinacolone (18 g), bp 130 °C (2 mm): NMR (CS_2) δ_{CMe_3} 1.1, δ_{CH_2} 3.7, δ_{Ar} 6.8–7.2.

Anal. Calcd for $C_{10}H_{14}OS_2$: C, 56.03; H, 6.6. Found: C, 55.95; H, 6.57. The ketone (7.5 g) in CS_2 (40 mL) was added dropwise to a stirred suspension of $AlCl_3$ (5.8 g) in CS_2 (80 mL) and stirring was continued for 22 h. The mixture was poured onto ice and hydrochloric acid and extracted with ether. The organic layer was washed, dried, and evaporated; the residue was distilled under vacuum to afford 3.2 g of **9**: bp 113 °C (2 mm); NMR (CS_2) δ_{CMe_3} 1.35, δ_2 6.84, δ_5 7.17, δ_6 7.03, J_{5-6} = 5.25 Hz, J_{2-5} = 1.5 Hz.

Anal. Calcd for $C_{10}H_{12}S_2$: C, 61.17: H, 6.17. Found: C, 61.37; H, 6.20.

(B). 2,5-Dibromothieno[3,2-*b*]thiophenes. These compounds were prepared from the thieno[3,2-*b*]thiophenes according to the following general procedure. To a solution of the thieno[3,2-*b*]thiophene (0.01 mol) in acetic acid (150 mL) *N*-bromosuccinimmide (0.02 mol) was added in small portions and the mixture was stirred for 2 h. The solution was poured onto water and extracted with chloroform several times; the organic layer was separated, washed with water and $NaHCO_3$ solution, and dried. The solvent was evaporated and the residue crystallized from ethanol or distilled under vacuum.

2,5-Dibromothieno[3,2-*b*]thiophene (10). Mp 128–129 °C (lit.[12] 129.5–131 °C).

2,5-Dibromo-3,6-dimethylthieno[3,2-*b*]thiophene (11). Yields 89%; mp 140–142 °C (lit.[1] 140–142 °C).

2,5-Dibromo-3,6-diphenylthieno[3,2-*b*]thiophene (12). Yields 90%; mp 252–254 °C; NMR (CS_2) $\delta_{C_6H_5}$ 7.38.

Anal. Calcd for $C_{18}H_{10}Br_2S_2$: C, 48.02; H, 2.24; Br, 35.50; S, 14.24. Found: C, 48.03; H, 2.26; Br, 35.37; S, 14.26.

2,5-Dibromo-3-*tert*-butylthieno[3,2-*b*]thiophene (13). Yields 92%; bp 150 °C (1 mm); NMR (CS_2) δ_{CMe_3} 1.52, δ_6 6.92.

Anal. Calcd for $C_{10}H_{10}Br_2S_2$: C, 33.9; H, 2.85. Found: C, 34.02; H, 2.90.

2,5-Dibromo-3-methylthieno[3,2-*b*]thiophene (14). Yields 85%; mp 74–75 °C; NMR (CS_2) δ_{CH_3} 2.25, δ_6 7.08.

Anal. Calcd for $C_7H_4Br_2S_2$: C, 26.94; H, 1.29. Found: C, 26.98; H, 1.28.

2,5-Dibromo-3-phenylthieno[3,2-*b*]thiophene (15). Yields 92%; mp 118–120 °C; NMR (CS_2) δ_6 7.0, $\delta_{C_6H_5}$ 7.38.

Anal. Calcd for $C_{12}H_6Br_2S_2$: C, 38.52; H, 1.62. Found: C, 38.38; H, 1.63.

(C). Synthesis of Potential 2,5-Dihydroxythieno[3,2-*b*]thiophenes (1–6). The syntheses of these compounds have been carried out according to the general procedure described below for the parent compound (**1**). Details on the workup of the reaction mixtures are also reported for the single products, whose physical and spectral data are collected in Table I.

Thieno[3,2-*b*]thiophen-2,5(3*H*,6*H*)-dione (1a) and Thieno[3,2-*b*]thiophen-2,5(6*H*,7*H*)-dione (1b). To a stirred solution of *n*-butyllithium (prepared from 0.42 g of Li) in ether, cooled at −60 °C, an ethereal solution of 2,5-dibromothieno[3,2-*b*]thiophene (**10**) (3 g) was added dropwise. The resulting solution was stirred for 30 min at −30 °C and then treated, at −70 °C, with *n*-butyl borate (10 g) in ether. The mixture was left to gradually reach room temperature during 5 h and then shaken with 2 N HCl (25 mL). The layers were separated and the aqueous phase extracted with ether. The ethereal solution was extracted with three portions of 100 mL of cold 2 N NaOH and the alkaline solution was acidified with cold 2 N H_2SO_4; the separating diboronic acid was dissolved in ether and 35% hydrogen peroxide (20 mL) was added. The mixture was vigorously stirred, under nitrogen, for 15 h. The ethereal solution was washed several times with water and dried over Na_2SO_4, and the solvent was evaporated under nitrogen. The residue was washed with pentane.

An NMR spectrum of the solid residue (1.3 g) showed the presence of **1a** and small amounts of **8** (R_3 = R_6 = H); bubbling HCl gas into

the solution caused the rapid and complete transformation of **1a** into **1b**.

A portion of the solid residue was washed with cold carbon disulfide, which left undissolved the pure thieno[3,2-*b*]thiophen-2,5(3*H*,6*H*)-dione (**1a**), mp 104–105 °C; NMR (CS_2) δ 3.62.

Anal. Calcd for $C_6H_4O_2S_2$: C, 41.84; H, 2.35; S, 37.23. Found: C, 41.58; H, 2.34; S, 37.5. The remaining part of the solid residue and the part dissolved in CS_2 were chromatographed through a silica gel column using light petroleum ether (9:1) as eluent. The first fractions contained the yellow thieno[3,2-*b*]thiophen-2,5-dione[4] (**8**) (0.1 g), mp 155–156 °C. Fractions were then collected which contained the thieno[3,2-*b*]thiophen-2,5(6*H*, 7*H*)-dione (**1b**).

3,6-Dimethylthieno[3,2-*b*]thiophen-2,5(6*H*, 7*H*)-diones (2b and 2b'). The NMR spectrum of the crude residue (3.6 g) obtained from the reaction of **11** (7.5 g) showed the presence of compounds **2b** and **2b'** in the ratio of 60:40, together with lower amounts of **7a** (R_3 = R_6 = Me) and **8** (R_3 = R_6 = Me). The components were separated by column chromatography as described above for the reaction of **1**. The first fractions contained the yellow dione **8**[4] (0.2 g), mp 151–152 °C. Further elution afforded a mixture of the two isomers **2b** and **2b'** (2.5 g); crystallization from acetone–pentane gave pure **2b**, mp 130–132 °C. The solution of this compound, as well as those containing the two isomers in different proportions, when treated with HCl gas, gave a mixture of **2b** and **2b'** in the ratio of 85:15. Finally, fractions were collected containing compound **7b**[1] (0.5 g), mp 125–127 °C.

3,6-Diphenylthieno[3,2-*b*]thiophen-2,5-dione (8) (R_3 = R_6 = Ph). The reaction carried out on **12** (2.7 g) afforded as the sole product the dione **8** (1.3 g), mp 224–225 °C.[4,13]

3-Methylthieno[3,2-*b*]thiophen-2,5(6*H*,7*H*)-dione (5b). Reaction of **14** (5.5 g) afforded a solid residue (2.8 g) which was chromatographed to give the following fractions: (i) compound **8** (R_3 = Me; R_6 = H) (0.1 g), mp 91–93 °C,[4] (ii) compound **7a** (R_3 = Me; R_6 = H)[1] (0.7 g) which on standing gradually transforms in a mixture of **7a** and **7b**,[1] and (iii) compound **5b** (1.4 g), mp 109–110 °C from ethanol.

3-Phenylthieno[3,2-*b*]thiophen-2,5(6*H*,7*H*)-dione (6b). The reaction carried out on 7.5 g of **15** afforded 3.7 g of residue which was worked up in the usual way to give (i) the dione **8** (R_3 = Ph; R_6 = H) (0.1 g), mp 124–126 °C,[1] (ii) compound **7a** (R_3 = Ph; R_6 = H)[1] (0.4 g), and (iii) the product **6b** (2.8 g), mp 145–147 °C from ethanol.

3-*tert*-Butylthieno[3,2-*b*]thiophen-2,5(6*H*,7*H*)-dione (4b) and 6-*tert*-Butylthieno[3,2-*b*]thiophen-2,5(6*H*,7*H*)-dione (4b'). The reaction was carried out on 5 g of **13**. The solid residue (3.2 g) was constituted by **8** (R_3 = CMe_3; R_6 = H), **7a** (R_3 = CMe_3; R_6 = H) and an equimolecular mixture of **4b** and **4b'**. The various components were separated by column chromatography in the usual way. The first fractions contained the dione **8**, mp 133–135 °C[4] (0.2 g); then 3-*tert*-butylthieno[3,2-*b*]thiophen-2(3*H*)-one, **7a** (0.7 g), mp 53–55 °C,[1] was collected. The following fractions contained mixtures, in different proportions, of **4b** and **4b'**; evaporation of the solvent left 2 g of residue. The mixture was crystallized from ethanol to afford pure 3-*tert*-butylthieno[3,2-*b*]thiophen-2,5(6*H*,7*H*)-dione (**4b**), mp 108–110 °C (1.6 g). This compound, as well as the mixtures with the isomeric **4b'**, when treated with HCl gas, gave a mixture of **4b** and **4b'** in the ratio of 90:10.

Acknowledgment. Financial support from the CNR, Rome, is gratefully acknowledged.

Registry No.—**1a**, 65701-76-0; **1b**, 65701-77-1; **2b**, 61414-32-2; **2b'**, 65701-78-2; **4b**, 65701-79-3; **4b'**, 65701-80-6; **5b**, 65701-81-7; **6b**, 65701-82-8; **7a** (R_3 = R_6 = Me), 56411-84-8; **7a** (R_3 = Me; R_6 = H), 56411-82-6; **7a** (R_3 = Ph; R_6 = H), 56411-81-5; **7a** (R_3 = CMe_3; R_6 = H), 56411-80-4; **7b** (R_3 = R_6 = Me), 56411-85-9; **7b** (R_3 = Me; R_6 = H), 56411-83-7; **8** (R_3 = R_6 = H), 60749-71-5; **8** (R_3 = R_6 = Me), 60749-72-6; **8** (R_3 = R_6 = Ph), 51752-01-3; **8** (R_3 = Me; R_6 = H), 60749-73-7; **8** (R_3 = Ph; R_6 = H), 60749-76-0; **8** (R_3 = CMe_3; R_6 = H), 60749-75-9; **9**, 65701-83-9; **10**, 25121-87-3; **11**, 56412-13-6; **12**, 65701-84-0; **13**, 65701-85-1; **14**, 65701-86-2; **15**, 65701-87-3; 3-mercaptothiophene, 7774-73-4; bromopinacolone, 5469-26-1; 3-thienylthiopinacolone, 65701-88-4; thieno[3,2-*b*]thiophene, 251-41-2; 3,6-dimethylthieno[3,2-*b*]thiophene, 56412-11-4; 3,6-diphenylthieno[3,2-*b*]thiophene, 21210-92-4; 3-methylthieno[3,2-*b*]thiophene, 1723-34-8; 3-phenylthieno[3,2-*b*]thiophene, 35022-15-2.

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Acid-Catalyzed Reaction of 1,6-Dioxaspiro[4.4]nonane with Ferrocene

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1,6-Dioxaspiro[4.4]nonane reacts with ferrocene in the presence of aluminum chloride or boron trifluoride etherate to give 2-ferrocenyl-2-(3-hydroxypropyl)tetrahydrofuran (**5**). Treatment of **5** with methyl Grignard gives 4-methyl-4-ferrocenylheptane-1,7-diol (**7**). Reaction of **5** with trifluoroacetic acid gives ferrocenylbis(3-trifluoroacetoxypropyl)carbonium trifluoroacetate (**8a**). Treatment of **8a** with aqueous base gives 4-ferrocenyl-3-heptene-1,7-diol (**6**). With trifluoroacetic acid as catalyst, 1,6-dioxaspiro[4.4]nonane reacts with ferrocene to give a mixture of **5**, **6**, 4,4-diferrocenylheptane-1,7-diol (**3**), and 1,1'-bis[4-(4-ferrocenyl-1,7-dihydroxy)heptyl]ferrocene (**9**). Ferrocene and the ferrocene derivatives exist in an equilibrium condition in this reaction.

A few diferrocenylmethane derivatives with alkyl or substituted alkyl groups attached to the quaternary carbon have been reported.[1,2] They are made by the acid-catalyzed reaction of ketones with ferrocene. Compound **2**, R' = CH_2CH_2OH, and derivatives of **2**, R' = $CH_2CO_2CH_3$, have been used to chemically attach ferrocene derivatives onto specially designed polyurethane systems.[3] One objective of the present work was to prepare 4,4-diferrocenylheptane-1,7-diol (**3**) as a constit-

Table I. ^{1}H-NMR Spectra of 1,6-Dioxaspiro[4.4]nonane–Ferrocene Reaction Products

Compd	Registry no.	Chemical shift, δ (ppm) (Me_4Si)[a]			
		CH_2CH_2	OCH_2	Fc	Other
5[b,d,e]	60583-71-3	1.2–2.5 (m)	3.56 (t, 6), 4.00 (t, 6)	3.9–4.3 (m, 9 H)	
8a[b,f]	65465-65-8	1.8–3.2 (m)	4.51 (t, 5)	4.98 (t, 2, 2 H), 5.01 (s, 5 H), 6.42 (t, 2, 2 H)	
6[b,d,e]	60635-84-9		3.65 (t, 6)	4.03 (s, 5 H), 4.25 (m, 4 H)	2.1–2.7 (m, =C(CH_2–)-) 5.68 (t, 7, =C(H)-) 1.4–2.0 (m, -CH_2–)
3[b,d,e]	60583-73-5	1.6–2.3 (m)	3.68 (t, 6)	4.06 (s, 10 H), 4.13 (m, 8 H)	
3[c,g]		1.4–2.1 (m)	3.44 (q, 5)	4.01 (s, 10 H), 4.11 (m, 8 H)	4.24 (t, 5, -OH)
9[c,g]	60583-70-2	1.3–2.2 (m)	3.42 (q, 5)	3.82 (m, 8 H), 4.03 (s, 10 H), 4.11 (m, 8 H)	4.22 (t, 5, -OH)
7[b,d,e]	60583-72-4	1.3–1.7 (m)	3.40 (t, 6)	3.9–4.3 (m, 9 H)	1.25 (s, -CH_3)

[a] Multiplicity of signal and coupling constant (Hz) in parentheses. [b] Measurements at 60 MHz, 27 °C. [c] Measurements at 100 MHz, 60 °C. [d] D_2O added. [e] $CDCl_3$. [f] CF_3CO_2H. [g] $(CD_3)_2SO$.

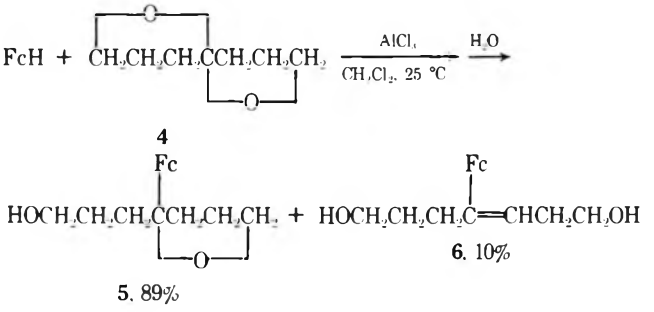
uent for directly incorporating ferrocenyl groups in polyurethane systems.[4]

$$\begin{array}{c} \text{Fc} \\ \text{RCH}_2\text{CCH}_2\text{R}' \\ \text{Fc} \end{array}$$

Fc = $C_5H_5FeC_5H_4$

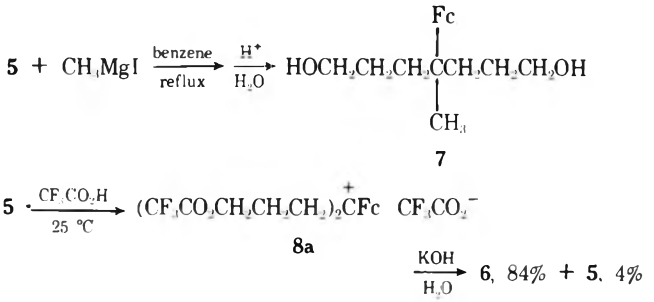
1, R = R′ = H[1]
2, R = H; R′ = $CH_2CO_2CH_3$, CH_2CH_2OH[2]
3, R = R′ = CH_2CH_2OH

The acid-catalyzed reaction of the ketone derivative, 1,6-dioxaspiro[4.4]nonane[5] (**4**), with ferrocene could conceivably generate **3** with the desired four functional groups, two hydroxyl and two ferrocenyl, in one operation. It was found that the course of this reaction depends upon the catalyst used. With aluminum chloride the reaction goes half-way. The principal product isolated is 2-ferrocenyl-2-(3-hydroxypropyl)tetrahydrofuran (**5**). The small amount of 4-ferrocenyl-3-heptene-1,7-diol (**6**) is probably formed by reaction of **5** with

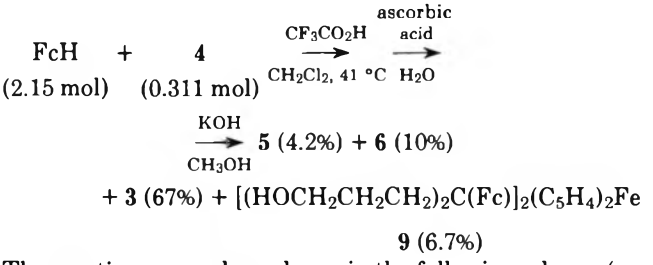


aqueous hydrogen chloride formed when the reaction mixture is poured into water at the end of the reaction. Only one ketal ether ring is opened and only one ferrocenyl group is attached to the ketal skeleton even though 2 mol of aluminum chloride and 4 mol of ferrocene are used per mol of **4**. With boron trifluoride etherate as catalyst the principal product is also **5**. Treatment of **5** with methyl Grignard reagent[6] gives 4-methyl-4-ferrocenylheptane-1,7-diol (**7**), and with trifluoroacetic acid[7,8] ferrocenylbis(3-trifluoroacetoxypropyl)carbonium trifluoroacetate (**8a**)[9] is formed. The ferrocenylcarbonium ion, **8a**, is isolable (NMR[8,10,11] Table I) and stable in trifluoroacetic acid for 12 days at 25 °C in air. Treatment of **8a** with base abstracts a proton to give **6**. The small amount of **5** isolated may arise from some initial **5** that was oxidized by trifluoroacetic acid[12] to a ferricenium derivative, preventing ether cleavage, and subsequently recovered after reduction with ascorbic acid.

With trifluoroacetic acid as catalyst the reaction of **4** with



ferrocene gives **3** and 1,1′-bis[4-(4-ferrocenyl-1,7-dihydroxy)heptyl]ferrocene (**9**) in addition to **5** and **6**.



The reaction proceeds as shown in the following scheme (eq 1–3). The product **3** (as **3a**) is

$$4 + \text{FcH} \xrightarrow{\text{CF}_3\text{CO}_2\text{H}} \mathbf{5a} \xrightarrow{\text{CF}_3\text{CO}_2\text{H}} \mathbf{8a} \quad (1)$$

$$\mathbf{8a} + \text{FcH} \overset{K_1}{\rightleftarrows} \mathbf{3a} \quad (2)$$

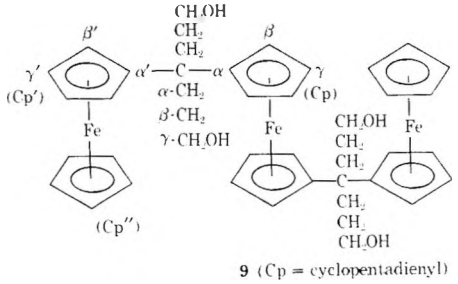
$$\mathbf{8a} + \mathbf{3a} \overset{K_2}{\rightleftarrows} \mathbf{9a} \quad (3)$$

formed from **8a** and ferrocene and similarly **9** (as **9a**) from **8a** and **3a**. Some of **5a** is trapped by oxidation to a ferricenium derivative and is recovered as **5** by reduction with ascorbic acid. Base converts **8a** into **6**. Reverse reactions of (2) and (3) were demonstrated qualitatively by treatment of **3a** and **9a** with trifluoroacetic acid (16 hr, 25 °C) followed by aqueous sodium hydroxide to give, in each case, mixtures of ferrocene, **6**, **3**, and **9**, resolvable by thin-layer chromatography on alumina and silica gel plates. An equilibrium ferrocene alkylation–dealkylation reaction involving an α-ferrocenylcarbonium ion has been reported.[13] Since reactions 2 and 3 are equilibrium reactions, it is evident that the concentration of **3a** with respect to **8a** and **9a** is favored by increased FcH concentration.[14] By using a 7 to 1 M ratio of FcH to **4**, as indicated in the previous experiment, **3** is the predominant product. By taking advantage of the equilibrium **9** could be prepared in quantity if desired.

Table II. ^{13}C-NMR Spectrum of 9, 25.14 MHz, 40 °C

^{13}C position[a]	No. of ^{13}C	Chemical shifts, ppm (Me_4Si)
Cp-α	2	99.66
Cp-β	4	66.86
Cp-γ	4	65.81
Cp′-α'	2	99.80
Cp′-β'	4	67.39
Cp′-γ'	4	66.52
Cp″	10	68.53
—C—	2	38.32
CH_2-α	4	27.87
CH_2-β	4	34.46
CH_2-γ	4	61.95

[a] Position designation:



9 (Cp = cyclopentadienyl)

Elemental analyses and proton NMR data are consistent with the structures of **3, 5, 6, 7,** and **9.** In addition the ^{13}C NMR spectrum of the more complex molecule, **9,** is reported, Table II. A compound with a structure similar to **9,** 1,1′-bis[2-(2-ferrocenyl-4-carbomethoxybutyl]ferrocene, was isolated from the acid-catalyzed reaction of methyl levulinate with ferrocene.[2]

Experimental Section

Aluminum Chloride Catalyzed Reaction of 1,6-Dioxaspiro[4.4]nonane (4) with Ferrocene. To $AlCl_3$ (3.0 g, 0.023 mol), suspended in 100 mL of CH_2Cl_2 and flushed with N_2, was added dropwise over 15 min with stirring 1.28 g (0.0100 mol) of **4** and 7.44 g (0.0400 mol) of ferrocene dissolved in 100 mL CH_2Cl_2. The reaction temperature was initially 25 °C and warmed to 35 °C during the addition. Stirring was continued at 25 °C with N_2 atmosphere for 16 h. The reaction mixture was then poured into 200 mL of ice water and a little ascorbic acid was added to dispel the blue color (ferricenium ion) of the aqueous phase. The organic phase was separated and poured onto a 50 × 160 mm column of activity III (dry column grade) neutral alumina packed in CH_2Cl_2. Unreacted ferrocene, 5.52 g (0.0297 mol), was eluted with CH_2Cl_2. Using a 2:1 mixture of CH_2Cl_2 and $CH_3CO_2C_2H_5$ as solvent a large yellow band was eluted to give 2.80 g (0.008 92 mol) (89% yield) of 2-ferrocenyl-2-(3-hydroxypropyl)-tetrahydrofuran (**5**). Recrystallization from a 1:1 mixture of pentane and cyclohexane gave **5,** mp 50–53 °C.

Anal. Calcd for $C_{17}H_{22}O_2Fe$: C, 64.98; H, 7.06; Fe, 17.78; mol wt, 314. Found: C, 64.95; H, 6.81; Fe, 17.53; *m/e,* 314.

The remaining small yellow band at the top of the column was eluted with 4% CH_3OH in CH_2Cl_2 to give 0.31 g (0.000 99 mol) (10% yield) of 4-ferrocenyl-3-heptene-1,7-diol (**6**), mp 88–90 °C (after recrystallization from ethyl ether).

The reaction was repeated using ferrocene, 7.44 g (0.040 mol), **4,** 1.28 g (0.010 mol), and 3.6 mL (0.03 mol) of boron trifluoride etherate. After 2 h of stirring at 25 °C, workup gave 1.72 g (55% yield) of **5.**

Reaction of 5 with Methylmagnesium Iodide. Magnesium (1.2 g, 0.050 mol) was reacted with 7.1 g (0.050 mol) of methyl iodide in 25 mL of ether to form a solution of CH_3MgI. Then **5,** 1.08 g (0.0034 mol), was dissolved in 25 mL of ether and added to the CH_3MgI solution. A yellow precipitate formed immediately and then dissolved. Dry benzene (25 mL) was added and the ether was evaporated under reduced pressure. The benzene solution was refluxed for 2.5 h. Ice water was added to destroy excess Grignard reagent and then 6 N HCl was added to dissolve the magnesium salts. The benzene phase was separated and washed with saturated aqueous sodium chloride. The washed benzene phase was poured onto a dry 36 × 250 mm alumina column. The chromatogram was developed with ethyl acetate. The most rapidly moving band contained 0.46 g of **5.** The more slowly moving band was cut out of the column and extracted with methanol to give 0.38 g (0.0012 mol) (34% yield) of 4-methyl-4-ferrocenylheptane-1,7-diol (**7**), mp 109–110 °C. Recrystallization from carbon tetrachloride raised the mp to 111–112 °C.

Anal. Calcd for $C_{18}H_{26}O_2Fe$: C, 65.46; H, 7.94; Fe, 16.91; mol wt, 330. Found: C, 65.44; H, 8.26; Fe, 16.76; *m/e,* 330.

Preparation and Reaction of Ferrocenylbis(3-trifluoroacetoxypropyl)carbonium Trifluoroacetate (8a) with Base. Ferrocenylbis(3-trifluoroacetoxypropyl)carbonium trifluoroacetate was prepared by treating 2.80 g (0.00892 mol) of 2-ferrocenyl-2-(3-hydroxypropyl)tetrahydrofuran (**5**) dissolved in 15 mL of CH_2Cl_2 at 5 °C with 25 mL of CF_3CO_2H and then keeping it for 16 h at 25 °C. The volatiles were removed on the rotary evaporator (0.5 mm of pressure and 25 °C). The dark viscous residue was dissolved in 50 mL of CH_2Cl_2 and then treated with 100 mL of ice cold H_2O. The blue color of the aqueous phase was dispelled with ascorbic acid. Neutralization of the aqueous phase with 1 N KOH caused it to turn dark brown. The organic phase was separated and poured onto a 50 × 150 mm alumina (activity III, dry column grade) column. The chromatogram was developed and the first small band eluted with a 2:1 mixture of CH_2Cl_2 and $CH_3CO_2C_2H_5$ to give 0.12 g (4%) of **5.** The column was then treated with a 4% solution of CH_3OH in CH_2Cl_2 to elute the major yellow band leaving a small yellow band at the top of the column which was not investiated further. Evaporation of solvent left 2.35 g (84% yield) of 4-ferrocenyl-3-heptene-1,7-diol (**6**), mp 82–88 °C. This was recrystallized by dissolving it in 200 mL of ethyl ether, concentrating to 25 mL, and cooling to −10 °C overnight to give 1.56 g of glistening orange platelets of **6,** mp 88–90 °C.

Anal. Calcd for $C_{17}H_{22}O_2Fe$: C, 64.98; H, 7.06; Fe, 17.78; mol wt, 314. Found: C, 65.03; H, 7.00; Fe, 17.57; *m/e* 314.

The carbonium ion, **8a,** was formed by dissolving **5** (0.25 g) in 2 mL of CF_3CO_2H in an NMR tube. After 1 h at 25 °C, formation of **8a** was complete (see Table I for NMR).

Reaction of Ferrocenylbis(3-trifluoroacetoxypropyl)carbonium Trifluoroacetate (8a) with Ferrocene. 5 (1 g, 0.0032 mol) was dissolved in 10 mL of CF_3CO_2H at 25 °C and let stand for 2 h. The trifluoroacetic acid was removed under reduced pressure at 25 °C and ferrocene (5.41 g, 0.032 mol), dissolved in 25 mL of CH_2Cl_2, was added to the residue. The solution was stirred 40 h at 25 °C under an N_2 atmosphere and then treated with 50 mL of H_2O and enough ascorbic acid to reduce the ferricenium ion present. The phases were separated and the aqueous phase was extracted with 25 mL of CH_2Cl_2. The CH_2Cl_2 phases were combined, the CH_2Cl_2 was evaporated, and the residue was heated at 175 °C (0.25 mm) for 15 min to remove residual unreacted ferrocene. The nonvolatile residue was then dissolved in ethyl acetate containing 2% CH_3OH and chromatographed on a dry 36 × 250 mm alumina column. The major yellow band was excised, extracted with CH_3OH, and recrystallized from benzene to give 1.1 g (69% yield) of **3,** mp 168–171 °C. An additional recrystallization from CH_3OH gave **3,** mp 169–171 °C. No other bands of the column were separated and identified.

Reaction of Ferrocenylbis(3-trifluoroacetoxypropyl)carbonium Trifluoroacetate (8a) with 4,4-Diferrocenylheptane-1,7-diol (3). To 10 mL of CH_2Cl_2 was added 1.0 g (0.0020 mol) of **3.** To the stirred suspension (N_2 atmosphere, 25 °C) was added 0.84 g (0.0040 mol) of trifluoroacetic anhydride dissolved in 6 mL of CH_2Cl_2. The diol quickly dissolved. To this solution was added 0.63 g (0.0020 mol) of **5,** and 4 mL of CF_3CO_2H. After 40 h at 25 °C, N_2 atmosphere, the reaction mixture was added to ice water with enough ascorbic acid to discharge the blue color of the aqueous phase. The CH_2Cl_2 phase was separated and the volatiles were removed under reduced pressure to leave 2.5 g of residue. The residue was dissolved in 50 mL of CH_3OH and KOH was added until the solution remained basic. Most of the CH_3OH was removed under reduced pressure and then H_2O was added. The solids were dissolved in 4% CH_3OH in CH_2Cl_2 and chromatographed on alumina (dry clumn grade) to give 0.80 g of a mixture of **6** and **3.** TLC (SiO_2, ethyl acetate) showed approximately equal amounts of **3** and **6** in the mixture. Recrystallization of the mixture from CH_2ClCH_2Cl gave 0.40 g (0.00080 mol) of **3,** mp 169–171 °C. Continuing elution of the column with 10% CH_3OH in CH_2Cl_2 gave 0.40 g of material. Recrystallization from CH_3OH gave 0.30 g (0.00037 mol) of **9,** mp 202–204 °C.

Trifluoroacetic Acid Catalyzed Reaction of 4 with Ferrocene. To 1 L of CH_2Cl_2 was added 400 g (2.15 mol) of ferrocene and 40.0 g (0.311 mol) of **4.** The mixture was stirred and purged with N_2 for 5 min and then 296 g (2.60 mol) of trifluoroacetic acid was added. This re-

action mixture was heated at reflux for 5.5 h while maintaining the N_2 atmosphere and then poured into 1.5 L of ice water containing 10 g of ascorbic acid. When the blue color of the aqueous phase disappeared, the organic phase was separated and the voltatiles were removed under reduced pressure (1 mm) with warming (80 °C) leaving 503 g of unreacted ferrocene and trifluoroacetylated ferrocene derivatives. This residue was hydrolyzed by stirring and heating to boiling in 1 L of CH_3CH containing 40 g (0.71 mol) of KOH. The resulting mixture was poured into 3 L of ice water and allowed to stand several hours to permit crystallization of products. The solids were separated by filtration and dried on the filter by sucking air through to leave 437 g (theoretical amount is 440 g) of products and unreacted ferrocene. This was extracted with five 3-L portions of boiling CH_2Cl_2 leaving 2.2 g of undissolved yellow powder (impure **9**).

The reaction mixture was separated by chromatography. The five 3-L portions of extract were poured onto an 85 × 440 mm alumina column, activity III (column packed in CH_2Cl_2), in the order in which they were taken. All unreacted ferrocene had been eluted by the time the last 3-L portion had been added. Evaporation of CH_2Cl_2 from this eluate left 298 g (1.60 mol) of ferrocene. There remained four well-defined bands on the column. The two bottom bands were eluted with CH_2Cl_2. The material from the first one, 0.7 g, was not identified. The next band, 4.0 g (0.013 mol, 4.1% yield), was identified by NMR as **5**.

The third (major) band was eluted with 4 L of 1% CH_3OH in CH_2Cl_2, 2 L of 2% CH_3OH in CH_2Cl_2, and then 6 L of 4% CH_3OH in CH_2Cl_2. (Starting elution with 4% CH_3OH in CH_2Cl_2 may cause 4,4-diferrocenylheptane-1,7-diol (**3**) to crystallize in the alumina column.) Evaporation of solvent left 114 g of a mixture of **6** and **3**. This mixture was dissolved in 1.8 L of boiling CH_2ClCH_2Cl, filtered, concentrated to 600 mL, and cooled to give 101.3 g (0.202 mol, 65% yield) of **3**, mp 168–171 °C. [Solubility of **3** is 0.38 g/100 mL of CH_2CCH_2Cl at 25 °C, indicating the presence of an additional 2.5 g of **3** in the mother liquor for a total of 103.8 g (0.207 mol, 67% yield) of **3**.] The presence of **6** and **3** in the mother liquor was shown by thin-layer chromatography on SiO_2 plates. A sample of **3** was recrystallized from CH_3OH, mp 169–171 °C.

Anal. Calcd for $C_{27}H_{32}Fe_2O_2$: C, 64.82; H, 6.45; Fe, 22.33; mol wt, 500. Found: C, 64.65; H, 6.50; Fe, 22.24; *m/e* 500.

After removal of the major band the alumina column was treated with 2 L of 6% CH_3OH in CH_2Cl_2 and 2 L of 10% CH_3OH in CH_2Cl_2. This developed the remaining band into two bands and eluted one to give 2.0 g of material which was not identified. The remaining band was removed with 25% CH_3OH in CH_2Cl_2. Evaporation of solvent left 10.4 g of material which was combined with the 2.2 g of undissolved yellow powder left after the initial extraction with CH_2Cl_2. This was dissolved in 4 L of hot CH_3OH, filtered, concentrated to 500 mL, and cooled to give 7.5 g (0.0092 mol, 5.9% yield) of **9**, mp 202–205 °C. [Solubility of **9** is 0.19 g/100 mL of CH_3OH at 25 °C, indicating the presence of an additional 0.95 g of **9** in the mother liquor for a total of 8.5 g (0.0104 mol, 6.7% yield) of **9**.] Another recrystallization from CH_3OH raised the melting point to 203–205 °C.

Anal. Calcd for $C_{44}H_{54}Fe_3O_4$: C, 64.89; H, 6.68; Fe, 20.57. Found: C, 64.87; H, 6.70; Fe, 20.11.

Acknowledgment. Appreciation is expressed to Donald W. Moore of this Laboratory for NMR spectra and their interpretation.

Registry No.—**4**, 176-25-0; ferrocene, 102-54-5.

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(14) [**3a**] = (K_1/[CF_3CO_2H]) [**8a**][FcH]; [**3a**]^2 = (K_1/K_2) [**9a**][FcH].

Reaction of 6(7)-Diazopenicillanates and Diazocephalosporanates with Sulfenyl Chlorides. Preparation of 6(7)α-Methoxy-Substituted Thiol Penicillanates and Thiol Cephalosporanates

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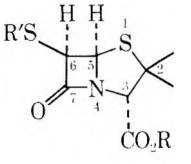
Reaction of diazo esters **3**, **10**, and **16** with sulfenyl chlorides in the presence of methanol gave 6(7)-α-methoxy thiol penicillanates and thiol cephalosporanates. Reaction of **10** and **16** with β,β,β-trichloroethoxycarbonylsulfenyl chloride in the presence of methanol gave the esters **12** and **19** which when treated with Zn–90% HOAc at 0 °C gave the mercaptans **13** and **20**. Mercaptans **13** and **20** were acylated by standard procedures.

A method has been developed in this laboratory for the preparation of sulfur analogues of penicillins and deacetoxycephalosporins of the general structures **1** and **2** where R′ can be either an alkyl group or an acyl group.[1] The isolation of cephalosporin derivatives from species of *Streptomyces* containing an α-methoxy group in the 7 position which exhibited greater activity than cephalosporin C against gram-negative organisms[2] suggested that the sulfur analogues **1** and **2** might also show increased activity with the introduction of an α-methoxy group in the 6(7) position. We wish to report here the preparation of such derivatives by reaction of the diazo esters **3**, **10**, and **16** with sulfenyl chlorides in the presence of methanol.



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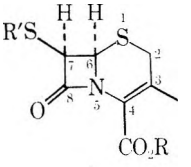

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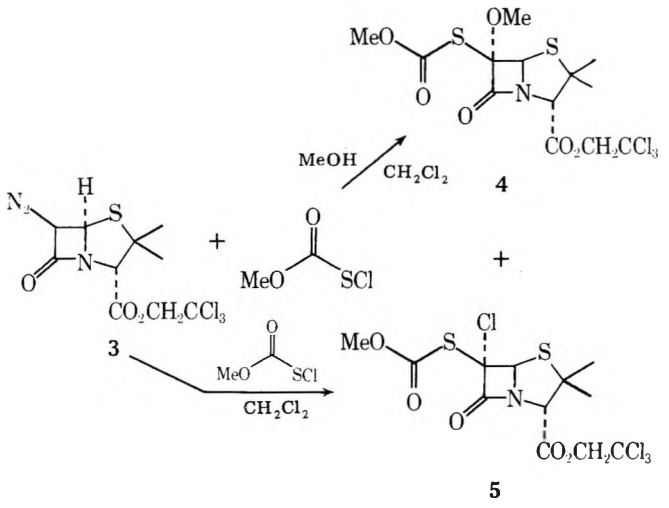
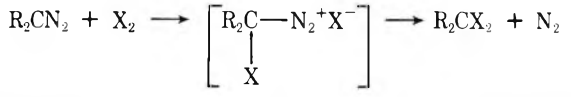
Scheme I



Results and Discussion

Treatment of the diazo ester **3** with carbomethoxysulfenyl chloride in methylene chloride containing an excess of methanol gave, after chromatography on silicic acid, the 6α-methoxy ester **4** in 78% yield along with a small amount (3%) of the 6α-chloro ester **5**. The 6α-chloro ester **5** was obtained in 88% yield by reaction of **3** with the sulfenyl chloride in the absence of methanol[3] (Scheme I).

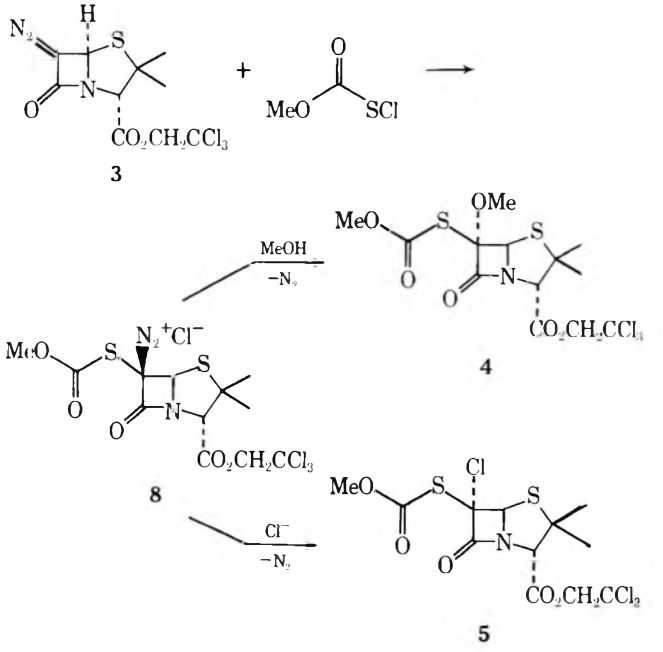
The stereochemistry at C-6 in **4** and **5** has been assigned from mechanistic considerations. Diazo compounds react readily with halogens giving geminal dihalides, the reaction proceeding through the diazonium intermediate shown below.[4] Reaction of **3** with the sulfur of the sulfenyl chloride



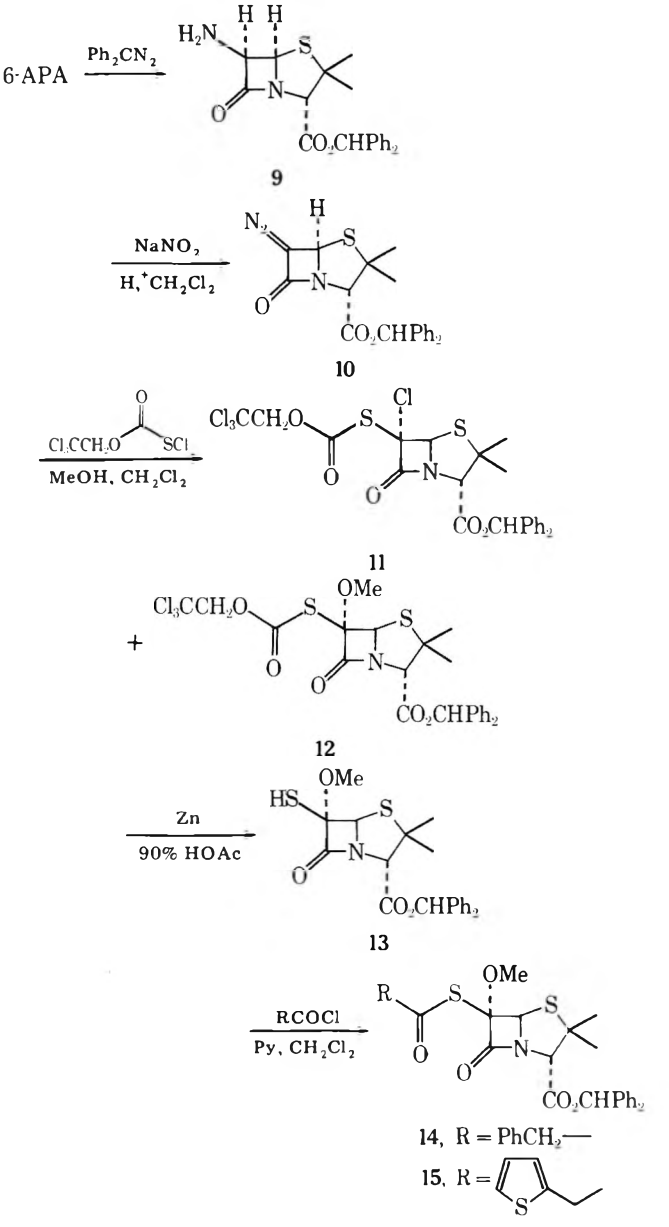
will initially give the diazonium intermediate **8**,[5] presumably with the stereochemistry indicated (see ref 6). Addition of methanol from the least hindered α face of the β-lactam ring[6] will give the 6α-methoxy ester **4** whereas addition of chloride ion will give **5**[7] (Scheme II).

Esterification of 6-APA with diphenyldiazomethane gave the benzhydryl amine **9** which was converted to the diazo ester

Scheme II



Scheme III

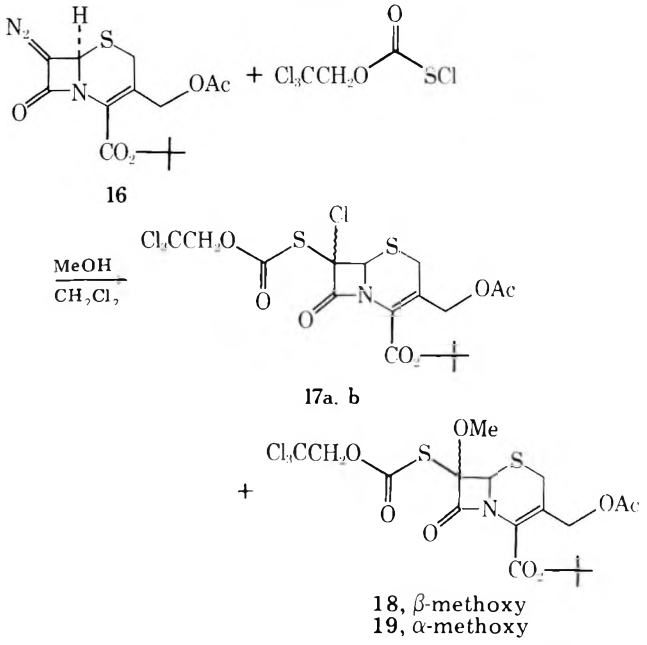


10 by treatment with sodium nitrite in 1 N $HClO_4$ and methylene chloride.[8] Reaction of **10** with β,β,β-trichloroethoxycarbonylsulfenyl chloride and an excess of methanol gave, after chromatography on silica gel,[9] the 6α-chloro ester **11** (1%) and the 6α-methoxy ester **12**[10] (70%). Removal of the trichloroethyl group from **12** with Zn–90% HOAc at 0 °C gave the mercaptan **13** in quantitative yield as a crystalline product. Acylation of **13** with phenylacetyl chloride and thiophene-2-acetyl chloride in methylene chloride containing an equivalent of pyridine gave the thiol esters **14** (77%) and **15** (83%), respectively (Scheme III).

In the cephalosporin series the mercaptan **20** was made by the same sequence of reactions used in the penicillin series. Reaction of the diazo ester **16** with β,β,β-trichloroethoxycarbonylsulfenyl chloride gave, after chromatography on silica gel (see ref 9), the 7α and β-chloro esters **17a** and **17b** as a mixture (oil) in 1% yield[11] and the 7β and α-methoxy esters **18** and **19** as crystalline products in 7% and 35% yields, respectively[12] (Scheme IV).

The assignment of the stereochemistry at C-7 in **19**, the major product in the reaction, is analogous to that given in the penicillin series. The fact that **18** and both epimers of **17** (in a ratio of approximately 2:1 by NMR integration of the C-6 proton in the crude reaction mixture) were isolated in rea-

Scheme IV



sonable quantities is presumably due to the fact that the dihydrothiazine ring does not shield the β face of the β-lactam ring to the same extent that the thiazolidine ring does in the penicillin series (vide supra).

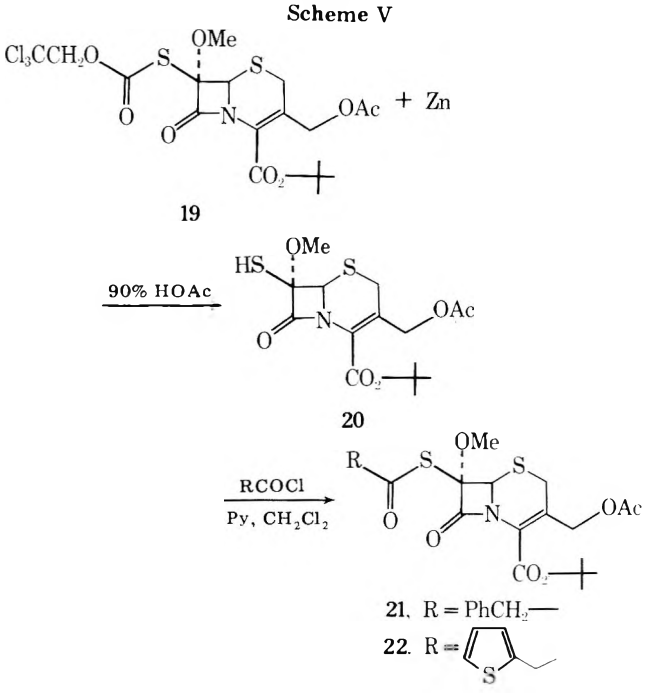
Removal of the trichloroethyl group from **19** in the same manner as described for **12** gave the mercaptan **20** as an unstable oil in quantitative yield. Acylation of **20** with phenylacetyl chloride and thiophene-2-acetyl chloride gave the corresponding esters **21** and **22** in 59% and 68% yields, respectively (Scheme V).

After removal of the protective groups[13] (see Experimental Section), the free acids were tested in vitro for bioactivity. Minimum inhibitory concentration (MIC) values are in micrograms per milliliter. Only the acids from **21** and **22** showed appreciable activity against the microorganisms used. Their values against *Bacillus subtilis* ATCC 6051 were <6.25 and 50, respectively.

Experimental Section

Melting points and boiling points are uncorrected; melting points were determined on a Fisher-Johns melting point apparatus. Nuclear magnetic resonance (NMR) spectra were recorded with a Varian Associates T-60 spectrometer and are reported in parts per million (δ) relative to tetramethylsilane as an internal standard. Infrared spectra (IR) were recorded on a Perkin-Elmer 237 spectrophotometer. High resolution mass spectra were recorded on a CEC-110B high-resolution Mattauch-Herzog mass spectrometer. Microanalysis was performed by Galbraith Laboratories, Inc., Knoxville, Tenn. Routine thin-layer chromatography was run on Baker-flex silica gel 1B-F TLC sheets. Preparative thick-layer chromatography was performed on EM Reagents precoated silica gel 60 F-254 plates (2 mm thickness). Column chromatography was performed with either Mallinckrodt silicic acid (100 mesh) or EM Reagents silica gel 60 (finer than 230 mesh).

Scheme V



β,β,β-Trichloroethyl 6-diazopenicillanate (3),[14] chlorocarbonylsulfenyl chloride,[15] carbomethoxysulfenyl chloride,[16] 7-diazocephalosporanic acid *tert*-butyl ester,[17] and thiophene-2-acetyl chloride[18] were prepared by literature procedures.

Synthesis of β,β,β-Trichloroethyl 6β-(Methoxycarbothiol)-6-chloropenicillanate (5). Carbomethoxysulfenyl chloride[16] (768.8 mg, 6.08 mmol) was added to an ice-cold solution of 2.1729 g (6.06 mmol) of the diazo ester **3**[14] in 50 mL of methylene chloride. There was an immediate evolution of gas. The solution was stirred at 0 °C for 30 min and then the solvent removed under reduced pressure. The residual oil was chromatographed on silicic acid using methylene chloride as an eluent. Isolation of the fastest moving fraction gave the chloro ester **5** (2.44 g, 88% as an oil; one spot on TLC): IR (CH_2Cl_2) 2960, 1790, 1765 sh, and 1725 cm^{-1}; NMR ($CDCl_3$) δ 1.55 (s, 3 H), 1.63 (s, 3 H), 3.93 (s, 3 H), 4.68 (s, 1 H), 4.83 (s, 2 H), 5.87 (s, 1 H); MS *m/e* 454.9000 (M^+, calcd for $C_{12}H_{13}NO_5Cl_4S_2$, 454.8990).

Isolation of a slower moving fraction gave 43.2 mg of an oil which was one spot by TLC; however, its NMR suggested the presence of more than one component. One of the components is identical (by NMR) with the product isolated in the preparation of **4** and believed to be the 6β-chloro ester **6** (see ref 3 and the next experimental procedure).

Synthesis of β,β,β-Trichloroethyl 6β-(Methoxycarbothio)-6-methoxypenicillanate (4). Carbomethoxysulfenyl chloride (1.0803 g, 8.54 mmol) was added to an ice-cold solution of the diazo ester **3** (3.0050 g, 8.38 mmol) in 50 mL of methylene chloride and 50 mL of methanol. There was an immediate evolution of gas. The solution was stirred at 0 °C for 30 min and the solvent removed under reduced pressure. The residual oil was chromatographed on silicic acid using methylene chloride as an eluent. Isolation of the fastest moving fraction gave the chloro ester **5** as an oil (132.1 mg, 3%) identical in all respects (NMR, IR, and TLC) with that obtained by treatment of the diazo ester **3** with carbomethoxysulfenyl chloride in the absence of methanol.

Isolation of a slower moving fraction gave 28.7 mg of an oil which was subjected to further chromatography on two 20 × 20 mm silica gel plates using methylene chloride–carbon tetrachloride as eluents. Isolation of the most polar fraction gave 18.9 mg (0.5%) of an oil whose spectral data are in complete agreement with the 6β-chloro ester **6**: IR (CH_2Cl_2) 2950, 1790, and 1760 cm^{-1}; NMR ($CDCl_3$) δ 1.58 (s, 3 H), 1.83 (s, 3 H), 3.92 (s, 3 H), 4.65 (s, 1 H), 4.78 (s, 2 H), 5.70 (s, 1 H); MS *m/e* 395.8868 ($M^+ - 59$, calcd for $C_{10}H_{10}NO_3Cl_4S_2$, 395.8856).

Isolation of the slowest moving fraction gave 2.97 g (78%) of the 6α-methoxy ester **4** as an oil (one spot on TLC): IR (CH_2Cl_2) 2950, 1775, 1755 sh, and 1715 cm^{-1}; NMR ($CDCl_3$) δ 1.55 (s, 3 H), 1.65 (s, 3 H), 3.68 (s, 3 H), 3.88 (s, 3 H), 4.63 (s, 1 H), 4.83 (s, 2 H), 5.68 (s, 1 H); MS *m/e* 450.9504 (M^+, calcd for $C_{13}H_{16}NO_6Cl_3S_2$, 450.9485).

Synthesis of Benzhydryl 6-Aminopenicillanate (9). A mixture of 5.400 g (25.0 mmol) of 6-APA and 4.850 g (25.0 mmol) of diphenyldiazomethane in 75 mL of methylene chloride and 25 mL of methanol was stirred at room temperature for 44 h. After approximately 24 h and 30 h, additional 1-g portions of diphenyldiazomethane were added. The solid was removed by filtration and the filtrate extracted with ice-cold dilute HCl. An emulsion formed which required more than 3 h to separate (during this time the mixture warmed to room temperature). The organic layer was separated and the aqueous layer extracted twice with methylene chloride (emulsions). The aqueous layer was partitioned with methylene chloride and made basic with $NaHCO_3$. After extraction with methylene chloride, drying ($MgSO_4$), and removal of the solvent under reduced pressure (no heat), the benzhydryl ester (2.99 g, 31%) was isolated as an oil: IR (CH_2Cl_2) 3380, 3050, 2960, 1775, and 1735 cm^{-1}; NMR ($CDCl_3$) δ 1.28 (s, 3 H), 1.60 (s, 3 H), 1.80 (s, 2 H), 4.40 (d, 1 H, J = 4.0 Hz), 4.47 (s, 1 H), 5.37 (d, 1 H, J = 4.0 Hz), 6.82 (s, 1 H), 7.20 (s, 10 H).

Synthesis of Benzhydryl 6-Diazopenicillanate (10). Ice water (100 mL), sodium nitrite (232.5 mg, 3.37 mmol), and 3 mL of 1 N $HClO_4$ were added (in that order) to an ice-cold solution of the amine

in 100 mL of methylene chloride and the mixture was vigorously stirred (mechanical stirrer) at 0 °C for 2 h. The organic layer was separated, washed with cold saturated NaCl, and dried (Na_2SO_4). Removal of the solvent under reduced pressure (no heat) gave a yellow oil which was dissolved in ether–petroleum ether and after standing at approximately −15 °C overnight, the product crystallized (420 mg, 75%). Recrystallization from ether–petroleum ether gave an analytically pure sample: mp 93.0–94.0; IR (CH_2Cl_2) 2090, 1760, and 1700 sh; NMR ($CDCl_3$) δ 1.27 (s, 3 H), 1.65 (s, 3 H), 4.47 (s, 1 H), 6.12 (s, 1 H), 6.88 (s, 1 H), 7.30 (s, 10 H).

Anal. Calcd for $C_{21}H_{19}N_3O_3S$: C, 64.10; H, 4.87; N, 10.68; S, 8.15. Found: C, 64.11; H, 4.90; N, 10.52; S, 8.06.

Synthesis of β,β,β-Trichloroethoxycarbonylsulfenyl Chloride. Chlorocarbonylsulfenyl chloride[15] (43.5 mL, 0.52 mol) was added dropwise over 30 min to an ice-cold solution of 50 mL (0.52 mol) of β,β,β-trichloroethanol and 42 mL (0.52 mol) of pyridine in 300 mL of methylene chloride. After the addition, the mixture was stirred at 0 °C for 1.5 h and at room temperature for 1.5 h. The mixture was washed with ice water and ice-cold saturated NaCl. The organic layer was dried ($MgSO_4$) and the solvent removed under reduced pressure.

After removal of the solvent, an oily crystalline material remained (crystalline material believed to be $[Cl_3CCH_2OCOS]_2$). The crystalline material was removed by crystallization from a minimum amount of ether. This process was repeated until as much crystalline material as possible was removed. The remaining yellow liquid was distilled under reduced pressure: fraction collected 54–59 °C (0.25 mm; external bath temperature, 80–90 °C); NMR ($CDCl_3$) δ 5.0 (singlet).

Synthesis of Benzhydryl 6β-(β,β,β-Trichloroethoxycarbothio)-6-chloropenicillanate (11). The diazo ester **10** was prepared as described above. After removal of the Na_2SO_4 by filtration, the methylene chloride solution of **10** was cooled to 0 °C and used in the following reaction.

β,β,β-Trichloroethoxycarbonylsulfenyl chloride (243.8 mg, 5.00 mmol; 1 equiv based on starting benzhydryl amine) was added to the above ice-cold solution of **10**. The solution was stirred at 0 °C for approximately 30 min and then the solvent was removed under reduced pressure. The residual oil was chromatographed on silica gel 60 (>230 mesh) using methylene chloride as an eluent. Isolation of the major fraction gave the 6α-chloro ester **11** (593 mg, 20%; oil) as the only identifiable β-lactam component: IR (CH_2Cl_2) 3040, 2950, 1790, and 1740 cm^{-1}; NMR ($CDCl_3$) δ 1.28 (s, 3 H), 1.60 (s, 3 H), 4.58 (s, 1 H), 4.73 (d, 1 H, J = 10.0 Hz), 4.93 (d, 1 H, J = 10.0 Hz), 5.80 (s, 1 H), 6.83 (s, 1 H), 7.23 (s, 10 H).

Synthesis of Benzhydryl 6β-(β,β,β-Trichloroethoxycarbothio)-6-methoxypenicillinate (12). The diazo ester **10** (starting with 2.8364 g, 7.43 mmol of benzhydryl amine **9** in 150 mL of methylene chloride) was prepared as described above. After removal of the Na_2SO_4 by filtration, the solution was cooled to 0 °C and 150 mL of methanol added.

β,β,β-Trichloroethoxycarbonylsulfenyl chloride (1.800 g, 7.38 mmol) was added to the above ice-cold solution. After stirring at 0 °C for 15 min and removal of the solvent under reduced pressure, the residual oil was chromatographed on silica gel 60 (>230 mesh) using methylene chloride as an eluent. Isolation of a minor fraction gave the 6α-chloro ester **11** (54 mg, 1%) identical in all respects (IR, NMR, and TLC) with that obtained from the reaction of **10** with β,β,β-trichloroethoxycarbonylsulfenyl chloride in the absence of methanol.

Isolation of the major fraction gave the 6α-methoxy ester **12** (3.16 g, 70%) as an oil (1 spot on TLC) as the only other β-lactam component: IR (CH_2Cl_2) 1775 and 1740 cm^{-1}; NMR ($CDCl_3$) δ 1.28 (s, 3 H), 1.60 (s, 3 H), 3.68 (s, 3 H), 4.60 (s, 1 H), 4.85 (s, 2 H), 5.70 (s, 1 H), 6.92 (s, 1 H), 7.33 (s, 10 H); MS m/e 603.0130 (M^+, calcd for $C_{25}H_{24}NO_6Cl_3S_2$, 603.0111).

Synthesis of Benzhydryl 6β-Mercapto-6-methoxypenicillanate (13). The 6α-methoxy ester **12** (1.2346 g, 2.04 mmol) was dissolved in 30 mL of 90% HOAc and the solution cooled to 0 °C before 1.6 g of zinc dust was added. The mixture was stirred at 0 °C for 5 h. Removal of the zinc by filtration through celite into a flask containing ice water and washing of the zinc with methylene chloride gave a two-phase system. The aqueous layer was made basic with $NaHCO_3$ and extracted with the organic layer. Separation of the organic layer, extraction of the aqueous layer with several methylene chloride–zinc washings, drying ($MgSO_4$), and removal of the solvent under reduced pressure (no heat) gave the mercaptan **13** as a crystalline product in quantitative yield. Recrystallization from methylene chloride–petroleum ether gave an analytically pure sample: mp 127.5–129.0 °C; IR (CH_2Cl_2) 3030, 2950, 1775, and 1740 cm^{-1}; NMR ($CDCl_3$) δ 1.30 (s, 3 H), 1.67 (s, 3 H), 2.55 (s, 1 H), 3.50 (s, 3 H), 4.55 (s, 1 H), 5.40 (s, 1 H), 6.85 (s, 1 H), 7.25 (s, 10 H).

Anal. Calcd for $C_{22}H_{23}NO_4S_2$: C, 61.52; H, 5.40; N, 3.26; S, 14.93. Found: C, 61.58; H, 5.41; N, 3.23; S, 14.93.

Synthesis of Benzhydryl 6β-(Phenylacetylthio)-6-methoxypenicillanate (14). A solution of 397.8 mg (9.26 mmol) of the mercaptan **13** in 20 mL of methylene chloride was cooled to 0 °C before 122 μL (9.22 mmol) of phenylacetyl chloride and 75 μL (9.27 mmol) of pyridine were added. The solution was stirred at 0 °C for 3 h and then extracted with ice-cold dilute HCl and aqueous $NaHCO_3$ and dried ($MgSO_4$), and the solvent removed under reduced pressure. After chromatography on silica gel 60 (>230 mesh) using methylene chloride as an eluent, the 6α-methoxy ester **14** (389 mg, 77%) was isolated as an oil: IR (CH_2Cl_2) 3050, 2925, 1770, 1740, and 1705 cm^{-1}; NMR ($CDCl_3$) δ 1.22 (s, 3 H), 1.45 (s, 3 H), 3.50 (s, 3 H), 3.78 (s, 2 H), 4.45 (s, 1 H), 5.63 (s, 1 H), 6.77 (s, 1 H), 6.9–7.3 (m, 15 H).

Synthesis of Benzhydryl 6β-(Thiophene-2-acetylthio)-6-methoxypenicillanate (15). In the same manner as described for the preparation of **14**, the 6α-methoxy ester **15** was isolated as an oil (83%) after chromatography on silica gel 60 (>230 mesh) using methylene chloride as an eluent: IR (CH_2Cl_2) 3050, 2960, 1775, 1740, and 1705 cm^{-1}; NMR ($CDCl_3$) δ 1.23 (s, 3 H), 1.48 (s, 3 H), 3.53 (s, 3 H), 3.98 (s, 2 H), 4.48 (s, 1 H), 5.70 (s, 1 H), 6.7–7.5 (m, 14 H).

7-Aminocephalosporanic acid *tert*-butyl ester was prepared according to the literature[19] and purified in the following manner. After removal of the solvent under reduced pressure (no heat), the crude product (dark brown) was dissolved in methylene chloride and extracted with ice-cold dilute HCl. The aqueous layer (kept cold) was extracted with methylene chloride (twice), partitioned with methylene chloride, and made basic with $NaHCO_3$. After separation of the organic layer, repeated extraction of the aqueous layer with methylene chloride (four times), drying ($MgSO_4$), and removal of the solvent under reduced pressure (no heat), the product was isolated as a light yellow crystalline material. Recrystallization from methylene chloride (minimum amount)–ether–petroleum ether gave 7-aminocephalosporanic acid *tert*-butyl ester as a white crystalline product. The yield of the diazo ester **16** depends on the purity of this starting material.

Synthesis of *tert*-Butyl 7-(β,β,β-Trichloroethoxycarbothio)-7-chlorocephalosporanates (17a and 17b). A vigorously stirred (mechanical stirrer) solution of *tert*-butyl 7-aminocephalosporinate (2.000 g, 6.10 mmol) in 200 mL of methylene chloride was cooled to 0 °C before 200 mL of ice water, 18.000 g (0.261 mmol) of sodium nitrite, and 1.150 g (6.04 mmol) of p-TsOH·H_2O were added in that order. After 5 min, a total of 1.660 g (8.73 mmol) of p-TsOH·H_2O was added gradually over 40 min. After the last addition, the mixture was stirred at 0 °C for 15 min and then the organic layer separated (kept cold), washed with cold saturated NaCl, and dried (Na_2SO_4). The Na_2SO_4 was removed by filtration and the filtrate cooled to 0 °C before the addition of 1.20 g (4.92 mmol; 0.8 equiv based on starting amine) of β,β,β-trichloroethoxycarbonylsulfenyl chloride. The solution was stirred at 0 °C for 15 min and then the solvent removed under reduced pressure and the residual oil chromatographed on silica gel 60 (>230 mesh) using 100:1 methylene chloride/ether (v/v) as an eluent. The chloro esters **17a** and **17b** (365 mg of oil, 11%) were isolated as a mixture of epimers in a ratio of approximately 2:1 by NMR integration of the C-6 protons: IR (CH_2Cl_2) 2950, 1790, and 1735 cm^{-1}; NMR ($CDCl_3$) δ 1.63 (s, 18 H), 2.15 (s, 6 H), 3.3–3.7 (m, 4 H), 4.7–5.4 (m, 10 H; C-6 protons are singlets at 5.17 and 5.27 in a ratio of 1:2, respectively).

The mixture of **17a** and **17b** (254 mg) was chromatographed on 100 g of silica gel 60 (>230 mesh; dried at 125 °C for 12 h prior to use) using 200:1 methylene chloride/ether (v/v) as an eluent. Fractions collected were monitored by NMR analysis. Three fractions were collected. The middle fraction was a mixture of epimers.

Less polar fraction (20 mg of oil): IR (CH_2Cl_2) 2925, 1790, and 1735 cm^{-1}; NMR ($CDCl_3$) δ 1.57 (s, 9 H), 2.10 (s, 3 H), 3.2–3.6 (m, 2 H), 4.5–5.3 (m, 5 H, C-6 proton singlet at 5.17).

More polar isomer (32 mg of oil): IR (CH_2Cl_2) 2950, 1790, and 1735 cm^{-1}; NMR ($CDCl_3$) δ 1.60 (s, 9 H), 2.12 (s, 3 H), 3.22 (d, 1 H, J = 18.0 Hz), 3.55 (d, 1 H, J = 18.0 Hz), 4.6–5.4 (m, 5 H; C-6 proton singlet at 5.27).

Synthesis of *tert*-Butyl 7-(β,β,β-Trichloroethoxycarbothio)-7-methoxycephalosporanates (18 and 19). A vigorously stirred (mechanical stirrer) solution of *tert*-butyl 7-aminocephalosporanate (2.000 g, 6.10 mmol) in 200 mL of methylene chloride was cooled to 0 °C before 200 mL of ice water, 18.000 g (.261 mmol) of sodium nitrite, and 1.150 g (6.04 mmol) of p-TsOH·H_2O were added in that order. After 5 min a total of 1.660 g (8.73 mmol) of p-TsOH was added gradually over 40 min. After the last addition, the mixture was stirred at 0 °C for 10 min and then the organic layer separated (kept cold), washed with cold saturated NaCl, and dried (Na_2SO_4). The Na_2SO_4

was removed by filtration and the filtrate (approximately 400 mL) cooled to 0 °C before 100 mL of methanol and 1.20 g (4.92 mmol; 0.8 equiv based on starting amine) of β,β,β-trichloroethoxycarbonylsulfenyl chloride were added in that order. The solution was stirred at 0 °C for 30 min and then the solvent removed under reduced pressure. The residual oil was chromatographed on silica gel 60 (>230 mesh) using 100:1 methylene chloride/ether (v/v) as an eluent. Isolation of the least polar β-lactam fraction gave the α and β-chloro esters **17a** and **17b** as a mixture (43 mg of oil, 1%) identical in all respects (IR, NMR and TLC) with the mixture obtained by treatment of the diazo ester **16** with β,β,β-trichloroethoxycarbonylsulfenyl chloride in the absence of methanol.

Isolation of a slower moving fraction gave the 7β-methoxy ester **18** as an oil which crystallized on standing (232 mg, 7%). Recrystallization from methylene chloride–petroleum ether gave an analytically pure sample: mp 95–97 °C; IR (CH_2Cl_2) 2970, 1780, and 1725 cm^{-1}; NMR ($CDCl_3$) δ 1.63 (s, 9 H), 2.15 (s, 3 H), 3.32 (d, 1 H, J = 18.0 Hz), 3.63 (d, 1 H, J = 18.0 Hz), 3.72 (s, 3 H), 4.7–5.3 (m, 5 H; C-6 proton singlet at 5.15).

Anal. Calcd for $C_{18}H_{22}NO_8S_2Cl_3$: C, 39.25; H, 4.03; N, 2.54; Cl, 19.31; S, 11.64. Found: C, 39.19; H, 4.11; N, 2.48; Cl, 19.29; S, 11.85.

Isolation of the slowest moving fraction gave the 7α-methoxy ester **19** as an oil which crystallized on standing (1.18 g, 35%). Recrystallization from methylene chloride–petroleum ether gave an analytically pure sample: mp 85.0–87.5 °C; IR (CH_2Cl_2) 2950, 1775, and 1735 cm^{-1}; NMR ($CDCl_3$) δ 1.57 (s, 9 H), 2.10 (s, 3 H), 3.25 (d, 1 H, J = 18.0 Hz), 3.62 (d, 1 H, J = 18.0 Hz), 3.73 (s, 3 H), 4.6–5.3 (m, 5 H; C-6 proton singlet at 5.10).

Anal. Calcd for $C_{18}H_{22}NO_8S_2Cl_3$: C, 39.25; H, 4.03; N, 2.54; Cl, 19.31; S, 11.64. Found: C, 39.41; H, 4.16; N, 2.45; Cl, 19.44; S, 11.76.

Synthesis of *tert*-Butyl 7β-Mercapto-7-methoxycephalosporanate (20). In the same manner as described for the preparation of **13**, the mercaptan **20** was isolated as an unstable oil in quantitative yield: IR (CH_2Cl_2) 2950, 2920, 1775, and 1725 cm^{-1}; NMR ($CDCl_3$) δ 1.58 (s, 9 H), 2.10 (s, 3 H), 2.55 (s, 1 H), 3.30 (d, 1 H, J = 18.0 Hz), 3.57 (d, 1 H, J = 18.0 Hz), 3.60 (s, 3 H), 4.80 (d, 1 H, 13.0 Hz), 4.88 (s, 1 H), 5.13 (d, 1 H, J = 13.0 Hz).

Synthesis of *tert*-Butyl 7β-Mercapto-7-methoxycephalosporanate (20). In the same manner as described for the preparation mercaptan **20** was isolated as an oil and used immediately in the following reaction.

A solution of 239 mg (0.64 mmol) of the mercaptan in 10 mL of methylene chloride was cooled to 0 °C before 52 μL (0.64 mmol) of pyridine and 84 μL (0.64 mmol) of phenylacetyl chloride were added in that order. The solution was stirred at 0 °C for 2.75 h and then extracted with ice-cold dilute HCl, aqueous $NaHCO_3$, and dried ($MgSO_4$), and the solvent removed under reduced pressure. After chromatography on silica gel 60 (>230 mesh) using 50:1 methylene chloride/ether (v/v) as an eluent, the 7α-methoxy ester **21** was isolated as an oil (184 mg, 59%) which crystallized on standing. Recrystallization from ether–petroleum ether gave an analytically pure sample: mp 78–80 °C; IR (CH_2Cl_2) 2950, 1775, 1735 sh, and 1720 cm^{-1}; NMR ($CDCl_3$) δ 1.62 (s, 9 H), 2.13 (s, 3 H), 3.20 (d, 1 H, J = 18.0 Hz), 3.60 (d, 1 H, J = 18.0 Hz), 3.62 (s, 3 H), 3.92 (s, 2 H), 4.77 (d, 1 H, J = 14.0 Hz), 5.08 (d, 1 H, J = 14.0 Hz), 5.10 (s, 1 H), 7.30 (s, 5 H).

Anal. Calcd for $C_{23}H_{27}NO_7S_2$: C, 55.97; H, 5.51; N, 2.84; S, 12.99. Found: C, 56.12; H, 5.48; N, 2.78; S, 12.99.

Synthesis of *tert*-Butyl 7β-(Thiophene-2-acetylthio)-7-methoxycephalosporanate (22). In the same manner as described for **21**, the 7α-methoxy ester **22** was isolated as an oil (206 mg, 68%) which crystallized on standing. Recrystallization from ether–petroleum ether gave an analytically pure sample: mp 78–80 °C; IR (CH_2Cl_2) 2950, 1775, 1735 sh, and 1720 cm^{-1}; NMR ($CDCl_3$) δ 1.62 (s, 9 H), 2.10 (s, 3 H), 3.15 (d, 1 H, J = 17.0 Hz), 3.53 (d, 1 H, J = 17.0 Hz), 3.60 (s, 3 H), 3.73 (s, 2 H), 4.70 (d, 1 H, J = 13.0 Hz), 5.00 (d, 1 H, J = 13.0 Hz), 5.03 (s, 1 H), 6.8–7.4 (m, 3 H).

Anal. Calcd for $C_{21}H_{25}NO_7S_3$: C, 50.58; H, 5.03; N, 2.80; S, 19.21. Found: C, 50.62; H, 5.20; N, 2.75; S, 19.31.

General Procedures for Removal of Protective Groups. For removal of the trichloroethyl group from **4**, see ref 1.

For 21 and 22. The esters were dissolved in cold trifluoroacetic acid, and the solution was stirred at 0 °C for 1 h. The TFA was removed by distillation under reduced pressure (2 mm; reaction flask kept in ice bath while TFA was removed) and the residue freeze-dried from benzene. The acids of **21** and **22** were isolated as white solids and bioassayed without purification.

For **12** the benzhydryl group was removed in the same manner as described for the removal of the *tert*-butyl group from **21** and **22**. After freeze drying, the residue was purified in the following manner. The acid was dissolved in methylene chloride and extracted with aqueous $NaHCO_3$. The aqueous layer, after being extracted several times with methylene chloride, was partitioned with methylene chloride, cooled with ice, and acidified with dilute HCl. Extraction with methylene chloride, drying ($MgSO_4$), and removal of the solvent under reduced pressure (no heat) gave the pure acid of **12**.

For 14 and 15. The esters (70–80 mg) were dissolved in 10 mL of CH_2Cl_2 and the solution was cooled to −77 °C (CO_2–acetone) before the addition of 0.5 mL of trifluoroacetic acid. The solution was warmed to approximately −10 °C (NaCl–H_2O–ice) and stirred at that temperature for 5–6 h. The solution was cooled to −77 °C and 75–100 mL of benzene added. After the contents of the flask solidified, the acids of **14** and **15** were isolated by freeze drying and bioassayed without purification.

In all cases the spectral data were in complete agreement with the structures of the free acids. The NMR spectra showed only signals corresponding to the free acid. Signals corresponding to the protons of the ester protecting group were totally absent, indicating a purity of >95% of the free acid.

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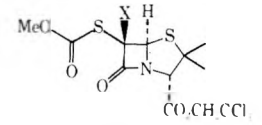
Registry No.—**3,** 51056-24-7; **4,** 65293-10-9; **5,** 65293-11-0; **6,** 65293-12-1; **9,** 47547-28-4; **10,** 65293-13-2; **11,** 65293-14-3; **12,** 65293-15-4; **13,** 65293-16-5; **14,** 65293-17-6; **15,** 65354-55-4; **16,** 58249-92-6; **17a,** 65354-56-5; **17b,** 65293-18-7; **18,** 65293-19-8; **19,** 65293-20-1; **20,** 65293-21-2; **21,** 65293-22-3; **21** acid, 65293-23-4; **22,** 65293-24-5; **22** acid, 65293-25-6; carbomethoxysulfenyl chloride, 26555-40-8; 6-APA, 551-16-6; diphenyldiazomethane, 883-40-9; chlorocarbonylsulfenyl chloride, 2757-23-5; β,β,β-trichloroethanol, 115-20-8; β,β,β-trichloroethoxycarboxylsulfenyl chloride, 65293-26-7; phenylacetyl chloride, 103-80-0; thiophene-2-acetyl chloride, 39098-97-0.

References and Notes

(1) J. C. Sheehan, T. J. Commons, and Y. S. Lo, *J. Org. Chem.*, **42**, 2224 (1977).
(2) E. H. Flynn, "Cephalosporins and Penicillins: Chemistry and Biology", Academic Press, New York, N.Y., 1972, Chapter 15.
(3) In the preparation of **4**, a fraction was isolated which after additional chromatography (see Experimental Section) 18.9 mg (<1%) of an oil was isolated whose spectral data (NMR, IR, and mass spectra) are in complete agreement with the epimeric 6β-chloro ester **6**.



6. X = Cl
7. X = OMe

This component (<1%) was also observed in the preparation of **5**; however, it was not obtained pure. The epimeric 6β-methoxy ester **7** was not isolated in the preparation of **4**. If formed, and very possibly it was, the amount would be small and it could have been lost during the chromatography.
(4) P. A. S. Smith, "The Chemistry of Open-Chain Organic Nitrogen Compounds", Vol. 2, W. A. Benjamin, Inc., New York, N.Y., 1966, Chapter 10, p 234.
(5) In sulfenyl chlorides of the general structure $RS^+–Cl^-$, the ionized form is as indicated. This is consistent with **3** reacting at sulfur and not chlorine giving **8**. N. Kharasch, "Organic Sulfur Compounds", Vol. 1, Pergamon Press, New York, N.Y., 1961, Chapter 32.
(6) The effect of the thiazolidine ring in penicillins in directing attack to the α face of the β-lactam ring is well known: see ref 1.
(7) There is an instant and rapid evolution of nitrogen upon addition of the sulfenyl chloride to **3**. An analogous mechanistic argument has been presented by B. G. Christensen and co-workers for the formation of a single 6β-bromo-6-methoxypenicillanate when benzyl 6-diazopenicillanate is stirred in MeOH–CH_2Cl_2 containing 1 equiv of NBA: L. D. Cama, W. J. Leanza, T. R. Beattie, and B. G. Christensen, *J. Am. Chem. Soc.*, **94**, 1408 (1972).
(8) Although the diazo ester **10** is crystalline and can be obtained analytically pure by recrystallization from ether–petroleum ether, better overall yields are realized if **10** is not isolated (see Experimental Section).
(9) In the case of the benzhydryl penicillanates (and the *tert*-butyl cephalosporanates; vide infra), there is some decomposition during the chromatography. Silica gel was used instead of silicic acid, and a solvent system was chosen such that the products were isolated within 24 h.
(10) The structure of **11** was authenticated by treatment of the diazo ester **10**

with the sulfenyl chloride in the absence of methanol. The epimers (at C-6) of **11** and **12** were not observed. However, if formed it is unlikely they would survive the chromatography: see ref 3 and 9.

(11) The 7-chloro esters **17a** and **17b** were made by treatment of the diazo ester **16** with the sulfenyl chloride in the absence of methanol. After extensive chromatography on silica gel, which decomposed most of the material put on the column (see ref 9), a small amount of each epimer was isolated (see Experimental Section).

(12) The diazo ester **16**, made by the method of Wiering and Wynberg (ref 17), is a crystalline compound; however, again (see ref 8) better overall yields of **19** are obtained if **16** is not isolated. The lower yields in this series compared to the previous two in the penicillin series are attributed mainly to the low yield in the preparation of the diazo ester **16**.

(13) The benzhydryl group has not been used to protect the carboxyl in penicillins because the mild acidic conditions required to remove it destroy the penam system. In the absence of an acylamino group at the C-6 position, which readily reacts with the β-lactam ring to form azlactones, penicillins are more acid stable (see ref 2, p 258). It was therefore anticipated that in the case of the α-methoxy thiol penicillanates, the benzhydryl group could be removed under mild acidic conditions. The carboxyl of **12** was smoothly deprotected with trifluoroacetic acid at 0 °C. With **14** and **15**, these same conditions gave complete destruction of the penam system. However, satisfactory results were obtained when TFA was used with methylene chloride as a solvent (see Experimental Section).

(14) J. C. Sheehan, Y. S. Lo, J. Loliger, and C. Podewell, *J. Org. Chem.*, **39**, 1444 (1974).
(15) German Patent 1 224 720; *Chem. Abstr.*, **65**, 12112h (1966).
(16) G. Zumach and E. Kühle, *Angew. Chem., Int. Ed. Engl.*, **9**, 54 (1970).
(17) J. S. Wiering and H. Wynberg, *J. Org. Chem.*, **41**, 1574 (1976).
(18) U.S. Patent 3 129 224; *Chem. Abstr.*, **61**, 5659e (1964).
(19) E. H. W. Bohme, H. E. Applegate, J. B. Ensing, P. T. Funke, M. S. Puar, and J. E. Dolfini, *J. Org. Chem.*, **38**, 230 (1973).

Computer-Assisted Synthetic Analysis. Performance of Long-Range Strategies for Stereoselective Olefin Synthesis

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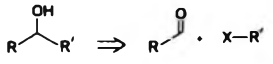
The Harvard program for computer-assisted synthetic analysis (LHASA) has been expanded to include a module which directs antithetic simplifications of olefinic target molecules. The new module employs a readily modifiable data base of C=C transforms (retroreactions) written in chemical English (CHMTRN). Transforms are selected via a unique set-matching process based on prescreen information extracted both from the target molecule and from the transform entries in the data table. Each transform has access to a considerable amount of subgoal power and is thus capable of generating quite long and sophisticated sequences. Several strategies, corresponding to effective plans for polyene synthesis, have been implemented. A number of sample antithetic analyses are included, and future extensions are discussed.

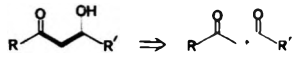
Synthetic methodology for the stereospecific and highly stereoselective construction of carbon–carbon double bonds has expanded dramatically in the last 15 years. Challenges presented by biogenetically interesting isoprenoid molecules, such as squalene[1] and farnesol,[2] and in particular by the insect juvenile hormones,[3] have stimulated development of a large number of versatile techniques for olefin synthesis.[4] To keep pace with these new methods, a special module for olefin synthesis has recently been added to the LHASA[5] computer program. The new package combines stereochemical sophistication[6] with a broad data base of chemical reactions, employing a variety of "strategies" to construct efficient and often elegant routes to polyolefinic molecules.

As previously described,[7] LHASA is an interactive program for synthetic analysis which employs straightforward graphical input and output. The program analyzes an input "target" molecule antithetically, generating a "tree" of potential synthetic precursors. Individual steps in the antithetic analysis correspond to "transforms" (retroreactions) which are chosen, or "keyed," by certain arrangements of functional groups and structural features in the target molecule.

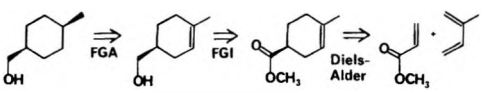
Early work on LHASA divided transforms into two categories, group oriented[8] and substructure oriented.[9] In the former category, an opportunistic, or breadth first, search through the data base selects transforms purely on the basis of arrangements of functionality. A Grignard transform, for instance, is keyed by the presence of a hydroxyl group:



and an Aldol condensation by (among other combinations) a carbonyl group and a hydroxyl separated by a "path" of two bonds:



In the latter category, certain powerful transforms generate antithetic pathways in a depth-first fashion. The existence of an appropriate substructure (for instance a ring of a certain size) is sufficient to key entry into the transform, and the existing functionality is modified as necessary for transform performance:



In this last example, the functionality in the target molecule was not correct for performance of the Diels–Alder disconnection. Accordingly, two nonsimplifying "subgoal" steps, a Functional Group Addition (FGA) of a C=C and a Functional Group Interchange (FGI) of the hydroxyl for the ester group, were performed by the program before the Diels–Alder transform. These steps, like the goal transform, were thoroughly evaluated by the program before display to ensure that they correspond to reasonable synthetic reactions. The subgoal powers of the LHASA program have recently been expanded to include sequential functional group interchange (SEQFGI),[10] double parallel functional group interchange (FGIFGI), and parallel functional group interchange–functional group addition (FGIFGA).

The new package for olefin syntheses combines features of both the group-oriented and substructure-oriented approaches, as described below. Considerable planning preceeded implementation of the module, with six important concepts guiding its development.

First, the data base for the package needed to reflect both the great diversity of new olefin syntheses and the stereochemical specificity of many of these new methods. The efficiency of a simple, functionality based search through all the transforms keyed by the presence of a C=C decreases dramatically with the addition of large numbers of new trans-

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forms. Accordingly, a fast and economical method for accessing the data base had to be devised.

Almost any recent olefin synthesis illustrates the degree to which functionality around a C=C can be modified after establishment of the C=C stereochemistry. A second requirement for an intelligent antithetic analysis, then, was the power to access several nonsimplifying, or subgoal, steps to transform the target structure to a precursor containing the functionality resulting from the C=C-forming reaction. In this sense each olefin transform would be like a substructure-oriented transform in the traditional group/substructure dichotomy. The C=C, like the six-membered ring in the Diels–Alder example above, would be a "key substructure" signaling entry into a depth-first search leading to the performance of the goal step, in this case the stereospecific C=C transform.

For syntheses of olefins containing more than one C=C, the number of precursor structures generated by a program capable of both broad and deep searches would often be unmanageable. Implementation of heuristically derived "strategies" would allow the program not only to choose individual transforms but actually to plan in advance the order in which to apply them. Strategies such as sequential application of the same transform, simultaneous disconnections at both ends of a chain, and disconnection of a central C=C (corresponding to a convergent synthesis) would limit the number of precursor structures and greatly enhance the sophistication of the resulting routes.

In an antithetic analysis using one of the strategies just mentioned, the "goal" of the analysis (e.g., two sequential applications of the Claisen rearrangement transform) is on a higher level than the goal of applying a single powerful transform. Accordingly, an extension of the normal subgoal structure would be necessary. Group-oriented transforms capable of disconnecting certain "strategic" bonds[11] might be used as subgoal steps, and in fact olefin transforms themselves could be used as subgoals to remove, antithetically, parts of a molecule blocking performance of the transforms required by the higher level strategy.

In order to decide which strategies would be most appropriate for a given target polyene, the program would have to make a C=C/transform match before any transforms were performed and displayed. Not only was a method for "prescreening" C=C's necessary, but the method had to be flexible enough to accommodate the addition of new transforms as well.

Finally, with a continuing commitment to the interactive nature of the LHASA program, the olefin module would allow the chemist to select for further processing precursor structures which appeared especially promising. This type of participation by the chemist would limit structure proliferation while obviating the need for overly restrictive tree-pruning heuristics in the program.

Implementation

Transform Selection.[12] The olefin package focusses on acyclic C=C's possessing *E* or *Z* character. Bonds whose synthesis would not require stereochemical sophistication are used only to key subgoal (FGI) transforms. Each acyclic *E* or *Z* C=C undergoes a special "perception" process prior to transform selection. First, a trisubstituted C=C is labeled as shown in Figure 1, with L, C, and T denoting respectively the "lone," "cis," and "trans" appendages on the olefinic atoms. For tetrasubstituted C=C's a fourth appendage label (X) is added, and for disubstituted bonds either the C or the T appendage disappears. Next, the labeled bond is scanned for structural features, both simple and complex, which are relevant to the transform selection process. Categories of molecular characteristics included correspond to those features which might potentially kill a C=C transform. Simple characteristics, like ring bonds and quaternary centers, are matched with the appendage atom and bond labels (see Figure 1) by FORTRAN code within the olefin package. More specialized features, such as the availability of various appendages from organocuprate reagents, are perceived by use of a binary search table.[9] A sample perception is shown in Figure 1. All of the perception information about a C=C is stored in a **perception set.** Sets are among the most frequently used data structures in LHASA. A set consists of a computer word (or words) in which each bit (valued 0 or 1) is assigned a unique meaning. In the perception set for the C=C in Figure 1, for example, bit 15 is on (= 1) signifying that there is a functional group on L3, bit 41 = 1 indicates a tertiary or quaternary center on C2, etc. One-hundred bits are sufficient to contain all the perception information necessary for prescreening of an arbitrary C=C.

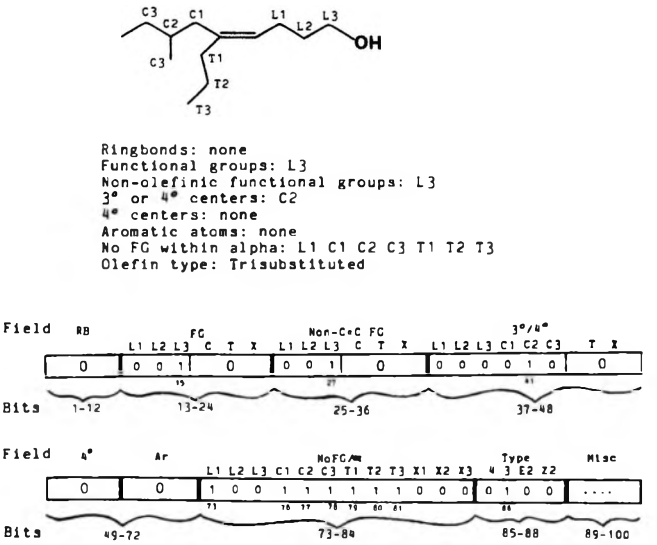


Figure 1. Sample perception set. Field abbreviations are as follows: RB = bonds which are ring bonds, FG = atoms bearing functional groups, Non-C=C FG = atoms bearing functional groups which are not C=C or C≡C, 3°/4° = atoms bonded to three or four other carbons, 4° = atoms bonded to four other carbons, Ar = atoms in aromatic rings, No FG/α = atoms not bearing a functional group whose adjacent atoms do not bear a functional group, Type = C=C substitution type (4 = tetrasubstituted, 3 = trisubstituted, E2 = E disubstituted, Z2 = Z disubstituted), Misc = miscellaneous characteristics (omitted for simplicity). Atom labels X1, X2, and X3 refer to the fourth appendage on a tetrasubstituted C=C.

In order to use the perception set characteristics to select transforms, the program must know which of these characteristics would prohibit application of a given transform. Therefore, each transform has associated with it a **screening set,** again 100 bits long, with bit positions assigned exactly as in the perception sets. An "on" bit (= 1) in the screening set for a transform corresponds to a molecular characteristic which should kill that transform. For easy modification by the chemist, the transform information necessary for creation of the screening sets is included at the top of a transform entry in the chemical English (CHMTRN)[13a] version of the data table under the comment heading ". . . Kill Specifiers for Prescreen," as shown in the sample transform entry in Figure 2. The CHMTRN assembler, TBLTRN,[13b] constructs the screening sets from the kill specifiers before LHASA is actually run.

After C=C perception is complete, a logical comparison (ANDing) operation is performed between the perception and screening sets, resulting in a set which is the intersection of the two input sets. Only when two corresponding bits are on in the input sets will a "1" appear in that position in the resultant set. Thus, if the resultant set in a comparison is nonzero, a feature was found which would block application of the

```
Transform 410
Name Claisen Rearrangement
...TL 3243(1969), JACS v.92 741,4461,4463(1970),v.95 553(1973)
Rating 30
...Kill Specifiers for Prescreen
Ringbond Trans2, Functional*group Trans1
No*FG*within*alpha Trans3
Olefin*type Tetrasubstituted Z*Disubstituted
Spacing*1*5 Well*defined*T*first Well*defined*L*last
...
If there is a functional group on alpha to atom*3  &
        offpath then go to Block4
If there is a functional group on beta to atom*3  &
        offpath then go to Block3
If there is a functional group on gamma to atom*3  &
        offpath then go to Block4
Block3 Designate the group as group one
    If hetero1*1 is nitrogen then go to Block6
    If the first group is carbonyl or: ester then go to Block2
    Go to Block4
Block6 If the first group is amide*3 then go to Block2
    Exchange the group for an amide*3 and*then go to Block5
Block4 Exchange the group for an ester on beta to atom*3 offpath
Block5 If unsuccessful then reject
Block2 Designate the group on beta to atom*3 offpath as group one
    If alpha to carbon1*1 is the same as alpha to atom*3
    Save as 1 the previous locant
    Kill if there is a hetero atom alpha to saved*atom 1
    Subtract 10 if atom*3 is a quaternary*center
    ....
            If there is a multiple bond in the first group  &
                then break it
            If first group is carbonyl then join saved*atom 1  &
                and carbon1*1
            If first group is carboxyl then attach an ether  &
                to carbon1*1
            Attach an ether to carbon1*1
            Separate saved*atom 1 and atom*3
            Double bond*3
            Single bond*5
            Attach a hydroxyl to atom*5
```

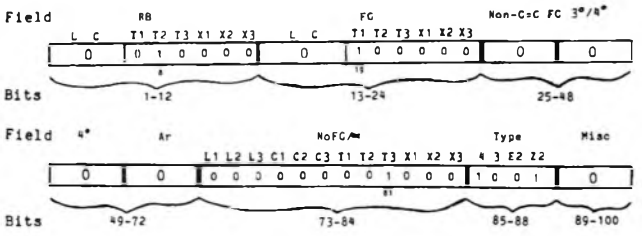
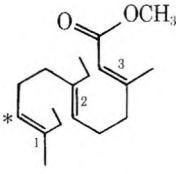


Figure 2. Sample transform entry with screening set for Claisen rearrangement transform. See Figure 1 for explanations of field abbreviations and appendage atom and bond labels.

transform concerned, while a zero resultant set indicates that the transform is appropriate for the C=C being perceived. The set that results from ANDing the perception set in Figure 1 with the screening set in Figure 2 is nonzero, since bit 81 is on in both sets. Thus, the program would not attempt the Claisen rearrangement transform for the target in Figure 1. In this fashion, a complete list of transforms applicable to each C=C is compiled *before* the actual transform entries are evaluated. This list not only serves as an extremely efficient means of transform selection but also provides direct input to the strategy selection process.

Strategy Selection. As mentioned above, the olefin package selects strategies by using heuristics which correspond to the most effective problem-solving techniques employed by a synthetic chemist. Strategy for olefinic target structures with only one C=C is simple. All the appropriate transforms (preceeded by subgoal steps, if necessary) are applied systematically and exhaustively (i.e., opportunistically). For polyenes, a hierarchy of three strategies is available. That which seems most powerful is attempted first, and if it fails, the next, etc. A given polyene strategy operates on a "chain" of C=C's. Strings of consecutive C=C's are identified and ordered according to length in a "chain perception" process which precedes strategy execution.

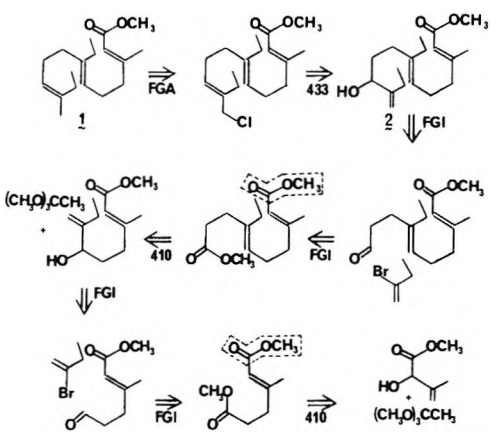
Sequential application of the same reaction is frequently an effective approach to polyene synthesis.[14] The antithetic analogue of this approach is the "sequential disconnection" strategy. This strategy is reserved for dienes and trienes, since a convergent approach is almost always more efficient for higher polyenes. Only certain transforms are given sequential disconnection power. Each such transform has a section in its CHMTRN data table entry giving information on the connectivity and spacing necessary for the sequential disconnection. For example, the specifiers "Spacing*1*5 Well*defined*T-*first Well*defined*L*last" in the Claisen rearrangement transform (see Figure 2) require that the two (or three) C=C's to be sequentially disconnected be in a 1,5 relationship, with the L appendage of one bond connected to the T appendage of the other, and that the bond with the "free" T appendage be disconnected first. (In contrast to the sequential Claisen rearrangement, which requires the well-defined 1,5-diene spacing, certain other transforms are labeled "undefined" with regard to spacing.) Analysis of Cecropia juvenile hormone triene ester **1** provides several antithetic sequential disconnection routes.



1

One of these routes involves disconnection by sequential application of the Claisen rearrangement transform. (While other lines of analysis are also generated by the program, they will not be discussed here in detail.) Perception of the chain containing C=C's 1, 2, and 3 indicates that bond 1 lacks a three-carbon T appendage but that bonds 2 and 3 form an appropriate "subchain" for disconnection by sequential application of the Claisen rearrangement transform. As indicated by the "Well*defined*T*first" specifier in the transform entry, the sequential Claisen rearrangement must *first* operate on the "free" T appendage of the 2,3 subchain. A problem is encountered, however, when the program attempts to exchange (via the CHMTRN command "Exchange the group for an ester on beta to atom*3 offpath") (see Figure 2) the C=C on atom T3 of bond 2 (the starred atom) for an ester, since the simple FGI chemistry does not include any stereospecific olefin syntheses. Bond 1 is thus recognized as a block to the higher-level goal of performing the sequential disconnection of bonds 2 and 3. To remove this block the program disconnects bond 1 opportunistically, using the appropriate olefin transforms, thereby paving the way for the sequential disconnection. Several structures are generated in the opportunistic disconnection of bond 1. At this juncture the program

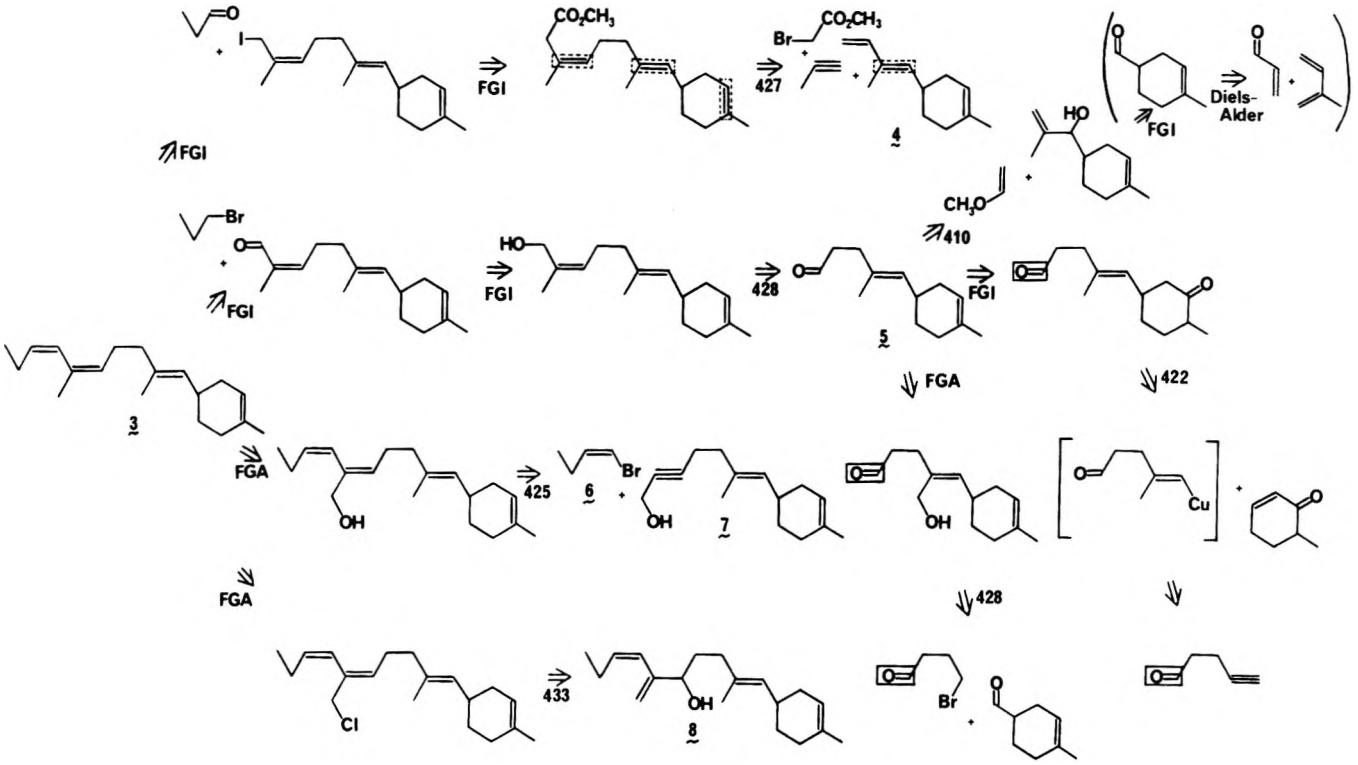
Scheme I.[17] Sequential Application of the Claisen Rearrangement Transform[a]



Sequential Disconnection of Juvenile Hormone Triene Ester

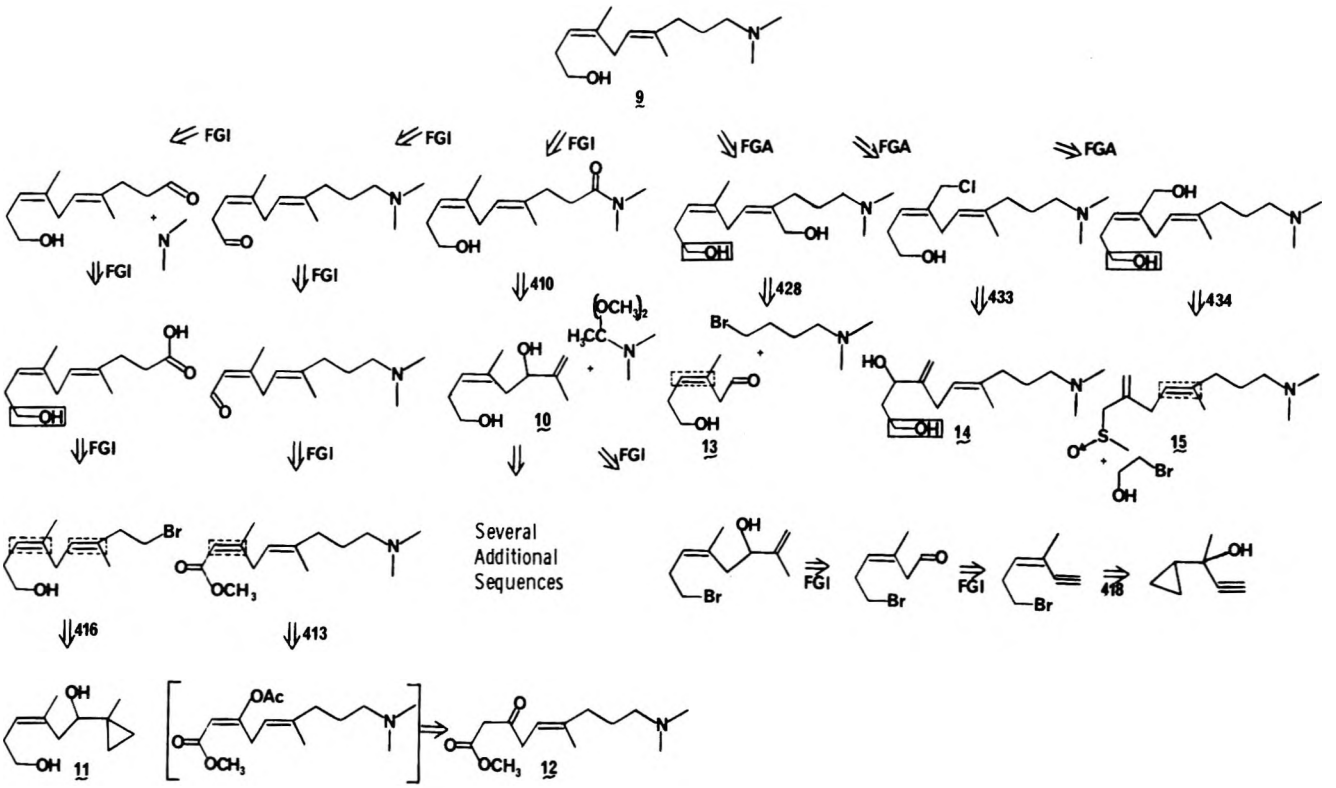
[a] Transform code numbers (see Table I) are as follows: 410 = Claisen rearrangement, 433 = allylic rearrangement with $SOCl_2$.

Scheme II.[17] Convergent Strategy[a]



[a] Transform code numbers (see Table I) are as follows: 410 = Claisen rearrangement, 422 = conjugate addition by vinyl copper reagent, 425 = R_2AlH reduction of propargylic alkoxide, 427 = alkylation of acetylenic borate, 428 = double Wittig with formaldehyde, 433 = allylic rearrangement with $SOCl_2$.

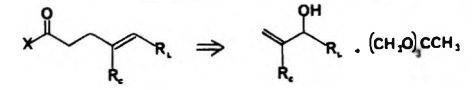
Scheme III.[17] Linear Strategy[a]



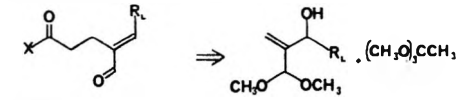
[a] Note that for the $RCH_2Br \rightarrow RCH_2CH_2NMe_2$ conversion leading to structure 11, LHASA finds six chemically reasonable sequences. To avoid node proliferation, only one of these is displayed. Transform code numbers (see Table I) are as follows: 410 = Claisen rearrangement, 413 = 1,4 addition–elimination, 416 = Julia synthesis, 418 = Julia synthesis on tertiary carbinol, 428 = double Wittig with formaldehyde, 433 = allylic rearrangement with $SOCl_2$, 434 = allylic sulfoxide rearrangement.

Table I. The Following Transforms Form the Data Base for the Olefin Package in LHASA

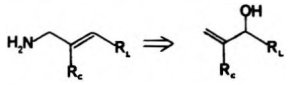
TRANSFORM 410
CLAISEN REARRANGEMENT
TL 3243(1969), JACS 92 741,4461,4463(1970); 95 553(1973)



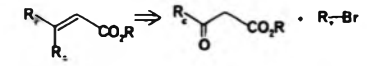
TRANSFORM 411
ACETAL CLAISEN REARRANGEMENT
TL 3469(75)



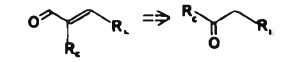
TRANSFORM 412
TRICHLOROACETIMIDATE REARRANGEMENT
JACS 96 597(74), 98 2901(76)



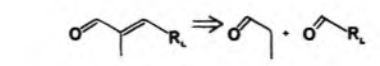
TRANSFORM 413
1,4 ADDITION-ELIMINATION
CHEM LETT 1097(1973), TL 925(1974)



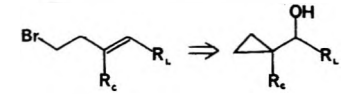
TRANSFORM 414
ALPHA-CHLORO ALDEHYDE ELIMINATION
TL 2465(73)



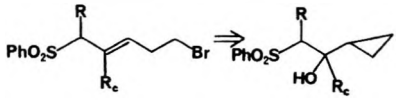
TRANSFORM 415
DIRECTED ALDOL CONDENSATION
NEUERE METHODEN DER PRAP. ORG CHEM, BAND VI, P.42 (70)
ACIE 7 7(68)



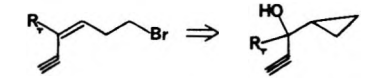
TRANSFORM 416
JULIA SYNTHESIS
JACS 90 2882(1968), TL 111(1973)



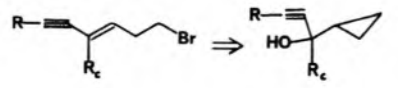
TRANSFORM 417
JULIA SYNTHESIS ON TERTIARY CARBINOL
TL 3445 (1974)



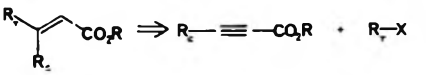
TRANSFORM 418
JULIA SYNTHESIS ON TERTIARY CARBINOL
TET. 28 3739(1972)



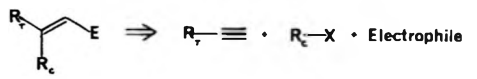
TRANSFORM 419
JULIA SYNTHESIS ON TERTIARY CARBINOL
TL 745(76)



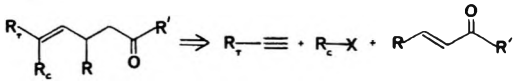
TRANSFORM 420
ORGANOCUPRATE ADDITION TO PROPARGYLIC ESTER
JACS 94 4395(1972), TL 1277,1281(1973); JOC 38 2733(1973)
JACS 97 1197(75), JOC 41 3629(76)



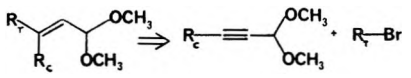
TRANSFORM 421
ELECTROPHILIC ATTACK BY VINYL COPPER COMPLEX
SYN 245(76), TET 32 1675(76), TL 2023(77)
J ORGMET CHEM 40 C49(72), 77 269,281(74)



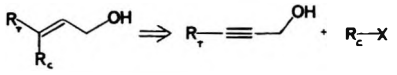
TRANSFORM 422
CONJUGATE ADDITION BY VINYL COPPER REAGENT
JACS 99 253 (77)



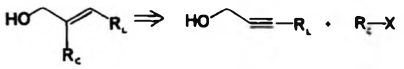
TRANSFORM 423
ORGANOCOPPER ADDITION TO PROPARGYLIC ACETAL
TL 2313 (76)



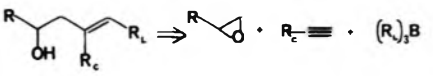
TRANSFORM 424
LAH REDUCTION OF PROPARGYLIC ALCOHOL
JACS 89 4245(1967), JOC 38 2733(1973), TL 1983(1973)



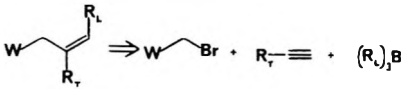
TRANSFORM 425
R2ALH REDUCTION OF PROPARGYLIC ALKOXIDE
JACS 92 6314(1970)



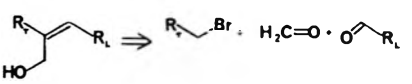
TRANSFORM 426
EPOXIDE OPENING BY ALKYNYL BORATE
TL 2741(1973), TET 30 3037(74), BUT CHEM LETT 397(75)



TRANSFORM 427
ALKYLATION OF ACETYLENIC BORATE
TL 795,4491(73); 3327(75)



TRANSFORM 428
DOUBLE WITTIG WITH FORMALDEHYDE
JACS 92 226,6635-7(1970); TL 3231(77)



TRANSFORM 429
DOUBLE WITTIG WITH TWO ALDEHYDES
JACS 92 226,6635-7(1970); TL 3231(77)

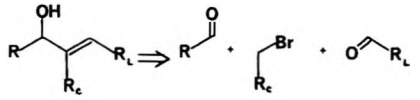
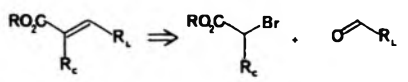
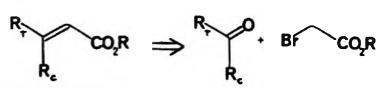


Table I (*continued*)

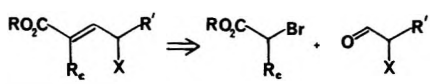
TRANSFORM 430
EMMONS-WADSWORTH-HORNER WITH ALDEHYDE
BCSJ 40 2968(1967), JACS 83 1733(1961), CHEM REV 87(74)



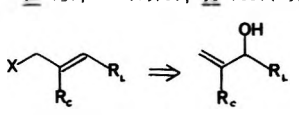
TRANSFORM 431
EMMONS-WADSWORTH-HORNER WITH KETONE
JACS 90 3769(1968), CHEM REV 87(74)



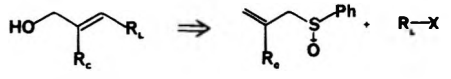
TRANSFORM 432
WITTIG REACTION TO GAMMA-HALO TIGLATE
TL 1679(75), 167(77)



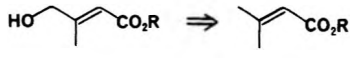
TRANSFORM 433
ALLYLIC REARRANGEMENT WITH SOCL2
BSCF 3568(1969), PNAS 68 1294(1971),
JACS 92 737,4461(1970), 95 7067(1973)



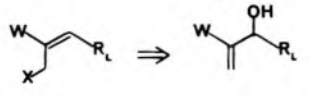
TRANSFORM 434
ALLYLIC SULFOXIDE REARRANGEMENT
CHEM COMM 702 (72), TL 1389(73), ACR 7 147 (74)
JOC 38 2245,2572(73)



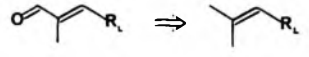
TRANSFORM 435
ALLYLIC SULFOXIDE REARRANGEMENT OF UNSAT. ESTER
TL 4215 (76)



TRANSFORM 436
ALLYLIC REARRANGEMENT OF VINYL-WITHDRAWING GROUP
TL 2751,2755 (74); JACS 98 3384 (76)

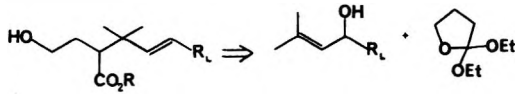


TRANSFORM 437
SELENIUM DIOXIDE OXIDATION
JACS 94 7154(72), 93 4835(71)

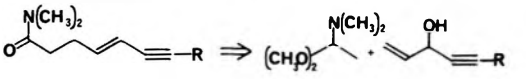


TRANSFORM 438
THIO-CLAISEN REARRANGEMENT
JACS 95 2693 (1973)

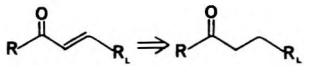
TRANSFORM 439
CYCLIC ORTHOESTER CLAISEN REARRANGEMENT
TL 847 (74)



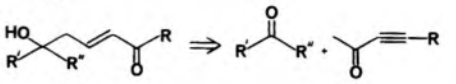
TRANSFORM 440
CLAISEN REARRANGEMENT OF ACETYLENIC ALCOHOL
TL 2607 (76)



TRANSFORM 441
ALPHA-KETO SULFOXIDE ELIMINATION
JACS 98 4887 (76)

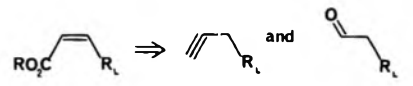


TRANSFORM 442
BETA-DIKETONE ENOL ETHER TRANSPOSITION
JACS 98 2351 (76)

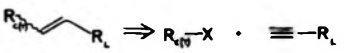


TRANSFORM 443
ALKYLATION OF DIMETHYLTHIO-ALLYLLITHIUM
JACS 93 1724 (1971)

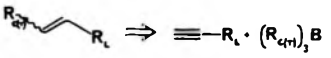
TRANSFORM 444
MODIFIED FAVORSKI REARRANGEMENT
PROC CHEM SOC 148 (64)



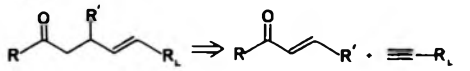
TRANSFORM 445
ACETYLENE REDUCTION
MARCH 361,593; HOUSE 19,91,124,172,205,252; B+P 106,162
ORGANOMET CHEM SYN 1 249(71),CHEM COMM 17,452(76)
TL 1815(72), 1927(75); JACS 96 316(74)
JOC 41 2214,2215,3484(76), 42 579(77)
SYN 625,816(76)



TRANSFORM 446
HYDROBORATION OF TERMINAL ACETYLENE
JACS 95 5786,6456 (1973)

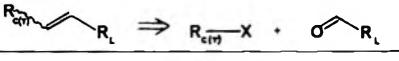


TRANSFORM 447
CONJUGATE ADDITION OF VINYL ALUMINUM COMPLEX
CJC 51 2098 (1973)

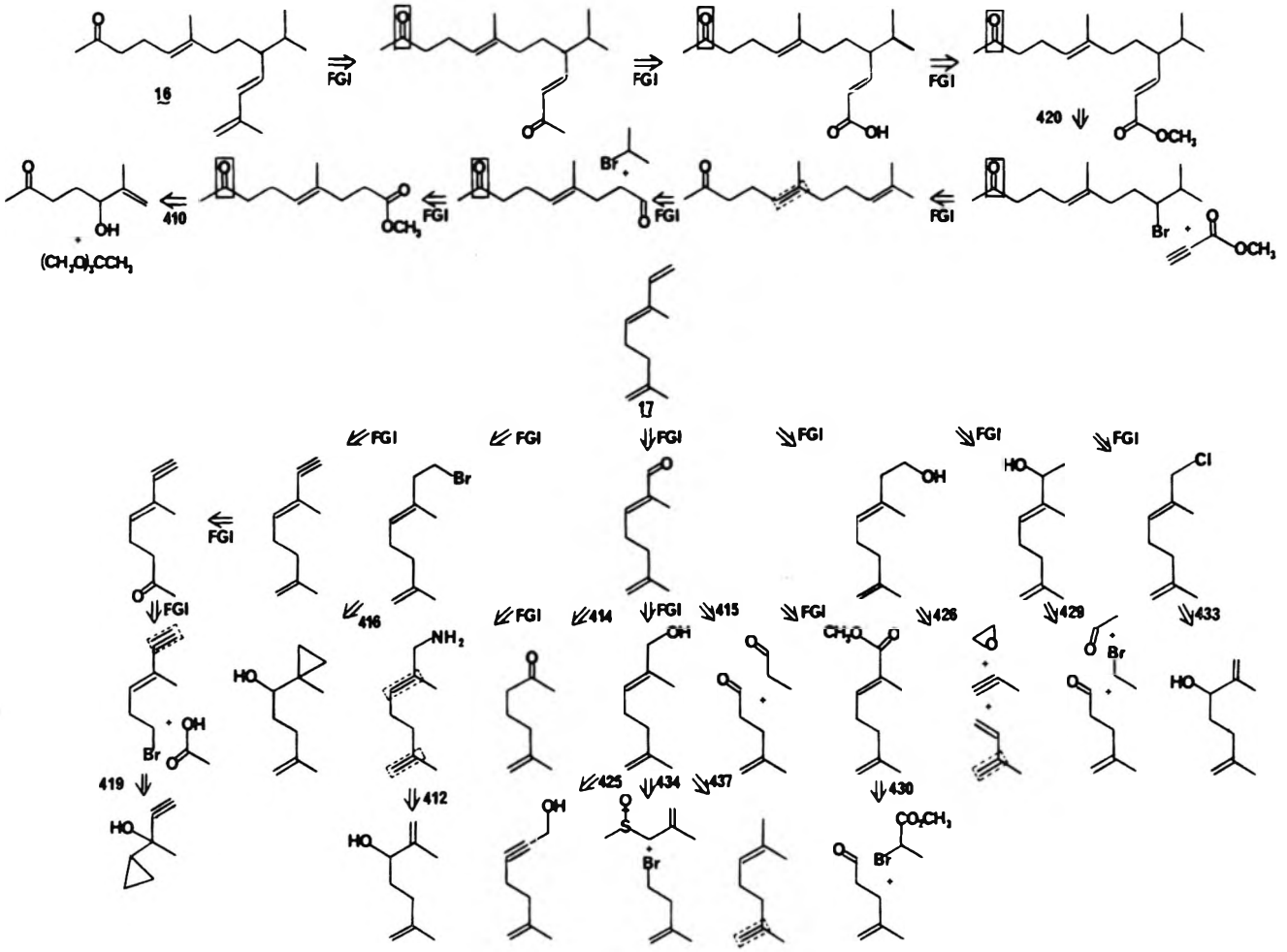


TRANSFORM 448
ALKYLATION OF VINYL CUPRATE
TL 2583 (71), 3461 (76)
J ORGMET CHEM 40 C49 (72), 77 269 (74)

TRANSFORM 449
WITTIG REACTION WITH REACTIVE YLIDE
MARCH 702; HOUSE 682-709; B+P 141
JACS 88 5653(66), 89 2758(67), 91 5675(69)
ACIE 4 689(65), 5 126(65); ANN 708 1(67)



Scheme IV.[17] Additional Examples[a]



[a] Transform code numbers (see Table I) are as follows: 410 = Claisen rearrangement, 412 = trichloroacetimidate rearrangement, 414 = α-chloro aldehyde elimination, 415 = directed aldol condensation, 416 = Julia synthesis, 419 = Julia synthesis on tertiary carbinol, 420 = organocuprate addition to propargylic ester, 425 = R_2AlH reduction of propargylic alkoxide, 426 = epoxide opening by alkynyl borate, 429 = double Wittig with two aldehydes, 430 = Emmons–Wadsworth–Horner with aldehyde, 433 = allylic rearrangement with $SOCl_2$, 434 = allylic sulfoxide rearrangement, 437 = selenium dioxide oxidation.

gives the chemist the opportunity to choose from among these structures (such as **2**) the one(s) he wishes to process further. Intervention by the chemist here allows him to guide the antithetic analysis in the directions which seem most reasonable and thus to limit the proliferation of precursor structures. When *2* is selected, processing continues *within the same strategy* and the antithetic analysis shown in Scheme I results.[15,16]

Convergent syntheses in which a central C=C in a polyene is formed at the end of the route have been used on several occasions.[18] If no sequential disconnections are found for a triene, or if the target has a chain longer than three bonds, the program attempts to disconnect the central C=C(s) (corresponding to a convergent synthesis). In this strategy, a C=C chain is scanned from the center outward in two passes. On the first pass, only disconnections of disubstituted bonds are considered, since the methods for synthesis of disubstituted C=C's are usually more straightforward than those required to make trisubstituted bonds. If no disubstituted C=C disconnections succeed, a second pass is performed in which only trisubstituted C=C transforms are considered. Bonds in the center of a chain are given higher priority than those nearer the ends in order to divide the molecule into fragments of as equal size as possible. Scheme II shows a representative analysis. Processing of **3** in the convergent strategy results in a request for opportunistic disconnection of the central C=C. Four transforms are found in the opportunistic search, and the program asks the user to "Select one or more nodes from among **4, 5, 6, 7,** and **8.**" The antithetic route to **5** seems most reasonable, suffering from no functional group interference problems, using no FGA's, and having the advantage that it disconnects bond 1 as a subgoal. When **5** is selected, three transforms are suggested. It should be emphasized that each fragment from the initial convergent disconnection has access to the entire range of strategies. If structure **5** had been a triene, it would have been considered by the sequential and convergent strategies itself. In this case, **5** had only one *E* or *Z* acyclic C=C, which was disconnected opportunistically.

The third level in the current strategy hierarchy corresponds to a synthesis in which a chain is built up from one end to the other. This "linear disconnection" strategy is used for dienes which cannot be disconnected by sequential application of the same transform and for trienes and higher polyenes for which neither sequential nor convergent disconnection succeeds. Scheme III shows a typical analysis. Again, opportunistic search through the olefin transforms has been used as a subgoal to the higher goal of achieving one or more linear disconnections. First, all transforms for distal bonds (those at either end of a chain) are performed, and the chemist is allowed to choose structures for further processing. When structure **10** is selected, the linear analysis is completed by disconnection of the remaining C=C. The linear strategy, more than either of the others in the hierarchy, leads to a proliferation of precursors. To avoid using simplistic and

overly restrictive heuristics in the program, the chemist is allowed to intervene in two ways. The first, already described, involves the choice of structures for further processing. The second operates as follows. Simple subgoals (FGI, SEQFGI, and FGA) are arranged in a hierarchy with the simplest (FGI) first and the one often requiring the most rigorous conditions (FGA) last. Four passes are made through the olefin transforms appropriate for a particular C=C, first with no subgoals, then with FGI capability, next with FGI and SEQFGI capability, and finally with FGI, SEQFGI, and FGA power. After each of the first three passes, if precursors have been generated in that pass, the chemist is asked if he wants to see deeper subgoals. If he responds "yes," processing continues with the next level of the hierarchy. If he says "no," he is then asked to choose from among the precursor structures which still contain *E* or *Z* acyclic C=C's, and processing continues. In Scheme III, for example, structure **10** results from the FGI level of the hierarchy, and the chemist has the option of seeing disconnections of the second C=C immediately. If more precursors to **9** are desired, the program will generate **11** and **12** at the SEQFGI level of the hierarchy and query the chemist again. If even deeper subgoals are desired, paths leading to **13**, **14**, and **15** will be grown. Similarly, in Scheme II, the chemist has the option of selecting structures for further processing before **6**, **7**, and **8** (whose routes involve FGA's) are generated.

The simple opportunistic disconnection strategy, normally accessed for monoenes or as a subgoal to one of the three higher-level strategies, has several interactive features of interest. It is possible for the chemist to select for antithetic analysis one or more specific C=C's in a polyene. The user may also choose a specific olefin transform, though this option is used primarily for debugging purposes. In addition, it is possible to override the normal subgoal hierarchy by depressing the "ALL SUBGOALS" button on the menu of processing options.[19] With this option selected, FGI, SEQFGI, and FGA capabilities are all accessed on the first pass through the appropriate transforms.

Additional Examples. The sophistication of any computer program for synthetic problem solving must be judged by the sequences it generates. The sample targets in Scheme IV have both been synthesized in the laboratory.[20] The olefin package in LHASA suggests a route (among others) to phenylsolanone (**16**) which is at least as inventive as the published synthesis. For ocimene (**17**), LHASA finds the published route and a large number of other reasonable pathways as well.

Future Extensions. Several extensions to the olefin package are envisioned for the near future. A strategy which can be highly effective for certain polyenes is one which applies simultaneous disconnections of identically substituted C=C's at opposite ends of a chain.[21] Performance of the goal transform in such a strategy would result in two identical disconnection products and a central fragment. Existing chain perception, transform selection, and identical appendage perception capabilities are sufficiently general to handle most of the problems associated with implementation of this strategy.

Another extension which will make efficient use of existing LHASA modules is the generation of stereoselective routes to epoxides, aziridines, episulfides, and cyclopropyl compounds. Target structures containing these functional group types will be preprocessed in "UNMASKING" mode,[13a,19] an option which accesses transforms capable of removing (antithetically) masked functionality, generating precursors containing only "core" functional groups. These unmasked precursors will then be processed by the olefin package.

Modification of the existing LHASA identical appendage perception modules to recognize near symmetry as well as perfect symmetry will allow convergent disconnections yielding similar, though nonidentical, fragments. In fact, disconnections in such a strategy need not break C=C's. The synthesis of squalene via sulfur-stabilized carbanion chemistry[22] is an excellent example. One possibility for implementation of such a strategy involves trial disconnections between central C=C's followed by identical appendage perception. Appendages would be classified as "potentially identical" on the basis of their carbon skeletons and subgoal chemistry could be requested to rectify differences in functionality.

An important goal in the antithetic simplification of bridged and fused polycyclic target structures is the disconnection of heuristically identified "strategic" bonds.[11] New heuristics could identify bonds blocking the performance of a higher-level strategy, and disconnection of this new type of strategic bond would then be a *subgoal* to that strategy. In addition, standardization of the entire transform-oriented data base (CHMTRN tables) and generalization of the methods for indexing and cross-referencing transforms will allow *all* transforms (not just FGI's and FGA's) to be used either as goals or as subgoals, enormously enhancing the subgoal power of the program.

An extension to the olefin package which is already being implemented involves control of C=C stereochemistry by (antithetic) reconnections to yield rings. Such reconnective chemistry exists in LHASA[23] but is not yet interfaced with the olefin package. The new, expanded reconnective package will interface efficiently with a ring executive capable of choosing among a variety of ring-synthesis strategies.

After several new strategies have been added, considerable effort will be devoted to the problem of selecting among these strategies intelligently. A large number of factors must be taken into account, among them chain length (number of C=C's), adjacent C=C separation (e.g., conjugated; 1,4; 1,5; etc.), C=C connectivity pattern (e.g., L appendage to adjacent T appendage), availability of transforms, and arrangement of nonolefinic functionality. Functional group interference must be accurately assessed along with the potential for both internal and external protection of interfering groups, and an optimal ordering of steps must be chosen.

It is gratifying to see, however, that despite the breadth of areas for future research, a recent review of pheromone synthesis[24] posed no problems which the current olefin package in LHASA did not handle efficiently.

Acknowledgments. We are grateful to the National Institutes of Health for financial assistance. The contributions of the other members of the LHASA group, especially Donald Barth, Harry Orf, and John Vinson, are greatly appreciated.

Appendix

For the transforms that form the data base for the olefin package in LHASA see Table I.

Supplementary Material Available: A complete listing of the CHMTRN version of the transforms (see Appendix) comprising the data table for the olefin package (30 pages). Ordering information is given on any current masthead page.

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Sulfene and the $^1CH_2/SO_2$ Potential Energy Surface[1a]

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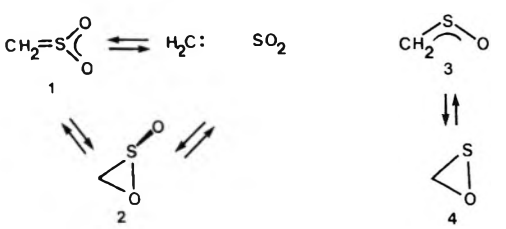
Sulfene, $CH_2{=}SO_2$ (**1**), is a highly reactive intermediate directly observable only at temperatures below −150 °C. Nonetheless it has been implicated in a variety of reactions in the gas phase and in solution. In particular its rearrangement to α-sultine **2**, the cheletropic fragmentation of **2** to $^1CH_2$ and SO_2, and its formation from the latter moieties have drawn attention. Exploration of the potential energy surfaces of these transformations has been undertaken by means of CNDO/B semiempirical calculations and compared with results for the corresponding hydrocarbon systems. Within the CNDO/B framework, the replacement of π-deficient $^1CH_2$ by π-rich SO_2 produces no fundamental mechanistic variations in the $CH_2{=}SO_2$ or α-sultine forming reactions relative to the $CH_2{=}CH_2$ or cyclopropane producing processes. Small but significant differences in the potential energy surfaces are, however, observed. These can be associated with the π-electron distributions of the reacting fragments. The electrocyclic ring closure of sulfene to α-sultine is predicted to follow an "allowed" pathway. It differs from the cyclization of the isoelectronic allyl anion (σ–π correlation) and sulfine (π–π_S correlation) in that a third type of orbital correlation is evident: π–n. High-lying nonbonding oxygen levels introduced by S oxidation are responsible. We suggest the existence of a four-membered ring cyclic sulfoxylate ester **8** on the sulfene potential surface and argue for its intervention in the chemistry of the previously postulated α-sultine. Other sulfene isomers are ruled out as unlikely transients. Finally the cheletropic addition of $^1CH_2$ to SO_2 to give sulfoxylate **8** is identified as an "electron pair excess" pericyclic reaction. The essential "forbiddeness" of this and related reactions is discussed.

Although sulfur trioxide is a stable and familiar laboratory reagent, the carbon analogue, sulfene (**1**), is a fleeting intermediate directly observable only at temperatures below ca. −150 °C.[2] The behavior of sulfene in solution is characterized by capture of electrophiles at carbon and nucleophiles at sulfur.[2,3] Oligomerization occurs in the absence of external addends.[4] When sulfene is generated in the gas phase at high temperatures, formaldehyde and SO are formed.[4b,5] It has been suggested that intramolecular cyclization to the α-sultine



2 precedes ultimate fragmentation.[5,6] More recently the preparation of transitory **2** at 25 °C has been claimed to result from the addition of methylene, $^1CH_2$, to SO_2[7] and from the peracid oxidation of thiocarbonyl *S*-oxides.[8]

In connection with our continuing fascination with sulfene,[9] sulfine **3**,[10] and oxathiirane **4**,[11] we have investigated the interconversion of the isoelectronic species **1**, **2**, and $^1CH_2/SO_2$ by the CNDO/B procedure.[12] [Throughout this paper, CH_2 is singlet ($^1CH_2$) unless indicated otherwise.] Besides possibly illuminating the above experimental findings, the triad is of interest for two additional reasons. Singlet methylene dimerizes to ethylene[13] and adds to C–C couble bonds to give cyclopropanes.[14] With regard to the first process, a study of the formation of sulfene **1** from CH_2 and SO_2 permits an inquiry into the consequences of the existence of π electrons in one of the combining fragments. A comparison of cyclopropane and α-sultine formation raises the additional question of symmetry and its absence in a pair of model cheletropic reactions. The electrocyclic ring opening of **2** to sulfene addresses the symmetry issue as well. Previous calculations on heteroelectrocylic reactions for oxathiirane **3**[11a] and related systems[15] suggest unexpected electronic features may be associated with the potential energy surface connecting end-point minima.

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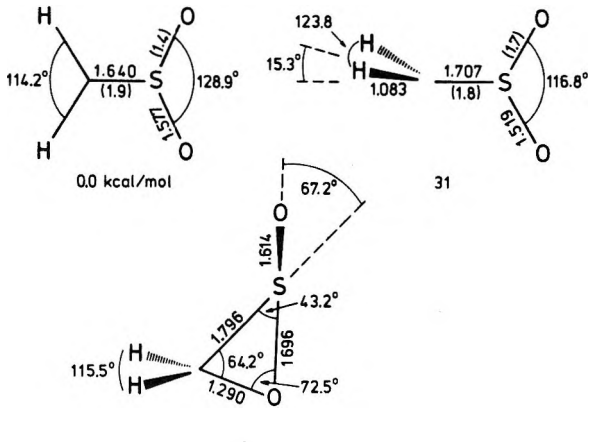


Figure 1. CNDO/B optimized geometries for planar sulfene **1**, twisted sulfene, and α-sultine **2**. Bond lengths are in Å; bond angles are in deg. Bond orders are given in parentheses. The relative calculated total energy is indicted beneath the structures (kcal/mol).

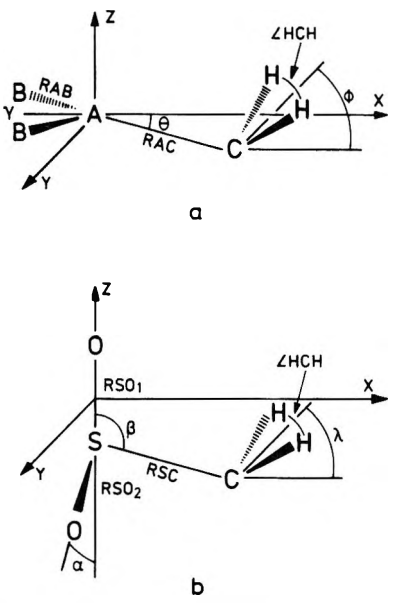
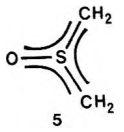


Figure 2. Reaction coordinate spaces for (a) the formation of sulfene from $^1CH_2$ and SO_2 and the dimerization of $^1CH_2$ to give ethylene; reaction coordinate is the A–C distance; optimized variables, γ, θ, ϕ, $\angle$HCH, and RAB (for RSO), and (b) α-sultine generation from $^1CH_2$ and SO_2; reaction coordinate is the S–C distance; optimized variables, α, β, λ, $\angle$HCH, and RSO_2.

Ground-State Structures

The ground state geometries of sulfene **1** and α-sultine **2** were optimized completely as a function of the total energy with CNDO/B. Sulfur d orbitals are not incorporated in the method. The resulting structures are given in Figure 1. Sulfene is predicted to be planar in agreement with the shape of its isoelectronolog, sulfur trioxide.[16] Distortion of either the CH_2 or the SO_2 moiety out of plane causes a rise in the calculated total energy. The carbon-rich isoelectronic species **5** is likewise predicted to be planar by the extended Hückel method.[17]



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Two additional features deserve comment. The S–O bond length (1.577 Å calcd) is clearly overestimated when compared with either SO_2 (1.431 Å)[18] or SO_3 (1.43 Å).[16] A similar long S–O distance was predicted for sulfine, $CH_2{=}SO$.[10,19] CNDO/B is consistently deficient in this regard. For molecules involving π-delocalized S–O bonds, the bond lengthening can be remedied by the explicit inclusion of sulfur 3d orbitals or by employment of a sufficiently large basis set.[20] Secondly the OSO bond angle is predicted to be considerably expanded relative to the calculated value for SO_2 (115°[12]). Qualitatively this may be attributed to negative charge localization on oxygen. The accompanying oxygen–oxygen electron repulsion is relieved by angle opening. Although CNDO/B gives reasonable dipole moments, comparison with CNDO/2 and STO-3G calculations suggests that charge buildup is somewhat exaggerated.[21] Consequently although the trend from SO_2 to sulfene seems reasonable, we suspect that $\angle OSO_{calcd}$ is overestimated.

Rotation about the C–S double bond in **1** is accompanied by inversion at carbon (cf. Figure 1). As $CH_2{=}SO_2$ travels to the energy maximum, the C–S bond order[22] drops from 1.9 to 1.8 and the S–O quantity simultaneously rises from 1.4 to 1.7. Coincident with bond loosening and tightening the moderate negative charge at carbon (−0.21) and the large positive charge at sulfur (+1.2) in **1** rise to −0.64 and +1.7 respectively, while the values at H and O are essentially unchanged (+0.12 → +0.13 and −0.62 → −0.63, respectively). The polar nature of planar sulfene is thus enhanced in the rotational transition state, a species probably best described as the σ-bonded union of carbanion and $R\text{–}SO_2^+$ fragments. The OSO angle and the S–O bond length reductions are in accord with electron transfer from oxygen to sulfur.

The overall structure of α-sultine **2** is reasonable[23] with the exception of the extended S–O bond length. The remarks directed at sulfene likewise apply here. For consistency in the calculations described below, the CNDO/B optimized geometries[12] of SO_2 and singlet CH_2 were employed at the reaction end points.

Potential-Energy Surfaces

For the transformations considered in the present study, the reaction coordinate method has been adopted. That is, a specific bond distance or bond angle was fixed at various values on the potential surface between the ground state structures under investigation. For fragmentations the calculations were performed out to a separation of 3–4 Å. At each of the intermediate points the remainder of the geometric parameters were varied until the CNDO/B total energy reached a minimum.

The S–C distance was chosen as the reaction coordinate for the combination of SO_2 and singlet CH_2 to give sulfene. A plane of symmetry bisecting the two fragments and a constant C–H bond length (1.098 Å) were assumed throughout. The five remaining variables are defined by Figure 2a (A = S, B = O). For the sake of comparison to the hydrocarbon analogue, the calculations were repeated for the dimerization of CH_2 (A = C, B = H). Four angles were optimized (θ, ϕ, γ, $\angle$HCH); the C–H bond distance was fixed at 1.098 Å.

α-Sultine formation from SO_2 and CH_2 utilized the S–C distance as the reaction coordinate and involved optimization of six variables. The separate S–O bond length and the four angles (α, β, λ, $\angle$HCH) are depicted in Figure 2b. The lowest energy approach of CH_2 on the S–O bond resulted from maintainance of carbon in the xz plane orthogonal to the yz plane containing the SO_2 unit. The xz plane furthermore contains the S–O bond under attack and bisects the HCH angle. Displacement of CH_2 from this plane proved to be an energy raising motion.

The least well-behaved potential surface was found to be the ring closure of sulfene **1** to α-sultine **2**. Initially the CSO angle was employed as reaction coordinate, with all other

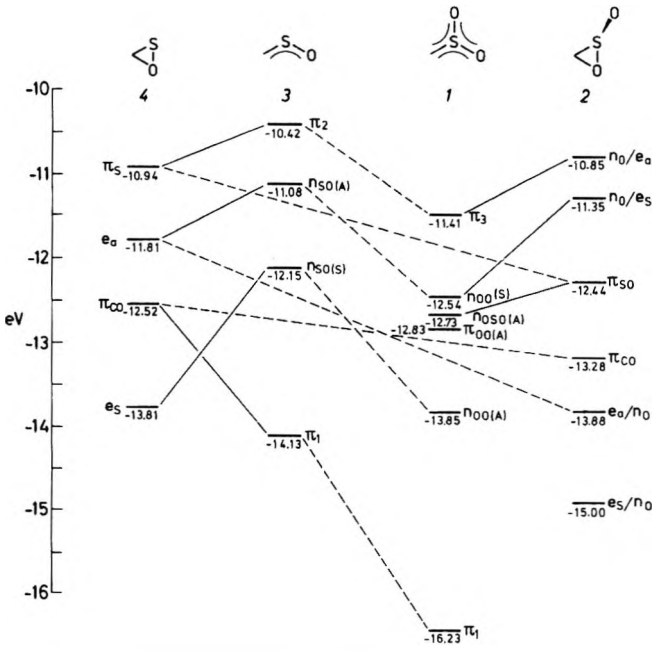


Figure 3. Oxidation of sulfine **3** and oxathiirane **4** and its consequences for the high-lying molecular orbitals (CNDO/B). Dashed lines connect **3** and **4** and the corresponding oxidized species **1** and **2**, respectively. The unbroken lines correlate acyclic and cyclic isomers (**3** → **4** and **1** → **2**).

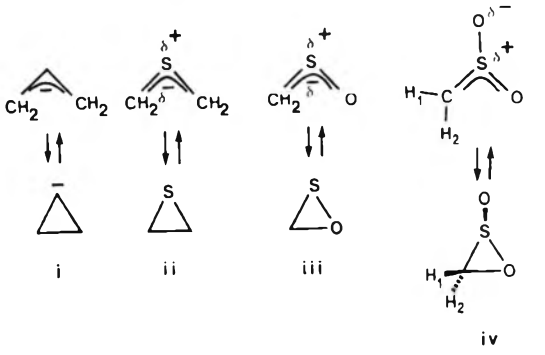
parameters being varied independently. Unfortunately discontinuities were encountered which are probably associated at least in part with the existence of the sulfene rotamer of Figure 1. Both this species and the ring closure maximum lie about 30 kcal/mol above sulfene **1**. Consequently in order to obtain a qualitative map of the cyclization, we finally incremented all bond angles between **1** and **2** and varied only the bond lengths C–S, C–O, and S–O.

The reaction coordinate approach has served in the theoretical study of reaction mechanisms at all levels of sophistication from extended Hückel to large basis set calculations which include CI. Nonetheless the recent work of Halgren and Lipscomb suggests that there are fundamental deficiencies in the selection of an arbitrary bond length or bond angle as guidepost along the potential surface.[24] Not only is there little assurance that the minimum energy pathway has been accurately plotted, but no guarantee can be provided for having traversed the lowest energy maximum, the transtion state. With these reservations in mind we compare our results to others derived by calculations using the same philosophy to construct the reaction pathway. Insofar as the "allowedness" or "forbiddeness" of a reaction is concerned,[25] the step-by-step details of molecular motion are less critical. An independent check on the qualitative course of the reaction can be made by reference to the orbital symmetry conservation principle,[26] its equivalent,[27] or a frontier orbital analysis. Likewise there is a reasonable precedent for expecting that the lack of sulfur d orbitals in CNDO/B will not influence the overall character of the predicted mechanisms.[28]

Sulfene–α-Sultine Interconversion.

The cyclization of sulfene to α-sultine **2** is profitably viewed as a member of the reaction series i to iv in which the allyl anion is progressively perturbed by sulfur and oxygen.

Transformations i–iii have been examined previously[11a,15,29] and have been found to proceed by an allowed route, that is all bonding MO's remain bonding throughout the computed reaction path. Closures i and ii require, of course, a conrotatory motion at the carbon termini. We find that reaction iv is



likewise allowed as is evident by the absence of a frontier orbital crossing in the orbital correlation diagram. Although two diasteriomeric transition states are conceivable, we have examined only that indicated by iv in which H_1 and the exo oxygen move out of the sulfene plane in the same direction.

Since sulfene **1** can be regarded as the *S*-oxide of sulfine **3**, it is instructive to inquire whether the replacement of the sulfur lone pair in the latter by –O leads to any fundamental changes in the electronic nature of the reaction. The CNDO/B energy barrier for sulfine cyclization is 16 kcal/mol,[10] whereas that for the corresponding sulfene closure is computed to be considerably higher, 26 kcal/mol. While the absolute values cannot be taken seriously, the relative barrier heights are reflected by well-defined changes in MO energies for reactions iii and iv.

The dashed lines of Figure 3 depict the consequences of oxidizing either sulfine **3** or oxathiirane **4** for several high-lying occupied MO's.[30] For each of the correlatable levels there is a significant drop in energy. To a first approximation introduction of the electronegative oxygen serves to lower the energy of comparable orbitals by an amount proportional to the change in the coulomb integral at sulfur. The more positively charged sulfur, or alternately the S–O unit, binds the associated electrons to a greater degree than the unoxidized sulfine sulfur.

Oxide formation ($R_nX: \rightarrow R_nX^+-O^-$) alters the overall composition of the MO manifold near the frontier gap by introducing new π-type and lone-pair levels. Relative to sulfine, sulfene is thus enriched by the nearly degenerate and relatively low energy antisymmetric n_{OSO} and π_{OO} orbitals of Figure 3. By contrast the orbitals in α-sultine **2** with no directly comparable counterparts in oxathiirane **4** are the two highest lying levels corresponding to delocalized nonbonding oxygen lone electron pairs (n_{O/e_a} and n_{O/e_s}).[31] The appearance of the latter is a straightforward consequence of adding oxygen-bearing nonbonding electrons to cycle **4**. The origin of the new MO's in sulfene is apprehended by referring to the situation for the π set in Figure 4. On the left side of the diagram thioformaldehyde and a single oxygen atom are brought together to produce the two allyl-like MO's of sulfine. On the right we start with three localized electron distributions, two of which arise from the symmetry-adapted oxygen p–π pair. The symmetric $\pi_{OO}(S)$ level combines with π_{CS} of thioformaldehyde leading to π_1 and π_3 of sulfene. The new MO is thus $\pi_{OO}(A)$. It should be noted that in Figure 4 no explicit consideration is given to the inductive effect of the added oxygens. In a similar manner the in-plane oxygen lone pairs interact with the σ framework of $H_2C{=}S$ to yield the three sulfene MO's $n_{OO}(S)$, $n_{OO}(A)$, and $n_{OSO}(A)$ (cf. Figure 3). The latter is the extra orbital relative to sulfine.

The remaining point concerns the way in which the MO's transform as sulfene and α-sultine are converted into one another. For symmetric systems exemplified by reactions i and ii, the antisymmetric π-HOMO's of the open species are deformed in textbook fashion into the σ-MO associated with the newly created bond in the three-membered rings, a π–σ cor-

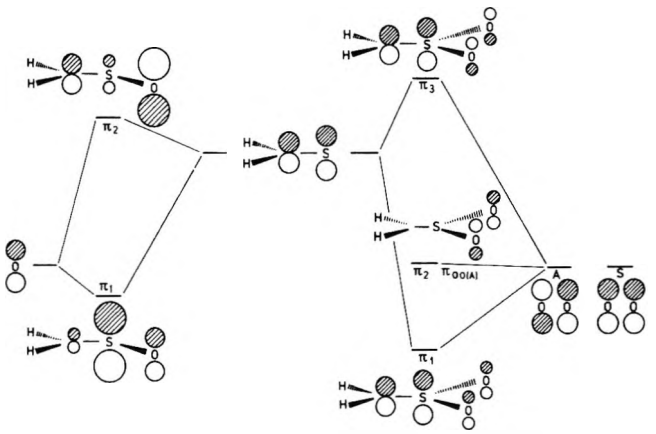


Figure 4. The PMO generation of π-MO's for sulfine 3 and sulfene 1 by the addition of one and two oxygen atoms respectively to thioformaldehyde.

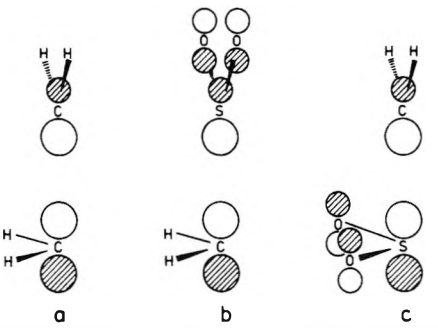


Figure 5. Possible initial reaction geometries for the combination of $^1CH_2$ and SO_2 to give ethylene (a) and sulfene 1 (b and c), respectively. The σ orbitals represent the HOMO for $^1CH_2$ and the highest energy, in-plane lone electron pair for SO_2. The p–π MO's correspond to the LUMO and HOMO for $^1CH_2$ and SO_2, respectively.

relation. For the unsymmetrical sulfine 3 we have previously suggested that the π-HOMO becomes the p–π sulfur lone pair in 4.[11a] Sulfene 1 within the CNDO/B framework exhibits yet another variation as indicated by the full lines on the right side of Figure 3. Thus the π-HOMO is reshaped as the high energy sulfoxide oxygen lone electron pair, a π–n correlation. Comparison of the sulfine/oxathiirane and sulfene/α-sultine HOMO and near-HOMO correlations (Figure 3) reveals that the former are energy releasing while the latter are energy consuming. It is tempting to speculate that the calculated barrier differential of 10 kcal/mol for cyclization of 1 and 3 owes its origin to this inverted behavior. In any case the relationship of reactions i–iv would appear to be superficial at the level of MO interchange, a conclusion supported by the theoretical behavior of other hetero systems isoelectronic with the allyl/cyclopropyl anion couple.[15]

Hoffmann and co-workers have studied the ring opening of ethylene episulfide (reaction ii) and that of the corresponding three-ring sulfoxide and sulfone by EH.[17] Whereas for ii there is a clear-cut preference for controtatory interconversion, monooxidation leads to the prediction that the disrotatory path becomes competitive. Dioxidation to the sulfone is accompanied by a crossover so that disrotation is indicated. No mention of the orbital correlation patterns as a function of oxygen content was made.

Sulfene from Singlet CH_2 and SO_2

The dimerization of singlet methylene involves the union of two high-energy fragments across a non-least-motion potential-energy surface.[13] The lone electron pair of one CH_2 is initially directed at the empty p orbital of the other; the planes subtended by each three-atom unit are nearly perpendicular (Figure 5a). The exothermic reaction ultimately produces planar ethylene.

The replacement of one CH_2 by SO_2 introduces a second fragment with both σ and π electrons. Furthermore the σ-sulfur electrons of SO_2 are delocalized considerably as a result of their mixing with the oxygen lone pairs. Although in principle SO_2 may attack the empty p-AO of CH_2 (Figure 5b) or CH_2 may impinge on the π system of SO_2 (Figure 5c), the latter can be discounted on the basis of the high degree of electron–electron repulsion to be encountered in such a transition state. The calculations described below reflect fully this expectation. The former σ-SO_2/p-CH_2 pathway is of interest relative to CH_2 dimerization since the presence of either the SO_2 π system or the diluted sulfur lone pair might make unanticipated stereoelectronic demands on the transition state.

Both the CH_2/CH_2 and CH_2/SO_2 combinations have been explored with CNDO/B as synopsized by the geometric variables of Figure 2a. At an RAC separation beyond 2.1 Å, the potential surfaces are rather flat. Full optimization is achieved only at great expense. Thus we restricted our comparison to the more important bond-forming portion of the reactions. Table I lists optimized parameters for both hyperplanes. Neither reaction exhibited an activation barrier.

Table I. The Dimerization of Singlet CH_2 and the Combination of CH_2 and SO_2 as Prescribed by Figure 2a (Å, deg)

	RAC	RSO	γ	$\angle$HCH	θ	ϕ
CH_2/CH_2	∞		104.4	104.4		
	2.30		104.6	104.6		
	2.00		108.6	105.1	0.6	83.7
	1.80		110.0	109.4	1.7	73.1
	1.60		121.2	121.2	0.0	0.0
	1.45		117.1	117.1	0.0	0.0
	1.376		114.9	114.9	0.0	0.0
CH_2/SO_2	∞	1.517	115.7	104.4		
	2.20	1.517	115.7	104.4		
	2.00	1.520	118.5	107.7	2.1	65.4
	1.90	1.530	121.1	113.3	2.6	54.3
	1.80	1.552	126.2	118.0	2.1	29.5
	1.72	1.567	128.6	116.9	0.0	0.0
	1.640	1.577	128.9	114.2	0.0	0.0

The overall non-least-motion paths for ethylene and sulfene production are quite similar as are the changes in the total charge distribution. In both cases the fragment serving as AB_2 sacrifices electrons to CH_2 until the point at which ϕ falls below 90°. Through the $\phi = 90 \rightarrow 0°$ phase the electron flow is reversed until the final balance is established. A similar two-stage charge adjustment was computed for the thermal cheletropic decomposition of diazirine.[32] The calculated electron transfer is in complete accord with a description of the reactions in PMO terms as shown in Figure 5a,b. As soon as the orthogonality of the virtual π-type orbitals on the attacking nucleophile and the σ lone pair of the electrophilic CH_2 is broken ($\phi < 90°$), the latter are capable of back donation and initiation of ultimate bond formation. It should be mentioned that the planar least-motion route to sulfene from CH_2 and SO_2 has also been examined. In agreement with quantitative and qualitative precedent, frontier orbital crossing appears as a signal of the energetic expense of this forbidden approach pathway.

The level correlation diagrams for our model processes are likewise similar (Figure 6). In particular the HOMO lone pair of methylene is smoothly transformed into the C–C and C–S π orbitals, respectively. This is depicted graphically for CH_2/SO_2 in Figure 7. At the start of the reaction the SO_2

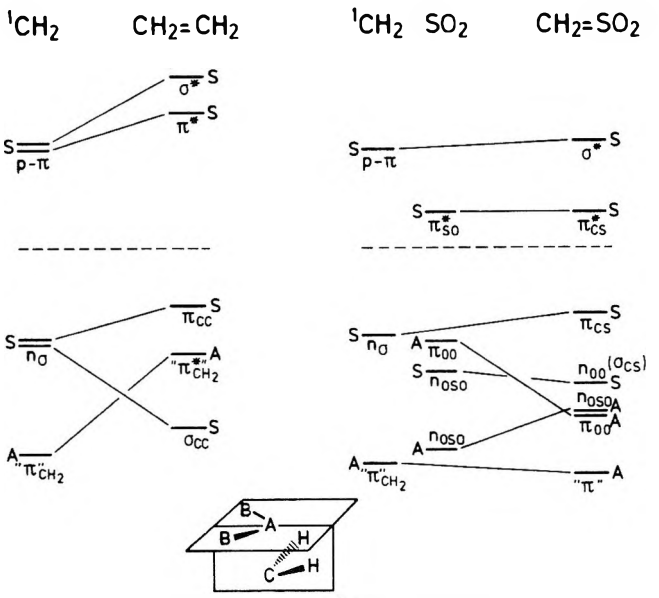


Figure 6. Level correlation diagrams (CNDO/B) for the non-least motion formation of ethylene and sulfene 1 from $^1CH_2/^1CH_2$, and $^1CH_2/SO_2$, respectively; cf. Figure 2a for the pathway definition and Figure 7 for deformation of the HOMO during sulfene formation.

moiety is devoid of electron density. Formation of the C–S bond is accompanied by rotation of the CH_2 group such that the original carbon sp^2 component is molded into a pure p contribution. Simultaneously the electron density at H vanishes while that at SO_2 grows in.[33]

In the CH_2/CH_2 reaction the second methylene electron pair (i.e., AB_2) is carried into the σ_{CC} orbital of $CH_2{=}CH_2$. The SO_2 lone pair (n_{OSO}) experiences an equivalent fate since it correlates with the sulfene level exhibiting mixed σ_{CS} and n_{OO} character. The other MO change of interest is connection of the nonbonding SO_2 π_{OO}-HOMO with its counterpart in sulfene (π_{OO}(A)). Thus both the hydrocarbon and heteroatom reactions are comparable in their essential details. No special electronic effects appear to arise from the substitution of SO_2 for CH_2 in the combination process supporting the suggestion that sulfene is experimentally accessible by this route.

Before leaving this section it is necessary to point out the existence of some fairly serious discrepancies between the CH_2 dimerization trajectory constructed here and that derived from an extended Hückel treatment.[13] First and foremost bond formation with CNDO/B occurs at very short C–C distances over a relatively compressed reaction coordinate (1.38–2.1 Å). The comparable EH values span the range 1.38–4.0 Å. Secondly the deviation of the unconstrained CH_2 from the x axis of Figure 2a is slight as reflected by ϕ_{max} = 1.7°. Again EH allows for a looser approach of the methylenes ($\phi_{max} > 35°$).[34] We attribute these differences to the inclusion of closed-shell repulsion effects via overlap in EH and its neglect in CNDO/B and other ZDO semiempirical schemes.[35,36] Thus the CH_2/CH_2 and CH_2/SO_2 transition states are calculated to be somewhat tighter than is undoubtedly the case in reality. This observation in conjunction with the above remarks concerning the reliability of the reaction coordinate technique forces us to place no quantitative significance on the geometric relationships of Table I. It is expected, nonetheless, that the computed hyperplanes mirror relative qualitative elements of the reactions under scrutiny.

A final point concerns the relative energy of the CH_2 on SO_2 vs. the SO_2 on CH_2 approaches indicated by Figure 5. For fixed geometry[38] fragments a calculation was performed for S–C distances ranging from 1.5 to 3.0 Å. At the lowest energy separation (ca. 1.75 Å) the SO_2 on CH_2 arrangement proved

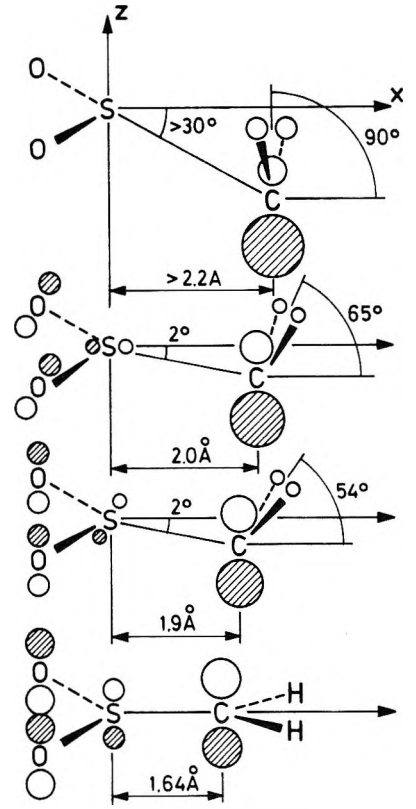


Figure 7. Transformation of the $^1CH_2$ HOMO lone pair to the sulfene π-HOMO as sulfene is formed from its fragments (CNDO/B); cf. Figure 6 for the full orbital correlation diagram.

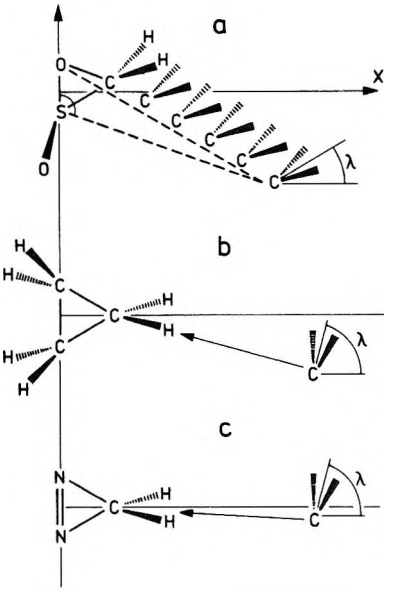


Figure 8. Pathway characteristics (CNDO/B) for the cheletropic addition of $^1CH_2$ to SO_2 (a), $CH_2{=}CH_2$ (b) and N_2 (c).

to be more stable by 13 kcal/mol in agreement with the energy-optimized pathway.

Addition of $^1CH_2$ to the OS=O Bond: α-Sultine

The coordinate space for α-sultine formation is depicted in Figure 2b. Optimization of the reaction pathway produced the instantaneous atomic positions indicated by Figure 8a. Variables β and λ are the essential quantities for determining the overall spatial disposition of the combining moieties.

Comparison of the results of the present study with the addition of $^1CH_2$ to $CH_2{=}CH_2$ (EH[14]) and N_2 (CNDO/B[32])

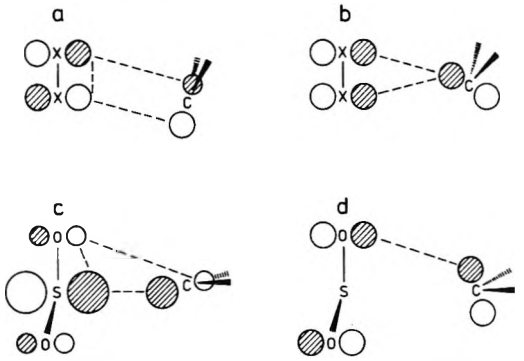


Figure 9. The frontier orbital description of the transition states for the allowed addition of $^1CH_2$ to a symmetric unsaturated functionality (X=X) and to the S=O bond of SO_2. Parts a and b depict $^1CH_2$(HOMO)/X=X(LUMO) and $^1CH_2$(LUMO)/X=X(HOMO), respectively. Parts c and d illustrate the $^1CH_2$(HOMO)/SO_2(LUMO) and $^1CH_2$(LUMO)/SO_2(HOMO) interactions, respectively. The orbital relationships are also useful for analyzing the transition states by the Hückel-Möbius method.

shows a significant although not fundamental difference. In the latter two cases λ varies from a maximum of 80–85° to a minimum of 0° (Figures 8b and 8c, respectively), whereas in the SO_2 addition it is found in the narrow range of 16–22°. In order to ensure that the computed differences are not the result of CNDO/B's tendency to produce early transition states, the $^1CH_2/CH_2$=CH_2–cyclopropane reaction was repeated with this parametrization and found to satisfactorily mimic the EH profile.[39] All three reactions can be analyzed quantitatively by considering the interaction of the frontier orbitals of the combining fragments. In Figure 9 (a and b) are shown the CH_2(HOMO)/X=X(LUMO) and CH_2(LUMO)/X=X(HOMO) interchanges, respectively. The non-least-motion paths are dictated by the requirement that the fragment orbitals of appropriate symmetry overlap as bonding sets in. Seen from the viewpoint of Dewar and Zimmerman,[27b,c] the X = N, CH_2 reactions involve four electrons in the transition state. The thermally "allowed" route demands an antiaromatic or a Möbius complex and necessitates a single orbital sign change (Figure 9a).

The parallel situation for union of SO_2 and CH_2 is depicted in Figure 9 (c and d). It should be noted that the replacement of the symmetrical X=X with SO_2 causes considerable change in the frontier density of the carbenophile. In particular in the LUMO of X=X the node is symmetrically disposed, while in SO_2 it lies much closer to oxygen. The result is that the sulfur contribution dominates the lowest virtual level of sulfur dioxide. Likewise the symmetry shown by the HOMO of X=X is lost completely by comparison with the S=O bond. The contribution of sulfur is exactly zero here. These differences mean that the lone electron pair of $^1CH_2$ will be directed strongly at sulfur along the approach trajectory in order to achieve maximum orbital overlap (Figure 9c). The diminutive λ reflecting the downward tilt of the CH_2 plane permits effective interaction with oxygen in both the HOMO and in the LUMO (Figure 9, c and d). A population analysis for the HOMO of the $^1CH_2/SO_2$ combination across the potential energy surface for α-sultine formation indicates that, although a considerable degree of asymmetry obtains, the basic pattern evidenced by the $^1CH_2/N_2$ addition[32] is maintained.

Finally, although the $^1CH_2/SO_2$ cheletropic union is allowed and electronically similar to cyclopropane formation, the α-sultine is not an obligatory intermediate. Alternatives are discussed below.

Other CH_2/SO_2 Transients and Transformations

Various reports on the intermediacy of α-sultine **2** offer two alternatives for its passage to products. The more popular

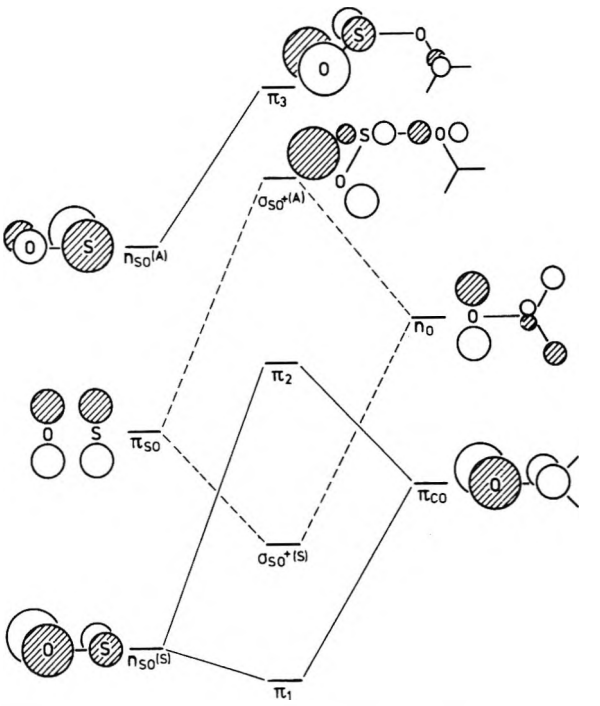
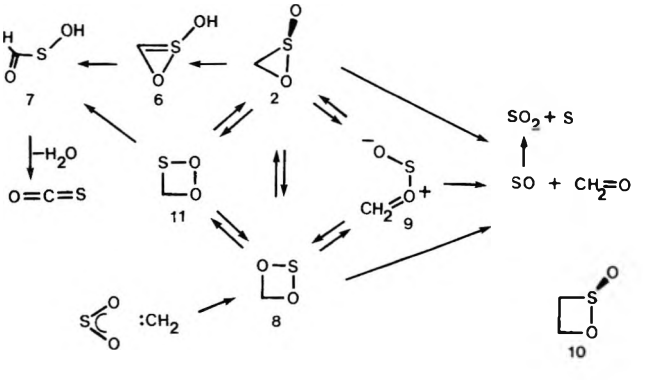


Figure 10. PMO interaction diagram for the formation of zwitterion **9** from ^1SO and CH_2=O.

speculation is ejection of SO to give the corresponding ketone or aldehyde.[4b,5] Singlet SO ultimately appears as SO_2, S_n, and polymer. A second decomposition route for **2** has been suggested to lead through species **6** and **7** and finally to carbonyl sulfide.[7]

Scheme I sketches three additional possibilities which have not been considered previously. The α-sultine might rearrange to the cyclic sulfoxylate ester **3** (1,3,2-dioxathietane) or undergo electrocyclic ring opening to the zwitterionic species **9**. Both transformations of **2** are favorable from the point of view of strain release. Of particular interest cyclic sulfoxylates are known as stable compounds in larger rings.[40] Furthermore, although the sulfinate ester → sulfoxylate ester interconversion is not known, the reverse process has been observed.[41] CNDO/B suggests the energy gain from **2** to **8** to be 37 kcal/mol. The acyclic dipolar species **9** in principle is accessible from both **2** and **8**; however, it is calculated to be thermochemically less stable than either of the cyclic isomers by 45 and 82 kcal/mol, respectively. Part of the energy difference undoubtedly resides in the well-known CNDO/INDO underestimate of strain in small rings, a quantity of 10–20 kcal/mol.[42] Significantly zwitterion **9** is likewise energy rich relative to ^1SO and CH_2=O (ΔE = 40 kcal/mol). An attempt to optimize the geometry of **9** resulted in a smooth stretching of the central S–O bond to give the latter fragments. No energy barrier was encountered. The computed lability of **9** can be

Scheme I



appreciated by reference to Figure 10 which pictures selected MO's in the PMO formalism.

The three highest lying occupied levels are all strongly antibonding. To a first approximation species **9** can be regarded as π isoelectronic with the butadiene dianion. For the latter the HOMO is the symmetrical π_3 with bonding between C_2 and C_3 but antibonding at the termini. In the unsymmetrical system **9**, the central node of the HOMO has moved in the direction of O^+ causing the bonding element to vanish. The next π level, π_2, likewise possesses a node between S and O^+. Finally the second highest lying level, the antisymmetric combination of the in-plane π(SO) and the oxygen lone electron pair of formaldehyde, is σ antibonding between the same atoms. The sum of the destablization associated with π_3, π_2, and σ_{SO^+} in **9** may be taken as the factor responsible for the barrierless dissociation to ^{1}SO and CH_2=O. Seen from the viewpoint of the latter species, the situation is much like the combination of a pair of He atoms. The first-order closed-shell repulsion between the filled orbitals dominates the fragment complex and is overall antibonding.

In view of this analysis we conclude that zwitterion **9** is most likely not involved in the further transformation of either **2** or **8**. Were **2** to begin to react by the electrocyclic pathway with initial cleavage of the CH_2–SO bond, the approach to the transition state would probably reflect the instability of **9** and thus lead to simultaneous O^+–SO rupture at the energy maximum. All in all an unsymmetrical cheletropic release of ^{1}SO seems to be the most suitable way of viewing the fragmentation of the α-sultine. There is ample precedent for this process.[43]

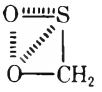
An equally attractive alternative and perhaps thermochemically preferred option is the rearrangement of **2** to **8** followed by a ($_\sigma 2_s + {}_\sigma 2_a$) cycloreversion to ^{1}SO and CH_2=O. Unsymmetrical heteropericyclic reactions often occur with reduced energy requirements relative to the symmetrical carbon analogue. And in certain cases where asymmetry creates a severe enough perturbation, the stereochemical distinction between various paths may be lost, all possible pathways being allowed and energetically competitive.[11a,15,44-46]

This appears to be the case for β-sultines **10** which fragment with a diminutive energy barrier[47] and with the capability for an in-plane ($_\sigma 2_2 + {}_\sigma 2_s$) dissociation.[28] Heteroelectrocyclic ring opening reactions likewise reflect both the energy reduction[48,49] and the stereochemical features[46,49] of perturbed processes. For this reason we have explored the unoptimized potential surfaces for both isomerization of α-sultine **2** to sulfoxylate **8** and fragmentation of the latter by an in-plane pathway. Conversion of **2** → **8** is calculated to cost 42 kcal/mol. The corresponding orbital correlation diagram shows that the filled MO's of starting material and product transform smoothly into one another indicative of an allowed, concerted process. The planar breakdown of sulfoxylate **8** to ^{1}SO and formaldehyde is accompanied by a frontier orbital crossing characteristic of a forbidden mechanism.[25] By implication the suprafacial–antarafacial route is preferred. Given the high content of heteroatoms in **8**, the concerted path may nonetheless occur easily relative to other possible pathways. In any case the high temperatures at which β-sultine **2** is postulated from certain precursors[4b,5] appear sufficient for promoting the **2** → **8** → ^{1}SO/CH_2=O sequence.

Both the latter and the cheletropic loss of ^{1}SO from α-sultine **2** appeal to us as energetically more feasible than enolization to the antiaromatic thiaoxirene **6** as suggested by Hiraoka.[7] The CNDO/B calculation places the thermochemical stability of this species at a value comparable with zwitterion **9**. The work which led to the postulation of intermediate **6** utilized photochemical and electron impact methods which might have generated a vibrationally or an electronically excited sultine. While it is difficult to comment on the fate of the latter, our calculations suggest that vibrational deexcitation to the energetic thiaoxirene system is not particularly competitive with other energy dispersal alternatives. The motivation for proposing **6** was the persistent appearance of carbonyl sulfide from the photolysis of sulfene precursors. Other mechanisms, however, can be written to accommodate this result.

For example, α-sultine **2** might rearrange to the 1,2,3-dioxathietane (**11**) followed by a hydrogen shift–ring opening step to give *S*-hydroxythioformic acid **7**. The ring expansion of **2** to **11**, unlike **2** → **8**, exhibits a frontier orbital crossing within the CNDO/B formalism. Significantly the latter passes through a three-center transition state with two lone pair bearing heteroatoms (**12**), whereas the energy maximum for the former contains three heteroatoms (**13**).

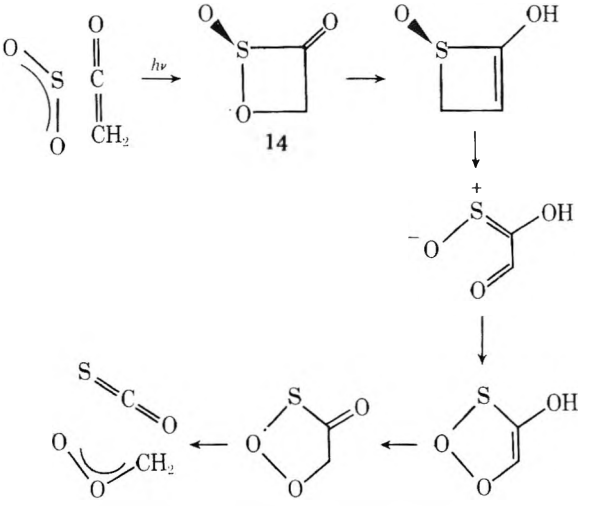
12



13

As we have pointed out previously,[15] pericycles with an excess of nonbonding electrons tend to express themselves via correlation diagrams reflecting nearly avoided crossings. A cheletropic example is considered in the next section. The presence of several heteroatoms may, however, facilitate a lowered energy barrier as mentioned above by effecting the necessary state mixing required for a "feasible" reaction.[50]

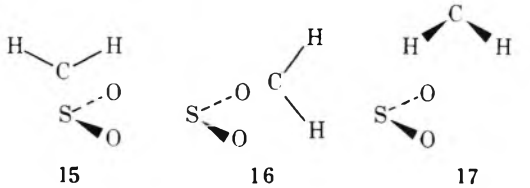
An additional alternative to the formation of small amounts of SCO obtained by irradiation of mixtures of ketene and SO_2[7] is the following. The initial reagents may cycloadd to give the 2,3-oxathietan-3-one-2 oxide **14** and transform as indicated



to ultimately produce carbonyl sulfide and the Criegee intermediate. Each of the steps finds a close analogy in related reactions.

The Cheletropic Addition of $^1CH_2$ to SO_2

The formation of sulfoxylate **8** by the cheletropic addition of $^1CH_2$ to SO_2 is shown in Scheme I. Since this appeared to be an attractive mechanistic route to COS via **8**, **11**, and **7**, and because to our knowledge simple carbenes are not known to participate in cheletropic ring formations to give four-mem-

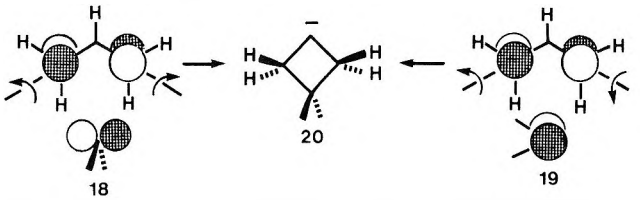


15 **16** **17**

bered cycles,[51] several reaction trajectories for the $^1CH_2/SO_2 \rightarrow$ 8 combination were examined with CNDO/B. These are indicated by structures **15–17.** Each of the explicitly computed reactions proved to exhibit a frontier orbital crossing.

The situation is illuminated by first referring to the isoelectronic carbon system, the allyl anion, $^1CH_2$, and the cyclobutyl anion **20.**

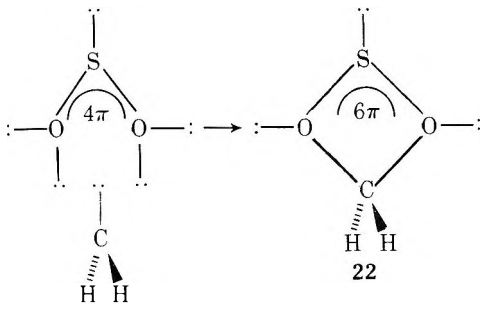
Thermal combination of $^1CH_2$ and $(CH_2CHCH_2)^-$ by a least-motion path (**18**) obeys the orbital symmetry conservation principle provided the allyl anion undergoes a disrotatory deformation. Structure **18** indicates the appropriate combination of anion–HOMO and $^1CH_2$–LUMO. Similarly the non-least-motion trajectory (**19**) is acceptable, if the allyl



18 20 19

anion reacts by a conrotation. Thus, as pointed out by Woodward and Hoffmann,[26] the two approaches of $^1CH_2$ are complementary and coupled to stereochemically distinct changes at the $C_3H_5^-$ termini. Equally important, the ability of the allyl anion to rotate during reaction breaks the σ–π separation and allows the π-HOMO to be transformed into σ_{CC} in the cyclobutyl anion, a σ–π correlation.

A consideration of the $SO_2/^1CH_2$ case clearly shows that although the system is isoelectronic with the carbon structures, the possibility for achieving a thermally allowed reaction path does not exist. Lewis type structures for the hetero process are shown by **21** and **22.**



21 22

The fragment π orbitals (**21**) contain four electrons, the σ, six nonbonding pairs. In the planar product sulfoxylate **22,** the π system has six electrons, whereas the corresponding σ count is three nonbonding pairs and two C–O σ bonds. The comparison is unchanged by allowing the four-membered ring to assume a puckered conformation. Formally starting material and product differ by the double excitation of a nonbonding electron pair from **21** to **22.** That is, they correspond to different electronic configurations. Although a similar description applies to the carbon species **18–20,** a mechanism is available whereby the costly excitation is bypassed, namely rotation about the CH–CH_2 bonds during ring closure. The terminal hydrogen nuclei move through space and simultaneously carry the electrons in the C–H bonds from the σ to the π framework. The net result is a configurational type interchange.

The SO_2 moiety lacks such a mechanism. By virtue of the σ–π separation inherent in the MO formalism, the in-plane lone pairs are unable to "rotate" into the system of **22** during the cheletropic addition. Consequently, since neither the linear (**15, 16**) nor the nonlinear (**17**) trajectories are coupled to an orbital transposition on SO_2, all reaction paths are forbidden[25] and require state mixing for a successful traverse of the path from $^1CH_2/SO_2$ to **22.** This is an example of a general class of reactions with an "excess" of nonbonding electrons. The point at which allowed routes are prohibited arises when the number of lone pairs replacing hydrogens prevents the ground state configurational mixing described above for the allyl anion. Another case would be the cycloaddition of formaldehyde and singlet O_2.[52]

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Registry No.—**1,** 917-73-7; **2,** 65621-95-6; **3,** 40100-16-1; **4,** 53283-22-0; $^1CH_2$, 2465-56-7; SO_2, 7446-09-5.

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(34) In our coordinate system the CH_2 (or SO_2) nucleophile is positioned at the origin, whereas in the previous work[13] the electrophilic partner was so fixed.
(35) It has been shown that the neglect of overlap required by the ZDO theoretical framework can favor biradicaloid over synchronous transition states[36] and result in serious underestimation of nonbonded lone pair–lone pair repulsions.[37] For example, CNDO/2 and INDO produce weakly repulsive or attractive potential energy curves for the direct interaction of lone electron pairs. Application of the "water test"[37] (orthogonal approach) to CNDO/B results in a properly repulsive potential at all oxygen separations; nonetheless at 1.5 Å the destablization energy is 5 eV compared with 11 eV for EH. The corresponding 4-31G value is 8.8 eV.
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Diazenium Cations. 3. Formation and Oxidation of a *cis*-Trialkylhydrazine: *cis*-Azomethinimines[1]

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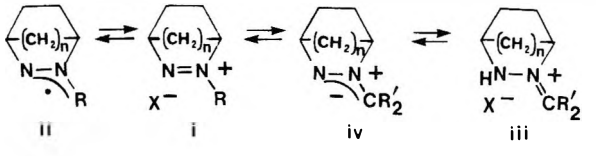
Isopropyl-substituted bicyclic diazenium cations i are readily isomerized via ylides iv to the corresponding *exo*-methylene iminium salts iii. Thus, in the presence of nucleophiles both are potential precursors to the little studied *cis*-trialkylhydrazine system. Treatment of either i or iii with CN^- under an inert atmosphere causes attack at carbon and leads to the corresponding oxygen-labile hydrazine. Facile air oxidation presumably generates a trialkylhydrazyl radical which ultimately results in production of azoalkane **6** and the tetrasubstituted cyanohydrazine **7**. Evidence is presented to show that **6** arises via an intermediate azomethinimine (**10c**) followed by protonation and subsequent dealkylation. The bicyclic hydrazine **7** is formed from a second intermediate, diazenium cation **11**, which experiences CN^- attack at nitrogen. The presence of an ylide intermediate is substantiated by demonstrating that azomethinimines iv are easily generated from a new series of both salts i and iii. Although in most instances the 1,3 dipoles were only trapped, isolation succeeded for a diphenyl derivative.

The recent isolation of bicyclic diazenium cations i has permitted exploratory studies of the chemistry of this many faceted function. Derivatives with R = H and alkyl show charge-transfer behavior[1-3] and facile electrochemical reduction to hydrazyl radicals ii.[4] When the substituent is 2,5-dinitrophenyl, chemical electron transfer leads to a complex equilibrium of open- and closed-shell species.[2] Simple protiodiazenium cations (i, R = H) are alkylated by alcohols of all kinds and serve as particularly efficient precursors to the *tert*-butyl cations.[1,2] Substituents bearing a proton α to $=N^+<$ (e.g., R = *i*-Pr) undergo rearrangement to the *exo*-iminium salt iii.[1] The reaction can be utilized for synthesis of the latter.



In the present discussion further examples of tautomeric pairs i and iii are reported. Their utility in the generation of azomethinimines iv is described. Furthermore, the preparation of a labile *cis*-trialkylhydrazine and its facile air oxidation have been investigated.

Trialkylhydrazine Formation and Oxidation. In principle, the iminium salts iii should be capable of accepting a nucleophile at carbon to produce the corresponding *cis*-tri-

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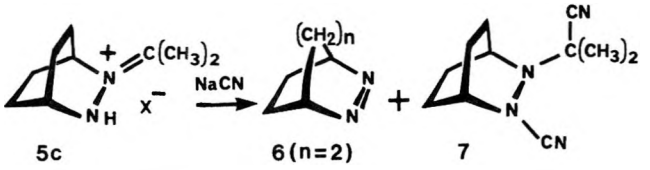
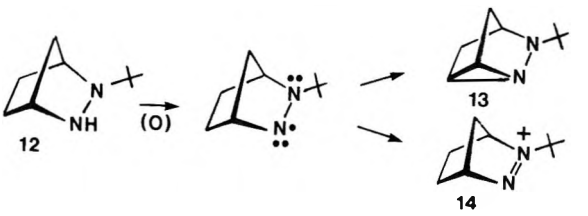


alkylhydrazines, a class of compounds with only a few representatives.[5,7] Our initial attempts to exploit this reaction employed the weakly basic cyanide ion and derivative **5c** (X = Br). Surprisingly, the combination of the latter and sodium cyanide in chloroform led to diazabicyclooctane (DBO) **6** and dicyanohydrazine **7** in 23 and 38% yields, respectively. The origin of these products is outlined in Scheme I. Evidence for it is developed below.

The key intermediate separating **5c** and **6** and **7** can be intercepted by running the above reaction under an inert atmosphere followed by careful workup in the absence of air. The oxygen-labile trisubstituted hydrazine **8** is thus obtained from both iminium salt **5c** and the diazenium species **9c** as an oil in 92% yield. Proof of structure rests on spectroscopic data, elemental analysis, and further transformation. The substance exhibits CN stretching in the infrared spectrum at 2220 cm^{-1} and a molecular ion at *m/e* 179 in the mass spectrometer. Its NMR spectrum displays characteristic NH absorption at τ 6.45, bridgehead protons at τ 7.03, and the hydrocarbon backbone and methyl groups between τ 7.7 and 8.6. Treatment of the oil with 1 equiv of phenyl isothiocyanate delivered the *N*-phenylthiosemicarbazide, indicating cyclization with elimination of HCN. Upon standing in air or under the influence of a stream of oxygen, hydrazine **8** is rapidly converted to azobicycle **6**, cyanohydrazine **7**, and acetone. The latter has been demonstrated both by NMR spectroscopy and GLC. The most plausible connectors between hydrazine **8** and the products are ylide **10** and the diazenium cation **11**.[8]

Bicyclo[2.2.1] trialkylhydrazine **12** has recently been shown to be air-oxidized to *N-tert*-butyl-2,3-nortricyclene (**13**) and



quinone-oxidized to diazenium salt **14** presumably by way of a hydrazyl radical.[7] A similar transformation for the bridge-expanded hydrazine **8** can be invoked to rationalize the intermediacy of salt **11** (see Scheme II).

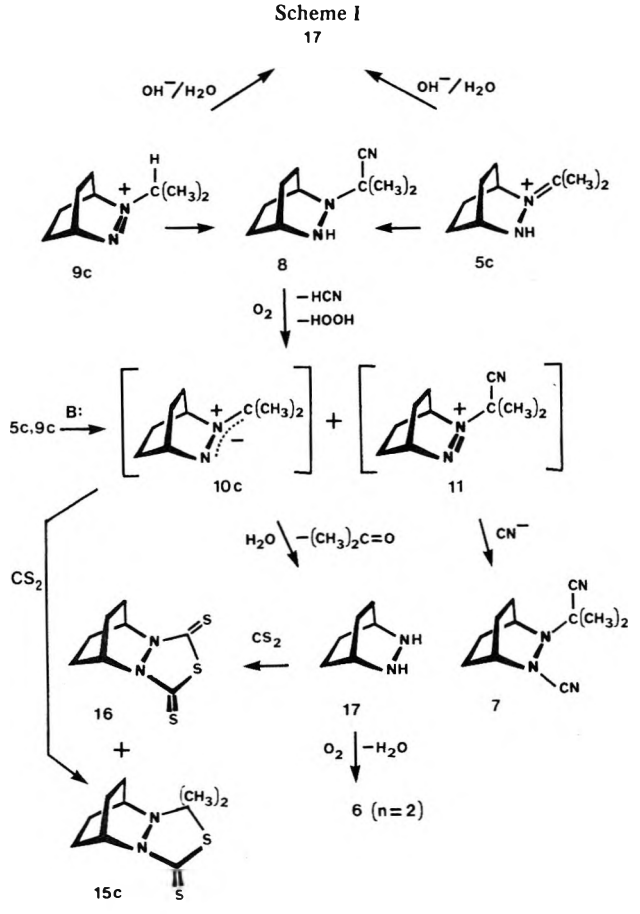
Testimony that these reactions are operating under the conditions necessary for oxidation of hydrazine **8** has been gathered as follows. Byproducts of the air oxidation of trialkylhydrazine ought to be the reduced species HO_2^- and H_2O_2. Indeed, within a few minutes of the introduction of oxygen to a dilute acetonitrile solution of **8**, the pH rises from 7 to 10 and a starch iodide probe develops the characteristic color of iodine.

Furthermore, in the presence of base (CN^-, HO_2^-) unreacted hydrazine **8** might be expected to eliminate hydrogen cyanide with the formation of azomethinimine **10c**. Accordingly, salts **5c** and **9c** upon treatment with triethylamine at room temperature in the presence of an excess of CS_2 both lead to the thiadiazole adduct **15c** in good yield, 66 and 65%, respectively. Although stable to CS_2, hydrazine **8** under identical conditions likewise furnishes **15c** (67%).[9] Verification of the structure is deferred to a subsequent section. A second product, thiadiazolidinedithione **16**, can be isolated in 18–25% yield from all three reactions unless the amine base is rigorously dried (see below). The 1,3 dipole **10c** is thereby suggested as the common intermediate for the reaction trio. The observation that cyanohydrazine **8** arises from both tautomers **5c** and **9c** leads further support to the intermediacy of **10c**. Ylides of this type are well known as 1,3 dipoles,[10] while a bicyclic homologue of **10c** has been generated by a separate route.[5,6] In agreement, air oxidation of **8** in a 10-mol excess of CS_2 furnishes thiadiazole **15c** as the major product (54%) along with the bicyclic dithione **16** (16%). A control experiment in which adduct **15c** was treated with CS_2 and Et_3N led to the quantitative recovery of starting material, indicating that **16** is not derived from **15c**. Dithione **16** is, however, produced in 83% yield from the simple bicyclic hydrazine **17** and CS_2/Et_3N and is therefore implicated as an intermediate in the oxidation of cyanohydrazine **8**. The formation of thiadiazolidinedithiones from hydrazines and CS_2 has been reported by Thorn.[11]

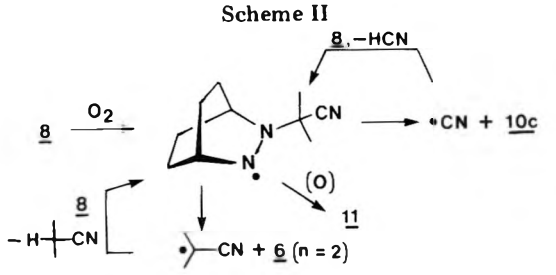
Although the formation of azomethine **10c** by the action of bases (CN^-, HO_2^-) generated during the air oxidation of **8** is consistent with the experiments described above, we cannot rule out its direct formation by loss of the cyanide radical from the intermediate hydrazyl radical. Radical chain decomposition could be sustained by subsequent CN· abstraction of hydrogen from **8** to regenerate hydrazyl (see Scheme II).

Another possible hydrazyl radical decomposition pathway involves the loss of the 2-cyanopropyl radical to give DBO **6** ($n = 2$). Hydrogen abstraction by the former would generate

Scheme I



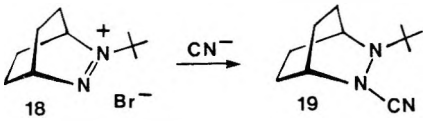
Scheme II



additional hydrazyl and 2-cyanopropane. A search for the latter by GLC and combined GLC–MS demonstrated its absence, however, and indicates that DBO **6** arises from another source, i.e., hydrazine **17**.

The presence of bicycle **17** is inferred both from the isolation of azo **6** and dithione **16**, as well as from the behavior of salts **5c** and **9c** under basic conditions. The salts are stable in aqueous solution as evidenced by their indefinite stability in D_2O as monitored by NMR spectroscopy. However, the addition of dilute aqueous NaOH to either material causes immediate and complete hydrolysis to hydrazine **17** and acetone. Any ylide generated during the oxidation of cyanohydrazine 8 can scavenge a proton from either water or H_2O_2, resulting in the formation of diazenium cation **9c** or the thermodynamically preferred[1] iminium cation **5c**. The resulting hydroxide or hydroperoxide in turn rapidly converts the tautomer formed to hydrazine **17** and subsequently to DBO **6** (n = 2) and water.

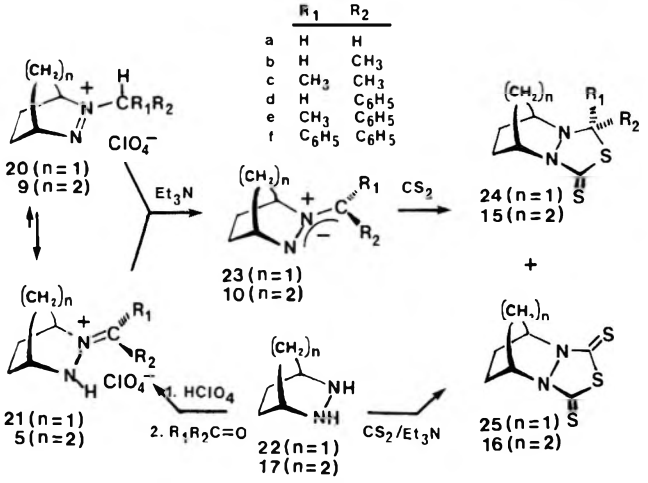
Generation of the azomethinimine **10c** from cyanohydrazine **8** releases a mole of HCN. Subsequent attack of cyanide ion from this source or from the reaction with **5c** or **9c** employing sodium cyanide on the diazenium species **11** accounts for the appearance of the dicyanohydrazine **7**. In order to confirm this event, the *tert*-butyl diazenium salt **18** (X = Br) was treated with NaCN at room temperature to give the cyanohydrazine **19** in quantitative yield.



The structures of cyanohydrazines **7** and **19** are confirmed by combustion analysis and spectroscopy, and in the latter case by its synthesis. Both compounds show a weak cyano stretch in the infrared spectra at 2220 cm^{-1} and exhibit NMR traces resembling that of cyanohydrazine **8**. Of significance is the appearance of split bridgehead protons (**7**, τ 6.48 and 6.70; **19**, τ 6.60 and 6.82) which reflect the differing electronic demands of adjacent N–CN and N–CC_3 moieties. These same protons for the monocyano compound **8** appear as a broad unresolved singlet.

The circumstantial evidence surrounding the intervention of azomethinimine **10c** and the possibility that cations **5c** and **9c** might serve as convenient precursors to the ylides iv in general stimulated efforts to generate the dipoles in a more controlled fashion. Although our goal in this regard was not fully realized, bicyclic ylides iv can be easily generated and trapped, and in one case isolated. Preparation of the appropriate starting materials is described in the following section.

Preparation of Diazenium and Iminium Salts. Diazenium cations **20** and **9** were prepared as reported previously[1] by alkylating DBH and DBO **6** (n = 1 and 2, respectively) with alkyl halides and silver perchlorate in methylene chloride. Yields ranged from 63 to 100% (Table I). In a few cases, although the NMR spectra of the salts were uncontaminated with impurities, completely satisfactory combustion analyses could not be obtained. We have noted previously that traces of base, including halide ions, catalyze rearrangement to the iminium tautomer.[1] And unless moisture is very carefully excluded the prototopic shift is accompanied by the further formation of bicyclic hydrazines (e.g., **17** and **22**).



The same problem arises of course in attempts to obtain pure samples of the iminium species **21** and **5**. These can sometimes be prepared by the controlled rearrangement of **20** and **9**.[1] A more satisfactory method consists of treating the corresponding bicyclic hydrazine hydroperchlorates with an excess of the appropriate aldehyde or ketone in dry 2-propanol (49–80%). The derivatives so obtained are listed in Table I.

Ylide Formation and Capture. Passage of the diphenyliminium cation **20** (R_1 = R_2 = C_6H_5) through a column of basic alumina leads to a bright yellow solution which delivers the stable azomethinimine **23** (R_1 = R_2 = C_6H_5) in 38% yield. Similar conditions proved to be unsuitable for the isolation of other azomethinylides in this series. Neither low temperatures nor a range of bases were successful. Nevertheless, in situ formation of the bicyclic zwitterions **10** and **23** was demonstrated by their 1,3-dipolar cycloaddition with CS_2. Treatment of either **5**, **9**, **20**, or **21** in an excess of CS_2 with more than 1 equiv of anhydrous triethylamine led to a yellow solution which faded to colorless within 10 min. The corresponding adducts **24** and **15** were obtained in most cases accompanied by dithiones **16** and **25**. As for **16**, the constitution of **25** was determined by its preparation from **22**. The yields of the two products are listed in Table II.

Although every attempt was made to dry the solvents, reagents, and starting materials prior to deprotonation of **5**, **9**, **20**, and **21**, the dithione byproducts **16** and **25** were persistent in their appearance. Since we have shown that the latter are not produced by way of **15** and **24**, we can only surmise that traces of moisture linger in the reaction system in spite of efforts to remove it. Alternatively, the triethylamine used may have been contaminated by the potent dealkylating agent diethylamine.[12] GLC examination of redistilled and alumina-treated triethylamine showed less than 0.1% of the latter, however.

Carbon disulfide can in principle cycloadd to the azomethinylides **10** and **23** to give either **15** and **24** or **26**. Only one isomer was consistently isolated from the reactions. Furthermore, unheated crude product mixtures were routinely monitored by NMR spectroscopy, but no differences from spectra of analytical samples were observed. Thus, it appears as though either the reaction proceeds regiospecifically or the kinetic product rapidly rearranges to the thermodynamically stable species. We assign the 1,3,4-thiadiazole-2-thione structure to **15**/**24** on the basis of ^1H and ^{13}C NMR spectroscopy. Adduct **24c** (R_1 = R_2 = CH_3) exhibits two methyl groups at τ 8.33 and 8.48. Methyl absorption for the corresponding bridge-expanded bicycle **15c** (R_1 = R_2 = CH_3) appears at τ

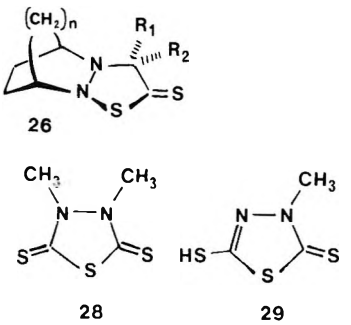


Table I. Physical Data for Diazenium and Iminium Salts (X = ClO_4)

Salt	Registry no.	n	R_1	R_2	Mp, °C (solvent)[a]	Yield %	^1H NMR, τ ($CDCl_3/Me_4Si$)	Formula	Analysis,[j] % C	H	N
20a	65621-96-7	1	H	H	150–152 dec	72	4.33[b] (1 H, broad s) 4.52 (1 H, broad s) 5.63 (3 H, s) 7.7–8.8 (6 H, m)	$C_6H_{11}N_2ClO_4$	34.2 34.3	5.3 5.4	13.3 13.2
20b	65621-97-8	1	H	CH_3	74–76	100	4.31[c] (1 H, broad s) 4.55 (1 H, broad s) 5.32 (2 H, q, J = 6 Hz) 7.5–8.6 (6 H, m) 8.45 (3 H, t, J = 6 Hz)	$C_7H_{13}N_2ClO_4$	37.4 37.4	5.8 6.1	12.5 12.5
20c	64671-88-1	1	CH_3	CH_3	122–124	99	4.11[c] (2 H, broad s) 4.78 (1 H, septet, J = 7 Hz) 7.3–8.6 (6 H, m) 8.30 (3 H, d, J = 7 Hz) 8.34 (3 H, d, J = 7 Hz)	$C_8H_{15}N_2ClO_4$	40.3 39.4	6.3 6.3	11.7 11.6
9a	65621-99-0	2	H	H	118–120	99	4.25[f] (1 H, broad s) 4.62 (1 H, broad s) 5.40 (3 H, s) 7.7–8.5 (8 H, m)	$C_7H_{13}N_2ClO_4$	37.4 37.1	5.8 5.8	12.5 12.5
9b	65622-01-7	2	H	CH_3	72–74	90	4.35[d] (1 H, broad s) 4.79 (1 H, broad s) 5.22 (2 H, q, J = 7 Hz) 7.7–8.6 (8 H, m) 8.43 (3 H, t, J = 7 Hz)	$C_8H_{15}N_2ClO_4$	40.2 39.6	6.3 6.3	11.8 11.6
9c	64672-05-5	2	CH_3	CH_3	227–228 (EtOH)	91	4.14[c] (1 H, broad s) 4.35 (1 H, broad s) 4.71 (1 H, septet, J = 7 Hz) 7.6–8.5 (8 H, m) 8.31 (6 H, d, J = 7 Hz)	$C_9H_{17}N_2ClO_4$	42.8 42.5	6.8 6.5	11.1 11.2
9d	65622-03-9	2	H	Ph	100–102	95	2.49[d] (5 H, broad s) 4.00 (2 H, s) 4.20 (1 H, broad s) 4.58 (1 H, broad s) 7.7–8.7 (8 H, m)	$C_{13}H_{17}N_2ClO_4$	51.9 51.7	5.7 5.6	9.3 9.4
9f	65622-05-1	2	Ph	Ph	62–66	69	2.75[g] (10 H, broad s) 4.36 (1 H, broad s) 4.56 (1 H, broad s) 4.73 (1 H, broad s) 8.21 (8 H, m)	$C_{19}H_{21}N_2ClO_4$[i]	60.6 55.0	5.6 6.0	7.4 8.2
21d	65622-07-3	1	H	Ph	164–166	80	1.4–2.7[f] (6 H m) 5.00 (1 H, broad s) 5.87 (1 H, broad s) 9.08 (6 H, broad s)	$C_{12}H_{15}N_2ClO_4$	50.3 49.0	5.3 5.4	9.8 10.1
21e	65622-09-5	1	CH_3	Ph	82–84	74	2.72[e] (5 H, broad s) 3.40 (1 H, broad s) 5.32 (1 H, broad s) 5.92 (1 H, broad s) 7.35 (3 H, s) 7.54–8.38 (6 H, m)	$C_{13}H_{17}N_2ClO_4$	51.9 50.4	5.7 5.5	9.3 9.3
21f	65622-11-9	1	Ph	Ph	244–246 ($CHCl_3$)	64	2.45[h] (10 H, broad s) 2.80 (1 H, broad s) 4.98 (1 H, broad s) 5.74 (1 H, broad s) 7.3–8.2 (6 H, m)	$C_{18}H_{19}N_2ClO_4$	59.6 59.5	5.3 5.4	7.7 7.7
5d	65622-13-1	2	H	Ph	222–223	69	1.1–2.5[f] (6 H, m) 5.41 (1 H, broad s) 6.34 (1 H, broad s) 6.60 (1 H, broad s) 8.03 (8 H, broad s)	$C_{13}H_{17}N_2ClO_4$	51.9 51.7	5.7 5.8	9.3 9.4
5e	65622-15-3	2	CH_3	Ph	128–130	49	2.2–2.7[e] (5 H, m) 5.49 (1 H, broad s) 6.24 (1 H, broad s) 7.19 (3 H, s) 7.5–8.3 (8 H, m)	$C_{14}H_{19}N_2ClO_4$	53.4 51.8	6.1 6.3	8.9 9.1
5f	65622-17-5	2	Ph	Ph	240–242	85	2.40[f] (10 H, broad s) 5.54 (1 H, broad s) 6.43 (1 H, broad s) 6.57 (1 H, broad s) 7.5–8.3 (8 H, m)	$C_{19}H_{21}N_2ClO_4$	60.6 60.2	5.6 5.1	7.4 7.1

[a] Where no solvent is given, the crude crystalline product was washed repeatedly with dry ether to provide the analytical sample. [b] CD_2Cl_2/CD_3OD. [c] $CD_2Cl_2/CDCl_3$. [d] CD_2Cl_2. [e] $CDCl_3$. [f] Me_2SO-d_6. [g] CD_3CN. [h] Acetone-d_6. [i] The crude product showed the expected NMR spectrum, but all attempts to purify it led to the iminium tautomer (see Experimental Section). [j] The calculated values are on the first line and the values found appear on the second line.

Table II. Physical Data for CS_2 Adducts and Yields for Dithiones 16 and 25

Adduct	Registry no.	n	R_1	R_2	Mp °C (solvent)	Yield, % (CS_2 adduct, **16**, or **25**)	^1H NMR, τ ($CDCl_3$/Me_4Si)	Formula	Analysis[h] % C	H	N
24a	65651-34-5	1	H	H	85–86[b] (CCl_4)	15 **4 (25)**	5.13 (1 H, broad s) 5.39, 5.62 (2 H, AB, J = 7 Hz) 6.22 (1 H, broad s) 7.5–8.3 (6 H, m)	$C_7H_{10}N_2S_2$	45.2 45.0	5.4 5.6	15.1 15.2
24b		1	H	CH_3	111–112[a] (CCl_4)	57 **17 (25)**	*a*	$C_8H_{12}N_2S_2$	48.0 48.0	6.0 6.3	14.0 14.0
24c	65622-18-6	1	CH_3	CH_3	108–110 (EtOAC/petroleum ether)	60 **0 (25)**	5.20 (1 H, broad s) 6.25 (1 H, broad s) 7.7–8.6 (6 H, m) 8.33 (3 H, s) 8.46 (3 H, s)	$C_9H_{14}N_2S_2$	50.5 50.1	6.6 6.4	13.1 12.9
24d		1	H	Ph	172–174[a] (CH_2Cl_2)	48 **11 (25)**	*a*	$C_{13}H_{14}N_2S_2$	59.5 59.4	5.4 5.6	10.7 10.5
24e		1	CH_3	Ph	126–127[a] (CH_2Cl_2/Et_2O)	31 **0 (25)**	*a*	$C_{14}H_{16}N_2S_2$	60.9 61.0	5.8 5.9	10.1 10.2
24f	65622-19-7	1	Ph	Ph	130 dec (Et_2O)	84 **0 (25)**	2.71 (5 H, s) 2.75 (5 H, s) 5.20 (1 H, broad s) 6.31 (1 H, broad s) 7.7–9.2 (6 H, m)	$C_{19}H_{18}N_2S_2$	67.4 67.2	5.4 5.3	8.3 8.2
15a[f]	65622-20-0	2	H	H	124–126[c] (acetone)	20 **25 (16)**	5.30[e] (1 H, broad s) 5.68 (2 H, s) 6.90 (1 H, broad s) 7.7–8.5 (8 H, m)	$C_8H_{12}N_2S_2$	48.0 48.0	6.0 5.8	14.0 14.5
15b	65622-21-1	2	H	CH_3	134–136[d] (acetone)	24 **19 (16)**	5.00 (1 H, broad s) 5.02 (1 H, q, J = 6 Hz) 6.80 (1 H, broad s) 7.6–8.5 (8 H, m) 8.44 (3 H, d, J = 6 Hz)	$C_9H_{14}N_2S_2$	50.5 50.5	6.6 6.4	13.1 13.1
15c[g]	65622-22-2	2	CH_3	CH_3	163–164 (EtOH)	66 **22 (16)**	5.00 (1 H, broad s) 6.63 (1 H, broad s, J = 7 Hz) 7.8–8.5 (8 H, m) 8.35 (6 H, s)	$C_{10}H_{16}N_2S_2$	52.6 52.6	7.1 7.0	12.3 12.3
15d	65622-23-3	2	H	Ph	184–186 (CCl_4)	78 **0 (16)**	2.3–2.8 (5 H, m) 4.07 (1 H, s) 4.95 (1 H, broad s) 7.02 (1 H, broad s) 7.6–8.6 (8 H, m)	$C_{14}H_{16}N_2S_2$	60.9 60.3	5.8 6.0	10.1 10.2
15e	65622-24-4	2	CH_3	Ph	72–74 (EtOAC/pertroleum ether)	59 **0 (16)**	2.3–3.1 (5 H, m) 5.02 (1 H, broad s) 6.89 (1 H, broad s) 7.97 (1 H, s) 7.8–8.5 (8 H, m)	$C_{15}H_{18}N_2S_2$	62.1 59.7	6.3 6.4	9.7 9.0
15f	65651-39-0	2	Ph	Ph	184–186 (benzene/petroleum ether)	40 **0 (16)**	2.83 (10 H, s) 5.12 (1 H, broad s) 6.74 (1 H, broad s) 7.8–9.0 (8 H, m)	$C_{20}H_{20}N_2S_2$	68.2 68.2	5.7 5.6	8.0 8.0

[a] See Experimental Section for details. [b] Purification: PLC; silica gel PF (254 + 366), 2.5 mm; benzene/petroleum ether/acetone, 7:5:1. [c] Purification: column chromatography; silica gel 60, 0.063–0.200 mm; benzene/petroleum ether/acetone, 3:3:1. [d] Purification: column chromatography; silica gel 60, 0.063–0.200 mm; benzene/petroleum ether, 1:2. [e] Solvent, CD_2Cl_2. [f] ^{13}C NMR: ($CDCl_3$/Me_4Si) 173.3 (1 C), 55.1 (1 C), 54.7 (1 C), 50.7 (1 C), 23.9 (2 C), 22.0 (2 C) ppm. [g] ^{13}C NMR: ($CDCl_3$/Me_4Si) 171.8 (1 C), 76.4 (1 C), 51.1 (1 C), 49.8 (1 C), 26.5 (4 C), 24.8 (2 C) ppm. [h] The calculated values are on the first line and the values found appear on the second line.

8.35. These values are superimposable with C–CH_3 resonances for the similar heterocycle **27** (τ 8.36).[13]

More instructive, the ^{13}C spectrum of compound **15a** (Table II) shows six peaks, one at 173.3 ppm and the remainder between 20 and 60 ppm downfield from Me_4Si ($CDCl_3$). The dimethyl derivative **15c** delivers a similar pattern with a single low field carbon at 171.8 ppm. The latter is assignable to N—^{13}C=S. Thicarbonyl ^{13}C absorptions for **27, 28,** and **29** are at 193, 180, and 187 ppm, respectively.[13,15] On the contrary, dithiomethyl acetate, an acyclic model for the alternative adduct **26,** displays ^{13}C=S absorption at 233 ppm.[16]

Conclusion

Bicyclic diazenium and iminium cations are readily interconverted via the azomethinimines iv (**10** and **23**). The latter ylides can be generated from either cation precursor and prompted to undergo a 1,3 cycloaddition to CS_2. Although we have not explored the efficacy of other dipolarophiles, there

is little doubt that a variety of synthetic goals may be achieved by choosing the appropriate reagent.[6]

Cations i and iii likewise react with weak nucleophiles such as CN^-. If R in i does not bear a proton α to $=N^+$, the nucleophile attacks the divalent nitrogen of the diazenium moiety to give a tetrasubstituted cyanohydrazine such as **7** and **19**. Where the mobile α proton is present, the diazenium species i behaves precisely as iminium cation iii and leads to trialkylhydrazine **8**. Our work does not allow a decision as to whether CN^- first attacks nitrogen as in **11** followed by rearrangement via ylide iv and HCN or whether CN^- functions as a base, catalyzing the transformation of i to iii and subsequently attaching itself to carbon. In any case, the resulting trialkylhydrazine mimics the redox lability of the previously reported example **12**. The behavior of salts i and iii under the influence of other nucleophiles is under investigation.

Experimental Section

General. Microanalyses were performed by the Microanalytical Laboratory, Department of General and Organic Chemistry, The H.C. Ørsted Institute, University of Copenhagen. Melting points were measured with a Büchi instrument and are uncorrected. IR spectra were recorded with a Perkin-Elmer 257 or 337 grating spectrophotometer and UV–vis spectra with a Cary 15 or Unicam SP 1800 recording spectrophotometer. Mass spectra were obtained on an AEI MS-902 apparatus. The NMR spectra were measured with Varian A-60 and Bruker HX-90E (^{13}C) spectrometers. GLC analyses were accomplished with a Perkin-Elmer F 11 gas chromatograph and a Pye Unicam 104 chromatograph. Both were equipped with a flame ionization detector. Reagent grade solvents and liquid reagents (alkyl halides, triethylamine, and CS_2) were all treated by passage through a column of basic alumina (2 × 5 cm) just prior to use. All ketones and aldehydes used were passed through a column of neutral alumina (2 × 5 cm) just before use. 2-Propanol was purified by distillation over CaH_2. Silver perchlorate, finely powdered, was dried and stored over concentrated H_2SO_4.

2-(2-Cyano-2-propyl)-2,3-diazabicyclo[2.2.2]octane (8) and 2-(2-Cyano-2-propyl)-3-cyano-2,3-diazabicyclo[2.2.2]octane (7). To a solution of iminium perchlorate **9c** ($X = ClO_4$)[1] (500 mg, 2.14 mmol) in chloroform (40 mL) cooled to 0 °C under N_2 was added a solution of NaCN (300 mg, 6.12 mmol) in distilled water (10 mL), and the mixture was stirred for 0.5 h. Upon addition the initial light yellow color of the reactants changed immediately to red and remained so throughout the reaction. The organic layer was separated, washed with saturated NaCl (3 × 25 mL), dried ($MgSO_4$), filtered, and stripped of solvent under reduced pressure to yield a light orange oxygen-sensistive oil (**8**; 360 mg, 2.01 mmol, 94%). Attempted recrystallization led to decomposition and further conversion: IR ν_{max} ($CHCl_3$) 3500–3200 (s), 2225 (s) cm^{-1}; NMR ($CDCl_3/Me_4Si$) τ 6.45 (1 H, broad s, J = 10 Hz, NH, exchanged with D_2O), 7.03 (2 H, broad s, J = 13 Hz), 6.9–7.2 (8 H, m), 8.66 (6 H, s); MS *m/e* 179 (M^+, 0.014), 178 (0.027), 177 (0.18), 152 (0.24, −HCN), 97 (0.45), 41 (0.82), 29 (1.0). Anal. Calcd for $C_{10}H_{17}N_3$: C, 67.0; H, 9.6; N, 23.5. Found: C, 66.7; H, 9.5; N, 23.7.

Chromatography (PLC; silica gel, 2 × 100 cm; EtOAc, 2 elutions) of a second portion of the oil (950 mg) resulted in two fractions (R_f 0.45 and 0.68, respectively) which were extracted with ether. The first fraction was relieved of solvent in vacuo to produce white solid DBO **6** (126 mg, 1.15 mmol, 20%): mp 138–140 °C; the NMR spectrum was identical with authentic DBO **6** (n = 2).

The second fraction was stripped of solvent and recyrstallized (hexane) to give white crystals of the dicyanohydrazine **7** (380 mg, 1.86 mmol, 35%): mp 114–115 °C; IR ν_{max} ($CHCl_3$) 2220 (w) cm^{-1}; NMR ($CDCl_3/Me_4Si$) τ 6.48 (1 H, broad s, J = 6 Hz), 6.70 (1 H, broad s, J = 6 Hz), 7.5–8.2 (8 H, m), 8.42 (6 H, s) Anal. Calcd for $C_{11}H_{16}N_4$: C, 64.7; H, 7.9; N, 27.4. Found: C, 64.8; H, 8.0; N, 27.3.

Bubbling a stream of O_2 into a solution of hydrazine **8** (60 mg) in CD_3CN (1 mL) in an NMR tube caused the conversion to **6** and **7** within 5 min and acetone (τ 7.90) appeared simultaneously. The presence of acetone was further confirmed by IR spectroscopy (ν_{max} (neat/KBr) 1720 (C=O) cm^{-1}) and GLC (Carbowax 1500, 45 °C, flow rate 50 mL/min, 3.2 min; the retention time was identical with that of authentic material). The reaction mixture was likewise investigated for 2-cyanopropane by comparison with standard solutions containing the latter, acetone, and acetonitrile (GLC; polypropylene glycol, 38 °C). Its absence was substantiated by examination of the reaction solution and standards with combined GLC–MS [poly(1,4-butanediol) succinate, 40 °C; Finnigan MS 1015 S/L (70 eV)]. The pH of the solution was monitored with indicator paper calibrated in 0.5 pH increments and reached a maximum value of 10.5. The presence of an oxidant was established by a strong positive test with starch iodide paper.

The above reactions gave identical results when diazenium bromide **9c** (X = Br) was employed instead of the above perchlorate.

Characterization of Cyanohydrazine 7 with PhNCS: 2,4,6-Triaza-3-thio-4-phenyl-5,5-dimethyltricyclo[5.2.2.0^{2,6}]undecane. Cyanohydrazine **7** (113 mg, 0.63 mmol) in CH_2Cl_2 (10 mL) was treated with PhNCS (108 mg, 0.80 mmol) in CH_2Cl_2 (10 mL) for 1 h (25 °C). Removal of the solvent in vacuo gave a white semisolid. Recrystallization (EtOH) yielded a microcrystalline solid (163 mg, 0.57 mmol, 90%): mp 149–150 °C; IR ν_{max} (KBr) 1510 (s), 1460 (s), 1300 (s), 1215 (s), 1205 (s), 700 (s) cm^{-1}; NMR ($CDCl_3/Me_4Si$) τ 2.73 (5 H, broad), 5.60 (1 H, broad), 6.80 (1 H, broad), 7.40–8.60 (8 H, m), 8.70 (6 H, m). Anal. Calcd for $C_{16}H_{21}N_3S$: C, 66.9; H, 7.4; N, 14.6; S 11.2. Found: C, 70.0; H, 7.4; N, 14.7; S, 11.4.

2,6-Diaza-3-thio-4-thia-5,5-dimethyltricyclo[5.2.2.0^{2,6}]undecane (15c) and 2,6-Diaza-3,5-dithio-4-thiatricyclo[5.2.2.0^{2,6}]-undecane (16). A. A solution of diazenium salt **9c** ($X = I^-$)[1] (2.04 g, 7.29 mmol) and CS_2 (10.6 g, 14.8 mmol) in CH_2Cl_2 (100 mL) under N_2 was treated dropwise with a solution of Et_3N (860 mg, 8.00 mmol; distilled from KOH) in CH_2Cl_2 (10 mL). The reaction was stirred for 1 h at 25 °C, the organic phase was washed with saturated NaCl (4 × 25 mL) and dried ($MgSO_4$), and the solvent was removed under reduced pressure to yield a solid (1.54 g). Chromatography of the curde solid on two plates (20 × 100 cm silica gel; CH_2Cl_2, 1 elution) furnished two main bands (R_f 0.25 and 0.75), which were extracted with CH_2Cl_2. The substance with R_f 0.75 was recrystallized to give white solid **15c** (1.10 g 4.82 mmol, 66%), mp 163–167 °C. For further physical characteristics, see Table II.

The compound with R_f 0.25 is white solid dithione **16** (370 mg, 1.61 mmol, 22%): mp 222–223 °C (MeOH); IR ν_{max} (KBr) 1440 (s), 1180 (s) cm^{-1}; NMR ($CDCl_3/Me_4Si$) τ 4.63 (2 H, broad s, J = 7 Hz), 7.95 (8 H, m); UV λ_{max} (CH_3OH) 266 nm (log ϵ 4.2), 338 (4.2). Anal. Calcd for $C_8H_{10}N_2S_3$: C, 41.7; H, 4.4; N, 12.2; S, 41.8. Found: C, 41.8; H, 4.3; N, 12.2; S, 41.6.

B. A solution of iminium salt **5c** ($X = ClO_4$)[1] (700 mg, 2.78 mmol) and CS_2 (2.11 g, 27.8 mmol) in CH_2Cl_2 (30 mL) under N_2 was treated dropwise with a solution of Et_3N (280 mg, 2.78 mmol; distilled from KOH) in CH_2Cl_2 (10 mL). The reaction immediately turned dark orange but gradually faded to light yellow after stirring for 1 h at 25 °C. After workup and chromatography of the crude reaction products as specified above, identical products were isolated, i.e., the CS_2 adduct **15c** (410 mg, 1.80 mmol, 65%) and the dithione **16** (164 mg, 0.690 mmol, 25%). No other products were observed.

Reaction of Cyanohydrazine 8 with CS_2/Et_3N. A solution of cyanohydrazine **8** (9.00 mg, 5.00 mmol) and CS_2 (3.80 g, 50.0 mmol) in CH_2Cl_2 (35 mL) under N_2 was treated dropwise with a solution of Et_3N (500 mg, 5.00 mmol; distilled from KOH). The resulting orange solution was stirred for 1 h at 25 °C, worked up as above, and chromatographed (PLC; silica gel; CH_2Cl_2, 2 elutions) to produce two main bands with R_f 0.25 and 0.75, respectively. Extraction with CH_2Cl_2 and solvent removal delivered dithione **16** (213 mg, 0.890 mmol, 18%) and CS_2 adduct **15c** (766 mg, 3.36 mmol, 67%).

Reaction of Cyanohydrazine 8 with CS_2/O_2. A solution of freshly prepared cyanohydrazine **8** was dissolved in CD_3CN in an NMR tube and shown to be homogeneous by NMR spectroscopy. Addition of a large excess of CS_2 in $CDCl_3$ caused no change in the spectrum. Bubbling O_2 into the solution promoted the rapid formation of DBO **6** (n = 2), dicyanohydrazine **7**, and the adduct **15c**. Continued O_2 introduction led to the complete disappearance of cyanohydrazine **8** and its replacement by the latter compounds (NMR). On a preparative scale a mixture of **8** (1.00 g, 5.55 mmol) and CS_2 (5.30 g, 55.5 mmol; dried over $MgSO_4$) in CH_3CN (50 mL) was stirred and subjected to a stream of O_2 gas for 1.0 h. Removal of the solvent under reduced pressure gave an orange solid (1.37 g). A portion (300 mg) was chromatographed (PLC; silica gel; CH_2Cl_2, 2 elutions) to give six bands. Those with R_f values of 0.25 and 0.75 were removed, extracted (CH_2Cl_2), and stripped to give off-white solids, the CS_2 adduct **15c** (151 mg, 0.66 mmol, 54%) and dithione **16** (46 mg, 0.20 mmol, 16%).

Treatment of CS_2. Adduct 15c with CS_2/Et_2N (Control Experiment). A solution of adduct **15c** (250 mg, 1.5 mmol) and CS_2 (300 mg, 4.25 mmol) in CH_2Cl_2 (30 mL) was treated dropwise with a solution of Et_3N (152 mg, 1.5 mmol; distilled from KOH) in CH_2Cl_2 (5 mL). The mixture was stirred for 1 h at 25 °C. TLC (silica gel, CH_2Cl_2) indicated only one spot, corresponding to starting material. Removal of solvent under reduced pressure gave a yellow residue that was triturated with ether (2 × 10 mL) to yield an off-white solid (260 mg).

The material had an NMR spectrum identical with that of starting material. No other product was observed. Adduct **15c** is thus inert to conversion to dithione **16** under these conditions.

Preparation of Dithione 16 from 2,3-Diazabicyclo[2.2.2]octane (17). DBO **6**[17,18] was catalytically reduced (Pd/C, EtOAc) on a Paar hydrogenation apparatus to 2,3-diazabicyclo[2.2.2]octane (**17**).[18] The consumation of DBO was confirmed by NMR spectroscopy. Hydrazine **17** (1.12 g, 10.0 mmol) in CH_2Cl_2 (25 mL) under N_2 was combined with CS_2 (7.6 g, 100 mmol) in CH_2Cl_2 (25 mL) and then treated dropwise with anhydrous Et_3N (1.01 g, 10 mmol; distilled over KOH) in CH_2Cl_2 (10 mL). The solution rapidly became yellow; stirring was continued for 0.5 h. TLC (silica gel, CH_2Cl_2) evidenced only one product. The solvent was removed under reduced pressure to yield an off-white solid. Trituration with ether gave a white powder of dithione **16** (1.88 g, 8.16 mmol, 82%), mp 223–224 °C (EtOH).

2,6-Diaza-3,5-dithio-4-thiatricyclo[5.2.1.0^{2,6}]decane (25). 2,3-Diazabicyclo[2.2.1]heptane (**22**) hydrobromide[1] (200 mg, 1.11 mmol), CS_2 (15 mL), Et_3N (10 mL), and CH_2Cl_2 (15 mL) were combined as described above, and the mixture was stirred for 4 h. The solvent was removed in vacuo, and the oily residue was dissolved in CH_2Cl_2 (50 mL), stripped to give a solid, and recrystallized (CCl_4) to give white crystals of the dithione **25** (40 mg, 0.21 mmol, 18%): mp 208–210 °C; NMR ($CDCl_3$/Me_4Si) τ 4.71 (2 H, broad s), 7.82 (6 H, broad s); IR ν_{max} (KBr) 1440 (s), 1185 (s) cm^{-1}. Anal. Calcd for $C_7H_8N_2S_3$: C, 38.9; H, 3.7; N, 12.9. Found: C, 38.8; H, 3.8; N, 12.6.

Reaction of Iminium Iodide 5c (X = I) and Diazenium Iodide 9c (X = I) with Aqueous Base. A sample of iminium iodide **5c** (X = I)[1] (65 mg) was dissolved in $CDCl_3$ and shaken with 2 drops of D_2O in an NMR tube. The NMR spectrum is nearly superimposable with that taken in dry solvent [($CDCl_3$/Me_4Si/D_2O) τ 4.02 (2 H, broad s, J = ca. 10 Hz), 4.15 (1 H, septet, J = 7 Hz), 7.3–8.4 (8 H, m), 8.26 (6 H, d, J = 7 Hz)], demonstrating that the system is stable to water. The D_2O/DSS spectrum is very similar and also stable. Addition of 1 drop of 20% NaOD (Merck) caused an immediate collapse of the observed spectrum and the appearance of the spectrum of hydrazine [($CDCl_3$/Me_4Si/D_2O) τ 6.5 (broad s), 7.10 (2 H, broad s, J = 6 Hz), 7.8–8.7 (8 H, m)].[18] Acetone appeared at τ 7.82 (s).

A parallel experiment was carried out with diazenium iodide **9c** (X = I) (65 mg) with identical results.

Preparation of 2-*tert*-Butyl-3-cyano-2,3-diazabicyclo[2.2.2]octane (19). To a solution of diazenium bromide **18**[1] (600 mg, 2.43 mmol) in $CHCl_3$ (23 mL) was added a solution of NaCN (300 mg, 6.12 mmol) in distilled water (10 mL). The mixture was stirred for 0.5 h, and the organic phase was separated, washed with saturated NaCl (2 × 15 mL), dried ($MgSO_4$), filtered, and stripped of solvent to give white solid **19** (400 mg, 2.07 mmol, 85%): mp 76–77 °C (hexane); IR ν_{max} ($CHCl_3$) 2220 (w) cm^{-1}; NMR ($CDCl_3$/Me_4Si) τ 6.60 (1 H, broad s), 6.82 (1 H, broad s), 7.9–8.5 (8 H, m), 8.78 (6 H, s). Anal. Calcd for $C_{11}H_{16}N_3$: C, 68.4; H, 9.9; N, 21.7. Found: C, 68.5; H, 9.9; N, 21.7.

Preparation of Diazenium Cations 9 and 20: Alkylation of Bicyclic Azoalkanes. The general procedure for the compounds listed in Table I is that given in ref 1 for **9c** (X = ClO_4). Variations from the procedure are noted below in A–C. All diazenium salts exhibit ν_{max} (KBr) 1150–1060 (broad s, ClO_4^-) cm^{-1} in the infrared spectrum.

A. 2-Methyl-2-azonia-3-azabicyclo[2.2.1]hept-2-ene Perchlorate (20a, X = ClO_4). Diazabicyclo[2.2.1]hept-2-ene[17,18] (226 mg, 2.35 mmol), $AgClO_4$ (490 mg, 2.35 mmol), CH_2Cl_2 (15 mL), and CH_3I (10 mL) were combined as above. The resulting perchlorate salt is difficultly soluble in CH_2Cl_2 and in most other organic solvents. In order to separate it from AgI, the solids were filtered and washed with dry MeOH (3 × 10 mL). The filtrates were combined and stripped of solvent, and the resulting solid was washed with dry ether and dried in a desiccator to yield white crystals of **20a** (X = ClO_4) (362 mg, 1.65 mmol, 72%), mp 150–152 °C dec (explosion). Care must be taken to exclude moisture from the system. Any trace of water leads to a mixture of isomers **20a** and **21a**, as is readily ascertained by NMR spectroscopy.

B. 2-Benzyl-2-azonia-3-azabicylo[2.2.2]oct-2-ene Perchlorate (9d, X = ClO_4). DBO **6** (1.33 g, 12.1 mmol), $AgClO_4$ (2.60 g, 12.5 mmol), CH_2Cl_2 (25 mL), and $PhCH_2Br$ (25 mL) were combined as above. The diazenium perchlorate is difficultly soluble in CH_2Cl_2. Thus, the reaction solids were filtered and washed with CH_2Cl_2 (5 × 10 mL) in order to separate the product from AgBr. The combined filtrates were stripped in vacuo to give a solid. Excess $PhCH_2Br$ was removed by washing with dry ether. After drying under vacuum, colorless crystals of **9d** (X = ClO_4) (3.46 g, 11.5 mmol, 95%) were obtained, mp 100–102 °C.

C. 2-Diphenylmethyl-2-azonia-3-azabicyclo[2.2.2]oct-2-ene Perchlorate (9f, X = ClO_4). DBO **6** (1.00 g, 9.10 mmol), $AgClO_4$ (2.00 g, 9.60 mmol), CH_2Cl_2 (50 mL), and $(Ph)_2CHBr$ (5.00 g, 20.2 mmol) were combined as above. The product was dissolved by washing the filtered reaction precipitate with CH_2Cl_2 (5 × 10 mL). The combined filtrates were stripped in vacuo and washed with dry ether (5 × 10 mL), yielding white crystals of **9f** (X = ClO_4) (2.36 g, 6.28 mmol, 69%), mp 62–66 °C. Recrystallization (EtOH) causes rearrangement to tautomer **5f** (X = ClO_4), as does utilization of the general procedure below.

Preparation of Iminium Cations 5 and 21: Condensation of Bicyclic Hydrazine Hydroperchlorates with Aldehydes and Ketones. The general procedure for compounds listed in Table I is illustrated by the following.

2-Benzylidene-2-azonia-3-azabicyclo[2.2.2]octane Perchlorate (5d, X = ClO_4). The hydrazine hydroperchlorate of **17**[1] (100 mg, 0.475 mmol) was dissolved in a mixture of *i*-PrOH (15 mL) and benzaldehyde (15 mL). The solution was refluxed for 1 h and allowed to stand (25 °C) under nitrogen overnight. The resulting white crystals were filtered and washed with dry ether (4 × 10 mL), yielding analytically pure product **5d** (X = ClO_4) (100 mg, 0.333 mmol, 69%), mp 222–223 °C.

Variations from this procedure are noted below in A–C. Two iminium cations (B and C) were best obtained by alkylation and in situ tautomerization. All salts showed ν_{max} (KBr) 1150–1060 (broad s, ClO_4^-) cm^{-1} in the infrared spectrum.

A. 2-Methylphenylmethylidene-2-azonia-3-azabicyclo-[2.2.2]octane Perchlorate (5e, X = ClO_4). The hydrazine hydroperchlorate of **17** (500 mg, 2.36 mmol) and acetophenone (2.80 g, 23.6 mmol) in *i*-PrOH (25 mL) were refluxed for 0.5 h. The reaction mixture was stored at −25 °C overnight under nitrogen. The solvent was evaporated and the oily residue crystallized by boiling it in a mixture of ether (10 mL) and ethyl acetate (2 mL). The resulting white crystals were filtered, washed with dry ether, and dried under vacuum to give **9e** (X = ClO_4) (362 mg, 1.15 mmol, 49%), mp 128–130 °C.

B. 2-Diphenylmethylidene-2-azonia-3-azabicyclo[2.2.1]heptane Perchlorate (21f, X = ClO_4). DBH **6** (n = 1) (1.00 g, 10.4 mmol), $AgClO_4$ (2.15 g, 10.4 mmol), and $(Ph)_2CHCl$ (2.10 g, 10.4 mmol) in $CHCl_3$ (50 mL) were stirred (24 h, 25 °C) under nitrogen. The reaction mixture was filtered and stripped of solvent. The partially transformed diazenium product **20f** was completely rearranged by recrystallization ($CHCl_3$), yielding white crystals of **21f** (X = ClO_4) (2.40 g, 6.61 mmol, 64%), mp 244–246 °C.

C. 2-Diphenylmethylidene-2-azonia-3-azabicyclo[2.2.2]octane Perchlorate (5f, X = ClO_4). A mixture of DBO **6** (600 mg, 5.45 mmol), $AgClO_4$ (1.13 g, 5.45 mmol), $(Ph)_2CHBr$ (13.5 g, 54.5 mmol), and Al_2O_3 (2.00 g, neutral) was stirred (4 h, 25 °C) under nitrogen in CH_2Cl_2 (25 mL), filtered through Celite, stripped of solvent, and washed with dry ether (5 × 15 mL), yielding colorless crystals of **5f** (X = ClO_4) (1.74 g, 4.62 mmol, 85%), mp 240–242 °C.

2-Diphenylmethylidene-2-azonia-3-azabicyclo[2.2.1]heptane Azomethinimine (23f). Diazenium cation **20f** (X = ClO_4) (900 mg, 2.47 mmol) was dissolved in $CHCl_3$ (400 mL) and passed through a column packed with basic alumina (activity III, 2 × 5 cm) under N_2. The resulting yellow solution was evaporated to give a yellow solid. Recrystallization (dry ether) yielded yellow crystals of **23f** (250 mg, 0.950 mmol, 38%), mp 111–113 °C. Repeated recrystallization yielded an analytical sample: NMR ($CDCl_3$/Me_4Si) τ 1.8–3.1 (10 H, m), 5.40 (1 H, broad s), 5.51 (1 H, broad s), 7.9–8.8 (6 H, m); IR ν_{max} (KBr) 1510 (s), 1490 (s), 1420 (s), 1210 (s), 1150 (s), 1120 (s) cm^{-1}. Anal. Calcd for $C_{18}H_{18}N_2$: C, 82.4; H, 6.9; N, 10.7. Found: C, 82.4; H, 7.0; N, 10.5.

Generation of Ylides 10 and 23 and Capture by Carbon Disulfide to Give 15, 16, 24, and 25. The general procedure for compounds listed in Table II is the following.

2,6-Diaza-3-thio-4-thiatricyclo[5.2.1.0^{2,6}]decane (24a). Diazenium perchlorate **20a** (X = CLO_4) (989 mg, 4.71 mmol) was dried (over H_2SO_4) and suspended in a mixture of CH_2Cl_2 (75 mL) and CS_2 (75 mL) under N_2. To the stirred suspension was added Et_3N (20 mL) dropwise. The salt dissolved within a few minutes as the reaction mixture turned yellow. Stirring was continued for 2 h under N_2 followed by solvent removal in vacuo. The oily residue was taken up in CH_2Cl_2 (20 mL), and the major part of the excess amine was removed by washing with water (3 × 20 mL). The organic phase was dried ($MgSO_4$) and the solvent stripped. The dark brown oily product showed the presence of **24a** and **25** by NMR spectroscopy. The mixture was separated by PLC (silica gel PF (254 + 366), 2.5 mm; benzene/petroleum ether/acetone, 7:5:1). A total of 260 mg was isolated from the plate: (i) 10 mg of unidentified material; (ii) 40 mg of white crystalline **25** (0.19 mmol, 4%), mp 208–210 °C; the NMR spectrum and melting point were identical with an independently prepared sample; (iii) 130 mg of white cyrstalline **24a** (0.698 mmol, 15%), mp 85–86 °C; recrystallization (CCl_4) provided an analytical sample (85

mg, 0.46 mmol), mp 85–86 °C (cf. Table II); (iv) 80 mg; the NMR spectrum showed a mixture of **24a, 25,** and an unidentified compound with absorption at ($CDCl_3$/Me_4Si) τ 4.86 and 6.71.

Different separation procedures were utilized for the various adduct derivatives. All CS_2 adducts showed characteristic strong IR absorptions in two regions: ν_{max} (KBr) 1180–1140 (s) and 1140–1120 (s) cm^{-1}.

Variations are noted below and in Table II. For further physical characteristics of the CS_2 adducts, Table II should be consulted.

A. 2,6-Diaza-3-thio-4-thia-5-methyltricyclo[5.2.1.0^{2,6}]decane (24b). Diazenium salt **20b** (X = ClO_4) (350 mg, 1.56 mmol), CH_2Cl_2 (20 mL), CS_2 (20 mL), and Et_3N (15 mL) were combined as above. The NMR spectrum of the product mixture (241 mg) showed **24b** and **25** in a ratio of 3:1 (ca. 57 and 17%, respectively). Column chromatography (silica gel 60, 0.063–0.200 mm; benzene/petroleum ether, 1:1) gave a small amount of **24b,** which was recrystallized (CCl_4) to give white crystals (20 mg, 0.10 mmol, 6%), mp 111–112 °C. The NMR spectrum showed a 1:1 mixture of two geometrical isomers: ($CDCl_3$/Me_4Si) τ 4.90 (1 H, q, J = 6 Hz), 5.18 (1 H, J = 6 Hz), 4.95 (1 H, broad s), 5.20 (1 H, broad s), 6.21 (1 H, broad s), 6.41 (1 H, broad s), 8.42 (3 H, d, J = 6 Hz), 8.49 (3 H, d, J = 6 Hz), 7.8–8.6 (12 H, m).

B. 2,6-Diaza-3-thio-4-thia-5-phenyltricyclo[5.2.1.0^{2,6}]decane (24d). Diazenium cation **20d** (X = ClO_4) (290 mg, 1.01 mmol), CH_2Cl_2 (20 mL), CS_2 (20 mL), and Et_3N (15 mL) were combined as above to yield a mixture of **24d** and **25** (150 mg). The two products were separated by washing the latter with ethyl acetate to extract **24d.** The residue, **25** (24 mg, 0.11 mmol, 11%), was identified by its melting point and NMR spectrum.

Compound **24d** was stripped of solvent and recrystallized (CH_2Cl_2/ethyl acetate) to yield white crystals (130 mg, 0.481 mmol, 48%), mp 172–174 °C. The NMR spectrum of pure **24d** showed a mixture of two isomers (2:3): (CD_2Cl_2/Me_4Si) τ 2.2–2.8 (10 H, m), 3.88 (1 H, s), 4.17 (1 H, s), 4.90 (1 H, broad s), 5.17 (1 H, broad s), 6.38 (1 H, broad s), 6.48 (1 H, broad s), 7.3–8.5 (12 H, m).

C. 2-6-Diaza-3-thio-4-thia-5-methyl-5-phenyltricyclo-[5.2.1.0^{2,6}]decane (24e). Cation **20e** (X = ClO_4) (165 mg, 0.550 mmol), CH_2Cl_2 (15 mL), CS_2 (15 mL), and diisopropylethylamine (10 mL) were combined as above to yield a mixture of the two geometrical isomers of **24e** as evidenced by the NMR spectrum. Recrystallization (CH_2Cl_2/ether) afforded white crystals (47 mg, 0.17 mmol, 31%), mp 126–127 °C. The NMR spectrum showed a 1:1 mixture of the two isomers: ($CDCl_3$/Me_4Si) τ 2.1–2.7 (10 H, m), 4.85 (1 H, broad s), 5.16 (1 H, broad s), 6.30 (2 H, broad s), 7.84 (3 H, s), 8.00 (3 H, s), 7.7–8.6 (12 H, m).

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Registry No.—**5c** (X = ClO_4), 64801-48-5; **5c** (X = I), 64801-47-4; **6** (n = 1), 2721-32-6; **6** (n = 2), 3310-62-1; **7,** 65621-79-6; **8,** 65621-80-9; **9c** (X = Br), 64672-02-2; **9c** (X = I), 64672-03-3; **16,** 65621-81-0; **17,** 280-49-9; **17** hydroperchlorate, 64671-91-6; **18,** 57163-60-7; **19,** 65621-82-1; **20g** (X = ClO_4), 65621-84-3; **20e** (X = ClO_4), 65621-86-5; **20f** (X = ClO_4), 65621-88-7; **22** HBr, 39158-98-0; **23f,** 65621-89-8; **24b** (isomer I), 65651-38-9; **24b** (isomer II), 65701-03-3; **24d** (isomer I), 65701-04-4; **24d** (isomer II), 65621-90-1; **24e** (isomer I), 65621-91-2; **24e** (isomer II), 65701-05-5; **25,** 65621-93-4; 2,4,6-triaza-3-thio-4-phenyl-5,5-dimethyltricyclo[5.2.2.0^{2,6}]undecane, 65621-92-3; benzaldehyde, 100-52-7; acetophenone, 98-86-2.

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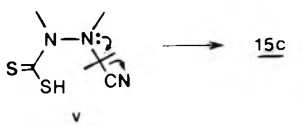
(8) Hydrogen cyanide addition to a bicyclic azomethinimine has been reported to lead to the corresponding trialkylhydrazine without mention of attendant difficulties.[7]
(9) It is conceivable that cyanohydrazine **8** is a strong enough base to promote a reversible self-elimination of HCN or nucleophilic enough to add CS_2 to give v, which might spontaneously close to **15c.** However, these possibilities are eliminated by the observation that **8** is unchanged in the presence of CS_2 unless treated with either Et_3N or O_2.



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Deuterium and the Octant Rule for Ketones. Syntheses and Circular Dichroism Data of Chiral 4-Deuterioadamantan-2-ones

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The syntheses of optically active (1*R*)-4(e)-deuterioadamantan-2-one (**5**), (1*R*)-4(a)-deuterioadamantan-2-one (**18**), and the (1*S*)-4,4-dideuterioadamantan-2-one (**21**) are described. To achieve this goal we developed a new general route for chiral adamantanones. From the circular dichroism data of **5**, **18**, and **21** in isooctane we must conclude that deuterium as a substituent β to the carbonyl behaves in a dissignate manner.

Numerous examples of asymmetric molecules owing their chirality to deuterium substitution are known.[1,2] Detailed and exact information about the influence of deuterium on the $n\pi^*$ Cotton effects of chiral ketones is lacking, however. The data Djerassi published[3] on (*R*)-3-deuteriocyclopentanone has limited use because of the lack of conformational integrity of the cyclopentane system: the Cotton effect of (*R*)-3-deuteriocyclopentanone reflects either the influence of deuterium by itself or this influence in combination with that of chiral conformations[4] of the cyclopentanone ring system.

As is well known, an exact knowledge of the conformation of the molecule is essential for useful interpretation of Cotton effects data. In the case of chirality due to deuterium it is clear that minor conformational ambiguities may swamp the small deuterium effects. The choice of the rigid adamantane framework for an examination of the influence of deuterium substitution on the $n\pi^*$ carbonyl Cotton effect is evident in light of Snatzke's earlier contributions.[5,11,12]

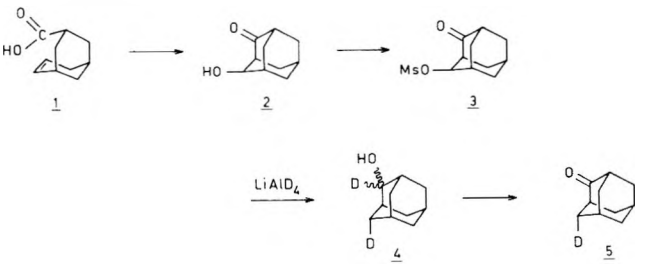
This paper reports the details of the syntheses and circular dichroism data of (1*R*)-4(e)-deuterioadamantan-2-one (**5**),[6] the (1*R*)-4(a)-deuterioadamantan-2-one (**18**), and the (1*S*)-4,4-dideuterioadamantan-2-one (**21**).[7]

Synthesis. The starting material in our synthesis was the *endo*-bicyclo[3.3.1]non-6-en-3-carboxylic acid[8] (**1**). Resolution of this acid was achieved using (+)-dehydroabietylamine. The diastereomeric salts could be separated by fractional crystallization from 96% ethanol. Decomposition of the salt $[\alpha]_{578}$ +77.8° gave an optically active acid (+)-(**1**), $[\alpha]_{578}$ +130.7°.

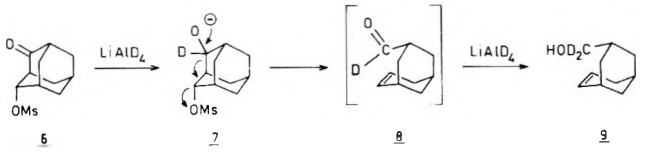
In a separate experiment optically active acid **1**, $[\alpha]_{578}$ +115.9°, was converted to a mixture of diastereomeric amides using the acid chloride[9] of **1** and optically pure (−)-α-phenylethylamine, $[\alpha]_D$ −39° (neat). Analytical separation of these amides by high-pressure liquid chromatography was possible and an enantiomeric excess of 77 ± 3% was established for the acid **1**, $[\alpha]_{578}$ +115.9°. The extrapolated absolute rotation of acid **1** would be $[\alpha]_{578}$ −151 ± 6° (it must be realized that extrapolation of optical rotations, itself dependent on concentration, cannot give entirely exact data). The acid **1** with $[\alpha]_{578}$ +126.4° used in our further work has an optical purity of 84 ± 3%. This is extrapolated from the value of the absolute rotation (with its inherent failings).

The acid **1** could be transformed readily to an epimeric mixture of 4-hydroxyadamantan-2-ones by treatment with acetic anhydride and boron trifluoride etherate in benzene.[10] The optical purity of the 4(a)- and 4(e)-hydroxyadamantan-2-ones (**2** and **10**) was almost identical to that of acid **1**, as could be verified on the CD data of **2** and **10**.[11] The only previous synthesis of optically active 4-hydroxyadamantan-2-ones was elegantly achieved by Snatzke using the laborious and low yield route starting with Meerwein's ester.[11,12] Our new route as described above proceeds in an overall yield of 84% starting with acid **1** as compared to 30% of the old route starting with 2-carboxyadamantan-4,8-dion. The 4(a)-hydroxyadamantan-2-one (**2**) was isolated from the mixture and

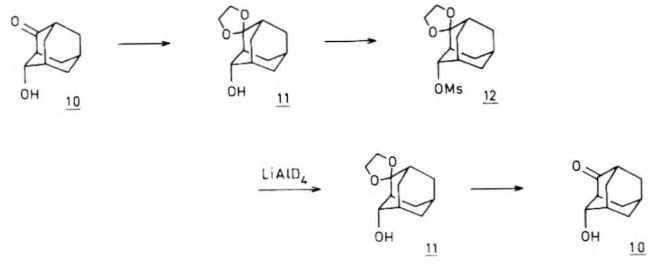
Scheme I. Synthesis of 4(e)-Deuterioadamantan-2-one (5)



Scheme II. Ring Opening of 6



Scheme III. Attempted Synthesis of 18



treated with methanesulfonyl chloride in dry pyridine to give the 4(a)-methylsulfonyloxyadamantan-2-one (**3**)[8] (Scheme I). Reduction of this ketone **3** with 5 equiv of lithium aluminum deuteride in dry ether furnished the alcohols **4** which were oxidized to the 4(e)-deuterioadamantan-2-one (**5**) (deuterium equatorial >95%). This percentage of equatorial deuterium was established by ^{1}H NMR analysis of the separated sets of axial and equatorial hydrogens, a separation which was induced through addition of Eu(fod)$_3$ in chloroform-*d*.[14]

To synthesize the epimeric 4(a)-deuterioadamantan-2-one (**18**) we first tried a route as described above via the 4(e)-methylsulfonyloxyadamantan-2-one (**6**). The reduction of this compound resulted in ring opening of the adamantane system[8] (as shown in Scheme II) giving the 3-hydroxydideuteriomethylbicyclo[3.3.1]non-6-ene **9**, among other products. To circumvent this ring opening we tried a route via the ethylene ketal of 4(e)-methylsulfonyloxyadamantan-2-one (**12**) (see Scheme III). Reduction of this ketal **12** with lithium aluminum deuteride almost exclusively attacks the sulfur atom giving the 4(e)-hydroxyadamantan-2-one (**10**), after hydrolysis of the ketal.

For the successful preparation of 4(a)-deuterioadamantan-2-one (**18**) we introduced deuterium at the equatorial

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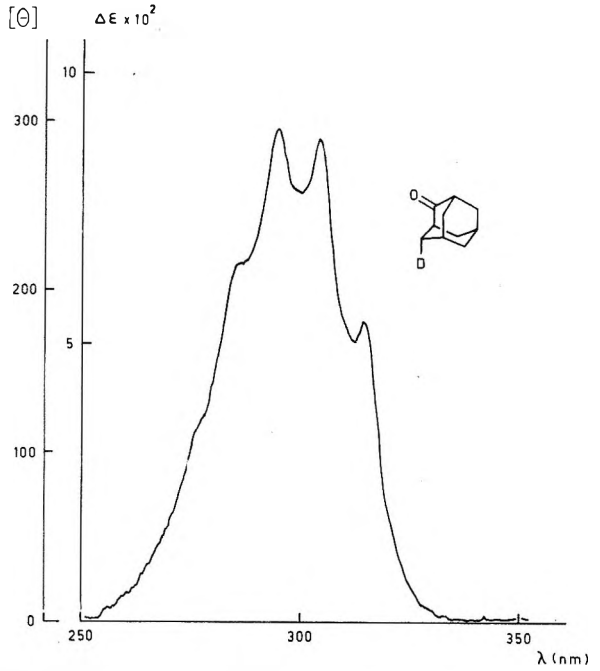
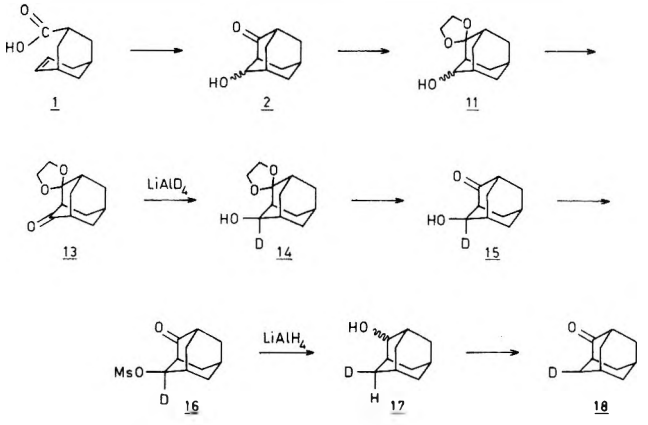
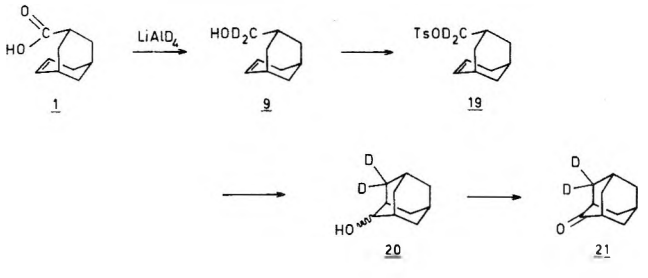


Figure 1. Circular dichroism spectrum of 4(e)-deuterioadamantan-2-one in isooctane (one scan).

Scheme IV. Synthesis of 4(a)-Deuterioadamantan-2-one (18)



Scheme V. Synthesis of 4,4-Dideuterioadamantan-2-one (21)



position in the 4(a)-hydroxyadamantan-2-one as shown in Scheme IV. The epimeric mixture of optically active 4-hydroxyadamantan-2-ones (**2** and **10**) was subsequently ketalized with ethylene glycol, oxidized with chromic acid, reduced with lithium aluminum deuteride, and hydrolyzed. The highly stereoselective formation of the axial epimer of **14** over the equatorial one (as determined from the integration of the peaks of both epimers of the 4-hydroxy-4-deuterioadamantan-2-ones, separated using HPLC) reflects steric control of the reducing agent by the ketal group.[8,15] The 4(a)-hydroxy-4(e)-deuterioadamantan-2-one (**15**) was now transformed to the 4(a)-deuterioadamantan-2-one (**18**) in exactly the same manner as described above for the 4(e)-deuterioadamantan-2-one (**5**) except that lithium aluminum hydride was used as reducing agent instead of the lithium aluminum deuteride. The percentage of axial deuterium was established as described above[14] (deuterium axial >95%).

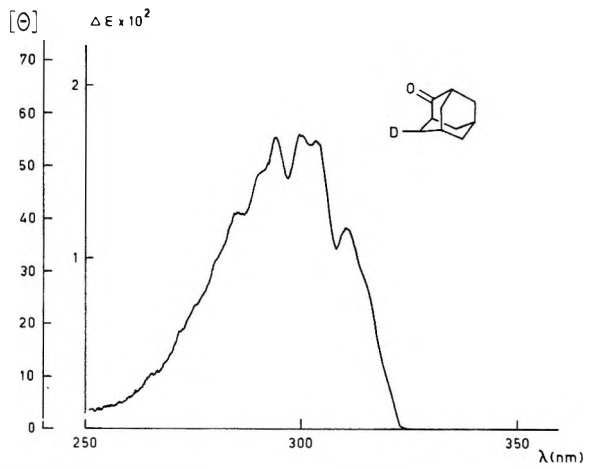


Figure 2. Circular dichroism spectrum of 4(a)-deuterioadamantan-2-one in isooctane (one scan).

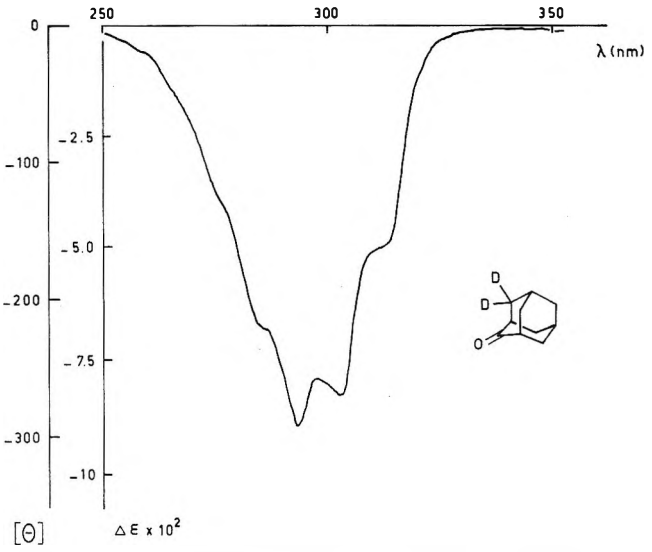


Figure 3. Circular dichroism spectrum of 4,4-dideuterioadamantan-2-one in isooctane (one scan).

The 4,4-dideuterioadamantan-2-one (**21**) was prepared as shown in Scheme V.[7] The unsaturated carbinol **9** was prepared by lithium aluminum deuteride reduction of the carboxylic acid **1**. Reaction of this alcohol **9** with *p*-toluenesulfonyl chloride in dry pyridine yielded the corresponding tosylate (**19**). In the solvolysis of this compound (**19**) two reactions occur:[16] a direct conversion to the desired alcohol **20**, and the formation of its tosylate via internal return. Hydrolysis of the latter in boiling 96% ethanol then furnished alcohol **20** in excellent yield. The 4,4-dideuterioadamantan-2-one (**21**) was obtained by oxidation with chromic acid in acetone.

Results

The absolute configuration of the *endo*-bicyclo[3.3.1]non-6-en-3-carboxylic acid (**1**), $[\alpha]_{578}$ +130.7°, could be assigned as (3*R*) on the basis of its transformation to the (1*S*)-4,4-dimethyladamantan-2-one.[7,13] The assignment (3*R*) for acid **1** correlated also with the absolute configurations that could be expected for the 4(a)- and 4(e)-hydroxyadamantan-2-ones (**2** and **10**). Through the known chemical correlations it is clear that the absolute configurations of all of the compounds discussed in this paper are now established. The molecules as

Table I. Rotations and Deuterium Content of 5, 18, and 21

Compd[b]	Specific rotation[a] at λ, nm 578	546	436	365	% deuterium
5 (0.39)	[+2.7°]	[+3.2°]	[+8.4°]	[+22.7°]	97
18 (0.48)		[+1.1°]	[+2.4°]	[+5.2°]	96
21 (0.53)	[−3.4°]	[−4.0°]	[−8.3°]	[−20.4°]	98

[a] Rotations are taken in isooctane. For the precision of the data see Discussion. Note solvent effect for **21**, $[\alpha]_{578}$ −2.8° (ethanol). [b] Concentration in parentheses.

drawn in this paper depict these absolute configurations (for nomenclature see Experimental Section).[17]

The 4(e)-deuterioadamantan-2-one (**5**) with an absolute configuration,[5] which can be described as (1*R*), showed a positive Cotton effect for the nπ^* transition. A positive Cotton effect is also observed for the (1*R*)-4(a)-deuterioadamantan-2-one (**18**) while the (1*S*)-4,4-dideuterioadamantan-2-one (**21**) showed a negative Cotton effect. Table I lists the rotations of **5**, **18**, and **21** at four different wavelengths together with the percentages of deuterium incorporated.

Since the optical purities of the starting material **1** and of the 4-hydroxyadamantan-2-ones (**2** and **10**) are known as 84 ± 3%, we assume that the optical purity of these deuterated adamantanones is in the order of 84% (see Discussion). To our knowledge direct determination of the optical purity of a ketone, which optical activity is solely due to deuterium substitution, has never been realized. Nevertheless we prepared the diastereomeric cylic thioketals of **21** using enantiomerically pure (*S*)-(+)-butane-2,3-thiol in order to test the limit of our recently developed ^{13}C method for enantiomeric excess determination.[18] No separation of signals was observed. Thus the enantiomeric excess of these ketones is based upon that of the percursors.

The CD data of the three deuterated adamantan-2-ones are depicted above. The n–π^* transition shows a surprisingly strong Cotton effect with $\Delta\epsilon$ of +0.090 at 295 nm in isooctane for the 4(e)-deuterioadamantan-2-one (**5**). The 4(a)-deuterioadamantan-2-one (**18**) exhibits a weaker Cotton effect with $\Delta\epsilon$ of +0.017 at 294 nm in isooctane, while the 4,4-dideuterioadamantan-2-one (**21**) gives a value of $\Delta\epsilon$ of −0.088 in the same solvent at the same wavelength.

Discussion

The CD data of the epimeric ketones **5** and **18** show that deuterium as perturber in the β equatorial position in a cyclohexanone system has much more influence on the nπ^* transition than deuterium in the β axial position has. This is generally observed for chiral perturbers β to the carbonyl chromophore in a cyclohexanone system.[19]

The CD spectrum of the 4(e)-deuterioadamantan-2-one (**5**) could be a composite of two superimposed spectra namely that of the 4(e)-deuterioadamantan-2-one (**5**) (>95%) and of its epimer **18** (<5%). An estimate of 1% of the magnitude of possible error introduced into the spectrum of **5** by the presence of 5% of the 4(a)-deuterioadamantan-2-one (**18**) can be made from the CD data knowing that the percentage axial deuterium is also >95%. For the 4(a)-deuterioadamantan-2-one (**18**), this error is in the order of 25%. In addition to the possible error given above, and the fact that deuterium is not 100% incorporated (see Table I), there remains the possibility of some optical fractionation of the intermediates and final products during purification.[20] For the dideuterio compound **21** optical fractionation and the fact that 98% deuterium is incorporated are possible errors.

An octant projection of **5** and **18** places deuterium in both compounds in the (−) back octant.[21] For each of the compounds a positive Cotton effect is observed for the nπ^* transition. For the 4,4-dideuterioadamantan-2-one (**21**) the two deuterium atoms are in the (+) back octant but **21** shows a negative Cotton effect in the CD spectrum.

We therefore conclude that deuterium behaves dissignate according to the nomenclature of Kirk and Klyne[22] (anti-octant in the old nomenclature). The reason for this behavior might be sought in the low refractivity of deuterium compared to that of hydrogen[23] and/or in the fact that the C–D bond length is shorter than the C–H bond length.[24]

Experimental Section

General. Melting points were determined on a Mettler FP_2 apparatus. Infrared spectra were recorded on a Unicam SP200 infrared spectrophotometer. ^1H-NMR spectra were recorded on a Varian A60 instrument or a Varian XL-100 using tetramethylsilane as an internal standard. Mass spectra (M) were obtained on a AEI MS 902 instrument; only the parent peak is given. Gas liquid chromatography was carried out on all compounds on a Varian aerograph 1400 apparatus showing no difference in retention times for the deuterated and analogous undeuterated compounds. Optical activity was measured on a Perkin-Elmer 241 polarimeter using 10-cm cells. Circular dichroism was measured on a Cary 60 apparatus in a 1-cm cell. Both measurements were done at room temperature (20–22 °C). High-pressure liquid chromatography was carried out on a Waters LC Model 6000 A and a Prep 500 apparatus.

(3*R*)-*endo*-Bicyclo[3.3.1]non-6-en-3-carboxylic Acid (1). The racemic compound was synthesized as described by Faulkner and McKervey.[8b] The racemic acid **1** (50 g) and (+)-dehydroabietylamine (86 g) were heated under reflux for 2 h in 1100 mL of 96% ethanol. The hot solution was cooled very slowly to room temperature. The salt, $[\alpha]_{578}$ +77.8° (c 0.5 96% ethanol), obtained after nine crystallizations, was decomposed with 10% hydrochloric acid and the *endo*-bicyclo[3.3.1]non-6-en-3-carboxylic acid was extracted into ether (3 × 75 mL). The combined ether layers were treated with 2 N aqueous sodium hydroxide and the alkaline layer was acidified with 2 N hydrochloric acid, extracted with ether (3 × 50 mL), dried, and evaporated giving the (+)-*endo*-bicyclo[3.3.1]non-6-en-3-carboxylic acid (**1**) as a white crystalline compound, $[\alpha]_{578}$ +130.7° (c 0.5, 96% ethanol). Spectral and physical data are identical with published values.[8a,b] To a solution of acid **1** (50 mg, $[\alpha]_{578}$ +115.9°, c 1.0 in 96% ethanol) in benzene oxylyl chloride (400 mg) was added. After stirring for 15 min the solvent and the excess of oxalyl chloride were evaporated. The acid chloride of **1** was then dissolved in ether and placed in an ice bath.

Adding optically pure (−)-α-phenylethylamine, $[\alpha]_D$ −39° (4 equiv), in ether gave a white precipitate. After being stirred for 1 h, the mixture was washed with 1 N hydrochloric acid, 10% aqueous sodium hydroxide, and water. The solution was dried and the solvent evaporated, giving a white solid (80 mg). This solid could be separated into diastereoisomers using HPLC, stainless steel column, i.d. 1/8 in., packed with Lichrosorb Si 60, 5 μ with hexane/methylene chloride as eluent.

The ratio of diastereomers was determined by integration of the peak areas (Spectra-Physics Autolab system I in line with HPLC) and found to be 8.85:1.15 (77%). Both peaks were separate and their identity was established by collecting and identifying the two amide fractions: IR (Nujol) 3400 (NH), 1640, 1540 (C=O); NMR ($CDCl_3$) δ 5.78 (5 H), 5–6 (3 H), 1.2–2.7 (14 H including doublet CH_3 at δ 1.37, J = 7 Hz); *m/e* 269.

(1*R*)-4(e)- and (1*R*)-4(a)-Hydroxyadamantan-2-one (10 and 2). A solution of (+)-*endo*-bicyclo[3.3.1]non-6-en-3-carboxylic acid (**1**) (1.39 g, $[\alpha]_{578}$ +125.6°, *c* 1.0, 96% EtOH), acetic anhydride (8 g), and distilled boron trifluoride etherate (2.4 g) in dry benzene (25 mL) was stirred at room temperature for 1 h. After cooling, cold water was added, the benzene was evaporated, and the solution was made alkaline with 10% aqueous sodium hydroxide. The mixture was heated to reflux for 1 h in order to hydrolyze the initially formed acetates. After cooling, the mixture was extracted with chloroform (4 × 50 mL) and the extract was washed with water and dried. Evaporation gave a white solid (1.1 g) of 4(e)- and 4(a)-hydroxyadamantan-2-one (**10** and **2**). The epimers were separated using a Waters Prep 500 apparatus, with a Preppak-500/silica cartridge at a flow rate of 250 mL/min. Elution with hexane–acetone (4:1) gave 4(e)-hydroxyadamantan-2-one (**10**) (yield 0.2 g (15%); $[\alpha]_{578}$ +5.0° (c 0.54, dioxane)) and 4(a)-hydroxyadamantan-2-one (**2**) (yield 0.9 g (69%); $[\alpha]_{578}$ −15.6° (c 0.48, dioxane)). All spectra data including the chiroptical properties were identical with the literature.[11,12]

(1*R*)-4(a)-Methylsulfonyloxyadamantan-2-one (3). 4(a)-

Methylsulfonyloxyadamantan-2-one (3) was synthesized from 2, $[\alpha]_{578}$ −15.6°, as described[8] ($[\alpha]_{578}$ −3.7° (c 0.45, dioxane)).

(1*R*)-4-Deuterioadamantan-2-deuterio-2-ol (4). A solution of 4(a)-methylsulfonyloxyadamantan-2-one (3) (0.24 g, $[\alpha]_{578}$ −3.8°, c 0.4, dioxane) in ether was added dropwise to a stirred slurry of lithium aluminum deuteride (0.4 g) in ether at 0 °C. After stirring at room temperature for 30 min, the suspension was heated under reflux for 1 h. The cooled suspension was treated with ice water and the aqueous layer was extracted with ether (3 × 25 mL). The combined ether layers were washed with water and dried. Evaporation gave a white solid (0.14 g). Crystallization from hexane at −40 °C gave the 4-deuterioadamantan-2-deuterio-2-ol (4): yield 0.12 g (78%); mp 257–260 °C; IR (Nujol) 3300 (OH), 2100, 2140 cm^{-1} (CD); NMR ($CDCl_3$) no signal at δ 3.85; *m/e* 154.

(1*R*)-4(e)-Deuterioadamantan-2-one (5). 4-Deuterioadamantan-2-deuterio-2-ol (4) (0.10 g) in acetone (20 mL) was treated with Jones reagent[25] with stirring until the first permanent red color appeared. Propan-2-ol was added to remove the excess of Jones reagent. After evaporation of acetone, water was added. Successively extraction with ether (3 × 25 mL), drying, and evaporation gave a white solid. Purification was done using HPLC on a 30-cm stainless steel column, o.d. ¼ in. packed with Lichrosorb Si 60, 5μ with hexane/CH_2Cl_2, 1:1 as eluent. Sublimation at 120 °C (20 mm) afforded the 4(e)-deuterioadamantan-2-one (5): yield 0.06 g (60%); $[\alpha]_{578}$ +2.7° (c 0.37, isooctane); mp 254–256 °C; IR (Nujol) 1720 (C=O), 2320, 2160 cm^{-2} (CD); NMR ($CDCl_3$) δ 2.65–2.45 (2 H), 2.30–1.70 (12 H); *m/e* 151.

Determination of the Percentage of Axial and Equatorial Deuterium. To the 4-deuterioadamantan-2-ones in deuteriochloroform a solution of tris(6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanedionato)europium (3 g in 3 mL of $CDCl_3$) was added until complete separation of the signals for the unequivalent protons of the adamantanone system was obtained in the ^1H NMR spectrum. The percentage of axial and equatorial deuterium β to the carbonyl could be determined from the integration of the peak areas of these protons. The experimental data for the integration of the peak areas of the protons α and β axial, β equatorial, γ, and δ to the carbonyl were respectively for compound 5 46-93-73-47-47 and for compound 18 41-65-85-41-42 (arbitrary units).

These data and the percentages of deuterium incorporated in both compounds (see Table I) allow a reliable estimate of >95% equatorial deuterium for 5 and >95% axial deuterium for 18 to be made.

(1*S*)-4,4-Ethylendioxoadamantan-2-one (13). A solution of 2 and 10 (1.1 g) prepared as described above and ethylene glycol (2 g) in anhydrous benzene containing 10 mg of *p*-toluenesulfonic acid was heated for 16 h using a Dean-Stark water separator. Ether was added and the mixture was extracted with aqueous sodium hydrogencarbonate and water. After drying the etheral extract and evaporating the solvent, the residue was treated with Jones reagent[25] as described above for 5. The 4,4-ethylendioxoadamantan-2-one (13) was chromatographed over alumina (Merck, Aluminum oxide 90 active, neutral). Elution with hexane/ether 3:1 gave a colorless oil: yield 0.81 g (66%); $[\alpha]_{578}$ −9.2° (c 0.55, hexane); IR (liquid) 1710, 1730 (C=O), 1110 cm^{-1} (COC); NMR ($CDCl_3$) δ 3.97 (4 H), 2.65–2.40 (2 H), 2.4–1.7 (10 H); *m/e* 208. Anal. Calcd for $C_{12}H_{16}O_3$: C, 69.21; H, 7.74. Found: C, 69.04; H, 7.84.

(1*R*)-4(a)-Hydroxy-4(e)-deuterioadamantan-2-one (15). A solution of 4,4-ethylendioxoadamantan-2-one (13) (0.62 g) ($[\alpha]_{578}$ −9.2°, c 0.55, hexane) in anhydrous ether (20 mL) was added dropwise to a slurry of lithium aluminum deuteride (0.7 g) in anhydrous ether (25 mL). After stirring under reflux for 30 min the cooled mixture was treated as described for 4. Hydrolysis of the acetal could be achieved through boiling the acetal alcohol 14 (0.61 g) in 10% aqueous acetone with a few drops of concentrated hydrochloric acid. After evaporation of the acetone, water was added and the aqueous layer was extracted with chloroform (3 × 30 mL). The combined chloroform layers were washed with saturated sodium hydrogencarbonate and dried. Evaporation gave the 4(a)-hydroxy-4(e)-deuterioadamantan-2-one (0.38 g). After chromatography under the same conditions as for 2 pure 15 could be obtained: yield 0.32 g (57%); $[\alpha]_{578}$ −10.8° (c 0.32 dioxane); mp 214–218 °C; IR (Nujol) 3460 (OH), 2050, 2120 cm^{-1} (CD); NMR ($CDCl_3$) no signal at δ 4.25; *m/e* 167.

(1*R*)-4(a)-Methylsulfonyloxy-4(e)-deuterioadamantan-2-one (16). Starting with 4(a)-hydroxy-4(e)-deuterioadamantan-2-one (15) prepared above 4(a)-methylsulfonyloxy-4(e)-deuterioadamantan-2-one (16) was synthesized according to the procedure described by Faulkner and McKervey.[8b] The *dl* ketone melted at 109–111 °C; we found for 16: mp 88–89 °C; $[\alpha]_{578}$ −1.6° (c 0.32, dioxane); NMR ($CDCl_3$) no signal at δ 5.22; *m/e* 245.

(1*R*)-4-Deuterioadamantan-2-ol (17). A solution of 4(e)-deuterio-4(a)-methylsulfonyloxyadamantan-2-one (16) (0.15 g, $[\alpha]_{578}$ −1.6°, c 0.32, dioxane) was treated with lithium aluminum hydride (0.13 g) exactly as described for 4. Crystallization from hexane at −40 °C afforded the 4-deuterioadamantan-2-ol (17): yield 0.08 g (85%); IR (KBr disk) 3280 (OH), 2100, 2200 cm^{-1} (CD); NMR ($CDCl_3$) signal at δ 3.85 (HCOH); *m/e* 153.

(1*R*)-4(a)-Deuterioadamantan-2-one (18). 4-Deuterioadamantan-2-ol (17) (0.08 g) was treated with Jones reagent as described above for the (1*S*)-4(e)-deuterioadamantan-2-one (5). Purification by HPLC and sublimation afforded the 4(a)-deuterioadamantan-2-one (18) (same conditions as for 5): yield 0.05 g (63%); mp 250–253 °C; $[\alpha]_{546}$ +1.2 ± 0.4° (c 0.48, isooctane); IR (KBr disk) 1725 (C=O), 2100, 2180 cm^{-1} (CD); NMR ($CDCl_3$) δ 2.65–2.45 (2 H), 2.30–1.70 (11 H); *m/e* 151.

(3*R*)-3-Hydroxydideuteriomethylbicyclo[3.3.1]non-6-ene (9). A solution of *endo*-bicyclo[3.3.1]non-6-en-3-carboxylic acid (1) (1.9 g, $[\alpha]_{578}$ +126.4°, c 0.5, 96% ethanol) in ether (100 mL) was added dropwise to a stirred slurry of lithium aluminum deuteride (3.8 g) in ether (20 mL). The mixture was then heated under reflux for 2 h. After treatment of the cooled extract with water, the aqueous layer was extracted with ether (4 × 50 mL). The combined ether layers were washed with water and dried. Evaporation gave 1.64 g of a yellow oil. After short-path distillation at 170 °C (20 mm) the 3-hydroxydideuteriomethylbicyclo[3.3.1]non-6-ene (9) was obtained as a colorless oil: yield 1.52 g (87%); $[\alpha]_{578}$ +185.5° (c 1.0, 96% ethanol); IR (liquid) 3400 (OH), 1645 (C=C), 2100, 2200 cm^{-1} (CD); NMR ($CDCl_3$) δ 5.5–6.0 (2 H, vinyl protons), 1.3–2.5 (11 H), no doublet at δ 3.57; *m/e* 154. Anal. Calcd for $C_{10}H_{14}D_2O$: C, 77.86; H, 9.15; D, 2.61. Found: C, 77.12; H, 9.13; D, 2.60.

(1*S*)-4,4-Dideuterioadamantan-2-ol (20). 9 (1.28 g) was added to a stirred solution of *p*-toluenesulfonyl chloride (1.58 g) in dry pyridine (100 mL) at 0 °C. The mixture was kept at 8 °C for 48 h and then was poured into cold water and extracted with ether (3 × 50 mL). The extract was washed successively with 10% hydrochloric acid, saturated aqueous sodium hydrogencarbonate, and water and dried. Evaporation gave an oil (19) which was immediately dissolved in 96% ethanol (100 mL) and heated under reflux overnight. After evaporation of the solvent water was added and extraction with ether (3 × 50 mL) gave (after drying and evaporation) a white compound. Crystallization from hexane gave 4,4-dideuteroadamantan-2-ol (20): yield 0.74 g (59%); $[\alpha]_{578}$ +0.7° (c 2.0, 96% ethanol); mp 258–260 °C; IR (KBr disk) 3250 (OH), 2205, 2100 cm^{-1} (CD); *m/e* 154. Anal. Calcd for $C_{10}H_{14}D_2O$: C, 77.86; H, 9.15; D, 2.62. Found: C, 77.75; H, 9.18; D, 2.62.

(1*S*)-4,4-Dideuterioadamantan-2-one (21). 4,4-Dideuterioadamantan-2-ol (20) (0.55 g) in acetone (25 mL) was treated with Jones reagent[25] exactly as described above for (+)-4(e)-deuterioadamantan-2-one (5). Purification through sublimation afforded the (−)-4,4-dideuterioadamantan-2-one (21): yield 0.52 g (94%); $[\alpha]_{578}$ −2.8° (c 1.0, 96% ethanol); mp 251–253 °C; IR (KBr disk) 1720 (C=O), 2100, 2200 cm^{-1} (CD); NMR ($CDCl_3$) δ 2.65–2.45 (2 H), 2.30–1.70 (10 H); *m/e* 152. Anal. Calcd for $C_{10}H_{12}D_2O$: C, 78.90; H, 7.95; D, 2.65. Found: C, 79.08; H; 8.06; D, 2.65.

Registry No.—(+)-1, 64889-20-9; (3*R*)-1, 64937-51-5; (3*R*)-1 dehydroabietylamine salt, 64998-10-3; (3*R*)-1 acid chloride, 64937-52-6; (3*R*)-1 (−)α-phenylethylamide derivative, 65404-82-2; (3*S*)-1 (−)-α-phenylethylamide derivative, 65450-99-9; (1*R*)-2, 27863-77-0; (1*R*)-3, 65437-67-4; (1*R*)-4 isomer 1, 65404-83-3; (1*R*)-4 isomer 2, 65437-69-6; (1*R*)-5, 65437-68-5; (3*R*)-9, 65404-84-4; (1*R*)-10, 27863-78-1; (1*S*)-13, 65404-85-5; 14, 65404-86-6; (1*R*)-15, 65404-87-7; (1*R*)-16, 65404-88-8; 17, 65404-89-9; (1*R*)-18, 65404-90-2; 19, 65404-91-3; 20, 65404-92-4; (1*S*)-21, 65494-21-5; (+)-dehydroabietylamine, 1446-61-3; (−)-2-phenylethylamine, 2627-86-3.

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(5) After this work had been completed and during the preparation of this manuscript D. A. Lightner, T. C. Chang, and J. Horwitz, *Tetrahedron Lett.*, 3019 (1977), reported the synthesis by the old laborious route[11] of the chiral 4(e)-deuterioadamantan-2-one. In a short communication we previously announced the preparation of the dideuterio compound **21**.[7] Although the spectral data Lightner reports for the chiral 4(e)-deuterioadamantan-2-one agrees well with our data,[20] we suggest that the assignment of the absolute

configuration as reported by Lightner is in error. Thus the molecule as represented by Lightner in his figure has the configuration (1*R*) and not (1*S*) as stated in the text.
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Kinetics and Mechanisms of the Thermal Decomposition of Triphenyl-1,2-dioxetane

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Triphenyl-1,2-dioxethane (**1**) was prepared and the kinetics of thermolysis in benzene and methanol were studied in order to more clearly define stepwise vs. concerted reaction paths in dioxethane decompositions. Activation parameters in benzene are E_a = 23.3 ± 0.3 kcal/mol, log A = 12.04 ± 0.19, $\Delta H^{\ddagger}$ = 22.6 ± .3 kcal/mol, $\Delta S^{\ddagger}$ = −5.6 ± 0.9 eu, and in methanol E_a = 23.3 ± 0.5 kcal/mol, log A = 12.07 ± 0.34, $\Delta H^{\ddagger}$ = 22.6 ± 0.5 kcal/mol, $\Delta S^{\ddagger}$ = −5.5 ± 1.5 eu. Activation parameters were calculated for **1**, based on stepwise O–O and C–C initiated bond ruptures of the dioxetane ring. The calculated values for the O–O process are E_a = 25.1 kcal/mol, log A = 12.8, $\Delta H^{\ddagger}$ = 24.4 kcal/mol, $\Delta S^{\ddagger}$ = −1.86 eu, and for the C–C process E_a = 35.2 kcal/mol, log A = 13.9, $\Delta H^{\ddagger}$ = 34.5 kcal/mol, $\Delta S^{\ddagger}$ = +3.2 eu. Considering the experimental activation parameters for **1** in comparison to calculated activation parameters, based on the O–O stepwise process and in comparison to experimental activation parameters for other dioxetanes, the O–O stepwise process appears most reasonable for **1**. The lack of any significant solvent effect in proceeding from benzene to methanol is also consistent with a stepwise thermolysis of **1**.

The formation of excited state molecules in the thermolysis of dioxetanes has attracted the interest of chemists in recent years.[1] Two mechanisms have been suggested for the thermolysis of these four-ring peroxides, namely, a concerted mechanism and a stepwise process initiated with peroxide bond rupture. These two mechanisms may represent the two ends of a mechanistic sequence, where the stepwise process merges into the concerted mode as the lifetimes of the stepwise biradical species decrease.

Of the simply substituted dioxetanes that we have studied to date, it appears that the kinetic data could be most readily accommodated by a stepwise thermolysis mechanism.[2] For example, observed experimental activation parameters are in good agreement with those calculated based on a stepwise process. The progressive replacement of methyl groups by up to two phenyl groups caused little or no change in the activation parameters. In addition, the predominance of triplet excited state carbonyl products relative to excited state singlets can be explained in a conventional manner without violating spin conservation.[2b]

These data suggest that we have been viewing dioxetanes that undergo decomposition at the stepwise end of the mechanistic spectrum. Dioxetanes of this type, with simple alkyl substitution or with up to two phenyl substituents, produce predominantly triplets in low to moderate efficiency.[2d] We are now interested to proceed toward the concerted end of this potential mechanistic spectrum. Some of the questions that arise in this survey are: (i) what type of substitution on the dioxetane ring is required to promote a concerted process; (ii) how large a change in activation parameters will be observed over the entire stepwise to concerted reaction spectrum; (iii) and how will efficiencies and electronic states of the carbonyl products vary over the mechanistic spectrum?

One of our approaches in an attempt to proceed to the concerted end of the mechanistic spectrum is to progressively place phenyl substituents on the dioxetane ring.[2] We now report our kinetic results with the most highly phenyl substituted dioxetane prepared to date, i.e., triphenyl-1,2-dioxetane. Kinetic studies were made in benzene and methanol solvent. The latter solvent was used to provide the most favorable conditions for a concerted process.[2a]

Results

Triphenyl-1,2-dioxetane (**1**) was prepared by standard procedures from triphenylethylene. Numerous attempts were made to purify **1** by recrystallization and chromatography. Occasionally, **1** would partially survive silica gel column

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Table I. First-Order Dependence in Triphenyl-1,2-dioxetane and the Effect of Triphenylethylene on the Rate[a]

10^4[1], M	Added $[(C_6H_5)_2C{=}CHC_6H_5]$, M	$10^4\,k$,[b] s^{-1}
1.60	0	5.60 ± 0.03
16.0	0	5.30 ± 0.02
1.60	1.20×10^{-2}	5.60 ± 0.05

[a] In benzene at 59.90 °C with 5.40×10^{-4} M DBA. [b] By least squares with standard error.

Table II. Effect of Temperature on the Rate of Decomposition of Triphenyl-1,2-dioxetane (1) in Benzene[a,b]

Temp, °C	$10^4\,k$,[c] s^{-1}	Temp, °C	$10^4\,k$,[c] s^{-1}
40.10	0.550 ± 0.004	59.90	5.58 ± 0.02
50.05	1.88 ± 0.07	59.90	5.65 ± 0.03
50.30	2.08 ± 0.03	70.00	14.4 ± 0.1
59.82	5.35 ± 0.11	70.00	14.5 ± 0.1
59.90	5.28 ± 0.03	77.85	33.7 ± 0.5
59.90	5.30 ± 0.05	77.90	32.7 ± 0.5

[a] [1] = 4.20×10^{-5} M. [b] Rates determined by following the decay of emission from DPA, with [DPA] = 5.40×10^{-4} M. All measurements were made with aerated solutions. [c] Rate coefficients were obtained by a least-squares fit and they are reported with standard error within a given measurement. The values were determined with a Hewlett-Packard 65 calculator, using Stat-Pac 1-22A.

chromatography. On most occasions, decomposition of 1 would occur on the column, even though the column was treated with EDTA and operated at low temperatures.[3] No significant improvement in purity was found with our attempts to recrystallize **1**. Due to these problems, we were usually forced to use samples of 1 for kinetic studies without chromatographic purification. However, similar rate coefficients were obtained from samples that were purified by chromatography or unpurified. Purified samples were employed for the product studies. By GLC analysis it appears that the major impurity in samples of 1 was triphenylethylene. For example, a sample with 7.40×10^{-3} M 1 contained 5.39×10^{-3} M of this olefin. Similar attempts to purify the bromohydroperoxide precursor to 1 met with failure. In fact, the bromohydroperoxide appeared even more susceptible to decomposition on the silica gel column than did **1**.

The only products that were identified from the thermolysis of 1 were benzaldehyde and benzophenone. With an initial dioxetane concentration of 7.40×10^{-3} M in benzene–carbon tetrachloride (3:1), thermolysis at 45 °C to completion gave apparent yields of benzaldehyde and benzophenone by GLC of 110 and 111%, respectively. Apparently, some decomposition of 1 occurred prior to the thermolysis, which was undetected, and gave yields in excess of 100%.

Kinetic Data. Rates of decomposition of **1** were measured by monitoring light emission from added 9,10-diphenylanthracene (DPA) or 9,10-dibromoanthracene (DBA). Good first-order plots were obtained and the first-order rates were confirmed by varying the initial concentration of 1 by tenfold (cf., Table I). In addition, it was shown that the major contaminant in the sample of **1**, i.e., triphenylethylene, did not alter the rate when this olefin was added at 1.20×10^{-2} M (cf., Table I). Activation parameters were determined from the kinetic data presented in Table II for thermolysis in benzene solvent. Similar rate data as a function of temperature for the thermolysis of 1 in methanol containing EDTA are given in Table III. The activation parameters, which result from the data of Tables II and III, are given in Table IV.

Table III. Effect of Temperature on the Rate of Decomposition of Triphenyl-1,2-dioxetane (1) in Methanol Containing EDTA[a]

Temp, °C	$10^4\,k$,[b] s^{-1}	Temp, °C	$10^4\,k$,[b] s^{-1}
37.08	0.487 ± 0.009	55.10	3.56 ± 0.03
37.08	0.511 ± 0.003	55.01	3.59 ± 0.06
45.10	1.09 ± 0.007	59.98	7.20 ± 0.10
50.20	2.19 ± 0.02	59.95	6.60 ± 0.11
50.20	2.31 ± 0.02	59.87	6.42 ± 0.07
52.99	2.60 ± 0.02	62.42	7.95 ± 0.05
52.99	2.77 ± 0.02	62.42	8.42 ± 0.20

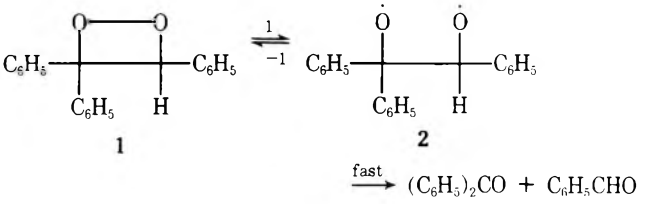
[a] [1] = 6.14×10^{-4} M, [DPA] = 4.70×10^{-4} M (45–62 °C) and 1.25×10^{-3} M (37 °C). All measurements were made with aerated solutions. [b] Least-squares fit with standard error.

Table IV. Experimental Activation Parameters for the Thermolysis of Triphenyl-1,2-dioxetane (1) in Benzene and in Methanol[a]

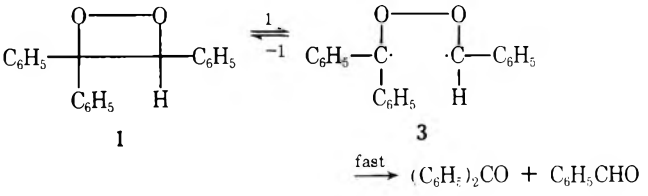
Solvent	E_a[b]	log A	$\Delta H^{\ddagger}$[b,c]	$\Delta S^{\ddagger}$[d]
Benzene	23.3 ± 0.3	12.04 ± 0.19	22.6 ± 0.3	−5.6 ± 0.9
MeOH	23.3 ± 0.5	12.07 ± 0.34	22.6 ± 0.5	−5.5 ± 1.6

[a] Activation parameters are obtained by a least-squares fit and they are given with standard error. [b] kcal/mol. [c] At 60 °C. [d] eu.

Scheme I



Scheme II



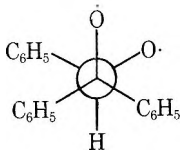
Calculation of Activation Parameters. Previously we showed that activation parameters for the thermolysis of dioxetanes could be well estimated by use of the hypothetical two-step O–O bond initiation process shown in Scheme I for 1.[2] Although this simple scheme can be used to estimate the activation parameters, a more detailed mechanism which involved singlet and triplet biradicals was required to explain the known photoemission or stimulated emission properties of dioxetane thermolyses.[2b] However, in both this extended biradical mechanism and the simple two-step scheme, the rate-determining step is O–O bond homolysis. Thus, Scheme I is an adequate model from which to calculate activation parameters.

In addition to calculating activation parameters based on Scheme I, it was necessary to consider the thermolysis of 1 proceeding by a C–C initiated homolysis process as shown in Scheme II. The necessity for considering Scheme II is due to the resonance stabilized biradical **3**, which when reflected to the transition state in the first step could sufficiently alter the activation parameters to make them competitive with Scheme I.

Activation energies based on Schemes I and II are calculated from eq 1.[4] The value of $\Delta H^{\circ}_{1,-1}$ in eq 1 is determined

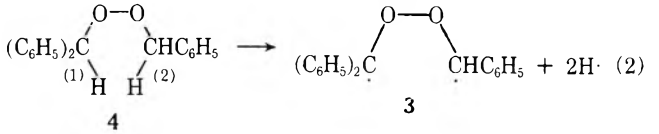
$$E_a = \Delta H^\circ_{1,-1} + E_{-1} \quad (1)$$

by the difference of heats of formation between the product and reactant. The heats of formation may be estimated by group additivity methods[4] or by a combination of the latter method and bond dissociation energies. Some group, gauche, and cis contributions that are required to estimate ΔH_f° for **1, 2,** and **3** are not reported. For example, corrections were made to reported group contributions where bonding was to aliphatic carbon (C), whereas bonding was required to benzene carbon (C_B). These corrections were made by noting comparable changes from replacing C_B with C in reported groups and the corrections are usually small. A satisfactory method for estimating gauche interactions, based on using one-half cyclohexane *A* values, was previously reported and is used here.[2b] With **2** in its most stable conformation as shown below,



2

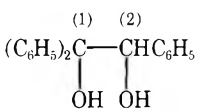
there are the following gauche corrections along with their estimates: [gauche O,O] = 0.35 kcal/mol, 2 [gauche Ph,O] = 2 × 1.55 = 3.1 kcal/mol, and [gauche Ph,Ph] = 1 .55 kcal/mol.[5] The first two gauche interactions were estimated as one-half the cyclohexane *A* value for hydroxy and for phenyl, respectively. The [gauche Ph,Ph] interaction was also estimated as one-half the phenyl *A* value. This may somewhat underestimate this interaction, but it appears to be the best estimate that can be made. The cis O,O interaction in **1** was estimated as before by using one-half of the phenyl *A* value.[2b] The previously employed strain energy of 25 kcal/mol for dioxetanes was used here.[2b] Due to the lack of appropriate group additivity values, a combination of bond dissociation energy and group additivity methods were employed to estimated ΔH_f° for the carbon biradical **3.**[7] Briefly, the method was based on eq 2, where ΔH_f° of **4** was calculated by the group additivity



4 **3** (2)

method, ΔH_f° for the hydrogen atom was obtained from tables,[4] and the heat of reaction ($\Delta H_r^\circ{}_{4,3}$) was obtained as the sum of the estimated bond dissociation energies. From these values, ΔH_f° of **3** was calculated ($\Delta H_f^\circ{}_3 = \Delta H_r^\circ{}_{4,3} + \Delta H_f^\circ{}_4 - 2\Delta H_f^\circ{}_H$). The C_2–H bond dissociation energy was estimated as $D_{C_2\text{-}H} = D_{(CH_3)_2CH\text{-}H} + E_{Ph}$resonance + $E_{\alpha\text{-}O}$resonance, where $D_{(CH_3)_2CH\text{-}H}$ = 95 kcal/mol,[4] E_{Ph}resonance is the benzyl resonance energy (−10 kcal/mol),[8] and $E_{\alpha\text{-}O}$resonance is the resonance energy of an α-oxy radical (−1.3 kcal/mol).[10] The C_1–H bond dissociation energy was estimated as $D_{C_1\text{-}H} = D_{(CH_3)_3C\text{-}H} + E_{Ph_2}$resonance + $E_{\alpha\text{-}O}$resonance, where $D_{(CH_3)_3C\text{-}H}$ = 92 kcal/mol. Unfortunately, we were unable to find reliable data to estimate E_{Ph_2}resonance. This value is taken as an average of the benzyl (−10 kcal/mol)[8] and trityl (−14.2 kcal/mol)[11] resonance energies on a per phenyl group ([−10 + (−14.2/3)]/2 = −7.4 kcal/mol) basis. Thus, E_{Ph_2}resonance is estimated to be −14.8 kcal/mol (=2 × (−7.4)).

Activation entropies and *A* factors for initial (O–O) bond rupture (Scheme I) and for intital (C–C) bond rupture (Scheme II) are estimated as follows. Intrinsic entropies of **1, 4,** and **5** are obtained directly from group additivity values, equating C_B carbons to ordinary C carbons, and using an S° ring correction of 26.0 eu/mol for the dioxetane.[4] The entropy losses in proceeding from the acyclic peroxide **4** to the carbon



5

biradical **3** and from **5** to the oxy biradical **2** are then estimated. Comprising $\Delta S^\circ{}_{4\to3}$ is the entropy loss due to the six vibrational motions of the two hydrogen atoms removed in going from **4** to **3** (mainly two HCO bends), and the entropy losses produced when the sixfold (therefore low rotational barrier) internal rotations of the three phenyl groups in **4** are restricted to torsional or highly hindered rotational motions (due to the development of radical resonance stabilizations) in **3.** Rotational barriers of the phenyl groups in **4** and **3** are estimated to be 1.5 (C-1), 1.5 (C-1), and 1.0 (C-2) kcal/mol and 13.0 (C-1), 5.0 (C-1), and 13.0 (C-2) kcal/mol, respectively. Treating the latter restricted rotors as torsions, the corresponding frequencies can be calculated to be 59, 37, and 59 cm^{-1}, respectively.[13] Therefore, $\Delta S^\circ{}_{4\to3} = -2S^\circ(\text{Ph}\to\infty)_{V_0}$ = 1.5 kcal − $S^\circ(\text{Ph}\to\infty)_{V_0}$ = 1.0 $kcal^{-2}(HCO)_{1150cm^{-1}} + 2S$(59 cm^{-1} torsion) + S(37 cm^{-1} torsion) = −2(8.3) − 8.6 − (0.1) + 2(4.5) + 5.5 = −10.8 eu/mol. The back activation entropy for ring closure of **3** to **1** ($\Delta S^\ddagger_{-1}$) is equated to minus the entropy of the internal rotation about the O–O bond in **3.** This is the reaction coordinate for the (−1) reaction in

$$4 \underset{-1}{\overset{1}{\rightleftharpoons}} 3$$

An estimated reduced moment of about 335 amu Å^2 for this internal rotation gives a free rotor partition function of Q_f = 114 and a free rotor entropy of about 10.4 eu/mol.[14] Setting the rotational barrier at $V_0 \simeq$ 9.5 kcal, a hindered internal rotation entropy of about 7.5 eu/mol is calculated, and thus, $\Delta S^\ddagger_{-1} \simeq -7.5$ eu/mol. For Scheme II, one obtains $S^{\circ\ddagger} = [S^\circ{}_4 + \Delta S^\circ{}_{4\to3} + \Delta S^\ddagger_{-1}]_{intrinsic} + R \ln(\eta^\ddagger/\sigma^\ddagger) = [167.6 - 10.8 - 7.5] + R \ln(2/1) = 150.6$ eu/mol. Also one obtains $S^\circ{}_1 = S^\circ{}_1$(intrinsic) + $R \ln(\eta/\sigma) = 150.2 + R \ln[2/(2)^3] = 147.4$ eu/mol and thus for Scheme II, $\Delta S^\ddagger = (S^{\circ\ddagger} - S^\circ{}_1) = 3.2$ eu/mol or $A_{est} = (ekT/h)e^{\Delta S^\ddagger/R} = 7.9 \times 10^{13}/s^{-1}$.

The transition state entropy of Scheme I is similarly obtained by the difference method, starting from the entropy of **5.** Removal of the two hydrogen atoms to produce the oxy biradical (2) involves the entropy loss of the hydrogen atom vibrations (again, essentially just the entropy associated with two HOC bends of 1150 cm^{-1} each) and the entropy loss associated with the two hydroxy group internal rotations. For rotational barriers of about 1.0 kcal, the entropy change $\Delta S^\circ{}_{5\to2} \simeq -2S^\circ(HOC)_{1150cm^{-1}} - 2S^\circ(\text{HO}\to\infty)_{V_0} = 1.0 = -0.1 - 2(4.6 - 0.2) = -8.9$ eu/mol. The intrinsic entropy of **2** is therefore, $S^\circ{}_2 = S^\circ{}_5 + \Delta S^\circ{}_{5\to2} = 163.6 - 8.9 = 154.7$ eu/mol. The activation entropy for ring closure of the oxy biradical **2** to **1,** $\Delta S^\ddagger_{-1}$, of Scheme I is equated to minus the entropy of internal rotation about the C–C bond. For this reaction coordinate internal rotation, a reduced moment of inertia of about 125 amu Å^2 is estimated, which gives a free rotor entropy of 9.4 eu and a hindered rotor entropy of 6.4 eu for a potential barrier of 10.8 kcal/mol. The pertinent entropies for Scheme I are than estimated as: $S^{\circ\ddagger} = [S^\circ{}_2 + \Delta S^{\circ\ddagger}{}_{-1}]_{intrinsic} + R \ln(\eta^\ddagger/\sigma^\ddagger) = [154.7 - 6.4] + R \ln(2/(2)^3) = 145.5$ eu/mol and $\Delta S^\ddagger = S^{\circ\ddagger} - S^\circ{}_1 = (145.5 - 147.4) = -1.86$ eu/mol or $A_{est} = (ekT/h)e^{\Delta S^\ddagger/R} = 6.2 \times 10^{12}\ s^{-1}$.

The pertinent data that were used to calculate the activation parameters for the processes given in Schemes I and II are given in Table V. From these data, $\Delta H^\circ{}_{1,-1}$ and the activation parameters for Schemes I and II are given in Table VI. The E_{-1} values of 8.5[2b] and 6.7[15] kcal/mol are those that have been used previously for dioxetanes and cyclobutanes.

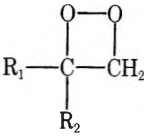
Table V. Thermochemical Parameters for Triphenyl-1,2-dioxetane, Biradicals 2 and 3, and Related Species

Species	Registry no.	$\Delta H_f°$, kcal/mol	$S°_{intrinsic}$, eu	$S°$,[a] eu
1	65293-77-8	75.68	150.2	147.4
2	65354-53-2	92.27	154.7	151.9
3	65354-54-3	104.2	156.8	155.4
4	55504-20-6	48.8	167.6	163.4
5	464-72-2		163.6	160.8

[a] $\sigma_1 = 2^3$, $n_1 = 2$; $\sigma_2 = 2^3$, $n_2 = 2$; $\sigma_3 = 2$ (the three phenyl group rotors have been treated here as vibrations), $n_3 = 1$; $S°_{real} = S°_{intrinsic} + R \ln (n/\sigma)$.

Discussion

Activation parameters for thermolysis of triphenyl-1.2-dioxetane (1) in benzene (E_a = 23.3 kcal/mol, log A = 12.04, $\Delta S^{\ddagger}$ = −5.6 eu) are similar to those that we have found for dioxetanes **6a–d** in aprotic nonpolar solvents.[2bc] In the series **6a–d,** the experimental E_a values range from 22.7 to 24.3 kcal/mol with log A (and $\Delta S^{\ddagger}$) ranging from 12.10 (−5.3 eu) to 12.83 (−2.0 eu). A comparison of experimental activation parameters in series **6a–d** with 1 suggests a common mecha-



6a, $R_1 = R_2 = CH_3$
b, $R_1 = CH_3$; $R_2 = C_6H_5$
c, $R_1 = R_2 = C_6H_5$
d, $R_1 = R_2 = C_6H_5CH_2$

nism, where substituent effects have little influence. Since phenyl substitution is expected to stabilize a developing π-carbonyl bond in a concerted process, the comparison of experimental activation parameters strongly suggests a stepwise decomposition.[2] The stepwise route, which was previously suggested to explain the kinetic data and the preponderance of triplet excited state carbonyl products (T_1) relative to S_1 products, is given in Scheme III.[2b]

Further confirmation of the dioxetane thermolysis mechanism can be made by comparison of experimental and calculated activation parameters, where the latter are based on a stepwise process. Two separate processes were considered, as outlined in Schemes I and II. These two processes, which involve O–O and C–C initiated bond breaking, bracket the concerted process, where a lower activation energy is expected than for either stepwise mode.[2]

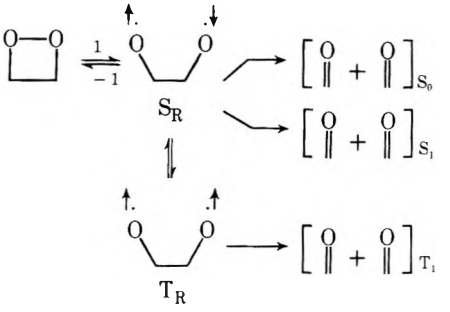
Calculated activation parameters for dioxetanes **6a–d,** based on an O–O initiated stepwise model, were in good agreement with experimental values.[2] A small increase in calculated E_a values was found with increasing steric effects.[16] For example, the calculated activation energy increased by 3.2 kcal/mol in preceding from 1,2-dioxetane to tetramethyl-1,2-dioxetane. This is qualitatively supported by the available experimental activation energies. Thus, 3,3-dimethyl-1,2-dioxetane (**6a**) and tetramethyl-1.2-dioxetane are reported to have E_a values of 23.0[2c] and 25.7–27.6[1d,17] kcal/mol, respectively. In proceeding from 3,3-diphenyl-1,2-dioxetane (**6b**) to triphenyl-1,2-dioxetane (1), an increase in E_a is expected due to steric effects. In terms of calculated E_a values for the O–O initiated process, this is noticed where the calculated values for **6b** and 1 are 22.9[2b] and 25.1 kcal/mol, respectively. In benzene solvent, the experimental E_a values are nearly identical for **6b** and 1 (22.1[2b] and 23.3 kcal/mol, respectively). Although the activation energy for 1 is somewhat lower than predicted by the O–O initiated stepwise process, the differences are probably within the experimental error and limits of the calculated values.

Table VI. Calculated Activation Parameters for Schemes I and II

Scheme	$\Delta H°_{1,-1}$[a]	E_{-1}[a]	E_a[a]	log A	$\Delta H^{\ddagger}$[a,b]	$\Delta S^{\ddagger}$[c]
I	16.59	8,5	25.1	12.8	24.4	−1.86
II	28.5	6.7	35.2	13.9	34.5	3.2

[a] kcal/mol. [b] At 60 °C. [c] eu.

Scheme III



Since heavy phenyl substitution could possibly change the mechanism of dioxetane thermolysis from (O–O) to (C–C) initiated stepwise rupture, calculations based on this latter mechanism (Scheme II) were made. Indeed, the calculated activation energy for Scheme II does approach the experimental E_a value and the E_a value calculated on the basis of (O–O) bond homolysis. However, the calculated E_a value for Scheme II (35.2 kcal/mol) does appear to be significantly higher than the experimental E_a value (23.3 kcal/mol). It should be noted though that there is no doubt significant error in the calculated E_a value for Scheme II.

The calculated entropy of activation for the (O–O) homolysis process (−1.86 eu), as obtained from Scheme I, is in the range of the experimental values for 1 in benzene (−5.6 eu) and methanol (−5.5 eu). This calculated value is also in the range of $\Delta S^{\ddagger}$ values for dioxetanes **6a–d** (−5.3 to −2.0 eu).[2bc] The calculated $\Delta S^{\ddagger}$ value based on Scheme II (C–C initiated homolysis) of +3.2 eu is more positive than the calculated value for (O–O) homolysis by 5 eu. This would tend to favor the (C–C) homolysis process; however, the difference is not great in terms of rate. For example, if the experimental E_a value for 1 is used and rate coefficients are calculated with the calculated $\Delta S^{\ddagger}$ values for the O–O and C–C homolysis processes, one obtains k_{C-C}/k_{O-O} = 13 at 60 °C.

A further comparison of experimental and calculated activation parameters for 1 can be made in terms of rate coefficients. From the calculated activation parameters given in Table VI for the O–O homolysis process (Scheme I), a rate coefficient of 2.09×10^{-4} s^{-1} is calculated at 60 °C. This may be compared with the rate coefficient calculated with experimental activation parameters for 1 at 60 °C in benzene (5.52×10^{-4} s^{-1}). In terms of relative rates, this comparison yields $k_{exptl}/k_{O-O,calcd}$ = 2.6. With the calculated activation parameters given in Table VI for the C–C homolysis process (Scheme II), a rate coefficient of 6.31×10^{-10} s^{-1} is obtained at 60 °C. In terms of relative rates, this gives $k_{exptl}/k_{C-C,calcd} = 3.3 \times 10^5$ ($=2.09 \times 10^{-4}/6.3 \times 10^{-10}$). Thus with our best estimates for O–O and C–C calculated activation parameters, the calculated O–O parameters yield a rate coefficient that is in excellent agreement with the observed value. In contrast, the C–C calculation parameters produce a rate coefficient that differs by over five orders of magnitude from the observed value. Considering both the agreement of the observed activation pa-

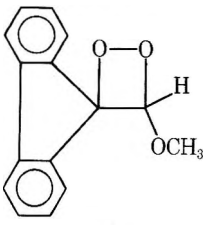
rameters with calculated parameters and the correspondence with experimental activation parameters in the series **6a–d**, it appears most reasonable that **1** is undergoing thermolysis by an O–O stepwise homolysis process.

Previously, we have used methanol to probe the mechanism of dioxetane thermolysis.[2a] Based on the decrease in enthalpy of activation in changing from an aprotic to a protic solvent in the β scission of the *tert*-butoxy radical,[18] we expected a similar solvent response for a concerted dioxetane decomposition. As seen from Table IV, the activation parameters for **1** are nearly identical in benzene and in methanol. This result is consistent with a stepwise decomposition mode for **1** in both benzene and methanol solvent, and it is not expected for a concerted process. The solvent effect results are then in agreement with the previous kinetic analysis above.

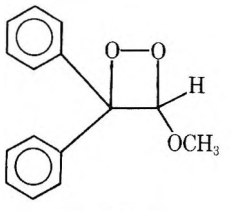
An important question that can be raised is, what magnitude of change in activation parameters is expected in proceeding from a stepwise to a concerted dioxetane thermolysis? Intimately related to this question is how substituents will influence the activation parameters of a concerted reaction. Presently, these questions are probably best answered by empirical correlations, rather than by means of calculations. Thermochemical kinetic calculations are not applicable to activation energy estimates for concerted reactions. In addition, molecular orbital calculations must be highly sophisticated in order to obtain a realistic description of the reaction surface, let alone to obtain reliable energy differences. For example, an ab initio calculation of the pyrolysis of cyclobutane[19] was required to demonstrate the biradical intermediate nature of the reaction as opposed to the earlier extended Hückel view of the reaction.[20] It can be noted that recent generalized valence bond (GVB) calculations of the thermolysis of 1,2-dioxetane are in agreement with a stepwise biradical process.[21]

An example of a concerted reaction where substituent effects have been studied is found in the pyrolysis of cyclobutenes. Substitution of methyl and of phenyl groups at the 3 position in cyclobutene increases the rate of pyrolysis by factors of 10^{22} and 2000,[23] respectively. In terms of activation energy, this corresponds to about a 5 kcal/mol decrease in E_a per phenyl substituent at the 3 and 4 positions in cyclobutene. In the concerted electrocyclic ring opening of cyclobutenones, replacement of one and two methyl groups by phenyl groups at the 4 position lowers $\Delta G^{\ddagger}$ by 3.1 and 2.3 kcal/mol, respectively.[24] In both of these reactions a π bond is developing in the transition state at the site of substitution. With these concerted electrocyclic ring openings as models, a significant lowering of E_a would be expected for phenyl substitution in dioxetanes, if the reaction were concerted.

Recently, reports of dioxetane thermolyses have appeared that are suggestive of a concerted decomposition. Activation parameters for the thermolysis of dioxetanes **7** and **8** are E_a

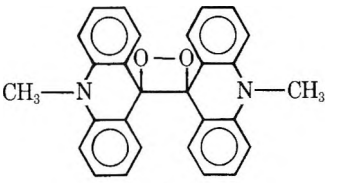


7



8

= 21.0 kcal/mol, log A = 11.6 and E_a = 26.1 kcal/mol, log A = 13.5, respectively.[25] These data, along with the unusual singlet excited state carbonyl production from **7**, may be indicative of a concerted decomposition of **7**. The unusually low activation energies observed in the thermolysis of **9** in benzene (E_a = 17.2 kcal/mol, $\Delta S^{\ddagger}$ = −5 eu) and in methylene chloride (E_a = 17.8 kcal/mol, $\Delta S^{\ddagger}$ = −1.1 eu) are also suggestive of a concerted decomposition.[26] Thus, it appears that significant decreases in activation energy can be anticipated when dioxetanes are suitably substituted to effect a concerted decomposition. Considering the similarity in activation energies, upon substituting the dioxetane ring with up to three phenyl groups, there appears to be little evidence for a concerted process with **6a–d** and **1**. However, if there is a smooth continuum from a stepwise to a concerted process, it will be difficult to detect the concerted character in dioxetanes near the stepwise end of this reaction spectrum.



9

In summary, the thermolysis of alkyl-substituted dioxetanes and those with phenyl substitution up to three phenyl groups are most reasonably interpreted as undergoing an O–O stepwise initiated decomposition. This interpretation is based on the similarity of experimental activation parameters with varying phenyl substitution, the similarity in experimental activation parameters upon changing from aprotic to a polar protic solvent, and in the agreement between experimental and calculated parameters based on an O–O initiated stepwise process. The decrease in the experimental activation energy for **1**, compared to the calculated value, is too small, compared to the error in these values, to be indicative of progress to a concerted mechanism. Thus, it appears that the stepwise mechanism is common to simply substituted four-membered ring compounds with the progressive introduction of oxygen in the series cyclobutane,[27] oxetane,[28] and simply substituted dioxetanes. In addition, the stepwise decomposition of dioxetanes has the added attribute of explaining the direct production of triplet carbonyl products[1d] without violation of spin conservation.

Experimental Section[29]

Triphenylethylene. This olefin was prepared by a previously reported method in 64% yield by means of a Grignard reaction, starting with benzyl chloride and benzophenone. Recrystallization from 95% ethanol gave a white solid: mp 70.0–70.5 °C (lit.[30] mp 68–69 °C); NMR spectrum (10% deuteriochloroform solution) $(C_6H_5)_2$ 7.31 (broad singlet, 10.0); (C_6H_5) 7.08 (broad singlet, 5.0); (=**CH**—C_6H_5) 6.98 (singlet 1.0).

1-Bromo-1,1,2-triphenyl-2-hydroperoxyethane. 1,3-Dibromo-5,5-dimethylhydantoin (MC/B) (1.4g, 4.9 mmol) was added in portions to a solution of triphenylethylene (2.5g, 9.8 mmol) and hydrogen peroxide (49 mmol) in 50 mL of tetrahydrofuran at −40 °C under a nitrogen atmosphere. The hydrogen peroxide THF solution was previously prepared from anhydrous THF and 98% hydrogen peroxide (FMC). The solution was then dried over anhydrous magnesium sulfate at 25 °C for 24 h prior to use. The temperature of the reaction mixture was maintained between −35 and −45 °C for 1.5 h and then the temperature was allowed to warm slowly to room temperature over 0.5 h. Stirring was continued for an additional 1.5 h at room temperature. The reaction mixture was then quenched in a separatory funnel containing 50 mL of ether and 25 mL of ice-cold aqueous 5% sodium bicarbonate solution. The ether fraction was further washed with sodium bicarbonate and then with cold water and finally dried over magnesium sulfate. The ether was removed under reduced pressure and the remaining yellow oil was dissolved in carbon tetrachloride. The NMR spectrum of this solution indicated a solvent dependent peroxy proton absorption at 8.7 ppm and integration of this absorption relative to the aromatic protons indicated a 60% yield of the bromohydroperoxide. The methine proton was observed at 6.08 ppm. This was further confirmed by iodometric titration.[31] Isolation of the hydroperoxide by recrystallization and by silica gel column chromatography was attempted without success.

Triphenyl-1,2-dioxetane (1). A 0.5 M sodium methoxide solution in methanol containing 2 mol % Na_2EDTA was prepared and 1.2 mL of this solution was added dropwise to a cooled (ca. 5 °C) mixture of

the bromohydroperoxide (0.5 mmol) in 5 mL of methanol (saturated with Na_2EDTA for 1 h prior to use) under a nitrogen atmosphere. The solution was stirred for an additional 0.5 h at 5–10 °C and then it was quenched with 8 mL of ice-cold water. This mixture was rapidly extracted with four 2 mL-portions of cold carbon tetrachloride. The latter extracts were further washed with cold water and dried over magnesium sulfate. An iodometric biamperometric titration[32] of this solution indicated that 1 had been formed in a 17% yield. The NMR spectrum showed the absence of the bromohydroperoxide, since no methine proton absorption was observed at 6.08 ppm. The dioxetane ring proton of 1 was buried in the aromatic envelope. A considerable effort was made to purify 1 by recrystallization and chromatography on silica gel. Recrystallization attempts failed but periodically one could obtain a partially purified sample of 1 by chromatography on silica gel. Although attempts were made to use low-temperature chromatography, it appeared that small-scale chromatography at room temperature using carbon tetrachloride as the eluent was about as satisfactory as any method.

Product Studies. A sample of 1 was purified by silica gel column chromatography and thermally decomposed in benzene–carbon tetrachloride (3:1) solvent. The thermolysis was carried out at 45 °C for greater than 20 half-lives in a sealed tube which was purged with nitrogen. The initial concentration of 1 was obtained from an iodometric biamperometric titration.[32] By NMR analysis, less than 10% of the bromohydroperoxide, based on 1, was present and benzaldehyde was not detected, although possibly 10% (based on 1) could be undetected. After thermal decomposition, the reaction mixtures were analyzed by GLC on a 5% methyl vinyl silicone column (6 ft × ⅛ in) at 110 °C vs. *o*-dichlorobenzene as an internal standard. Retention times (min) are: benzaldehyde (3.0), *o*-dichlorobenzene (4.5), benzophenone (12.0), and triphenylethylene (30). Yields of products were calculated by reference to a standard mixture of these components. Peak areas were determined by digital integration and the final yields are the average of five analyses.

Kinetic Methods. Rate measurements were made by light emission methods according to a previously reported method.[2a,b] The primary acceptor and light emitter in these studies was DBA in benzene solvent and DPA in methanol solvent. The kinetic data as well as the activation parameters were processed by means of a least-squares program.

Acknowledgment. We thank the U.S. Army Research Office for support of this research.

Registry No.—Triphenylethylene, 58-72-0; 1-bromo-1,1,2-triphenyl-2-hydroperoxyethane, 65293-78-9; 1,3-dibromo-5,5-dimethylhydantoin, 77-48-5.

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(8) The benzyl resonance energy was obtained as: E_{ph}resonance = $D_{C_6H_5CH_2-H} - D_{CH_3CH_2-H} = 88^9 - 98^4 = -10$ kcal/mol.

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(10) The resonance energy for the α-oxy radical is taken as the difference between the average activation energies for methyl radical hydrogen atom abstraction from dimethyl ether (E_a = 9.7 kcal/mol)[9] and from ethane (E_a = 11.0 kcal/mol)[9].

(11) The resonance energy of the trityl radical is taken as the difference between the activation energies for the thermolysis of 2,2′-azoisobutane (43.5 kcal/mol)[12a] and benzeneazotriphenylmethane (29.3 kcal/mol).[12b] This assumes initial single bond homolysis for each compound.

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(13) Hindered internal rotations can be treated as torsional vibrations if the condition $V_0 > RT$ holds. The frequency of the torsion is given by $W(cm^{-1}) = 21.56\ n/2\pi\ (V_0/2Ir)^{1/2}$, where n is the foldness of the rotation, V_0 is the barrier to rotation in calories, and Ir is the reduced amount of inertia in amu Å^2. See ref 4, p 45.

(14) The free rotor partition function is obtained from the relationship, $Q_f = 0.360/n(Ir\,T)^{1/2}$, where n is the symmetry of the rotation, Ir is the reduced moment of inertia in amu Å^2, and T is the temperature in K. The free rotor entropy is then, $S_f^\circ = (R/2) + R \ln Q_f$.

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Decarbonylation and Decarboxylation by Lithium in Hexamethylphosphoramide[1]

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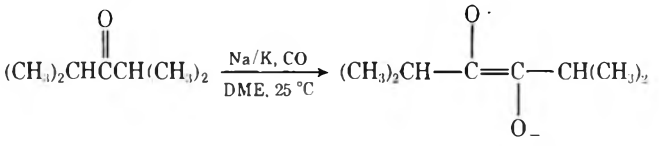
A series of strained-ring ketones and esters were reduced with lithium in hexamethylphosphoramide and the paramagnetic reduction products identified by ESR spectroscopy. Diphenylcylopropenone yielded *trans*-stilbene radical anion, *o*-phenylene carbonate yielded *o*-benzosemiquinone, bicyclo[4.2.1]nona-2,4,7-trien-9-one yielded cyclooctatetraene radical anion, and phthaloyl peroxide yielded the biphenylene radical anion. Tetramethylcyclobutane-1,3-dione can be reduced to yield the same radical anion detected in the acyloin condensation of dimethyl 2,2,4,4-tetramethyl-3-ketoglutarate, which is assigned to 3,3,5,5-tetramethyl-4-oxocyclopentane-1,2-semidione. Diisopropyl ketone is also carbonylated by potassium and carbon monoxide in dimethoxyethane to yield the *trans*-diisopropylsemidione, which is also detected in the reduction of tetramethylcyclobutane-1,2-dione by lithium in hexamethylphosphoramide–tetrahydrofuran mixtures.

It has been previously reported that potassium in THF or DME at 25 °C converts some strained-ring monoketones, such as 2,2,4,4-tetramethylcyclobutanone, 7-norbornenone, or 9-ketobenzonorbornene, into semidiones.[3-5] One interpretation is that the initially formed ketyl undergoes decarbonylation forming $K^+CO^-\cdot$, which reacts with another molecule of the ketone. Some proof for the second step of this process is furnished by the observation that whereas diisopropyl ketone fails to yield a ketyl or semidione detectable by ESR spectroscopy upon reduction by Na/K in DME at 25 °C, a solution of diisopropyl ketone saturated with carbon monoxide yields the known[6] *trans*-diisopropylsemidione detectable by ESR spectroscopy. However, the reaction is not general and numerous other ketones fail to yield the semidione under these conditions.



a^H = 1.9(2), 0.03(12) G

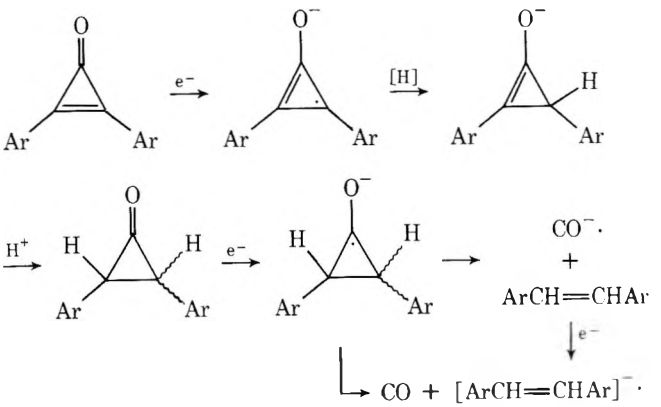
g = 2.00486

During an investigation of the reducing properties of the system HMPA/Li we have observed some further examples of decarbonylation as well as an example of bisdecarboxylation. Decarbonylation products were detected by ESR spectroscopy when diphenylcyclopropenone, o-phenylene carbonate, or bicyclo[4.2.1]nona-2,4,7-trien-9-one were treated with HMPA/Li in a static system (Table I).

Diphenylcyclopropenone, when treated with HMPA/Li in a static or flow system (~0.1 s between mixing and detection), yielded the *trans*-stilbene radical anion which is readily distinguished from the known diphenylacetylene radical anion. The strength of the ESR signal appeared to be increased by the addition of THF to the solution. A plausible explanation is that reduction to diphenylcyclopropanone preceded decarbonation as shown in Scheme I.

Treatment of diphenylcyclopropenone with Na/K in DME at room temperature gave a different result. An ESR signal formed only slowly, but after 18 h of reaction a strong ESR signal for a species with a^H = 5.30(2), 2.65(4), and 0.50(4) G was observed. Under the same conditions diphenylacetylene gave a^H = 4.8(2), 2.65(4), and 0.65(4) G,[15] whereas diphenyl radical anion has a^H = 5.46(2), 2.73(4), and 0.43(4) G. It seems most likely that in DME the reaction of diphenylcyclopropenone with Na/K has involved the cleavage of a phenyl group which is eventually converted to biphenyl radical anion, possibly via the coupling of phenyl radicals with the phenide ion.[16,17]

Scheme I

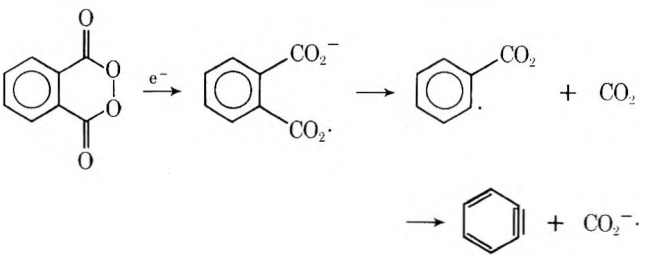


$$C_6H_5\cdot + K \rightarrow C_6H_5K \xrightarrow{C_6H_5\cdot} [C_6H_5\text{–}C_6H_5]^-\cdot K^+$$

Diphenylcyclopropenone also will give the CO insertion reaction under some conditions. When the ketone in Me_2SO is mixed in a flow cell with potassium *tert*-butoxide, an unstable radical that is not the ketyl can be detected. Upon stopped flow the ESR signal of this species disappears, and slowly the ESR signal of diphenylcyclobutene-1,2-semidione[18] appears; a^H = 1.30(2), 1.20(4), 0.48(4) G (experimental results of Dr. T. Morita).

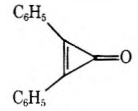
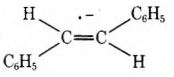
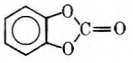
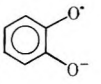
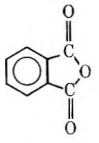
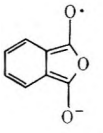
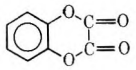
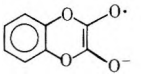
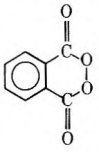
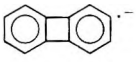
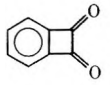
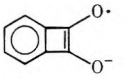
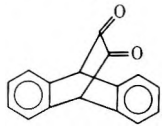
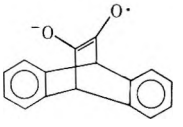
In the case of *o*-phenylene carbonate and bicyclo[4.2.1]nona-2,4,7-trien-9-one the reaction appears to involve a simple chelatropic expulsion of carbon monoxide from the ketyl with the formation of the *o*-benzoquinone and cyclooctatetraene radical anions. α-Diones such as diphenylcyclobutenedione,[18] benzocyclobutanedione,[13] or dibenzobicyclo[2.2.2]octane-2,3-dione[14] can be converted to the semidione radical ions under reductive conditions without decarbonylation.

o-Phthaloyl peroxide gave the radical anion of biphenylene upon reaction with HMPA/Li. Solutions of the peroxide in



0022-3263/78/1943-2242$01.00/0

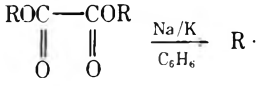
Table I. Radical Anions Observed by ESR Spectroscopy at 25 °C

Carbonyl compound	Registry no.	Hyperfine splitting constants, G (equiv protons)	Obsd radical anions	Registry no.	Lit. ref
	886-38-4	a^H = 4.35(2), 4.00(2), 3.05(2), 1.95(2), 0.82(3), 0.3(2)		34467-73-7	7
	2171-74-6	a^H = 3.4(2), 1.35(2), a^{Li} = 0.42(1)[a]		20526-43-6	8
	34733-74-9	a^H = 3.3(8)		34510-85-5	9
	85-44-9	a^H = 2.22(2), 0.20(2) (slow flow required)		34533-03-4	10
	16536-36-0	a^H = 0.18(4)		65761-22-0	11
	4733-52-2	a^H = 2.7(0.4), 0.2(2)		34478-97-2	12
	6383-11-5	a^H = 3.7(2), 1.9(2) (CH_3CN, $(C_2H_5)_4N^+$)		54165-46-7	13
	22612-93-7	a^H = 0.18(8) (Me_2SO, K^+)		17441-61-1	14

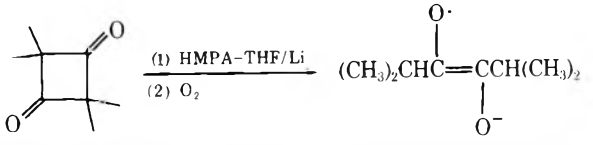
[a] Observed only after UV irradiation.

HMPA showed no indication of the formation of biphenylene by UV, and it is concluded that the biphenylene results from benzyne formation by decarboxylation of the first formed unstable radical anion.

The reaction is not surprising because benzoyl peroxide itself is readily cleaved by one-electron transfer agents. 1,2-Benzoxylate yielded the radical anion without decarboxylation as did phthalic anhydride. Berndt has reported the formation of persistent free radicals by the reductive decarboxylation of acyclic oxalic diesters, but this reaction occurs rather slowly.[19]



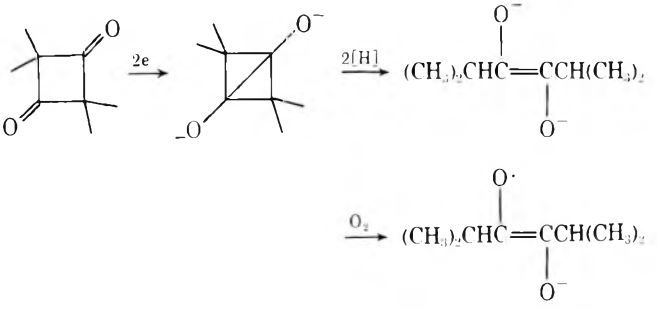
Reduction of 2,2,4,4,-tetramethylcyclobutane-1,3-dione with HMPA/Li at 25 °C failed to yield an ESR signal without added THF. With an HMPA/THF ratio of 35:65, reduction



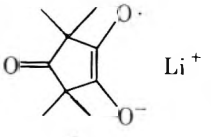
followed by a brief exposure to air produced *trans*-diisopropylsemidione in low yield.[6] In this case decarbonylation may not be involved; for example, see Scheme II.

With HMPA/THF = 67:33 the reaction of the dione with lithium gave a species with a^{Li} = 0.60, a^C = 7.8, 4.9 G. This is

Scheme II

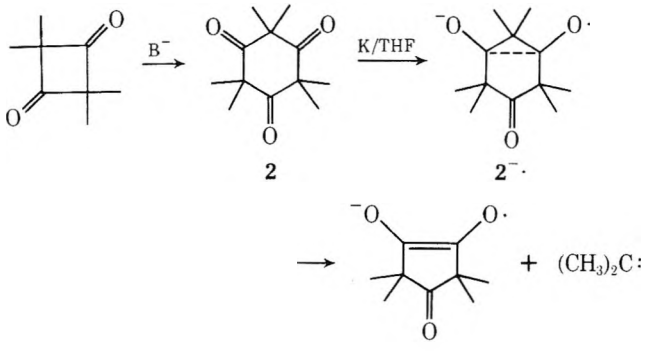


not the *cis*-diisopropylsemidione which has a^H = 2.2, $a_{CH_3}{}^H$ = 0.16, a^{Li} = 0.65 G,[6] but it is the same species Ward has ascribed to the tetramethylcyclobutane-1,3-dione ketyl (DME/K, 25 °C, a^C = 7.6, 5.0 G).[20] However, ketyls generally have $a_{CO}{}^C$ in the range of 40–50 G.[4] Moreover, 2,2,4,4-tetramethylcyclobutanone ketyl ($a_{CO}{}^C$ = 50, $a_{CH_3}{}^C$ = 13.4 G) decomposed in THF above −50 °C to yield 2,2,4,4-tetramethylcyclopentane-1,2-semidione ($a_{CH_3}{}^C$ = 6 G).[4] We believe the observed species is most likely the semidione 1 formed by a decarbonylation–carbonylation process. The values of a^C in cyclic 1,2-semidiones are typically in the range of $a_{CO}{}^C$ =



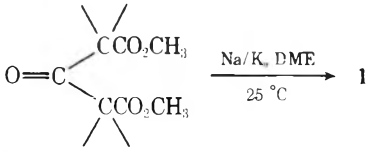
1

Scheme III

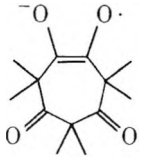


1–1.5, a_α^C = 5–6, $a_\beta^C \cong$ 6–8 G.[4] HMPA(35%)–THF(65%) containing lithium and excess lithium iodide rapidly produced a strong ESR signal for **1** without the formation of the *trans*-diisopropylsemidione. Apparently high lithium ion concentrations favor the decarbonylation process over the reductive rearrangement process of Scheme II.

Final proof for the correctness of the assignment of structure **1** was furnished by the acyloin condensation of dimethyl 2,2,4,4-tetramethyl-3-ketoglutarate with Na/K alloy in DME at 25 °C wherein the species with a^C = 7.6 and 5.0 G was observed. The acyloin condensation is known to involve semidione radical anions as intermediates.[21]



Tetramethylcyclobutane-1,3-dione is known to yield **2** in the presence of base at elevated temperatures.[22] Furthermore, **2** can be reduced by lithium in ammonia to a *cis*-cyclopropanediol via $2^{-}\cdot$.[23] This suggested that $2^{-}\cdot$ might be a precursor to **1**, or that **3** might actually be the species observed



in the reduction of tetramethylcyclobutane-1,3-dione. However, attempted reductions of **2** by K/THF at 25 or −80 °C have produced no detectable ESR signals and the proposed sequence of Scheme III as well as structure **3** are excluded.

Experimental Section

Diphenylcyclopropenone,[24] *o*-phenylene carbonate,[25] bicyclo[4.2.1]nona-2,4,7-trien-9-one,[26] *o*-phthaloyl peroxide,[27] dimethyl 2,2,4,4-tetramethyl-3-ketoglutarate,[28] and 2,2,4,4,6,6-hexamethylcyclohexane-1,3,5-trione[22] were synthesized by literature procedures.

Reduction with HMPA/Li was conducted by dissolving the substrate in one leg of a H-cell[29] and a pellet of freshly cut lithium in the other leg. The HMPA solutions were thoroughly deoxygenated by prepurified nitrogen or argon, mixed, and allowed to drain into a fused silica flat ESR cell attached to the H-cell. For flow experiments the HMPA solutions were discharged from motor-driven glass syringes through polyethylene tubing and mixed in a fused silica cell (Varian Associates V-4549A) with a dead volume of 0.05 mL. Reductions by Na/K alloy were conducted by stirring an ethereal solution of the substrate with an excess of the alloy under nitrogen or carbon monoxide followed by transfer of a sample of the reduced solution to the ESR cell. Reductions by potassium in THF were performed by adding a degassed THF solution of the substrate to a potassium mirror under vacuum.[3] ESR spectra were determined using a Varian E-3 spectrometer.

Registry No.—HMPA, 680-31-9; lithium, 7439-93-2.

References and Notes

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Cyclization and Polymerization of ω-(Bromoalkyl)dimethylamines[1]

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We have examined the kinetics of S_N2 ring closure of 3-bromopropyldimethylamine (**1**) (C-3) to a four-membered ring and of 6-bromohexyldimethylamine (**5**) (C-6) to a seven-membered ring as part of a study of steric factors in substitution reactions. We have made a few measurements on the cyclization of the C-5 homologue **4** and the polymerization of the C-8 homologue **6**. At 25 °C in methanol the rates for cyclization (k_1) and for polymerization (k_2) are as follows (10^5 s^{-1} and 10^5 M^{-1} s^{-1}): C-3, 5.3, 2.9; C-5, 1130, —; C-6, 1.7, 1.5; and at 80 °C $k_2 = 85 \times 10^{-5}$ M^{-1} s^{-1} for C-8. Both four-membered ring formation and seven-membered ring formation dominate over polymerization in solutions more dilute than 0.1 M. Thermodynamic data for ring-closure reactions have been summarized and it is shown that the classical explanation of ring-closure effects gives the wrong ratio for five-membered vs. six-membered ring closure by a factor of about 10^4 and the wrong ratio for four-membered vs. seven-membered ring closure by about 10^{12}.

Current interest in substitution reactions of the S_N2 type embraces a number of different aspects ranging from detailed theoretical studies[2,3] and mechanistic considerations of possible ion pair intermediates[4,5] to the energetics of solvent effects[6-8] and the computation of steric effects.[9-12] We are particularly interested in steric effects and are obtaining experimental data on ring closure reactions since these may provide valuable examples for testing the computations.

The general features of ring-closure reactions are well known; in the competition between cyclization and polymerization, cyclization wins out for formation of five-membered or six-membered rings.[13] Ring-closure reactions have been reviewed by Capon,[15] Page,[14] and Stirling,[16] and recently Baldwin[17] has proposed some general correlations.

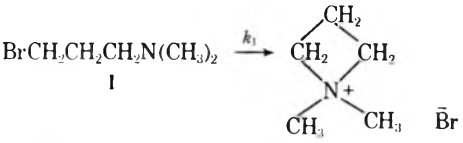
The classical explanation of the relative rates of closure of rings is based on a competition between hindrance of ring strain, which is large for three-membered and four-membered rings, smaller for five, and negligible for six, and the monotonically decreasing probability of the ends reaching each other.[18] There is also transannular hydrogen crowding in intermediate rings (8–12 atoms).

The energy factors are intriguing. For the prototype ring closures pentane to cyclopentane and hexane to cyclohexane, the six-membered ring is favored by about 3 kcal/mol based on $\Delta G°_f$.[14] In some S_N2 reactions the rate constants for closure of the five-membered ring are faster than closure to the six-membered ring by factors of about 100 to 1000. This amounts to about 3 to 4 kcal/mol. There is accordingly a discrepancy of some 6 to 7 kcal/mol that needs an adequate theoretical explanation. In other words, the product rings are not good models for the transition states.[14] We return to this question in the Discussion.

Other steric factors are also important. Alkyl substitution on the backbone accelerates the rate of ring closure.[18,19] This is often called the gem-dialkyl effect, and several examples are known.[20-22] The magnitude of the gem-dimethyl effect is sometimes predictable from consideration of enthalpies of conversion of substituted alkanes to substituted cycloalkanes.[19]

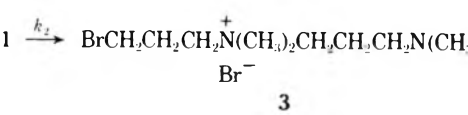
Results

In this study we have examined the rate of the thermal S_N2 reactions of 3-bromopropyldimethylamine **1**, and of related homologues in methanol. We are mainly interested in relatively large rate differences among a series of compounds, and the purpose of the present study was to explore the general characteristics of the reactions. There have been several studies of cyclizations of primary amines,[23-26] but numerous possibilities for side reactions have raised some questions of interpretation.[26] The tertiary bromoamines such as **1** (and **4**, **5**, and **6**) can still undergo a variety of reactions, but cyclization (eq 1) and polymerization (eq 2) predominate. The principal



$$\mathrm{BrCH_2CH_2CH_2N(CH_3)_2} \xrightarrow{k_1} \mathrm{Br^-} \quad (1)$$

1



$$\mathbf{1} + \mathbf{1} \xrightarrow{k_2} \mathrm{BrCH_2CH_2CH_2\overset{+}{N}(CH_3)_2CH_2CH_2CH_2N(CH_3)_2\ Br^-} \quad (2)$$

3

$\mathrm{Br(CH_2)_nN(CH_3)_2}$ **4**, $n = 5$; **5**, $n = 6$; **6**, $n = 8$

disadvantage is that cyclic products such as **2** and polymer such as **3** are not in general easy to separate nor to analyze, although **2** itself can be determined by NMR.

It is well known that reactions between amines and alkyl halides, often called Menshutkin reactions,[27] are particularly sensitive to solvent effects.[6-8] The reactions in alcohols show an intermediate rate, and the rates are only moderately sensitive to small amounts of water. In most of our studies we used the hydrobromide salts of **1** and its homologues. The salt was dissolved in methanol and prepared for reaction by adding a known amount of a solution of sodium hydroxide in methanol. This in effect introduces a small amount of water (2% maximum, usually much less).

The reactions of **1**, **4**, and **5** are more or less first order. The detailed kinetics are in principle complex: there is a competition between first-order cyclization (eq 1) and second-order polymerization (eq 2). With a large excess of alkali (mostly $NaOCH_3$) there is a direct second-order reaction which we designate k_{base}. Reactions 1 and 2 also are subject to a salt effect, eq 3 (acceleration).

$$k_1 = k_1°(1 + b'[\mathrm{salt}])$$
$$k_2 = k_2°(1 + b'[\mathrm{salt}]) \quad (3)$$

There is one other complicating feature in that dimer **3** (eq 2) does not cyclize appreciably under the present conditions, and hence the reaction is not strictly of the first plus second order type. It is nevertheless possible to effect a reasonable dissection based on an analysis of the apparent first-order constants obtained over an extended fraction of the reaction using eq 4.

$$k_1(\mathrm{apparent}) = k_1 + k_2[\mathrm{bromoamine, initial}]/2 \quad (4)$$

We have, however, computed k_1, k_2, and b' of eq 3 by a least-squares procedure based on numerical integration of eq 5. In

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Table I. Rate Constants for Cyclization (k_1) and Polymerization (k_2)[a]

	C-3 (1),[g] 25 °C	C-5 (4),[h] 25 °C	C-6 (5),[i] 25 °C	C-8 (6),[j] 80 °C
$10^5 k_1$[b]	5.3	1130[c]	1.7	...
$10^5 k_2$[d]	2.9	...	1.5	85[e,f]
b' (eq 3)	0.4	...	0.4	...

[a] Solvent is methanol; rate constants have std dev of about 15%. [b] In s^{-1}. [c] Extrapolated. [d] $M^{-1} s^{-1}$. [e] 0.5×10^{-5} at 25 °C. [f] $k_{base} = 3 \times 10^{-3}$ $M^{-1} s^{-1}$ at 80 °C. [g] Registry no.: 53929-74-1. [h] Registry no.: 65102-10-5. [i] Registry no.: 65102-11-6. [j] Registry no.: 63411-31-4.

Table II. Yields of Dimethylazetidinium Bromide (2)

Concn of 1, M	% yield of 2, obsd	% yield of 2, calcd[a]
0.02	100	99
0.1	89	94
0.2	90	...
0.5	75	77
1.0	63	63

[a] From eq 5 and rate constants in Table I by numerical integration.

these equations A stands for bromoamine **1** or **5**, and Z is dimer or polymer having reactive end groups.

$$\mathrm{A(1)} \xrightarrow{k_1} \text{cyclic product(2)} + \mathrm{Br^-}$$

$$\mathrm{A} + \mathrm{A} \xrightarrow{k_2} \mathrm{Z(3)} + \mathrm{Br^-}$$

$$\mathrm{A} + \mathrm{Z} \xrightarrow{2k_2} \mathrm{Z} + \mathrm{Br^-} \qquad (5)$$

$$\mathrm{Z} + \mathrm{Z} \xrightarrow{k_2} \mathrm{Z} + \mathrm{Br^-}$$

$$\mathrm{A} + \text{base} \xrightarrow{k_{base}} \mathrm{AOCH_3}$$

$$\mathrm{Z} + \text{base} \xrightarrow{k_{base}} \mathrm{ZOCH_3}$$

The relevant rate constants are summarized in Table I, product data for **1** are presented in Table II, and Arrhenius equation parameters are in Table III. The approximate k_{base} for **1** and for **5** is about 1×10^{-5} $M^{-1} s^{-1}$. The reported rate constant for reaction for *n*-butyl bromide and sodium methoxide in methanol at 25 °C is 0.9×10^{-5} $M^{-1} s^{-1}$.[28]

Discussion

Since the purpose of our studies has been to explore overall effects of structure on reactivity, we have not sought to carry out the range of experiments necessary to evaluate in detail the effects of temperature on the cyclization or the polymerization, nor have we sought to explore salt effects in detail. Our studies do establish the fact that closure to four-membered rings and to seven-membered rings will usually dominate in solutions more dilute than 0.1 M, and they provide the necessary guidelines to show when serious departures may be anticipated.

Our data also show that competition from direct reaction with methoxide ion is not important in the presence of 0.1 M sodium methoxide, nor are other intermolecular substitution reactions important at such concentrations. These conclusions are significant in that they serve to validate the various previous studies of cyclization of primary bromoalkylamines, whose behavior had been in some doubt.[26] With the primary amines it is, of course, necessary to use an excess of base to avoid complexities of acid–base competition between reactants and products.

Table III. Arrhenius Parameters for Overall Reaction

	$A \times 10^{-10}$/ s^{-1}[a]	E/kcal mol^{-1}[a]	Temp range, °C
C-3 (1)	34.151	21.510 ± 0.1	25, 35, 40, 45
C-5 (4)	2.270	16.781 ± 0.5	−2, −11, −22
C-6 (5)	2.537	20.695 ± 0.12	25, 35, 45, 55
C-8 (6)	0.1443	19.761 ± 1.3	60, 70, 80

[a] Units for C-8 are s^{-1} M^{-1}. Error limits on A are 10% for **1**, 20% for **5**, and a factor of 2 for **4** and **6**. A and E are correlated; they are given to enough places to reproduce the rate constants without round-off error. The solvent was methanol, concentrations were 0.2 M or less, and the principal reaction is cyclization for **1**, **4**, and **5** and polymerization for **6** (C-8).

Table IV. Rates of Cyclization of $H_2N(CH_2)_nBr$ in Water at 25 °C[24,25]

($H_2NCH_2CH_2Br$)	0.036
$H_2N(CH_2)_3Br$	0.0005
$H_2N(CH_2)_4Br$	30.0[a]
$H_2N(CH_2)_5Br$	0.5
$H_2N(CH_2)_6Br$	0.001
$H_2N(CH_2)_4Cl$	0.0075
$H_2N(CH_2)_5Cl$	0.00011

[a] Rough estimate; not measured.

We shall not attempt to review the literature, but our studies now indicate that most of the previous work based on primary amines can be accepted as valid measures of cyclization rates. The Freundlich data is an example (Table IV). In these studies the relative rate for cyclization to six-membered vs. seven-membered rings is about 500 while we find about 650; the relative rate of seven- vs. four-membered rings is 2 while we find 1/3 for the dimethylamino series.

Table V summarizes the enthalpies, entropies, and free energies of representative cyclization reactions. In making such comparisons it is advisable to be sure that the reactions are isostructural, that, for example, hydrogen removal consistently comes from methyl as in the first nine entries. The entries show the modern assignment of strain ($\Delta\Delta H$), of entropy ($\Delta\Delta S$), and of overall strain plus entropy effects ($\Delta\Delta G$). For a given sized ring the data do correlate the gem-dimethyl effect, cyclization to 1,1-dimethylcyclohexane being favored over cyclization to cyclohexane.

Table VI summarizes the ring closure data of Table V. If cycloalkanes are taken as models for the cyclization process, then the $\Delta\Delta G$ values of Table VI summarize the classical predictions. Because of the large values of the strain energy terms ($\Delta\Delta H$), the formation of four-membered rings is predicted to be slower than formation of seven-membered rings by $\Delta G \sim 17$ kcal/mol or about 10^{12}. Experimentally the rates are about equal. The relative rates for five-membered rings and six-membered rings are also in the wrong order. The prediction is a ratio of 1/300 and the observed ratio is perhaps 1000. It is clear that rate predictions based on the classical explanation are of limited value.

Experimental Section

3-Bromopropyldimethylamine (1). 3-Dimethylaminopropanol (21 g) was added to 50 mL of 48% hydrobromic acid and the flask was swept with nitrogen. The mixture was heated rapidly to 110–120 °C and held there for about 4 h. Solvent was removed at water pump pressure and the residue was further dried by azeotropic distillation

Table V. Enthalpy, Entropy, and Free Energy of Cyclization, Based on Formal Reactions

Product	Registry no.	ΔS^b	ΔH	ΔG^b	$\Delta\Delta S^{b,c}$	$\Delta\Delta H^c$	$\Delta\Delta G^{b,c}$
		$2RCH_3 \rightarrow RCH_2CH_2R + H_2$					
Alkane[d]		−5.1	10.2	11.7	0	0	0
Cyclopropane	75-19-4	17.1	37.6	32.5	22.2	27.4	20.8
Cyclobutane	287-23-0	14.2	36.5	32.3	19.3	26.4	20.6
Cyclopentane	287-92-3	11.5	16.5	13.1	16.7	6.4	1.4
Cyclohexane	110-82-7	3.3	10.5	9.5	8.4	0.4	−2.2
Cycloheptane	291-64-5	4.4	16.4	15.0	9.5	6.2	3.4
Cyclooctane	292-64-8	1.0	19.8	19.5	6.1	9.6	7.8
1,1-Dimethylcyclopentane[e]	1638-26-2	15.0	15.7	10.9	20.1	5.5	−0.8
1,1-Dimethylcyclohexane[e]	590-66-9	8.2	9.9	7.5	13.3	−0.3	−4.2
		$RCH{=}CH_2 + R'CH_3 \rightarrow R(CH_2)_3R'$					
Alkane[d]		−29.0	−19.9	−11.4	0	0	0
Cyclopropane		−7.0	7.9	10.0	21.9	27.7	21.4
Cyclobutane		−9.6	6.4	9.3	19.4	26.3	20.7
Cyclopentane		−12.7	−13.5	−9.7	16.3	6.4	1.7
Cyclohexane		−20.7	−19.5	−13.3	8.3	0.4	−1.9
Cycloheptane		−19.4	−13.6	−7.8	9.5	6.2	3.6
Cyclooctane		−22.9	−10.2	−3.4	6.1	9.6	8.0
		$RCH(CH_3)_2 + R'CH_3 \rightarrow RC(CH_3)_2CH_2R'$					
Alkane[d]		−10.2	9.2	12.2	0	0	0
1,1-Dimethylcyclopentane		10.4	13.5	10.4	20.6	4.3	−1.8
1,1-Dimethylcyclohexane		3.3	8.2	7.3	13.5	−1.0	−4.9
		$RC{\equiv}CH + R'CH_3 \rightarrow$ *cis*-$RCH{=}CHCH_2R'$					
cis-Alkene		−25.3	−31.1	−23.6	0	0	0
Cyclobutene	822-35-5	−6.5	−8.5	−6.5	18.8	22.6	17.6
Cyclopentene	142-29-0	−9.6	−26.6	−23.8	15.7	4.5	−0.2
Cyclohexene	110-83-8	−13.9	−30.8	−26.7	11.4	0.3	−3.1
		cis-R—CH=CHR′ → cycloalkene + H_2					
Alkane (from 1st line above)		−5.1	10.2	11.7	0	0	0
Cyclobutene		14.6[f]	32.7	26.4[f]	19.7	22.5	14.7
Cyclopentene		11.3	14.6	9.3	16.5	4.4	−2.4
Cyclohexene (from 2-hexene)		6.8	11.2	9.2	11.9	1.1	−2.5
Cyclohexene (from 3-hexene)		7.0[f]	10.1	8.0[f]	12.2	−0.1	−3.7

[a] Primary data (kcal/mol) are for gaseous hydrocarbons at 25 °C from ref 29. [b] Entropy and free energy corrected to molar concentration basis (correction is 6.35 gibbs). [c] $\Delta\Delta Q$ values are ΔQ(cyclic) − ΔQ(alkane). [d] Average of four typical examples. [e] Averages of values for 2,2-dimethylalkane and 3,3-dimethylalkane. [f] Corrected for symmetry of *cis*-alkene (R ln 2).

Table VI. Average $\Delta\Delta Q$ Values for Ring Closure[a]

Product	Symmetry number (σ)[b]	$\Delta\Delta S$(avg)	$\Delta\Delta H$(avg)	$\Delta\Delta G$(avg)	$\Delta\Delta S_{int}$ (avg)[c]
Cyclopropane	6	22.1	27.6	21.7	25.9
Cyclobutane	8	19.4	26.4	20.6	23.5
Cyclopentane[d]	10	16.3	5.6	0.4	20.8
Cyclohexane[d]	6	9.2	−0.2	−2.8	12.9
Cycloheptane	1	9.5	6.2	3.4	9.5
Cyclooctane	8	6.1	9.6	7.8	10.2

[a] Based on $\Delta\Delta Q$ values in Table V (omitting cycloalkenes); units kcal/mol. [b] As recommended in ref 30. [c] $\Delta\Delta S$(avg) + R ln σ. [d] $\Delta\Delta S$ for dimethyl examples was reduced by R ln σ before averaging so as to convert to common basis. The std dev of $\Delta\Delta S$ is 0.6 based on cyclopentane and cyclohexane (6 df); std dev of averages is about 0.3, 95% confidence limits of averages is about 0.8; bias is uncertain.

and then stored over phosphorus pentoxide and sodium hydroxide pellets. The salt was recrystallized from methanol followed by addition of ether. Various preparations had titratable and total bromide of 100 ± 3% (range). At slightly higher temperatures reduction occurs as a side reaction and *n*-propyldimethylamine is formed.

Other members of the series were prepared analogously: 6-bromohexyldimethylamine was prepared from 6-dimethylamino-1-methoxyhexane by the above hydrobromic acid procedure. The sequence employed was 1,6-dibromohexane to 6-bromo-1-methoxyhexane to 6-dimethylamino-1-methoxyhexane.

Marvel and others have prepared these compounds previously by treatment of bromophenoxyalkanes with hydrobromic acid.[31,32]

Kinetic Measurements. A weighed sample of the salt was dissolved in methanol and to this was added an exact equivalent or a known excess of a solution of sodium hydroxide in methanol. For studies above 50 °C the samples were sealed in ampules. Reactions were quenched with dilute nitric acid and the bromide ion was titrated with silver nitrate solutions using a potentiometric end point. Representative data are reported in Table VII.

Computations. The kinetics data were treated either as first order or second order using LSKIN1[33] or LSKIN2.[34] Sets of kinetic data were then processed using the general least-squares program GENLSS[34] which was provided with a subroutine for numerical integration of eq 5 including all salt effects. The results were further checked by performing representative computations using REMECH.[35,36]

Product Studies. Representative runs for **1** were examined by GLC for the presence of $(CH_3)_2NCH_2CH_2CH_2OCH_3$ or $(CH_3)_2NCH_2CH{=}CH_2$, which were synthesized independently. Amounts present were very small.

The *N,N*-dimethylazetidinium ion (**2**) shows a triplet for $CH_2N(+)$

Table VII. Representative Rate Data for 3-Bromopropyldimethylamine (1)[a]

Initial concn, M		$k_{obsd} \times 10^5$/
1	$LiNO_3$	s^{-1} [b]
0.02	...	5.0
0.02	0.40	6.0
0.10	...	5.7
0.50	...	7.2
1.01	...	11.1

[a] Solvent methanol, 25 °C. [b] Apparent first-order rate constant.

at about 0.8 ppm lower field than the triplet for the polymer, and the separation permits an analysis for the amount of cyclic products. The difference is smaller for the C-6 compound.

Registry No.—3-Dimethylaminopropanol, 3179-63-3.

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Effect of Hexadecyltrimethylammonium Bromide on the Thiolysis of *p*-Nitrophenyl Acetate

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Micelles of hexadecyltrimethylammonium bromide produce a rate increase of ca. 50-fold in the thiolysis of *p*-nitrophenyl acetate by thiophenoxide anions. The distribution constants between the water and the micellar phase, determined spectrophotometrically, of *p*-Cl, *p*-CH_3, *p*-CH_3O, and thiophenoxide anions were 20×10^3, 8.2×10^3, 2.7×10^3, and 4.8×10^3 M^{-1}, respectively. The calculated distribution constants of all four undissociated thiophenols were of the order of 1×10^3 M^{-1}. The apparent p*K*s of the thiophenols were lowered upon incorporation into the micellar phase. The entire rate increase produced by hexadecyltrimethylammonium bromide in the thiolysis of *p*-nitrophenyl acetate by thiophenoxides can be explained on the basis of concentration of the reagents on the micellar phase.

Only a limited number of nucleophiles have been unequivocally demonstrated to participate in covalent catalysis by enzymes.[1] Among these, the SH group of cysteine residues shows an unusually high reactivity when situated in the active site of "SH enzymes" such as papain,[2] ficin,[3] bromelin,[4] or glyceraldehyde-3-phosphate dehydrogenase.[5] The nucleophilic reactivity of SH groups in proteins can range from those which are extremely reactive to those which are nonreactive or "masked".[6,7] Although the details are far from clear, there is general agreement that this wide range of reactivities can be attributed to differing microenvironments of the potentially reactive SH group. Unusually high SH reactivities are also found with low molecular weight compounds such as coenzyme A (CoASH) and glutathion (GSH), which participate covalently as coenzymes in a number of enzyme-catalyzed reactions.[6,7] Since the reactivities of the SH groups of GSH or CoASH are entirely within the expected range[8] (on the basis of comparison with other mercaptans), the SH group of both GSH and CoASH must be "activated" by the apoenzyme, much in the same manner as active site SH groups.

Since micelles serve as models of the (possible) role of charged and/or neutral interphases on nucleophilic reactivity (for recent reviews on micelles see 9–12) the study of micellar effects on SH reactivity has relevance to the question of the reactivity differences found in biological systems. There is indeed evidence that micelles affect, markedly in some cases, the rates of different SH reactions:[8,13-16] (1) The rate of reaction of *N*-dodecanoyl-*dl*-cysteine (DCS) with chloroacetamide, iodoacetamide, and *p*-nitrophenyl acetate (NPA) is increased by 5–7-, 60–100-, and 100–200-fold, respectively, upon addition of hexadecyltrimethylammonium bromide (CTAB).[13] On the other hand, incorporation of DCS into negative micelles leads to a decrease of the apparent reactivity of the SH group.[13] (2) The rate of reaction of alkyl mercaptans

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with NPA is accelerated by up to 10^4-fold upon addition of alkyl trimethylammonium bromide detergents.[14] (3) The formation of mixed micelles of thiols (like β-mercaptoethylammonium) and oleic acid has been proposed to explain the thiol-catalyzed cis–trans isomerization of oleic acid.[15] (4) CTAB increases 3×10^3-fold the reaction rate of thiophenoxide anion with 2,4-dinitrofluorobenzene.[16] (5) The rate of thiolysis of NPA by GSH and CoASH is accelerated by CTAB micelles by factors of 100 and 300, respectively.[8]

The rate increase observed for many reactions upon addition of detergents above the critical micelle concentration (CMC) can often be explained on the basis of concentration of the reagents in the micellar phase and changes in the apparent pK of a nucleophile, without requiring the postulation of changes in the intrinsic reactivity of the attacking nucleophile.[17] Before attributing the observed rate effect of micelles to changes in nucleophile reactivity (a pertinent analysis can be found in ref 18) it is thus necessary to correct these rates for concentration effects and distribution of the ionic species between the aqueous and micellar phases.

In this work, we demonstrate that the rate increase produced by CTAB on the reaction between thiophenoxide and NPA can be explained entirely on the basis of concentration of the reagents in the micellar phase; consequently, intrinsic effects of the micellar phase on reactivity must be of little or no importance in this system.

Experimental Section

CTAB (E. Merck, Darmstadt pro Analysis grade Lot 252534) was extracted with ether and recrystallized three times from acetone–ethanol. Thiophenol (Eastman Kodak Co.) was vacuum distilled. p-Methoxythiophenol (Aldrich Chem. Co.) was used as received. p-Methyl- and p-chlorothiophenol were recrystallized from ethanol–water. Thiophenyl acetate was prepared from acetic anhydride and thiophenol and purified by vacuum distillation (bp 110 °C (13 mmHg)).[19]

p-Nitrophenyl acetate (Sigma Chem. Co.) and 5,5′-dithiobis(p-nitrobenzoic acid) (BDH Biochemicals) were used without further purification. All other reagents were analytical grade. Water which had been deionized and twice distilled in glass was used throughout.

Methods. The CTAB concentration of stock solutions was determined by bromide titration.[20] Thiophenol concentrations in stock solutions in deareated ethanol were determined by measuring the free SH content.[21]

Kinetics. The thiolysis of NPA was followed by measuring the appearance of p-nitrophenoxide (405 nm) in a Gilford recording spectrophotometer equipped with a thermostated cell compartment (Forma Scientific Circulating Bath) maintained at 30 ± 0.2 °C. The reaction mixture was temperature equilibrated in the cell compartment and reaction was initiated by adding (0.01 mL) a stock solution of NPA ($1–2 \times 10^{-3}$ M) in CH_3CN. The total organic solvent in the reaction never exceeded 0.8% (v/v). All solutions were deareated under vacuum and flushed with N_2.

Apparent first-order rate constants (thiophenol/NPA:10/1) were obtained from log $(DO_\infty - DO_t)$ vs. time plots (Hewlett Packard Model 10 simple linear regression program), which were linear for (at least) 4 half-lives. Second-order rate constants were obtained from

$$k_2 = \frac{k_\psi - k_w}{|\mathrm{RSH}|_T} \tag{1}$$

where k_ψ is the observed apparent first-order rate constant in the presence of thiophenol and k_w is the observed first-order rate constant for the spontaneous hydrolysis of NPA under the same conditions (pH, CTAB) in the absence of the thiophenol. $|\mathrm{RSH}|_T$ is the total concentration of added thiophenol, which, under the conditions employed (vide infra), is totally dissociated.

These results were confirmed (Figures 1A and 1B) by measuring the variation of the observed rate constant with thiophenol concentration, both in the absence (Figure 1A) and in the presence (Figure 1B) of CTAB.

Determination of pK of Thiophenols. The effect of CTAB on the apparent pK of the thiophenols was determined at a single (saturating) CTAB concentration. Spectral data obtained for thiophenol and thiophenoxide anion both in the presence and absence of CTAB were utilized in the following equation:

$$K = \frac{[H^+](1 - (E_{AH}/E_\psi))}{(E_{A^-}/E_\psi) - 1} \tag{2}$$

where E_ψ is the observed extinction coeficient $(A_\psi/(\mathrm{RSH})_T)$ at particular H^+ concentration and wavelength and E_{AH} and E_{A^-} are the extinction coefficients of the thiophenol and thiophenoxide anions at the same wavelength. Appropriate controls assured that Lambert–Beer law was obeyed at the CTAB (4×10^{-3} M) and thiophenol (ca. 2×10^{-5} M) concentrations used.

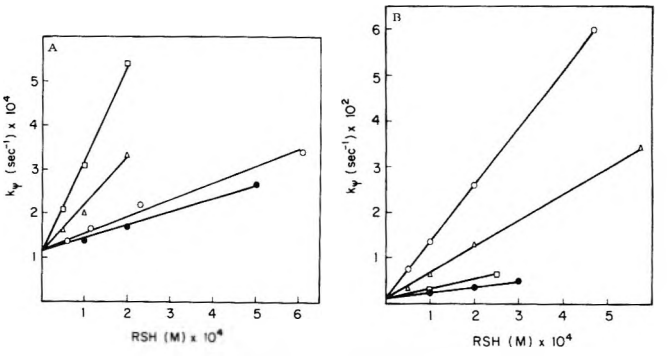

Figure 1. Effect of the variation of thiophenol concentration on the rate of thiolysis of NPA. All reactions were done in 0.02 M borate buffer pH 8.5 with ca. 5×10^{-6} M NPA. A: (●) p-chlorothiophenol; (○) thiophenol; (△) p-methylthiophenol; (□) p-methoxythiophenol. B (all reactions contained 4×10^{-3} M CTAB): (●) p-chlorothiophenol; (□) thiophenol; (△) p-methylthiophenol; (○) p-methoxythiophenol.

Determination of Distribution Constants between the Water and Micellar Phases. According to the phase-separation model,[17,18] the distribution constant (K_a) for the thiophenoxide anions can be defined as

$$K_a \simeq \frac{C_m}{C_w}\bar{V} \tag{3}$$

where C_m and C_w are the concentrations of the anion in the micellar and aqueous phases, respectively, and $\bar{V}$ is the molar volume of the micellized detergent. Using this model and assuming that the volume of the micellar "phase" is small compared to the total volume of the solution, it can be shown that

$$C_T = C_m C_D \bar{V} + C_w \tag{4}$$

where C_D is the concentration of micellized detergent and C_T is the total anion concentration.

From eq 3 and 4, it can be shown that

$$E_\psi = \frac{K_a C_D}{(1 + K_a C_D)} \times E_m + \left(1 - \frac{K_a C_D}{(1 + K_a C_D)}\right) \times E_w \tag{5}$$

where E_ψ is the observed extinction coefficient at a particular wavelength and detergent concentration and E_m and E_w are the extinction coefficients of the anion in the micellar and aqueous phases, respectively.

Rearranging eq 5, one obtains a linearized form of this equation that permits the determination of K_a.

$$\frac{1}{E_\psi - E_w} = \frac{1}{K_a(E_M - E_w)} \times \frac{1}{C_D} + \frac{1}{(E_m - E_w)} \tag{6}$$

Typical results, showing the effect of CTAB on the spectra of thiophenoxides and plots of eq 6, are presented in Figures 2A and 2B. The distribution constants for the undissociated thiophenols were calculated as described by Berezin and co-workers from the K_a and the effect of CTAB on pK.[22]

Results

We have previously shown that CTAB exerts a marked effect on the UV spectra of thiophenoxide anion.[16] These spectral changes were used to calculate both distribution constants and apparent pK shifts of the thiophenols (Experimental Section). The relevant spectral data are presented in Table I.

Table II summarizes the results for the effect of CTAB on

Table I. Effect of CTAB on the Spectra of Thiophenols

Compd	Registry no.	RSH[a] λ_{max}, nm	RSH[a] E, M^{-1} cm^{-1}	R_S^-[b] λ_{max}, nm	R_S^-[b] E, M^{-1} cm^{-1}	RSH + CTAB[c] λ_{max}, nm	RSH + CTAB[c] E, M^{-1} cm^{-1}	R_S^- + CTAB[d] λ_{max}, nm	R_S^- + CTAB[d] E, M^{-1} cm^{-1}
Thiophenol	108-98-5	237.8	271	262.5	12600	238.0	252	275.0	9468
p-Methoxythiophenol	696-63-9	239.0	753	262.5	14097	241.0	650	270.0	16632
p-Chlorothiophenol	106-54-7	245.0	1041	270.0	15143	247.0	1650	285.0	15500
p-Methylthiophenol	106-45-6	238.0	511	265.0	12634	240.0	522	276.0	12426

[a] In 0.01 M HCl. [b] Borate buffer, 0.02 pH 8.5. [c] In 0.01 M HCl containing 4×10^{-3} M CTAB. [d] In 0.02 M borate buffer pH 8.5 containing 4×10^{-3} M CTAB.

Table II. Distribution Constants of Thiophenols between Water and CTAB and Effect of CTAB on the Apparent pK of Thiophenols

Compd	$K_{a(SH)} \times 10^{-3}$[a]	$K_a \times 10^{-3}$[b]	pK[c]	pK_m[d]
p-Chlorothiophenol	1	20 ± 5	6.5	5.3
Thiophenol	1	4.7 ± 0.8	6.8	6.2
p-Methylthiophenol	1	8.2 ± 0.5	7.1	6.3
p-Methoxythiophenol	0.93	2.7 ± 0.4	7.0	6.6

[a] Calculated according to ref 22. [b] Calculated from eq 6. [c] pK in the water see ref 29 for independent measurements. [d] Apparent pK in the presence of 4×10^{-3} M CTAB, calculated from eq 2.

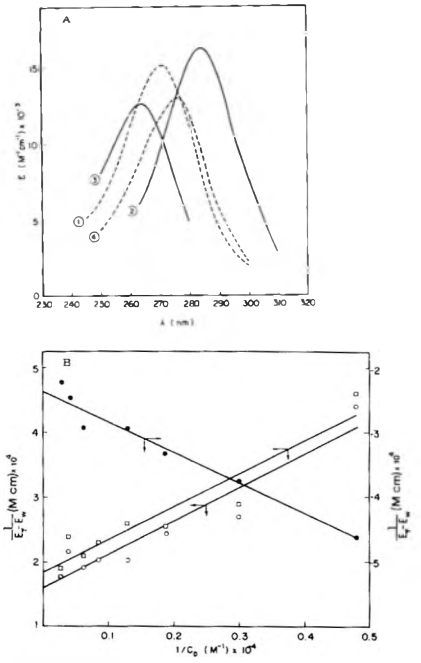

Figure 2. Effect of CTAB on the spectra of thiophenoxide anions. All spectra were obtained in 2×10^{-2} borate buffer pH 8.5. A: (1) *p*-chlorothiophenol; (2) *p*-chlorothiophenol, with added 4×10^{-3} M CTAB; (3) *p*-methylthiophenol; (4) *p*-methylthiophenol, with added 4×10^{-3} M CTAB. B (determination of K_a of thiophenoxide according to eq 6): (●) 250 nm; (○) 285 nm; (□) 275 nm.

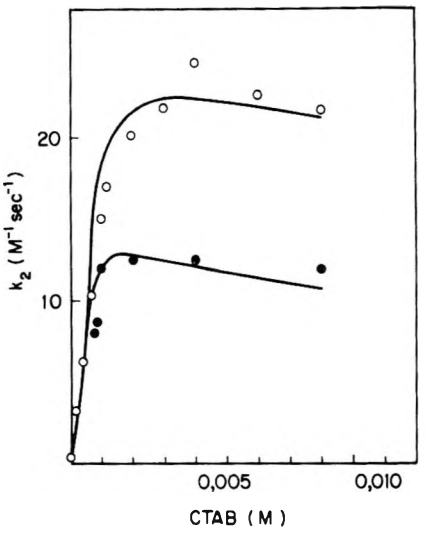

Figure 3. Effect of CTAB on the thiolysis of NPA: (●) *p*-chlorothiophenol in 2×10^{-2} M borate buffer pH 8.5; (○) thiophenol in phosphate buffer 4.5×10^{-2} M pH 7.8. The curves were calculated using eq 7 (see text). The concentration of NPA used was usually 5×10^{-6} M and the thiophenols 5×10^{-5} M.

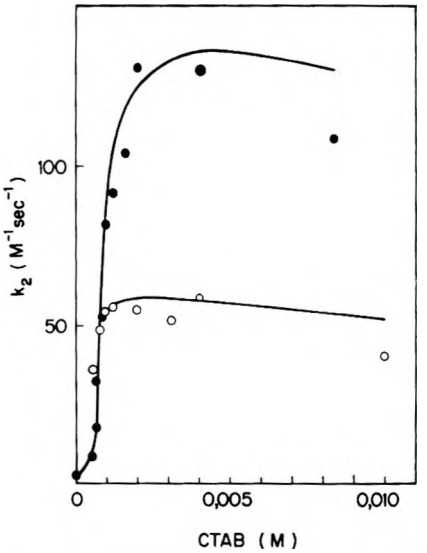

Figure 4. Effect of CTAB on the thiolysis of NPA: (○) *p*-methylthiophenol; (●) *p*-methoxythiophenol. Reactions were done in 2×10^{-2} M borate buffer pH 8.5; curves were calculated using eq 7 (see text). The concentration of NPA used was usually 5×10^{-6} M and the thiophenols 5×10^{-5} M.

the apparent pK of substituted thiophenols and the corresponding distribution constants between the aqueous and micellar phases of both the protonated and unprotonated forms of the thiophenols. From the pK values it is evident that all of the thiophenols should be completely dissociated under our kinetic conditions (pH >7.8), especially in the presence of CTAB. Thus, the second-order rate constants for thiolysis of NPA represent those for the reaction between the thiophenoxide anions and NPA.

The addition of CTAB causes ca. a 50-fold increase in the rate of thiolysis of NPA by the thiophenoxide anions (Figures 3 and 4, Table III). The products of these reactions are, in all cases, *p*-nitrophenoxide and the corresponding thiophenyl acetate. On the basis of known reaction rates for hydrolysis of thiol esters,[1,8,23] it can be anticipated that the resulting thioesters should be stable under our reaction conditions.

Table III. Effect of CTAB on the Thiolysis of NPA by Thiophenoxides

Compd	Registry no.	k_{2w}, M^{-1} s^{-1} [a]	k_{2max}, M^{-1} s^{-1} [b]	k_{2M}, M^{-1} s^{-1} [c]	K_a, M^{-1} [d]
p-Chlorothiophenoxide	35337-68-9	0.30	12.7	0.19	15000
Thiophenoxide	13133-62-5	0.36	25.0	0.39	3900
p-Methylthiophenoxide	26330-85-8	1.08	59.4	0.91	7700
p-Methoxythiophenoxide	26971-83-5	2.29	130.0	2.18	2300

[a] Second-order rate constant in the aqueous phase. [b] Observed maximum second-order rate constant in the presence of CTAB (see Figures 3 and 4). [c] Calculated values for the second-order rate constant in the CTAB phase (eq 7 see text). [d] Best fit value for the distribution constant (eq 7 see text).

Conclusive evidence for such stability was obtained by demonstrating a quantitative correspondence between the decrease of the free SH content and the production of p-nitrophenoxide, both in the presence (4×10^{-3} M) and absence of CTAB, and the stability of thiophenyl acetate under all reaction conditions described in this work.

The second-order rate constants increase sharply at CTAB concentrations above 5×10^{-4} M. Independent conductimetric data confirm that, under our kinetic conditions, the CMC of CTAB is, in fact, lowered from 9×10^{-4} M[11] to 5×10^{-4} M.

The effect of CTAB on the rate of thiolysis was quantitatively analyzed using a phase-separation model[17]

$$k_2 = \frac{(k_{2M}/\overline{V})K_aK_bC_D + k_{2w}}{(1 + K_aC_D)(1 + K_bC_D)} \quad (7)$$

where k_2 is the observed second-order rate constant, k_{2M} and k_{2w} are the second-order rate constants in the micellar and aqueous phases, respectively, and K_a and K_b are the distribution constants of the thiophenoxide and NPA, respectively.

Equation 7 was fitted to the experimental data (Figures 3 and 4) in the following manner. Taking $K_b = 27$ M^{-1},[18] CMC $= 5 \times 10^{-4}$ M (vide supra), and $\overline{V} = 0.37$ M^{-1} [18] and using the corresponding experimental values for k_{2w} (Table III), the best values for K_a and k_{2M} were obtained by successive iterations. The initial value for K_a was obtained from the results presented in Table II. An initial estimate of k_{2M} can be obtained by an examination of the maximum catalytic enhancement in the following manner. From eq 7 it can be shown that:[17]

$$\left|\frac{k_{2max}}{k_{2w}}\right| = \frac{k_{2M}}{k_{2w}\overline{V}} \times \frac{K_a \times K_b}{(K_a^{1/2} + K_b^{1/2})^2} \quad (8)$$

where k_{2max} is the maximum second-order rate constant obtained by addition of detergent. When $K_a \gg K_b$ eq 8 reduces to

$$\lim_{K_a \gg K_b} \left|\frac{k_{2max}}{k_{2w}}\right| = \frac{k_{2M}}{k_{2w}} \times \frac{K_b}{\overline{V}} \quad (9)$$

For $K_b = 27$ M^{-1} and $\overline{V} = 0.37$ M^{-1}

$$\lim_{K_a \gg K_b} \left|\frac{k_{2max}}{k_{2w}}\right| = \frac{k_{2M}}{k_{2w}} \times 77 \quad (10)$$

which predicts a maximum rate enhancement of 77 if $k_{2M} = k_{2w}$. Since the maximum rate enhancements found are no larger than 50, an initial value of $k_{2M} = k_{2w}$ is fully justified. The best fit values of k_{2M} and K_a are presented in Table III. It should be noted that the latter are within experimental error of the values of K_a obtained from the absorption data. Moreover, the second-order rate constants in the micellar phase (k_{2M}) (with the exception of p-chlorothiophenoxide) are essentially equal to those in the aqueous phase (k_{2w}).

Discussion

The interpretation of micellar effects on reactions between hydrophobic nucleophiles and micelle-incorporated substrates has been greatly facilitated by an analysis, due to Berezin and co-workers,[17] in which the concentration of substrates in the micellar phase can be explicitly taken into account. It can be shown[24] that this treatment may be applied rigorously (that is, micelles can be considered as a separate pseudophase) when the concentration of the substrates is not sufficient to saturate the micellar phase and the substrates partition independently of each other.

The analysis of the effect of CTAB on the thiolysis of NPA demonstrates unequivocally that the rate acceleration can be attributed exclusively to concentration of the substrates in the micellar phase. The calculated second-order rate constants for thiolysis of NPA by thiophenoxide, p-methylthiophenoxide, and p-methoxythiophenoxide in the micellar phase are, within experimental error, identical to the second-order rate constants measured in the absence of CTAB. The calculated second-order rate constant for the thiolysis of NPA by p-chlorothiophenoxide is lower in the micellar phase than in water. Even in this case a net acceleration is observed, since this decrease in rate is outweighed by the concentration of NPA and p-chlorothiophenoxide in the micellar phase.

The distribution constants for the thiophenoxide anions increase in the order

$$p\text{-MeO} < p\text{-H} < p\text{-Me} < p\text{-Cl}$$

On the other hand, the distribution constants for the undissociated thiophenols are smaller than those for the corresponding anions and have a constant value of ca. 1×10^3 M^{-1}. This difference between the distribution constants for the protonated and unprotonated forms of the thiophenols indicates that the association of the thiophenoxides with the micelle has a strong electrostatic component. Furthermore, the association of the thiophenoxides with CTAB exhibits a dependence on the para substituent; analogous substituent effects have been observed in other studies of the incorporation of negatively charged aromatic derivatives in CTAB.[25,26]

In conjunction with the substituent effects on K_a there is a corresponding shift in the apparent pKs of the thiophenols in the order

$$p\text{-MeO} < p\text{-H} < p\text{-Me} < p\text{-Cl}$$

In view of the lack of micellar effects on reactivity, this pK shift can be attributed to the increased solubilization of the thiophenoxide anions as compared to the thiophenols.

The data presented above strongly suggest that the lack of micellar effects on the second-order rate constants is related to the position of the thiophenoxide ions in the CTAB micelle. The relative orders and magnitudes of the association constants for the thiophenoxide anions and the thiophenols suggest, as has been previously shown for cases of other negatively charged aromatics,[11] that the principal interaction involved in the association of the thiophenoxide(s) with the micelle is that between the positive surfactant head group and the aromatic ring. Such an interaction would tend to restrict the environment of the negatively charged sulfur to the aqueous limit of the Stern layer. This environment, and the

fact that nucleophilic attack of the thiophenoxide anions is probably not rate limiting in this case,[27] would minimize the effect of the interface on the reaction rate.

We emphasize, however, that the absence of significant intrinsic rate effects on the thiolysis of NPA by thiophenoxides in CTAB cannot be taken as general phenomenon, i.e., the lack of an effect of charged interfaces on the reactivity of SH groups. Indeed preliminary investigations[14] of the thiolysis of NPA by long-chain alkyl mercaptans, which is not limited by the same restrictions, show that the catalytic factors are much higher than those predicted on the basis of eq 9 with $k_{2M} = k_{2w}$.

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Registry No.—CTAB, 57-09-0; NPA, 830-03-5.

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Addition of Organocopper(I) Reagents to α,β-Acetylenic Sulfoxides[1a]

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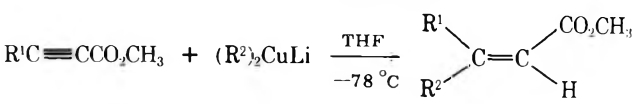
α,β-Acetylenic sulfoxides (**2**) reacted readily with monoalkylcopper reagents (**1**) at −78 °C in tetrahydrofuran to afford high yields of β-alkylated α,β-ethylenic sulfoxides (**3**). As in the analogous reaction with α,β-acetylenic esters, the addition was highly stereoselective, giving the product of a cis addition to the triple bond almost exclusively. The product sulfoxides were oxidized almost quantitatively with *m*-chloroperbenzoic acid to produce the corresponding sulfones (**12**) stereospecifically, thus providing a highly stereoselective synthesis of isomeric α,β-ethylenic sulfones. The structures of these compounds, and thus the cis nature of the addition reaction, were established on the basis of their ^{1}H NMR spectra, and in the case of (*Z*)- and (*E*)-1-(ethanesulfonyl)-2-methyl-1-hexene (**14a** and **14b**) were confirmed unambiguously by an alternate stereospecific synthesis of each isomer. The reaction of (*E*)-2-iodo-1-(ethanesulfonyl)-1-hexene (**21**) with methylcopper bis(diisopropyl sulfide) gave **14a**, while (*E*)-2-iodo-1-(ethanesulfonyl)propene (**20**) and the corresponding *n*-butylcopper complex gave **14b**. In contrast to the clean addition of monoalkylcopper reagents to acetylenic sulfoxides, lithium di-*n*-butylcuprate reacted with **2a** and **2b** to also give ethyl *n*-butyl sulfoxide. This cleavage product presumably resulted from attack at the sulfoxide sulfur rather than additive attack on the triple bond.

The chemistry of organocopper(I) reagents represents an ever-expanding topic of investigation that has received a great deal of attention in recent years.[2] In particular, the conjugate addition reactions of organocopper(I) reagents with α,β-unsaturated carbonyl compounds and related substances have been actively investigated since 1966, when it was demonstrated that such species were the reactive intermediates in the copper-catalyzed conjugate additions of Grignard reagents to α,β-unsaturated ketones.[3] α,β-Acetylenic esters also undergo a facile conjugate addition reaction with lithium diorganocuprates,[4] with cis addition taking place exclusively.



In contrast, an investigation of the reaction of lithium dialkylcuprates with a number of α,β-ethylenic sulfur compounds[5] has shown that with these substrates conjugate addition, if it occurs at all, is more difficult than with α,β-ethylenic carbonyl compounds, and that competing side reactions are more prevalent.

At the time this work was initiated, no additions of organocopper(I) reagents to α,β-acetylenic sulfur compounds had

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Table I. Addition of Monoalkylcopper Reagents (1) to α,β-Acetylenic Sulfoxides (2)

R^1	Registry no.	R^2	Registry no.	% cis addition	Product	Registry no.	% yield
CH_3 (1a)	1184-53-8	CH_3 (2a)	25558-06-9		4	65832-85-1	100
CH_3 (1a)		n-C_4H_9 (2b)	54088-87-8	>96[a]	5a	54088-88-9	100
n-C_4H_9 (1b)	34948-25-9	CH_3 (2a)		98.8[a]	5b	54088-89-0	98
CH_3 (1a)		C_6H_5 (2c)	65832-84-0	100[b]	6a	65832-86-2	93
C_6H_5 (1c)	3220-49-3	CH_3 (2a)		100[b]	6b	65832-87-3	100
CH_3 (1a)		H (2d)	36565-71-6	100[c]	7	65832-88-4	81
n-C_4H_9 (1b)		n-C_4H_9 (2b)			8	65832-89-5	97
n-C_4H_9 (1b)		C_6H_5 (2c)		100[b]	9a	65832-90-8	97.5
C_6H_5 (1c)		n-C_4H_9 (2b)		100[b]	9b	65832-91-9	100
n-C_4H_9 (1b)		H (2d)		100[b]	10	65832-92-0	96.5
C_6H_5 (1c)		C_6H_5 (2c)			11	57642-54-3	100

[a] Determined by GLC analysis after oxidation of the sulfoxide to the sulfone. [b] Determined by NMR. No indication in the sulfoxide, or the sulfone derived from it, of any of the trans addition product. [c] NMR of the sulfoxide was complicated by contamination with unidentified nonisomeric material and was ambiguous; NMR of the sulfone derived from it indicated only the product of cis addition.

Table II. Oxidation of α,β-Ethylenic Sulfoxides (3) to α,β-Ethylenic Sulfones (12)

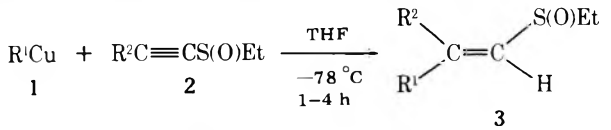
Sulfoxide, mmol	Peracid,[a] mmol	Sulfone, % yield	Registry no.
4, 1.50	1.50	**13**, 100	65832-93-1
5a, 1.57	1.65[b]	**14a**, 99	54088-92-5
5b, 2.57	2.75[c]	**14b**, 88	54088-91-4
6a, 2.76	2.76	**15a**, 100	58202-55-4
6b, 1.44	1.44	**15b**, 100	65832-94-2
7, 1.07	1.07	**16**, 66	65832-95-3
8, 1.505	1.58[b]	**17**, 100	58202-53-2
9a, 2.76	2.76	**18a**, 100	58202-56-5
9b, 1.44	1.44	**18b**, 100	58202-54-3
10, 0.817	0.817	**19**, 95	65832-96-4

[a] 85% m-chloroperbenzoic acid. [b] 5% excess. [c] 7% excess.

been reported. It was anticipated, however, that, since acetylenic substrates are more subject to nucleophilic attack than their ethylenic analogues,[6] acetylenic organosulfur compounds would readily undergo conjugate addition reactions with organocopper reagents. This expectation has been justified and we have briefly described the results of our investigation of the addition of monoalkylcopper reagents and lithium diorganocuprates to α,β-acetylenic sulfoxides.[7] The data presented herein represent a more complete account of that work. During the course of this investigation a preliminary account of the conjugate addition of Grignard reagents to α,β-acetylenic sulfides in the presence of stoichiometric amounts of cuprous halides was reported by other workers.[8a] Subsequently they have published brief reports of similar additions to acetylenic sulfoxides[8b] and sulfones[8c] which completely support the findings to be presented here.

Results and Discussion

RCu Additions. Monoalkylcopper reagents (1) were found to react with α,β-acetylenic sulfoxides (2) in a highly stereoselective manner to produce excellent yields of β-alkylated α,β-ethylenic sulfoxides (3) (Table I). In all cases the product

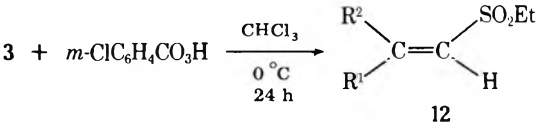


3

of a cis addition of R^1 and H to the triple bond was formed almost exclusively. Addition took place even with a terminal acetylenic sulfoxide (**2d**) with no observable abstraction of the acetylenic proton by the organometallic reagent.

In all reactions involving the possible formation of geometrical isomers, the NMR spectra of the crude ethylenic sulfoxides showed the stereoselective formation of essentially only *one* isomer, it usually being clear, when each isomer was available (**5, 6, 9**), that the members of each (*E*)-(*Z*) pair were distinguishable by NMR. In the case of **6**, the NMR spectra of each isomer appeared very similar, and there was some doubt that the differences between the two spectra were real, possibly being due to solvent effects instead. When the two presumed isomers were combined to give an approximately 1:1 mixture, however, the NMR spectrum showed without question two distinctly different compounds.

The direct GLC analysis of the sulfoxide products of these reactions (as well as the acetylenic sulfoxide starting materials) proved to be difficult due to thermal decomposition[9] of these compounds at the temperatures (>125 °C) necessary to elute them from even nonpolar (SE-30, SF-96) columns. The corresponding sulfones, however, were quite stable thermally and were readily obtained from the sulfoxides. Treatment of the sulfoxides, **3**, with 1.0 equiv of m-chloroperbenzoic acid in chloroform at 0 °C for 24 h produced almost quantitative yields of the α,β-ethylenic sulfones, **12** (Table II).

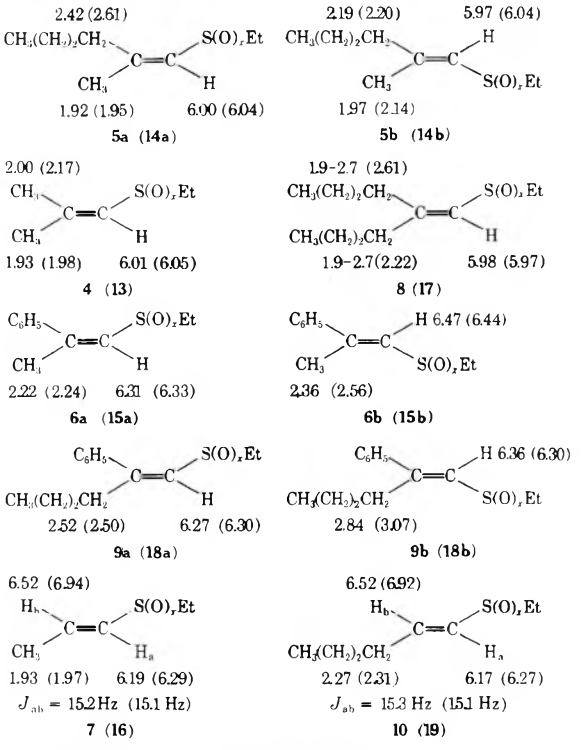


12

In all cases involving the oxidation of a *single* sulfoxide geometrical isomer, only *one* sulfone isomer (as shown by NMR and, in some cases, by GLC) was formed with retained configuration.

Structural Assignments. In order to determine the stereochemistry of the organocopper(I) addition reactions it was necessary to determine unambiguously the stereochemical structure of the olefinic products. This was carried out using three independent approaches. The structure of each isomer of sulfoxides **5, 6,** and **9** (and the corresponding sulfones **14, 15,** and **18**) was deduced from a comparison of the NMR spectra of the two isomers in each pair, primarily of the chemical shift values of their allylic methyl and methylene protons. In the case of the disubstituted olefins **7** and **10** (and the corresponding sulfones **16** and **19**) the stereochemistry was determined on the basis of the magnitude of the olefinic proton coupling constant. Finally, these structural assignments were confirmed in two cases by a stereospecific alternate synthesis of the isomeric sulfones **5a** and **5b**. These were shown to be identical to the sulfones derived from the sulfoxide products of the addition of respectively **1a** to **2b** and **1b** to **2a**.

Table III. NMR Data for α,β-Ethylenic Sulfoxides (3) and Sulfones (12; the Sulfone δ Values are in Parentheses)[a]



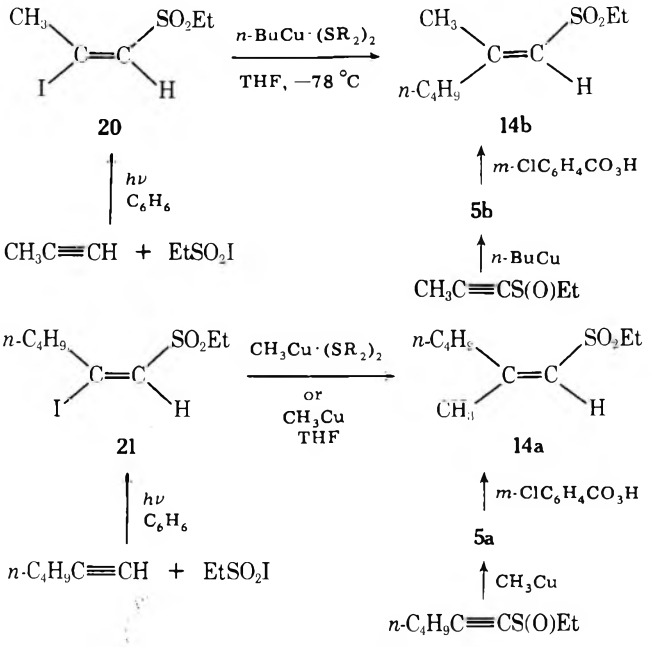
[a] 10–20% (v/v) in $CDCl_3$, ppm (δ) downfield from tetramethylsilane: sulfoxide, $x = 1$ (sulfone, $x = 2$).

The ^{1}H-NMR absorptions due to the allylic methyl and methylene protons in the ethylenic sulfoxides, **3**, and the corresponding sulfones, **12**, were expected to appear further downfield when they were cis to the sulfur functionality than when they were trans to the sulfoxide or sulfone group.[10,11] Therefore, the (*E*) structure was assigned to sulfoxide **5b** and sulfone **14b**, which have their allylic methyl absorption at lower field and their allylic methylene signal at higher field than **5a** and **14a**, respectively (Table III). The values for the allylic methyl and methylene protons in these compounds also matched very closely those for the corresponding methyl groups in **4** and **13** and the corresponding methylene groups in **8** and **17**. In a similar fashion the (*E*) configuration was assigned to sulfoxides **6b** and **9b** and sulfones **15b** and **18b** and the (*Z*) configuration to **6a**, **15a**, **9a**, and **18a**. These assignments were further substantiated by an examination of the chemical shifts of the vinyl protons in these aromatic systems. Those vinyl protons cis to a phenyl group were expected to be deshielded to a greater extent by its induced magnetic field than those trans to it, which would be essentially unaffected by the diamagnetic anisotropy of the aromatic ring. The NMR spectra of the above mentioned aryl compounds were in complete agreement with this prediction in all of the structural assignments made above.

When addition product **3** and its derived sulfone **12** were disubstituted olefins, the olefinic protons were found to have an NMR coupling constant of approximately 15 Hz (this was especially evident with the sulfones **16** and **19**), indicating a trans arrangement about the double bond. The assignment of a trans geometry for these compounds was also supported by the presence of a strong band in the 960–980-cm^{-1} region of the infrared spectra of sulfoxides **7** and **10**, while there was virtually no absorption in the 665–730-cm^{-1} region that could be attributed to a cis olefin.

Alternate Synthesis of 14a and 14b. The addition of sulfonyl iodides to acetylenes to produce iodovinyl sulfones (e.g., **20** and **21**) has been shown to take place in a trans fashion exclusively.[12] Replacement of the halogen by an alkyl or aryl group would then lead to a sulfone of the same kind (**12**) as that obtained from sulfoxide **3**. Simple vinyl halides have been shown to undergo this type of displacement of halogen by lithium diorganocuprates, with almost complete retention of stereochemistry.[13,14] Although the reaction of iodovinyl sulfones with cuprous phenylacetylide[12,15] was under investigation in this laboratory concurrent with the present study, a similar reaction with simple alkyl or aryl organocopper(I) reagents had not been previously reported.

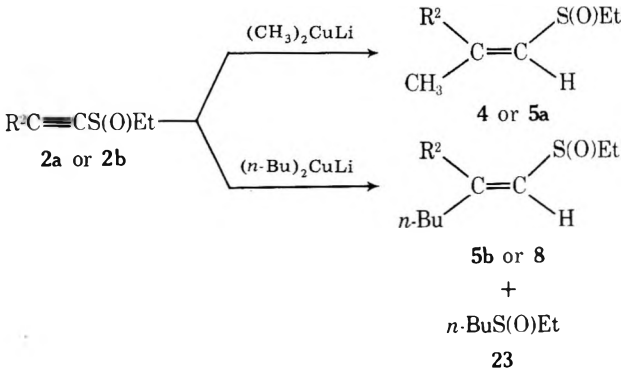
We have found that the reaction of **20** with an *n*-butylcopper bis(diisopropyl sulfide) complex leads to the highly stereospecific formation of **14b** in 88% yield.[7] The same reaction with lithium di-*n*-butylcuprate, or the similar reaction of **21** with lithium dimethylcuprate,[16] however, gave nonstereospecific coupling, resulting in 20:80 (with $(n\text{-Bu})_2$CuLi) and 64:36 (with Me_2CuLi after 3.5 h; 54:46 after 4.5 h) mixtures of **14a** and **14b**. The reaction of **21** with a methylcopper bis-



(diisopropyl sulfide) complex also gave highly stereospecific coupling, although it also gave, after 5 h at −78 °C, considerable amounts of recovered **21**, and a by-product, **22**. Fortunately, reacting *uncomplexed* methylcopper with **21** for 8 h at −78 °C resulted in almost complete consumption of the iodovinyl sulfone, although sizable quantities of **22** were still produced. Happily, the stereospecificity of this reaction was, if anything, slightly higher. The identity of **22** has been established by other workers in this laboratory as being *n*-BuCH=CHSO$_2$Et of predominantly the cis configuration.[17] This presumably arose through protonation of a vinyl copper species formed via copper–halogen exchange between the organocopper reagent and the iodovinyl sulfone, in a manner similar to that observed with simple vinyl halides.[13] Working up the reaction by adding an excess of methyl iodide prior to protonation[13] decreased slightly the amount of **22** formed but did not eliminate it. Another investigation in this laboratory based upon and performed subsequent to this work has uncovered experimental conditions, which efficiently prevent this undesired side reaction. A study of the reaction of organocopper(I) reagents with iodovinyl sulfones[15] has shown that methylcopper reacts smoothly with **21** at 0 °C in THF to give **14a** exclusively to the total exclusion of **22**.

R_2CuLi Additions. While monoalkylcopper reagents added cleanly to **2**, some lithium diorganocuprates also gave a by-product resulting from cleavage of the acetylenic sulfoxide.

Although lithium dimethylcuprate added normally to **2a** (83%) and **2b** (97.5%, >96% cis addition), lithium di-*n*-butylcuprate reacted to give appreciable quantities of ethyl-*n*-butyl sulfoxide (**23**) as well. Apparently the more reactive



lithium di-*n*-butylcuprate can attack the acetylenic sulfoxide at sulfur to displace an acetylide, as well as adding to the triple bond. The less reactive lithium dimethylcuprate, in contrast, was only capable of additive attack on the triple bond. It might be argued that this cleavage product could be arising from small amounts of *n*-butyllithium present in the reaction mixture, rather than from $(n\text{-Bu})_2\text{CuLi}$. Indeed, *n*-butyllithium did react with **2a** under the same conditions to give predominantly cleavage to **23**, as well as lesser amounts of 1-ethylsulfinylpropadiene (**24**) (resulting from isomerization of the starting acetylenic sulfoxide).

$$\underset{\textbf{2a}}{CH_3C{\equiv}CS(O)Et} + n\text{-BuLi} \xrightarrow[-78\ ^\circ C]{THF} \textbf{23} + \underset{\textbf{24}}{H_2C{=}C{=}CHS(O)Et}$$

In spite of this result, however, we do not favor this explanation for several reasons. An accidential slight excess of *n*-butyllithium was precluded in these reactions by using a 2% excess of cuprous iodide in the formation of the diorganocuprate. In addition it was considered highly improbable that an error in quantities could have occurred sufficiently large to produce the observed yields of **23** (on the order of 20% as determined by GLC after oxidation of the sulfoxide products to sulfones). Furthermore, it has been shown that alkyllithiums are *not* present in solutions of lithium diorganocuprates due to an equilibrium with the monoalkylcopper

Experimental Section

General. Infrared spectra were recorded on either a Beckman IR-33 or a Perkin-Elmer Model 137B infracord infrared spectrometer. NMR spectra were recorded on a Varian A-60A instrument. Mass spectra were obtained on a Hitachi RMU-6A mass spectrometer. Microanalyses were performed by Dr. C. S. Yeh and staff, Purdue University. Analytical and preparative gas–liquid phase chromatography (GLC) were performed on a Wilkins (Varian) Aerograph Autoprep Model A-700 instrument having a thermal conductivity detector and using helium as a carrier gas. Column A: 8 ft × 0.25 in., 15% neopentyl glycol isophthalate on 60–80 mesh Chromasorb W; column B: 10 ft. × 0.25 in., 10% OV-17 on 60–80 mesh, acid washed, dimethyldichlorosilane treated (AW/DMCS) Chromosorb W; column C: 6.5 ft. × 0.375 in., 10% GE SF-96 on 60–80 mesh, AW/DMCS Chromosorb W.

Reagent grade tetrahydrofuran (THF) was distilled from lithium aluminum hydride under nitrogen immediately before use. Anhydrous methanol was stored over 3A molecular sieves. Cuprous iodide was purchased from Research Organic/Inorganic Chemical Corp. and was purified by the method of Posner and Sterling.[19] Diisopropyl sulfide and 85% *m*-chloroperbenzoic acid were obtained from Aldrich Chemical Co. and were used without further purification. Methyllithium (manufactured from methyl chloride by Foote Mineral Co.) was purchased from Matheson Coleman and Bell, and *n*-butyl- and phenyllithium were obtained from Alfa Inorganics (Ventron). They were stored in the cold under nitrogen and were standardized by a modified Gilman double titration method.[20]

Apparatus for experiments requiring dry conditions were either flame or oven dried and cooled under a stream of nitrogen. During work-up of the reactions, general drying of the solvent was performed over anhydrous magnesium sulfate and the solvent was removed on a rotary evaporator in vacuo at water aspirator pressure.

Preparation of α,β-Acetylenic Sulfoxides (2). These were prepared from the corresponding α,β-acetylenic sulfides[21] by oxidation with 1.0 equiv of *m*-chloroperbenzoic acid in chloroform at 0 °C for 24 h.[22]

1-(Ethanesulfinyl)-1-hexyne (**2b**) was obtained from 1-(ethylthio)-1-hexyne[23] in 86% yield: bp 72 °C (0.20 mm) (75 °C (0.17 mm)); IR (neat) 2205 (s, C≡C), 1078 cm^{-1} (s, S→O); NMR ($CDCl_3$ δ 0.93 (distorted t, 3 H), 1.38 (t, *J* = 7.25 Hz, 3 H), 1.15–2.0 (m, 4 H), 2.47 (broadened t, 2 H), 2.99 (q, *J* = 7.25 Hz, 2 H). Anal. Calcd for $C_8H_{14}OS$: C, 60.72; H, 8.92; S, 20.26. Found: C, 61.02; H, 8.81; S, 20.01.

1-(Ethanesulfinyl)-2-phenylethyne (**2c**) was obtained crude, after removing traces of solvent in vacuo at 4 mm, in quantitative yield from 1-(ethylthio)-2-phenylethyne.[23] This was used as such in subsequent organocopper(I) reactions, the NMR indicating it contained no major impurities, since it was found to decompose with vigorous evolution of a gas upon attempted distillation at approximately 90 °C (0.2 mm): IR (neat) 2185 (s, C≡C), 1075, 1035 (s, S→O), 761, 692 (s, C_6H_5), 1607, 1583, 1499, 1452, 835 cm^{-1}; NMR ($CDCl_3$) δ 1.49 (t, *J* = 7.25 Hz, 3 H), 3.13 (q, *J* = 7.25 Hz, 2 H), 7.42 (m, 5 H).

General Procedure for the Addition of R^1Cu (1) to α,β-Acetylenic Sulfoxides (2). A quantity of cuprous iodide 2% in excess of the number of moles of organolithium reagent to be used was weighed into a round-bottom flask containing a magnetic stirring bar and having a side arm fitted with a rubber septum stopper. After fitting with a gas inlet adapter tube (with stopcock) and oven drying, the flask was connected to a mercury bubbler via the adapter tube and was cooled while flushing with prepurified nitrogen introduced through the septum stopper via a syringe needle. A dry THF was then injected, the volume of which, in combination with the volume of organolithium solution to be used, resulted in an approximately 0.25 M solution of the organocopper(I) reagent. The resulting stirred suspension was placed in a cooling bath (0 °C for MeLi and PhLi, −10 °C for *n*-BuLi) and a solution of the organolithium reagent was injected over a 1–2-min period. The more stable organocopper(I) reagents (methyl and phenyl) were allowed to stir at 0 °C for 10 min and then cooled to −78 °C for 15 min, while the less stable *n*-butyl reagents were cooled in a dry ice–acetone bath immediately. Into this solution of RCu (25 mol % in excess of the acetylenic sulfoxide) was then rapidly injected a 0.25 M solution (precooled to −78 °C) of **2** in THF. After stirring at −78 °C for 1–4 h, the reaction was quenched by injecting 5–10 mL of anhydrous methanol (precooled in a syringe to −78 °C) and then pouring the resulting mixture into a saturated aqueous ammonium chloride solution. Extraction with dichloromethane (3 × 25 mL), drying, and evaporation in vacuo usually gave essentially pure ethylenic sulfoxide **3** (Table IV). During the aqueous workup, an orange, yellow, or yellow-grey to silver-grey solid was usually formed. During the extractions, this was found for the most part in the more dense dichloromethane layer. No attempt was made

Table IV. Experimental Data for the Reaction of R^1Cu (1) with $R^2C{\equiv}CS(O)Et$ (2)

R^1Cu	CuI, mmol	R^1Li, mmol	Acetylene, mmol	Time, h	Product, % yield
1a	3.37	3.30[a]	**2a**, 2.64	2.0	**4**[f]
1a	3.82	3.74[b]	**2b**, 2.99	1.5	**5a**[f]
1b	3.87	3.87[c]	**2a**, 3.1	2.0	**5b**, 98
1a	7.575	7.425[a]	**2c**, 5.94	2.0	**6a**, 93
1c	3.67	3.60[d]	**2a**, 2.88	4.0	**6b**[f]
1a	1.68	1.65[a]	**2d**, 1.32	2.0	**7**, 81
1b	3.95	3.87[c]	**2b**, 3.1	1.0	**8**, 97
1b	7.21	7.07[e]	**2c**, 5.66	2.0	**9a**, 98
1c	3.67	3.60[d]	**2b**, 2.88	4.0	**9b**[f]
1b	2.00	1.96[e]	**2d**, 1.57	2.0	**10**, 97
1c	7.72	7.56[d]	**2c**, 6.05	4.0	**11**[f]

[a] 1.65 M methyllithium in diethyl ether. [b] 1.78 M methyllithium in diethyl ether. [c] 1.76 M *n*-butyllithium in *n*-hexane. [d] 1.80 M phenyllithium in 70:30 benzene–diethyl ether. [e] 2.02 M *n*-butyllithium in *n*-hexane. [f] Quantitative.

to prevent this solid from being drawn off with the organic extracts, since it was easily removed later along with the drying agent by filtration. Purification for microanalysis was usually accomplished by molecular distillation at reduced pressure. (Satisfactory analyses could not be obtained for the sulfoxides **4, 5a, 5b,** and **6a,** although they were obtained for the corresponding sulfones.)

1-(Ethanesulfinyl)-2-methylpropene (4): IR (neat) 1646, 800 (m, $R_2C{=}CHR$), 1049, 1024 (s, S→O), 2965, 2940, 2900, 1453, 1385, 1265, 1173, 976, 859 cm^{-1}; NMR ($CDCl_3$) δ 1.25 (t, J = 7.5 Hz, 3 H), 1.93 (d, J = 1.25 Hz, 3 H), 2.00 (d, J = 1.25 Hz, 3 H), 2.75 (q, J = 7.5 Hz, 2 H), 6.01 (m, 1 H).

(*Z*)-1-(Ethanesulfinyl)-2-methyl-1-hexene (5a): IR (neat) 2985, 2960, 2895, 1464 (s, CH), 1637, 797 (m, $R_2C{=}CHR$), 1050, 1026 (s, S→O), 1389, 1262, 1170, 1101, 973, 932, 731 cm^{-1}; NMR ($CDCl_3$) 0.93 (distorted t, 3 H), 1.27 (t, J = 7.5 Hz, 3 H), 1.1–1.8 (m, 4 H), 1.92 (d, J = 1.4 Hz, 3 H), 2.42 (broadened t, 2 H), 2.72 (q, J = 7.5 Hz, 2 H), 6.00 (m, 1 H).

(*E*)-1-(Ethanesulfinyl)-2-methyl-1-hexene (5b): IR (neat) 2985, 2960, 2900 (s, CH), 1642, 809 (m, $R_2C{=}CHR$), 1050, 1026 (s, S→O), 1465, 1390, 1265, 1170, 1117, 978, 936, 865, 740; NMR ($CDCl_3$) δ 0.92 (distorted t, 3 H), 1.24 (t, J = 7.5 Hz, 3 H), 1.1–1.8 (m, 4 H), 1.97 (d, J = 1.1 Hz, 3 H), 2.19 (broadened t, 2 H), 2.73 (q, J = 7.5 Hz, 2 H), 5.97 (m, 1 H).

(*Z*)-β-(Ethanesulfinyl)-α-methylstyrene (6a): IR (neat) 1624 (w, shoulder, C=C), 1045, 1023 (s, S→O), 835 and/or 804 (m, $R_2C{=}CHR$), 767, 701 (s, C_6H_5), 3080, 3055, 3000, 2960, 2940, 2900, 1607, 1580, 1501, 1447, 1383, 1329, 1265, 1190, 1165, 1135, 1080, 972, 922, 729 cm^{-1}; NMR ($CDCl_3$) δ 1.22 (t, J = 7.5 Hz, 3 H), 2.22 (d, J = 1.4 Hz, 3 H), 2.74 (q, J = 7.5 Hz, 2 H), 6.31 (q, J = 1.4 Hz, 1 H), 7.32 (s, 5 H).

(*E*)-β-(Ethanesulfinyl)-α-methylstyrene (6b) was purified for microanalysis by molecular distillation at 70 °C (0.15 mm): IR (neat) 1615 (m, C=C), 1046, 1027 (s, S→O), 812 (s, $R_2C{=}CHR$), 753, 696 (s, C_6H_5), 3080, 3050, 3000, 2960, 2900, 1581, 1505, 1451, 1390, 1311, 1261, 1235, 1194, 1168, 1078, 975, 924 cm^{-1}; NMR ($CDCl_3$) δ 1.30 (t, J = 7.5 Hz, 3 H), 2.36 (d, $J \approx$ 1.25 Hz, 3 H), 2.85 (q, J = 7.5 Hz, 2 H), 6.47 (q, $J \approx$ 1.25 Hz, 1 H), 7.40 (m, 5 H). Anal. Calcd for $C_{11}H_{14}OS$: C, 68.00; H, 7.26; S, 16.50. Found: C, 68.10; H, 7.46; S, 16.35.

(*E*)-1-(Ethanesulfinyl)propene (7) was purified for microanalysis by molecular distillation at 52 °C (0.2 mm): IR (neat) 1646 (w, C=C), 1052, 1028 (s, S→O), 960 (s, *trans*-RCH=CHR), 3040, 3005, 2965, 2945, 2900, 1452, 1425, 1385, 1320, 1283, 1242, 1178, 1140, 1097, 813, 788, 760, 739, 620 cm^{-1}; NMR ($CDCl_3$) δ 1.25 (t, J = 7.5 Hz, 3 H), 1.93 (d, $J \approx$ 5.2 Hz, 3 H), 2.74 (q, J = 7.5 Hz, 2 H), 6.19 (d, $J \approx$ 15.2 Hz, 1 H), 6.52 (doublet, $J \approx$ 15.2 Hz, of distorted quartets, $J \approx$ 5.2 Hz, 1 H). Anal. Calcd for $C_5H_{10}OS$: C, 50.81; H, 8.53; S, 27.12. Found: C, 50.90; H, 8.59; S, 27.00.

1-(Ethanesulfinyl)-2-(*n*-butyl)-1-hexene (8) was purified for microanalysis by molecular distillation at 85 °C (0.15 mm): IR (neat) 2985, 2960, 2895 (s, CH), 1632, 820 (m, $R_2C{=}CHR$), 1050, 1029 (s, S→O), 1470, 1391, 1265, 1168, 1140, 1119, 976, 790, 735 cm^{-1}; NMR ($CDCl_3$) δ 0.93 (distorted t, 6 H), 1.27 (t, J = 7.5 Hz, 3 H), 1.1–1.9 (m, 8 H), 1.9–2.7 (m, 4 H), 2.74 (q, J = 7.5 Hz, 2 H), 5.98 (s, 1 H). Anal. Calcd for $C_{12}H_{24}OS$: C, 66.61; H, 11.18; S, 14.82. Found: C, 66.44; H, 11.33; S, 14.90.

(*Z*)-1-(Ethanesulfinyl)-2-phenyl-1-hexene (9a) was purified for microanalysis by molecular distillation at 86 °C (0.10 mm): IR (neat) 3080, 3050 (w, CH), 2980, 2955, 2895 (s, CH), 1624 (w, C=C), 1043, 1022 (s, S→O), 840 and/or 814 (m, $R_2C{=}CHR$), 772, 700 (s, C_6H_5), 1606, 1580, 1501, 1461, 1450, 1424, 1388, 1330, 1261, 1187, 1165, 1137, 1116, 1080, 970, 938, 920, 727 cm^{-1}; NMR ($CDCl_3$) δ 0.87 (distorted t, 3 H), 1.22 (t, J = 7.5 Hz, 3 H), 1.1–1.6 (m, 4 H), 2.52 (broadened t, 2 H), 2.74 (q, J = 7.5 Hz, 2 H), 6.27 (t, J = 1.25 Hz, 1 H), 7.31 (m, 5 H). Anal. Calcd for $C_{14}H_{20}OS$: C, 71.14; H, 8.53; S, 13.56. Found: C, 70.92; H, 8.69; S, 13.50.

(*E*)-1-(Ethanesulfinyl)-2-phenyl-1-hexene (9b) was purified for microanalysis by molecular distillation at 91 °C (0.2 mm): IR (neat) 3085, 3055 (m, CH), 2985, 2960, 2895 (s, CH), 1610, 822 (m, $R_2C{=}CHR$), 1050, 1029 (s, S→O), 757, 700 (s, C_6H_5), 1580, 1505, 1464, 1452, 1390, 1316, 1265, 1240, 1169, 1140, 1114, 976, 929, 880 cm^{-1}; NMR ($CDCl_3$) δ 0.87 (distorted t, 3 H), 1.32 (t, J = 7.5 Hz, 3 H), 1.1–1.8 (m, 4 H), 2.84 (q, J = 7.5 Hz, overlapping a broadened t, 4 H), 6.36 (s, 1 H), 7.37 (s, 5 H). Anal. Calcd for $C_{14}H_{20}OS$: C, 71.14; H, 8.53; S, 13.56. Found: C, 71.35; H, 8.57; S, 13.28.

(*E*)-1-(Ethanesulfinyl)-1-hexene (10) was purified for microanalysis by molecular distillation at 58 °C (0.15 mm): IR (neat) 2990, 2960, 2900 (s, CH), 1644 (m, C=C), 1060, 1030 (s, S→O), 973 (s, *trans*-RCH=CHR), 1426, 1390, 1320, 1280, 1263, 1140, 930, 788 cm^{-1}; NMR ($CDCl_3$) δ 0.92 (distorted t, 3 H), 1.26 (t, J = 7.5 Hz, 3 H), 1.1–1.8 (m, 4 H), 2.27 (d of overlapping, broadened t, 2 H), 2.73 (q, J = 7.5 Hz, 2 H), 6.17 (d, J = 15.3 Hz, 1 H), 6.52 (doublet, J = 15.3 Hz, of distorted triplets, J = 6.0 Hz, 1 H). Anal. Calcd for $C_8H_{16}OS$: C, 59.95; H, 10.06; S, 20.00. Found: C, 59.74; H, 10.18; S, 20.03.

β-(Ethanesulfinyl)-α-phenylstyrene (11). The crude product was recrystallized from cyclohexane to give 0.927 g (59.7%) of analytically pure light yellow crystals: mp 99–100.5 °C; IR (KBr) 1046, 1017 (s, S→O), 865 (m, $R_2C{=}CHR$), 765, 699 (s, C_6H_5), 3085, 3020, 2995, 2965, 2940, 2905, 1602, 1581, 1506, 1455, 1420, 1390, 1345, 1320, 1275, 1230, 1171, 1139, 1088, 971, 930, 808, 780, 732 cm^{-1}; NMR ($CDCl_3$) δ 1.26 (t, J = 7.5 Hz, 3 H), 2.83 (q, J = 7.5 Hz, 2 H), 6.82 (s, 1 H), 7.31 (s, 10 H). Anal. Calcd for $C_{16}H_{16}OS$: C, 74.96; H, 6.29; S, 12.51. Found: C, 74.76; H, 6.18; S, 12.57.

Oxidation of α,β-Ethylenic Sulfoxides (3) to α,β-Ethylenic Sulfones (12). To a 0.15–0.17 M solution of α,β-ethylenic sulfoxide (used as it was isolated directly from an organocopper(I) addition reaction) in chloroform at 0 °C was added 1.0 equiv of solid 85% *m*-chloroperbenzoic acid. After stirring at 0 °C for 24 h, the reaction mixture was washed twice with a solution made up of equal volumes (usually 10–20 mL each) of a 10% Na_2SO_3 solution and a saturated $NaHCO_3$ solution. Drying and evaporation in vacuo usually gave an almost quantitative yield of essentially pure α,β-ethylenic sulfone (Table II). These compounds were purified for microanalysis by preparative GLC.

1-(Ethanesulfonyl)-2-methylpropene (13) had a GLC retention time of 11.6 min on column A at 190 °C and 45 mL/min and was collected for microanalysis from column B under similar conditions: IR (neat) 1660, 814 (s, $R_2C{=}CHR$), 1321, 1298, 1149 (s, SO_2), 3075, 3020, 2980, 2960, 2925, 1469, 1439, 1400, 1256, 1199, 1098, 1070, 1000, 892, 730 cm^{-1}; NMR ($CDCl_3$) δ 1.34 (t, J = 7.5 Hz, 3 H), 1.98 (d, J = 1.35 Hz, 3 H), 2.17 (d, J = 1.25 Hz, 3 H), 3.00 (q, J = 7.5 Hz, 2 H), 6.05 (m, 1 H). Anal. Calcd for $C_6H_{12}O_2S$: C, 48.62; H, 8.16; S, 21.63. Found: C, 48.80; H, 8.41; S, 21.47.

(*Z*)-1-(Ethanesulfonyl)-2-methyl-1-hexene (14a) had a GLC retention time of 21.3 min on column A at 190 °C and 45 mL/min and was collected for microanalysis from column B under similar conditions: IR (neat) 2990, 2960, 2900 (s, CH), 1649 (s, C=C), 1320, 1290, 1144 (s, SO_2), 805 (m, $R_2C{=}CHR$), 1473, 1403, 1398, 1249, 1065, 993, 889, 865, 832 cm^{-1}; NMR ($CDCl_3$) δ 0.93 (distorted t, 3 H), 1.32 (t, J = 7.5 Hz, 3 H), 1.13–1.83 (m, 4 H), 1.95 (d, $J \approx$ 1.5 Hz, 3 H), 2.61 (broadened t, 2 H), 2.98 (q, J = 7.5 Hz, 2 H), 6.04 (broadened s, 1 H). Anal. Calcd for $C_9H_{18}O_2S$: C, 56.80; H, 9.53; S, 16.85. Found: C, 57.04; H, 9.57; S, 16.71.

(*E*)-1-(Ethanesulfonyl)-2-methyl-1-hexene (14b) had a GLC retention time of 29.0 min on column A at 190 °C and 45 mL/min and was collected for microanalysis from column B under similar conditions: IR (neat) 2990, 2960 (s, CH), 2900 (m, CH), 1641 (s, C=C), 1312, 1284, 1135 (s, SO_2), 800 (m, $R_2C{=}CHR$), 3075, 1464, 1427, 1393, 1241, 1179, 1055, 986, 938, 878, 717 cm^{-1}; NMR ($CDCl_3$) δ 0.92 (distorted t, 3 H), 1.30 (t, J = 7.0 Hz, 3 H), 1.1–1.85 (m, 4 H), 2.14 (d, $J \approx$ 1.5 Hz, 3 H), 2.20 (broadened t, 2 H), 2.99 (q, $J \approx$ 7.0 Hz, 2 H), 6.04 (m, 1 H). Anal. Calcd for $C_9H_{18}O_2S$: C, 56.80; H, 9.53; S, 16.85. Found: C, 56.72; H, 9.35; S, 16.63.

(*Z*)-β-(Ethanesulfonyl)-α-methylstyrene (15a) was collected for microanalysis from column C, retention time 9.7 min at 195 °C and 60 mL/min: IR (neat) 1636, 852 or 797 (m, $R_2C{=}CHR$), 1310, 1283, 1140 (s, SO_2), 770, 702 (s, C_6H_5), 3015, 2975, 2910, 1610, 1585, 1505, 1464, 1445, 1423, 1385, 1345, 1240, 1199, 1085, 1050, 1035, 981, 925, 736 cm^{-1}; NMR ($CDCl_3$) δ 1.20 (t, J = 7.5 Hz, 3 H), 2.24 (d, J = 1.45 Hz, 3 H), 2.67 (q, J = 7.5 Hz, 2 H), 6.33 (q, J = 1.45 Hz, 1 H), 7.37 (s, 5 H). Anal. Calcd for $C_{11}H_{14}O_2S$: C, 62.82; H, 6.71; S, 15.24. Found: C, 63.05; H, 6.53; S, 15.03.

(*E*)-β-(Ethanesulfonyl)-α-methylstyrene (15b) was collected for microanalysis from column C, retention time 14.6 min at 195 °C and 60 mL/min: IR (neat) 1620 (m, C=C), 1310, 1283, 1135 (s, SO_2), 830 or 812 (s, $R_2C{=}CHR$), 760, 697 (s, C_6H_5), 3085, 3010, 2970, 2905, 1582, 1506, 1453, 1420, 1390, 1240, 1197, 1080, 1050, 1005, 983, 924, 620 cm^{-1}; NMR ($CDCl_3$) δ 1.40 (t, J = 7.5 Hz, 3 H), 2.56 (d, $J \approx$ 1.25 Hz, 3 H), 3.09 (q, J = 7.5 Hz, 2 H), 6.44 (q, $J \approx$ 1.25 Hz, 1 H), 7.42 (s, 5 H). Anal. Calcd for $C_{11}H_{14}O_2S$: C, 62.82; H, 6.71; S, 15.24. Found: C, 62.67; H, 6.91; S, 15.07.

(*E*)-1-(Ethanesulfonyl)propene (16) was collected for microanalysis from column B, retention time 8.4 min at 185 °C and 30 mL/min: IR (neat) 3075, 3010, 2975, 2910 (w, CH), 1659, 964 (m, *trans*-RCH=CHR), 1320, 1300, or 1287, and 1137 (s, SO_2), 1452, 1426, 1390, 1247, 1056, 822, 789, 754, 711 cm^{-1}; NMR ($CDCl_3$) δ 1.32 (t, J = 7.5 Hz, 3 H), 1.97 (dd, J = 1.2, 6.5 Hz, 3 H), 2.98 (q, J = 7.5 Hz, 2 H), 6.29 (doublet, J = 15.1 Hz, of quartets, J = 1.2 Hz, 1 H), 6.94 (doublet, J = 15.1 Hz, of quartets, J = 6.5 Hz, 1 H). Anal. Calcd for $C_5H_{10}O_2S$: C, 44.75; H, 7.51; S, 23.89. Found: C, 44.98; H, 7.54; S, 23.80.

1-(Ethanesulfonyl)-2-(*n*-butyl)-1-hexene (17) was collected

for microanalysis from column B, retention time 25.6 min at 185 °C and 120 mL/min, and retention time 34.2 min on column A at 192 °C and 45 mL/min, reduced to 17.5 min at 120 mL/min: IR (neat) 2985, 2960, 2900 (s, CH), 1633, 821 (m, R_2C=CHR), 1313, 1283, 1138 (s, SO_2), 1425, 1390, 1290, 1056, 985, 939, 880, 790, 717 cm^{-1}; NMR ($CDCl_3$) δ 0.93 (distorted t, 6 H), 1.36 (t, J = 7.5 Hz, 3 H), 1.15–2.0 (m, 8 H), 2.22 (broadened t, 2 H), 2.61 (broadened t, 2 H), 3.00 (q, J = 7.5 Hz, 2 H), 5.97 (s, 1 H). Anal. Calcd for $C_{12}H_{24}O_2S$: C, 62.02; H, 10.41; S, 13.80. Found: C, 62.20; H, 10.22; S, 14.00.

(*Z*)-1-(Ethanesulfonyl)-2-phenyl-1-hexene (18a) was collected for microanalysis from column C, retention time 8.9 min at 225 °C and 60 mL/min: IR (neat) 2980, 2960 (s, CH), 2895 (m, CH), 1630, 840 (m, R_2C=CHR), 1310, 1281, 1128 (s, SO_2), 780, 700 (s, C_6H_5), 3080, 3060, 1609, 1582, 1502, 1462, 1451, 1422, 1390, 1240, 1192, 1082, 1051, 1031, 1008, 980, 940, 730 cm^{-1}; NMR ($CDCl_3$) δ 0.88 (distorted t, 3 H), 1.20 (t, J = 7.5 Hz, 3 H), 1.15–1.7 (m, 4 H), 2.50 (broadened t, 2 H), 2.63 (q, J = 7.5 Hz, 2 H), 6.30 (t, $J \approx$ 1.25 Hz, 1 H), 7.35 (s, 5 H). Anal. Calcd for $C_{14}H_{20}O_2S$: C, 66.63; H, 7.99; S, 12.70. Found: C, 66.50; H, 8.11; S, 12.45.

(*E*)-1-(Ethanesulfonyl)-2-phenyl-1-hexene (18b) was collected for microanalysis from column C, retention time 9.5 min at 225 °C and 60 mL/min: IR (neat) 2990, 2960 (s, CH), 2900 (m, CH), 1617, 830 (s, R_2C=CHR), 1315, 1285, 1140 (s, SO_2), 770 or 755, 700 (s, C_6H_5), 3090, 3060, 1583, 1507, 1466, 1455, 1423, 1392, 1242, 1089, 1056, 1020, 987, 930, 880, 620 cm^{-1}; NMR ($CDCl_3$) δ 0.87 (distorted t, 3 H), 1.42 (t, J = 7.5 Hz, 3 H), 1.1–1.7 (m, 4 H), 3.07 (m, 2 H), 3.08 (q, J = 7.5 Hz, 2 H), 6.30 (s, 1 H), 7.38 (s, 5 H). Anal. Calcd for $C_{14}H_{20}O_2S$: C, 66.63; H, 7.99; S, 12.70. Found: C, 66.87; H, 8.05; S, 12.45.

(*E*)-1-(Ethanesulfonyl)-1-hexene (19) was collected for microanalysis from column B, retention time 21.6 min at 190 °C and 30 mL/min: IR (neat) 2990, 2965, 2900 (s, CH), 1647, 989 (m, *trans*-RCH=CHR), 1324, 1289, 1141 (s, SO_2), 3080, 1479, 1429, 1395, 1244, 1058, 935, 889, 835, 732 cm^{-1}; NMR ($CDCl_3$) δ 0.92 (distorted t, 3 H), 1.32 (t, J = 7.5 Hz, 3 H), 1.1–1.8 (m, 4 H), 2.31 (m, 2 H), 2.98 (q, J = 7.5 Hz, 2 H), 6.27 (doublet, J = 15.1 Hz, of triplets, J = 1.1 Hz, 1 H), 6.92 (doublet, J = 15.1 Hz, of triplets, J = 6.0 Hz, 1 H). Anal. Calcd for $C_8H_{16}O_2S$: C, 54.51; H, 9.15; S, 18.19. Found: C, 54.37; H, 9.33; S, 18.30.

Alternate Synthesis of (*E*)-1-(Ethanesulfonyl)-2-methyl-1-hexene (14b). Diisopropyl sulfide (3.6 mL, 0.5 mL/mmol of CuI)[24] was injected into an ice-cold suspension of 1.368 g (7.18 mmol) of cuprous iodide in 20.5 mL of THF. After cooling to −10 °C, 4.0 mL (7.04 mmol) of 1.76 M *n*-butyllithium in *n*-hexane were injected over a 2 min period, followed by immediate cooling to −78 °C. Into this solution of *n*-butylcopper bis(diisopropyl sulfide) (2.5 equiv) was injected a solution (precooled to −78 °C) of 0.733 g (2.82 mmol, 1.0 equiv) of (*E*)-2-iodo-1-(ethanesulfonyl)propene (**20**)[25] in 11.3 mL of THF. After 5 h at −78 °C; 5 mL of anhydrous methanol was injected and the resulting reaction mixture was then poured into 25 mL of saturated ammonium chloride solution. Extraction with dichloromethane (3 × 25 mL), drying, and evaporation gave 2.092 g of light yellow *solid*, whose NMR showed the desired product and also an extremely large isopropyl absorption, possibly due to some kind of copper–diisopropyl sulfide complex. Bubbling air through a pentane solution of this material resulted in the precipitation of a fine yellow solid, which was filtered off. Evaporation of the pentane filtrate then gave 0.471 g (88%) of crude 1-(ethanesulfonyl)-2-methyl-1-hexene. GLC analysis on column A at 190 °C and 45 mL/min indicated that this was 93% pure and was predominantly the desired (*E*) isomer ((*E*):(*Z*) = 97.5:2.5), with NMR, IR, and GLC retention time identical to the sulfone, **14b**, obtained by oxidation of the product of the addition of *n*-butylcopper to 1-(ethanesulfinyl)propyne.

Reaction of Lithium Di-*n*-butylcuprate with (*E*)-2-Iodo-1-(ethanesulfonyl)propene (20). A solution of 0.687 g (2.64 mmol) of **20** in 10.5 mL of THF, precooled to −78 °C, was added rapidly to a solution of 5.0 equiv of lithium di-*n*-butylcuprate at −78 °C, prepared from 2.563 g (13.46 mmol) of cuprous iodide in 38 mL of THF and 15.0 mL (26.40 mmol) of 1.76 M *n*-butyllithium in *n*-hexane. After 0.5 h at −78 °C a 5-mL aliquot was withdrawn in a precooled syringe and injected into 1 mL of anhydrous methanol at −78 °C. Pouring into 5 mL of saturated NH_4Cl, extraction with dichloromethane (3 × 5 mL), drying, and evaporation in vacuo gave a yellow liquid. GLC analysis on column A at 190 °C and 45 mL/min showed that 69.7% of this material was a mixture of 1-(ethanesulfonyl)-2-methyl-1-hexenes, **14a:14b** = 19.5:80.5. In addition, 22.4% of this crude product was made up of two materials with retention times of 8.05 and 9.9 min, in a ratio of 72.5:27.5. These are probably the cis and trans isomers, respectively, of 1-(ethanesulfonyl)propene, arising from a vinyl copper species formed by copper–halogen exchange between the organocuprate and the iodovinyl sulfone.

The remainder of the reaction mixture was treated after 5.5 h with 3.2 mL (4.86 g, 26.40 mmol) of 1-iodobutane (precooled to −78 °C) and then stirred at 0 °C for 4 h. Working up in the same manner as before gave a yellow liquid. GLC analysis showed a similar **14a:14b** ratio of 28:72, but the amount of by-product at 7.8 and 9.5 min was much smaller.

Alternate Synthesis of (*Z*)-1-(Ethanesulfonyl)-2-methyl-1-hexene (14a). A solution of 0.598 g (1.98 mmol) of (*E*)-2-iodo-1-(ethanesulfonyl)-1-hexene (**21**)[12] in 7.9 mL of THF (precooled to −78 °C) was added to 2.5 equiv of methylcopper bis(diisopropyl sulfide) at −78 °C, prepared in the same manner as the *n*-butylcopper complex from 1.038 g (5.45 mmol) of cuprous iodide and 2.725 mL of diisopropyl sulfide in 14.1 mL of THF and 3.0 mL (4.95 mmol) of 1.65 M methyllithium in diethyl ether. After stirring for 5 h at −78 °C, 5 mL of anhydrous methanol (precooled to −78 °C) was injected, and the reaction mixture then poured into 40 mL of saturated ammonium chloride. Extraction with dichloromethane (3 × 25 mL), drying, and evaporation in vacuo gave 1.51 g of white *solid*. Bubbling air through a pentane solution of this material, followed by filtration and evaporation of the filtrate in vacuo, gave 0.446 g of a pink liquid. GLC analysis of this material on column B at 190 °C and 45 mL/min showed that there was still starting iodovinyl sulfone **21** present. To the extent that 1-(ethanesulfonyl)-2-methyl-1-hexene was formed, however, the (*Z*) isomer was formed stereospecifically (**14a:14b** = 94.5:5.5). In addition, there was a pair of by-product peaks at 9.9 and 12.3 min, in a ratio of 2:98 (**14:21:22** = 50.2:33.4:16.4). The NMR also showed the desired (*Z*) isomer, **14a**, and the iodovinyl sulfone, **21**, and showed further vinyl absorption in the δ 6.2–6.5 region due to the by-product, **22**.

Reaction of Methylcopper with (*E*)-2-Iodo-1-(ethanesulfonyl)-1-hexene (21). A solution of 0.598 g (1.98 mmol) of **21** in 7.9 mL of THF (precooled to −78 °C) was added to 2.5 equiv of methylcopper at −78 °C prepared from 0.962 g (5.05 mmol) of cuprous iodide in 16.8 mL of THF and 3.0 mL (4.95 mmol) of 1.65 M methyllithium in diethyl ether. After stirring for 8 h at −78 °C, a 13.0-mL aliquot was withdrawn in a precooled syringe and injected into 5 mL of anhydrous methanol at −78 °C. Pouring into 40 mL of saturated ammonium chloride, extraction with dichloromethane (3 × 15 mL), drying, and evaporation in vacuo gave 0.203 g of material. GLC analysis on column B showed that essentially all of the iodovinyl sulfone had been consumed but that substantial amounts of by-product were still present (**14:21:22** = 71.9:4.9:23.2), although the formation of 1-(ethanesulfonyl)-2-methyl-1-hexene was still stereospecific (**14a:14b** = 96.3:3.7).

To the remainder of the reaction mixture was added a solution of 1.54 mL (3.515 g, 24.7 mmol) of methyl iodide in 5 mL of THF (precooled to −78 °C). After stirring for an additional 2 h, injection of 5 mL of precooled anhydrous methanol and work-up exactly as before gave 0.190 g of liquid. GLC analysis showed there was only a moderate decrease in the amount of by-product, with little change otherwise.

Addition of Lithium Dimethylcuprate to 1-(Ethanesulfinyl)-propyne (2a). A solution of 0.413 g (3.56 mmol) of **2a** in 14.2 mL of THF (precooled to −78 °C) was added to a solution of 1.25 equiv of lithium dimethylcuprate, prepared from 0.865 g (4.54 mmol) of cuprous iodide in 12.8 mL of THF and 5.0 mL (8.9 mmol) of 1.78 M methyllithium in diethyl ether. After stirring at −78 °C for 2 h, 5 mL of anhydrous methanol (precooled to −78 °C) was injected. Pouring into 25 mL of saturated ammonium chloride, extraction with dichloromethane (3 × 25 mL), drying, and evaporation in vacuo gave 0.393 g (83%) of essentially pure 1-(ethanesulfinyl)-2-methylpropene (**4**).

Addition of Lithium Dimethylcuprate to 1-(Ethanesulfinyl)-1-hexyne (2b). Lithium dimethylcuprate, prepared from 0.727 g (3.82 mmol) of cuprous iodide in 11.8 mL of THF and 4.2 mL (7.48 mmol) of 1.78 M methyllithium in diethyl ether, was reacted with 0.473 g (2.99 mmol) of **2b** in 12.0 mL of THF at −78 °C for 1.5 h. Quenching and workup exactly as in the previous reaction gave 0.507 g (97%) of essentially pure (*Z*)-1-(ethanesulfinyl)-2-methyl-1-hexene (**5a**). Oxidation of 0.253 g (1.45 mmol) of this material in 8.5 mL of chloroform with 0.310 g (0.263 g peracid, 1.53 mmol, 5% excess) of 85% *m*-chloroperbenzoic acid at 0 °C for 24 h gave, after workup, 0.284 g (103%) of sulfone. GLC analysis on column A showed that the 1-(ethanesulfonyl)-2-methyl-1-hexene formed was >95.6% (*Z*) isomer **14a**.

Reaction of Lithium Di-*n*-butylcuprate with 1-(Ethanesulfinyl)propyne (2a). Lithium di-*n*-butylcuprate, prepared from 0.751 g (3.94 mmol) of cuprous iodide in 11.1 mL of THF and 4.4 mL (7.74 mmol) of 1.76 M *n*-butyllithium in *n*-hexane, was reacted with 0.360 g (3.1 mmol) of **2a** in 12.4 mL of THF at −78 °C for 2 h. Addition of 5 mL of precooled anhydrous methanol and then pouring into 25 mL

of saturated ammonium chloride, followed by extraction with dichloromethane (3 × 25 mL), drying, and evaporation in vacuo, gave 0.516 g of yellow liquid. The NMR and IR spectra of this material were slightly different from those of the expected **5b**, the NMR possibly indicating the presence of another compound. Oxidation of this 0.516 g of material in 5.0 mL of chloroform with 0.601 g (0.511 g of peracid, 2.96 mmol) of 85% *m*-chloroperbenzoic acid in 12.0 mL of chloroform at 0 °C for 12 h and then at room temperature for 12 h gave, after workup, 0.557 g of yellow liquid. Again the IR and NMR were similar but not identical to those of the expected **14b**.

GLC analysis of this oxidation product, on column A at 190 °C and 45 mL/min, while showing the expected 1-(ethanesulfonyl)-2-methyl-1-hexenes (**14a:14b** = 3.2:96.8, at 20.9 and 29.1 min, respectively), also showed a second component at 12.1 min. A sample of this by-product, mp 47–48.5 °C, was isolated by collection from column A and was identified as ethyl *n*-butyl sulfone (lit.[26] mp 50–50.5 °C) by comparison of its IR, NMR, and mass spectra with those of an authentic sample.[27] The GLC area ratio of 1-(ethanesulfonyl)-2-methyl-1-hexenes to ethyl *n*-butyl sulfone was 81:19. The isolation of this sulfone by-product indicated that ethyl *n*-butyl sulfoxide (**23**) was being formed as a by-product in the di-*n*-butylcuprate addition reaction.

Reaction of Lithium Di-*n*-butylcuprate with 1-(Ethanesulfinyl)-1-hexyne (2b). Lithium di-*n*-butylcuprate, generated from 0.753 g (3.95 mmol) of cuprous iodide in 11.1 mL of THF and 4.4 mL (7.74 mmol) of 1.76 M *n*-butyllithium in *n*-hexane, was reacted with 0.491 g (3.1 mmol) of **2b** in 12.4 mL of THF at −78 °C for 1.0 h. Quenching and workup as in the previous experiment gave 0.615 g of liquid. Oxidation of 0.410 g of this material (⅔ of the total 0.615-g yield, theoretically 2.07 mmol of sulfoxide) with 0.442 g (0.376 g of peracid, 2.17 mmol, 5% excess) of 85% *m*-chloroperbenzoic acid in 13 mL of chloroform at 0 °C for 24 h gave, after workup, 0.460 g of liquid. GLC analysis on column as before showed this to be a mixture of 1-(ethanesulfonyl)-2-(*n*-butyl)-1-hexene (at 36.0 min) and ethyl *n*-butyl sulfone (at 10.3 min) in a ratio of 83:17.

Reaction of 1-(Ethanesulfinyl)propyne (2a) with *n*-Butyllithium. A solution of 0.409 g (3.52 mmol) of **2a** in 14.1 mL of THF was reacted with a solution of 2.0 mL (3.52 mmol) of 1.76 M *n*-butyllithium in *n*-hexane, dissolved in 12.1 mL of THF, at −78 °C for 2 h. Injection of 5 mL of precooled anhydrous methanol followed by workup gave 0.471 g of yellow liquid. The IR and NMR of this material indicated that it was predominantly ethyl *n*-butyl sulfoxide (**23**), with small amounts of ethanesulfinylpropadiene (**24**),[22a] and virtually no addition product **5b**. The propadiene **24** was indicated in the IR by a small, sharp peak at 1952 cm^{-1} (C=C=C) and in the NMR by an apparent triplet ($J \approx 6.5$ Hz) at δ 6.15 (-**CH**=C=CH_2) and a doublet (J = 6.5 Hz) at δ 5.30 (CH=C=**C**H_2). Oxidation of 0.235 g of this material (½ of the total 0.471-g yield, theoretically 1.76 mmol of sulfoxide) with 0.376 g (0.320 g of peracid, 1.85 mmol, 5% excess) of 85% *m*-chloroperbenzoic acid in 11 mL of chloroform at 0 °C for 24 h gave, after workup, 0.270 g of yellow liquid. The IR and NMR similarly showed that this was predominantly ethyl *n*-butyl sulfone, with a small amount of ethanesulfonylpropadiene[22a] (IR 1980 cm^{-1} (C=C=C); NMR δ 6.22 (dd, -**CH**=C=CH_2), 5.52 (d, J = 6.5 Hz, -CH=C=**C**H_2)). GLC analysis on column A showed ethyl *n*-butyl sulfone at 10.2 min.

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Nucleophilic Borohydride: Selective Reductive Displacement of Halides, Sulfonate Esters, Tertiary Amines, and *N,N*-Disulfonimides with Borohydride Reagents in Polar Aprotic Solvents

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Sodium borohydride in polar aprotic solvents (HMPA, Me_2SO, sulfolane) furnishes a convenient and effective source of nucleophilic hydride which may be utilized for the reductive displacement of primary and secondary alkyl halides, sulfonate esters, tertiary amines, and disulfonimides. This latter procedure provides a method for reductive deamination of amines. The mildness of borohydride allows a number of chemoselective transformations without damage to groups normally affected by harsher reagents such as $LiAlH_4$ (i.e., COOR, COOH, CN, NO_2). Sodium trimethoxyborohydride is also an effective hydride source and is particularly valuable with substrates sensitive to borane (i.e., alkenes). A procedure for the two-steps-in-one conversion of alcohols to hydrocarbons is described, along with a convenient synthesis of unsymmetrical tertiary amines. The synthetic utility, scope, and limitations of the reagent system are presented.

Introduction

The eminence of borohydride in the arsenal of reductive weapons available to organic chemists is well established, primarily because of the relative chemoselectiveness, stability, convenience, and inexpense of the reagent in effecting certain important reductive transformations.[1] However, the mildness of the reagent also limits the application of borohydride to a relatively few, easily reduced functional groups such as acid chlorides, aldehydes, and ketones; others, including carboxylic acids, esters, cyano, amido, nitro, most alkenes, halides and sulfonate esters remain untouched under usual conditions.[2]

Some time ago, we envisioned that the utility of borohydride might be augmented by deployment in polar aprotic solvents, such as dimethyl sulfoxide (Me_2SO), sulfolane, and hexamethylphosphoramide (HMPA), which markedly accelerate nucleophilic substitution reactions (S_N2) without greatly enhancing other types of attack such as carbonyl additions.[3] Thus, types of reductions which involve displacement of a σ-bonded functional group by nucleophilic hydride should be enhanced in such solvents. In fact, preliminary investigations by us[4a] and others[4b,c,d] suggested that indeed the reductive removal of halides and sulfonate esters in Me_2SO, sulfolane, HMPA, or DMF were quite effective while other normally resistant groups remained intact. Since the preliminary reports, the reagent system, especially using Me_2SO, has been successfully utilized for a number of mild and selective transformations.[5] This article incorporates a systematic and exploratory investigation of the scope and synthetic utility of such reductions with regard to the chemoselectivity and range of useful leaving groups which may be effectively removed by displacement with borohydride and, to a lesser extent, sodium trimethoxyborohydride. Summarily, the investigations reported here encompass: (a) the selective reduction of alkyl and aryl halides and sulfonate esters;[4a,5v] (b) the direct conversion of alcohols to hydrocarbons;[5v] (c) the reduction of quaternary ammonium salts to tertiary amines including a convenient synthesis of unsymmetrical examples;[5v] and (d) the reductive deaminations of amines via reductive displacement of disulfonimides.[5w]

For convenience, the results are tabulated systematically in Tables I–V and considered separately below according to leaving groups.

Results and Discussion

Reductions of Alkyl and Benzyl Halides and Sulfonate Esters.[6] Borohydride anion behaves as an effective source of nucleophilic hydride anion in a variety of polar aprotic solvents including Me_2SO,[4a,b] sulfolane,[4a] HMPA,[4d] DMF,[4c] or diglyme[4b] and may be utilized for the reductive displacement of halides[4] (except fluoride), sulfonate esters,[4] and methyl sulfate anion.[4b] A wide variety of successful conversions are presented in Table I representing the culmination of our efforts during the past several years along with selected examples from the literature. The results illustrate that a variety of experimental conditions are adequate for effective displacements. Thus, primary and secondary iodides, bromides, chlorides, sulfonate esters, and primary benzylic halides are smoothly converted to hydrocarbons at temperatures between 25 and 100 °C using a zero to twofold molar excess of borohydride (entries 1–27, 40–53). Reductions in HMPA are often quite rapid as evidenced by production of dodecane in 87% yield from 1-iodododecane in 90 s at 25 °C (entry 2). Reductions in sulfolane occur less rapidly (entries 2, 6, and 12 vs. 3, 8, and 11), especially with chlorides. If the substrate is devoid of other reducible functional groups, temperatures of 70–100 °C appear to offer maximum yield in minimum reaction time; thus, for example, decane is produced from 1-iododecane in 93% yield in 15 min at 80 °C (Me_2SO, entry 1) while 1-chloropropylbenzene affords propylbenzene in 90% yield in 2 h at 70 °C (HMPA, entry 12). Although secondary examples require longer reaction times, the yields of hydrocarbon products are still good to excellent (entries 18–27).

The reductions of benzhydryl chloride and bromide in Me_2SO afforded substantial quantities of benzhydrol along with the expected diphenylmethane (entries 48 and 52). The corresponding reductions in sulfolane or HMPA gave only the hydrocarbon (entries 49, 52, and 53). The divergent path leading to the alcohol conceivably may arise via either: (a) an initial displacement of halide by Me_2SO to give a sulfonium salt, which is subsequently attacked at oxygen by borohydride[7] to generate benzhydrol (path a, Scheme I); or (b) borohydride induced α elimination of HCl to afford diphenylcarbene which attacks Me_2SO to provide benzophenone[8] followed by borohydride reduction (path b). This latter path was rejected since dimer formation from the carbene (tetra-

Scheme I

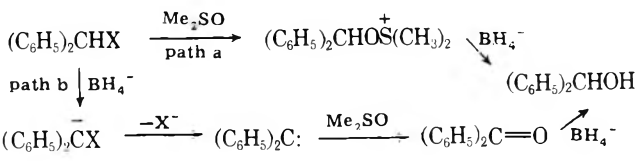

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Table I. Reduction of Halides and Sulfonate Esters in Polar Aprotic Solvents

Entry	Compd	Registry no.	Reducing Agent (mol ratio)[d]	Solvent	Time, h	Temp, °C	Product	% yield[a] (isolated)
			Primary Halides and Sulfonate Esters					
1	1-Iododecane	2050-77-3	$NaBH_4$[e] (2)	Me_2SO	0.25	85	Decane	93
2	1-Iodododecane	4292-19-7	$NaBH_4$ (1)	HMPA	0.025	25	Dodecane	87
3	1-Iododecane		$NaBH_4$ (2)	Sulfolane	0.25	100	Decane	93
4	1-Iodooctane	629-27-6	$NaBH_4$ (5.3)	Diglyme	1.0	45	Octane	91[b]
5	1-Bromodecane	112-29-8	$NaBH_4$ (2)	Me_2SO	1.5	85	Dodecane	94
6	1-Bromododecane	143-15-7	$NaBH_4$ (1)	HMPA	0.022	25	Dodecane	73
7	1-Bromododecane		$NaBH_4$ (2)	Me_2SO	1.5	85	Dodecane	95
8	1-Bromododecane		$NaBH_4$ (2)	Sulfolane	1.5	100	Dodecane	96
9	ω-Bromoundecanoic acid	2834-05-1	$NaBH_4$ (2)	Me_2SO	2.5	25	Undecanoic acid	(98)
10	1-Chlorododecane	112-52-7	$NaBH_4$ (2)	Me_2SO	4	85	Dodecane	91 (80)
11	1-Chlorododecane		$NaBH_4$ (2)	Sulfolane	6	100	Dodecane	85
12	1-Chloropropylbenzene	934-11-2	$NaBH_4$ (4)	HMPA	2	70	Propylbenzene	90
13	Chloromethyl phenyl sulfone	7205-98-3	$NaBH_4$ (3)	HMPA	13	110	Methyl phenyl sulfone	91
14	*n*-Dodecyl tosylate	10157-76-3	$NaBH_4$ (2)	Me_2SO	2	85	Dodecane	87 (85)
15	*n*-Dodecyl tosylate		$NaBH_4$ (2)	Sulfolane	2	100	Dodecane	88
16	Ethyl tosylate	80-40-0	$NaBH_4$ (5.3)	Diglyme	1.0	45	Ethane	35[b]
17	2-Phenyl-1,3-propanediol ditosylate	1570-96-3	$NaBH_4$ (2.2)	Me_2SO	2.75	70	2-Phenylpropane	(54–69)
			Secondary Halides and Sulfonate Esters					
18	2-Iodooctane	557-36-8	$NaBH_4$ (3)	Me_2SO	1	85	Octane	82
19	2-Iodooctane		$NaBH_4$ (3)	Sulfolane	1	100	Octane	81
20	2-Bromododecane	13187-99-0	$NaBH_4$ (3)	Me_2SO	18	85	Dodecane	86
21	2-Bromododecane		$NaBH_4$ (3)	Sulfolane	18	100	Dodecane	69
22	2-Chlorooctane (sealed tube reaction)	628-61-5	$NaBH_4$ (6)	Me_2SO	48	85	Octane	67
23	2-Chlorodecane	1002-56-8	$NaBH_4$ (3)	Me_2SO	18	85	Decane	(68)
24	Ethyl 2-bromohexanoate	615-96-3	$NaBH_4$ (2)	Me_2SO	0.75	15	Ethyl hexanoate	86
25	Ethyl 5-bromovalerate	14660-52-7	$NaBH_4$ (4)	HMPA	0.5	25	Ethyl valerate	85
26	α-Bromo-4-phenylacetophenone	135-73-9	$NaBH_4$ (4)	HMPA	1	25	4-(α-Hydroxyethyl)biphenyl	79
27	Cyclododecyl tosylate	27092-44-0	$NaBH_4$ (3)	Me_2SO	24	85	Cyclododecane	(54)
			Allylic Halides					
28	Cinnamyl bromide	4392-24-9	$NaBH_4$ (4)	HMPA	0.5	25	β-Methylstyrene	47
					2	25	β-Methylstyrene	39
29	Cinnamyl bromide		$NaBH_4$ (8)	80% HMPA[g]	0.5	25	β-Methylstyrene	82
30	Cinnamyl bromide		$NaBH(OCH_3)_3$[f] (3)	HMPA	1	50	β-Methylstyrene	78
31	Cinnamyl chloride	2687-12-9	$NaBH_4$ (4)	HMPA	0.5	70	β-Methylstyrene	0
32	Cinnamyl chloride		$NaBH_4$ (8)	80% HMPA[g]	0.5	70	β-Methylstyrene	81
33	Cinnamyl chloride		$NaBH(OCH_3)_3$ (4)	HMPA	1	50	β-Methylstyrene	60
34	1-Chloro-2-ethyl-2-hexene	65588-46-7	$NaBH_4$ (4)	HMPA	1	70	3-Methyl-3-heptene	0
35	1-Chloro-2-ethyl-2-hexene		$NaBH_4$ (8)	80% HMPA[g]	0.5	70	3-Methyl-3-heptene	71
36	1-Chloro-2-ethyl-2-hexene		$NaBH(OCH_3)_3$ (4)	HMPA	1.75	70	3-Methyl-3-heptene	82
37	3-Chloro-2-phenyl-1-propene	3360-52-9	$NaBH_4$ (8)	80% HMPA[g]	0.5	70	α-Methylstyrene	90
38	3-Chloro-2-phenyl-1-propene		$NaBH(OCH_3)_3$ (4)	HMPA	2	70	α-Methylstyrene	86
39	Phenylpropargyl chloride	3355-31-5	$NaBH_4$ (8)	80% HMPA[g]	0.5	70	1-Phenyl-1-propyne	64
			Benzylic Halides					
40	*p*-Nitrobenzyl bromide	100-11-8	$NaBH_4$ (2)	Me_2SO	1.5	25	*p*-Nitrotoluene	(95)
41	α,2,6-Trichlorotoluene	2014-83-7	$NaBH_4$ (2)	Me_2SO	2.5	25	2,6-Dichlorotoluene	(85)
42	α,2,6-Trichlorotoluene		$NaBH_4$ (6)	Sulfolane	2	100	2,6-Dichlorotoluene	76
43	α-Phenylethyl bromide	585-71-7	$NaBH_4$ (7)	65% Diglyme		45	Ethylbenzene	80[c]
							Styrene	1
							α-Phenylethanol	14
44	α-Phenylethyl bromide		$NaBH_4$ (3)	Me_2SO	1	85	Ethylbenzene	79
45	α-Phenylethyl bromide		$NaBH_4$ (3)	Sulfolane	1	100	Ethylbenzene	82
46	α-Phenylethyl chloride	672-65-1	$NaBH_4$ (4)	HMPA	10	70	Ethylbenzene	98
47	Benzhydryl bromide	776-74-9	$NaBH_4$	80% Diglyme			Diphenylmethane	87[c]
48	Benzhydryl bromide		$NaBH_4$ (3)	Me_2SO	24	25	Diphenylmethane	62
							Benzhydrol	33
49	Benzhydryl bromide		$NaBH_4$ (3)	Sulfolane	1	100	Diphenylmethane	93
50	Benzhydryl chloride	90-99-3	$NaBH_4$	65% Diglyme 1 M NaOH			Diphenylmethane	99[c]
51	Benzhydryl chloride		$NaBH_4$ (6)	Me_2SO	24	35	Diphenylmethane	61
							Benzhydrol	32

Table I (*continued*)

Entry	Compd	Registry no.	Reducing Agent (mol ratio)[d]	Solvent	Time, h	Temp, °C	Product	% yield[a] (isolated)
52	Benzhydryl chloride		$NaBD_4$ (3)	HMPA	11	50	Diphenylmethane-d_1	100
53	Benzhydryl chloride		$NaBH_4$ (3)	Sulfolane	1	100	Diphenylmethane	94
54	Trityl chloride	76-83-5	$NaBH_4$ (4)	HMPA	1	70	Triphenylmethane	85
55	Trityl chloride		$NaBH_4$ (6)	Me_2SO	1.5	85	Triphenylmethane	(90)
			Vinylic Halides					
56	β-Bromostyrene	103-64-0	$NaBH_4$ (8)	80% HMPA[g]	24	70	Ethylbenzene	2
							Phenylacetylene	8
							β-Bromostyrene	52
							Styrene	26
57	β-Bromostyrene		$NaBH(OCH_3)_3$ (4)	HMPA	3.5	70	Phenylacetylene	84
							Styrene	8
			Dihalides					
58	Styrene dibromide	6607-46-1	$NaBH_4$ (4)	Me_2SO	1.5	85	Ethylbenzene	65
59	Styrene dibromide		$NaBH_4$ (4)	Sulfolane	1.5	100	Ethylbenzene	64
60	Styrene dibromide		$NaBH(OCH_3)_3$ (4)	HMPA	1	70	Ethylbenzene	2
							Phenylacetylene	62
							Styrene	24
61	1,2-Dibromooctane	6269-92-7	$NaBH_4$ (4)	HMPA	2	70	Octane	84
62	1,2-Dibromooctane		$NaBH(OCH_3)_3$ (8)	HMPA	2	70	Octane	66
							1-Octene	12
							2-Bromooctane	11

[a] Yields were determined by GLC using internal standards and predetermined detector response factors unless specified otherwise. [b] Reference 4b. [c] Reference 4d. [d] Molarity of reducing agent/molarity of compound. [e] Registry no.: 16940-66-2. [f] Registry no.: 16940-17-3. [g] 20% H_2O.

phenylethene) was not observed and from the absence of deuterium incorporation at the methine position of the alcohol upon reaction with $NaBD_4$ in Me_2SO as required by path b. Similar alcohol side products were not observed for less activated benzyl halides (aryl, alkylaryl, entries 40–46). The highly activated, but hindered, tertiary benzyl halides trityl chloride and bromide also afforded no alcohol product (entries 54 and 55), presumably because of facile ionization of any generated sulfonium ion to give a trityl carbonium ion which is trapped by hydride.[9] Other tertiary halides which contain α hydrogens undergo rapid elimination to alkenes which are subsequently hydroborated; in fact, coupled with treatment with a carboxylic acid, the procedure provides a convenient reductive method for converting tertiary halides to hydrocarbons.[4a,10] Vicinal dihalides are smoothly converted to the corresponding hydrocarbons (entries 58, 59, and 61), in contrast to $LiAlH_4$ reductions which predominately afford olefins[1d,11] or $NaBH_3CN$ which gives mixtures of hydrocarbons and alkenes.[6k,l] Thus, borohydride may be utilized to hydrogenate double bonds in sensitive compounds by way of bromination and reduction. The related derivative $NaBH(OCH_3)_3$ was less successful in that products resulting from incomplete reduction and/or elimination were concomitantly produced (entries 60 and 62). This latter behavior may be due to the presence of methoxy anion formed by disproportionation of the reagent.[12] Likewise, reduction of the vinylic halide β-bromostyrene was not successful with either $NaBH_4$ or $NaBH(OCH_3)_3$, the latter giving elimination to phenylacetylene (entry 57) while the former reluctantly afforded a mixture of reduction and elimination products (entry 56).

The reduction of allylic halides with BH_4^- is complicated by the production of borane, which may further react with alkene products via hydroboration.[10] Thus, attempts to dehalogenate cinnamyl derivatives or 1-chloro-2-ethyl-2-hexene in HMPA gave only a meager amount of the desired alkene product at ambient temperature (entry 28) and virtually none at 70 °C (entries 31 and 34). This problem could be alleviated by conducting the reductions in 4:1 HMPA/H_2O mixture (entries 29, 32, 35, and 27). Apparently, the initially formed borane is hydrolyzed rapidly enough to prevent attack on the product. A propargyl chloride was also successfully reduced in this solvent system (entry 39). Interestingly, a small amount (13%) of propylbenzene was produced with cinnamyl chloride in aqueous HMPA (entry 32), indicating some double bond reduction.[13] Nevertheless, the reagent system appears to offer an attractive method for allylic and propargylic halide removal. Alternatively, $NaBH(OCH_3)_3$ provides good yields of alkenes, since this reagent cannot provide a hydroborating species (entries 30, 33, and 36).

The reductive removal of functional groups is extended by a convenient two-steps-in-one method for conversion of alcohols to hydrocarbons.[14a,b] The process involves the in situ conversion of the alcohol to the iodide with methyltriphenoxyphosphonium iodide[14c] in sulfolane or HMPA and subsequent reduction with BH_4^-. Results for a variety of representative examples along with general reaction conditions are presented in Table II. Thus, primary, secondary, and benzyl alcohols are effectively reduced without concomitant attack of other functional groups such as cyano and nitro. Sodium trimethoxyborohydride is also effective for the reduction and prevents any offending hydroboration of alkene-containing substrates such as cinnamyl alcohol (entry 6).

For synthetic applications, borohydride offers several apparent advantages. First the chemoselectivity available allows the reductive removal of halides and sulfonate esters selectively without affecting a number of other sensitive groups. Thus, esters (entries 24 and 25),[5a,g,h,s] carboxylic acids (entry 9), nitro (entry 40),[5f] cyano (entry 5, Table II),[5h,i] sulfone (entry 13), and, under special conditions as discussed, alkenes (entries 29, 30, 32, 33, 35, 36, 37, and 38);[5b,k,i,r,s] α-halo ketones afford concomitant carbonyl reduction (entry 26). In addition, the products are uncontaminated with alkene side products from elimination, a result which is probably at least partly attributable to the aforementioned hydroboration of any unwanted alkene. When other reducible groups are present, it is usually advisable to conduct the reductions at moderate

Table II. Conversion of Alcohols to Hydrocarbons with Methyltriphenoxyphosphonium Iodide in Sulfolane or Hexamethylphosphoramide

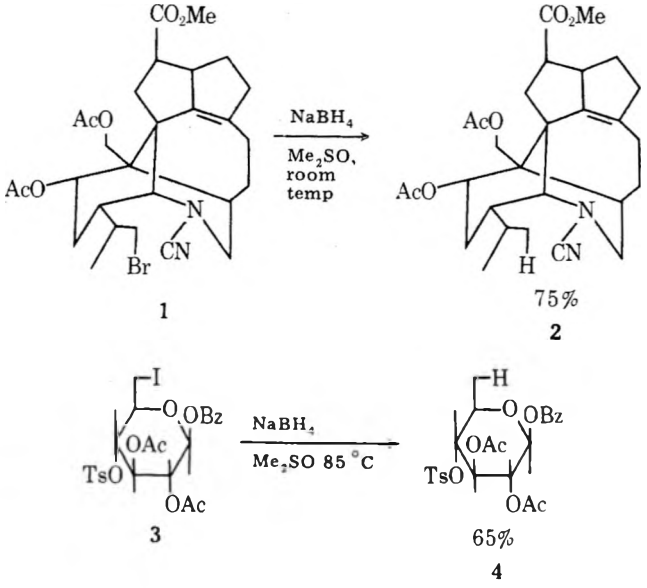
Entry	Compd	Registry no.	Ratio[a] of hydride/ alcohol	Solvent	T, °C	Time, h (Time, reduction)	% yield hydrocarbon[b]
1	1-Decanol	112-30-1	6	Sulfolane	85	0.5 (0.5)	90
2	1-Decanol		6	HMPA	85	0.5 (0.5)	78
3	2-Decanol	1120-06-5	6	Sulfolane	85	0.5 (0.5)	62
4	*m*-Nitrobenzyl alcohol	619-25-0	6	Sulfolane	30	1.0 (2.0)	71
5	7-Hydroxyheptane nitrile	17976-80-6	6	Sulfolane	85	0.5 (1.0, 40 °C)	70
6	Cinnamyl alcohol	104-54-1	9[c]	Sulfolane	40	0.5 (2.5)	73

[a] Solutions were 1.0 in the alcohol and a 0.5 mol excess of methyltriphenoxyphosphonium iodide was employed. [b] Determined by GLC using internal standards and appropriate detector response factors. [c] Sodium trimethoxyborohydride used.

Table III. Dealkylation of Quaternary Ammonium Salts with Hydrides in Polar Aprotic Solvents

Entry	Compd	Registry no.	Hydride (ratio of hydride/ compd)	Solvent	Temp, °C	Time, h	% yield products (Ratio)	
1	Phenyltrimethylammonium iodide	98-04-4	$NaBH_4$ (3)[a]	Me_2SO	85	7.0	89	
2			$NaBH_4$ (3)[a]	Me_2SO	120	1.0	96	
3			$NaBH_4$ (3)[a]	Sulfolane	120	1.0	95	
4			NaH (6)[b]	HMPA	100	2.75	96	
5			$NaBH_4$ (3)	HMPA	85	5.0	96	
6	Phenyldimethylethylammonium iodide	1006-07-1	$NaBH_4$ (3)[a]	Me_2SO	120	1.0	7[c]	82[d]
7			$NaBH_4$ (3)[b]	HMPA	100	1.0	6[c]	85[d]
8	Phenyldimethylisopropylammonium iodide	35616-26-3	$NaBH_4$ (3)[a]	Me_2SO	120	1.5	13[c] (6.4)	84[e]
9			$NaBH_4$ (3)[b]	HMPA	100	1.0	16[c] (4.9)	79[e]
10	Tripropylmethyl ammonium iodide	3531-14-4	$NaBH_4$ (6)[b]	HMPA	175	9.0	54[f]	18[g]
11	Trimethyldodecylammonium bromide	1119-94-4	$NaBH_4$ (6)[b]	HMPA	175	9.0	65[h]	
12	*N,N*-Dimethylaniline + ethyl iodide (1:2 ratio)	121-69-7	$NaBH_4$ (3)	Me_2SO	120	2.0	8[c] (9.9)	79[d]

[a] Solution 0.267 M in compound. [b] Solution 0.40 M in compound. [c] *N,N*-Dimethylaniline. [d] *N*-Methyl-*N*-ethylaniline. [e] *N*-Methyl-*N*-isopropylaniline. [f] Tripropylamine. [g] Dipropylmethylanine. [h] *N,N*-Dimethyldodecylamine. [i] Amine and iodide heated in Me_2SO at 50 °C for 16 h followed by addition of borohydride.



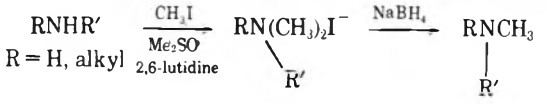
1 2 3 4

temperatures (i.e., 15–25 °C) to prevent undesirable overreductions. For instance, while nitro groups are inert at 25 °C (entry 40), higher temperatures afford azoxy, azo, and amine derivatives.[2a] Recent examples extracted from the literature of the usefulness and selectivity possible with the reducing system are illustrated by the conversion of **1** to **2** in Me_2SO at room temperature[5h] and the reductive removal of iodo from the carbohydrate derivative **3** (to **4**).[5g] Finally, with sensitive alkene-containing substrates, $NaBH(OCH_3)_3$ provides an acceptable alternative (vide infra).

Reduction of Quaternary Ammonium Salts. Synthesis of Tertiary Amines. The reductive removal of alkyl groups from quaternary ammonium salts is an often sought and substantially investigated synthetic technique. Conceptually, the process may often be regarded as an expulsion of a tertiary amine and the most successful techniques have generally employed some nucleophilic reagent usually in combination with S_N2 enhancing solvents.[16] This section describes the utility of $NaBH_4$ in polar aprotic solvents for this transformation coupled with a convenient synthesis of tertiary amines, including unsymmetrical varieties.

Phenyltrimethylammonium iodide was chosen for exploratory investigation and the displacement rate with borohydride in HMPA, Me_2SO, and sulfolane at 75 °C was monitored by GLC as presented in Figure 1. As qualitatively observed for halide displacements and with other systems, HMPA provided the fastest reduction rate, requiring ~5 h for complete conversion. At higher temperatures, (i.e., 100 °C for HMPA, 120 °C for Me_2SO and sulfolane), effective reduction in all three solvents was usually obtained within 1 h (entries 2–3, 6–12).[17] Thus, in the absence of sensitive groups, the higher temperatures are recommended for convenience. The results for a variety of dealkylations are presented in Table III, from which several noteworthy points are evident. First, in cases where a choice is available, a methyl is attacked preferentially to a primary group as expected for a bimolecular substitution reaction (entries 6–9). Thus, the procedure can be used to prepare unsymmetrical amines via alkylation of a

Table IV. Conversion of Primary and Secondary Amines to Tertiary Amines by Alkylation–Demethylation in Me_2SO



Amine (0.01 mol)	Registry no.	CH_3I,[a,b] mol	$NaBH_4$, mol	% yields[b]	
Aniline	62-53-3	0.05	0.07	75	
N-Methylaniline	100-61-8	0.04	0.06	78	
N-Ethylaniline	103-69-5	0.04	0.06	5[c]	71[d]
N-Methyl-*N*-ethylaniline	613-97-8	0.02	0.03	8[c]	79[d]

[a] Amine, methyl iodide, and 0.01 mol of 2,6-lutidine heated at 50 °C for 16 h, followed by addition of $NaBH_4$ and heating at 120 °C for 2 h. [b] Yields determined by GLC using internal standards and corrected for detector response. [c] *N,N*-Dimethylaniline. [d] *N*-Methyl-*N*-ethylaniline.

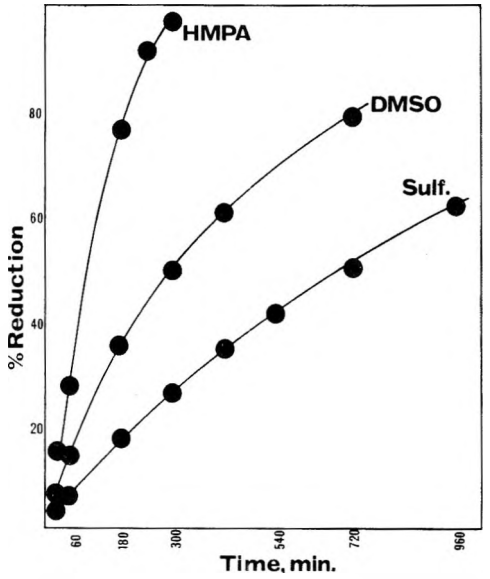


Figure 1. Sodium borohydride reduction of phenyltrimethylammonium iodide at 75 °C: solutions 0.40 M in phenyltrimethylammonium iodide, 1.20 M in $NaBH_4$. The percent reductions were determined by GLC using internal standards and are corrected for detector response.

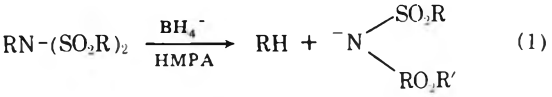
tertiary amine containing an *N*-methyl group followed by demethylation. The higher percentage of isopropyl removal over ethyl (compare entries 6 and 8) suggests that at least part of the dealkylation proceeds by Hofmann elimination in which borohydride or the halide counterion serves as the base. As seen from the table, the reduction of tetraalkyl salts proceeds much less readily than anilinium examples (compare entries 1–9 with 10 and 11), reflecting the increased base strength and, hence, the decreased leaving ability of trialkylamines over aryl derivatives. The relatively strenuous conditions required (i.e., 175 °C, 9 h) tempers the selectivity of the reaction somewhat since several other functional groups (i.e., NO_2, CO_2R, halide) probably could not survive these conditions. An interesting result is shown by entry 4 in which sodium hydride in HMPA functions as an effective nucleophile toward the methyl salt, affording a 96% yield of the tertiary amine. This represents one of the few cases where an alkali metal hydride apparently functions as a displacing nucleophile.[6s] Since NaH is a poor reducing agent toward most functional groups, this suggests that very selective displacements may be attainable with alkali metal hydrides under the proper conditions, a topic which is being explored.

Noting that both alkylation of amines to produce quaternary salts (Menschutkin reaction) and subsequent reductive dealkylation both involve S_N2 type processes, a convenient two-steps-in-one synthetic procedure was suggested for direct alkylation–demethylation to generate tertiary amines as demonstrated in Table IV. The method involves treatment of a primary, secondary, or tertiary amine with excess methyl iodide in Me_2SO using 2,6-lutidine to remove HI[18] followed by reduction with BH_4^- without prior isolation of the intermediate quaternary salt. The results in Table IV indicate the procedure to be effective for producing tertiary amines in good yields (considering that two steps are involved) with a high predominance of the demethylated product.

Reductive Deamination of Primary Amines via *N,N′*-Disulfonamides. The activation of hydroxyl groups for displacement or elimination via conversion to suitable leaving groups (i.e., sulfonate esters, halides) has enjoyed considerable success and has led, at least partially, to the great importance of alcohols as synthetic intermediates. Unfortunately, the analogous functionalization and utilization of amines is primitive in comparison, primarily because most nitrogen derivatives are relatively strong bases, and, consequently, poor leaving groups. Apparently, the incorporation of even a strong electron-withdrawing group on a nitrogen is not normally sufficient to stabilize the departing amine derivative anion.

One successful recent approach to this problem has involved stabilization of the developing leaving anion by the incorporation of two powerful withdrawing groups, principally sulfonyl[19] or carbonyl moieties.[20] In fact, use of the former (as disulfonimides) has generated several synthetic applications for substitution and elimination reactions;[19] evidently, the disulfonimide anion is sufficiently stable and nonbasic to allow facile ejection.

Along the above lines, we envisioned that BH_4^- in S_N2 enhancing solvents should provide sufficiently potent nucleophilic hydride to displace disulfonamides (i.e., eq 1) and thus

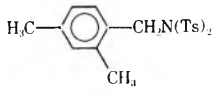
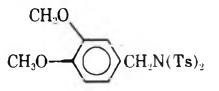
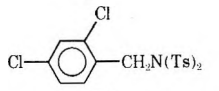
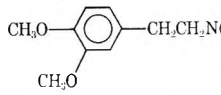
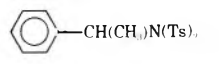


(1)

introduce a convenient approach to the reductive deamination of primary amines. This section describes our successful efforts in this area along with the scope and limitations encountered. A preliminary account of this investigation has previously appeared.[5w]

Any general and useful synthetic approach requires that essential intermediates, in this case disulfonimides, be conveniently available via reliable and high yielding methods. Fortunately, Baumgarten and DeChristopher have described a generally excellent procedure to disulfonimides by way of readily obtainable sulfonamides.[19c] In our hands, this method was quite sufficient for unhindered amines located on primary carbons, but less successful when the amino group is flanked by alkyl groups. Thus, while the disulfonimides of 2-amino-

Table V. Reduction of Disulfonimides with Borohydride in HMPA

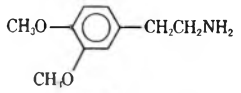
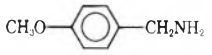
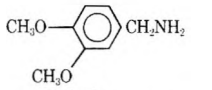
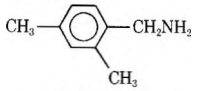
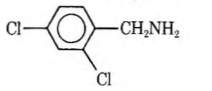
Entry	Compd[a]	Registry no.	Ratio of MBH_4^-/M compd	Temp, °C	Time, h	% yield of hydrocarbon[b] (Isolated)
1	$CH_3(CH_2)_9N(Ts)_2$	56079-36-8	2	25	48	30
2			2	110	46	43
3			2	150	4.0	80
4			2	175	4.0	84
5			2	175	8.0	88
6			4	175	8.0	91
7			4 ($NaBH_3CN$)	175	26.5	23
8			3 ($LiBHEt_3$)[c]	reflux	8.0	0[d]
9	$CH_3(CH_2)_9N(Bs)_2$	56079-37-9	2	150	4.0	73
10	$CH_3(CH_2)_{11}N(Ts)_2$	56079-38-0	2	175	4.0	68
11		65588-47-8	2	150	4.0	(78)
12		56079-40-4	2	175	4.0	(78)
13		65588-48-9	2	175	4.0	(32)
14		65588-49-0	2	175	12	22[f]
15		65588-50-3	2	150	6.0	(64)
16	$C_6H_5(CH_2)_4N(Ts)_2$	65588-51-4	2	175	4.0	88
17	$CH_3(CH_2)_9N(SO_2CF_3)_2$	65588-52-5	2	25	120	36
18			2	100	5.0	33
19			2 (18-crown-6)	100	5.0	33
20			2	175	4.0	36
21	$CH_3(CH_2)_9N(Ns)_2$	65588-53-6	2	150	4.0	0
22			2 (18-crown-6)	Reflux	22.0	0
23	$CH_3(CH_2)_6CH(CH_3)N(Bs)_2$	65588-54-7	4	175	8.0	66
					19.0	73
24	Cyclododecyl–$N(Ts)_2$	56079-41-5	4	175	20	Trace[e]
25	Cyclooctyl–$N(Ts)_2$	65588-55-8	4	175	18	23
26	$CH_3CH(CH_3)(CH_2)_3CH(CH_3)$-$N(Ts)_2$	65588-56-9	2	175	4.0	54
27		65588-57-0	3	175	4.0	77

[a] Solutions were 0.2 M. [b] Yields were determined by GLC using internal standards and corrected for detector response. [c] Solvent was a 1:1 mixture of THF and HMPA. [d] A 96% yield of *n*-decyl-*p*-toluenesulfonamide was isolated. [e] A 71% yield of cyclododecyl-*p*-toluenesulfonamide was isolated. [f] A 51% yield of *N*-(2,4-dichlorobenzyl)-*p*-toluenesulfonamide was also isolated.

nonane, cyclooctylamine and cyclododecylamine were procured the yields were modest, while all attempts to prepare sulfonimides of other, more severely hindered amines (i.e., 1-adamantyl, *exo*-2-aminonorborane, aminodiphenylmethane) were singularly unsuccessful although the intermediate sulfonamides were readily obtained. Since these results potentially restrict the utilization of disulfonamides, we explored a variety of approaches in hopes of finding a viable synthetic alternative. Since the problem involved the introduction of the second sulfonyl group, the general sulfonation procedure (DMF, NaH as base)[19c] was modified in several minor ways (solvents, times, and temperatures), but unfortunately with no success. Likewise, the use of the thallium salt of the sulfonamide, reported to improve displacement of the second sulfonyl halide,[22] also led to no improvement in our hands. As a last resort, the very potent electrophilic reagent *p*-toluenesulfonyl perchlorate was employed,[23] but again to no avail. Evidently, sulfonamide anions severely resist addition of a second sulfonyl moiety in even moderately hindered environments, which suggests an unusually inflated steric requirement for sulfonimides. Indeed, Bartsch and co-workers[19k] have recently noted an extreme regioselectivity in the elimination of disulfonimides to afford almost exclusively the Hofmann alkene, a result attributed to an abnormally great bulkiness of the disulfonimide leaving group.[19k,24] Apparently the steric requirement of the $-N(SO_2)_2$ portion equals or even surpasses that of the trimethylammonium ion! In any case, with this final synthetic frustration, our efforts to find an acceptable procedure for hindered sulfonimides were abandoned.

Initial reductive investigations with *N*-(*n*-decyl)-*N*,*N*-di(*p*-toluene)sulfonimide established that replacement of the disulfonimide anion by hydride (to give decane) was obtainable in reasonable reaction times (4–8 h) at 150–175 °C in HMPA using a twofold molar excess of BH_4^-. The progress of the reductions was conveniently monitored by GLC and the products were readily obtained by dilution with water and extraction with an organic solvent (i.e., cyclohexane). In this fashion, a number of successful conversions to hydrocarbons were accomplished as presented in Table V.

Table VI. Sulfonamides and Disulfonimides

Amine	Registry no.	Sulfonamide[a] Mp, °C	Sulfonamide[a] Registry no.	Disulfonimide[a] mp, °C
$CH_3(CH_2)_9NH_2$	2016-57-1	62–63[b]	1228-64-4	51–53
$CH_3(CH_2)_9NH_2$		75–77[c]	65588-58-1	75–77
$CH_3(CH_2)_9NH_2$		86–87[d]	65588-59-2	122–123
$CH_3(CH_2)_{11}NH_2$	124-22-1	172–174[b]	1635-09-2	36–37
$C_6H_5(CH_2)_4NH_2$	13214-66-9	50–53[b]	5435-06-3	71–73
	120-20-7	129–131[b]	14165-67-4	119–121
	2393-23-9	122–124[b]	54879-64-0	148–150
	5763-61-1	127–129[b]	65588-60-5	156–158
	94-98-4	88–89[b]	54879-65-1	146–147.5
	95-00-1	111–113[b]	65588-61-6	187–188
$CH_3(CH_2)_6CH(CH_3)NH_2$	13205-58-5	liq[c,e]	65588-62-7	79–80
$(CH_3)_2CH(CH_2)_3CH(CH_3)NH_2$	543-82-8	50–52[b,e]	65588-63-8	72–74
$C_6H_5CH(CH_3)NH_2$	98-84-0	77–80[b]	4809-56-7	153–155
Cyclododecylamine	1502-03-0	152.5–154[b]	65588-64-9	202–204 dec
Cyclooctylamine	5452-37-9	64–66[b]	16801-74-4	197–198

[a] Satisfactory combustion analytical data for C and H (±0.3%) were reported for these compounds. [b] *p*-Toluenesulfonyl derivative. [c] *p*-Bromobenzenesulfonyl derivative. [d] *p*-Nitrobenzenesulfonyl derivative. [e] Product obtained as a mixture of the sulfonamide and disulfonimide.

Several alternatives were pursued in attempts to discover less vigorous experimental conditions, but with only limited success. In hopes of further enhancing the leaving ability of the disulfonimide anion, the strongly electron-withdrawing trifluoromethylsulfonyl[19i] and *p*-nitrophenylsulfonyl groups were incorporated into the disulfonimide derivatives. However, with the former, the yield of hydrocarbon product was consistently low under a variety of conditions (including the use of the phase transfer reagent 18-crown-6,[25] entries 19 and 22), although room temperature (25 °C) could be employed. The invariance of yield conceivably reflects a competition between displacement and elimination to give an alkene; the absence of the latter in the product mixture probably stems from the aforementioned hydroboration by generated borane (vide infra). Utilization of the *p*-nitrobenzene derivative resulted in no detectable yield of hydrocarbon (entries 21 and 22). Furthermore, an attempt at improvement by employing the more potent hydride delivering reagent $LiBH(C_2H_5)_3$ ("Super Hydride")[6g,h,i,16q,26] was surprisingly unsuccessful, affording only *N*-decyl-*p*-toluenesulfonamide (entry 8) resulting either by attack at nitrogen (or sulfur) or initial halide induced elimination of *p*-toluenesulfinic acid and subsequent reduction of the resulting *N*-tosylimine **5**. This latter path was discarded, since the corresponding reduction with $LiBD(C_2H_5)_3$ gave the sulfonamide without concomitant incorporation of deuterium at the carbon adjacent to nitrogen. Apparently, the coupled steric requirements of the bulky triethylborohydride and sulfonimide groups preclude approach even to an adjacent primary carbon.[27] Predictably, BH_3CN^- was considerably less successful than BH_4^- as a hydride source, affording only a mediocre yield of hydrocarbon product under strenuous conditions (entry 7).

$CH_3(CH_2)_8CH{=}NTs$

5

At this stage our attempts to temper the reaction conditions were abandoned. Nevertheless, the general procedure is effective for deamination of unhindered primary, benzylic, and certain secondary disulfonimides in good to excellent yields (entries 1–6, 9–13, 15, 16, 23, 24, 26, and 27). The relatively congested cyclododecyldisulfonimide gave exclusive S–N bond cleavage (entry 24), again reflecting the steric requirement of the leaving group coupled with the reluctance of the system to undergo S_N2 displacements.[28] The corresponding cyclooctyl derivative (entry 25) afforded cyclooctane, albeit in low yield (23%).

Summary

Sodium borohydride in polar aprotic solvents (Me_2SO, HMPA, and sulfolane) provides a convenient and effective source of nucleophilic hydride which may be utilized for the reductive displacement of a number of functional leaving groups. Successful, selective conversions to hydrocarbons are accomplished for primary, secondary, and triaryl tertiary halides and sulfonates esters, quaternary ammonium salts, and unhindered primary and secondary disulfonimides.[29] Alcohols are conveniently transformed to hydrocarbons via initial in situ conversion to iodides followed by reduction. Likewise, unsymmetrical tertiary amines result from exhaustive alkylation of amines to quaternary salts and subsequent demethylation with BH_4^-. With substrates susceptible to hydroboration (i.e., allylic and other alkene containing molecules), aqueous HMPA or use of $NaBH(OCH_3)_3$ provides viable alternatives.

Experimental Section

All melting points and boiling points are uncorrected. Infrared spectra were taken on a Perkin-Elmer Model 457 spectrometer either as films or in potassium bromide disks. Proton nuclear magnetic resonance spectra were obtained on a Varian A-60 spectrometer using

tetramethylsilane as an internal standard. Microanalyses were performed by Chemanalytics Inc., Tempe, Ariz. Gas chromatography (GLC) was performed on a Hewlett-Packard Model 5250B instrument. Yields of products were determined by GLC using internal standards and were corrected for detector response.

Materials. Sodium borohydride from Alfa Inorganics was used as obtained. Hexamethylphosphoramide, (HMPA), dimethyl sulfoxide (Me_2SO), and sulfolane were distilled from BaO (HMPA) or CaH_2 and stored over molecular sieves. Alkyl halides, alcohols, amines, and other reagents were obtained commercially and usually distilled or recrystallized before use. Sulfonate esters and quaternary salts were prepared by standard procedures. Disulfonimides were prepared via the sulfonamides from the corresponding amines. In all cases, IR and NMR data were consistent with assigned structures.

Reductions with Sodium Borohydride: General Procedure. The reductive methods used for halides, sulfonate esters, quaternary ammonium salts, and disulfonimides are similar and straightforward. The appropriate quantities of reagents, as provided in the tables, were reacted at the indicated temperatures for the required times as determined by GLC. Workup involved simply dilution with water and extraction with an organic solvent, usually cyclohexane, $CHCl_3$, or ether. For reductions in HMPA, $CHCl_3$ should be avoided since this solvent preferentially complexes with HMPA. An internal standard was then added to the organic solution for analysis by GLC. For preparative isolations, the organic phase was washed with water or brine to remove residual reduction solvent, dried ($MgSO_4$), and concentrated at reduced pressure.

The reductions of alcohols to alkanes listed in Table II were conducted in a similar manner. A solution of the alcohol and methyltriphenoxyphosphonium iodide[14c] in the proper solvent was reacted under the conditions presented in Table II. The $NaBH_4$ was then cautiously added (the reaction is initially very vigorous) and stirring continued for the appropriate time. Water was then slowly added, followed by cyclohexane and an internal standard. The cyclohexane solution was analyzed by GLC. For preparative isolations, the organic solution was washed with dilute aqueous NaOH (to remove small amounts of phenol) and twice with water, dried ($MgSO_4$), and concentrated at reduced pressure.

The following reduction is presented as a representative example of the general procedure used for all leaving groups. A solution of *N*-(2,5-dimethylbenzyl)-*N*,*N*-di(*p*-toluene)sulfonimide (3.55 g, 8 mmol) and $NaBH_4$ (605 mg, 16 mmol) in 40 mL of HMPA was heated for 4 h at 150 °C, diluted with water, and extracted three times with cyclohexane. The cyclohexane solution was washed three times with water, dried, and concentrated on a rotary evaporator to give 852 mg of colorless oil. Flash distillation at reduced pressure (Kugelrohr apparatus) afforded 747 mg (78%) of 1,2,5-trimethylbenzene product, identified by comparison with an authentic sample.

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References and Notes

(1) For excellent reviews of borohydride as well as other metal hydride reductions see: (a) H. O. House, "Modern Synthetic Reactions", W. A. Benjamin, New York, N.Y., 1972, Chapter 2; (b) E. R. H. Walker, *Chem. Soc. Rev.*, **5**, 23 (1976); (c) H. C. Brown, "Boranes in Organic Chemistry", Cornell University Press, Ithaca, N.Y., 1972; (d) N. G. Gaylord, "Reductions with Complex Metal Hydrides", Interscience, New York, N.Y., 1956; (e) for a comprehensive and excellent review of the use of BH_4^- in conjunction with metal catalysts, including industrial applications, see R. C. Wade, D. G. Holak, A. H. Hughes, and B. C. Hui, *Catal. Rev., Sci. Eng.*, **14**, 211 (1976).

(2) Exceptions include the following. (a) The reduction of aromatic nitro groups in Me_2SO or pyridine to amines, azoxy, or azo compounds [see R. O. Hutchins, D. W. Lamson, L. Rua, C. Milewski, and B. Maryanoff, *J. Org. Chem.*, **36**, 803 (1971); H. J. Shine and E. Mallory, *ibid.*, **27**, 2390 (1962); G. Otani, Y. Kikugawa, and S. Yamada, *Chem. Pharm. Bull.*, **16**, 1840 (1968); (with metal complexes) Y. Arai, A. Mijin, and Y. Takahashi, *Chem. Lett.*, 743 (1972); K. Hanaya and T. Ono, *J. Chem. Soc. Jpn.*, **92**, 1225 (1971); K. Hanaya, N. Fujita, and H. Kudo *Chem. Ind. (London)*, 794 (1973); B. Loubinoux, J. J. Chanof, and P. Caubere, *J. Organomet. Chem.*, **88**, C4 (1975)], or using Pd/C catalysis to give amines [T. Neilson, H. Wood, and A. Wylie, *J. Chem. Soc.*, 371 (1962)] or various heterocycles [cf., R. T. Coutts and M. Wohlebe, *Can. J. Chem.*, **52**, 3432 (1974)]. (b) Alkenes activated by electron-withdrawing substituents are often smoothly reduced to the saturated derivatives: see J. H. Schaulle, G. J. Walter, and J. G. Moxin, *J. Org. Chem.*, **39**, 755 (1974); S. B. Kadin, *ibid.*, **31**, 620 (1966); J. A. Meschino and C. H. Bond, *ibid.*, **28**, 3129 (1963); J. A. Marshall and R. D. Carroll, *ibid.*, **30**, 2748 (1965); H. LeMoal, R. Carrie, and M. Bargain, *C. R. Held. Seances Acad. Sci.*, **255**, 2541 (1960); L. Berlinquet, *Can. J. Chem.*, **33**, 1119 (1955); G. W. K. Cavill and F. B. Whitfield, *Proc. Chem. Soc., London*, 380 (1962); H. Shechter, D. E. Ley, and E. B. Roberson, Jr., *J. Am. Chem. Soc.*, **78**, 4984 (1956); A. I. Meyers and J. S. Sircan, *J. Org. Chem.*, **32**, 4134 (1967); A. Hassner and C. Heathercock, *ibid.*, **29**, 1350 (1964). (c) Borohydride anion in carboxylic acid solvents reductively alkylates certain heterocyclic amines [see G. W. Gribble, P. D. Lord, J. Skotnicki, S. E. Dietz, J. T. Eaton, and J. L. Johnson, *J. Am. Chem. Soc.*, **96**, 7812 (1974); G. W. Gribble and P. W. Heald, *Synthesis*, 650 (1975); P. Marchini, G. Liso, A. Reho, F. Liberatore, and F. M. Moracci, *J. Org. Chem.*, **40**, 3453 (1975)]; the reagent system also reduces amides to the corresponding amines [see, N. Umino, T. Iwakuma, and N. Itoh, *Tetrahedron Lett.*, 763 (1976)], selectively reduces aldehydes in the presence of ketones [G. W. Gribble and D. C. Ferguson, *J. Chem. Soc., Chem. Commun.*, 535 (1975)], reduces nitrimines to nitramines [M. J. Haire, *J. Org. Chem.*, **42**, 3446 (1977)], converts certain arylmethanols to hydrocarbons [G. W. Gribble, R. M. Leese, and B. E. Evans, *Synthesis*, 172 (1977)], and transforms to-sylhydrazones to hydrocarbons [R. O. Hutchins and N. R. Natale, *J. Org. Chem.*, in press (1978). (d) The reduction of certain esters has also been noted: see, for example, S. Takahashi and S. A. Cohen, *ibid.*, **35**, 1505 (1970); M. S. Brown and R. Rapoport, *ibid.*, **28**, 3261 (1963). (e) Borohydride also has been used sparingly for the reduction of imines to amines: see, for instance, K. A. Schellenberg, *ibid.*, **28**, 3259 (1963); P. R. Farina, L. J. Farina, and S. J. Benkovic, *J. Am. Chem. Soc.*, **95**, 5409 (1973); A. I. Meyers, H. W. Adickes, I. R. Politzer, and W. N. Beverung, *ibid.*, **91**, 965 (1969); A. I. Meyers, G. R. Malone, and H. W. Adickes, *Tetrahedron Lett.*, 3715 (1970). (f) Infrequent reduction of amides has also been reported: see, for example, Y. Kikugawa, S. Ikegame, and S. Yawada, *Chem. Pharm. Bull. Jpn.*, **17**, 98 (1969).

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(17) A note of caution is in order at this point. HMPA has been shown to be a carcinogen and, in addition, is relatively expensive. For small-scale reactions and using adequate and careful precautions, handling this material, in our opinion, does not offer severe problems. With large-scale reactions however, Me_2SO might be preferred considering safety and expense.

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(20) S. B. Kadin, *J. Org. Chem.*, **38,** 1348 (1973).

(21) The reluctance of hindered systems to add a second sulfonyl moiety has been noted previously (ref 19c and communications with Professors Baumgarten and Glass), and apparently stems from an unusually severe steric requirement of sulfonimides, see ref 19k.

(22) H.-L. Pan and T. L. Fletcher, *Synthesis*, 39 (1975).

(23) F. Klages and F. E. Malecki, *Justus Liebigs Ann. Chem.*, **691,** 15 (1966).

(24) The related phthalimido and succinimido groups also present relatively large steric environments as evidenced by their reluctance to occupy axial positions in cyclohexane; see H. Booth and G. C. Gidley, *Tetrahedron Lett.*, 1449 (1964).

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(26) S. Krishnamurthy, R. M. Schubert, and H. C. Brown, *J. Am. Chem. Soc.*, **95,** 8486 (1973).

(27) The preference for S–N over C–N cleavage has been noted by others even with small nucleophiles such as hydroxide, cyanide, or mercaptide; see, for example, ref 19e, and 19f and references cited therein.

(28) This sluggish behavior of 12-membered rings toward S_N2 reactions has been previously noted: see P. J. C. Fierens and P. Verschelden, *Bull. Soc. Chim. Belg.*, **61,** 427, 609 (1952); L. Schotsmans, P. J. C. Fierens, and T. Verlie, *ibid.*, **68,** 580 (1959).

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Onium Ions. 18.[1] Static Protonated and Exchanging Diprotonated Ambivalent Heteroorganic Systems: Hydroxylamines, Acetone Oxime, and Dimethyl Sulfoxide

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Monoprotonated aliphatic hydroxylamines, acetone oxime, and dimethyl sulfoxide as their fluoroantimonate salts (prepared from the corresponding hydrochloric acid salts) in SbF_5–SO_2ClF (or SO_2) solution were studied to determine the site of protonation. Subsequently, diprotonation was also investigated in HSO_3F–SbF_5 (magic acid) solution. From the ^1H and ^{13}C NMR data of the static and exchanging species it was possible to determine the site of monoprotonation, as well as an indication of diprotonation. MINDO/3 calculations were also carried out on the parent, mono-, and diprotonated forms of dimethyl sulfoxide. The calculated and experimental results gave good agreement.

Weak bases (**1**) are protonated in strong acids of increasing strength. Whether a static protonated form (**2**) is observed depends primarily upon the relative acidity constant. In some cases, an equilibrium between **1** and **2** was observed in sulfuric and fluorosulfuric acid solutions, due to the very weak basicity of the studied compounds.[2,3] With the use of mixtures of fluorosulfuric acid and antimony pentafluoride (magic acid) the acidity constant H_0 can be greatly increased, allowing the complete protonation of weaker bases, forming the static protonated onium ions.[4]

$$\underset{\mathbf{1}}{RX:} \overset{H^+}{\rightleftharpoons} \underset{\mathbf{2}}{\overset{+}{R}XH}$$

When two or more heteroatoms are present in a molecule frequently more than one site can be protonated in magic acid solution, forming static heteroorganic dications. This is the case with some anilines,[5] trihydroxy- and trimethoxybenzenes,[6] dinitriles,[7] amino acids,[8] guanidines, ureas,[9] azobenzenes, and hydrazines.[5] Most of these compounds form highly stabilized systems where the two charges are usually separated by one or more atoms. An exception is the case of diprotonated hydrazines, where the two charged centers are adjacent to each other. Due to the ability of nitrogen to stabilize the charge, diprotonated hydrazines can even be isolated as stable salts from aqueous hydrochloric acid solutions.

Even in superacid media it is not expected that weak ambivalent bases will be completely diprotonated, forming a stable static species. An even more unlikely possibility would be the formation of the geminally doubly protonated perhydronium ion (**4**) via protonation of the hydronium ion (**3**). However, such a species could be involved in an exchange process in superacidic media.

$$\underset{\mathbf{3}}{HA} + H_3O^+: \rightleftharpoons \underset{\mathbf{4}}{H_4O^{2+}} + A^-$$

In the present study we have investigated, by ^1H and ^{13}C NMR spectroscopy, monoprotonated hydroxylamines, acetone oxime, and dimethyl sulfoxide as their fluoroantimonate salts prepared from the hydrochloric acid salts in SbF_5–SO_2ClF solution and determined the site of monoprotonation. Subsequently, we also studied the possible diprotonation in HSO_3F–SbF_5 solution. Since the sites of possible diprotonation are adjacent to each other, the possibility of diprotonation was investigated in terms of basicity of the sites being protonated. We also carried out MINDO/3 calculations of the heat of formation and charge distributions for dimethyl sulfoxide and its mono- and diprotonated derivatives. The results were compared with the experimental (NMR) results.

Results and Discussion

When hydroxylamine hydrochloride is dissolved in a solution of SbF_5–SO_2ClF, the formed fluoroantimonate salt shows two absorptions in the ^1H NMR spectrum at −80 °C at $\delta_{^1H}$ (Me_4Si) 6.87 and 8.47 (Table I). From the multiplicities of the

$$NH_2OH{\cdot}HCl \xrightarrow[-80\ °C]{SbF_5\text{–}SO_2ClF} \overset{+}{H_3N}\text{–}OH\ Sb_2F_{10}Cl^-$$

coupling patterns and integration of the peak areas, the resonances were assigned to the hydroxyl and ammonium protons, respectively. When the temperature of the solution was raised, the doublet due to the ammonium group further broadened due to the ^{14}N quadruple effect. The quartet of the hydroxyl group, however, remained unaffected by change of temperature.

When antimony pentafluoride was replaced with magic acid, the proton absorption due to the hydroxyl group broadened and displayed no fine coupling. The ammonium group's absorption collapsed to a broadened singlet. When the temperature was raised the hydroxyl peak broadened and eventually merged into the baseline. This effect is reversible with no decomposition occurring and indicates an exchange process through diprotonated hydroxylamine (see subsequent discussion).

$$\overset{+}{H_3}NOH \overset{HSO_3F\text{–}SbF_5\text{–}SO_2ClF}{\rightleftharpoons} \overset{+}{H_3}N\text{–}\overset{+}{O}H_2$$

The same temperature dependence effects are observed for *N*-methylhydroxylamine hydrochloride, trimethylamine oxide hydrochloride, and acetone oxime hydrochloride. In the ^1H NMR spectra the hydroxyl absorption in each of the above cases is observed even at −80 °C. Lowering the temperature results in a broad absorption at the same ^1H NMR chemical shift as observed in SbF_5–SO_2ClF solution (Table I).

The hydrogen chloride salt of dimethyl sulfoxide is stable and can be isolated from an ethereal solution.[10,11] When this salt was dissolved in a solution of SbF_5–SO_2, the formed fluoroantimonate displayed two sharp singlets in the ^1H NMR spectrum at $\delta_{^1H}$ 6.26 (s) and 3.18 (s), corresponding to the absorptions of the hydroxyl and methyl groups, respectively. The ^1H NMR spectrum of the solution showed no temperature dependence between −20 and −80 °C.

When dimethyl sulfoxide is dissolved in a solution of

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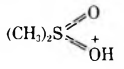
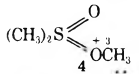
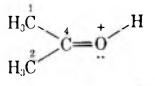
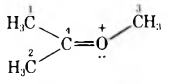
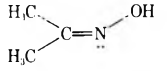
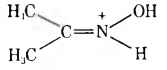
0022-3263/78/1943-2268$01.00/0

Table I. ^{1}H NMR Parameters of the Hydroxylamines, Acetone Oxime, and Dimethyl Sulfoxide in Strong Acid Solution

Registry no.	No.	Species	Solvent	Temp, °C	δ_{1H} (Me$_4$Si) NH_3	OH	CH_3
5470-11-1	5	$NH_3^+OH\ Cl^-$	SbF_5–SO_2ClF	−80	8.47 (bd)	6.87 (q)	
			HSO_3F–SbF_5–SO_2ClF	−80	8.53 (bs)	7.00 (b)	
					NH_2		
4229-44-1	6	$CH_3N^+H_2OH\ Cl^-$	SbF_5–SO_2ClF	−20	8.60 (b)	7.18 (t)	3.66 (t)
			HSO_3F–SbF_5–SO_2ClF	−80	8.65 (bs)		3.53 (t)
				−100	8.73 (b)	7.30 (b)	3.60 (b)
7651-88-9	7	$(CH_3)_3N^+OH\ Cl^-$	SbF_5–SO_2	−38		7.42 (s)	3.59 (s)
			HSO_3F–SbF_5–SO_2	−60			3.86 (s)
				−100		7.30 (bs)	3.60 (s)
					=NH		
4154-71-6	8	$HON^+H{=}C(CH_3)_2\ Cl^-$	SbF_5–SO_2ClF	−80	11.13 (bs)	8.20 (s)	2.80 (s), 2.86 (s)
127-06-0		$HON{=}C(CH_3)_2$	HSO_3F–SbF_5–SO_2ClF	−10			2.88 (s), 2.80 (s)
				−60	11.21 (bs)		2.88 (s), 2.81 (s)
				−100	11.32 (bs)	8.40 (vb)	2.85 (b)
26394-12-7	9	$(CH_3)_2S{=}OH^+\ Cl^-$	SbF_5–SO_2	−20		6.26 (s)	3.18 (s)
67-68-5	10	$(CH_3)_2S{=}O$	HSO_3F–SbF_5–SO_2	−20			3.36 (s)
				−100		6.53 (s)	3.38 (s)

Table II. ^{13}C NMR Chemical Shifts [a] of Protonated (Methylated) Heteroorganic Compounds

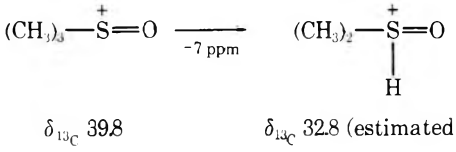
Registry no.	No.	Species	δ_{13C} (Me$_4$Si) 1	2	3	4
1184-78-7	11	$(CH_3)_3\overset{+}{N}{-}O^-$	62.1			
	7	$(CH_3)_3\overset{+}{N}{-}OH$	58.3			
	10	$(CH_3)_2S{=}O$	37.1			
	9	$(CH_3)_2S{=}\overset{+}{O}H$	34.3			
47987-92-8	12	$(CH_3)_3\overset{+}{S}{=}O$	39.8			
22396-69-6	13	$(CH_3)_2S{=}\overset{+}{O}CH_3$	32.7		60.4	
75-18-3	14	$(CH_3)_2\ddot{S}$	16.3			
18683-32-4	15	$(CH_3)_2\overset{+}{S}H$	19.5			
676-84-6	16	$(CH_3)_3S^+$	26.5			
67-71-0	17	$(CH_3)_2SO_2$	41.5			
26428-10-4	18		40.7			
65465-71-6	19		38.7		63.4	
67-64-1	20 [b]	$(CH_3)_2\overset{4}{C}{=}\ddot{O}$	30.2			205.1
43022-03-0	21 [c]		30.2	31.6		248.5
41798-19-0	22 [c]		27.0	32.2	68.8	245.1
	23		16.1	22.8		156.1
	24		18.2	21.8		181.8

[a] All of the ^{13}C NMR chemical shifts are referenced from external Me$_4$Si. All of the measurements were performed at −60 °C except where indicated otherwise. [b] These chemical shifts were obtained from ref 22. [c] The ^{13}C NMR data was measured in ref 17.

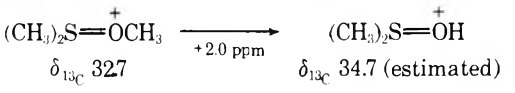
HSO_3F–SbF_5–SO_2 at −20 °C, the hydroxyl absorption is not observed in the ^{1}H NMR spectrum. On cooling the solution to −100 °C a slightly broadened singlet is observed at δ 6.53. The fact that there is no coupling with the methyl hydrogens led Modena[12] to assign the absorption at δ_{1H} 6.26 to the OH group (O-protonation) rather than to the SH group, as suggested in our preceding work.[13] However, since the absorption at δ 6.26 is broadened, it could indicate the possibility of coupling or an exchanging system.

It also appeared difficult to determine the site of protonation on the basis of ^{13}C NMR chemical shift data.[12] In order to estimate the ^{13}C NMR shifts of S- and O-protonated dimethyl sulfoxide, the ^{13}C NMR spectra of protonated and methylated dimethyl sulfide and dimethyl sulfone were used as models for the S and O derivatives of dimethyl sulfoxide, respectively. Table II shows that the replacement of the methyl group of trimethylsulfonium iodide by hydrogen results in a shielding of the methyl carbon resonance by 7.0 ppm.

Applying this value to the chemical shift of the trimethylsulfoxonium iodide[10,14] we could estimate the ^{13}C NMR resonance of S-protonated Me_2SO as $\delta_{^{13}C}$ (Me_4Si) 32.8. The *O*-



methyl derivative of dimethyl sulfone was slowly formed (1 h) when the sulfone was treated with an equimolar amount of CH_3F–SbF_5 in SO_2 at −30 °C. The methyl carbons bound to sulfur were shielded by 2.0 ppm relative to the protonated sulfone. Based on the ^{13}C NMR absorption of the O-methylated Me_2SO,[5] it is possible to estimate the carbon resonance of O-protonated Me_2SO as $\delta_{^{13}C}$ (Me_4Si) 34.7. Thus, the ex-



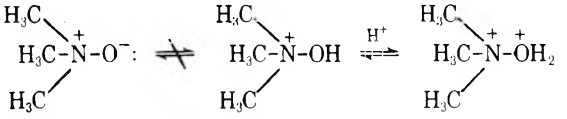
perimentally observed shift of $\delta_{^{13}C}$ 34.3 is close to the estimated value of the O-protonated form, but the S-protonated form deviates only slightly. The ^{13}C NMR chemical shifts in Table II are those of the static species indicated and are not in equilibrium.

Recent Raman spectroscopic studies by Spiekermann and Schrader[15] have indicated that the mono-O-protonated structure is formed in magic acid solution containing dimethyl sulfoxide. This is in accord with the general chemical background of acid-catalyzed reactions of dimethyl sulfoxide, indicating that a proton adds at oxygen, as well as the NMR spectroscopic data of Modena and the data described in the present work. Observed temperature-dependent behavior in superacid media raised the question of whether or not the diprotonation of dimethyl sulfoxide is involved in an exchange process.

When the hydrochloride salts of hydroxylamines, acetone oxime, and dimethyl sulfoxide were dissolved in a solution of antimony pentafluoride–sulfuryl chloride fluoride (or sulfur dioxide), the corresponding monoprotonated fluoroantimonate salts were obtained. The ^1H NMR spectra were usually not temperature dependent, and the site of protonation could be unequivocally determined from the spectra. When the same precursors were dissolved in a solution of HSO_3F–SbF_5–SO_2ClF (or SO_2), the NMR spectra were temperature dependent and did not display sharp absorptions or fine coupling. As the temperature of the solutions was lowered, the absorptions corresponding to the monoprotonated species started to be resolved in the ^1H NMR spectra. Thus, it appears that in the strong superacidic system an exchange reaction is taking place.

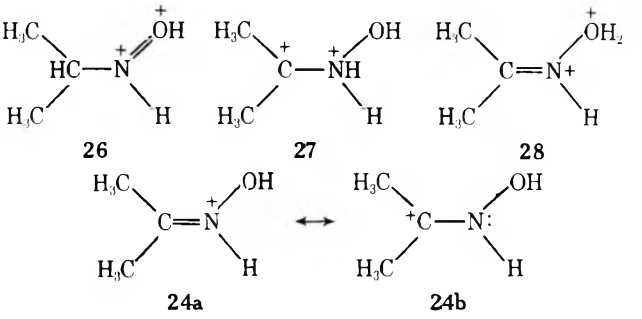
The observed exchange of the hydroxyl proton can be best explained through the intermediacy of an N,O (S,O) diprotonated species. In the ^1H NMR spectra of the monoprotonated species in SbF_5–SO_2ClF (or SO_2) (not a proton source) no exchange is observed. Thus, the exchange phenomenon with HSO_3–SbF_5 cannot be due to deprotonation to the neutral species followed by reprotonation. Although it can be concluded that exchange occurs through a diprotonated species, these obviously unstable (through charge–charge repulsion) species have not been directly observed under nonexchanging conditions.

In HSO_3F–SbF_5 solution trimethylamine oxide hydrochloride (**7**) is not in equilibrium with trimethylamine oxide (**11**). Rather, the basicity of the oxygen of **7**, despite the adjacent ammonium center, allows it to be protonated in HSO_3F–SbF_5, forming the diprotonated ion **25**. However, even the strong acidity of HSO_3F–SbF_5 is not large enough to



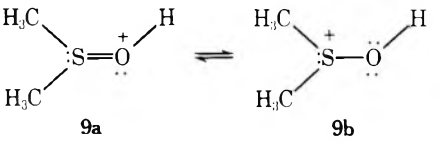
completely protonate **7**, which results in an equilibrium between **7** and **25**. As the temperature of the solution is lowered, the absorptions for the thermodynamically more stable monoprotonated ion **7** are observed in the ^1H NMR spectrum. Even at −120 °C some exchange is still taking place as evidenced by the slightly broadened absorptions. N-Protonated hydroxylamine (**5**) and N-methylated hydroxylamine (**6**) exhibit the same temperature-dependent behavior in their ^1H NMR spectra. In each case the second protonation can take place only on the nonbonded electron pair of the oxygen atom. This is not the case, however, for acetone oxime and dimethyl sulfoxide.

For N-protonated acetone oxime there are conceivably three possible sites for a second protonation: the iminium carbon (**26**), the nitrogen (**27**), and the oxygen (**28**). N-Pro-



tonated acetone oxime (**24**) is stabilized primarily by two resonance structures similar to those described for iminium ions.[16] Thus, due to their basicities, protonation at carbon (**26**) or nitrogen (**27**) is not considered feasible. This is confirmed by the NH absorption in the ^1H NMR spectrum and by the ^{13}C NMR shift of the iminium carbon. The hydroxyl absorption of $\delta_{^1H}$ 8.2 is shielded by 6 ppm from that of protonated acetone, indicating that the former site is more basic. Again diprotonation at the oxygen atom leads to exchange.

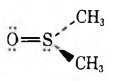
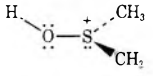
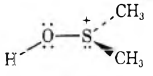
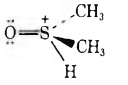
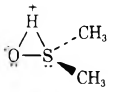
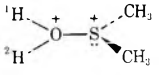
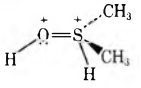
There is considerable evidence from IR, Raman, and NMR data of the various salts and strong acid solutions of dimethyl sulfoxide pointing toward O-protonation. Since the hydrochloric acid salt of dimethyl sulfoxide forms the static monoprotonated fluoroantimonate **9** in SbF_5–SO_2 solution (evidenced by the temperature independence of the ^1H NMR spectrum), it is possible to attain unequivocal structural information from its ^1H and ^{13}C NMR spectra. Resonance forms **9a** and **9b** contribute to the overall structure. In comparison



with the previously discussed protonated oximes, imines,[16] and ketones[17] (Tables I and II), it might have been expected that **9a** should be a major contributor to the overall structure, resulting in restricted rotation about the S–O bond. However, the ^1H and ^{13}C NMR spectra show only one methyl absorption, indicating free rotation about the S–O bond. Thus, the hydroxysulfonium ion (**9b**) is the major contributor to the overall structure of monoprotonated dimethyl sulfoxide (**9**).

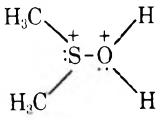
O-Protonated dimethyl sulfoxide is comparable to the *N*-hydroxytrimethylammonium ion (**7**) except that one of the methyl groups on nitrogen is replaced by a nonbonded pair

Table III. MINDO/3 Calculations of Heats of Formation, Bond Order, and Charge Densities for Dimethyl Sulfoxide and its Mono- and Diprotonated Ions

No.	Species	Geometry: Bond lengths, Å		Geometry: Angles, deg		ΔH_f, kcal/mol	S–O bond order	Charge density	
10		O–S	1.48	OSC	106.7	−47.7 (−46.9)[a]	0.791, 0.380, 0.447	−0.617	+0.853
		S–C	1.81	HCS	107.5				
		C–H	1.09						
9		H–O	0.936	HOS	144.2	80.1	0.603, 0.241, 0.279	−0.461	+0.865
9		H–O	0.935	HOS	131.3	83.2	0.678, 0.174, 0.282	−0.461	+0.775
30		H–S	1.40	HSO	237.8	153.2	0.705, 0.474, 0.365	−0.486	+1.168
31		H–O	1.33	HOS	56.2	183.0	0.733, 0.101, 0.258	−0.370	+0.666
		H–S	1.33	OHS	67.6				
29[b]		S–O	1.61	HOS[1]	133.2	370.7	0.583, 0.131, 0.130	−0.238	+0.667
		H–O[1]	0.966	HOS[2]	121.9				
		H–O[2]	0.980						
32		H–O	0.936	HOS	144.2	429.7	0.623, 0.277, 0.215	−0.458	+1.06
		H–S	1.40	HSO	237.8				

[a] Experimental value: *Natl. Bur. Stand. (U.S.), Circ.*, **500** (1952). [b] Registry no.: **29**, 65465-72-7.

of electrons. It is thus expected that the second protonation, as implied by the larger contribution of **9b** to **9**, will occur on oxygen, forming **29**. This is confirmed by the ^1H NMR spec-



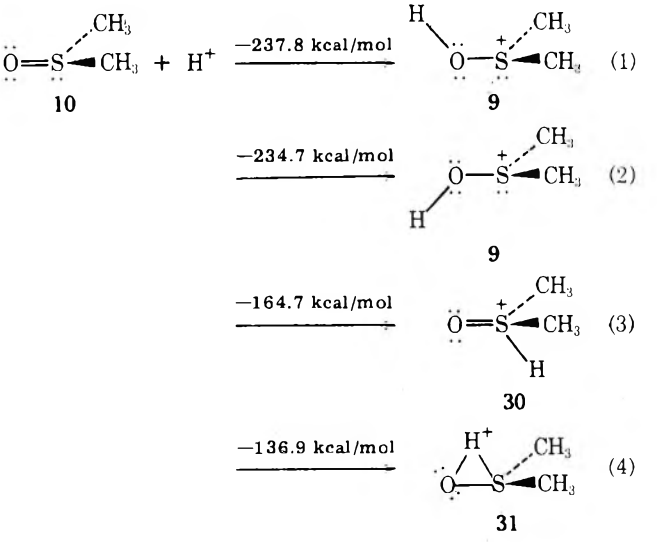
29

trum in HSO_3F–SbF_5, which only showed the temperature dependence of the hydroxyl absorption.

MINDO/3 Calculations of Mono- and Diprotonated Dimethyl Sulfoxide. Since the experimental evidence suggests that mono- and diprotonation of dimethyl sulfoxide take place in strong acid solutions on the oxygen atom, MINDO/3 calculations were carried out on the various possible structures of mono- and diprotonated dimethyl sulfoxide to investigate the most stable cations and to relate the energetics of the possible forms. The MINDO program was calibrated with respect to the heat of formation of dimethyl sulfoxide and its S–O bond length. Indeed, the required constants for the S–O bond were not available in the original QCPE 279 version of the MINDO program. The two parameters, α and β, required to evaluate the core repulsion integral and the resonance integral, respectively, were determined by a two-dimensional variation procedure that led to the values $\alpha_{SO} = 1.8$ and $\beta_{SO} = 0.51$. The results of the MINDO/3 calculations for the model compound Me_2SO and its protonated derivatives are summarized in Table III.

From the heats of formation in Table III it is possible to estimate the energetics of the sites of mono- and diprotonation of dimethyl sulfoxide. In Scheme I the monoprotonation reactions are given. As can be seen from the data, O-protonation of dimethyl sulfoxide is an extremely favorable process compared to either the formation of S-protonated or hydrogen-bridged structures. It is interesting to note that there are two relative minima for O-protonation with an energy difference of only 3.1 kcal/mol for the syn and anti forms. Thus, the O-protonated cation is the most stable species, as observed experimentally. This is reasonable if the charge densities of the

Scheme I

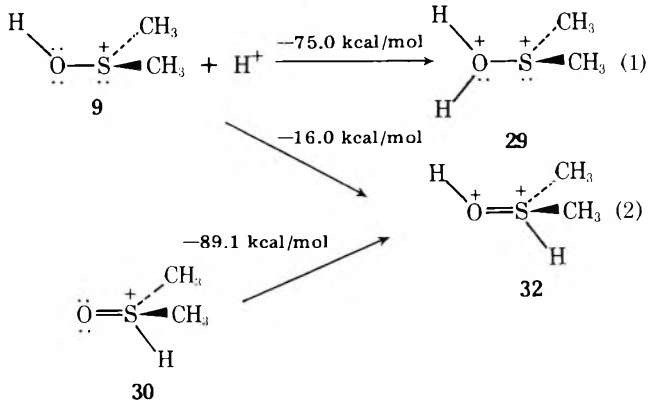


oxygen and sulfur atoms are considered before and after protonation. In dimethyl sulfoxide the charge on oxygen is −0.617 and on sulfur it is +0.853. After O-protonation the charge on oxygen increased to −0.461 while that on sulfur remained approximately the same. With S-protonation the charge on sulfur increased substantially to +1.168, whereas it remained approximately the same on oxygen. Upon O-protonation there is a lessening of the dipole of the S–O bond, whereas the charge difference in S-protonation increases, indicating a less stable system. Electrostatic addition to oxygen is thus favored.

From the data of Table III, Scheme II depicts the energetics of the formation of syn-O-protonated dimethyl sulfoxide and the diprotonated species. From the syn-O-protonated dimethyl sulfoxide, O-protonation is again found to be the most favorable. From the relative charges on sulfur and oxygen the electrostatic addition to oxygen to form **29** is expected.

The MINDO/3 results agree well with the experimental observation in strong acids. The values for the heat of reaction from Schemes I and II are not expected to agree experimen-

Scheme II



tally due to the solvation effect of the proton. The heat of formation of the proton (+365.5 kcal/mol) should be considerably lower[18] since the de facto protonating agent is $H_2O_3{}^+SF$ and not the naked proton itself. This will make the reactions less favorable energetically, but the relative energies of different O- and S-protonated species should not be affected.

Conclusions

The solutions of the hydrochloric acid salts of *N*-hydroxylamines, acetone oxime, and dimethyl sulfoxide in SbF_5–SO_2ClF (SO_2) gave the monoprotonated fluoroantimonates. Their ^1H and ^{13}C NMR spectra allowed the determination of the site of protonation. In HSO_3F–SbF_5–SO_2ClF (or SO_2) it was possible from the ^1H NMR data to show that a second protonation takes place, resulting in exchange with the monoprotonated species. Since oxygen is the only basic site in the *N*-hydroxytrimethylammonium ion, it was unequivocally shown that the second protonation occurs on oxygen. When considering all of the possible sites for the second protonation of acetone oxime, it was concluded from the ^1H NMR data that exchange was occurring through protonation on oxygen. In the case of dimethyl sulfoxide, it was also determined from the ^1H NMR data that a second protonation on oxygen causes exchange of the hydroxyl proton. MINDO/3 calculations were also carried out on dimethyl sulfoxide and its mono- and diprotonated ions. The results in all cases showed mono- and diprotonation at oxygen to be most favorable, in agreement with the experimental data.

It was thus possible to demonstrate that diprotonated species can be formed in superacidic media. Such species could be involved in some acid-catalyzed reactions.

Experimental Section

Starting Materials. Hydroxylamine hydrochloride and dimethyl sulfoxide were commercially available of highest purity (Baker Chemical Co.), as were trimethylamine oxide dihydrate, dimethyl sulfone, and dimethyl sulfide (Eastman Chemical Co.) and acetone oxime (Air Products).

Trimethylamine oxide (2 g) was prepared by heating the dihydrate under vacuum (~1 mm) at 150 °C for 2 h. Trimethylamine oxide hydrochloride was prepared from the dihydrate as reported.[20]

The hydrochloride salts of acetone oxime[21] and dimethyl sulfoxide were prepared by dissolving equimolar amounts of dry HCl and the precursor in dry diethyl ether. The salt, which immediately precipitates out of solution, was filtered under a dry nitrogen atmosphere and stored in a desiccator.

Preparation of Solutions. The precursors (~0.5 g) were dissolved in SO_2 or SO_2ClF solutions and then carefully added to a solution of HSO_3F–SbF_5 or SbF_5 (~2 g), dissolved in SO_2ClF or SO_2 (~2 g) to give approximately 10% solutions. All of the solutions were kept in a dry ice–acetone bath.

Nuclear Magnetic Resonance Studies. The ^1H NMR spectra were obtained on a Varian Associates Model A-56/60 spectrometer equipped with a variable temperature probe and controller.

The ^{13}C NMR studies were performed on a Varian XL-100-15 spectrometer equipped for proton decoupling, with a variable temperature unit and a 620L computer with 16K data points. The instrument was run in the Fourier transform pulse mode with either proton decoupling or the fully coupled experiment with some nuclear Overhauser effect. The pulse width (H_1 field) in typical experiments was 2–15 μs, where a 42-μs pulse is equivalent to a 90° pulse. Acquisition times were between 0.3 and 0.8 s with pulse delays of 0–9 s depending on the experiment. The total number of transients for a suitable signal to noise ratio for each absorption varied from 100 to 7000 passes. The radio frequency was 25.16 MHz, with the absorption referenced from external Me_4Si in CCl_3F.

MINDO/3 Calculations. The experimental geometry of dimethyl sulfoxide[11] was used in all calculations of the parent compound and its protonated derivatives. For the protonated species all of the bond lengths, angles, and dihedral angles involving the attacking proton were completely optimized. In addition to these parameters, the S–O bond length was optimized for the O-diprotonated species.

Acknowledgment. Support of our work by the National Institutes of Health is gratefully acknowledged.

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Molecular Sieve Fluorination of Fluorobenzene Using Elemental Fluorine

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A new technique of fluorination which uses molecular sieves has been developed. Using elemental fluorine and this technique, monofluorination of fluorobenzene has been achieved with yields in excess of 19%. Under the optimum fluorinating conditions, the o- and *p*-difluorobenzenes were formed to the exclusion of meta. The polymers usually observed when using elemental fluorine were not found due to the localization of the substrate on the molecular sieves.

The study of direct fluorination of organic compounds was first attempted by Moissan[1] in 1886. Bockemuller[2] studied direct liquid-phase fluorination of aromatic compounds resulting primarily in the formation of addition products and polymers. Recently, Grakauskas[3] made a study of direct liquid-phase fluorination of several aromatic systems with limited success. Young[4] used thermochemical data to explain the failure of earlier workers. A 1961 publication of Baker and Eng[5] showed how molecular sieve beds could be employed in the chlorination of selected hydrocarbons.

The use of a molecular sieve bed in the fluorination of organic molecules interested the authors for the following reasons. In earlier reactions between elemental fluorine and organic molecules, complex mixtures were usually produced via progressive fluorination, cleavage, and in most cases polymerization. The present process gives a clean conversion to difluorobenzenes. If a respectable yield of monofluorinated product is to be obtained, the polymer formation should be reduced to a minimum. Through the use of molecular sieve beds it is possible to localize the substrate and hold it in a particular location throughout the fluorination, thereby preventing substrate radicals from coming into contact with other substrate molecules. Since such contact is necessary for polymerization, the desired effect should be achieved.

Earlier workers have ascribed the molecular degradation found during fluorination to the very exothermic nature of reactions between organic compounds and elemental fluorine. It has been found that fluorination reactions can be better controlled by leading the excess heat away from the reaction site. If the molecular sieves are maintained at low temperature throughout the fluorination, they could function as a third body and thereby dissipate the heat.

Since the substrate molecules are held stationary on the rather large surface area of the molecular sieve, any exothermic heat generated by the fluorination would be spread evenly over the entire molecular sieve surface, thereby preventing the development of localized hot spots.

Experimental Section

Fluorine is extremely hazardous primarily because the weak F–F bond in molecular fluorine (37.6 kcal/mol) leads to extraordinary reactivity. Based on our experience using elemental fluorine the following major safety precautions are recommended. Fluorine cylinders should be kept behind steel barricades and the valve operated remotely. Monel valves or high-nickel steel valves with Teflon packing are highly recommended. Stainless steel or Monel tubing (properly passified) is recommended for transfer of the gas. The reactor should be shielded and all lines containing fluorine under pressure should be located behind a heavy barricade. The latter precaution eliminates a potential danger in the event of rupture of pressure lines.

Elemental fluorine was obtained from Allied Chemical Corp. in 6-lb steel cylinders and was passed through a sodium fluoride trap to remove hydrogen fluoride impurities before use. PCR, Inc., supplied the fluorobenzene and the o- and *m*-difluorobenzenes. Pierce Chemical Co. supplied the *p*-difluorobenzene. The molecular sieves (13×, 1/16 in. diameter pellets) were a gift from the Linde Division, Union Carbide Corp.

Fluorine and nitrogen gases used in the reaction were measured by Hasting mass flowmeters. The flow rate of nitrogen and fluorine were regulated with Hoke Micro-mite valves.

The molecular sieve reactor was made from 14 in. of 2.5-in. o.d. copper tubing. In a typical reactor, 241 g of molecular sieve pellets were packed inside the reactor. Glass wool was placed at each end to prevent the molecular sieves from plugging the outlets. The tube endings outside the reactor were fitted with Hoke on–off diaphragm valves.

The oven used in loading and unloading the sieves was a tube furnace capable of receiving the reactor and having a maximum operating temperature of 600 °C.

During the course of this investigation the following procedures were carried out on a routine basis.

In the loading procedure (see Figure 1), the fluorobenzene vapor was flushed with nitrogen from the boiling flask, F, through valves, V_2 and V_3, onto the molecular sieve bed, which was previously heated to 200 °C. When the fluorobenzene began to condense into the cooled receiver, R, nitrogen was allowed to pass directly into the sieve bed in order to remove any unadsorbed substrate. The reactor was allowed to come to room temperature, and the apparatus was disassembled at tubing connectors, C_1 and C_2. The reactor was weighed and reassembled, as in Figure 2, in preparation for the fluorination. In the fluorinating procedure the reactor was cooled by dry ice, flushed with nitrogen, and then the prescribed amount of fluorine and nitrogen was allowed to pass through the respective flow transducers, FT, and through the trap, T, and into the reactor. Following this the reactor was flushed with nitrogen for 20 min to remove the excess fluorine.

In the unloading procedure an apparatus was used similar to that in Figure 1. The reactor was flushed with nitrogen at room temperature for 20 min and then the temperature was raised to 400 °C. The product was flushed from the reactor and condensed in receiver R, which was cooled by a mixture of dry ice and trichloroethylene.

Gas chromatography was used in the analysis of each reaction product. The conditions of analysis were similar to that of Seiler, Durrance, and Sams.[6] The retention times of fluorobenzene and of the three isomeric difluorobenzenes were identical with those of the authentic compounds. Through use of a disc integrator, peak areas were calculated and then compared to calibration curves which were obtained by using injections of known concentration.

Results

Early in this investigation, a series of experiments were carried out to determine the optimum fluorinating conditions based on the highest percent yield. Maintaining the fluorine to fluorobenzene ratio at 0.75, reactions were carried out at −185, −78, 25, and 100 °C following techniques similar to those described in the procedure. Since the percent of monofluorinated product was found to be 0.20, 5.87, 0.23, and 0.0%, respectively, −78 °C was considered to be the optimum reaction temperature. Additional experiments were carried out maintaining the fluorine to fluorobenzene ratio at 0.75 and the temperature at −78 °C while using different schedules for the introduction of fluorine. A series of experiments using both constant fluorine flow rates and stepwise increases in fluorine flow rates were conducted. These studies indicated that a flow rate of 10 mL of fluorine and 90 mL of nitrogen for the first hour, 20 mL of fluorine and 80 mL of nitrogen for the second hour, and 30 mL of fluorine and 70 mL of nitrogen for the third hour produced the highest percent of monofluorinated

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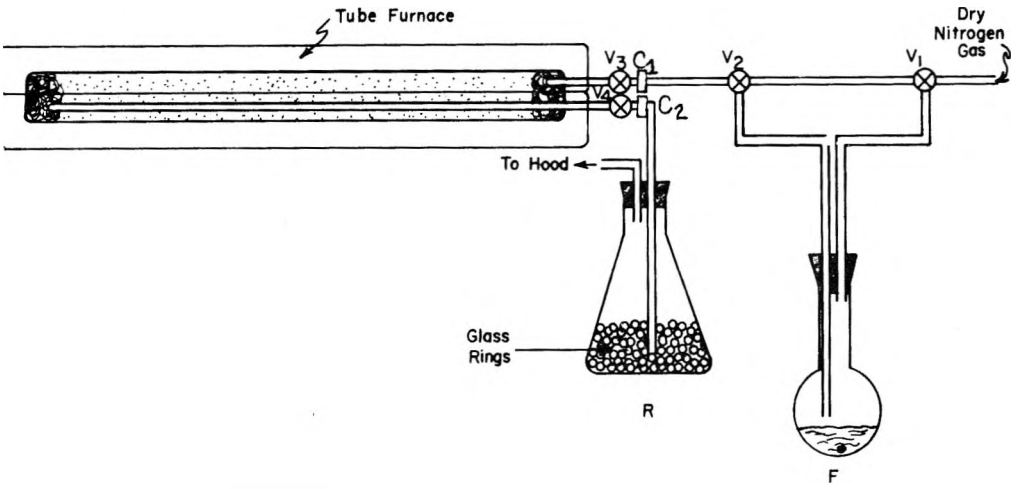

Figure 1. Apparatus used for loading and unloading the molecular sieve bed.

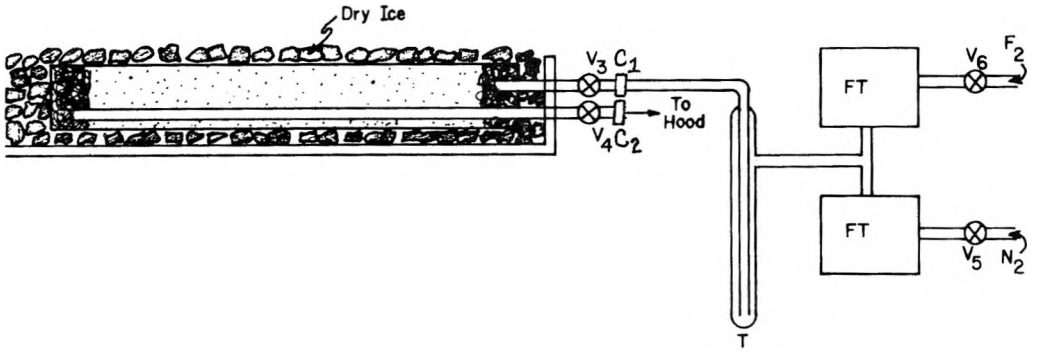

Figure 2. Apparatus used for fluorinating the substrate while on the molecular sieve bed.

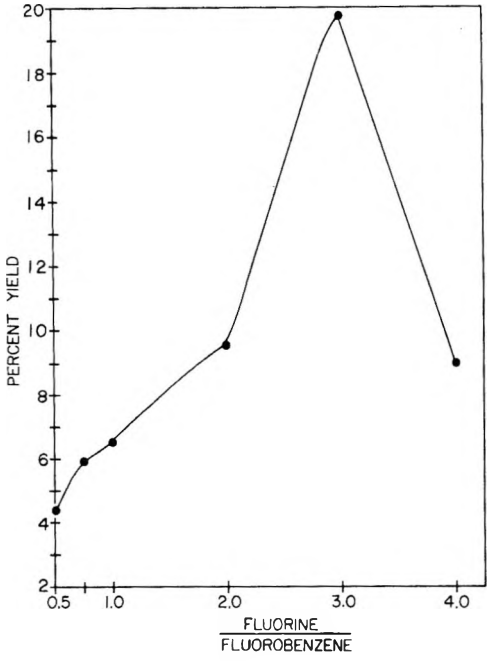

Figure 3.

products. This program of gradual increase in fluorine introduction was retained for the remaining experiments.

Attention was directed to determine the optimum fluorine to fluorobenzene ratio. Six reactions were carried out in which the temperature was maintained at −78 °C, the F_2 was introduced according to the 10/20/30 graded program, and the fluorine to fluorobenzene ratio was varied from 0.5 to 4.0. Table I and Figure 3 present the results of these experiments.

Table I

Fluorine/ fluorobenzene[a]	Difluorobenzene, % yield			
	Ortho	Meta	Para	Total
0.50	1.09	0.66	2.62	4.4
0.75	1.33	0.807	3.73	5.9
1.00	1.63	1.16	3.76	6.5
2.00	3.89	0.196	5.38	9.5
3.00	8.12	0	11.61	19.7
4.00	3.05	0	6.10	9.1

[a] The number of millimoles of fluorobenzene varied depending on the loading capacity of each individual reactor, the average being 280.

Discussion

Figure 3 shows that the percent difluorobenzene synthesized is increased from 4.4% when the ratio of fluorine to fluorobenzene was 0.5, hit a maximum of 19.7% when the ratio was 3, then decreased to 9.1% when the ratio was 4. This data shows that the highest efficiency with respect to the substrate occurs when the fluorine to fluorobenzene ratio is 3. Analysis of the substances recovered in the unloading procedure showed only fluorobenzene and the difluorobenzene isomers present.

Fluorination at the ratio of 3, as found in Table I, gave the highest percent overall yield of the difluorobenzenes, which was 19.7%. The remaining 80.3% of the product was unfluo-

rinated monofluorobenzene. Although significant amounts of meta isomer were found in experiments with fluorine to fluorobenzene ratios up through 2, it is interesting to note that no meta isomer was found when the fluorine to fluorobenzene ratios were 3 or greater. The fact that no polymers were found indicates that the technique used was successful in eliminating polymer formation.

Desirable characteristics inherent to the molecular sieve technique are: (1) substrate molecules are separated and localized, which ensures dimolecular reactions; (2) adsorptive properties of the molecular sieves permit loading and unloading a substance in a completely reversible fashion; (3) molecular sieves function as a third body to dissipate the heat of reaction; (4) heat of reaction is generated over a greater area; and (5) adsorbed substrate is not free to participate in polymer formation.

As may be seen from the procedure described earlier in this work, a complete fluorination can be carried out with minimal effort in a matter of hours. Although in a typical reaction the amount of products obtained are within the limits of experimental error, the molecular sieves were found to have lost approximately one-half of their active loading sites with each successive fluorination. Efforts to determine the cause of active site loss resulted in experiments which showed the endogenous hydrofluoric acid reacting with the silicates of the molecular sieves and reducing the number of loading sites. After several unsuccessful attempts to use the molecular sieves repeatedly, it was found that the gradual degradation of the molecular sieves represented an uncontrollable reaction parameter. In order to ensure reproducible results, each experiment in this study was begun with fresh unused molecular sieves, thereby overcoming the aforementioned difficulty.

Conclusion

Conditions have been optimized to form the greatest amount of difluorobenze product. Under the following conditions: temperature, −78 °C; fluorination schedule, 10/20/30; and fluorine to substrate ratio, 3; a maximum yield of 19.7% monofluorinated product was obtained. Despite the relatively high yield of desired products, there was no meta isomer found; however, measurable amounts of the meta isomer were observed in the experiments conducted at the lower ratios. The usual polymer formation, which is expected when elemental fluorine is allowed to react with organic substrates, was not observed due to aforementioned factors. Although this technique is easily accomplished, there is one drawback. The major difficulty lies in the fact that a completely inert molecular sieve has not been found; therefore, this work is being discontinued.

Registry No.—Fluorine, 7782-41-4; fluorobenzene, 462-06-6; *o*-difluorobenzene, 367-11-3; *m*-difluorobenzene, 372-18-9; *p*-difluorobenzene, 540-36-3.

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Notes

Reactions of α-Alkoxy-α,β-unsaturated Carbonyl Compounds[1]

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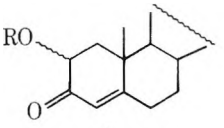
Received December 5, 1977

α-Alkoxy-α,β-unsaturated carbonyl compounds have attracted our attention because of their potential as addends in annulation and addition reactions. The products of these reactions, α-alkoxycarbonyl compounds (e.g., **1**), would be useful intermediates in the synthesis of natural products, e.g., cerin or β-ecdysone. It was uncertain, however, whether the unsaturated carbonyl of the addend would be sufficiently reactive to participate in the required reactions. Mesomeric electron donation from the alkoxy group[2] might make the system less susceptible to nucleophilic attack even as the carbonyl group is activating the alkene. As model compounds for study, we have chosen methyl α-methoxyacrylate (**2**) and 2-ethoxy-1-buten-3-one (**3**). We have investigated reactions of these compounds with nucleophiles (as a prelude to studies of the Robinson annulation), with lithium dialkylcuprates, and with dienes.



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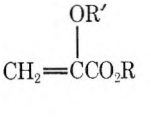
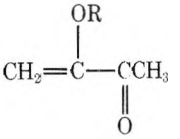
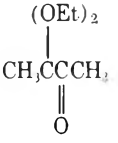


2, R = R′ = Me
6, R = Et; R′ = Me
7, R = R′ = Et



3, R = Et
5, R = Me



4

Compound **2** was prepared from methyl 2,3-dibromopropionate by the method of Ogata et al.[3] The enone **3**, originally obtained by Harris as an unidentified side product in the preparation of 3,3-diethoxy-2-butanone (**4**),[4] was prepared in our work by distilling ketal **4** from $KHSO_4$[5] (cf. the preparation of the methyl analogue, **5**[6]).

Although reactions of nucleophiles with **6**[7] and **7**[8] have been reported, no successful conjugate addition to any of these compounds has yet been described. Attempts to induce the addition of the sodium enolates of cyclohexanone, methylcyclohexanone, dimedone, or 2-carbethoxycyclohexanone to **2** or **3** were unsuccessful. Dimethyl sodiomalonate, however, was an effective nucleophile toward both **3** and **2**, giving **8** and **9**, respectively. The best yields (60%) of **8** were obtained by refluxing an ether–methanol solution of **3**, dimethyl malonate, and sodium methoxide for 24 h. By comparison, the analogous reaction with methyl vinyl ketone occurs within 2 h at room

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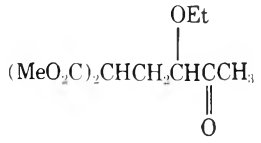

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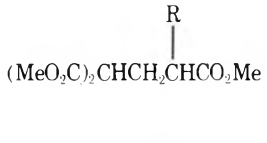
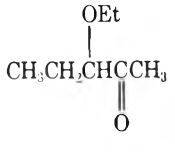


9, R = OMe
10, R = H
11, R = Me

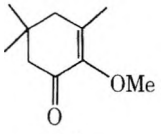
temperature.[9] The acrylate **2** was even more sluggish. When a solution of dimethyl malonate and **2** in ether–methanol was heated with sodium methoxide for 4 days, a 59% yield of **9** was obtained. In comparison, a 79% yield of **10**[10] was obtained from methyl acrylate after only 4 h under the same conditions.

Since Michael additions are, in general, only moderately susceptible to steric influence at the α carbon,[11] and since the α-substituted methyl methacrylate readily adds nucleophiles under the above conditions (60% yield of **11**[10] after 5 h), the steric bulk of the alkoxy group probably has only a slight role in decreasing the reactivity of **2** and **3**. The electronic factors which are probably responsible for most of this decrease may be of two types. The alkoxy group may act to stabilize the carbon–carbon double bond[2b] of the enone, thus retarding reactions in which that bond is affected. Or, the enolate intermediate in the Michael addition[12] may be destabilized by mesomeric electron donation from oxygen.[2a] The available data indicate that this destabilization may compete with stabilization by inductive electron withdrawal in the case of α-alkoxy, sp^2-hybridized carbanions.[2a,13] Sufficient evidence is not available to indicate which of these two electronic effects is primarily responsible for the deactivation of **2** and **3**.

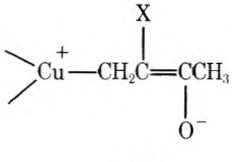
Another conjugate addition to **3**, that of lithium dimethylcuprate, has also been investigated. Relatively vigorous conditions (3 h at room temperature) are required in order to obtain an 85% yield of **12**. House and Umen found that alkoxyenone **13** also reacted more sluggishly than expected under these conditions.[14] The effect of the alkoxy group in



12



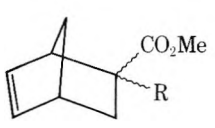
13



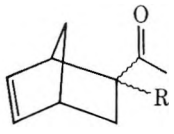
14

these cases is probably to slow the formation of the enolate-like intermediate, **14**, so that that step becomes rate determining.[15]

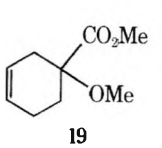
We have also investigated the reactivity of **2** and **3** toward dienes. The unsubstituted enones, methyl acrylate and methyl vinyl ketone, form adducts **15**[16] and **16**[17] respectively when treated with cyclopentadiene at room temperature. However, neither **2** nor **3** formed an adduct, detectible by GLC or TLC,



15, R = H
17a, R = OMe; *endo*-CO_2Me
b, R = OMe; *exo*-CO_2Me



16, R = H
18, R = OEt
21, R = OMe



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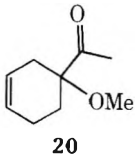

20

in methylene chloride or ether at room temperature, or in refluxing benzene or toluene. Acid catalysis (aluminum chloride or acetic acid) was likewise ineffective, The addition could be effected by heating the dienophile in a large excess of diene at 160–190 °C. Thus, **2** afforded a 54% yield of **17** and **3** afforded a 61% yield of **18** upon treatment with cyclopentadiene. Treatment of **2** and **3** with butadiene in a similar manner afforded cyclohexenes **19** (49% yield) and **20** (40% yield), respectively. Reactions of analogues **5**,[6] **6**,[7] and **7**[18] have with dienes also been reported to occur at high temperatures.

The exo and endo diastereomers of **17** were readily separated by preparative GLC. The structural assignments were made on the basis of the relative positions of the NMR signals of protons on the substituents at C-2 (signals due to endo-substituent protons are upfield from those due to the exo).[19] The ratio of substituent protons are upfield from those due to the exo).[19] The ratio of endo ester **17a** to exo ester **17b** was 38:62 as determined by GLC. Thus, **2** shows selectivity opposite to that shown by methyl acrylate (70:30) but very similar to that shown by methyl methacrylate (32:68).[20] The similarity in the endo:exo ratios obtained from **2** and methyl methacrylate indicates the presence of similar steric interactions[21] in the transition states. Thus, the decrease in dienophile reactivity must be caused by the electronic effects of the alkoxy group.

Despite the success of the separation of the diastereomers of **16**[7] and **21**,[6] we have been unable to separate the diastereomers of **18** by GLC or TLC. However, the ratio of *endo*-acetyl to *exo*-acetyl may be estimated from NMR signals at δ 2.20 and 2.30, respectively. The observed ratio of 1:2 is very much different from the 63:37 ratio found for the diastereomers of **21**.[6] The endo:exo ratio of the norbornenes obtained from methyl vinyl ketone is 83:17, while that from methyl isopropenyl ketone is 42:58.[22] Thus, the endo:exo ratio for **18** is that to be expected from steric interactions while that for **21** is surprisingly high. The reasons for this difference are not obvious.

Although these α-alkoxy-α,β-unsaturated carbonyl compounds are less reactive toward nucleophiles and dienes than the unsubstituted analogues, they will undergo conjugate additions and Diels–Alder reactions. Synthetically useful intermediates may be prepared if these reactions can be extended. We are attempting to apply the Michael additions of enone **3** in a Robinson annulation sequence.

Experimental Section

General. NMR spectra were recorded with a Varian T-60 spectrometer and are reported in ppm downfield from tetramethylsilane. Infrared spectra were recorded with a Perkin-Elmer 457 spectrophotometer using a thin film of the oil between sodium chloride plates. The UV spectra were recorded on a Beckmann DB-G spectrophotometer. Melting points were obtained with a Thomas-Hoover melting point apparatus and are uncorrected. The elemental analyses were performed by Galbraith Laboratories, Inc. An Aldrich Kugelrohr apparatus was utilized for bulb-to-bulb distillation. GLC was accomplished using: (A) a 2 ft × 0.25 in. 10% SE-30 column, (B) a 6 ft × 0.50 in. 20% SE-30 column, or (C) a 6 ft × 0.25 in. 20-M Carbowax column.

2-Ethoxy-1-buten-3-one (3). To a flask containing 5.53 g (34.5 mmol) of **4**[4] and 268 mg (2 mmol) of $KHSO_4$ was attached a short-path distillation head with a receiving flask containing 2 mL of saturated aqueous $NaHCO_3$. A 180 °C sand bath was used to quickly warm the contents of the flask. After completion of the distillation, the $NaHCO_3$ solution was extracted with 30 mL of ether. The ether solution was dried (Na_2CO_3) and concentrated in vacuo. The residue was distilled under vacuum (10 Torr), the fraction distilling between 40 and 50 °C being collected. Thus, 2.158 g of a 85:15 mixture of **3** and **4** was obtained. Further purification was accomplished by preparative GLC (column A). **3**: IR 1710, 1610 cm^{-1}; NMR ($CDCl_3$) δ 1.37 (t, J = 7 Hz, 3 H), 2.28 (s, 3 H), 3.80 (q, J = 7 Hz, 2 H), 4.42 (d, J = 2 Hz, 1 H), 5.18 (d, J = 2 Hz, 1 H); mass spectrum (70 eV) m/e 114 (P), 99, 70 (base),

44, 43; UV (95% C_2H_5OH) λ_{max} 250 nm (ϵ 4.2 × 10^3).

Methyl 2-Carbomethoxy-4-ethoxy-5-oxohexanoate (8). To a solution of 23 mg (1 mmol) of sodium in 3 mL of methanol and 15 mL of ether was added dropwise 789 mg (6.0 mmol) of dimethyl malonate. This was followed by dropwise addition of 838 mg of a mixture of **3** and **4** (4.2 mmol of **3**). The solution was then refluxed for 24 h. After cooling, it was acidified with 1 N HCl, washed twice with 10 mL of water, once with saturated aqueous $NaHCO_3$, and again with water. After drying ($MgSO_4$) and concentration in vacuo 1.12 g of a crude product was obtained. This crude product was found by GLC analysis using tetradecane as an internal standard to contain 620 mg of **8** (59% yield). Preparative GLC (Column B) was used to further purify **8**: IR 1750, 1735, 1715 cm^{-1}; NMR ($CDCl_3$) δ 1.20 (t, J = 7 Hz, 3 H), 2.20 (s, ≈3 H), 2.1–2.4 (m, ≈2 H), 3.2–3.7 (m, 3 H), 3.77 (s, 6 H); mass spectrum (70 eV) *m/e* 203, 187, 143 (base), 115. Anal. Calcd for $C_{11}H_{18}O_6$: C, 53.65; H, 7.37. Found: C, 53.37; H, 7.34.

Dimethyl 2-Carbomethoxy-4-methoxyglutarate (9). When 1.311 g (11 mole) of **2**,[3] 1.744 g (13 mmol) of dimethyl malonate, and 2.1 mmol of sodium methoxide in an ether–methanol solution were refluxed for 4 days and the product isolated as above, the yield of **9** was estimated by GLC (column A) to be 58%. The crude product was subjected to bulb-to-bulb distillation followed by preparative GLC. **9**: IR 1745 (very broad) cm^{-1}; NMR ($CDCl_3$) δ 2.47 (m, 2 H), 3.47 (s, 3 H), 3.68 (s, 3 H), 3.74 (s, 6 H), 3.7 (m, ≈2 H); mass spectrum (70 eV) *m/e* 217, 189, 130 (base). Anal. Calcd for $C_{10}H_{16}O_7$: C, 48.39; H, 6.50. Found: C, 48.60; H, 6.32.

3-Ethoxy-2-pentanone (12). To a solution of lithium dimethylcuprate, prepared from 1.457 g (7.6 mmol) of cuprous iodide and 9 mL of 1.6 M methyllithium at 0 °C, was added a solution containing 2.75 mmol of **3** in 2 mL of ether. The mixture was stirred at room temperature for 3 h after which time it was diluted with 50 mL of ether and washed with dilute ammonium hydroxide until the aqueous layer was colorless. The ether layer was dried (Na_2SO_4) and concentrated by distillation. One half of the crude material was subjected to preparative GLC (column B) from which was obtained **12**: IR 2980, 1717 cm^{-1}; NMR ($CDCl_3$) δ 0.93 (t, J = 7 Hz, 3 H), 1.23 (t, J = 7 Hz, 3 H), 1.67 (q, J = 7 Hz, 2 H), 2.13 (s, 3 H), 3.47 (q, J = 7 Hz, ≈2 H), 3.57 (t, J = 7 Hz, ≈1 H).

From the other half of the crude material was obtained 204 mg of a semicarbazone: mp 109–11 °C (lit.[23] mp 93–5 °C); NMR ($CDCl_3$) δ 0.90 (t, J = 7 Hz, 3 H), 1.2 (t, J = 7 Hz, 3 h), 1.5 (m, ≈2 H), 1.83 (s, ≈3 H), 3.37 (q, J = 7 Hz, 2 H), 3.67 (t, J = 7 Hz, 1 H), 5.83 (broad s, 2 H). Anal. Calcd for $C_8H_{17}O_2N_3$: C, 51.32; H, 9.15; N, 22.44. Found: C, 51.29; H, 8.90; N, 22.34.

***endo*- and *exo*-2-Carbomethoxy-2-methoxy-5-norbornene (17a and 17b).** A stainless steel bomb containing 1.005 g (8.7 mmol) of **2** and 5.04 g (77 mmol) of cyclopentadiene was heated at 165 °C for 12 h. The reaction mixture was chromatographed on silica gel. The portion eluting with chloroform yielded 850 mg of **17** (53% yield). The endo and exo isomers were separated by preparative GLC (column C). The reaction mixtures before column chromatography had been found by GLC to contain a 38:62 ratio of the isomers. They were identified as below.

Shorter retention time isomer (**17a**): IR 2950, 1730 cm^{-1}; NMR ($CDCl_3$) δ 1.5–2.1 (m, 4 H), 2.9 (m, ≈1 H), 3.1 (m, ≈1 H), 3.23 (s, 3 H), 3.71 (s, 3 H), 5.88 (d of d, J_1 = 3 Hz, J_2 = 6 Hz, 1 H), 6.28 (d of d, J_1 = 3 Hz, J_2 = 6 Hz, 1 H); mass spectrum (70 eV) *m/e* 182 (P), 117 (base). Anal. Calcd for $C_{10}H_{14}O_3$: C, 65.92; H, 7.74. Found: C, 65.93; H, 7.68.

Longer retention time isomer (**17b**): IR 2950, 1730 cm^{-1}; NMR ($CDCl_3$) δ 1.2–1.8 (m, 3 H), 2.27 (d of d, J_1 = 3 Hz, J_2 = 12 Hz, 1 H), 2.9 (m, 1 H), 3.13 (s, 3 H), 3.3 (m, 1 H), 3.80 (s, 3 H), 6.07 (d of d, J_1 = 3 Hz, J_2 = 6 Hz, 1 H), 6.40 (d of d, J_1 = 3 Hz, J_2 = 6 Hz, 1 H); mass spectrum (70 eV) *m/e* 182 (P), 117 (base).

Anal. Calcd for $C_{10}H_{14}O_3$: C, 65.92; H, 7.74. Found: C, 66.01; H, 7.73.

2-Ethoxy-2-acetyl-5-norbornene (18). In a stainless-steel bomb were placed 0.64 g of a mixture of **3** and **4** (4.2 mmol of **3**) and 3.7 g (55 mmol) of freshly distilled cyclopentadiene. The sealed bomb was kept in a sand bath at 160 °C for 40 h. Silica gel column chromatography of the reaction products afforded 464 mg (61% yield) of the Diels–Alder adduct, **18**, upon elution with benzene–chloroform (1:1). Preparative GLC (column C) afforded an analytical sample of the mixture of endo and exo isomers of **18**: IR 3050, 2970, 1710 cm^{-1}; NMR ($CDCl_3$) δ 1.17 (t, J = 7 Hz, *endo*-OCH_2CH_3), 1.22 (t, J = 7 Hz, *exo*-$O\text{-}CH_2CH_3$), 1.3–2.0 (m, 4 H), 2.20 (s, *endo*-$COCH_3$), 2.30 (s, *exo*-$COCH_3$), 2.7–3.4 (m, 4 H), 5.8–6.4 (m, 2 H).

Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C, 73.42; H, 8.84.

4-Carbomethoxy-4-methoxycyclohexene (19). A sealed bomb containing 2.03 g (17.4 mmol) of **2**, approximately 5 g (90 mmol) of butadiene, and 10 mg of hydroquinone was heated at 190 °C for 56 h. The reaction mixture was extracted with 100 mL of hot acetonitrile and the residue from the concentration of that solution was chromatographed on a silica gel column. The fraction eluted with benzene–chloroform (1:1) contained 1.45 g of **19** (49% yield). This material was further purified by bulb-to-bulb distillation. **19**: IR 1735, 1655 cm^{-1} NMR ($CDCl_3$) δ 2.0 (m, 4 H), 2.4 (m, 2 H), 3.24 (s, 3 H), 3.74 (s, 3 H), 5.64 (bs, 2 H); mass spectrum (70 eV) *m/e* 139, 112 (base). Anal. Calcd for $C_9H_{14}O_3$: C, 63.51; H, 8.29. Found: C, 63.56; H, 8.40.

4-Ethoxy-4-acetylcyclohexene (20). A solution of 978 mg of a mixture of **3** and **4** (4.3 mmol of **3**), 4 g (74 mmol) of butadiene, and 10 mg of hydroquinone in 5 mL of benzene was placed in a stainless-steel bomb and heated at 190 °C for 70 h. The reaction mixture was treated as above to give 290 mg (40% yield) of **20**. A bulb-to-bulb distillation afforded a sample of **20** for analysis: IR 3030, 1710, 1652 cm^{-1}; NMR ($CDCl_3$) δ 1.20 (t, J = 7 Hz, 3 H), 1.7–2.4 (m, 6 H), 2.20 (s, 3 H), 3.30 (q, J = 7 Hz, 2 H), 5.65 (br s, 2 H); mass spectrum (70 eV) *m/e* 125, 97, 80. Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 71.54; H, 9.73.

Registry No.—**2**, 7001-18-5; **3**, 65915-73-3; **4**, 51933-13-2; **8**, 65915-74-4; **9**, 65942-40-7; **12**, 65915-75-5; **12** semicarbazone, 65915-76-6; **17a**, 65915-77-7; **17b**, 65915-78-8; *exo*-**18**, 65915-79-9; *endo*-**18**, 65915-80-2; **19**, 65915-81-3; **20**, 65915-82-4; dimethyl malonate, 108-59-8; cyclopentadiene, 542-92-7; butadiene, 106-99-0.

References and Notes

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Synthesis of 8-Methoxy- and 11-Methoxybenz[*a*]anthraquinones via Diels–Alder Reaction of 1,4-Phenanthraquinone

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We have been interested in the synthesis of oxygenated derivatives of 7,12-dimethylbenz[*a*]anthracene (one of the most potent carcinogenic polycyclic aromatic hydrocarbons).[1,2] Since excellent methods[3,4] exist to convert 7,12-

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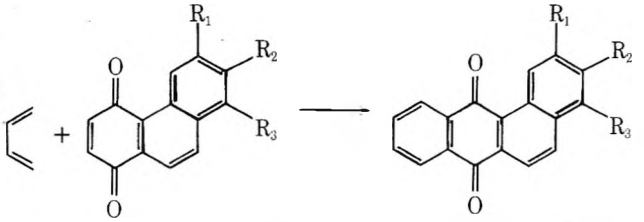
Scheme I



I, R_1, R_2, or R_3 = OCH_3 II, R_1, R_2, or R_3 = OCH_3

benz[*a*]anthraquinones into the corresponding 7,12-dimethylbenz[*a*]anthracene derivatives, synthesis of the former constitutes a solution to the problem.

Diels–Alder cycloadditions have been applied to the synthesis of related polycyclic aromatic compounds.[5–8] Thus, 2,3- and 4-methoxy-7,12-benz[*a*]anthraquinones may be prepared by a Diels–Alder reaction between 1,3-butadiene and 6-, 7-, or 8-methoxy-1,4-phenanthraquinone.[5] See Scheme I.

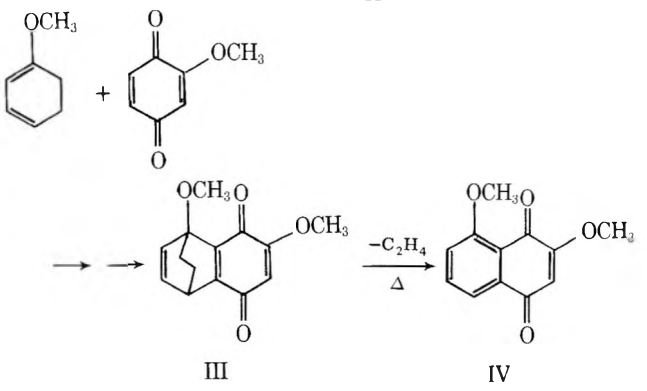
When reaction was attempted between 1-methoxy-1,3-butadiene and 1,4-phenanthraquinone, methanol was lost and only 7,12-benz[*a*]anthraquinone was isolated, even at low temperatures. Therefore, an alternative route was sought for the synthesis of the 8- and 11-methoxy-7,12-benz[*a*]anthraquinones.

Aromatic methoxy substituted compounds have been prepared via a Diels–Alder reaction[9,10] between a 1-methoxy-1,3-cyclohexadiene and 1,4-benzoquinone which gave an ethylene-bridged bicyclic intermediate, III, Scheme II. On pyrolysis, ethylene is eliminated in a retro-Diels–Alder reaction to give the aromatic methoxy compound IV.

In a similar fashion we reacted 1-methoxy-1,3-cyclohexadiene with 1,4-phenanthraquinone, Scheme III, to give in 75% yield two bridged bicycloadducts Va and Vb in a ratio of 18:82, as determined by NMR. The mixture of isomers was not separable on either silica or alumina thin layer chromatograms using a variety of solvent systems. After pyrolytic elimination of ethylene from the mixture, two products were isolated in quantitative yield. The isomers were separated by column chromatography in a ratio of 16:84, the more polar isomer predominating. They were identified by spectroscopic techniques (IR, NMR, UV, and high resolution mass spectrometry) and shown to be 8- and 11-methoxy-7,12-benz[*a*]anthraquinone (8-OMe-VI and 11-OMe-VI).

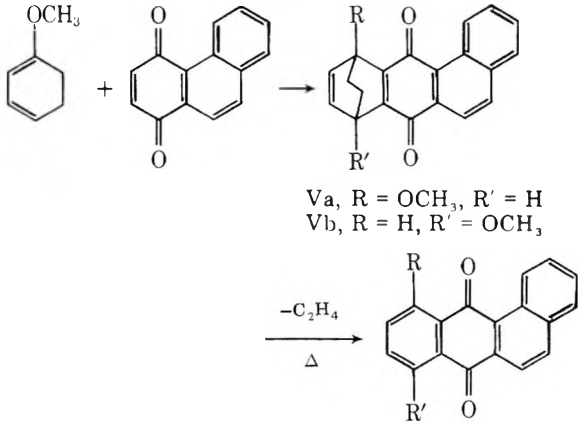
On the basis of steric interactions in transition state during the Diels–Alder reaction, one might expect that the 8-methoxy isomer (8-OMe-VI) would be predominant. In order to verify the structures of each isomer, experiments were done using lanthanide shift reagents, $Eu(fod)_3$ and $Pr(fod)_3$. It is expected that the shift reagent will chelate to the quinone carbonyl possessing an adjacent methoxy ether functionality and one would observe the most rapid shift for the methoxy methyl group in both isomers. The chemical shift of C_1–H in 7,12-benz[*a*]anthraquinones is unique at δ 9.7.[11] In the 11-methoxy isomer, the shift of the C_1–H should be more rapid than the shift of C_1–H in the 8-methoxy isomer where it is located considerably further from the coordinated shift reagent. This is indeed observed. The McConnel–Robertson equation for pseudocontact shifts in lanthanide-substrate interactions predicts that when the internuclear angle between the carbonyl–Eu–H falls between 55 and 125°, an upfield shift will be observed.[12] Consistent with this prediction, the C_1–H of 11-methoxy-7,12-benz[*a*]anthraquinone experiences a significant upfield shift on addition of $Eu(fod)_3$, whereas the C_1–H of 8-methoxy-7,12-benz[*a*]anthraquinone does not. Please see supplementary material for supporting data.

Scheme II



III IV

Scheme III



Va, R = OCH_3, R′ = H
Vb, R = H, R′ = OCH_3

11-OMe-VI, R = OCH_3, R′ = H
8-OMe-VI, R = H, R′ = OCH_3

Experimental Section

The National Cancer Institutes safety standards for research involving chemical carcinogens were followed.[13] IR spectra were determined in chloroform solution using matched 0.01-mm NaCl cells on a Perkin-Elmer 281 spectrometer and were calibrated against known bands in polystyrene. Ultraviolect spectra were obtained in 95% ethanol on a Beckman Acta M spectrometer. NMR spectra were determined on a Varian XL-100 instrument in the FT mode. Melting points were taken on a Hoover–Thomas apparatus and are uncorrected. High-resolution mass spectra were run at the California Institute of Technology Microanalytical Laboratory, Pasadena, Calif. on a duPont 21-492 mass spectrometer.

Preparation of Va and Vb. A solution of benzene (65 mL), 1,4-phenanthraquinone[5] (278.4 mg; 1.338 mmol), and 1-methoxy-1,3-cyclohexadiene[14] (1.367 g; 12.42 mmol) was heated overnight at 94 °C in a pressure bottle. After cooling, the solvent was evaporated and the residue was chromatographed on a column, 2.5 × 17 cm, packed with 51 g of Alumina (MCB, 80–325 mesh, activated) eluting initially with hexane to remove excess diene and possible polymeric products of the diene. The column was next eluted with 10% ethyl acetate/hexane to remove traces of unreacted 1,4-phenanthraquinone. The final eluting solvent was 30% ethyl acetate/hexane. The desired adducts were obtained as an orange solid, 298.9 mg (0.946 mmol, 75% yield). The product was identified as a mixture of Va and Vb from its NMR spectra and from further chemical studies: NMR (100 MHz) ($CDCl_3$) δ 9.5 (m, 1 H), 8.2–7.5 (m, 5 H), 6.7–6.3 (m, 2 H), 4.56 (m, 1 H), 3.75 (s, 3 H), 2.9–2.4 (m, 4 H).

Preparation of 8-OMe-VI and 11-OMe-VI. The isomeric mixture of Va and Vb (80.6 mg; 0.253 mmol) was sublimed at 150 °C (0.15 mm) over 2 h in a vacuum sublimator. Isolated from the cold finger was 73.6 mg (0.253 mmol, 100% yield) of a mixture of 8- and 11-methoxy-7,12-benzanthraquinone. The isomers were separated on a 2.5 × 45 cm column packed with 81 g of silica (TLC grade Silica H, E. Merck Co.) eluting with 50% ethyl acetate/hexane with 80 psi pressure across the column. Recovered after chromatography were 10.8 mg of the less polar 11-methoxy-7,12-benzanthraquinone (mp 195 °C) and 61.4 mg of 8-methoxy-7,12-benzanthraquinone (mp 184–185 °C).

Spectral properties of 11-methoxy-7,12-benz[*a*]anthraquinone: NMR (FT-100 MHz) ($CDCl_3$) δ 9.38 (m, 1 H), 8.33–7.30 (m 8 H), 4.08 (s, 3 H); IR ($CHCl_3$) 1670, 1595, 1465, 1450, 1330, 1310, 1280, 1240–10, 1075, 995, 855 cm^{-1}; UV (ethanol) λ (log ϵ) 390 (3.84), 285 (4.58), 233

(4.55), 212.5 (4.72); calcd for $C_{19}H_{12}O_3$, parent ion *m/e* 288.079, found 288.080.

Spectral properties of 8-methoxy-7,12-benz[*a*]anthraquinone: NMR (FT-100 MHz) ($CDCl_3$) δ 9.59 (m 1 H), 8.31–7.27 (m 8 H), 4.06 (s, 3 H); IR ($CHCl_3$) 1665, 1590, 1470, 1450, 1275, 995 cm^{-1}; UV (ethanol) λ (log ϵ) 386 (3.87), 282 (4.48), 231 (4.42), 211 (4.65); calcd for $C_{19}H_{12}O_3$, parent ion *m/e* 288.079, found 288.081.

Pr(fod)$_3$ Experiment. A solution of 114.7 mg of Pr(fod)$_3$ in 2 mL of $CDCl_3$ was added in small aliquots via syringe to prepared solutions of methoxybenz[*a*]anthraquinones (5–15-mg sample) in 0.5 mL of $CDCl_3$ in a NMR tube. The NMR spectra were recorded on a Varian XL-100 spectrometer in the FT mode. The shifts of the methoxy and C_1–H were recorded after each addition of praseodymium solution. For these data and plots of the chemical shift of the C_1–H vs. the sum of the shifts of the methoxy and C_1–H,[15] see the supplementary material in the microfilm edition.

Eu(fod)$_3$ Experiment. A solution of 188.1 mg of Eu(fod)$_3$ in 2 mL of $CDCl_3$ was added via syringe in small aliquots to a prepared solution of methoxybenz[*a*]anthraquinone (10–20-mg sample) in 0.5 mL of $CDCl_3$ in a NMR tube. After each addition of europium reagent, the NMR spectrum was recorded on a Varian XL-100 in the FT mode. The shifts of the methoxy and C_1–H were recorded. For these data and a plot of the chemical shifts of the C_1–H vs. the sum of the shifts of the C_1–H and methoxy,[15] see the supplementary material in the microfilm edition.

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Registry No.—Va, 65915-31-3; Vb, 65915-32-4; 8-OMe-VI, 65915-33-5; 11-OMe-VI, 65915-34-6; 1,4-phenanthraquinone, 569-15-3; 1-methoxy-1,3-cyclohexadiene, 2161-90-2.

Supplementary Material Available: observed proton shifts of 11-methoxy-7,12-benz[*a*]anthraquinone and 8-methoxy-7,12-benz[*a*]anthraquinone with Pr(fod)$_3$ (Tables I and II) and Eu(fod)$_3$ (Tables III and IV) and plots of the shift of C_1–H vs. the sum of C_1H and OCH_3 with Pr(fod)$_3$ and Eu(fod)$_3$ (Figures I and II) (4 pages). Ordering information is given on any current masthead page.

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A One-Flask Preparation of Analytically Pure $K_2Fe(CO)_4$

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The use of the highly nucleophilic tetracarbonylferrate dianion, $[Fe(CO)_4]^{2-}$, in organic and inorganic syntheses has markedly grown in recent years. Numerous useful carbon–carbon bond-forming reactions can be effected with this reagent.[1] It also serves as a starting material for the preparation of a variety of iron carbonyl π complexes (cyclobutadiene, trimethylenemethane, *o*-xylylene) and mixed metal complexes such as $[(CH_3)_2SnFe(CO)_4]_2$ and $[HgFe(CO)_4]_n$.[2] Syntheses of $[Fe_2(CO)_8]^{2-}$ and polynuclear clusters such as $H_2FeRu_2Os(CO)_{13}$ from $[Fe(CO)_4]^{2-}$ have recently been communicated.[3,4]

We report in this note a novel and convenient one-flask synthesis of analytically pure $K_2Fe(CO)_4$. While $K_2Fe(CO)_4$ has not been used as extensively as $Na_2Fe(CO)_4$ or $Na_2Fe(CO)_4$–dioxane, parallel reactivity has been observed for alkylation reactions,[5] and some useful organic transformations employing $K_2Fe(CO)_4$ have been reported.[6] Unlike $Na_2Fe(CO)_4$, $K_2Fe(CO)_4$ is not spontaneously flammable in air.

In typical procedures 1 equiv of $Fe(CO)_5$ was added to 2.1–2.5 equiv of commercially available K(*s*-$C_4H_9)_3BH$[7] at room temperature. After a 3–4 h reflux period, cooling afforded a 95–100% yield of analytically pure $K_2Fe(CO)_4$ as a white precipitate (eq i). After isolation by Schlenk or glove box techniques, additional reactions were carried out to provide chemical characterization (eq ii and iii).

$$Fe(CO)_5 \xrightarrow[3\text{ h, THF, }\Delta]{2K(s\text{-}C_4H_9)_3BH} K_2Fe(CO)_4\downarrow\ (100\%) \qquad \text{(i)}$$

$$K_2Fe(CO)_4 \xrightarrow[2.\ P(C_6H_5)_3]{1.\ n\text{-}C_8H_{17}Br} \text{nonanal (100\%)} \qquad \text{(ii)}^5$$
$$3.\ CH_3COOH$$

$$K_2Fe(CO)_4 \xrightarrow{2AuCl[P(C_6H_5)_3]} [Fe(CO)_4][AuP(C_6H_5)_3]_2\ (82\%)$$
$$\text{(iii)}^8$$

Production of $K_2Fe(CO)_4$ proceeds via the rapidly formed and spectroscopically observable intermediate metal formyl 1 (eq iv). This compound was originally synthesized by Collman and Winter by formylation of $Na_2Fe(CO)_4$[9] with formic acetic anhydride. More recently, we[10] and others[11,12] have found that salts of 1 may be formed by attack of suitable hydride donors upon $Fe(CO)_5$. Conversion of 1 to $K_2Fe(CO)_4$ is the slow step. Since at no time are $Fe(CO)_5$ and $[Fe(CO)_4]^{2-}$ simultaneously present, the binuclear complex $[Fe_2(CO)_8]^{2-}$ is not formed.[3] Other preparations of $[Fe(CO)_4]^{2-}$ require close monitoring to ensure this byproduct is not produced.[5]

$$Fe(CO)_5 \xrightarrow{H^-} \underset{1}{HC(O)Fe(CO)_4} \xrightarrow{H^-} \longrightarrow [Fe(CO)_4]^{2-} \qquad \text{(iv)}$$

For many years, $K_2Fe(CO)_4$ (of questionable purity) was available only by reaction of ethanolic or aqueous KOH with $Fe(CO)_5$.[13] More recently, $K_2Fe(CO)_4$ has been synthesized from elemental potassium[5] and its crystal structure has been determined.[14] However, this procedure is experimentally more elaborate than ours, and a recrystallization is required to produce $K_2Fe(CO)_4$ of comparable purity. Since K(*s*-$C_4H_9)_3BH$ is considerably more expensive than potassium, the utility of our procedure is greatest with small to medium scale preparations where analytically pure product is desired. Attempts to synthesize $Li_2Fe(CO)_4$ or $Na_2Fe(CO)_4$ by reaction of $Fe(CO)_5$ with $Li(C_2H_5)_3BH$, Li(*s*-$C_4H_9)_3BH$, $Na(C_2H_5)_3BH$, or $Na(CH_3O)_3BH$ were unsuccessful. Although trialkyl borohydrides can be readily prepared from MH (M = Li, Na, K) and trialkylboranes,[15] we have not found variations of our procedure exploying a catalytic amount of $(C_2H_5)_3B$ or (*s*-

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$C_4H_9)_3B$ and a stoichiometric amount of KH to be satisfactory.

This route to $K_2Fe(CO)_4$ extends previous work by us[10,16] on the synthesis of transition metal monoanions by trialkyl borohydride cleavage of metal carbonyl dimers. Exploratory experiments indicate that trialkyl borohydrides are not sufficiently strong reductants to produce more highly reduced species such as metal carbonyl trianions.[17] The conversion 1 → $K_2Fe(CO)_4$ poses an intriguing mechanistic question and is currently under investigation.

Experimental Section

General. All reactions were conducted under a N_2 atmosphere. THF was dried and deoxygenated by distillation from sodium benzophenone ketyl. Infrared spectra were obtained on a Perkin-Elmer Model 521 spectrometer, and elemental analyses were conducted by Gailbraith.

$K_2Fe(CO)_4$. To a dried 200-mL round-bottom flask was added 70 mL of 0.5 M K(*s*-$C_4H_9)_3BH$ (35 mmol)[7] followed by 2.2 mL of $Fe(CO)_5$ (3.22 g, 16.5 mmol). The reaction mixture was refluxed for 4 h. After cooling, the resultant white solid was filtered (in a glove box or via Schlenk techniques) and washed with 50 mL of hexane. After vacuum drying, 4.0 g of analytically pure $K_2Fe(CO)_4$ (16.2 mmol, 98%, mp 270–273 °C dec) was obtained. Anal. Calcd: C, 19.85; Fe, 22.60. Found: C, 19.94; Fe, 22.38.

Caution: Since the byproduct (*s*-$C_4H_9)_3B$ is spontaneously flammable when pure, we recommend that the waste solvents be treated with an appropriate amount of a mild oxidizing agent (clorox, dilute H_2O_2) before disposal.

$Fe(CO)_4[AuP(C_6H_5)_3]_2$. To a 25-mL round-bottom flask containing a magnetic stirring bar were added 0.051 g of $K_2[Fe(CO)_4]$ (0.207 mmol), 0.2052 g of $(C_6H_5)_3PAuCl$[18] (0.417 mmol), and 15 mL of THF. After being stirred for 12 h, the reaction mixture was gravity filtered. Methanol (15 mL) was added to the filtrate and the solution was concentrated to a cloud point on a rotary evaporator. Cooling to 0 °C for 12 h afforded brown-yellow crystals which were isolated by suction filtration, washed with methanol, and vacuum dried (0.1735 g). A second crop was obtained (0.0101 g) for a total yield of 0.184 g (0.169 mmol; 82% based upon $K_2[Fe(CO)_4]$) (IR (THF) 2002, 1929, 1893 cm^{-1}; mp 145–150 °C dec).

Nonanal from Octyl Bromide. This procedure is similar to the $[Fe(CO)_4]^{2-}$ assay reported by Collman.[5] To a 25-mL round-bottom flask was added 0.0945 g of $K_2[Fe(CO)_4]$ (0.0384 mmol), 0.08 mL of octyl bromide (0.463 mmol), and 0.1325 g of $(C_2H_5)_3P$ (0.508 mmol). The mixture was stirred for 12 h followed by addition of 200 μL of glacial acetic acid and 100 μL of tridecane. Gas chromatographic analysis (with reference to tridecane) indicated a 100% yield of nonanal based upon $K_2[Fe(CO)_4]$.

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Registry No.—Octyl bromide, 111-83-1; nonanal, 124-19-6; $K_2Fe(CO)_4$, 16182-63-1; K(*s*-$C_4H_9)_3BH$, 54575-49-4; $Fe(CO)_5$, 13463-40-6; $Fe(CO)_4[AuP(C_6H_5)_3]_2$, 16027-25-1; $(C_6H_5)_3PAuCl$, 14243-64-2.

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Thallium in Organic Synthesis. 50. A Convenient Synthesis of Thallium(I) Cyanide, a Useful Reagent in Organic Synthesis[1,2]

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Thallium(I) cyanide has previously been prepared either by precipitation from an aqueous solution of thallium(I) nitrate with potassium cyanide[4] or by exchange between aqueous potassium cyanide and the thallium(I) form of Dowex-50 ion exchange resin.[5] The first of these procedures requires repeated fractional recrystallization of the crude product and the use of CO_2-free water (to avoid the formation of thallium(I) carbonate); the second procedure requires a large excess of the cation exchange resin. Both procedures are complicated by the formation of complexes with counterions (e.g., K^+). For these reasons, thallium(I) cyanide has received little attention as a reagent for organic synthesis.

We wish to describe a convenient and quantitative preparation of anhydrous thallium(I) cyanide under nonaqueous conditions by the reaction of dry hydrogen cyanide with thallium(I) phenoxide, together with some preliminary results on the utilization of this reagent for the preparation of α-ketonitriles, cyanoformates, and trimethylcyanosilane.

Use of Thallium(I) Cyanide in Synthesis. Stirring equimolar amounts of thallium(I) cyanide and an aroyl chloride in ether or ethyl acetate as solvent at room temperature for 1–3 hr, followed by removal of insoluble thallium(I) chloride and evaporation of the solvent, gives aromatic α-ketonitriles. This simple entry into these intriguing intermediates is to be contrasted with the classical method for their preparation which involves distilling aroyl chlorides over heavy-metal cyanides such as mercuric cyanide, cuprous cyanide, or silver cyanide, or addition of pyridine to a mixture of an aroyl chloride and hydrogen cyanide in ether,[6] or by the utilization of phase transfer catalysis.[7] In some instances, our procedure is unquestionably the method of choice. For example, *p*-nitrobenzoylcyanide was obtained from *p*-nitrobenzoyl chloride and thallium(I) cyanide in 85% yield after 30 min at room temperature. By contrast, attempts to prepare this compound in satisfactory yield by previously available procedures have been reported to be singularly unsuccessful.[8] Representative conversions of aroyl chlorides to aromatic α-ketonitriles are summarized in Table I.

The reaction is not generally applicable to aliphatic α-ketonitriles, since the initially formed products dimerize under the reaction conditions. Thus, reaction of thallium(I) cyanide with acetyl, propionyl, or pivaloyl chloride in ether at room

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Table I. Aromatic and Aliphatic α-Ketonitriles, RCOCN

R	Registry no.	Time, h	Temp, °C	Yield,[a] %	IR absorption, cm^{-1} CO	IR absorption, cm^{-1} CN	Mp or bp, °C (mm) Obsd	Mp or bp, °C (mm) Lit.	Ref
C_6H_5	613-90-1	1	23	74	1690	2230	30–32	32–33	10
m-$CH_3C_6H_4$	5955-74-8	1.5	31	89	1700	2245	130–133 (40)	133 (40)	*b*
p-$CH_3C_6H_4$	14271-73-9	12	23	78	1670	2220	45–46[d]	49–49.5	*c*
p-$CH_3OC_6H_4$	14271-83-1	2	23	45	1675	2210	59.1	58–59	*b*
o-ClC_6H_4	35022-42-5	1.5	31	81	1675	2230	34–36	35	*e*
m-$NO_2C_6H_4$	61017-48-9	2	23	74	1700	2225	33–34	33–34	*f*
p-$NO_2C_6H_4$	6048-20-0	0.5	23	85	1700	2250	111[h]	116	*g*
2-Furyl	6047-91-2	3	31	84	1665	2245	25	25	*i*
2-Thienyl	6007-78-9	3	23	50	1645	2215	52.5	51.5	*j*
Cyclopropyl	6047-92-3	1	23	49	1700	2210	40–42 (11)	45–55 (12)	*k*
$(CH_3)_3C$	42867-40-3	1.5	23[l]	45	1720	2210	117–120 (760)	120	*m*

[a] Isolated yields determined on recrystallized or distilled material. [b] F. Asinger, A. Saus, H. Offermanns, and H.-D. Hahn, *Justus Liebigs Ann. Chem.*, **691**, 92 (1966). [c] R. L. Soulen, S. C. Carlson, and F. Lang, *J. Org. Chem.*, **38**, 479 (1973). [d] C_9H_7NO requires: C, 74.47; H, 4.86; N, 9.65. Found: C, 74.57; H, 4.85; N, 9.46. [e] *Beilstein*, Band X, 662 (1927). [f] L. Claisen and C. M. Thompson, *Chem. Ber.*, **12**, 1942 (1879). [g] A. Dornow and H. Grabhofer, *Chem. Ber.*, **91**, 1824 (1958). [h] $C_8H_4N_2O_3$ requires: C, 54.55; H, 2.29; N, 15.80. Found: C, 54.67; H, 2.55; N, 14.90. [i] E. Fischer and F. Brauns, *Chem. Ber.*, **46**, 892 (1913). [j] W. Steinkopf, *Justus Liebigs Ann. Chem.*, **540**, 14 (1939). [k] E. Zbiral and L. Fenz, *Monatsh. Chem.*, **96**, 1983 (1965). [l] Reaction run in *o*-dichlorobenzene. [m] B. A. Clement and R. L. Soulen, *J. Org. Chem.*, **39**, 97 (1974).

Table II. Aliphatic α-Ketonitrile Dimers, $(RCOCN)_2$

R	Registry no.	Time, h	Temp, °C	Yield,[a] %	IR absorption, cm^{-1} CO	IR absorption, cm^{-1} CN	Mp, °C
CH_3	65378-56-5	1	23	75	1760	2270	69–70[b]
C_2H_5	65378-57-6	0.5	23	48[c]	1775	2250	58
$(CH_3)_3C$	65378-58-7	1	23	60[d]	1765	2225	54.8

[a] Isolated yields determined on recrystallized material. [b] Lit. mp 69.4–70.2 °C (B. E. Tate and P. D. Bartlett, *J. Am. Chem. Soc.*, **78**, 5575 (1956)). [c] $C_8H_{10}N_2O_2$ requires: C, 57.82; H, 6.07; N, 16.85. Found: C, 57.62; H, 5.91; N, 16.82. [d] $C_{12}H_{18}N_2O_2$ requires: C, 64.84; H, 8.16; N, 12.60. Found: C, 64.67; H, 7.93; N, 12.41.

Table III. Cyanoformates, NCCOOR

R	Registry no.	Time, h	Temp, °C	Yield,[a] %	IR absorption, cm^{-1} CO	IR absorption, cm^{-1} CN	Bp, °C (mm) Obsd	Bp, °C (mm) Lit.[b]
CH_3	17640-15-2	7[c]	35	66	1755	2250	95–97 (760)	95–96 (760)
C_2H_5	623-49-4	1	76	91	1750	2250	110–112 (760)	115–116 (760)
$(CH_3)_2CHCH_2$	59873-30-2	1	76	87	1750	2250	75–76 (80)	52–53 (20)

[a] Isolated yields determined on redistilled material. [b] Reference 9. [c] Reaction run in diethyl ether.

temperature gave only the corresponding α-ketonitrile dimers. We did prepare pivaloyl cyanide in 45% yield utilizing *o*-dichlorobenzene as solvent, but attempts to extrapolate this result to other aliphatic acid chlorides failed. This simple procedure represents a convenient route to these aliphatic α-ketonitrile dimers, many of which have not been reported previously (see Table II).

Reaction of alkyl chloroformates with thallium(I) cyanide in refluxing ethyl acetate gives alkyl cyanoformates (see Table III); reaction with potassium cyanide in the presence of 18-crown-6 is much slower.[9]

Trimethylcyanosilane[10a,b] is easily prepared (84% yield) by heating a mixture of trimethylchlorosilane and thallium(I) cyanide for 10 h without solvent.

We are currently exploring further synthetic applications of anhydrous thallium(I) cyanide.

Experimental Section

Thallium(I) Cyanide. Dry hydrogen cyanide, generated in situ from sodium cyanide and sulfuric acid, was bubbled for a few minutes through a stirred suspension of 6.0 g of thallium(I) phenoxide in 200 mL of refluxing dry ether (35 °C). The heavy white precipitate which rapidly formed was collected by filtration, washed with ether, and dried to give 4.6 g (100%) of thallium(I) cyanide, IR ν 2048 cm^{-1} (lit.[5] 2048 cm^{-1}).

General Method for the Preparation of Aromatic α-Ketonitriles. A suspension of 5.0 g (0.022 mol) of thallium(I) cyanide in 50 mL of dry ether or ethyl acetate was stirred vigorously under the conditions specified in Table I. The appropriate aroyl chloride (0.020 mol) was then added, and stirring was continued for the indicated period of time. The insoluble thallium(I) chloride which had precipitated was removed by filtration through Celite, the filtrate was evaporated under reduced pressure to remove solvent, and the crude product was purified either by fractional distillation or by recrystallization (see Table I). The method for the preparation of aliphatic α-ketonitrile dimers is the same as described above; conditions are specified in Table II.

General Method for the Preparation of Alkyl Cyanoformates. To a refluxing mixture of 5 g (0.022 mol) of thallium(I) cyanide in 50 mL of dry ethyl acetate was added 0.020 mol of the alkyl chloroformate, and the mixture was heated under reflux for the period of time indicated in Table III. When reaction was complete (as indicated by the disappearance of the characteristic absorption band at 1770 cm^{-1}), the reaction mixture was cooled to room temperature and filtered through Celite to remove precipitated thallium(I) chloride. Solvent was removed under reduced pressure and the product was purified by distillation (see Table III).

Trimethylcyanosilane. A suspension of 4.7 g (0.020 mol) of thallium(I) cyanide in 13 g (0.12 mol) of freshly distilled trimethylchlorosilane was heated under reflux overnight, and the precipitated thallium(I) chloride was removed by filtration through Celite. Excess trimethylchlorosilane was removed by distillation, and the product was distilled at 115–117 °, yield 1.66 g (84%). The product was identified by comparison with an authentic sample.

Registry No.—RCOCl (R = C_6H_5), 98-88-4; RCOCl (R = m-$CH_3C_6H_4$), 1711-06-4; RCOCl (R = p-$CH_3C_6H_4$), 874-60-2; RCOCl

(R = p-$CH_3OC_6H_4$), 100-07-2; RCOCl (R = o-ClC_6H_4), 609-65-4; RCOCl (R = m-$NO_2C_6H_4$), 121-90-4; RCOCl (R = o-$NO_2C_6H_4$), 122-04-3; RCOCl (R = 2-furyl), 527-69-5; RCOCl (R = 2-thienyl), 5271-67-0; RCOCl (R = cyclopropyl), 4023-34-1; RCOCl (R = $(CH_3)_3C$), 3282-30-2; RCOCl (R = CH_3), 75-36-5; RCOCl (R = C_2H_5), 79-03-8; ClCOOR (R = CH_3), 79-22-1; ClCOOR (R = C_2H_5), 541-41-3; ClCOOR (R = $(CH_3)_2CHCH_2$), 543-27-1; hydrogen cyanide, 74-90-8; thallium, 7440-28-0; thallium(I) cyanide, 13453-34-4; trimethylcyanosilane, 7677-24-9; trimethylchlorosilane, 75-77-4.

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Total Synthesis of *Racemic* α-Santalene and of *Racemic* Teresantalic Acid[1a]

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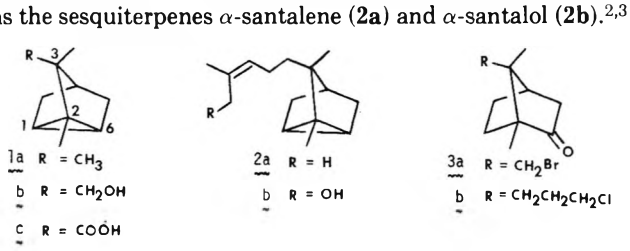
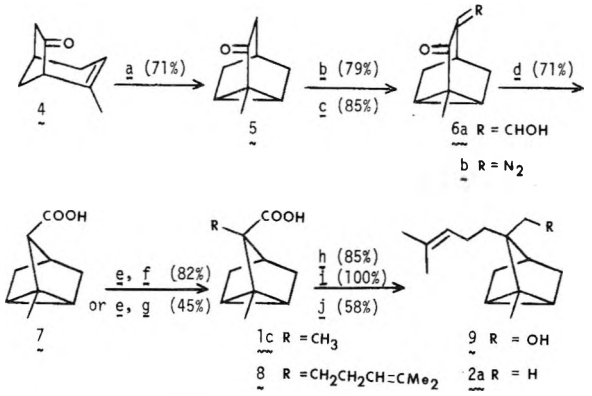
Representative examples of the tricyclene family of terpenes, characterized structurally by the presence of a 3,3-disubstituted 2-methylbicyclo[2.2.1.$0^{2,6}$]heptane skeleton, include the parent monoterpene tricyclene (**1a**) and its C-3 derivatives teresantalol (**1b**) and teresantalic acid (**1c**), as well as the sesquiterpenes α-santalene (**2a**) and α-santalol (**2b**).[2,3]



Although devoid of relative stereochemical relationships due to symmetry, these tricyclic carbon skeletons have attracted considerable synthetic interest. These efforts[4] have involved initial preparation of 7,7-disubstituted bicyclo[2.2.1]heptanones such as π-bromocamphor (**3a**)[4a] or chloro ketone **3b**[4b], cyclopropane ring closure via a carbene or carbenoid intermediate to generate the tricyclic skeleton, and subsequent functional group modification to yield the desired mono- and sesquiterpenes. We wish to report an alternative route to this general class of natural products which, via the intermediacy of tricyclic acid **7**, allows selective synthetic manipulation of *both* C-3 substituents of the tricyclene nucleus. This approach is illustrated by the total synthesis of *racemic* α-santalene (**2a**) and of *racemic* teresantalic acid (**1c**).

As shown in Scheme I, irradiation of the β,γ-unsaturated ketone **4**[5] in acetone resulted in a smooth rearrangement[6] to give the tricyclic α-methyl cyclopropyl ketone **5**. Conversion of **5** into the α′-formyl derivative **6a**, followed by treatment with tosyl azide yielded the diazo ketone **6b**,[7] which upon photolysis underwent ring contraction[8] to furnish the key intermediate, tricyclic acid **7**. Satisfactory generation of the dianion of acid **7** was achieved by exposure of **7** to lithium diisopropylamide (2.5 equiv, 50 °C)[9] *followed by* addition of n-butyllithium (1 equiv, 50 °C).[10,11] Alkylation of this dianion with methyl iodide yielded racemic teresantalic acid (**1c**). Alternatively treatment of the dianion with 5-iodo-2-methyl-2-pentene gave the 3,3-disubstituted acid **8**, which upon lithium aluminum hydride reduction yielded alcohol **9**, a structural isomer of the important natural product α-santalol (**2b**). Tosylation of alcohol **9** and reduction with lithium triethylborohydride furnished *racemic* α-santalene (**2a**).

Scheme I



[a] $h\nu$, acetone, 25 °C, 10 h. [b] NaH, ethyl formate, Et_2O/EtOH, 25 °C, 42 h. [c] Tosyl azide, Et_3N, CH_2Cl_2, 25 °C, 78 h. [d] $h\nu$, $NaHCO_3$, THF/H_2O, 25 °C, 45 min. [e] Lithium diisopropylamide (2.5 equiv), THF, 50 °C, 1 h; then n-BuLi (1 equiv) 50 °C, 1 h. [f] CH_3I, 25 °C, 16 h. [g] $Me_2C{=}CHCH_2CH_2I$, 25 °C, 20 h. [h] Lithium aluminum hydride, THF, reflux, 22 h. [i] Tosyl chloride, pyridine, 5 °C, 32 h. [j] Lithium triethylborohydride, THF, 25 °C, 72 h.

Experimental Section

General. All reactions were carried out in an inert nitrogen atmosphere and were routinely monitored by TLC or VPC using a Varian Aerograph 1200 instrument equipped with 5% SE-30 on Gas Chromosorb Q (100/120 mesh) ⅛ in. × 10 ft or 15% FFAP on Gas Chromosorb Q (100/120 mesh) ⅛ in. × 7 ft columns. Photochemical reactions were performed using a Hanovia 450 W, 3.7 A quartz high pressure mercury vapor lamp in a circulating ice-water cooled double-walled quartz immersion well. Photochemical solutions were deoxygenated by purging with dry nitrogen for 30 min and maintained at ca. 10 °C during irradiation. Melting points were determined on a Mel-temp apparatus and are uncorrected. Infrared spectra were obtained on a Perkin-Elmer Model 237B grading infrared spectrometer; ^{1}H-NMR spectra were measured on a Perkin-Elmer R-12 spectrometer, a Varian A-60 instrument equipped with cross correlation, or a Varian HA-100 instrument and chemical shifts are reported in ppm downfield (δ) from internal Me_4Si. ^{13}C-NMR spectra were obtained on a Bruker WH90 instrument and chemical shifts are reported in ppm downfield (δ) from internal Me_4Si. High-resolution mass spectra were obtained using a CEC Model 21-100 mass spectrometer. The microanalytical determination was done by Chemalytics, Inc., Tempe, Ariz.

2-Methyltricyclo[3.2.1.$0^{2,7}$]octan-3-one (5). Irradiation of 4-methylbicyclo[3.2.1]oct-3-en-6-one (3.91 g, 28.7 mmol) in acetone (300 mL) for 10 h resulted in complete disappearance of starting material. After evaporation of the acetone at reduced pressure, the dark residue was dissolved in Et_2O and filtered through aluminum oxide (30 g, activity III) and after evaporation of the solvent distilled to give 2.80 g (71%) of tricyclic ketone **5**: bp 45–47 °C (0.1 mm); IR (CCl_4) 3025 and 1690 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.10 (s, 3), 1.1–1.5 (m, 1), 1.5–2.0 (m, 4), 1.94–2.08 (br d, 2, J = 4 Hz), 2.0–2.6 (m, 2); ^{13}C NMR ($CDCl_3$) 209.8 (s), 44.2 (t), 35.6 (s), 31.9 (t), 30.6 (d), 28.8 (d), and 16.8 (q); mass spectrum, m/e (rel intensity) 136 (molecular ion, 24), 93 (32), 92 (100), and 79 (36). Anal. Calcd for $C_9H_{12}O$: m/e 136.0888. Found: m/e 136.0890.

4-Formyl-2-methyltricyclo[3.2.1.$0^{2,7}$]octan-3-one (6a). Sodium hydride (0.60 g, 25 mmol), ethyl formate (9.50 g, 12.8 mmol), ethanol (0.50 g, 10 mmol), and tricyclic ketone **5** (1.72 g, 12.6 mmol) were stirred at 25 °C for 42 h in diethyl ether (100 mL). The reaction mixture was extracted with 10% KOH (2 × 50 mL) and the organic

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phase was washed with brine and dried ($MgSO_4$) and the excess solvent was evaporated under reduced pressure to give 0.31 g of recovered tricyclic ketone **5.** The basic aqueous phase was chilled in an ice bath, acidified by addition of 10% HCl, and extracted with ether. The aqueous phase was saturated by addition of sodium chloride and reextracted with ether. The combined organic phases were washed with brine, dried ($MgSO_4$), and evaporated at reduced pressure to give a residue which was distilled to yield 1.34 g (79%) of formyl ketone **6a;** bp 55–58 °C (0.1 mm); IR (CCl_4) 3040, 1655, 1585, and 1035 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.22 (s, 3), 1.1–1.7 (m, 3), 1.7–2.7 (m, 4), 2.4–2.7 (m, 1), and 7.08 (s, 1).

4-Diazo-2-methyltricyclo[3.2.1.$0^{2,7}$]octan-3-one (6b). *p*-Toluenesulfonyl azide (3.00 g, 15 mmol), triethylamine (3.90 g, 38 mmol), and formyl ketone **6a** (1.40 g, 8.6 mmol) were stirred at 25 °C in methylene chloride (30 mL) in a light-protected flask for 3 days. The mixture was diluted with ether (100 mL), washed with 10% KOH (2 × 25 mL) and brine, dried ($MgSO_4$), and then evaporated at reduced pressure to give a residue which was purified by chromatography on silica gel (35 g) using pentane–ether mixtures (7:3 to 5:5, v/v) to yield 1.17 g (85%) of diazo ketone **6b,** a bright yellow oily residue which solidified upon standing: mp 50–52 °C; IR (CCl_4) 3035, 2075, 1645, 1635, 1375, 1250, 1150, 1025, 950, and 910 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.24 (s, 3), 1.5–2.3 (m, 6), and 2.95–3.20 (m, 1).

2-Methyltricyclo[2.2.1.$0^{2,6}$]heptane-3-carboxylic Acid (7). The crude diazo ketone **6b** (0.280 g, 1.73 mmol) was irradiated in water (250 mL) containing tetrahydrofuran (50 mL) and sodium bicarbonate (2.0 g) for 45 min. The reaction was monitored by observing the disappearance of the characteristic diazo absorption (2075 cm^{-1}) in the infrared spectrum. Sodium hydroxide (5 g) was dissolved in the reaction mixture, and then this mixture was extracted with diethyl ether (discarded), acidified by addition of 10% HCl, saturated with sodium chloride, and finally extracted several times with ether. The ether extracts were washed with brine, dried ($MgSO_4$), and evaporated under reduced pressure to give a residue that was purified by chromatography on silica gel (10 g) with ether to give 0.187 g (71%) of tricyclic acid **7** as a waxy solid, which was further purified by sublimation (60 °C, 0.3 mm): mp 71–72 °C; IR (CCl_4) 1700, 1425, 1420, 1300, 1295, 1240, 1230, 1220, and 855 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.95 (d of d, 1, J = 1.5, 5 Hz), 1.08 (d of d, 1, J = 1.5, 5 Hz), 1.15–1.6 (m, 3) 1.29 (s, 3), 1.83 (d, 1, J = 11 Hz), 2.15–2.35 (m, 1), and 2.29 (d, 1, J = 1.5 Hz); ^{13}C NMR ($CDCl_3$) δ 180.9 (s), 53.1 (d), 36.4 (d), 34.6 (t), 31.9 (t), 20.8 (s), 18.9 (d), 17.7 (d), and 13.7 (q); mass spectrum, *m/e* (rel intensity) 152 (molecular ion, 100), 111 (28), 107 (96), 93 (50), 92 (28), 91 (90), 81 (44), 79 (78), 77 (36), and 66 (36). Anal. Calcd for $C_9H_{12}O_2$: C, 71.02; H, 7.95; *m/e*, 152.0837 Found: C, 71.03; H, 7.80; *m/e*, 152.0835.

Teresantalic Acid (1c). To a stirred solution of diisopropylamine (0.40 g, 3.9 mmol) in THF (10 mL), a solution of *n*-butyllithium in hexane (1.5 M, 2.3 mL, 3.4 mmol) was added at −5 °C. This mixture was stirred for 15 min and then tricyclic acid **7** (0.210 g, 1.38 mmol) in THF (3 mL) was added. The resulting mixture was heated at ~50 °C for 1 h and then cooled to ca. −30 °C and *n*-butyllithium in hexane (1.0 mL, 1.5 mmol) was added. After warming to 10 °C for ca. 15 min, the mixture was heated at 50 °C for 1 h. A small aliquot of this mixture was quenched in D_2O, acidified with 10% HCl, and extracted with ether to give recovered acid **7,** which, when analyzed by GC/MS (3% OV-101), revealed a ratio of d_0/d_1 (*m/e* 152/153) of ca. 2.9, respectively.[10] The original dianion solution above was chilled to −5 °C, methyl iodide (1.0 g, 7 mmol) in THF (2 mL) was added, and the resulting mixture was stirred for 18 h at room temperature. The contents were poured into water (100 mL), acidified with 10% HCl, and extracted with ether. The aqueous phase was saturated with sodium chloride and extracted with additional ether. The combined organic phases were washed with brine, dried ($MgSO_4$), and evaporated at reduced pressure to give a residue, which after filtration through silica gel (5 g) with ether and sublimation (80 °C, 0.3 mm) yielded 190 mg of material which on the basis of VPC analysis was composed of 91% teresantalic acid (**1c**) and 9% recovered starting acid **7.** This corresponds to a yield of 82% of teresantalic acid (**1c**). Pure **1c** was obtained by recrystallization (EtOH): mp 160–162 °C (lit. mp [chiral material][12] 158 °C); IR (CCl_4) 1700, 1445, 1405, 1290, 1200, 1155, 1140, 1080, 1040, 975, 940, and 855 cm^{-1}; ^1H NMR δ 0.86 (br d, 1, J = 6 Hz), 1.0–1.9 (m, 3), 1.15 (s, 3), 1.23 (s, 3), 1.58, 1.77 (br d, 2, J = 5 Hz), and 1.9–2.1 (m, 1); mass spectrum, *m/e* (rel intensity) 166 (molecular ion, 54), 121 (100), 93 (80), and 74 (64). Anal. Calcd for $C_{10}H_{12}O_2$: *m/e* 166.0994. Found: *m/e* 166.0988.

2-Methyl-3-(4-methylpent-3-en-1-yl)tricyclo[2.2.1.$0^{2,6}$]heptane-3-carboxylic Acid (8). As described above for teresantalic acid (**1c**), tricyclic acid **7** (0.230 g, 1.5 mmol) was treated with lithium diisopropylamide (2.6 equiv) in THF for 1 h at ~50 °C, followed by addition of *n*-butyllithium (1 equiv), first at −30 °C and then at 50 °C for 1 h. The reaction mixture was cooled to −78 °C and 5-iodo-2-methyl-2-pentene[13] (1.3 g, 6.2 mmol) was added. The mixture was allowed to warm to room temperature and was stirred for 20 h. The mixture was poured into cold 10% KOH (50 mL) and extracted with pentane (3 × 50 mL). The aqueous phase was cooled in an ice bath, acidified with 10% HCl, saturated with sodium chloride, and then extracted with ether. The combined organic extracts were washed with brine and evaporated at reduced pressure to give a residue that was partitioned between pentane (150 mL) and saturated sodium bicarbonate (50 mL). After extraction of the aqueous phase with additional pentane (3 × 50 mL), the combined organic phases were dried ($MgSO_4$) and evaporated under reduced pressure to give crude alkylated acid **8.** Acidification of the bicarbonate phase (10% HCl), followed by normal workup, yielded 0.140 g of recovered starting acid **7.** Product **8** was purified by crystallization (CH_3CN) to give 62 mg (45%) of **8**: mp 97–98 °C; IR (CCl_4) 1695, 1450, 1410, 1375, 1290, 1260, 1230, 1200, 1175, and 860 cm^{-1}, ^1H NMR δ 0.86 (br d, 1, J = 6 Hz), 1.08 (br, 1, J = 6 Hz), 1.0–1.4 (m, 4), 1.26 (5.3), 1.4–1.8 (m, 2), 1.64 (d, 6, J = 8 Hz), 1.8–2.4 (m, 3), and 4.98–5.24 (br t, 1); ^{13}C NMR ($CDCl_3$) δ 12.6, 17.6, 19.7, 20.5, 23.9, 25.0, 25.7, 30.2, 31.4, 33.0, 37.5, 58.6, 124.3, 131.8, 183.5; mass spectrum, *m/e* (rel intensity) 254 (molecular ion, 10), 164 (14), 150 (22), 107 (24), 82 (100), and 69 (20). Anal. Calcd for $C_{15}H_{22}O_2$: *m/e*, 234.1620. Found: *m/e*, 234.1624.

3-Hydroxymethyl-2-methyl-3-(4-methylpent-3-en-1-yl)tricyclo[2.2.1.$0^{2,6}$]heptane (9). A mixture of tricyclic acid **8** (0.10 g, 0.43 mmol) and lithium aluminum hydride (0.03 g, 0.88 mmol) in THF (15 mL) was heated at reflux for 22 h. To the cooled solution ethyl acetate (0.1 g) was added, the volume was reduced by evaporation at reduced pressure, and the residue was treated with 10% KOH (5 mL), saturated sodium potassium tartrate (5 mL), and water. This mixture was extracted several times with pentane and the combined organic extracts were dried (Na_2SO_4) and then evaporated under reduced pressure to give 0.080 g (85%) of crude alcohol **9.** A sample of pure **9** (preparative VPC, 5% SE-30) showed: IR (CCl_4) 3620, 2450, 3040, 1450, 1370, 1285, 1080, 1030, 1005, 850, and 835 cm^{-1}; ^1H NMR δ 0.90 (AB d of d, 2, J = 6, 4 Hz), 1.0–1.6 (m, 5), 1.06 (s, 3), 1.66 (d, 6, J = 8 Hz), 1.6–1.9 (m, 3), 1.9–2.3 (m, 2), 3.64 (s, 2), and 5.06–5.30 (br t, 1); mass spectrum *m/e* (rel intensity) 220 (molecular ion, 14), 184 (44), 138 (18), 120 (26), 110 (36), 105 (34), 93 (32), and 69 (100). Anal. Calcd for $C_{15}H_{24}O$: *m/e*, 220.1827. Found: *m/e*, 220.1831.

α-Santalene (2a). Tricyclic alcohol **9** (0.040 g, 0.18 mmol) was treated with *p*-toluenesulfonyl chloride (0.06 g, 0.31 mmol) in pyridine (1 mL) at 5 °C for 32 h. Evaporation at reduced pressure and extraction with CCl_4 furnished, after evaporation, 0.07 g (102%) of crude tosylate **9** (R = OTs): ^1H NMR δ 1.00 (s, 3), 0.7–2.1 (m, 12), 1.63 (d, 6, J = 7 Hz), 2.47 (s, 3), 3.97 (s, 2), 4.88–5.25 (br, t, 1), 7.35 (d, 2, J = 8 Hz), and 7.85 (d, 2, J = 8 Hz). The crude tosylate (0.045 g, 0.12 mmol) was dissolved in THF (5 mL) and a THF solution of lithium triethyl borohydride (1 M, 2.0 mL, 2 mmol) was added. After this mixture was allowed to stand at room temperature for 3 days, it was cooled in an ice–water bath, and cold 10% KOH (5 mL) and 30% hydrogen peroxide (0.3 g) were cautiously added. After stirring for 1 h, the mixture was diluted with water (50 mL) and extracted with pentane. The combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated under reduced pressure to give 0.017 g of a residue which by VPC analysis contained α-santalene (**2a**) and the starting alcohol **9** in the ratio of 2.3:1. This corresponds to a 58% yield of **2a.** Pure **2a** was obtained by preparative VPC on 5% SE-30 and it was identical to natural α-santalene as judged by IR,[14] NMR,[15] and mass spectral data.[15] Synthetic racemic **2a** showed: IR (CCl_4) 3040, 1455, 1370, 1340, 1315, 1285, 1270, 1260, 1230, 1195, 1165, 1155, 1120, 1095, 1055, 1040, 970, 935, 905, 875, 850, 835, and 800 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.80 (s, 3), 0.98 (s, 3), 0.7–1.4 (m, 6), 1.64 (d, 6, J = 7 Hz), 1.4–2.2 (m, 5), and 4.96–5.74 (br t, 1); mass spectrum, *m/e* (intensity) 204 (molecular ion, 20), 189 (24), 161 (18), 122 (28), 121 (46), 107 (40), 95 (54), 94 (100), 93 (96), 91 (28), 89 (26), and 69 (36).

Registry No.—**1c,** 562-66-3; **2a,** 512-61-8; **5,** 65878-89-9; **6a,** 65878-90-2; **6b,** 65878-91-3; **7,** 65878-92-4; **8,** 65878-93-5; **9** tosylate, 65899-41-4; **9,** 65878-94-6; 4-methylbicyclo[3.2.1]oct-3-en-6-one, 53216-75-4; 5-iodo-2-methyl-2-pentene, 43161-11-1.

References and Notes

(1) (a) Financial support of this research by the Robert A. Welch Foundation is gratefully acknowledged; (b) Recipient of Chemistry Department Eastman Kodak Fellowship, 1976–77.

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(10) Quenching of the dianion with D_2O resulted in ca. 85% incorporation of deuterium at C-3; when the *n*-BuLi treatment was omitted, ca. 20–30% deuterium incorporation was observed.
(11) Preliminary attempts to generate the enolate of the methyl ester of **7** using lithium diisopropylamide were unsuccessful as judged by deuterium incorporation; however, see P. A. Grieco and Y. Masaki, *J. Org. Chem.*, **40**, 150 (1975).
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(15) We are indebted to Dr. Bruno Willhalm, Fermenish SA, Geneva for spectral data of natural α-santalene.

A New Synthesis for Δ^{24}-Sterols: Preparation of Cholesta-5,24-dien-3β-ol (Desmosterol)[1a,2]

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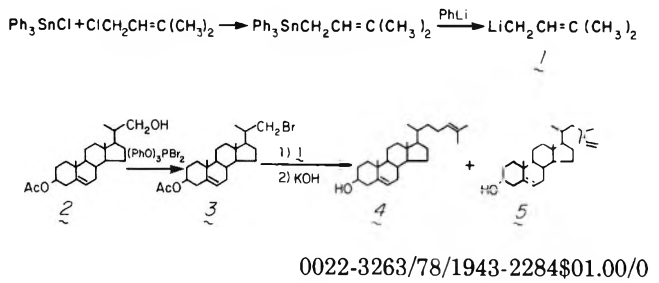
The new synthesis of Δ^{24} unsaturated sterols which involves the coupling reaction between dimethylallyllithium and a bromide is exemplified by the production of cholesta-5,24-dien-3β-ol (desmosterol; **4**) in Scheme I. The anticipated value of the new synthesis is in the preparation of other Δ^{24}- sterols. Reactions such as reductions of double bonds may be performed on the nuclear part of the sterol before the side chain with the labile Δ^{24} bond is added.

In this synthesis of desmosterol, 3β-acetoxy-23,24-dinorchol-5-en-22-ol (**2**), a known compound,[3,4] is converted into 3β-acetoxy-22-bromo-23,24-dinorchol-5-ene (**3**) with $(PhO)_3PBr_2$ in the presence of 1 mol of pyridine. This combination of reagents has been used[5] for the conversion of alkene or alkyne alcohols into bromides.

Preparation of compounds **4** was based on the analogous coupling reaction of allyllithium with 1-iodopentane to give 1-octene.[6] The required dimethylallyllithium reagent (**1**) was prepared by the transmetallation procedure of Seyferth and Weiner[7] involving a triphenyltin intermediate.

Scheme I



The coupling reaction produces the desired product and a minor by-product (**5**, ca. 3:1). The by-product has the same mol wt (as determined by MS) as the main product. The spectral data from **5** which include ^{13}C-NMR, ^{1}H-NMR, and IR determinations support structure **5**. The ^{13}C-NMR peaks at 109.7 and 149.8 ppm downfield from Me_4Si are comparable to the 108.1- and 148.1-ppm values for the vinyl protons of 3,3-dimethyl-1-butene.[8,9] The ^{1}H-NMR spectrum includes vinyl protons with chemical shifts and coupling constants similar to those of model compounds 3,3-dimethyl-1-butene[10] and 17 α-vinylestradiol.[11] The compound absorbs strongly at 907 cm^{-1} which is consistent with the IR absorption of a terminal methylene group. Previous studies[12,13] with allylic Grignard reagents indicate that the products formed are derived from the starting halide and/or the corresponding allylic isomer. This phenomenon appears to be occurring with the dimethylallyllithium in the coupling reaction causing the formation of 23,23-dimethyl-26,27-dinorcholesta-5,24-dien-3β-ol (**5**).

The new synthesis of desmosterol (**4**) is more practical than previously published preparations of this compound. The overall yield of desmosterol from the new synthesis is 14% when the 3β-acetoxy-23,24-dinorchol-5-en-22-ol starting material is prepared from commercially available 3β-acetoxy-23,24-dinorchol-5-en-22-oic acid by the Hayatsu method.[4] Compound **4** is produced from 3β-acetoxychol-5-en-24-oic acid in 9% yield,[14] and from 3β-acetoxy-26-norcholest-5-en-25-one in 36% yield,[15] but 3β-acetoxy-23,24-dinorchol-5-en-22-oic acid is a much more economical starting material. The nickel tetracarbonyl used to prepare π-(dimethylallyl)-nickel bromide in one synthesis[16] is highly toxic, and no yield is reported for the first step (Arndt–Eistert homologation) in another preparation.[16] The latter synthesis also uses 3β-acetoxy-23,24-dinorchol-5-en-22-oic acid as the starting material, and the yield of desmosterol from the homologue is 21%.

The new coupling reaction can be used for preparing Δ^{24} sterols with modified nuclear systems. Reactions such as hydrogenation which the Δ^{24} bond would not survive are performed before the addition of the Δ^{24} bond. The Fagerlund and Idler synthesis of desmosterol[14] can also be adapted for the preparation of other Δ^{24}-sterols. However, the limitations of yield and cost discussed in the synthesis of desmosterol would obtain.

Experimental Section

Melting points were determined on a Hoover Uni-Melt apparatus, under vacuum, and are uncorrected. IR spectra were taken on a Perkin-Elmer Model 521 spectrophotometer equipped with a KBr micropellet attachment. High-resolution MS spectra were determined on an A.E.I.M.S. 30. The ^{1}H-NMR spectrum was determined on a Bruker 270 MHz instrument, and the natural abundance, ^{1}H-decoupled, ^{13}C-NMR spectrum was obtained with an XL-100-15/VFT-100 instrument. The spectra were determined in $CDCl_3$, and chemical shifts are reported downfield from the Me_4Si internal standard. Microanalyses were carried out by M-H-W Laboratories, Garden City, Mich.

Dimethylallyltriphenyltin. This compound was produced from triphenyltin chloride (ICN Pharmaceuticals, Inc., Plainview, N.Y.; 10.9 g, 28.3 mmol) and 1-chloro-3-methyl-2-butene (Eastman, 4.6 g, 44 mmol).[7] The white solid was recrystallized from hexanes (50 mL), and the product (7.2 g, 17.19 mmol, 60.7%) which melted over several degrees was recrystallized from hexanes by removing the solvent at room temperature with nitrogen until crystals began to form. The many-sided irregular crystals melt at 71–72.5 °C and decompose in boiling hexanes: IR (KBr) 3060, 3050, 2964, 2910, 1694, 1657, 1651, 1426, 848, 807, 724, 710, 448 cm^{-1}. Anal Calcd for $C_{23}H_{25}Sn$ (420.147): C, 65.74; H, 5.99. Found: C, 65.82; H, 5.99.

3β-Acetoxy-22-bromo-23,24-dinorchol-5-ene (3). A 250-mL three-neck distilling flask equipped with a dropping funnel, drying tube, nitrogen inlet, and magnetic stirring bar was flame dried under a nitrogen atmosphere. Triphenyl phosphite (Aldrich, 5.4 g, 17.4 mmol) and ether (18 mL, freshly distilled from lithium aluminum

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hydride) were added to the cooled flask, and the solution was cooled on ice. Bromine (2.76 g, 17.2 mmol) was added dropwise with stirring. The ether was removed from the slightly yellow solid by vacuum distillation. The remaining solid was washed with ether which was removed by vacuum distillation while the flask was warmed periodically in a mineral oil bath held below 50 °C. The flask was transferred to an ice–salt bath. Compound **2**[3,4] (0.62 g, 1.65 mmol) in benzene[17] (94 mL, freshly distilled from lithium aluminum hydride) and pyridine (0.14 mL, 1.7 mmol, freshly refluxed in and distilled from BaO) were added to a fresh dropping funnel. The steroid solution was added over 10 min, the flask was allowed to warm to room temperature, and the mixture was stirred for 2 h. The mixture was washed with distilled H_2O (100 mL), and the aqueous layer was washed with benzene (50 mL). The combined benzene layers were warmed in a water bath and the solvent was removed under a stream of nitrogen. The crude material was chromatographed on Alumina F20 (102 g) in benzene–hexanes (increasing polarity from 1:1, v/v). The product (0.34 g, 0.77 mmol, 46.7%, mp 157–159.5 °C), which was eluted with benzene–hexanes 4:1, was rechromatographed on Alumina F20 and recrystallized from distilled MeOH to yield cubes: mp 157.5–158.5 °C; IR (KBr) 580 (CBr) cm^{-1}. Anal. Calcd for $C_{24}H_{37}O_2Br$ (437.452): C, 65.9; H, 8.5; Br, 18.3. Found: C, 65.98, H, 8.65; Br 18.32.

Cholesta-5,24-dien-3β-ol (Desmosterol, 4). A 15-mL three-neck distilling flask equipped with a magnetic stirring bar, dropping funnel, reflux condensor, nitrogen inlet, and drying tube was flame dried under nitrogen. Luer-lok syringes and needles were used for the transfer of all liquids. Lithium wire (2.4 cm, approximately 100 mg, 0.014 g-atom cut into six pieces) was added to the cooled flask, and the lithium was washed with ether (10 and 5 mL, freshly distilled from lithium aluminum hydride) from the dropping funnel. The washings were discarded, and fresh ether (1.2 mL) was added to the lithium. Freshly distilled bromobenzene (0.68 g, 4.3 mmol) was added to ether (2.4 mL) in the dropping funnel, and 10 drops of the mixture was added to the lithium. The remaining mixture was added in two equal portions after 5 and 12 min of stirring. The dark brown cloudy liquid (4 mL) was transferred to a 25-mL three-neck flask equipped with a nitrogen inlet, drying tube, and magnetic stirring bar and containing dimethylallyltriphenyltin (2.2 g, 5.25 mmol) in ether (10.4 mL). A cream-colored precipitate formed quickly, and stirring was discontinued after 5 min. The precipitate was allowed to settle, and the clear brown dimethylallyllithium solution (9 mL) was transferred to a three-neck distilling flask containing **3** (226 mg, 0.51 mmol). The flask was equipped with a reflux condensor, nitrogen inlet, drying tube, magnetic stirring bar, heating mantle, and a dropping funnel which supplies ether to maintain the reaction volume. The mixture was refluxed gently for 6.5 h. Saturated NH_4Cl (pH adjusted to 9 with NH_4OH) was added. The mixture was partitioned between distilled H_2O (20 mL) and ether (30 mL), and the aqueous layer was washed with ether (2 × 30 mL). The combined ether layers were warmed in a water bath, and the solvent was removed under a stream of nitrogen. The oily residue was saponified for 0.5 h with 5% alcoholic KOH (15 mL) and distilled H_2O (20 mL) and hexanes (40 mL) were added. The dried organic layer was chromatographed on a $AgNO_3$/silicic acid/Super-Cel column[18] (88.6 g) in benzene. Desmosterol (79.35 mg, 115–116.5 °C, 0.2 mmol, 39.2%) was rechromatographed on Alumina F20 (49 g) in benzene followed by benzene–EtOAc (1:1, v/v) and recrystallized from distilled MeOH (mp 119–119.5 °C) [lit. mp 120–122,[16] 120.5–121,[15] 117–118 °C[14]]: IR (KBr) 1373, 1056, 1022, 959, 950, 835, 800 cm^{-1}. Anal. Calcd for $C_{27}H_{44}O$: M^+ *m/e* 384.3389. Found: M^+ *m/e* 384.3421.

23,23-Dimethyl-26,27-dinorcholesta-5,24-dien-3β-ol (5). The isomer which is produced in the coupling reaction (26.65 mg, 191–195 °C) was also rechromatographed on Alumina F20 and recrystallized from distilled MeOH (mp 192–194 °C with sublimation): IR (KBr) 1469, 1461, 1457, 1444, 1434, 1378, 1372, 1360, 1290, 1061, 1053, 1023, 1006, 963, 956, 907, 839, 800, 782, 685, 668 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.8 (q, 1, J_{cis} = 10 Hz, J_{trans} = 17.2 Hz, $C_{24}CH$=), 5.35 (m, 1, C_6), 4.87 (d, 1, J = 11.7 Hz, C_{25}=$CH_{2_{cis}}$), 4.87 (d, 1, J = 16.25 Hz, C_{25}=CH_2 (trans)); ^{13}C NMR ($CDCl_3$) δ_c 149.8 (C_{24}), 121.86 (C_6), 109.7 (C_{25}). Anal. Calcd for $C_{27}H_{44}O$: M^+ *m/e* 384.3389. Found: M^+ *m/e* 384.3406.

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Registry No.—**1**, 50585-10-9; **2**, 55509-37-0; **3**, 58507-57-6; **4**, 313-04-2; **5**, 65733-48-4; triphenyltin chloride, 639-58-7; 1-chloro-3-methyl-2-butene, 503-60-6; dimethylallyltriphenyltin, 65733-49-5.

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General Procedure for the Synthesis of Mono-N-acylated 1,6-Diaminohexanes

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Studies in our laboratory required the ready availability of *N*-acrylyl-1,6-diaminohexane and *N*-(2-methylacrylyl)-1,6-diaminohexane in high purity. When attempts were made to prepare *N*-acrylyl-1,6-diaminohexane using the published procedure,[1] a product was isolated which agreed with the reported characteristics of the compound; however, analysis revealed the product to be bis(*N,N'*-acrylyl)-1,6-diaminohexane. In addition, the synthesis of monoacrylated product by reaction of acryloyl chloride and excess 1,6-diaminohexane gave poor yields due both to the preferential formation of the bis(N,N'-acrylated) product and to the similar physical properties of the bases, *N*-acrylyl-1,6-diaminohexane and 1,6-diaminohexane.

The key to the successful synthesis of mono-N-acylated 1,6-diaminohexanes is the protection of one of the amino groups of 1,6-diaminohexane by some readily removable group, particularly when this protecting group also favorably alters the solubility properties of the product so that its separation from the unsubstituted and disubstituted by-products is readily accomplished. Hence the easily removable, hydrophobic *tert*-butyloxycarbonyl[2] (Boc) group was used, which renders *N-tert*-butyloxycarbonyl-1,6-diaminohexane separable from the unreacted diamine and bis(*N,N'-tert*-butyloxycarbonyl)-1,6-diaminohexane.

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The introduction of the Boc group is accomplished with *S-tert*-butyloxycarbonyl-4,6-dimethyl-2-mercaptopyrimidine.[3] Isolation and purification of the desired *N-tert*-butyloxycarbonyl-1,6-diaminohexane as the hydrochloride is readily accomplished in approximately 60% yield. *N-tert*-Butyloxycarbonyl-1,6-diaminohexane is then reacted with the appropriate acid chloride, i.e., acryloyl and 2-methylacryloyl chloride, in the presence of tertiary base to yield *N-tert*-butyloxycarbonyl-*N'*-acrylyl-1,6-diaminohexane or *N-tert*-butyloxycarbonyl-*N'*-(2-methylacrylyl)-1,6-diaminohexane in excellent yield. Finally, the Boc group is removed with 3 M HCl in ethyl acetate to give in nearly quantitative yield the hydrochloride salts of monoacrylated 1,6-diaminohexanes.

Experimental Section

All melting points were determined in open capillary tubes and are reported uncorrected. Thin-layer chromatography was performed on precoated plates of silica gel G-60 F-254 (E. Merck). Compounds were applied in loads of up to 100 μg, and chromatograms were developed for 10–15 cm in the following solvent systems: A, $CHCl_3$–CH_3OH–CH_3CO_2H (9:1:1, v/v/v); B, butanone–CH_3CO_2H–H_2O (15:1:1); C, $CHCl_3$–CH_3OH (9:1); D, acetone–CH_3CO_2H–H_2O (9:1:1). Visualization was performed by UV, Cd/ninhydrin spray,[4] followed by treatment with Cl_2 gas and starch/NaI spray. Products gave single spots under these conditions.

***N-tert*-Butyloxycarbonyl-1,6-diaminohexane·HCl (1).** 1,6-Diaminohexane (23.2 g, 0.2 mol) was dissolved in dioxane (90 mL). To the stirred solution *S-tert*-butyloxycarbonyl-4,6-dimethyl-2-mercaptopyrimidine[3] (24.6 g, 0.1 mol) in dioxane (100 mL) was added slowly over a period of 3 h, and the reaction was allowed to proceed overnight. The precipitate (4,6-dimethyl-2-mercaptopyrimidine) was removed by filtration, and the filtrate was evaporated to 100 mL. The subsequent addition of water (150 mL) precipitated bis(*N,N'-tert*-butyloxycarbonyl)-1,6-diaminohexane (5.95 g, 0.02 mol) which was then removed by filtration. The dioxane was removed from the filtrate under reduced pressure and, following the addition of ~40 g of NaCl, the aqueous solution was extracted with EtOAc (50 mL, four times). The organic phase was pooled and evaporated under reduced pressure. The resulting oil was dissolved in water (100 mL) and acidified with 1 M HCl (70 mL) to a pH of 3. The aqueous phase was washed with EtOAc until the solution was colorless at which time the aqueous solution was saturated with NaCl. *N-tert*-Butyloxycarbonyl-1,6-diaminohexane·HCl crystallized and was isolated by filtration (18.3 g). The product was dissolved in C_2H_5OH (150 mL), decolorized with Norit, and filtered. The ethanol solution was evaporated to ~75 mL and added to 400 mL of acetone. The material, which crystallized shortly thereafter, was then filtered and dried: yield 14.6 g (58%); mp 162.5–163 °C; TLC R_f(A) 0.22, R_f(B) 0.20. Anal. Calcd for $C_{11}H_{25}N_2O_2Cl\cdot\frac{1}{4}H_2O$ (257.3): C, 51.4; H, 10.0; N, 10.9. Found: C, 51.5; H, 10.1; N, 10.5.

***N-tert*-Butyloxycarbonyl-*N'*-(2-methylacrylyl)-1,6-diaminohexane (2).** Compound 1 (7.58 g, 29.5 mmol) was suspended in $CHCl_3$ (200 mL) and cooled in an ice bath and triethylamine (8.74 mL, 63 mmol) was added. To the stirring suspension, 2-methylacryloyl chloride (3.0 mL, 30 mmol) dissolved in $CHCl_3$ (50 mL) was added dropwise. Following the addition, the solution was washed with water (100 mL, thrice), dried with Na_2SO_4, and evaporated in vacuo. The product crystallized upon the addition of hexane: yield 7.37 g (86%); mp 59–60 °C. A sample was recrystallized from benzene–hexane (1:10): mp 61–62 °C; TLC R_f(C) 0.58. Anal. Calcd for $C_{15}H_{28}N_2O_3$ (284.4): C, 63.4; H, 9.92; N, 9.85. Found: C, 63.4; H, 9.82; N, 9.69.

***N-tert*-Butyloxycarbonyl-*N'*-acrylyl-1,6-diaminohexane (3).** A sample of compound 1 (17.8 g, 70.4 mmol) was dissolved in CH_3OH and converted to the free base by elution through a Rexyn 201 (OH^-) column (2 × 50 cm, previously washed with CH_3OH). The CH_3OH was removed in vacuo and the resulting oil, after dissolution in $CHCl_3$ (250 mL) and addition of triethylamine (9.82 mL, 70.4 mmol), was added dropwise to a solution of acryloyl chloride (7.0 mL, 80 mmol) in $CHCl_3$ (250 mL) that was being stirred and kept at −5 to −10 °C. When the reaction solution reached room temperature, it was washed with water (250 mL, four times) and evaporated under reduced pressure and the material was crystallized from benzene: yield 15.9 g (83%), mp 107–109 °C. A sample was recrystallized from benzene: mp 108.5–109.5 °C; TLC R_f(C) 0.51. Anal. Calcd for $C_{14}H_{26}N_2O_3$ (270.4): C, 62.2; H, 9.69; N, 10.4. Found: C, 62.5; H, 9.63; N, 10.3.

***N*-(2-Methylacrylyl)-1,6-diaminohexane·HCl (4).** Compound 2 (2.56 g, 9.0 mmol) was dissolved in 3 M HCl–EtOAc (5 mL). After 30 min the solution was removed in vacuo and the oil was triturated with ether, filtered, and dried: yield 1.92 g (96%); mp 110–112 °C. Since the material was hygroscopic, a sample was converted to the free base by passage through a Rexyn 201 (OH^-) column and crystallized as the tosylate from C_2H_5OH–ether: mp 132–132.5 °C; TLC R_f(D) 0.28. Anal. Calcd for $C_{17}H_{28}N_2O_4S$ (356.5): C, 57.3; H, 7.92; N, 7.86. Found: C, 57.2; H, 7.76; N, 7.65.

***N*-Acrylyl-1,6-diaminohexane·HCl (5).** Compound 3 (2.38 g, 7.54 mmol) was treated with 3 M HCl–EtOAc as described above and the product was isolated in a 98% yield. The material polymerized on heating and melted at ~160 °C. For the purpose of analysis, the tosylate was prepared and crystallized as described for **4**: mp 145 °C (sharp); TLC R_f(D) 0.24. Anal. Calcd for $C_{16}H_{26}N_2O_4S$ (342.5): C, 56.1; H, 7.65; N, 8.18. Found: C, 56.1; H, 7.46; N, 7.96.

Note Added in Proof: The overall yield of *N-tert*-butyloxycarbonyl-1,6-diaminohexane·HCl (1) can be further increased by storing the by-product, bis(*N,N'-tert*-butyloxycarbonyl)-1,6-diaminohexane, in anhydrous Et_2O saturated with HCl gas at 25 °C. During the next 12 h, *N-tert*-butyloxycarbonyl-1,6-diaminohexane·HCl crystallizes free of 1,6-diaminohexane·2HCl.

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Registry No.—**1** HCl, 65915-94-8; **2**, 65915-95-9; **3**, 65915-96-0; **4**, 65915-97-1; **4** HCl, 65915-98-2; **4** tosylate, 65915-99-3; **5**, 7530-30-5; **5** tosylate, 65916-00-9; **5** HCl, 65916-01-0; 1,6-diaminohexane, 124-09-4; *S*-Boc-4,6-dimethyl-2-mercaptopyrimidine, 41840-28-2; 2-methylacryloyl chloride, 920-46-7; acryloyl chloride, 814-68-6.

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A New Synthesis of α-(2-Pyridyl) Ketones by Acylation of 2-Picolyllithium and 2,6-Lutidyllithium with *N,N*-Dimethylcarboxamides

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In connection with a study[2] of the synthesis and characterization of nickel(II), copper(II), and cobalt(II) complexes of various α-(2-hetaryl) ketones we required a series of α-(2-pyridyl) ketones of type **4**. The most widely used method for the synthesis of such compounds involves reaction of 2-lithiomethylpyridines (**1**) with an appropriate ester.[3-5] The mechanism of this process, as proposed by Levine and Raynolds,[5] involves initial reaction of **1** with the acylating ester to form **2**, which then reacts with more **1** either by proton abstraction to form the enolate of the desired ketone or by

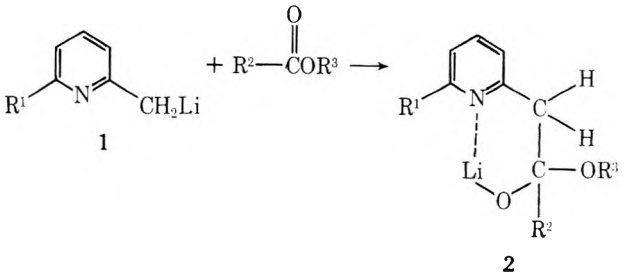

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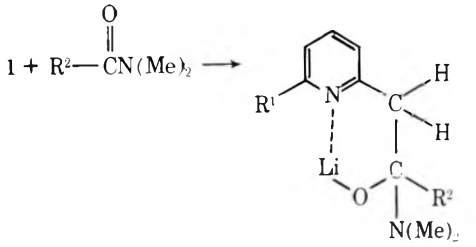
Table I
Acylation of 2-Picolylithium and 2,6-Lutidyllithium with *N,N*-Dimethylcarboxamides

Amide R^2	Registry no.	Ketone product R^1	R^2	No.	Registry no.	Yield, % S.A.[a]	I.A.[b]	Lit. yield, %	Bp, °C (Torr)	Lit. bp, °C (Torr)
CH_3	127-19-5	H	CH_3	**4a**	6302-02-9	79	69	18[c]	60–65 (0.4)	74–75 (1.5)[c]
$(CH_3)_2CH$	21678-37-5	H	$(CH_3)_2CH$	**4b**	10330-59-3	85	67	30[c]	80 (2)	79–85 (2)[c,d]
$(CH_3)_3C$	24331-71-3	H	$(CH_3)_3C$	**4c**	34552-04-0		57		78–83 (0.3)	51–53 (0.15)[d,e]
$C_6H_5CH_2$	18925-69-4	H	$C_6H_5CH_2$	**4d**	50550-53-3		69		133–138 (0.3)	*f*
C_6H_5	611-74-5	H	C_6H_5	**4e**	1620-53-7	51	41	40[c]	100–120 (1)	145–153 (3–4)[c]
CH_3		CH_3	CH_3	**4f**	65702-08-1	69		21[g]	67–72 (0.7)	105–106 (9.9)[g]
$(CH_3)_2CH$		CH_3	$(CH_3)_2CH$	**4g**	65702-09-2	66		31[g]	78–84 (0.7)	119–120.5 (9.5)[g]
$(CH_3)_3C$		CH_3	$(CH_3)_3C$	**4h**	65702-10-5	75			85 (0.7)	*h*

[a] Standard addition. [b] Inverse addition. [c] See ref 3. [d] See ref 8. [e] Calcd for $C_{11}H_{15}NO$: C, 74.54; H, 8.53; N, 7.90. Found: C, 74.15; H, 8.69; N, 7.86. [f] Calcd for $C_{14}H_{13}NO$: C, 79.59, H, 6.20; N, 6.63. Found: C, 79.32; H, 6.27; N, 6.64. [g] See ref 4. [h] Calcd for $C_{12}H_{17}NO$: C, 75.35; H, 8.96; N, 7.32. Found: C, 75.57; H, 9.11; N, 7.23.

displacement of alkoxide to form the lithium salt of a tertiary alcohol. Since the ionization and displacement reactions usually proceed at rates greater than the rate of formation of **2**, a molecular equivalent of **1** is consumed in a nonproductive fashion with respect to ketone formation. Therefore, a 2:1 molar ratio of **1**:acylating ester is routinely employed in these reactions.[3-5] Recently,[6] it has been found that efficient acylations of methylated heteroaromatics with nonenolizable esters can be accomplished with a 1:1 molar ratio of heterocyclic substrate:ester employing excess sodium hydride as the condensing agent. However, when the sodium hydride procedure was attempted with 2-picoline or quinaldine using ethyl acetate as the acylating agent, the rate of ester self-condensation to form ethyl acetoacetate was much more rapid than lateral acylation.[7] Photostimulated $S_{RN}1$ reactions of 2-halopyridines with ketone enolates provide a facile new route to certain ketones of type **4**, but such reactions afford mixtures of products with ketones capable of forming isomeric enolates, and certain enolates, such as those derived from alkyl aryl ketones, fail to react.[8]

Earlier reports[9,10] that *N,N*-dimethylcarboxamides react with organolithium reagents to form ketones prompted us to investigate the possibility of using these compounds for the acylation of lithio salts **1**. It seemed possible that addition of **1** to the amide carbonyl would produce intermediates such as **3**,[5,10] in which the dimethylamino function would serve to



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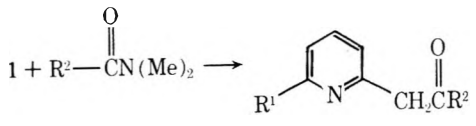
suppress proton abstraction as well as nucleophilic displacement, thereby leading mainly to ketonic products without requiring an extra equivalent of **1**.

Reaction of 2-picolyllithium (**1**, R^1 = H) with a representative series of *N,N*-dimethylcarboxamides afforded ketones **4a–e** in yields of 41 to 85%. Similar acylations of 2,6-lutidyllithium (**1**, R^1 = CH_3) afforded the corresponding α-(6-methyl-2-pyridyl) ketones **4f–h** in yields of 66 to 75%. Results of these experiments are summarized in Table I. In all cases the molar ratio of lithium reagent:acylating amide was 1:1, and



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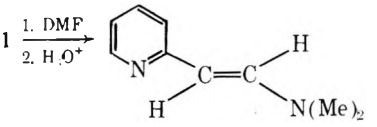
yields are based on the heterocycle. Addition of the metalated methylheteroaromatics to the acylating amide (inverse addition)[12] did not increase the yields over those obtained when the amide was added to the organometallic reagent (normal addition). For comparison purposes, yields of ketones **4a**, **4b**, and **4e–g** obtained previously by acylation of **1** (R^1 = H and R^1 = CH_3) with appropriate esters are included in Table I. These yields were recalculated on the basis of **1** as the limiting reagent in order to compare them with the present results. In four of five cases where comparisons can be made, the amide acylation procedure affords yields at least double those involving esters. In addition, no carbinol by-products were detected, whereas acylations of **1** (R^1 = H and R^1 = CH_3) with methyl acetate produce the corresponding tertiary alcohols in yields of 28 and 35%, respectively.[3-5] The steric requirements of the acylating amide exert only minor effects on these reactions as evidenced by the fact that the yields obtained with **1** (R^1 = CH_3) remain essentially constant as the amide R^2 residue is changed from methyl, to isopropyl, to *tert*-butyl. Successful acylation of **1** (R^1 = H) with *N,N*-dimethylphenylacetamide implies that amides containing relatively acidic α protons can be employed without difficulty.

Attempted acylation of **1** (R^1 = H) with DMF failed to afford 2-pyridylacetaldehyde. Instead, the normal hydrolytic work-up produced an unstable yellow oil with mass spectra and ^{1}H-NMR characteristics consistent with enamine structure **5**.



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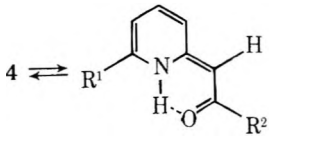
Pyridyl ketones **4** exist in solutions in equilibrium with their enamine tautomers **6**.[16] Comparison of the integrated intensities of the side-chain methylene and vinyl protons in the ^{1}H-NMR spectra of $CDCl_3$ solutions of **4a–h** provided a convenient method for determination of enamine content (Table II). Comparison of the enamine concentration data indicates that as the steric requirements of R^2 are increased, the amount of enamine present in solution also increases.[17] From a consideration of inductive effects alone, the enamine concentration might be expected to decrease with increasing methyl substitution at R^2. An increase in enamine content with R^2 = phenyl (**4c**) would be anticipated, since phenyl should increase the polarity of the carbonyl group, thereby



6

Table II
^{1}H-NMR Data for α-(2-Pyridyl) Ketones[a]

Ketone No.	R^1	R^2	δ CH_2 keto	δ CH enamine	% enamine[b]	Registry no.
4a[a]	H	CH_3	3.88	5.28	12	65702-11-6
4b	H	$CH(CH_3)_2$	4.00	5.40	16[c]	65702-12-7
4c	H	$C(CH_3)_3$	4.10	5.50	18	65702-13-8
4d	H	$CH_2C_6H_5$	3.94	5.28	22	65702-14-9
4e	H	C_6H_5	4.50	6.03	46	65702-15-0
4f	CH_3	CH_3	3.92	5.10	16	65702-16-1
4g	CH_3	$CH(CH_3)_2$	4.01	5.41	18[c]	65702-17-2
4h	CH_3	$C(CH_3)_3$	4.40	5.50	27[c]	65702-18-3

[a] Solvent = $CDCl_3$. Concentrations of ketones were ca. 25% by volume. Chemical shifts and integrated intensities of all other peaks were consistent with the assigned structures of **4a–h.** [b] Relative error ±2% or less, except where noted. [c] Relative error ±2.5%.

leading to stronger hydrogen bonding than when R^2 = alkyl. It appears that steric factors are more important than inductive effects with aliphatic R^2 groups and that the observed increase in enamine content with bulkier R^2 groups results mainly from relief of steric repulsions between these groups and the heterocyclic moiety in the pyridyl tautomers. Similar effects have been noted with β diketones.[18] Substitution of a methyl group at the 6 position of the pyridine ring in **4f–h** causes an increase in enamine content over that observed with the corresponding unmethylated ketones **4a–c.** Since addition of a 6-methyl group should contribute little to the steric requirements of the pyridine residue, it is suggested that the methyl group increases the basicity of the ring nitrogen and that the enamine form is stabilized by stronger hydrogen bonding in the methylated ketones.

Experimental Section

Melting points were taken on a Thomas-Hoover Mel-Temp apparatus and are uncorrected; boiling points are also uncorrected. Infrared spectra were measured on films, melts, or in Nujol mulls on potassium bromide plates. Spectra were recorded on a Beckman IR-5, a Beckman 20-AX, or a Perkin-Elmer 621 spectrophotometer where band positions were calibrated using polystyrene. Proton magnetic resonance (^{1}H-NMR) spectra were recorded on a JEOL PS 100 spectrometer. Chemical shifts are reported in δ in parts per million (ppm) downfield from tetramethylsilane as in internal standard. Mass spectra were obtained using a Hitachi Perkin-Elmer RMU-7 double-focusing mass spectrometer. The analyzer tube and the ion source were maintained at a pressure less than 10^{-6} Torr. Microanalyses were carried out in this Department on a Perkin-Elmer Model 240 C, H, and N elemental analyzer.

N,N-Dimethylamides were prepared by the method of Lecomet.[19] This involved dissolving the appropriate acid chloride in ether and passing dimethylamine gas through the solution until moist litmus paper above the solution turned blue. The solution was filtered to remove the precipitated dimethylammonium chloride. The ether was removed at aspirator pressure and the final products were purified by distillation.

Tetrahydrofuran (THF) was distilled from sodium hydride and stored under argon. *n*-Butyllithium (2 M in hexane) was obtained from Alpha-Ventron. All other chemicals were reagent grade and were used without further purification.

3-Methyl-1-(2-pyridyl)-2-butanone (4b). The following procedure is intended to be used as a model for the preparation of ketones **4.**

Standard Addition. 2-Picolyllithium (**1,** R^1 = H) was prepared by the method of Smith et al.[11] This involved the placing of 2-picoline (47.2 g, 0.50 mol) in a 2-L three-necked flask containing 200 mL of THF which was purged with argon and stirred mechanically. The solution was cooled in a dry ice/2-propanol bath and 2 M *n*-butyllithium (0.50 mol in hexane) was added dropwise through a pressure-equalizing dropping funnel. The bath was removed and the temperature was allowed to rise to ambient. The cooling bath was then replaced and a solution of 58 g (0.5 mol) of *N,N*-dimethylisobutyramide in 200 mL of anhydrous ether was added dropwise to the picolyllithium. The solution was allowed to warm to ambient temperature and 200 mL of water was added cautiously followed by 31 mL of concentrated HCl. The water layer was checked to ensure basicity, after which the ethereal layer was removed. The water layer was extracted with three 100-mL portions of chloroform and the extracts were combined with the ethereal layer and dried over Na_2SO_4. The volume was reduced at aspirator pressure and 65 °C. The crude product was vacuum distilled to afford 69.4 g (85%) of **4b,** bp 80 °C (2 Torr) [lit.[3] bp 79–85 °C (2 Torr)]. The ^{1}H-NMR and IR spectra of **4b** were identical with those of an authentic sample.[8]

Inverse Addition. 2-Picolyllithium (0.25 mol) was prepared and diluted with 200 mL of anhydrous ether. The solution was added dropwise to a solution of 26.5 g (0.25 mol) of *N,N*-dimethylisobutyramide in 200 mL of anhydrous ether. The product was worked up as in the previous procedure to afford 67% of **4b.**

Enamine 5. To a solution of 109 g (1.5 mol) of DMF in 300 mL of anhydrous ether cooled in a dry ice/2-propanol bath was added 1.0 mol of 2-picolyllithium over a period of 10 h. The reaction mixture was allowed to warm to room temperature and was then poured into 200 mL of 6 N HCl. The ethereal layer was separated. The aqueous layer was made basic and extracted with three 50-mL portions of chloroform. The organic layers were combined, dried (Na_2SO_4), and concentrated at 25 °C (0.25 Torr). Vacuum distillation afforded a light yellow oil, bp 75 °C (0.4 Torr), which began to decompose rapidly even at −5 °C. A sample of this product had: ^{1}H NMR ($CDCl_3$) δ 2.84 (s, 6 H, $N(CH_3)_2$), 5.22 (d, J = 7 Hz, 1 H, vinyl H), 6.88 (m, 2 H, PyH-3,5), 7.5 (d, J = 7 Hz, 1 H, vinyl H, superimposed on the multiplet for PyH-4, 1 H), and 8.43 (m, 1 H, PyH-6); mass spectrum *m/e* 148 (M^+).

Acknowledgment. We are pleased to acknowledge financial support from the National Institute of Neurological and Communicative Disorders and Stroke, Grant No. NS10197. Thanks are due to Mr. Dale Dreiling for providing technical assistance during this study.

Registry No.—1 (R′ = H), 1749-29-7; 1 (R′ = Me), 34667-18-0; **5,** 20973-84-6.

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The Utility of Hexachlorodisilane for the Deoxygenation of Nitrones, 2*H*-Imidazole 1-Oxides, 5*H*-Pyrazole 1-Oxides, and Related *N*-Hydroxy Compounds

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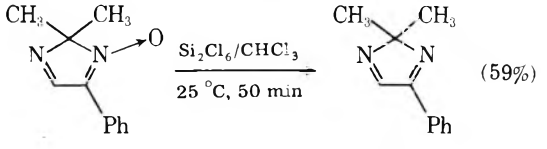
Several reports describing the use of trichlorosilane for the reduction of phosphine oxides to phosphines[1] and for the reductive deoxygenation of several types of S→O bonds[2] have appeared. Subsequently, the utility of hexachlorodisilane (Si_2Cl_6) in similar applications has been described[3,4] and extended to the reduction of phosphine sulfides,[5] amine oxides,[3] azo *N*-oxides,[6] azo *N,N'*-dioxides,[6] and aryl nitro compounds;[7] selected nonhalogenated disilanes have also been found to deoxygenate several classes of *N*-oxides under suitably vigorous conditions.[7,8]

In conjunction with several studies currently in progress we required a mild, selective technique for the reductive cleavage of N–O bonds in nitrones, 2*H*-imidazole 1-oxides, 5*H*-pyrazole 1-oxides, and related *N*-hydroxy substituted heterocycles. We report here that Si_2Cl_6 is a satisfactory and potentially general reagent for the deoxygenation of a variety of such substances; furthermore, the reductions we have studied were found to proceed cleanly and under remarkably mild conditions (see Experimental Section) and were quite selective in several cases where standard procedures[9] for the deoxygenation of *N*-oxides either yielded rearranged products of deoxygenation, or were not sufficiently selective with regard to avoidance of further reduction of the C=N bond of the initial deoxygenation products (e.g., in the case of Zn/HOAc) to be of practical use.

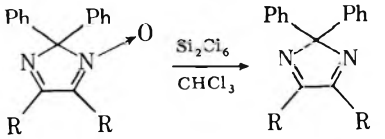
We first recognized the potential usefulness of Si_2Cl_6 in the deoxygenation of 2*H*-imidazole 1-oxides while attempting to establish the structure of the previously unreported *N*-oxide **1** (one of several products formed in the thermally induced



1 **2**

cyclization–rearrangement of *N*-nitroso-3-methyl-2-phenyl-2-butenaldimine[10]) by deoxygenating it to obtain **2**, the parent 2*H*-imidazole. As indicated below, treatment of **1** with Si_2Cl_6 afforded **2** in 59% yield (isolated and purified) under the conditions shown.

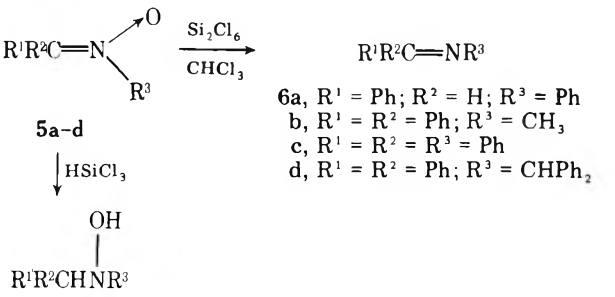
To further assess the generality of this surprisingly mild N–O deoxygenation procedure, the known 2*H*-imidazole 1-oxides **3a** and **3b**[11] were prepared and treated with Si_2Cl_6



3a,b **4a**, R = CH_3; **b**, R = Ph

under similar conditions; the corresponding pure 2*H*-imidazoles, **4a** and **4b**, were isolated in 75% and 79% yield, respectively.

The obvious similarity of the N → O containing moiety of **1**, **3a**, and **3b** to that of nitrones led to an extension of the deoxygenation procedure to the reduction of the acyclic nitrones **5a–d**; the isolated yields of the corresponding imines



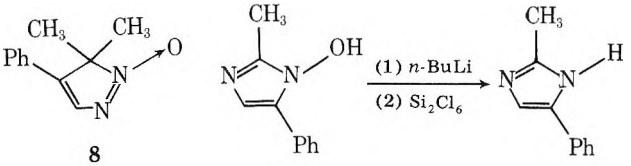
5a–d **6a**, R^1 = Ph; R^2 = H; R^3 = Ph; **b**, R^1 = R^2 = Ph; R^3 = CH_3; **c**, R^1 = R^2 = R^3 = Ph; **d**, R^1 = R^2 = Ph; R^3 = $CHPh_2$

7a, **7b**

6a–d in pure form were uniformly in the range of ca. 70–80%.

For comparison, the reactions of **5a** and **5b** with $HSiCl_3$ were also run. In both cases, the corresponding *hydroxylamines* (**7a** and **7b**) were the major products. Although the desired deoxygenations were not achieved in these two cases, such reductions of nitrones to hydroxylamines using relatively inexpensive $HSiCl_3$ may have some potential economic advantages over reported procedures[12] which utilize either $LiAlH_4$ or $NaBH_4$ as reductant for this purpose.

Finally, in studies related to that which afforded **1**,[10] two other previously unreported N–O containing heterocycles, **8** and **9**, were encountered. The key to their identification in each instance was their facile Si_2Cl_6-mediated reductive



8 **9** **10**

deoxygenation to the corresponding parent heterocycle; viz. **8** yielded 3,3-dimethyl-4-phenyl-3*H*-pyrazole,[13] and **9** (via its oxyanion)[10] yielded **10**; the latter *dehydroxylation* of an *N–OH* containing heterocycle is also unexampled in the reductions known, till now, to be effected by Si_2Cl_6.

Experimental Section[14]

Preparation of 2*H*-Imidazole 1-Oxides (1, 3a, and 3b), Nitrones (5a–d), and the 1-Hydroxyimidazole 9. 4,5-Dimethyl-2,2-diphenyl-2*H*-imidazole 1-oxide (**3a**),[11] 2,2,4,5-tetraphenyl-2*H*-imidazole 1-oxide (**3b**),[11] α,*N*-diphenylnitrone (**5a**),[15a] α,α-diphenyl-*N*-methylnitrone (**5b**),[15b] α,α,*N*-triphenylnitrone (**5c**),[15c] and α,α-diphenyl-*N*-benzhydrylnitrone (**5d**)[15d] were prepared according to published procedures. The 2*H*-imidazole 1-oxide **1** and the 1-hydroxyimidazole **9** were obtained as products in an ongoing study of the cyclization–rearrangement reactions of *N*-nitroso-2-phenyl-2-butenaldimines.[10]

2,2-Dimethyl-4-phenyl-2*H*-imidazole (2). To a solution of 2,2-dimethyl-5-phenyl-2*H*-imidazole 1-oxide (**1**) (92 mg, 0.49 mmol) in 5 mL of $CHCl_3$ at 25 °C and under N_2 was added dropwise 187 mg (0.66 mmol) of Si_2Cl_6 (PCR, Inc.). After the resulting mixture was stirred for an additional 50 min at 25 °C it was added to 4 mL of cold aqueous NaOH (10%). The resulting white suspension was diluted further with H_2O and extracted with $CHCl_3$. The extracts were dried over anhydrous Na_2SO_4 and K_2CO_3. Removal of the $CHCl_3$ in vacuo afforded 65 mg (77%) of crude **2** which, after chromatography over neutral Al_2O_3 (Woelm; dry column) using CH_2Cl_2 as developer and eluent, yielded 50 mg (59%) of nearly pure **2** as a light yellow solid. An analytical sample of **2** was obtained by sublimation at 32 °C (0.5 mm): mp 48.5–50 °C; NMR ($CDCl_3$) δ 1.56 (s, 6), 7.35–7.62 (m, 3), 7.85–8.12 (m, 2), 8.38 (s, 1); IR (CCl_4) 1615, 1538, 1452, 1358, 1348, 1267, 1220, 1165, 932, 695, and 588 cm^{-1}; IR (CS_2) additional peak at 773 cm^{-1}; UV λ_{max} (cyclohexane) 208 nm (ε 29 200), 221 (12 300), 258 (9410), 278 (2670 sh) and 289 (960); mass spectrum (70 eV) *m/e* (rel intensity) M^+ 172 (43), 145 (100), 104 (69), 89 (4), 77 (15), 69 (58), 51 (8), and 42 (32). Anal. Calcd for $C_{11}H_{12}N_2$: C, 76.71; H, 7.02; N, 16.26. Found: C, 76.74; H, 6.97; N, 16.23.

The spectral properties and melting point of the product were identical with those of an authentic sample of **2** prepared as follows by condensation of ammonia, acetone, and phenylglyoxal.[16] Ammonia

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(NH_3) gas was rapidly bubbled through a solution of acetone (300 mg, 5.17 mmol) in 10 mL of dry diethyl ether (Et_2O) at 25 °C. After 5 min, a solution of phenylglyoxal (130 mg, 0.970 mmol) in dry Et_2O (4 mL) was added dropwise to the acetone–ammonia mixture, following which ammonia was bubbled through the reaction mixture for an additional 10 min. The flask was stoppered, and the reaction mixture was stirred overnight at 25 °C and then refluxed for 2 h. The residue which remained after the Et_2O was removed was subjected to dry column chromatography over neutral Woelm Al_2O_3 (activity grade III). Elution with CH_2Cl_2–CCl_4 (5:1) afforded 120 mg (72%) of nearly pure 2,2-dimethyl-4-phenyl-2*H*-imidazole (**2**) which, after sublimation at 30 °C (0.6 mm), yielded material having mp 48.5–50 °C. A mixture melting point of **2** with the product obtained by deoxygenation of **1** with Si_2Cl_6, as described above, showed no depression.

General Procedure for the Deoxygenation of 2*H*-Imidazole 1-Oxides (3a, 3b) and Nitrones (5a–d) with Si_2Cl_6. Hexachlorodisilane (Si_2Cl_6) obtained from Aldrich and from PCR was used without purification. The substituted 2*H*-imidazole 1-oxide or nitrone was dissolved in a given amount of $CHCl_3$ or tetrahydrofuran (THF) and Si_2Cl_6 (1.0 to 1.2 mol equiv) was added slowly via a syringe at ice-bath temperature (0–5 °C). The ice bath was removed and the reaction mixture was allowed to stand at ambient temperature for 0.5 to 1.0 h. The reaction mixture was again cooled to 0–5 °C and maintained at that temperature as an excess of cold aqueous NaOH (20%) solution was added with rapid stirring. The organic phase was separated and washed with 5% $NaHCO_3$ and saturated NaCl solutions and dried ($MgSO_4$). The solvent was removed at reduced pressure.

4,5-Dimethyl-2,2-diphenyl-2*H*-imidazole (4a). A solution of 4,5-dimethyl-2,2-diphenyl-2*H*-imidazole 1-oxide (**3a**; 1.32 g, 0.005 mol) in 10 mL of $CHCl_3$ was treated with Si_2Cl_6 and worked up according to the general procedure to yield 1.11 g of a crude yellow solid (mp 160–191 °C) which afforded 0.99 g (80%) of pure **4a**, mp 197–198.5 °C, upon recrystallization from ethanol: NMR ($CDCl_3$) δ 2.29 (s, 6) and 6.9–7.8 (m, 10); mass spectrum (70 eV) *m/e* (rel intensity) M^+ 248 (4.3), 208 (14.8), 207 (100), 206 (5.3), 167 (19.0), 166 (96.1), 165 (87.9), 164 (6.9), 163 (5.1), 139 (5.0), 115 (2.7), 113 (1.8), 104 (3.7), 103 (2.7), 83 (9.7), 82 (14.9), 81 (10.4), 76 (4.6), 69 (3.5), and 62 (2.9). Three additional recrystallizations from ethanol afforded an analytical sample of **4a**: mp 198–198.4 °C. Anal. Calcd for $C_{17}H_{16}N_2$: C, 82.22; H, 6.49; N, 11.28. Found: C, 82.34; H, 6.42; N, 11.14.

2,2,4,5-Tetraphenyl-2*H*-imidazole (4b). A solution of 776 mg (2.00 mmol) of 2,2,4,5-tetraphenyl-2*H*-imidazole 1-oxide (**3b**) in 5 mL of $CHCl_3$ was deoxygenated and worked up as outlined above to yield 585 mg (79%) of pure **4b**, mp 197.8–198.2 °C (lit.[11] 199–201 °C).

Benzylidineaniline (6a). A solution of α,*N*-diphenylnitrone (**5a**; 1.97 g, 0.010 mol) in 20 mL of anhydrous THF (freshly distilled from $LiAlH_4$ and CaH_2) was deoxygenated with Si_2Cl_6 according to the general procedure to yield a yellow oil which was triturated with petroleum ether. Removal of the solvent from the resulting petroleum ether solution afforded 1.39 g (77%) of **6a** as a yellow solid: mp 46.5–48.5 °C (lit.[17a] 47–49 °C). Recrystallization from EtOH–H_2O raised the melting point to 49.7–51.0 °C; a mixture melting point with authentic **6a** was 49–50 °C.

***N*-Methylbenzophenone Ketimine (6b).** A solution of α,α-diphenyl-*N*-methynitrone (**5b**; 634 mg, 3.00 mmol) in 2 mL of $CHCl_3$ was treated with Si_2Cl_6 as described above to afford 427 mg (73%) of pure **6b** as a pale yellow oil after evaporative distillation of the crude product at 100–105 °C (0.7 mm): NMR ($CDCl_3$) 3 H singlet at δ 3.13 (lit.[17b] δ 3.13).

***N*-Phenylbenzophenone Ketimine (6c).** A solution of α,α,*N*-triphenylnitrone (**5c**; 276 mg, 1.01 mmol) in 5 mL of $CHCl_3$ upon deoxygenation with Si_2Cl_6 in the usual manner afforded 192 mg (74%) of pure **6c**, mp 111–112.5 °C, upon recrystallization from EtOH–H_2O (lit.[17c] 112–113 °C); a mixture melting point with authentic **6c** was 112–113 °C.

***N*-Benzhydrylbenzophenone Ketimine (6d).** Deoxygenation of α,α-diphenyl-*N*-benzhydrylnitrone (**5d**; 1.09 g, 0.003 mol) with Si_2Cl_6 in 8 mL of $CHCl_3$ according to the general procedure yielded 1.015 g of white solid (mp 135–140 °C) which afforded 0.832 g (80%) of pure **6d** upon recrystallization from ethanol: mp 151–151.5 °C (lit.[17d] 149–150 °C).

Benzylphenylhydroxylamine (7a). A solution of α,*N*-diphenylnitrone (**5a**; 985 mg, 5.00 mmol) in 10 mL of anhydrous THF was reduced with 0.8 mL (ca. 8 mmol) of $HSiCl_3$ using the procedure described below for the reduction of **5b** to **7b**. A yellow solid (970 mg) was obtained which was triturated with a small amount of pentane to afford, upon removal of the supernatant pentane solution, 665 mg (67%) of **7a** (87 ± 2% pure by NMR assay) as slightly yellow crystals, mp 75–80 °C. The product resisted attempts at further purification by recrystallization from several solvents. Further trituration with hexane afforded a small amount of pure benzylphenylhydroxylamine (**7a**): mp 87–88 °C (lit.[18a] 86 °C); NMR (CCl_4) δ 4.21 (s, 2), 5.63 (br s, 1) and 6.8–7.4 (m, 10).

***N*-Methyl-*N*-benzhydrylhydroxylamine (7b).** Trichlorosilane ($HSiCl_3$; 0.8 mL, ca. 0.008 mol; treated with quinoline and distilled before using) was added slowly via a syringe to a solution of nitrone **5b** (1.056 g, 0.005 mol) in 4 mL of $CHCl_3$ at ca. −30 °C (dry ice–acetone bath) and under N_2. The reaction mixture was allowed to stand at ambient temperature. After 20 min it was transferred slowly via pipet into 6 mL of cold aqueous NaOH (20%) solution while stirring thoroughly. The product was extracted with 10 portions of CH_2Cl_2 and the combined extracts were dried (Na_2SO_4). Removal of the solvent in vacuo left 0.972 g (91%) of crude *N*-methyl-*N*-benzhydrylhydroxylamine (**7b**) as colorless crystals, mp 79–81 °C, which could be recrystallized efficiently from cyclohexane to afford pure **7b**: mp 81.5–82 °C (lit.[18b] 82 °C); NMR (CCl_4) δ 2.24 (s, 3), 4.48 (s, 1), 5.93 (br s, 1, OH), 6.8–7.4 (m, 10).

2-Methyl-4(5)-phenylimidazole (10). *n*-Butyllithium (1.2 mmol; 0.6 mL of a 2 M solution in hexane obtained from Ventron) was added dropwise with stirring to a cold (0–5 °C) slurry of 1-hydroxyl-2-methyl-5-phenylimidazole (**9**; 200 mg, 1.20 mmol) in 7 mL of dry THF under N_2. After 3 min, Si_2Cl_6 (0.23 mL [350 mg], 1.3 mmol) was added, by means of a syringe, to the vigorously stirred reaction mixture at 0–5 °C. The reaction mixture was heated at 35 °C for 1 h and then poured into 25 mL of saturated aqueous Na_2CO_3 solution and extracted with $CHCl_3$. The combined extracts were washed with H_2O and brine, dried (Na_2SO_4), and concentrated in vacuo. Dry-column chromatography over alumina (Woelm; activity grade III) eluting with 4% EtOH in $CHCl_3$ afforded 72 mg (40%) of ca. 95% pure 2-methyl-4(5)-phenylimidazole (**10**). A sample of **10** which was recrystallized from $CHCl_3$–Et_2O (1:4) exhibited mp 159–160.5 °C (lit.[19] 161 °C); ^1H NMR ($CDCl_3$) δ 2.35 (s, 3), 7.13–7.80 (m, 6) and 11.6 (br s, 1); ^1H NMR ($CDCl_3/CD_3OD$) δ 2.38 (s, 3), 4.64 (s, 1), 7.10 (s, 1), and 7.15–7.72 (m, 5); ^{13}C NMR ($CD_3OD/CDCl_3$) δ (downfield from Me_4Si) 13.5 [rel. intensity, 15.6], 116.0 [21.0], 124.7 [45.7], 125.6 [10.3], 126.8 [28.7] and 128.8 [44.0]; IR ($CHCl_3$) 3470, 2960, 1610, 1588, 1452, 1406, 1156, 1136, 1105, 955, 945, and 560 cm^{-1}; UV λ_{max} (EtOH) 203 nm (ϵ 16 300) and 267 (15 200).

The spectral properties and melting point of **10** were identical with those of an authentic sample of **10** obtained as follows. Ammonia (NH_3) gas was bubbled through a solution of acetaldehyde (130 mg, 3.0 mmol) in 10 mL of dry Et_2O. After 5 min, 130 mg (1.0 mmol) of phenylglyoxal in 4 mL of dry Et_2O was added dropwise to the reaction mixture. The addition of NH_3 was continued during the addition and for 5 min longer. The reaction mixture was then stirred overnight at 25 °C followed by 3 h at reflux temperature. Concentration of the resulting solution followed by dry-column chromatography of the residue afforded 110 mg (70%) of nearly pure **10** which exhibited mp 159–160.5 °C after recrystallization from $CHCl_3$–Et_2O (1:4). A mixture melting point with **10** obtained by deoxygenation of **9** as described above showed no depression.

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Registry No.—**1**, 65776-47-8; **2**, 65776-48-9; **3a**, 57891-99-3; **3b**, 57892-00-9; **4a**, 65776-49-0; **4b**, 7196-81-8; **5a**, 1137-96-8; **5b**, 7500-79-0; **5c**, 4504-13-6; **5d**, 5076-57-3; **6a**, 538-51-2; **6b**, 13280-16-5; **6c**, 574-45-8; **6d**, 5350-59-4; **7a**, 3376-40-7; **7b**, 27865-53-8; **9**, 65776-50-3; **10**, 13739-48-5; Si_2Cl_6, 13465-77-5; $HSiCl_3$, 10025-78-2; *N*-nitroso-2-phenyl-2-butenaldimine, 65776-51-4; *N*-nitroso-3-methyl-2-phenyl-2-butenaldimine, 65776-52-5; acetone, 67-64-1; phenylglyoxal, 1074-12-0; acetaldehyde, 75-07-0.

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Nucleophilic Substitution Reactions of *N*-Alkyldi(trifluoromethane)sulfonimides. Role of the Solvent Hexamethylphosphoric Triamide

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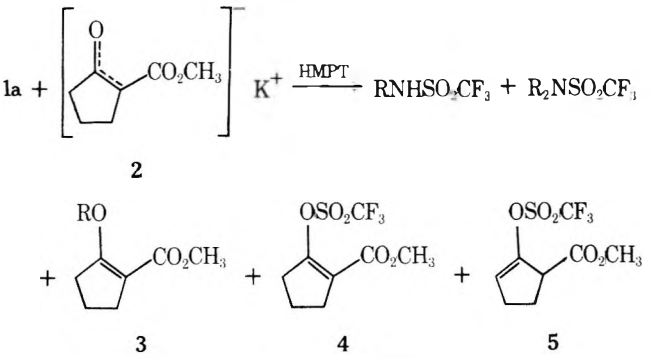
Nucleophilic substitution reactions of *N*-alkyldi(trifluoromethane)sulfonimides **1** have been reported.[1] Analogous reactions with other sulfonimides have also been investigated.[1b,2] To ascertain the synthetic utility of these reactions the alkyl group of the *N*-alkyldi(trifluoromethane)sulfonimide was varied and an assortment of nucleophiles were used.

$RN(SO_2CF_3)_2$

1a, R = *n*-C_6H_{13}
b, R = $C_6H_5CH_2CH_2$
c, R = $CH_3OCH_2CH_2$
d, R = $(CH_3)_2CHCH_2$
e, R = $CH_3CH_2OCOCH_2$

The results of these studies, all done using HMPT as solvent, are recorded in Tables I and II. In addition the reaction of sulfonimide **1a** with **2** afforded the products shown below. The compounds present after 233 h were *n*-hexyltrifluoromethanesulfonamide, *N,N*-di-*n*-hexyltrifluoromethanesulfonamide, **3**, **4**, and **5** in 30, 15, 39, ca. 10, and ca. 5% yield, respectively, as determined by quantitative GC analysis. Each of the products was isolated and compared with authentic material. The last two compounds were characterized by their IR, NMR, and UV spectra and elemental analysis and compared with material prepared according to the method of Stang and Dueber.[3]



These results show that nucleophilic displacements on *N*-alkyldi(trifluoromethane)sulfonimides by iodide ion to give the corresponding alkyl iodide occur in synthetically useful yields. Others have reported[1b,2b] synthetically useful displacement reactions of halide ions with *N*-alkyldi(arene)-sulfonimides.[4] Substitution reactions of sulfonimides in which alkyl iodides are presumably intermediates have also been reported.[1a,2c,f] Thus, although some reactions of sulfonimides with nucleophiles result in S–N cleavage,[2d,e,5] either by attack at sulfur or elimination,[6,7] simple nucleophilic substitution of the sulfonimide group can be achieved in many cases by a two-step sequence:[1a,2c,f] first displacement with iodide ion and then nucleophilic substitution on the alkyl iodide so obtained. An alternative to this sequence which also involves a key role for HMPT in nucleophilic substitution reactions is outlined below.

The displacements on sulfonimides were studied in HMPT because nucleophilic substitution reactions occur faster in this solvent.[8] However, it became apparent that HMPT could function as a nucleophile toward sulfonimides. Thus, NMR spectroscopy revealed that a solution of **1a** in HMPT formed salt **6a** on standing at room temperature overnight. Addition of an aqueous solution of sodium tetraphenylboron resulted in the precipitation of a crystalline salt. This salt (**6a**, X = $B(C_6H_5)_4$) was characterized spectroscopically and by elemental analysis. Similarly, **6b** was formed from **1b** in HMPT. Several other reactions illustrating the nucleophilicity of HMPT have been previously reported.[9] These salts, **6**, which are usually prepared from the corresponding alcohols,[10] are known to be useful alkylating agents.[9e,10,11] Thus reaction of **6a** with sodium cyanide in HMPT produced heptanenitrile in 72% yield, with sodiodiethyl malonate the reaction gave diethyl *n*-hexylmalonate in 87% yield; and with sodiomalonitrile the reaction gave the corresponding mono- and dialkylated products in 79% yield. A minor change in the procedure for reacting **1a** with sodium cyanide results in a dramatic change in the course of the reaction. If **1a** is added to sodium cyanide in HMPT rapid reaction ensues but no significant amount of heptanenitrile forms. However, if a solution of **1a** in HMPT is allowed to stand at room temperature for 18 h and then sodium cyanide is added, heptanenitrile forms in good

$ROP^+[N(CH_3)_2]_3X^-$

6a, R = *n*-C_6H_{13}
b, R = $C_6H_5CH_2CH_2$

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Table I. Reactions of Sulfonimides 1a–e with Nucleophiles in HMPT[a]

$RN(SO_2CF_3)_2 + M^+X^- \rightarrow RX + RNHSO_2CF_3 + R_2NSO_2CF_3$

$RN(SO_2CF_3)_2$	Registry no.	M^+X^-	RX yield, %	$RNHSO_2CF_3$ yield, %	$R_2NSO_2CF_3$ yield, %
1b	65832-17-9	KI	53	2	0
		NaCN	2	8	39
		$NaCH(CO_2CH_2CH_3)_2$[b]	11	3	25
1c	65832-18-0	KI	39	8	0
		NaCN	5	14	40
		$NaCH(CO_2CH_2CH_3)_2$	51	0	19
1d	65832-19-1	KI	76	16	0
		NaCN	2	25	19
		$NaCH(CO_2CH_2CH_3)_2$	12	10	31
1e	65832-20-4	KI	64[c]	0	0
		NaCN	10	15	0
		$NaCH(CO_2CH_2CH_3)_2$[d]	0	2	0

[a] Yields are based on quantitative GC by comparison with authentic samples. The products were identified by comparison of IR and NMR spectra and GC retention times with authentic samples. [b] Also $[CH(CO_2CH_2CH_3)_2]_2$ is formed in 16% yield. [c] Combined yield of ethyl iodoacetate and corresponding ethyl ether formed from this iodide. [d] Also $CH_3CH_2OCOCH{=}C(CO_2CH_2CH_3)_2$ is formed in 18% yield.

Table II. Reactions of *N*-*n*-Hexyltrifluoromethanesulfonimide (1a) with Nucleophiles in HMPT[a]

$RN(SO_2CF_3)_2 + M^+X^- \rightarrow RX + RNHSO_2CF_3 + R_2NSO_2CF_3$
$R = n\text{-}C_6H_{13}$

M^+X^-	RX yield, %	$RNHSO_2CF_3$ yield, %	$R_2NSO_2CF_3$ yield, %
$NaCH(COCH_3)CO_2CH_2CH_3$	ca. 30	0	
$KOCOCH_3$	0		
$NaSC_6H_5$[b]	15	23	12
NaN_3	0	52	14
$TlCH(COCH_3)_2$	46	29	25
$NaCH(CN)_2$	0	47	18
H_2O[c]	40	0	0

[a] Yields are based on quantitative GC by comparison with authentic samples. The products were identified by comparison of IR and NMR spectra and GC retention times with authentic samples. [b] Also diphenyl disulfide is formed in 50% yield. [c] Under the conditions of this reaction 6a is formed in 40% yield and *n*-hexyl trifluoromethanesulfonate is formed in 10% yield.

yield. From the extensive work done by others on nucleophilic displacement reactions of salts **6** the formation of such salts from amines should be synthetically advantageous.

In sum nucleophilic displacement on *N*-alkyldi(trifluoromethane)sulfonimides in HMPT may involve direct displacement on carbon, direct displacement on sulfur, or displacement on carbon via solvent participation. There may well be other cases in which apparent direct displacement on carbon electrophiles in HMPT as solvent involves solvent participation. A possible example is the reduction of di(arene)sulfonimides by sodium borohydride in HMPT at 150–175 °C.[2e] We echo the warning of Anselmi et al.[9e] "that great care must be exercised in the evaluation of reactions involving catenoid transition states if carried out in HMPT".

Experimental Section

Infrared spectra were recorded on either a Perkin-Elmer Model 337 or Model 137 IR spectrophotometer. NMR spectra were measured using a 60 MHz Varian T-60 NMR spectrometer and employing tetramethylsilane as an internal standard. Ultraviolet spectra were determined using a Cary 14 UV spectrophotometer. Mass spectra were recorded on a Hitachi Perkin-Elmer Model RMU-6E double-focusing mass spectrometer. Elemental microanalyses were performed by Spang Microanalytical Laboratory, Ann Arbor, Mich. Melting points were determined in open, glass capillary tubes using a Thomas-Hoover melting point apparatus or on glass cover slips using a Thermolyne microstage melting point apparatus.

Carbon tetrachloride and acetonitrile were distilled from phosphorus pentoxide, diethyl ether was distilled from sodium metal, the amines and pyridine were distilled from calcium hydride, and HMPT was distilled under vacuum from sodium metal prior to use in reactions.

Preparation of Trifluoromethanesulfonimides. The trifluoromethanesulfonimides were prepared from the corresponding sulfonamides using the method of Baumgarten et al.[5] in ethyl ether (A) or acetonitrile (B) as solvent. The trifluoromethanesulfonamides were secured using the method of Gramstad and Haszeldine,[12] but with cyclohexane used as the solvent instead of ethyl ether.

***n*-Hexyldi(trifluoromethane)sulfonimide (1a):** B (56%); bp 50 °C (0.15 mm); IR (CCl_4) 1435, 1135 cm^{-1}; NMR (CCl_4) δ 0.70–2.10 (m, 11 H, aliphatic), 3.89 (t, J = 7 Hz, 2 H, NCH_2). Anal. Calcd for $C_8H_{13}F_6NO_4S_2$: C, 26.30; H, 3.59; S, 17.55. Found: C, 26.37; H, 3.83; S, 17.58.

n-Hexyltrifluoromethanesulfonamide: 79% yield; bp 83 °C (0.1 mm); IR (CCl_4) 3350, 3190, 1385, 1205 cm^{-1}; NMR (CCl_4) δ 0.80–1.75 (m, 11 H, aliphatic), 3.26 (m, 2 H, NCH_2), 5.17 (s, 1 H, NH). Anal. Calcd for $C_7H_{14}F_3NO_2S$: C, 36.05; H, 6.05; S, 13.75. Found: C, 36.06; H, 6.10; S, 13.80.

2-Phenylethyldi(trifluoromethane)sulfonimide (1b): B (61% yield); bp 84–85 °C (0.63 mm); IR (CCl_4) 1415, 1200 cm^{-1}; NMR (CCl_4) δ 3.02 (t, J = 7 Hz, 2 H, aliphatic), 4.02 (t, J = 7 Hz, 2 H, NCH_2), 7.20 (s, 5 H, aromatic). Anal. Calcd for $C_{10}H_9F_6NO_4S_2$: C, 31.17; H, 2.36; S, 16.64. Found: C, 31.20; H, 2.39; S, 16.75.

2-Phenylethyltrifluoromethanesulfonamide: (82% yield); bp 95–96 °C (0.25 mm); IR (CCl_4) 3200, 1375, 1195 cm^{-1}; NMR (CCl_4) δ 2.75 (t, J = 7 Hz, 2 H, aliphatic), 3.39 (m, 2 H, NCH_2), 5.20 (t, J = 5 Hz, 1 H), 7.12 (s, 5 H, aromatic). Anal. Calcd for $C_9H_{10}F_3NO_2S$: C, 42.69; H, 3.98; S, 12.66. Found: C, 42.78; H, 3.92; S, 12.75.

2-Methoxyethyldi(trifluoromethane)sulfonimide (1c): B (47% yield); bp 43 °C; IR (CCl_4) 1415, 1115 cm^{-1}; NMR (CCl_4) δ 3.31 (s, 3 H, CH_3O), 3.59 (t, J = 5 Hz, 2 H, OCH_2), 4.09 (t, J = 5 Hz, 2 H, NCH_2). Anal. Calcd for $C_5H_7F_6NO_5S_2$: C, 17.70; H, 2.08; S, 18.90. Found: C, 17.80; H, 2.11; S, 18.81.

2-Methoxyethyltrifluoromethanesulfonamide: 31% yield; bp 55–56 °C (0.32 mm); IR (CCl_4) 3975, 1365, 1180 cm^{-1}; NMR (CCl_4) δ 3.40 (m, 7 H), 6.00 (s, 1 H, NH). Anal. Calcd for $C_4H_8F_3NO_3S$: C, 23.19; H, 3.98; S, 15.48. Found: C, 23.14; H, 3.86; S, 15.52.

Isobutyldi(trifluoromethane)sulfonimide (1d): A (27%); bp 33–34 °C (0.55 mm); IR (CCl_4) 1420, 1120 cm^{-1}; NMR (CCl_4) δ 1.02 (d, J = 7 Hz, 6 H, Me), 2.08 (m, 1 H, CH), 3.70 (d, J = 7 Hz, 2 H, NCH_2). Anal. Calcd for $C_6H_9F_6NO_4S_2$: C, 21.37; H, 2.69; S, 19.01. Found: C, 21.43; H, 2.69; S, 19.06.

Isobutyltrifluoromethanesulfonamide: 79% yield; bp 47 °C (0.45 mm); IR (CCl_4) 3850, 3680, 1375, 1195 cm^{-1}; NMR (CCl_4) δ 0.96 (d, J = 7 Hz, 6 H, Me), 1.80 (m, 1 H, CH), 3.08 (d, J = 7 Hz, 2 H, NCH_2), 5.58 (s, 1 H, NH). Anal. Calcd for $C_5H_{10}F_3NO_2S$: C, 29.27; H, 4.91; S, 15.62. Found: C, 29.32; H, 4.87; S, 15.65.

Ethyl *N,N*-Di(trifluoromethanesulfonyl)glycinate (1e): A (34%); bp 78 °C (0.35 mm); IR (CCl_4) 1400, 1110 cm^{-1}; NMR (CCl_4) δ 1.32 (t, J = 7 Hz, 3 H, Me), 4.31 (q, J = 7 Hz, 2 H, CH_2O), 4.50 (s, 2

H, NCH_2). Anal. Calcd for $C_6H_7F_6NO_6S_2$: C, 21.50; H, 2.11. Found: C, 21.31; H, 2.34.

Ethyl *N*-trifluoromethanesulfonylglycinate: 54% yield; mp 93–94 °C; IR (CCl_4) 3950, 1195, 1140 cm^{-1}; NMR (CCl_4) δ 1.30 (t, J = 7 Hz, 3 H, Me), 3.96 (d, J = 6 Hz, 2 H, NCH_2), 4.25 (q, J = 7 Hz, 2 H, CH_2O), 5.60 (s, 1 H, NH). Anal. Calcd for $C_5H_8F_3NO_4S$: C, 25.54; H, 3.43; S, 13.63. Found: C, 25.66; H, 3.02; S, 13.72.

***N,N*-Di-*n*-hexyltrifluoromethanesulfonamide:** (23% yield); bp 109 °C (0.1 mm); IR (CCl_4) 1390, 1180; NMR (CCl_4) δ 0.80–1.80 (m, 11 H, aliphatic), 3.30 (t, J = 7 Hz, 2 H, NCH_2). Anal. Calcd for $C_{13}H_{26}F_3NO_2S$: C, 49.19; H, 8.25; S, 10.11. Found: C, 49.29; H, 8.26; S, 10.15.

Reaction of 1a with 2: A sample of **2** (0.35g, 1.9 mmol) prepared according to the method of Mayer and Alder[13] was dissolved in anhydrous HMPT (2 mL) and the solution was placed under an atmosphere of nitrogen. To this solution cooled in ice water was added a solution of **1a** (0.69 g, 1.9 mmol) dissolved in anhydrous HMPT (1.5 mL) over 1.5 h. After the addition the reaction mixture was allowed to warm to room temperature. After 233 h the reaction mixture was poured into saturated aqueous sodium bicarbonate solution (5 mL) and extracted with ethyl ether (5 × 4 mL). The combined ether extracts were washed successively with water (2 × 8 mL) and brine (2 × 8 mL) and dried over anhydrous magnesium sulfate. After removal of the solvent the residue was analyzed by quantitative GC using a 5 ft 10% Carbowax 20 M on Chromosorb W (DMCS treated) column at 120 °C. Each of the compounds in the product mixture was isolated by preparative GC and shown to be identical with authentic material. Authentic samples of **3–5** were secured as indicated below.

Authentic **3**, R = *n*-C_6H_{13}, was prepared from 1-bromohexane and **2** using the general method of Pond and Cargill.[14]

Preparation of 4 and 5. Following the method of Stang and Deuber[3] for the preparation of vinyl trifluoromethanesulfonates, trifluoromethanesulfonic acid anhydride[12] (3.73 g, 13.1 mmol) was rapidly added to a solution of methyl 2-ketocyclopentanecarboxylate (1.73 g, 12.0 mmol) and pyridine (1.03 g, 13.1 mmol) in carbon tetrachloride (30 mL) cooled in a −78 °C bath. The mixture was allowed to warm to room temperature and after 3 days the mixture was filtered and the solids and tars were mixed with water (40 mL) and extracted with carbon tetrachloride (5 mL). The extract and filtrate were combined, washed with water (2 × 10 mL), dried ($MgSO_4$), and concentrated by rotary evaporation. The residue was distilled to give a mixture of bp 53–57 °C (0.3 mm) consisting of unreacted ester and **4** and **5** (the ratio of **4** and **5** determined by GC analysis was 2.2:1). This mixture was separated by preparative GC using a 5 ft 5% SE-30 on Chromosorb W column (DMCS treated).

Vinyl trifluoromethanesulfonate (4): IR (CCl_4) 2950, 1725, 1655, 1425, 1350, 1205, 1170, 1140, 1050, 1000 cm^{-1}; NMR (CCl_4) δ 2.10 (m, 2 H), 2.78 (t, J = 7 Hz, 4 H), 3.80 (s, 3 H); UV (cyclohexane) λ_{max} (ϵ) 221 nm (12 000). Anal. Calcd for $C_8H_9F_3O_5S$: C, 35.04; H, 3.31; S, 11.69. Found: C, 35.24; H, 3.29; S, 11.62.

Vinyl trifluoromethanesulfonate (5): IR (CCl_4) 2950, 1740, 1650, 1420, 1330, 1205, 1170, 1060, 970 cm^{-1}; NMR (CCl_4) δ 2.40 (m, 5 H), 3.70 (s, 3 H), 5.80 (m, 1 H); UV (cyclohexane) λ_{max} (ϵ) 198 (4200) nm. Anal. Calcd for $C_8H_9F_3O_5S$: C, 35.04; H, 3.31; S, 11.69. Found: C, 35.19, H, 3.23; S, 11.60.

Reaction of Nucleophiles with Sulfonimides. The general procedure was to add the sulfonimide dissolved in anhydrous HMPT (1 to 2 M) to a solution of the salt (an amount equimolar to that of the sulfonimide plus 10%) dissolved in anhydrous HMPT and cooled in an ice–water bath. The solution was stirred at room temperature for 2–4 days. The mixture was then poured into water and extracted three times with ether. The combined ether extracts were washed successively with water and brine and dried over anhydrous magnesium sulfate. The solution was then analyzed by quantitative GC. In each case the product reported in Tables I and II was isolated by preparative GC and the IR and NMR spectra and GC retention times were compared with authentic samples

Reaction of Sulfonimide 1a with HMPT. A sample of sulfonimide **1a** (0.15 g, 0.42 mmol) was dissolved in anhydrous HMPT (0.4 mL) and placed under a dry nitrogen atmosphere. An NMR spectrum of the solution was measured immediately after mixing. This spectrum showed a signal at δ 4.20 (t, J = 7 Hz, CH_2N). After 17.5 h this signal was replaced by one at δ 4.25 (m, CH_2O). After 24 h the solution was cooled in an ice–water bath and a solution of sodium tetraphenylboron (0.34 g, 1.0 mmol) dissolved in water (10 mL) was added over 5 min. A voluminous precipitate formed. After stirring with cooling for 0.5 h, the mixture was filtered to afford solid **6a**, X = $B(Ph)_4$ (0.18 g, 73%), mp 160–161 °C. After recrystallization from absolute methanol colorless needles were obtained: first crop (0.16 g), mp 169–169.5 °C; second crop (0.01 g), mp 168–168.5 °C; purified yield of 69%; IR (KBr) 3050, 2925, 1575, 1475, 1450, 1420, 1300, 1180, 1155, 1050, 1030, 995 cm^{-1}; NMR (CD_3COCD_3) δ 0.70–1.88 (m, 11 H), 2.70–2.87 (d, J = 10 Hz, 18 H), 4.23 (m, 2 H), 6.89 (m, 12 H), 7.14 (m, 8 H); spin decoupling experiments gave the following results—irradiation at δ 1.63 caused the multiplet at δ 4.23 to collapse to a doublet with J = 6 Hz. Anal. Calcd for $C_{36}H_{51}BN_3OP$: C, 74.10; H, 8.76; N, 7.23. Found: C, 73.85; H, 8.82; N, 7.30.

Reaction of Sulfonimide 1b with HMPT. A solution of sulfonimide **1b** (0.26 g, 0.67 mmol) dissolved in HMPT (0.7 mL) was stirred at room temperature for 3 days. A solution of sodium tetraphenylboron (0.38 g, 1.1 mmol) in water (10 mL) was then added over 5 min while cooling in an ice–water bath. A voluminous precipitate formed. After stirring with cooling for 0.5 h the mixture was filtered and the precipitate was washed with water to afford **6b**, X = $B(Ph)_4$ (0.22 g, 51%). Recrystallization from ethanol gave a colorless solid (although only a modest amount of solid was obtained): mp 192–194 °C; IR (KBr) 3050, 2990, 1475, 1455, 1305, 1175, 1150, 1060, 1000 cm^{-1}. Ethanol was not the best choice for a recrystallization solvent for this compound.

Reaction of 6a with Nucleophiles. These reactions were all done in a similar way. A specific example is given in detail below.

A solution of sulfonimide **1a** (0.67 mmol) dissolved in HMPT (0.6 mL) was placed under a dry nitrogen atmosphere and stirred at room temperature for 20 h. To this solution cooled in an ice–water bath was added, over 0.5 h, a solution of diethyl sodiomalonate prepared by adding diethyl malonate (0.13 g, 0.81 mmol) in HMPT (0.2 mL) to sodium hydride (0.03 g, 57% mineral oil dispersion washed with ether, 0.81 mmol) suspended in HMPT (0.2 mL) at 0 °C over 0.75 h and stirred with cooling for an additional 1 h. After stirring at room temperature for 4 days the solution was poured into water (35 mL) and extracted with ethyl ether (3 × 10 mL). The combined ether extracts were washed successively with water (10 mL) and brine (10 mL) and dried over anhydrous magnesium sulfate. The mixture was filtered, the solvent was removed, and the residual oil was analyzed by quantitative GC at 165 °C on a 5 ft 10% SE-30 on Chromosorb W (DMCS treated) column. The oil was a mixture consisting of diethyl malonate, *N,N*-di-*n*-hexyltrifluoromethanesulfonamide, and diethyl *n*-hexylmalonate (87%). Samples of each product were obtained by preparative GC and their IR and NMR spectra and GC retention times were compared with those of authentic samples.

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Registry No.—**1a**, 35920-58-2; **2**, 61114-30-5; **4**, 65832-21-5; **5**, 65832-22-6; **6a** (X = $B(Ph)_4$), 65877-70-5; **6b** (X = $B(Ph)_4$), 65898-24-0; HMPT, 680-31-9; *n*-hexyltrifluoromethanesulfonamide, 52374-19-3; 2-phenylethyltrifluoromethanesulfonamide, 36458-24-9; 2-methoxyethyltrifluoromethanesulfonamide, 65832-23-7; isobutyltrifluoromethanesulfonamide, 65832-24-8; ethyl *N*-trifluoromethanesulfonylglycinate, 65832-25-9; *N,N*-di-*n*-hexyltrifluoromethanesulfonamide, 65832-26-0.

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An Improved Synthesis of α-Methylene γ-Lactones by Electrolysis of α-Carboxy-α-phenylthiomethyl-γ-butyrolactones

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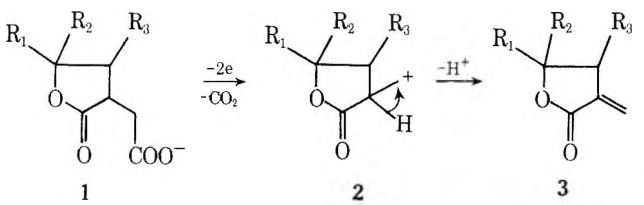
α-Methylene γ-lactone function, an important structural feature of biologically active natural products,[1] has received much attention and its synthetic attempts have been well documented in a recent publication.[2a,b] The reported methods for the preparation of α-methylene γ-lactone analogues[2] have been shown to employ largely severe conditions such as strong acids, bases, and heat in the crucial steps of the formation of the exo double bond. Recently, Ronald reported an interesting method for the preparation of *trans*-α-methylene-β,γ-tetramethylene-γ-butyrolactone from the corresponding α-carboxy-α-methylthiomethyl γ-lactone by three steps.[3] In this paper, we describe an improved one-step synthesis of α-methylene γ-lactones from α-carboxy-α-phenylthiomethyl-γ-butyrolactones, involving electrolytic elimination of both sulfenyl and carboxyl groups at room temperature.

Our preliminary challenges for the synthesis of the α-methylene γ-lactone group by electrodecarboxylation of the primary carboxylic acids **1** in pyridine–water–triethylamine (9:1:0.3 v/v)[4] at a current of 0.01–0.06 A/cm^2 (applied voltage 50–60 V) afforded **3** in 30–35% yields[5] via the intermediate **2**, indicating that the desired product **3**, which was exposed to a high applied voltage and also a high oxidation potential,[6] would undergo further anodic oxidation, causing decrease of the yield. This result suggests that the electrolysis at lower potential than that of **1** would promise a more favorable result. Besides, it is desirable that the product **3** should be removed immediately from the electrolysis solution. The advantage of allowing the anodic oxidation of the phenyl sulfide derivatives



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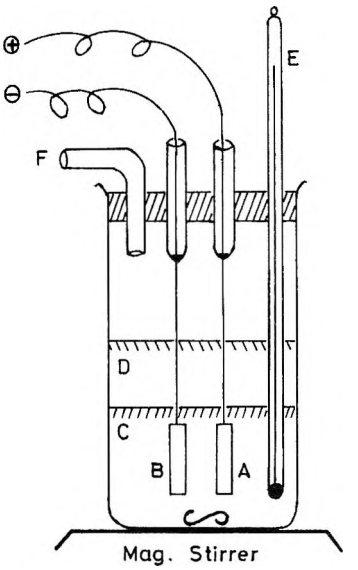
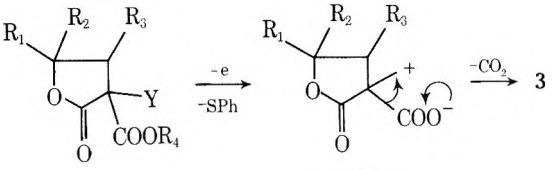


Figure 1. Electrolysis cell: (A) anode Pt plate (3 cm^2); (B) cathode Pt plate (3 cm^2); (C) aqueous phase; (D) organic phase; (E) thermometer; (F) gas lead pipe.

at the lower potential[7] rather than those of the carboxylic acids[6] led us to choose α-carboxy-α-phenylthiomethyl-γ-butyrolactone analogues **5** as a suitable compound for our synthetic purpose, since elimination of phenyl thiyl radical would be expected by one-electron oxidation on the sulfur atom of **5**,[7] affording the intermediate **7**, and subsequent loss of carbon dioxide would provide the desired **3**.



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4, Y = H; R_4 = H
5, Y = CH_2SPh; R_4 = H
6, Y = H; R_4 = Et

Improvement of the electrolysis for the continuous extraction of the products was made by employing a two-phase system, consisting of water and organic solvents as shown in Figure 1. By this procedure, the products are expected to move from the aqueous layer to the organic layer, while the substrates are electrolyzed in the aqueous phase. Electrolysis of the ammonium salt of **5** to the desired **3** was carried out in an aqueous layer, dissolving an excess amount of triethylamine and lithium perchlorate as supporting electrolytes (Table II). The aqueous layer as depicted in Figure 1 was covered with a mixed solution of ether and benzene (3:2) as an extracting solvent. The aqueous solution was electrolyzed in an undivided beaker under a current of 16–7 mA/cm^2 with applied voltage of 3.2–3.5 V (1.3–1.5 V vs. SCE) at 38–40 °C for 4–12 h using platinum electrodes (3 cm^2). Successfully, the desired **3** was obtained only by evaporation of the extracting solvent as a sole product along with diphenyl disulfide after 40–80 Faradays/mol of electricity were passed. The electrolysis conditions of **5** as well as the yields of **3** are shown in Table II.

Experimental Section

Melting points and boiling points are uncorrected. IR spectra were determined with a JASCO Model IRA-1 grating spectrometer. ^{1}H-NMR spectra were determined at 60 MHz with a Hitachi Model R-24 and ^{13}C-NMR spectra were determined at 25.05 MHz with a JEOL Fourier transform spectrometer, Model FX-100 with a JEC-980-16K memory computer. The chemical shift values are expressed in δ values

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Table I. Physical Properties, Yields, and Combustion Analyses of α-Carboxy-α-phenylthiomethyl γ-Lactones 5

Product 5			Registry	Mp,	IR, C=O cm^{-1}		^{1}H NMR, δ –CH_2S–	Yield,	Anal., % Calcd		Found	
R_1	R_2	R_3	no.	°C	Lactone	Acid	(multiplicity)	%[a]	C	H	C	H
n-C_8H_{17}	H	H	65651-96-9		1772	1710	3.52 (q, J = 7.5 Hz)	94	65.92	7.74	65.97	7.92
–$(CH_2)_5$–		H	65651-97-0		1765	1718	3.52 (q, J = 6.5 Hz)	92	63.74	6.29	63.58	6.57
H	–$(CH_2)_5$–		65651-98-1	124.2	1776	1722	3.51 (broad s)	94	63.74	6.29	63.72	6.47
H	–$(CH_2)_4$–		65651-99-2	141.4	1770	1698	3.56 (broad s)	95	62.74	7.92	62.72	6.07

[a] The yield is based on isolated 5.

Table II. Electrolysis Conditions[a] of 5 and Yields of α-Methylene γ-Lactones 3

Substrate 5			Registry	Amt added,	Solvent and electrolyte H_2O,	Et_3N,	$LiClO_4 \cdot 3H_2O$,	Current density,	Electricity, Faradays/	Time,	Yield of 3,
R_1	R_2	R_3	no.	mmol	mL	mg	mg	mA/cm^2	mol	h	%
n-C_8H_{17}	H	H	65651-99-8	0.193	15	182	200	16–10	80	12	92[c]
–$(CH_2)_5$–		H	52978-85-0	0.178	10	109	200	13–10	42	4	82
H	–$(CH_2)_5$– (β,γ-cis)		3725-04-0	0.093	15	109	120	13–7	48	4	77[d]
H	–$(CH_2)_4$– (β,γ-trans)		3727-53-5	0.147	10	109	200	13–7	30	5	73[e]

[a] The electrolysis was carried out at 38–40 °C. [b] Applied voltages were adjusted at 3.2–3.5 V. [c] Diphenyl disulfide was also obtained in 91% yield. [d] Physical data are as follows: bp 70–73 °C (0.015 mm, Kugelrohr) (lit.[11] bp 60–70 °C (0.05 mm)); ^{13}C NMR ($CDCl_3$) δ_C 24.3 (t), 27.4 (t), 30.7 (t), 31.2 (t), 31.8 (t), 43.1 (d), 82.3 (d), 122.0 (t), 140.3 (s), 170.3 (s). [e] Physical data are as follows: bp 70–72 °C (0.015 mm, Kugelrohr) (lit.[11] 70 °C (0.01 mm)); ^{13}C NMR ($CDCl_3$) δ_C 24.1 (t), 24.9 (t), 25.8 (t), 30.5 (t), 48.9 (d), 83.1 (d), 117.1 (t), 139.6 (s), 170.6 (s).

(ppm) relative to Me_4Si as an internal standard. Elemental analyses were performed in our laboratory.

α-Ethoxycarbonyl-γ-*n*-octyl γ-lactone (6, R_1 = n-C_8H_{17}, R_2 = R_3 = H) was prepared by the reaction of ethyl sodiomalonate (3.8 mmol) with 1,2-epoxydecane (4 mmol) in dry EtOH (2 mL) at 70 °C for 12 h. After workup in the usual manner, there was obtained 770 mg (75%) of 6 (R_1 = n-C_8H_{17}, R_2 = R_3 = H): bp 88–90 °C (0.015 mm, Kugelrohr); IR (neat) 1780 (lactone), 1735 cm^{-1} (ester); ^{1}H NMR ($CDCl_3$) δ 0.88 (t, J = 5 Hz, 3, CH_3), 1.28 (t, J = 7 Hz, 3, CH_3), 1.30 (br s, 14, CH_2), 1.80–2.90 (m, 2, CH_2), 3.31–3.80 (m, 1, CH), 4.26 (q, J = 7 Hz, 2, CH_2), 4.00–4.80 (m, 1, CH–O). Anal. Calcd for $C_{15}H_{26}O_4$: C, 66.64; H, 9.69. Found: C, 66.42; H, 9.80.

α-Carboxy-γ-*n*-octyl γ-lactone (4, R_1 = n-C_8H_{17}, R_2 = R_3 = H) was obtained by hydrolysis of 6 (R_1 = n-C_8H_{17}, R_2 = R_3 = H, 2.64 mmol) with NaOH (5.5 mmol) in aqueous 20% EtOH at room temperature for 15 h in 95% yield as a white solid: mp 63.5–64.5 °C (lit.[9] mp 58–59 °C); IR (Nujol) 1775 (lactone), 1718 cm^{-1} (COOH); ^{1}H NMR ($CDCl_3$) δ 0.87 (t, 3, CH_3), 1.27 (br s, 14, CH_2), 1.90–2.90 (m, 2, CH_2), 3.50–3.87 (m, 1, CH), 4.14–4.80 (m, 1, CH–O), 6.87 (br s, 1, COOH).

Similarly, **α-carboxy-γ,γ-pentamethylene γ-lactone** (4) was obtained in 98% yield by hydrolysis of 6 (R_1, R_2 = –$(CH_2)_5$–, R_3 = H) with aqueous ethanolic NaOH: mp 135–136 °C (lit.[10] 136 °C); IR (Nujol) 1757 (lactone), 1716 cm^{-1} (COOH); ^{1}H NMR ($CDCl_3$) δ 1.62 (br s, 10, CH_2), 2.37 (d, J = 10 Hz, 2, CH_2), 3.75 (t, J = 10 Hz, 1, CH), 7.99 (br s, 1, COOH).

α-Carboxy-β,γ-*cis*-pentamethylene γ-lactone (4, R_2, R_3 = –$(CH_2)_5$–, R_1 = H) was prepared by the reaction of β,γ-*cis*-pentamethylene γ-lactone[11] (1.4 mmol) with excess CO_2 using i-Pr_2NLi (2.5 mmol) in dry THF (5 mL) at –40 °C for 30 min. After workup in the usual manner, there was obtained 267 mg (96%) of 4 (R_2, R_3 = –$(CH_2)_5$–, R_1 = H) as a pasty oil: IR (neat) 1780 (lactone), 1720 cm^{-1} (COOH); ^{1}H NMR ($CDCl_3$) δ 1.10–2.30 (m, 10, CH_2), 2.75–3.48 (m, 1, CH), 3.37 (d, J = 8 Hz, 1, CH), 4.74 (t, d, J = 8, 4 Hz, 1, CH), 9.14 (br s, 1, COOH). Anal. Calcd for $C_{10}H_{14}O_4$: C, 60; 59; H, 7.12. Found: C, 60.76; H, 7.22.

Similarly, **α-carboxy-β,γ-*trans*-tetramethylene γ-lactone**[13] (4, R_2, R_3 = –$(CH_2)_4$–, R_1 = H) was obtained in 97% yield from β,γ-*trans*-tetramethylene γ-lactone:[12] IR (neat) 1775 (lactone), 1720 cm^{-1} (COOH); ^{1}H NMR ($CDCl_3$) δ 1.10–2.60 (m, 9, CH_2, CH), 3.38 (d, J = 13 Hz, 1, CH), 2.60–3.50 (m, 1, CH–O), 9.52 (br s, 1, COOH).

α-Ethoxycarbonyl-α-ethoxycarbonylmethyl-γ-*n*-octyl γ-Lactone (8). To a mixture of EtONa (1.5 mmol) and 6 (R_1 = n-C_8H_{17}, R_2 = R_3 = H, 0.9 mmol) in dry EtOH (1.5 mL) $BrCH_2CO_2Et$ (1.2 mmol) was added. After stirring for 48 h at room temperature, the white slurry was quenched with cold water and taken up in ether–benzene (1:1). The organic layer was washed with brine, dried (Na_2SO_4), and concentrated. The residue was chromatographed (SiO_2, hexane–ether 4:1) to give 270 mg (84%) of 8: bp 136–138 °C (0.015 mm, Kugelrohr); IR (neat) 1775 (lactone), 1735 cm^{-1} (ester); ^{1}H NMR ($CDCl_3$) δ 0.90 (t, 3, CH_3), 1.27 (t, 6, CH_3), 1.30 (br s, 14, CH_2), 2.40–3.53 (m, 4, CH_2), 4.16 (q, 2, CH_2), 4.24 (q, 2, CH_2), 4.40–4.90 (m, 1, CH–O). Anal. Calcd for $C_{19}H_{32}O_6$: C, 64.02; H, 9.05. Found: C, 64.14; H, 9.10.

Similarly, **α-ethoxycarbonyl-α-ethoxycarbonylmethyl-γ,γ-pentamethylene γ-lactone** (9) was obtained in 82% yield by the reaction of 6 (R_1, R_2 = –$(CH_2)_5$–, R_3 = H) with $BrCH_2CO_2Et$: bp 103–104 °C (0.015 mm, Kugelrohr); IR (neat) 1768 (lactone), 1735 cm^{-1} (ester); ^{1}H NMR ($CDCl_3$) δ 1.25 (t, 3, CH_3), 1.28 (t, 3, CH_3), 1.20–2.10 (m, 10, CH_2), 2.59 (ABq, J = 14 Hz, 2, CH_2), 3.05 (ABq, J = 18 Hz, 2, CH_2), 4.02 (q, 2, CH_2), 4.27 (q, 2, CH_2). Anal. Calcd for $C_{16}H_{24}O_6$: C, 61.52; H, 7.74. Found: C, 61.71; H, 7.89.

α-Carboxymethyl-γ-*n*-octyl γ-Lactone (1, R_1 = n-C_8H_{17}, R_2 = R_3 = H). A mixture of 8 (300 mg, 0.84 mmol), aqueous 48% HBr (3 mL), and AcOH (6 mL) was stirred at 130 °C for 10 h. The volatile materials were rotoevaporated and the residue was recrystallized from benzene to give 162 mg (75%) of 1 (R_1 = n-C_8H_{17}, R_2 = R_3 = H): mp 91–92 °C; IR (Nujol) 1780 (lactone), 1705 cm^{-1} (COOH); ^{1}H NMR ($CDCl_3$) δ 0.87 (t, 3, CH_3), 1.28 (br s, 14, CH_2), 1.98–2.30 (m, 4, CH_2), 4.10–4.70 (m, 1, CH–O), 9.05 (br s, 1, COOH). Anal. Calcd for $C_{14}H_{24}O_4$: C, 65.60; H, 9.44. Found: C, 65.80; H, 9.51.

Similarly, **α-carboxymethyl-γ,γ-pentamethylene γ-lactone (1, R_1, R_2 = –$(CH_2)_5$–, R_3 = H)** was obtained in 77% yield by hydrolysis of 9 with aqueous 48% HBr: mp 133.5–134.5 °C; IR (Nujol) 1764 (lactone), 1730 cm^{-1} (COOH); ^{1}H NMR ($CDCl_3$) δ 1.64 (br s, 10, CH_2), 2.26–3.30 (m, 5, CH_2, CH), 9.30 (br s, 1, COOH). Anal. Calcd for $C_{11}H_{16}O_4$: C, 62.25; H, 7.60. Found: C, 62.27; H, 7.59.

Electrolysis apparatus used for the electrolysis of 1 and 5 is outlined in Figure 1. A simple undivided cell, 2 cm in diameter and 10 cm high, fitted with a gas lead pipe, a thermometer, a magnetic stirrer bar, and too smooth platinum electrodes (1.5 × 2 cm^2), being placed parallel to each other 5 mm apart was used.

Electrochemical Synthesis of 3 from 1 in a Homogenious Pyridine–Water Solution. A stirred solution of 1 (R_1 = n-C_8H_{17}, R_2 = R_3 = H, 150 mg, 0.6 mmol), Et_3N (0.3 mL), and water (1.0 mL) in pyridine (9.0 mL) was electrolyzed in a beaker (35 mL) fitted with platinum electrodes (3 cm^2) at 50–60 V (0.01–0.06 mA/cm^2) at 32–39 °C for 5 h. The reaction mixture was acidified with cold aqueous 10% tartaric acid and extracted with ether–benzene (1:1). The organic layer was washed with brine, dried (Na_2SO_4), and concentrated. The resi-

due was chromatographed (SiO_2, hexane–ether 4:1) to give 38 mg (30%) of **3** ($R_1 = n\text{-}C_8H_{17}$, $R_2 = R_3 = H$) as an oil: bp 98 °C (0.015 mm, Kugelrohr); IR (neat) 1768 (lactone), 1666 cm^{-1} (C=C); ^1H NMR ($CDCl_3$) δ 0.87 (t, 3, CH_3), 1.29 (br s, 14, CH_2), 2.27–3.32 (m, 2, CH_2), 4.49 (q, J = 7 Hz, 1, CH–O), 5.59 (t, J = 3 Hz, 1, HC=C), 6.18 (t, J = 3 Hz, 1, HC=C); ^{13}C NMR ($CDCl_3$) δ_C 14.1 (q), 22.7 (t), 29.2 (t, 2), 29.3 (t), 29.4 (t), 31.8 (t), 33.6 (t), 36.3 (t), 77.6 (d), 121.8 (t), 134.7 (s), 170.3 (s). Anal. Calcd for $C_{13}H_{22}O_2$: C, 72.24; H, 10.54. Found: C, 72.39; H, 10.48.

α-Methylene-γ,γ-pentamethylene γ-lactone[2d] (**3**, R_1, R_2 = $-(CH_2)_5-$, R_3 = H) was obtained in 35% yield by the electrolysis of **1** (R_1, R_2 = $-(CH_2)_5-$, R_3 = H) in the same manner as described in the preceding experiment: bp 73 °C (0.02 mm, Kugelrohr); IR (neat) 1762 (lactone), 1663 cm^{-1} (C=C); ^1H NMR ($CDCl_3$) δ 1.73 (br s, 10, CH_2), 2.74 (t, J = 3 Hz, 2, CH_2), 5.45 (t, J = 3 Hz, 1, HC=C), 6.06 (t, J = 3 Hz, 1, HC=C); ^{13}C NMR ($CDCl_3$) δ_C 22.5 (t, 2), 24.8 (t), 37.5 (t, 3), 36.6 (t), 38.4 (s), 122.1 (t), 135.5 (s), 169.9 (s).

α-Carboxy-α-phenylthiomethyl-γ-*n*-octyl γ-Lactone (**5**, R_1 = $n\text{-}C_8H_{17}$, $R_2 = R_3$ = H). To a cooled (−70 °C) solution of $i\text{-}Pr_2NLi$ (161 mg, 1.50 mmol) in dry THF (1.0 mL) was added dropwise a solution of **4** ($R_1 = n\text{-}C_8H_{17}$, $R_2 = R_3$ = H, 122 mg, 0.5 mmol) in dry THF (1.5 mL). After stirring for 15 min at −70 °C, the dry ice bath was removed and the mixture was allowed to stand for several minutes until the temperature reached 0 °C. Then, to the mixture cooled with an ice–water bath at 0 °C, a solution of freshly prepared phenylthiomethyl iodide[14] (254 mg, 1.02 mmol) in dry THF (1.5 mL) was added dropwise with stirring and the mixture was stirred for 3 h. The mixture was quenched with cold water and acidified with cold aqueous 10% HCl. The organic phase was separated and the aqueous phase was extracted with CH_2Cl_2. The combined extracts were washed with cold brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was chromatographed (SiO_2, hexane–AcOEt 2:1) to give 172 mg (94%) of **5** ($R_1 = n\text{-}C_8H_{17}$, $R_2 = R_3$ = H) as a pasty oil.

Physical constants together with elemental analyses of the analogous compounds **5** prepared from the corresponding γ-lactone-α-carboxylic acids **4** are shown in Table I.

A General Procedure for Electrochemical Synthesis of 3 from 5 in a Two-Layer System. A stirred solution of **5** ($R_1 = n\text{-}C_8H_{17}$, $R_2 = R_3$ = H, 69 mg, 0.19 mmol), $LiClO_4 \cdot 3H_2O$ (1.3 mmol), and Et_3N (1.8 mmol) in water, being covered with 5 mL of ether and benzene (3:2), was electrolyzed in a beaker fitted with platinum electrodes (3 cm^2) at a constant applied voltage of 3.5 V (ca. 1.4 V vs. SCE), current density 10–16 mA/cm^2, for 12 h (ca. 80 Faradays/mol). The organic phase that separated was washed with brine and dried (Na_2SO_4). Removal of the solvent and the following chromatography (SiO_2, hexane–ether 4:1) of the residue gave 37 mg (92%) of **3** ($R_1 = n\text{-}C_8H_{17}$, $R_2 = R_3$ = H) as an oil. The electrolysis conditions of **5** as well as the yield of the α-methylene γ-lactone **3** are shown in Table II.

Registry No.—**1** ($R_1 = n\text{-}C_8H_{17}$; $R_2 = R_3$ = H), 65652-01-9; **1** (R_1, R_2 = $(CH_2)_5$; R_3 = H), 65652-02-0; **4** ($R_1 = n\text{-}C_8H_{17}$; $R_2 = R_3$ = H), 65652-03-1; **4** (R_1, R_2 = $(CH_2)_5$; R_3 = H), 65652-04-2; **4** (R_2, R_3 = $(CH_2)_5$; R_1 = H), 65652-05-3; **4** (R_2, R_3 = $(CH_2)_4$; R_1 = H), 4354-68-1; **6** ($R_1 = n\text{-}C_8H_{17}$; $R_2 = R_3$ = H), 14872-59-4; **6** (R_1, R_2 = $(CH_2)_5$; R_3 = H), 58022-89-2; **8**, 65701-65-7; **9**, 65652-06-4; ethyl sodiomalonate, 996-82-7; 1,2-epoxydecane, 2404-44-6; β,γ-*cis*-pentamethylene γ-lactone, 3724-99-0; β,γ-*trans*-tetramethylene γ-lactone, 34905-87-8.

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A Convenient Preparation of 2-Substituted Benzothiazoles[1]

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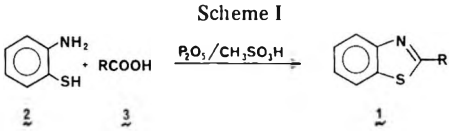
The availability of 2-substituted benzothiazoles (**1**) depends on preparative routes in which the fused thiazole ring is constructed from acyclic reactants.[2] Since many compounds containing this heterocyclic nucleus are of industrial[3] or biological[4] interest, methods for the preparation of 2-substituted benzothiazoles have been extensively studied.[2] Recently we have become interested in benzothiazoles as synthetically useful units[5] and required a broad and facile entry to this ring system.

Though in principle the direct condensation of 2-aminothiophenol (**2**) with the appropriate carboxylic acid (**3**) provides the most direct route to the 2-substituted benzothiazoles (**1**), in practice this direct route has been difficult to carry out conveniently in the laboratory.[6] Generally a reactive carboxylic acid derivative, e.g., an acid chloride,[2] acid anhydride,[2] imino ester,[2] or *N*-ethoxycarbonylthioamide,[7] has been employed, and obviously this method requires an extra step. Although polyphosphoric acid (PPA)[8] and more recently polyphosphate ester (PPE)[9] have been employed for the direct condensation of carboxylic acids with 2-aminothiophenol, both methods afford variable yields of the 2-substituted benzothiazoles (**1**) and the former requires high reaction temperatures (ca. 200 °C).

We would like to report that 2-substituted benzothiazoles (**1**) are obtainable directly from 2-aminothiophenol (**2**) and the corresponding carboxylic acid (**3**) by treatment with P_2O_5/CH_3SO_3H (1/10, w/w)[10] and warming (Scheme I). The reaction as illustrated by the examples in Table I is generally effective for a wide range of aliphatic and aromatic carboxylic acids. The general procedure involves treating a mixture of P_2O_5/CH_3SO_3H (1/10, w/w) and **2** (ratio of 1.5 g/1.0 mmol) with 1 equiv of the required carboxylic acid and warming for ca. 10 h followed by aqueous basic workup.

The reaction does not appear to be useful for α,β-unsaturated carboxylic acids. Whereas 2-styrylbenzothiazole (**1j**) was obtained in 57% from *trans*-cinnamic acid and **2**, less than 20% of 2-(2-methylpropenyl)benzothiazole (**1k**) was obtained from 3,3-dimethylacrylic acid and **2** under the described conditions. Furthermore, the α-trialkylated carboxylic acid, pivalic acid

Scheme I



2 **3** **1**

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Table I
Preparation of 2-Substituted Benzothiazoles (1) from 2-Aminothiophenol (2) and Carboxylic Acids (3)

Entry	R	Reaction time (temp, °C)	Yield,[a] %
a	CH_3	1 h (25) 10 h (70)	93[b]
b	$CH_3(CH_2)_5$	1 h (25) 10 h (75–80)	96[c]
c	$PhCH_2$	1 h (25) 10 h (75)	89[c]
d	3-Pyridyl-CH_2	1 h (25) 10 h (75–80)	86[d]
e	Cyclohexyl	1 h (25) 10.5 h (80–85)	88[e]
f	$(CH_3)_2CH$	15 h (25) 8 h (70)	74[c]
g	3-$MeOC_6H_4$	1 h (25) 10 h (95)	85[f]
h	4-ClC_6H_4	10 min (25) 17.5 h (90–95)	83[g]
i	2-Furyl	1 h (25) 10 h (75–80)	84[h]
j	PhCH=CH	1 h (25)[i] 10 h (55)	57[j]
k	$(CH_3)_2C$=CH	1 h (25) 10 h (55)	19[k]
l	$(CH_3)_3C$	1 h (25)[l] 10 h (75–80)	<10

[a] Yield after purification by column chromatography (SiO_2). All products exhibited the reported or expected ^{1}H-NMR, IR, mass spectral characteristics and were identical in all respects to authentic material (when available). [b] Identical in all respects to distilled commercial material (Aldrich). [c] For previous characterization see J. Metzger and H. Plank, *Bull. Soc. Chim. Fr.*, 1692 (1956); R. Guglielmetti, E. J. Vincent, J. Metzger, J. Berger, and R. Garnier, *ibid.*, 4195 (1967). [d] For preparation of authentic material see ref 4a. [e] For preparation of authentic material see ref 5. [f] Mp 81–82 °C (lit. mp 82–83 °C): F. A. Babiehev, L. A. Kirpianova, and T. A. Dashevskaya, *Urk. Khim. Zh. (Russ. Ed.)*, **32**, 706 (1966); *Chem. Abstr.*, **65**, 13682a (1966). [g] Mp 115–116 °C (lit.[4c] mp 117–118 °C). [h] Mp 103–104.5 °C (lit. mp 105 °C): M. T. Bogert and A. Stull, *J. Am. Chem. Soc.*, **47**, 3078 (1925). [i] Weight (g) of P_2O_5/CH_3SO_3H (1/10, w/w): mmol substrate was 2:1. [j] Mp 110–111 °C (lit. mp 112 °C): D. M. Brown and G. A. R. Kon, *J. Chem. Soc.*, 2147 (1948). [k] Mp 78–80 °C (lit. mp 81–82 °C): E. B. Knott, *ibid.*, 3793 (1965). [l] Evolution of gas evident, presumably CO and isobutylene.

(**3l**), appears to decarbonylate under the reaction conditions (evolution of gas).

The ease with which the reagent P_2O_5/CH_3SO_3H (1/10, w/w) may be handled, especially on large preparative scales, is particularly noteworthy.[10] This fact coupled with the reagent's ability to promote the direct condensation of a wide range of carboxylic acids (**3**) with 2-aminothiophenol (**2**) in high yields makes this procedure a particularly convenient and attractive method for the direct preparation of 2-substituted benzothiazoles when compared to related direct condensation methods.[2,6,8,9]

Experimental Section[11]

Preparation of 2-Substituted Benzothiazoles. The General Procedure is Illustrated with 2-Methylbenzothiazole (1a). A 4.5-g solution of P_2O_5/CH_3SO_3H (1/10, w/w)[10] was treated sequentially with 2-aminothiophenol (3.0 mmol, 376 mg) and acetic acid (3.0 mmol, 180 mg). The resulting solution was stoppered and magnetically stirred at 25 (1 h) and 70 °C (10 h). After cooling, the solution was slowly added to ca. 50–75 mL of aqueous 5% $NaHCO_3$[12] and the resulting solution was made basic to pH paper by the addition of aqueous 10% NaOH. Extraction of the aqueous phase ($CHCl_3$) followed by drying of the combined organic phases ($MgSO_4$) and evaporation of the solvent in vacuo afforded the crude product as a yellow oil. Chromatography (20 g SiO_2, 20 × 1.5 cm, CH_2Cl_2 to 20% Et_2O: CH_2Cl_2 gradient elution) afforded 415 mg (447 theoretical, 93%) of pure 2-methylbenzothiazole (**1a**), as a colorless liquid identical in all respects with distilled authentic material (Aldrich).

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Registry No.—**1a**, 120-75-2; **1b**, 65718-88-9; **1c**, 6265-94-7; **1d**, 33928-36-8; **1e**, 40115-03-5; **1f**, 17626-86-7; **1g**, 10002-44-5; **1h**, 6265-91-4; **1i**, 1569-98-8; **1j**, 1483-30-3; **1k**, 1628-61-1; **1l**, 17626-88-9; **2**, 137-07-5; **3a**, 64-19-7; **3b**, 111-14-8; **3c**, 103-82-2; **3d**, 501-81-5; **3e**, 98-89-5; **3f**, 79-31-2; **3g**, 586-38-9; **3h**, 74-11-3; **3i**, 88-14-2; **3j**, 140-10-3; **3k**, 541-47-9; **3l**, 75-98-9.

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(11) Melting points are uncorrected. Infrared spectra (IR) were obtained in $CHCl_3$ for solids or as neat films for liquids and recorded on a Perkin-Elmer 267 spectrophotometer. ^{1}H-NMR spectra were obtained on a Varian A-60 or CFT-20/HFT-80 spectrophotometer in $CDCl_3$ with tetramethylsilane as an internal standard. Mass spectra were recorded on an AEI-MS9 spectrophotometer at 70 eV.
(12) When working on large preparative scales workup is facilitated by pouring directly onto aqueous 10% NaOH.

Photoreaction of Hexafluorobenzene with Cyclohexane: Evidence for Substitution and Addition Mechanism

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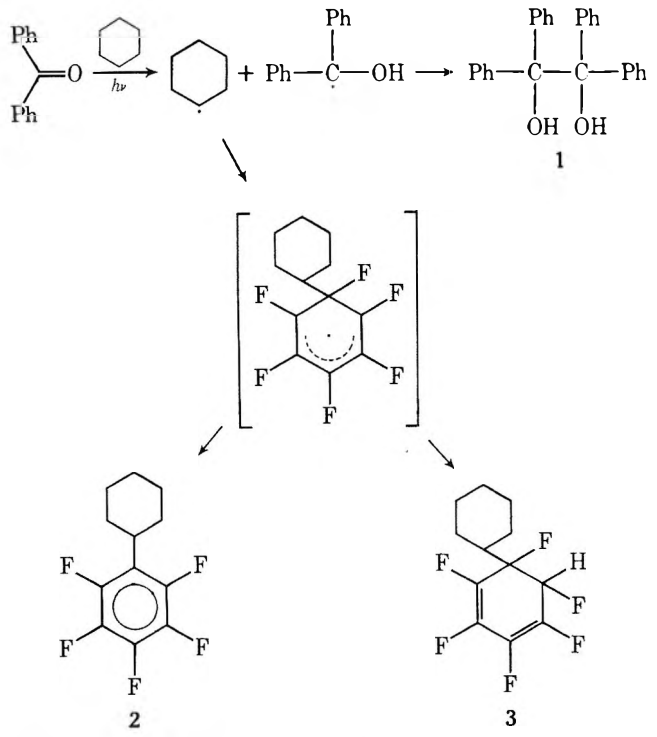
Light-induced substitution reactions of aryl fluorides have been recently reviewed.[1] Bryce-Smith and co-workers[2] have recently observed cine-substitution by nucleophilic substitution of fluorobenzene and difluorobenzenes with primary and secondary amines and found evidence for the addition–elimination mechanism. Irradiation of solutions of hexafluorobenzene in cyclohexane and cyclooctane gives hydrogen fluoride and a complex mixture containing cyclohexylpentafluorobenzene and other radical coupling products.[3]

0022-3263/78/1943-2297$01.00/0

Scheme I



We now report that 24-h irradiation of a solution of hexafluorobenzene in cyclohexane in the presence of benzophenone with λ 300–350 nm at T = 25 °C leads to the formation of three products. A white crystalline product, which precipitated from solution and was filtered off, was easily recognized as 1,1,2,2-tetraphenyl-1,2-dihydroxyethane (**1**). The filtrate was evaporated in vacuo and the crude reaction mixture was analyzed by ^{19}F-NMR spectroscopy and separated by preparative TLC. The main product formed (**2**, 61%, mp 43–44 °C) shows in its ^{19}F spectrum three signals: δ_F −148.5 (2 F, dd), −165.0 (1 F, t), −169.5 (2 F, td), with the coupling constants 24 and 9 Hz; in its mass spectrum it shows the following fragments *m/e* 250 (M^+, 53, calcd for $C_{12}F_5H_{11}$ *m/e* 250.0781, found *m/e* 250.0780), 208 (9), 195 (9), 194 (100), 181 (31). From the spectroscopic data we established that cyclohexylpentafluorobenzene was formed. The minor product (**3**, 23%, oil product) formed shows in its ^{19}F-NMR spectrum six multiplets: δ_F −146.25 (dm), 146.85 (dd), −152.25 (dm), −153.75 (dm), −164.25 (dm), and −170.25 (ddm) with the following coupling constants $^2J_{F2,H}$ = 60 Hz, $^3J_{F1,F2}$ = 21 Hz and $^3J_{F3,F4}$ = $^3J_{F5,F6}$ = 24 Hz. Product **3** was converted by heating to product **2**. Product **3** shows in its mass spectrum the following fragments: *m/e* 250 (M^+ − HF, 52%, calcd for $C_{12}H_{11}F_5$ *m/e* 250.0781, found *m/e* 250.0785), 194 (100), 183 (90), 182 (60), 121 (44), 82 (36). On the basis of the spectroscopic data and chemical transformations, we established the structure of the product **3** as 1-cyclohexyl-1,2,3,4,5,6-hexafluoro-3,5-cyclohexadiene.

Reduction of the irradiation time from 24 to 6 h or prolongation to 60 h affected only the overall yield of the products but not the ratio of the substitution and addition products (**2**/**3** = 3:2, determined by ^{19}F NMR), which reduced the possibility of the formation of substitution product (**2**) by photoelimination of **3**, as was suggested by photonucleophilic substitution reactions of fluorobenzene and difluorobenzenes.[2] On the basis of the above mentioned observations, the mechanism presented in Scheme I is suggested. In the presence of benzophenone a cyclohexyl radical is formed, which then reacts with hexafluorobenzene forming radical species A, transforming by two different paths to **2** and **3**.

Being interested in the effect of ring magnitude of the cycloalkene on photosubstitution and addition reactions, we also studied the reactions with cyclopentane and cycloheptane. The reaction with cyclopentane resulted in the formation of 1-cyclopentylpentafluorobenzene in very low yield (2%) and greater amounts of 1,1,2,2-tetraphenyl-1,2-dihydroxyethane and cyclopentylcyclopentane, while the reaction with cycloheptane under the conditions mentioned above failed. Photosubstitution reactions with some *n*-alkanes, i.e., *n*-hexane and *n*-heptane, also did not occur.

It is known that free-radical substitutions with fluorosubstituted aromatic molecules occur readily using aryl radicals, and extensive studies have been made using diaryl peroxides as the source of these radicals.[4] Arylation of pentafluorobenzene does indeed occur using dibenzoyl peroxide, but $(C_6F_5COO)_2$ gives only tar.[5] The thermal reaction (T = 70 °C) of hexafluorobenzene in cyclohexane solution in the presence of dibenzoyl peroxide did not result in the formation of cyclohexylpentafluorobenzene (**2**) or 1-cyclohexyl-1,2,3,4,5,6-hexafluoro-3,5-cyclohexadiene (**3**) as in the case of the photoinitiated reaction but only polymeric material was isolated.

Experimental Section

Irradiation was carried out in a Rayonet Photochemical Chamber, Reactor Model RPR-100, with RPR 253.7 nm, RPR 300 nm, and RPR 350 nm lamps. IR spectra were recorded by using a Perkin-Elmer 257 spectrometer, ^{1}H- and ^{19}F-NMR spectra were determined by a Jeol JNM-PS-100 from CCl_4 solution with Me_4Si and CCl_3F as internal standards, and mass spectra were recorded on a CEC 21-110 spectrometer. Melting points were determined on a Kofler apparatus and are uncorrected. Gas liquid partition chromatography was carried out on a Varian Aerograph Model 1800 and preparative TLC on Merck-PSC-Fertigplatten Kieselgel F 254.

Materials. The hexafluorobenzene and benzophenone were obtained from commercial sources and purified to conform with published physical and spectral data. Solvents were purified by literature methods[6] and stored over molecular sieves.

Irradiation of Hexafluorobenzene. Hexafluorobenzene (1 mmol, 186 mg) and 2 mmol (364 mg) of benzophenone were dissolved in 18 mL of cyclohexane. The solution was irradiated at room temperature for 24 h with 300- or 350-nm lamps. 1,1,2,2-Tetraphenyl-1,2-dihydroxyethane was filtered off and the solvent was evaporated in vacuo. The reaction mixture was analyzed by NMR and the products were separated by preparative TLC and 153 mg (61%) of cyclohexylpentafluorobenzene (**2**, mp 43–44 °C) and 63 mg (23%, liquid product) of 1-cyclohexyl-1,2,3,4,5,6-hexafluorocyclo-3,5-hexadiene (**3**) were isolated. Mass spectrum of the product **2**, calcd for $C_{12}F_5H_{11}$ *m/e* 250.0781, found *m/e* 250.0780, *m/e* 250 (M^+, 53), 208 (9), 195 (9), 194 (100), 181 (31); NMR spectrum δ_{F_2,F_6} −148.5 (dd, $J_{F,F}$ = 24, 9 Hz), δ_{F_3,F_5} −169.5 (td, $J_{F,F}$ = 24, 9 Hz), δ_{F_4} −165 (t, $J_{F,F}$ = 24 Hz). Mass spectrum of the product *3*, calcd for $C_{12}F_6H_{12}HF$ *m/e* 250.0781, found *m/e* 250.0785, *m/e* 250 (M^+ − HF, 52), 194 (100), 183 (90), 182 (60), 121 (44), 82 (36); NMR spectrum δ_{F_1} −164.25 (dm, $^3J_{F_1,F_2}$ = 21 Hz), δ_{F_2} = −170.25 (ddm, $^2J_{F,H}$ = 60 Hz, $^3J_{F_1,F_2}$ = 21 Hz), δ_F −152.25 (dm), −153.75 (dm), −146.25 (dm), −146.85 (dd), δ_{CFH} 4.63 (dm, 1 H), δ_{CH} 2.72 (m, 1 H), δ_{CH_2} 1.06–1.94 (m, 10 H).

On heating at T = 150 °C, product **3** was transformed into product **2**. The separation of the crude reaction mixture formed by irradiation by preparative GLC (FFAP 30% on Chromosorb AW at T = 200 °C) gave only cyclohexylpentafluorobenzene.

Irradiation of hexafluorobenzene and benzophenone in cyclopentane gave, after GLC separation (FFAP 30% on Chromosorb AW at T = 170 °C), 2% of cyclopentylpentafluorobenzene (liquid product). Mass spectrum, calcd for $C_{11}F_5H_9$ *m/e* 236.0624, found *m/e* 236.0630, *m/e* 236 (M^+, 4), 139 (30), 123 (39), 85 (39), 84 (47), 69 (30), 67 (62), 41 (100); NMR spectrum δ_{F_2,F_6} −145.5 (dd, $J_{F,F}$ = 24, 9 Hz), $\delta_{F_3,F_5-165.75}$ (td, $J_{F,F}$ = 24, 9 Hz), δ_{F_4} −152.25.

References and Notes

(1) J. Cornelisse and E. Havinga, *Chem. Rev.*, **75**, 353 (1975).
(2) D. Bryce-Smith, A. Gilbert, and S. Krestonosich, *J. Chem. Soc., Chem. Commun.*, 405 (1976).
(3) D. Bryce-Smith, B. E. Connett, A. Golbert, and E. Kendrick, *Chem. Ind. (London)*, 855 (1966).
(4) R. D. Chambers, "Fluorine in Organic Chemistry", Wiley, New York, N.Y., 1973, p 313; W. A. Sheppard and C. M. Sharts, "Organic Fluorine Chemistry", W. A. Benjamin, New York, N.Y., 1969, p 200.
(5) P. A. Claret, G. H. Williams, and J. Coulson, *J. Chem. Soc. C*, 341 (1968);

G. H. Williams, *Intra-Sci. Chem. Rep.*, **3**, 229 (1969); P. H. Oldham, G. H. Williams, and B. A. Wilson, *J. Chem. Soc. B*, 1346 (1970).
(6) A. Weissberger, Ed., "Technique of Organic Chemistry", Vol. VII, Interscience, New York, N.Y., 1955.

Registry No.—**2**, 10304-79-7; **3**, 65915-27-7; hexafluorobenzene, 392-56-3; cyclohexane, 110-82-7.

Sodium Borohydride in Acetic Acid. A Convenient System for the Reductive Deoxygenation of Carbonyl Tosylhydrazones

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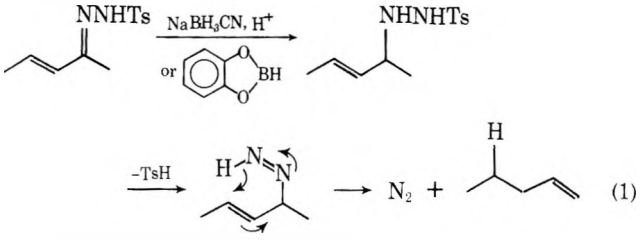
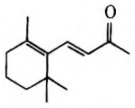
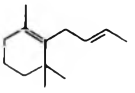
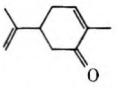
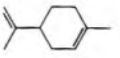
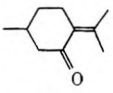
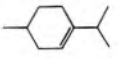
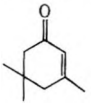
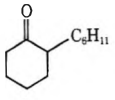
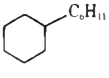
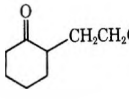
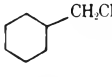
The reductions of carbonyl tosylhydrazones to hydrocarbons with sodium cyanoborohydride in acidic media[1] or with catecholborane[2] provide mild and selective alternatives to standard Wolf–Kishner deoxygenation.[1,2] With α,β-unsaturated derivatives, alkenes are usually furnished in which the double bond migrates to the position formerly occupied by the carbonyl (eq 1) even when such movement produces less thermodynamically stable positional isomers. Thus, alkene linkages may be moved from conjugation with aromatic rings or other π systems and the procedures offer a convenient pathway to exocyclic olefins.[1,2] The mechanism for this intriguing "alkene walk" reaction apparently proceeds through a diazene intermediate which deposits a hydride via a 1,5 migration as illustrated in eq 1.



(1)

The full synthetic potential of the methods are, however, hampered by the relative expense of both hydride reagents,

Table I. Reductive Deoxygenation of Tosylhydrazones with Sodium Borohydride–Acetic Acid

Tosylhydrazone	Registry no.	Method[a]	Time at 70 °C, h	Product	Registry no.	% yield isolated
	21195-61-9	A	2.5		13066-63-2	87
		B	1.0			89
		C	2.5			52
		B[b]	3.0			81
	41780-85-2	A	2.0		1003-64-1	72
		B	1.0			61
	21195-60-8	A	2.0		138-86-3	10
		B	1.5			70
	21195-64-2	B	1.5		500-00-5	51
	65226-90-6	B	4.0		1712-47-6	67
	65226-92-8	B	3.0		65226-94-0	57
	21195-62-0	B	5.0		503-44-6	18
$C_6H_5CH{=}CHCHO$	7318-33-4	A	1.5	$C_6H_5CH_2CH{=}CH_2$	300-57-2	42
		B	1.5			56
$C_6H_5CH{=}CHCOCH_3$	17336-65-1	B	3.0	$C_6H_5CH_2CH{=}CHCH_3$	1560-06-1	54
$CH_3(CH_2)_4CO(CH_2)_4CH_3$	65930-66-7	A	1.5	$CH_3(CH_2)_9CH_3$	1120-21-4	81
		B	1.5			84
	41780-66-9	A	2.0		92-51-3	61
		B	2.0			61
	13992-91-1	A	2.0		41010-09-7	68
		B	2.0			70
$o\text{-}OC_2H_5C_6H_4CHO$	65609-76-9	A	2.0	$o\text{-}OC_2H_5C_6H_4CH_3$	614-71-1	44
		B	3.0			80
$C_6H_5CO(CH_2)_2CH_3$	41780-81-8	B	4.0	$C_6H_5(CH_2)_3CH_3$	104-51-8	68

[a] Method C involved preparation and utilization of $NaBH(OAc)_3$ in benzene as described in ref 7f; this procedure appears inferior for the present application. [b] The tosylhydrazone prepared in situ in acetic acid from the ketone and tosylhydrazone followed by addition of $NaBH_4$.

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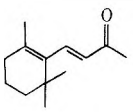
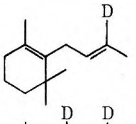
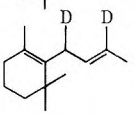
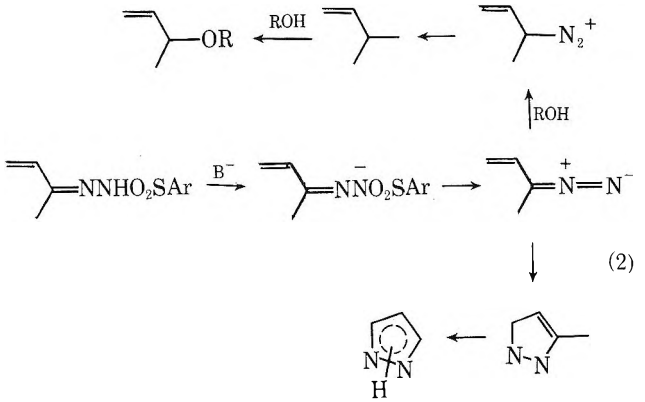
Table II. Deuterium Incorporation in the Reductive Deoxygenation of Tosylhydrazones

Tosylhydrazone	Method	Time at 70 °C, h	Product	Registry no.	% yield isolated
	A: $NaBD_4$, HOAc	1.5		16940-66-2	75
	D:[a] $NaBD_4$, DOAc	1.5		64-19-7	81
$C_6H_5CO(CH_2)_2CH_3$	A:[b] $NaBD_4$, HOAc	4.0	$C_6H_5CHD(CH_2)_2CH_3$	15681-89-7	60
	E:[c] $NaBD_4$, DOAc	4.0	$C_6H_5CD_2(CH_2)_2CH_3$	758-12-3	72

[a] Method D: the deuteride reagent (12.5 mmol) was dissolved in 10 mL of HOAc or DOAc and added to a slurry of 5 mmol of the tosylhydrazone in 10 mL of HOAc or DOAc. The solution was stirred at room temperature for 1 h and at 70 °C for 1.5 h and worked up as in method A. [b] A fivefold excess of $NaBD_4$ was used. [c] Method E: same as method D, fivefold excess of $NaBD_4$.

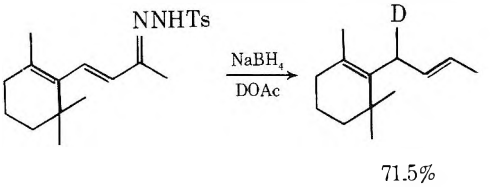
the relative inconvenience of handling moisture-sensitive catecholborane, at least for large scale and/or industrial applications, and the reluctance of $NaBH_3CN$ to attack aryl[3] and cyclic enone derivatives. Unfortunately, although $NaBH_4$ in the usual solvents (CH_3OH, C_2H_5OH, THF) reduces saturated tosylhydrazones to hydrocarbons,[4] the application to α,β-unsaturated cases fails, leading instead to allylic ethers and/or pyrazoles in alcohol solvents.[5] These divergent pathways have been attributed by Pagnoni and co-workers[5] to a decreased electrophilicity of conjugated imine π bonds which allows initial abstraction of the acidic N–H proton by the basic BH_4^- followed by elimination to a diazo ketone and subsequent conversion to ethers or pyrazoles as presented in eq 2.



(2)

The recent disclosures and exploitation of the utility of $NaBH_4$ in carboxylic acid solvents[7] suggested the possible advantage of this reagent system to circumvent the problems associated with conjugated (and aryl) tosylhydrazones. Thus, protonation of the imine nitrogen should increase the rate of nucleophilic attack while, concomitantly, preventing production of the offending tosylhydrazone anion.

This report presents the successful realization of the use of $NaBH_4$ in acetic acid as a convenient and relatively inexpensive alternative method for the reductive deoxygenation of most types of tosylhydrazones, including α,β-unsaturated and aryl cases. General experimental procedures have been developed for successful conversion of structural varieties, dependent upon the ease or reluctance of reduction. For unhindered aliphatic and several unsaturated systems, the procedure (method A) involves dissolving a 2.5 mol excess of $NaBH_4$ (conveniently handled in the pellet form) in glacial acetic acid (ca. 1.4 mL/mmol $NaBH_4$) while keeping the temperature between ca. 15 and 20 °C with an ice bath. To this solution (probably $NaBH(OAc)_3$)[7] is added the tosylhydrazone and the mixture is stirred at ambient temperature for 1 h and then at 70 °C for 1–4 h to complete the reduction. Workup is accomplished by pouring the solution into crushed ice, adjustment of the pH to ca. 9 with aqueous NaOH, and extraction with pentane or hexane. Evaporation and distillation (or recrystallization) provide the product hydrocarbon. For less electrophilic tosylhydrazones (aromatic and certain conjugated derivatives), a more vigorous procedure was required for adequate conversions (method B). Thus, the tosylhydrazone is slurried in glacial acetic acid (ca. 3.5 mL/mmol tosylhydrazone) and a 10 mol excess of $NaBH_4$ pellets is added at such a rate that foaming does not become an inconvenience. After addition, the solution is stirred at ambient temperature for 1 h and then at 70 °C for 1–4 h; workup is accomplished as in method A. Although the above procedures have not been completely optimized, we have found no need for an inert atmosphere, only adequate ventilation for hydrogen generated in the reaction. The results for a variety of structural types are presented in Table I and illustrate the versatility of the systems. The convenience and relative inexpense of the reagent suggest considerable utility for such transformations, especially on large scale. Furthermore, use of $NaBD_4$ in CH_3COOH or CH_3COOD allows the regioselective introduction of one or two deuterium atoms, respectively (i.e., eq 3 and Table II),



(3)

71.5%

thus augmenting applications of the procedure. With CH_3COOD, exchange of the tosylhydrazone N–H proton evidently is faster than reduction and hydride transfer to carbon.

A limitation was encountered involving isophorone tosylhydrazone which furnished only 18% of the desired rearranged alkene. Apparently, steric encumbrance to situating the required pseudoaxial diazene link over the ring (containing a pseudoaxial methyl) for hydride deliverance interupts the mechanism and allows other, unknown reactions to compete. Furthermore, nitro groups do not always survive the reaction conditions. Thus, *p*-nitrobenzaldehyde tosylhydrazone afforded a complex mixture of unidentified products and essentially no *p*-nitrotoluene.[8]

Experimental Section

Materials. $NaBH_4$ in pellet form was supplied by Alfa Inorganics (Ventron Corp.) and used as received. $NaBD_4$ (98% D) was obtained from Merck & Co., Inc. The carbonyl tosylhydrazones were prepared as previously described.[1a,b,2d] Drying of organic solvents was accomplished with anhydrous Na_2SO_4.

Tosylhydrazone Reductions. The general reduction procedures are described in the text and Table II. The following representative

descriptions are provided for each method.

Method A. A solution of $NaBH(OAc)_3$ was prepared by dissolving $NaBH_4$ pellets (25 mmol, 945 mg, 4 pellets) in glacial acetic acid (35 mL) with ice-bath cooling such that the temperature was maintained between 15 and 20 °C. To this was added β-ionone tosylhydrazone[1b] (3.60 g, 10 mmol) and the mixture was stirred at ambient temperature for 1 h followed by 2.5 h at 70 °C. The solution was then poured into crushed ice, made basic with aqueous NaOH, and extracted with three portions of pentane. The pentane solution was dried and concentrated on a rotary evaporator and the residue was carefully distilled at reduced pressure (Kugelrohr apparatus) to obtain 1.66 g (87%) of diene product, identical in all respects with an authentic sample.[1b]

Method B. To a stirred slurry of 6-undecanone tosylhydrazone (5.08 g, 15 mmol) in 50 mL of glacial acetic acid was added $NaBH_4$ pellets (ca. 5.67 g, 150 mmol, 24 pellets) at such a rate that foaming was not a problem (ca. 1 h). The solution was stirred at room temperature for 1 h and then at 70 °C for 1.5 h and worked up as in method A. Distillation at reduced pressure (Kugelrohr apparatus) yielded 1.96 g of undecane, identical with an authentic sample.

Method C. See Table I, footnote *a*.

Method D. A partial solution of β-ionone tosylhydrazone (1.80 g, 5 mmol) in 10 mL of CH_3COOD was prepared by warming for a few minutes under an N_2 atmosphere. To this was added a solution of $NaBD(OAc)_3$ prepared by carefully adding $NaBD_4$ (523 mg, 12.5 mmol) to CH_3COOD (10 mL). The solution was stirred at room temperature for 1 h followed by 1.5 h at 70 °C. Workup as before afforded 0.77 g (81%) of 4-(2-methylcyclohexenyl)-2-butene-*2,4-d*, which showed 95 ± 5% d_2 incorporation by NMR.

Method E. Similar to method D; solutions of $NaBD_4$ (1.046 g, 25 mmol) and propyl phenyl ketone tosylhydrazone (1.58 g, 5 mmol) were each prepared in 10 mL of CH_3COOD. The combined solution was stirred at room temperature for 1 h and at 70 °C for 4 h and worked up as before to give 0.48 g (72%) of 1-phenylbutane-*1,1-d*$_2$. Analysis by NMR indicated 95 ± 5% d_2.

Acknowledgments. The authors thank the donors of the Petroleum Research Fund, administered by The American Chemical Society, for support of this work. We also thank Ventron Corp. for a generous supply of $NaBH_4$ (pellet form).

Registry No.—$NaBH_4$, 16940-66-2; HOAc, 64-19-7; $NaBD_4$, 15681-89-7; CH_3COOD, 758-12-3.

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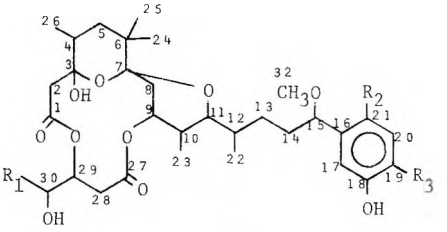
Communications

Toxins from Blue-Green Algae:[1] Structures of Oscillatoxin A and Three Related Bromine-Containing Toxins

Summary: Oscillatoxin A, a major toxic metabolite of a mixture of *Oscillatoria nigroviridis* and *Schizothrix calcicola* from Enewetak, has been identified from high-frequency ^1H and ^{13}C NMR studies as 31-nordebromoaplysiatoxin. Three minor bromine-containing toxic compounds from this algal mixture, viz., 21-bromooscillatoxin A, 19,21-dibromooscillatoxin A, and 19-bromoaplysiatoxin, have also been identified.

Sir: At one time a cyanophyte was suspected to be the primary causative organism of ciguatera, a disease associated with outbreaks of fish poisoning in the tropical and subtropical Pacific. While examining possible sources of the toxin in ciguateric fish of the Gilbert Islands, Banner found that two lipid-soluble toxins were present in *Schizothrix calcicola* from the atoll of Marakei, but neither toxin was characterized and both proved to be nonciguateric.[2]

In a previous communication[3] we reported the isolation of debromoaplysiatoxin (DAT, **1**) from a mixture of predominately two cyanophytes belonging to the Oscillatoriaceae tentatively identified as *Oscillatoria nigroviridis* and *Schizothrix calcicola*. We have now isolated from this algal mixture a second major toxic[4] component which we have named oscillatoxin A (OT-A, **2**) along with small amounts of 21-bromo- and 19,21-dibromooscillatoxin A (**3** and **4**) and 19-bromoaplysiatoxin (**5**). DAT and OT-A may be identical with or related to the two lipid-soluble toxins that Banner had detected in *S. calcicola* from Marakei.



1 $R_1 = {}^{31}CH_3$, $R_2 = R_3 = H$

2 $R_1 = R_2 = R_3 = H$

3 $R_1 = R_3 = H$, $R_2 = Br$

4 $R_1 = H$, $R_2 = R_3 = Br$

5 $R_1 = {}^{31}CH_3$, $R_2 = R_3 = Br$

Frozen *O. nigroviridis-S. calcicola* (8 kg wet weight) collected from the seaward reef flat of Enewetak Island was homogenized and extracted with a mixture of methylene chloride and methanol (1:2 by volume). Water was added to the filtrate and the methylene chloride layer was washed repeatedly with water, dried over anhydrous sodium sulfate, and evaporated

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Table I. Proton NMR Data for Oscillatoxin A (OT-A) in Acetone-d_6

δ, ppm[a]	No. of protons	Assignment[b]	Multiplicity, J (Hz)
8.25[c]	1	OH on 18	br s
7.13	1	20	t, $J_{19,20} = J_{20,21} = 7.5$
6.93	1	17	dd, $J_{17,19} = 2$, $J_{17,21} = 1$
6.84	1	21	dt, $J_{20,21} = 7.5$, $J_{17,21} = J_{19,21} = 1$
6.72	1	19	ddd, $J_{19,20} = 7.5$, $J_{17,19} = 2$, $J_{19,21} = 1$
5.22	1	29	m
5.21	1	9	m
4.34[c]	1	OH on 3	d, $J_{OH(3),4} = 2$[d]
4.14[c]	1	OH on 30	t, $J_{OH(30),30} = J_{OH(30),30'} = 6.5$
3.99	1	15	t, $J_{14,15} = J_{14',15} = 6.5$
3.92	1	11	dd, $J_{10,11} = 10.5$[e], $J_{11,12} = 2.5$
3.69	1	30	m[f]
3.67	1	30′	m[g]
3.17	3	OCH_3	s
2.96	1	28	m
2.93	1	28′	m
2.74	1	2	d, $J_{2,2'} = -13$
2.72	1	8 (eq)	dd, $J_{8,8'} = -14.5$, $J_{8,9} = 3$[h]
2.53	1	2′	d, $J_{2,2'} = -13$
1.95	1	14	tt, $J_{14,14'} = -13$, $J_{13,14} = 13$, $J_{13',14} = J_{14,15} = 6.5$
1.84	1	4	m
1.72	1	8′ (ax)	dd, $J_{8,8'} = -14.5$, $J_{8',9} = 3.5$[i]
1.70	1	10	m
1.62	1	5 (ax)	t, $J_{5,5'} = -13$, $J_{4,5} = 13$[e]
1.60	1	14′	dtd, $J_{14,14'} = -13$, $J_{13',14'} = J_{14',15} = 6.5$, $J_{13,14'} = 2$
1.53	1	12	m
1.40	1	13	m
1.32	1	13′	m
1.06	1	5′ (eq)	dd, $J_{5,5'} = -13$, $J_{4,5'} = 4$
0.86	3	26	d, $J_{4,26} = 7$
0.84	3	25	s
0.81	3	24	s
0.80	3	22	d, $J_{12,22} = 7$
0.73	3	23	d, $J_{10,23} = 7$

[a] Relative to $(CH_3)_4Si$ (δ = 0) and solvent peak (δ 2.06) as internal standards. [b] Based on extensive spin–spin decoupling experiments at 360 MHz. [c] Disappears on addition of D_2O. [d] W coupling. [e] Trans diaxial coupling. [f] Becomes dd on addition of D_2O ($J_{30,30'} = -10$, $J_{29,30} = 3$). [g] Becomes dd on addition of D_2O ($J_{30,30'} = -10$, $J_{29,30'} = 3$). [h] Diequatorial coupling. [i] Axial–equatorial coupling.

to give the crude extract (14.5 g). Column chromatography of this extract on Florisil yielded two toxic fractions. The first toxic fraction (1.3 g), eluted with hexane/chloroform (1:1), was separated further by column chromatography on silica gel H (TLC grade) and gel filtration on Sephadex LH-20 with chloroform/methanol (1:1) to produce 467 mg of nearly pure DAT (1) and 33.4 mg of a mixture of **2**, **3**, **4**, and **5**. LC of the latter mixture on Porasil A using chloroform/acetonitrile (85:15) yielded 6.5 mg of pure **5** and 15 mg of a mixture of **3** and **4**. The second toxic fraction (0.77 g), eluted from the Florisil column with chloroform, contained OT-A (2) as the major component. Gel filtration on Sephadex LH-20 using chloroform/methanol (1:1) followed by LC on Porasil A using chloroform/acetonitrile (85:15) gave pure **2**.

Comparison of the ^1H and ^{13}C NMR spectral data of OT-A and DAT suggested to us that OT-A was 31-nordebromoaplysiatoxin. The 360-MHz ^1H NMR spectrum of OT-A in acetone-d_6 (Table I) lacked a doublet at δ 1.14 for a methyl group on C-30 and it showed two 1 H signals at δ 3.67 and 3.69 for nonequivalent methylene protons on C-30 rather than one signal at 4.05 ppm for a methine proton on C-30. Also the signal for the hydroxyl proton on C-30, a doublet at δ 4.23 for DAT, appeared as a triplet (disappeared on the addition of D_2O) at δ 4.14 for OT-A. The remainder of the OT-A spectrum was identical with that of DAT. Aside from the difference at C-30, extensive proton spin–spin decoupling experiments verified that the rest of the OT-A structure, including relative stereochemistry (C-29 uncertain), was the same as that proposed for DAT.[5] The ^{13}C NMR spectrum of OT-A contained 31 signals, one less peak than the ^{13}C NMR spectrum of DAT (Table II). All but three of the OT-A carbon signals (C-28, C-29, C-30) resonated within 0.4 ppm of the corresponding signals for DAT. The OT-A signals for C-28, C-29, and C-30 showed chemical-shift differences from the DAT signals, +2.48, −1.40, and −3.89 ppm, respectively, as expected for removing the methyl substituent from C-30. In the off-resonance spectrum the C-30 signal was a triplet at δ 62.40 for OT-A, whereas it was a doublet at δ 66.29 for DAT. The very close correspondence between the chemical shifts of the remaining carbon signals for OT-A and DAT again showed that the two toxins have the same relative stereochemistry at C-3, C-4, C-7, C-9, C-10, C-11, C-12, and C-15.

Electron impact (EI) mass spectrometry failed to show a molecular ion for OT-A, but like the aplysiatoxins[5] did show a fragment ion peak due to the loss of water from the molecular ion. A high-resolution mass measurement (Found: (560.30084. Calcd for $C_{31}H_{44}O_9$: 560.29854) confirmed the

Table II. Carbon-13 NMR Data for Debromoaplysiatoxin (DAT) and Oscillatoxin A (OT-A) in Acetone-d_6

Chemical shift[a]			Chemical shift[a]		
DAT	OT-A	Assignment[b]	DAT	OT-A	Assignment[b]
169.56 (s)	169.28 (s)	1 or 27	46.11 (t)	46.18 (t)	
168.37 (s)	168.73 (s)	1 or 27	40.34 (t)	40.39 (t)	5
157.48 (s)	157.54 (s)	18	38.16 (s)	38.28 (s)	6
145.07 (s)	145.07 (s)	16	35.30 (t)	35.29 (t)	
128.97 (d)	128.98 (d)	20	34.87 (d)	34.86 (d)	
118.53 (d)	118.55 (d)	21	34.60 (d)	34.73 (d)	
114.16 (d)	114.18 (d)	19	33.89 (t)	36.37 (t)	28
113.84 (d)	113.92 (d)	17	33.41 (d)	33.48 (d)	
100.00 (s)	100.23 (s)	3 or 7	32.84 (t)	32.89 (t)	
97.98 (s)	98.22 (s)	3 or 7	30.41 (t)	30.45 (t)	13
85.03 (d)	85.06 (d)	11	26.02 (q)	26.08 (q)	25
73.44 (d)	72.04 (d)	29	22.81 (q)	22.85 (q)	24
72.46 (d)	72.59 (d)	9	16.96 (q)		31
68.99 (d)	69.17 (d)	15	15.74 (q)	15.75 (q)	26
66.29 (d)	62.40 (t)	30	12.80 (q)	12.82 (q)	22
55.82 (q)	55.85 (q)	32	12.27 (q)	12.32 (q)	23

[a] In ppm using acetone-d_6 (δ 29.20) as an internal reference. [b] Proton correlations are based on detailed single-frequency off-resonance decoupling experiments at 90 MHz.

elemental composition of this fragment ion.

The sign and magnitude of the optical rotations of OT-A, $[\alpha]^{25}_D$ + 67 ± 10° (EtOH, *c* 0.12), and DAT, $[\alpha]^{25}_D$ + 60.6 ° (EtOH, *c* 0.66), suggested that the two compounds have the same absolute configuration (C-29 uncertain).

Structures **3, 4,** and **5** were deduced on the basis of low- (100 MHz) and high-frequency (360 MHz) proton magnetic resonance studies. The ^{1}H NMR spectra of the compounds assigned structures **3** and **4** differed from the ^{1}H NMR spectrum of OT-A primarily in the aromatic region. An AMX pattern at δ 6.82 (dd, 1 H, *J* = 8.0, 2.0 Hz), 7.05 (d, 1 H, *J* = 2.0 Hz), and 7.44 (d, 1 H, *J* = 8.0 Hz) was consistent with a 3,4-disubstituted phenol moiety in **3.** The ^{1}H NMR spectrum of **4** contained only two singlets (δ 7.22 and 7.64) in the aromatic region, in agreement with a 2,4,5-trisubstituted phenol system. The ^{1}H NMR spectrum of **5** showed a doublet at δ 1.11, indicating the presence of a methyl group on C-30, and it exhibited only two aromatic proton signals at δ 7.21 (s) and 7.63 (s). Again, the EI mass spectra of **3, 4,** and **5** did not exhibit molecular ions, but characteristic M − H_2O peaks were observed and high-resolution measurements confirmed their elemental compositions.[6]

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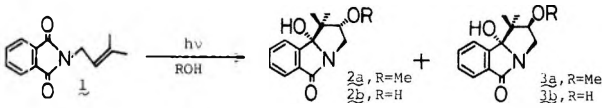
Photochemical Cyclization of *N*-2-Alkenyl- and *N*-3-Alkenylphthalimides

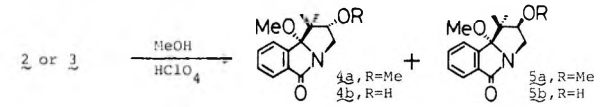
Summary: Photolysis of *N*-(3-methyl-2-butenyl)phthalimide (**1**) in methanol gave cyclic compounds **2a** and **3a** probably via successive processes; intramolecular electron transfer (**1** → **19**), polar addition of methanol (**19** → **20**), and cyclization of diradical (**20** → **2a** + **3a**).

Sir: It is well known that *N*-alkylated phthalimides undergo photochemical hydrogen abstraction reactions.[1] However, as far as we know, no examples of photochemical reactions of phthalimides with monoolefins have been published.[2] We now wish to report the first examples of photochemical reactions of phthalimides with monoolefins, in particular the intramolecular photochemical reactions of *N*-2-alkenyl- and *N*-3-alkenylphthalimides.

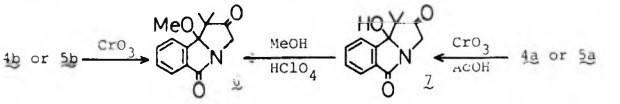
For example, a solution of *N*-(3-methyl-2-butenyl)-phthalimide (**1**) (5 mM) in methanol was irradiated under N_2



with a 300-W high-pressure Hg-arc lamp (Eikosha PIH-300) through quartz for about 5 h.[3] At this stage, the starting material had almost disappeared. After workup, two products were obtained. The structure and stereochemistry of the isomeric products ($C_{14}H_{17}NO_3$, mass *m/e* 247, elemental analyses) **2a** (41%, mp 98–99 °C) and **3a** (41%, mp 200–201 °C) were assigned as the following. **2a:** IR (KBr) 3400 (OH), 1685 cm^{-1} (amide); ^{1}H NMR ($CDCl_3$) δ 0.42 (s, 3 H, Me), 1.42 (s, 3 H, Me), 3.48 (s, 3 H, OMe), 3.5–3.9 (m, 3 H), 4.51 (s, 1 H, OH), 7.3–7.9 (m, 4 H). **3a:** IR (KBr) 3250 (OH), 1680 cm^{-1} (amide); ^{1}H NMR ($CDCl_3$) δ 0.32 (s, 3 H, Me), 1.40 (s, 3 H, Me), 3.07 (s, 1 H, OH), 3.27 and 3.62 (two dd, 2 H, NCH_2), 3.43 (s, 3 H, OMe), 4.37 (t, 1 H, methine), 7.3–7.8 (m, 4 H). The products **2a** and **3a** were resistant to acetylation by acetic anhydride–pyridine and to chromic acid oxidation, but they were converted to an equilibrium mixture of methyl ethers, **4a** (mp 89–90 °C)/**5a** (mp 98–99 °C) = 3:1, probably via a

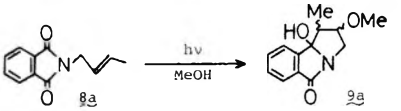


common stable tertiary carbonium ion, on treatment with a trace amount of acid ($HClO_4$) in methanol. Diols **2b** (mp 172–174 °C) and **3b** (mp 178–181 °C), which were obtained by photolysis of **1** in water–acetonitrile (v/v 1:8) in a yield of 70% (**2b**/**3b** = 1:1), were converted to an equilibrium mixture of monomethyl ethers **4b** (oil)/**5b** (oil) = 3:1 by a similar procedure. The secondary alcohol **4b** was easily oxidized to ketone **6** (50%, mp 108–110 °C) by Jones oxidation. The ketone **6** was

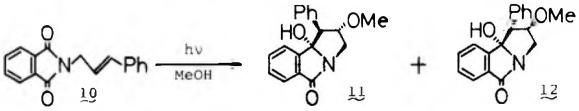


also obtained by the reverse manipulation; i.e., initial oxidation of **4a** accompanied by hydrolysis to **7** (72%, mp 200–202 °C) followed by methylation to give **6.** ^{1}H NMR spectra of **2a** and **3a** showed the presence of two kinds of *C*-methyl groups. The anisotropic shielding effect of the phenyl ring is probably responsible for the higher chemical shift of one of the two methyl groups. Similarly in **2–7** one of the two methyl groups had its ^{1}H NMR signals at δ 0.28–0.50. The stereochemistry of **2–5** was assigned on the basis of their ^{1}H NMR spectra. Thus, for the isomers **2** or **4,** the higher field shift of the methine protons compared to those of the corresponding isomers **3** or **5** (for example, **3a** − **2a** = 0.5, **3b** − **2b** = 0.58 ppm HCOMe) is explicable in terms of the same anisotropic effect seen for the methyl groups. Further support for these structures will be shown in connection with other photoproducts (vide infra). Photolysis (10 h) of **1** in acetonitrile resulted in recovery of the starting material.

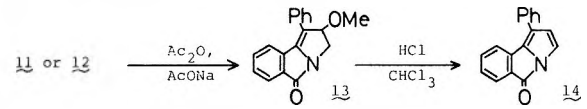
Irradiation of *N*-(2-butenyl)phthalimide (**8a**) in methanol gave the corresponding products **9a** (mixture, 75%), but *N*-allylphthalimide (**8b**) afforded no corresponding products on photolysis in methanol.



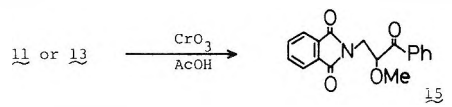
Photolysis of *N*-(3-phenyl-2-propenyl)phthalimide (**10**) in methanol gave **11** (68%, mp 162–164 °C) and **12** (17%, mp



189–191 °C). On refluxing **11** and **12** in acetic anhydride and sodium acetate for 0.5 h, respectively, we readily obtained the same dehydrated product **13** (pale yellow crystals, mp 164–166 °C). The product **13** was further converted to **14** (orange

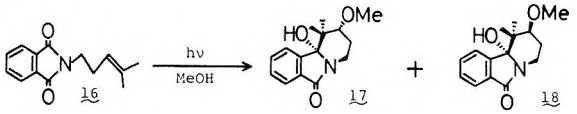


crystals, mp 113–115 °C) by treating with hydrochloric acid in chloroform. The main photoproduct **11** was quantitatively oxidized to **15** (mp 135–136 °C) by chromic acid oxidation in acetic acid. In a similar manner, **13** was oxidized to **15** (50%).



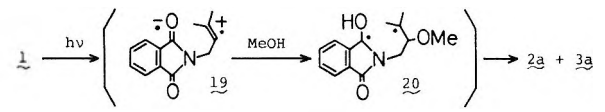
The structure of **11** was confirmed by X-ray diffraction. The stereochemistry of **12** is assigned on the basis of its ^{1}H NMR spectra compared with that of **11**: partial ^{1}H NMR (δ) of **11**, 4.1–4.4 (m, 2 H, two methine), 3.78 (m, 2 H, NC**H**$_2$); **12**, 4.92 (m, 1 H, **H**COMe), 3.74 and 3.50 (two dd, 2 H, NC**H**$_2$), 2.76 (d, 1 H, **H**CPh). On irradiation of **10** in methanol, the presence of a triplet quencher (penta-1,3-diene, 1 mol/L) did not significantly affect the rate of formation of the photoproducts, analogous to the case of photolysis of *N*-(dibenzylaminomethyl)phthalimide.[1e]

Irradiation of *N*-(4-methyl-3-pentenyl)phthalimide (**16**) in methanol gave the corresponding isomers **17**/**18** = 1:1 (84%).



These intramolecular photocyclizations of phthalimides may be reasonably explained by a mechanism involving initial one-electron transfer.[4] Thus, for example, in the photocyclization of **1**, the primary photoprocess may be one-electron transfer from the double bond (**1** → **19** in Scheme I) followed by polar addition of methanol to give a diradical (**19** → **20**)[5] which cyclizes to produce **2a** and **3a**.[6]

Scheme I



The reaction pattern of the photocyclization of *N*-alkenylphthalimide described above seems to be novel in the widely studied photochemistry of carbonyl compounds with olefins. The scope, limitation, and detailed mechanism of this reaction are under investigation.

Acknowledgment. We are indebted to Professor Masao Kakudo and Dr. Nobuo Tanaka of Osaka University (the Institute for Protein Research) for X-ray diffraction analysis.

References and Notes

(1) (a) Y. Kanaoka, *Yuki Gosei Kagaku Kyokai Shi*, **33**, 949 (1975), and papers cited therein; (b) Y. Sato, H. Nakai, T. Mizoguchi, and Y. Kanaoka, *Tetrahedron Lett.*, 1889 (1976); (c) Y. Sato, H. Nakai, T. Mizoguchi, Y. Hatanaka, and Y. Kanaoka, *J. Am. Chem. Soc.*, **98**, 2349 (1976); (d) H. J. Roth and D. Schwarz, *Arch. Pharm.*, **308**, 631 (1975); (e) J. D. Coyle and G. L. Newport, *Tetrahedron Lett.*, 899 (1977).

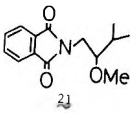
(2) Light-induced reaction of *N*-methylphthalimide with cycloalkenes has been reported, but the report described only an α-hydrogen abstraction from cycloalkenes.[2a] Photochemical oxetane formation of *N*-2-alkenyl alicyclic imides[2b] and photoaddition of dienes to *N*-methylphthalimide[2c] have been reported. (a) Y. Kanaoka and Y. Hatanaka, *Chem. Pharm. Bull.*, **22**, 2205 (1974); (b) K. Maruyama and Y. Kubo, *J. Org. Chem.*, **42**, 3215 (1977); (c) P. H. Mazzocchi, M. J. Bowen, and N. K. Narain, *J. Am. Chem. Soc.*, **99**, 7063 (1977).

(3) All new compounds gave satisfactory analytical results as well as reasonable spectral properties (IR, NMR, UV, and mass spectra).

(4) It is reported that in the photochemical reaction of aromatic esters with olefins in polar solvents, the exciplexes, once formed, dissociate into the radical ions.[4a-c] Furthermore, in the photohydrogen abstraction reaction of phthalimides, electron transfer (or CT) mechanisms are often regarded as playing an important role.[1] (a) R. A. Neunteufel and D. R. Arnold, *J. Am. Chem. Soc.*, **95**, 4080 (1973); (b) Y. Shigemitsu and D. R. Arnold, *J. Chem. Soc., Chem. Commun.*, 407 (1975); (c) A. J. Maroulis, Y. Shigemitsu, and D. R. Arnold, *J. Am. Chem. Soc.*, **100**, 535 (1978).

(5) Photosensitized anti-Markownikoff addition of alcohols (involving electron transfer) to olefins has been reported[4a-c] and the protonation of a carbonyl group from a CT complex by methanol has been postulated.[5a] The diradical is also a presumed intermediate in the intramolecular δ-hydrogen abstraction reaction of *N*-alkylphthalimides.[1] (a) P. J. Wagner and D. A. Ersfeld, *J. Am. Chem. Soc.*, **98**, 4515 (1976).

(6) Another mechanism for the photolysis of **1** is the possible intermediacy of *N*-(2-methoxy-3-methylbutyl)phthalimide (**21**) (via sensitized anti-Markownikoff addition of methanol to the double bond) followed by δ-hydrogen abstraction to **2a** and **3a**. However, in our hands **21** could not be isolated under various conditions. Furthermore, a photoreaction of **21** is anticipated to occur with preferential γ-hydrogen rather than δ-hydrogen abstraction as is observed in the photolysis of *N*-(3-methylbutyl)phthalimide.[1a]



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Diels–Alder Reaction of 1,4-Quinone Monobenzenesulfonimides

Summary: The Diels–Alder cycloaddition of a series of 1,4-quinone monobenzenesulfonimides with various 1,3-butadienes was investigated. The objective was to determine the influence of the benzenesulfonimide group on the regiochemistry of the cycloaddition as well as the relative dienophile double bond reactivity. The salient results are: (1) the regiochemistry of the cycloadditions is exclusively controlled by the benzenesulfonimide group; (2) the double bond in the quinone imine which is syn to the benzenesulfonimide is the more activated dienophilic position.

Sir: Synthetic strategy for the construction of a large number of naturally occurring quinones, including the biologically significant anthracycline antineoplastic antibiotics, utilizes a Diels–Alder cycloaddition of a quinone to a diene. However, this methodology often suffers both regiochemical and reactivity problems. That is, in the cycloaddition of a substituted benzoquinone with a substituted diene, the regiochemical problem concerns the orientation of the substituents in the final product, and the reactivity problem concerns the relative reactivity of the enone double bonds in the quinone dienophile.[1] These conflicts are dramatically illustrated in the elegantly simple synthesis of (±)-daunomycinone reported by Kende, Tsay, and Mills.[2] Here it was observed that the key intermediate, 5-methoxy-1,4,9,10-anthradiquinone (**1**), reacts with most electron-rich dienes at the internal 4a,9a double

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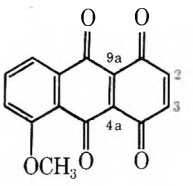


1

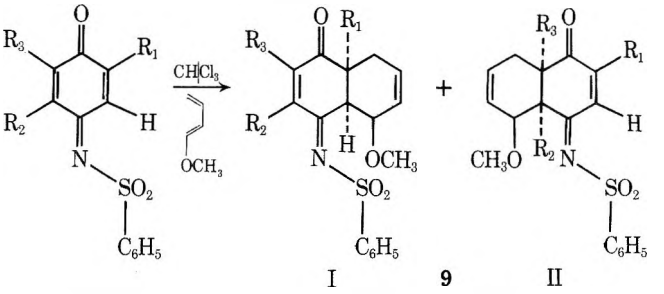
bond. The desired exclusive cycloaddition at the 2,3-double bond was accomplished with 2-acetoxy-1,3-butadiene, but both possible regioisomers resulted.

Our objectives concerning the above two problems were to study the Diels–Alder cycloadditions of a simple quinone derivative which could control both the regiochemistry and the double bond reactivity. Specifically, the cycloadditions of various 1,4-benzoquinone monobenzenesulfonimides with 1-methoxy-1,3-butadiene were initially investigated.[3] The salient results of this study are the following: (1) the benzenesulfonimide group markedly controls the regiochemistry of the reaction in that, for the examples described here, only those adducts **9** are formed which have the methoxy group at position 5 and the imide at position 4; (2) *remarkably, and counter to our initial expectation, the double bond which is syn to the benzenesulfonyl group is the more activated dienophile.*

When a chloroform solution of 1,4-benzoquinone monobenzenesulfonimide (**2**) and 10% molar excess of 1-methoxy-1,3-butadiene was allowed to stand at ambient temperature for 3 days, complete reaction occurred to give a 65% isolated yield of a mixture of the adducts **3** and **4** in a ratio of, respectively, 2:1.[4] Under these conditions the reaction is actually under thermodynamic control, since it was subsequently shown that the reaction is complete within 30 min and the ratio of **3**/**4** here is ~4:1. This kinetic ratio slowly changes to the equilibrium ratio of 2:1 as the reaction solution stands at ambient temperature over the 3-day period.[5] These isomers could not be separated by conventional methods, but the structural assignments were made (vide infra) on the basis of ^{1}H NMR analysis of the resulting mixture. No other regioisomers could be detected. Thus, the reaction appears to be regiospecific with respect to the electronic control of the imine vs. the carbonyl group, and regioselective with respect to the double bond reactivity. A complete stereochemical analysis of **3** and **4** has not been made. However, the indicated relative configuration of the chiral centers in the molecules is anticipated based upon the principle of endo cycloaddition. The stereochemistry of the imine moieties is readily assigned from the fact that the absorption for the vinyl proton at position 3 in the minor product, **4**, is deshielded relative to the analogous absorption in **3**. These appear respectively at δ 8.1 and 6.7. That the deshielded absorption is due to the *syn*-vinyl proton (with respect to the benzenesulfonyl group) is based upon the observation that the chemical shifts of the *syn*-vinyl protons in the quinone imines **2** and **5**–**8** all appear between δ 8.1 and 8.2.[6] Therefore, it is apparent that the proton on the syn double bond is experiencing a deshielding anisotropy effect of the benzenesulfonyl group.

In a manner analogous to the above, the cycloadditions of the quinone imines **5**–**8** with 1-methoxy-1,3-butadiene were investigated (3 days at ambient temperature), which gave, respectively, the adducts **9a,b, 9c,d, 9e,** and **9f** (Table I). Here again, the reactions were all observed to be regiospecific. For the symmetrical quinone imine **5**, where the difference in syn vs. anti double bond reactivity would be due only to the imine stereochemistry, the major isomer **9a** again was due to cycloaddition to the syn double bond as evidenced by the C-3 vinyl proton absorption at δ 8.1 for the minor isomer **9b** (25%), and δ 6.9 for the major isomer **9a** (49%). A reversal in the double bond reactivity was observed for the cycloaddition of

Table I



I 9 II

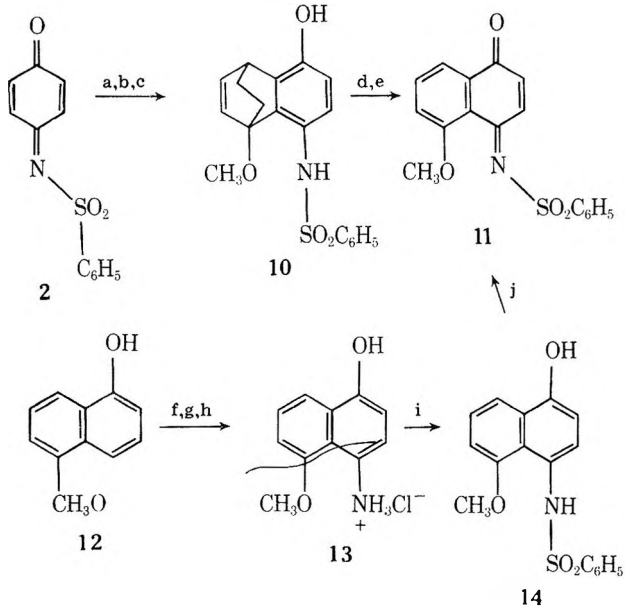
Quinone imine	R_1	R_2	R_3	I[c]	II[c]
2	H	H	H	**3**, 66%[a]	**4**, 33%[a]
2	H	H	H	**3**, 80%[b]	**4**, 20%[b]
5	CH_3	H	CH_3	**9a**,[8] 49%	**9b**,[8] 25%
6	CH_3	CH_3	H	**9c**, 27% (mp 173–175 °C)	**9d**, 55% (mp 121–123 °C)
7	H	CH_3	H	**9e**, 86% (mp 139–141 °C)	None
8	H	CH_3	CH_3	**9f**, 85% (mp 134–136 °C)	None

[a] NMR ratio after 3 days at room temperature. [b] NMR ratio after 30 min at room temperature. [c] All other % of I and II are actual isolated yield unless otherwise stated.

2,5-dimethyl-1,4-benzoquinone monobenzenesulfonimide (**6**). Here, the major product **9d** arises from cycloaddition to the anti double bond. This is not unexpected, since the 2,3-double bond (syn) would be activated by the benzenesulfonyl group, but deactivated by the methyl group at position 2. That is, for a cycloaddition occurring on the 2,3 double bond, "initial bond formation" would take place at position 2, and alkyl substitution at this site is known to retard the reaction.[7] The 5,6 double bond (anti), on the other hand, would gain no activation from the *anti*-benzenesulfonyl group, but would not be as greatly deactivated by the 5-methyl substituent, since "initial bond formation" would take place at the unsubstituted position 6. The influence of the methyl groups in **6** is apparently more important than the imine stereochemistry and thus preferential cycloaddition takes place at the anti-5,6 double bond to give **9d,** which shows the diagnostic low-field vinyl proton absorption at δ 8.1. For the quinone imines **7** and **8,** cycloaddition takes place, as expected, only at the unsubstituted syn double bond to give, respectively, **9e** and **9f.** Such assignments are clearly made by the fact that **9e** shows vinyl proton absorptions corresponding to three protons and **9f** to two protons.

To this point, the discussion has focused primarily upon the reactivity preference of the dieneophile double bond, and no persuasive arguments have been put forward regarding the regiospecificity of the cycloadditions. Such assignments of the regiostructures of **3, 4,** and **9a–f** are made on the basis of the following ^{1}H NMR data. Adduct **9d** shows a multiplet at δ 3.23 for the methine proton at position 5, which collapses to a singlet upon irradiation (decoupling) of the 6,7-vinyl protons. Adduct **9c** shows this same methine proton as a multiplet at δ 4.27, which collapses to a doublet (J = 5.5 Hz) upon decoupling the 6,7-vinyl protons. This resulting doublet is due to coupling to the methine proton at position 4a, which appears at δ 4.40 as a doublet (J = 5.5 Hz). Adduct **9f** shows the 5- and 4a-methine protons, respectively, as a multiplet at δ 4.28 and a doublet of doublets at δ 4.47. Decoupling in the 6,7-vinyl region causes the multiplet to collapse to a doublet (J = 3.9 Hz), and decoupling the 8a-methine proton at δ 2.81 results in collapse of the δ 4.47 doublet of doublets to a simple doublet (J = 3.9 Hz). The ^{1}H NMR spectrum of **3** and **9e** parallels that of **9f,** while **9b** is analogous to **9c.** Finally, the methine protons

Scheme I



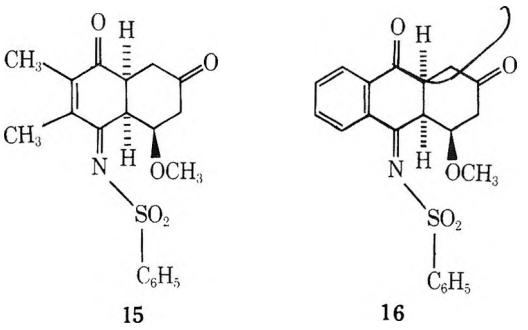
(a) $C_6H_7OCH_3/CHCl_3$/room temp. (b) KO*t*-Bu/THF. (c) H_3O^+. (d) $Pb(OCOCH_3)_4/CH_3CO_2H$. (e) C_6H_6, Δ. (f) $^+N_2C_6H_4SO_3^-$. (g) $Na_2S_2O_4/H_2O$. (h) Concentrated HCl. (i) $C_6H_5SO_2Cl$. (j) $Pb(OCOCH_3)_4$.

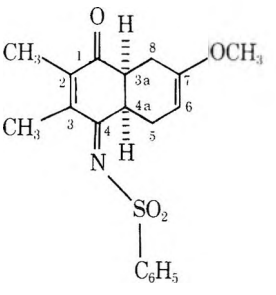
at position 5 in **4** and **9a**, which both appear at δ 3.60, collapse to doublets upon decoupling the 6,7-vinyl region. These data are consistent only with the indicated regiostructures of the adducts, i.e., **9a–f**.

In order to gain chemical conformation that the benzenesulfonimide group controls the regiochemistry of the cycloadditions, 1,4-benzoquinone monobenzenesulfonimide[6] (**2**) was treated with 1-methoxycyclohexa-1,3-diene to give the adduct which upon treatment with ^-O-*t*-Bu followed by acid workup to give the naphthol **10** in 35% yield (Scheme I):[9] mp 202–203 °C; NMR ($CDCl_3$) δ 9.3 (s, 1 H), 7.85 (s, 1 H). 7.8–6.7 (m, 7 H), 6.5–6.3 (m, 2 H), 4.13 (m, 1 H), 3.39 (s, 3 H), 1.9–1.0 (m, 4 H); IR (Nujol, cm^{-1}) 3315, 3500. This was oxidized with lead tetraacetate and pyrolyzed in refluxing benzene to give the quinone imine **11** (53%): mp 143–145 °C; NMR ($CDCl_3$) δ 8.5–7.2 (m, 8 H), 8.49 (d, 1 H, J = 10 Hz), 6.85 (d, 1 H J = 10 Hz), 3.7 (s, 3 H); IR (Nujol, cm^{-1}) 1650, 1600. This product was then independently synthesized starting with 1-hydroxy-5-methoxynaphthalene[10] (**12**). Here the naphthol was treated with *p*-sulfonylbenzenediazonium chloride and the resulting azo compound was reduced to the amine **13**, which was then treated with benzenesulfonyl chloride to give **14** (61%): mp 172–174 °C; NMR (acetone-d_6) δ 9.33 (s, 1 H), 8.75 (s, 1 H), 6.68–8.0 (m, 10 H), 3.81 (s, 3 H); IR (Nujol, cm^{-1}) 3600, 3510. Subsequent oxidation of **14** gave **11** in 90% yield.

In conjunction with our desire to utilize quinone imines as synthetic precursors to certain anthracycline antibiotics, it was of interest to see if 1,3-disubstituted-1,3-butadienes would undergo regiospecific cycloaddition. Thus, the reactions of 1-methoxy-3-(trimethylsiloxy)-1,3-butadiene[11] with 2,3-dimethyl-1,4-benzoquinone monobenzenesulfonimide and 1,4-naphthoquinone monobenzenesulfonimide were studied. In both cases the reaction proceeds smoothly to give a single adduct which upon mild hydrolysis with 0.1 N HCl/THF results, respectively, in **15** (mp 170–172 °C) (75%) and **16** (mp 147–149 °C) (80%). Their structures are based upon spectral and elemental analyses which are consistent with the arguments previously presented.

Finally, it was of interest to see if the same high degree of regiochemical control would be observed for quinone imine cycloadditions to the less strongly directing 2-methoxy-1,3-butadiene. Thus, an acetonitrile solution of **8** containing a catalytic amount of hydroquinone was treated with excess diene at 55 °C (6 h). Here the resulting adduct, **17**, mp 142–144 °C, was obtained in 75% purified yield, and again only one regioisomer could be detected by NMR analysis of the crude solid product. Decoupling experiments of the 220-MHz spectrum of **17** revealed that the low-field C-4a methine proton (δ 4.25) and the vinyl proton at C-6 (δ 4.48) were both coupled to one of the methylene protons at C-5 (δ 2.74) and such a result is consistent for only the regioisomer **17**.





References and Notes

(1) A number of unique resolutions to these problems have recently been reported. See, for example: W. W. Lee, A. P. Martinez, T. H. Smith, and D. W. Henry, *J. Org. Chem.*, **41**, 2296 (1976); T. R. Kelly, R. N. Goerner, Jr., J. W. Gillard, and B. K. Prazak, *Tetrahedron Lett.*, 3869 (1976); H. H. Inhoffen, H. Muxfeldt, V. Koppe, and J. H. Trosien, *Chem. Ber.*, **90**, 1448 (1957); R. A. Dickinson, R. Kubela, G. A. MacAlpine, Z. Stojanac, and Z. Valenta, *Can. J. Chem.*, **50**, 2377 (1972); N. Stojanac, A. Sood, Z. Stojanac, and Z. Valenta, *ibid.*, **53**, 616 (1975); T. R. Kelly, J. W. Gillard, R. N. Goerner, Jr., and J. M. Lyding, *J. Am. Chem. Soc.*, **99**, 5513 (1977); B.M. Trost, J. Ippen and W. C. Vladuchick, *ibid.*, **99**, 8117 (1977).

(2) A. S. Kende, Y. Tsay, and J. E. Mills, *J. Am. Chem. Soc.*, **98**, 1967 (1976).

(3) The cycloadditions of quinone imines with dienes has previously been reported by R. Adams. However, the regio- and stereochemistry of the adducts were not determined, see: R. Adams and W. Reifschneider, *Bull. Soc. Chim. Fr.*, 23 (1958).

(4) All new compounds reported here showed spectral and analytical properties in complete accord with their proposed structures.

(5) It is, of course, possible that this equilibration takes place by a reversibility of the Diels–Alder reaction rather than isomerization of the time double bond. However, in view of the mild reaction conditions (ambient temperature), this appears unlikely.

(6) These quinone imines were all prepared according to the methods described by Adams and Reifschneider; see ref 3.

(7) M. F. Ansell and A. H. Clements, *J. Chem. Soc.*, 269 (1971).

(8) The mixture of **9a** and **9b** could not be separated. However, spectral analysis of the mixture readily allowed the structural assignments of the individual isomers.

(9) This transformation is analogous to that previously reported in the quinone series, see: R. G. F. Giles and G. H. P. Roos, *J. Chem. Soc., Perkin Trans. 1*, 2057 (1976).

(10) The naphthol was prepared in 82% overall yield from 1,5-dihydroxynaphthalene by dimethylation (CH_3I/K_2CO_3/acetone) followed by monodemethylation ($C_2H_5SH/NaH/DMF$).[3]

(11) S. Danishefsky and T. Kitahara, *J. Am. Chem. Soc.*, **96**, 7807 (1974).

(12) The authors are grateful to the National Cancer Institute (CA 11890) for financial support of this work.

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Trialkylborohydrides

Trialkylborohydrides have recently been found by Professor John Gladysz and coworkers to be useful reagents for the reductive cleavage of transition metal-metal bonds.[1] Cleavage products are usually highly nucleophilic anions which are useful intermediates in organometallic and organic syntheses. Reactions are rapid and clean, and a number of high-yield, multistep sequences have been executed in a single flask. When lithium triethylborohydride (Aldrich's **Super-Hydride®** reagent) is used, by-products are hydrogen and readily volatilized triethylboron. Potassium salts are easily obtained using potassium tri-*sec*-butylborohydride (Aldrich's **K-Selectride®** reagent).

These procedures are more convenient than existing methods for metal anion synthesis. Representative reactions are depicted below.

$$[Co(CO)_4]_2 \xrightarrow{\text{Super-Hydride}} LiCo(CO)_4 \quad 100\%$$

$$[Mo(CO)_3C_5H_5]_2 \xrightarrow{\text{K-Selectride}} KMo(CO)_3C_5H_5 \quad 100\%$$

Transition metal monoanions are useful synthetic intermediates.[2] Numerous organometallic compounds are available by alkylation or acylation of these highly nucleophilic species. Cluster complexes and other compounds containing metal-metal bonds can be obtained by addition of an appropriate electrophile. Representative examples are given below.

$$[Mn(CO)_5]_2 \xrightarrow{\text{Super-Hydride}} LiMn(CO)_5 \xrightarrow{PhC(O)Cl} PhC(O)Mn(CO)_5 \quad 92\%$$

$$[Fe(CO)_2C_5H_5]_2 \xrightarrow{\text{K-Selectride}} KFe(CO)_2C_5H_5 \xrightarrow{Ph_3SnCl} Ph_3SnFe(CO)_2C_5H_5 \quad 93\%$$

Highly reactive anionic metal formyl complexes can be prepared readily *via* reduction of metal carbonyl compounds with trialkylborohydrides.[3]

$$L_nM\text{-}C{=}O \xrightarrow{\text{Super-Hydride}} Li^+L_nM^-CHO$$

The Fischer-Tropsch process is believed to involve a catalyst-surface-bound formyl group. Consequently, the study of metal formyl complexes has attracted recent attention because of the increasing economic importance of coal transformations.

Gladysz and coworkers also found that **Super-Hydride** rapidly and quantitatively cleaves elemental selenium.[4] Thus, dialkyl selenides and diselenides can be conveniently prepared in a one-flask operation *via* the following simple sequences:

$$Se + 2\ LiEt_3BH \longrightarrow Li_2Se \xrightarrow{2\ RX} R\text{-}Se\text{-}R$$

$$2\ Se + 2\ LiEt_3BH \longrightarrow Li_2Se_2 \xrightarrow{2\ RX} R\text{-}Se\text{-}Se\text{-}R$$

The utility of Collman's Reagent, $Na_2Fe(CO)_4$, in organic and inorganic syntheses is well known.[5] Recently, Gladysz and Tam reported a novel and convenient one-flask synthesis of the analytically pure potassium salt of Collman's Reagent *via* **K-Selectride** reduction of **iron pentacarbonyl**.[6]

$$Fe(CO)_5 \xrightarrow{\text{K-Selectride}} K_2Fe(CO)_4 \quad >95\%$$

Further applications of trialkylborohydrides for metal and metalloid anion syntheses should be forthcoming. Obviously, trialkylborohydrides promise to be extremely useful reagents for the organometallic chemist.

References:

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18,014-9	**K-Selectride®** (potassium tri-*sec*-butylborohydride), 0.5*M* in THF	**500ml $26.40**
17,972-8	**Super-Hydride®** (lithium triethylborohydride), 1*M* in THF	**500ml $23.10**
19,573-1	**Iron pentacarbonyl**	**250g $10.45; 1kg $27.50**