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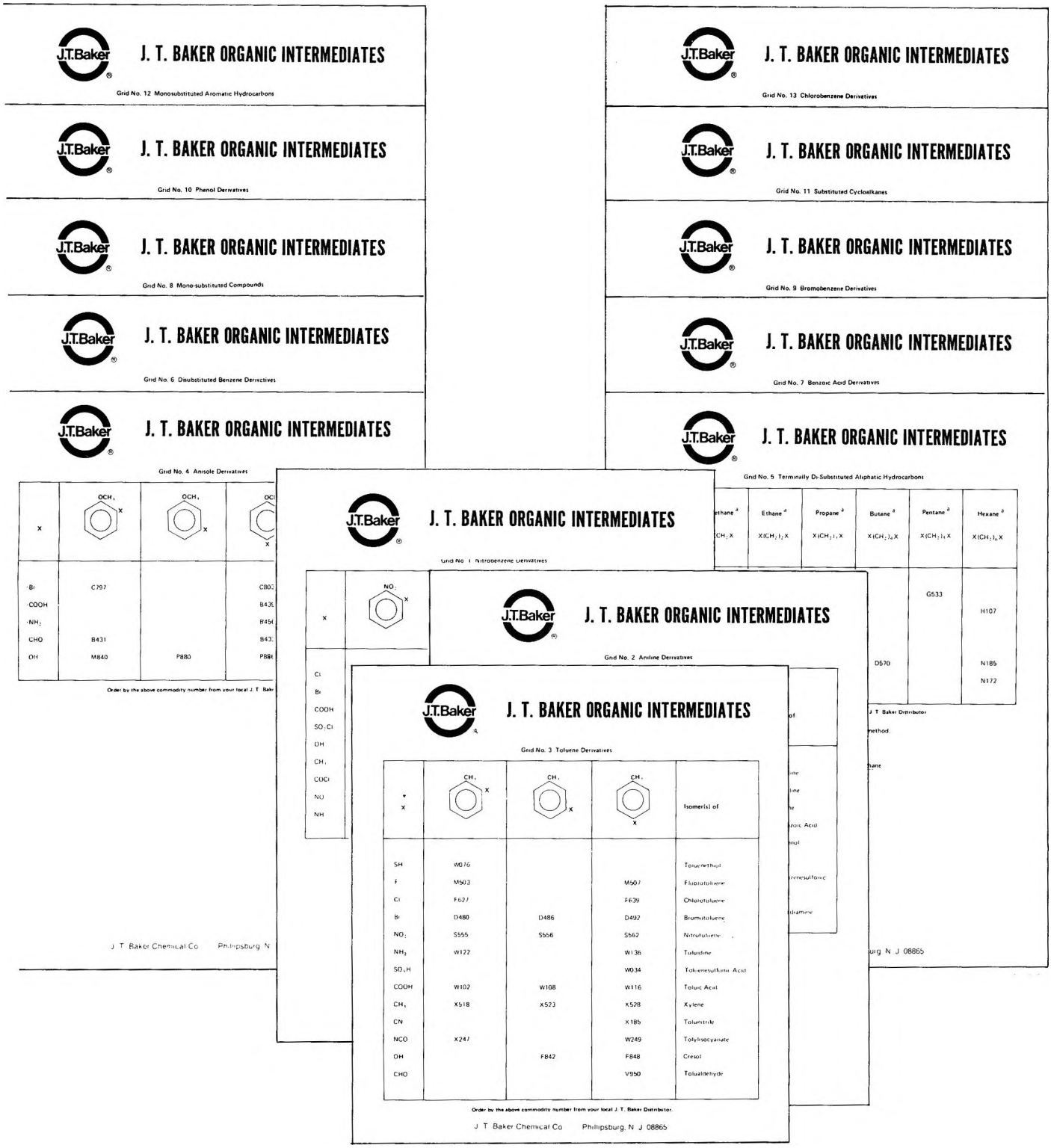

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COOH			B43
NH_2			B45
CHO	B431		B43
OH	M840	P880	P88

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				G533	H107
			D570		N185
					N172

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Br	
COOH	
SO_2Cl	
OH	
CH_3	
COCl	
NO	
NH	

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+ X	CH_3	CH_3	CH_3	Isomer(s) of
SH	W076			Toluenethiol
F	M503		M507	Fluorotoluene
Cl	F627		F639	Chlorotoluene
Br	D480	D486	D492	Bromotoluene
NO_2	S555	S556	S562	Nitrotoluene
NH_2	W122		W136	Toluidine
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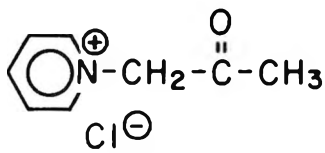

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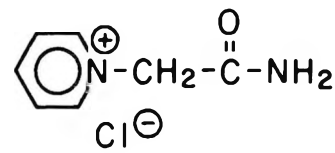

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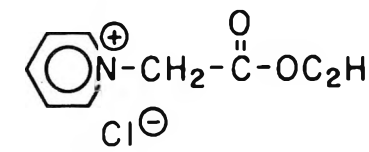

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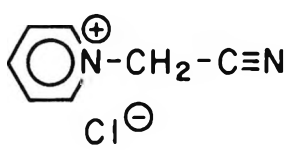

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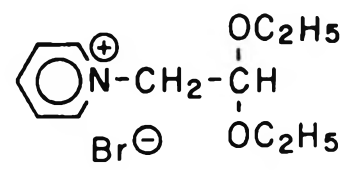

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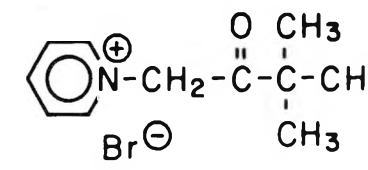

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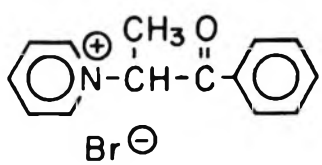

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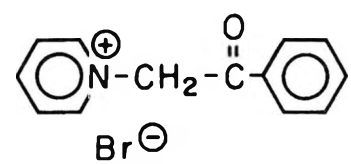

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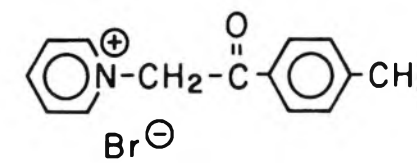

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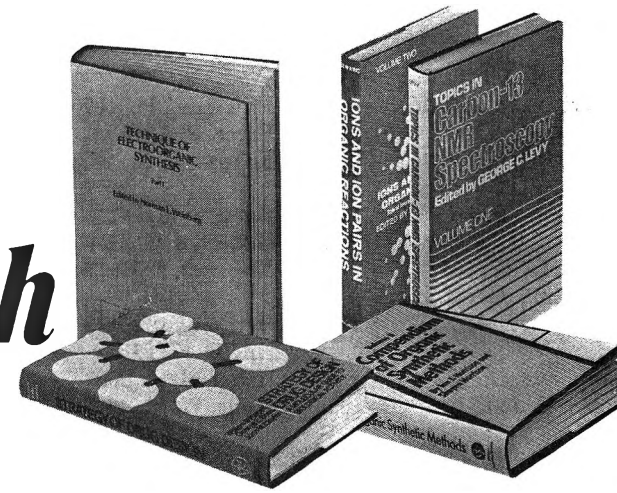

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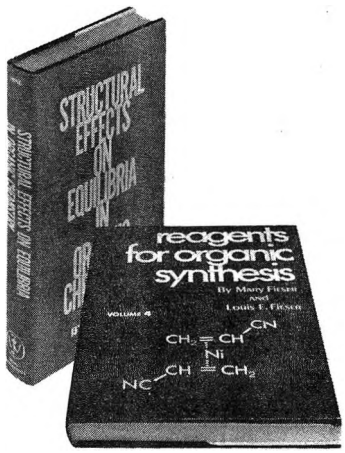

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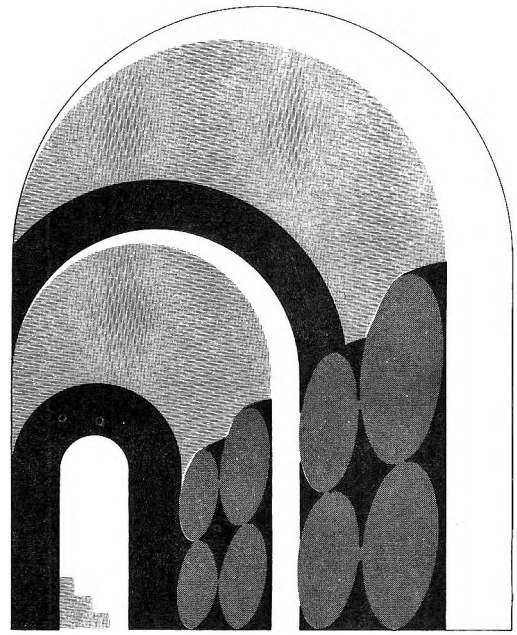

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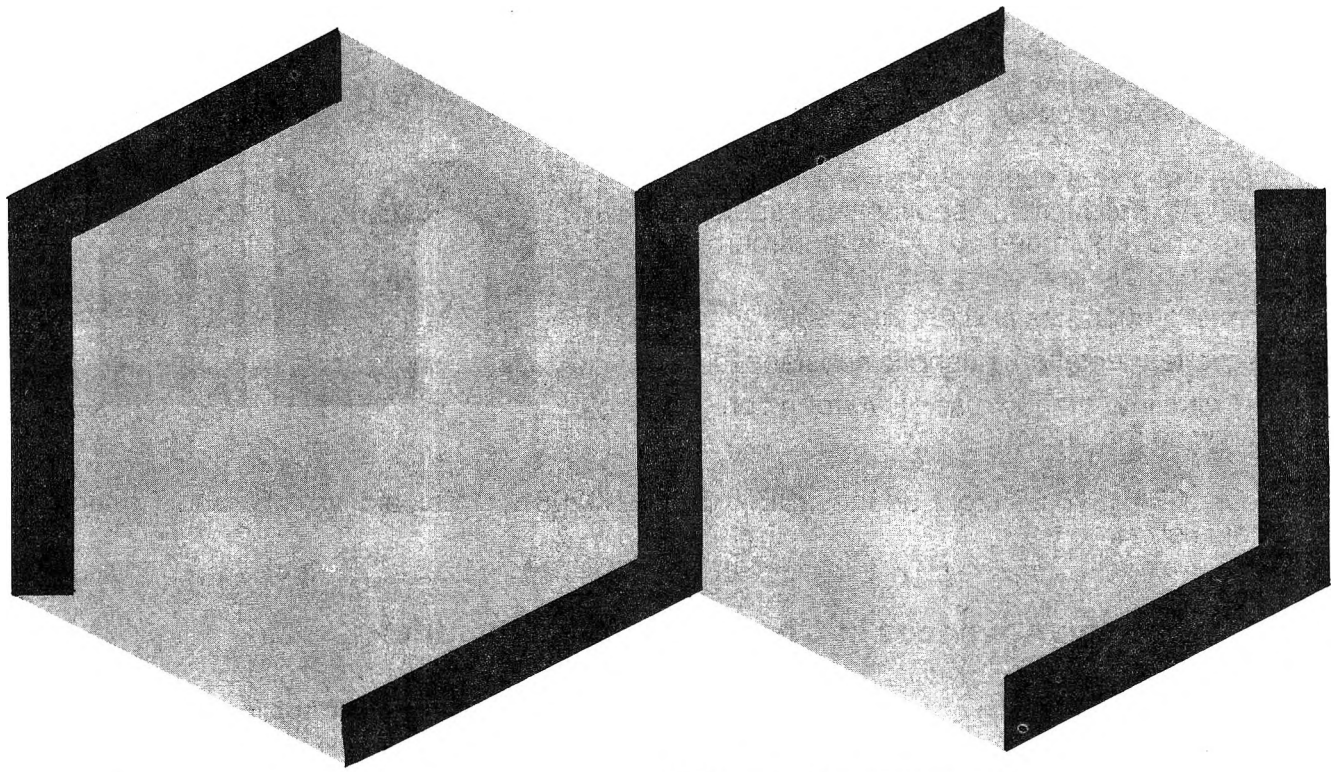

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Quinazolines and 1,4-Benzodiazepines. LXVI.[1] Reactions of a Nitrosoamidine with Nucleophiles

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Received April 12, 1974

N-Nitroso chloro diazepoxide **2** was found to react with a variety of nucleophilic reagents to yield 2-substituted benzodiazepines and diazomethane. This novel reaction was used for the synthesis of the 2-alkoxybenzodiazepines **3**, the 2-hydrazinobenzodiazepines **4** and **5**, the 2-aziridino derivative **6**, the 2-ethylthiobenzodiazepine **11**, the 2-oximinobenzodiazepines **12**, the 2-guanidino derivative **13**, and the 2-malonyl derivatives **14**. Reduction of the nitrosoamidine **2** with lithium aluminum hydride gave the known 4-hydroxybenzodiazepine **15**.

In a recent publication we reported that the nitrosoamidine group in compound **2** can be readily hydrolyzed under basic conditions to give the lactam **1**.[1] As a continuation of this work it has been found that the nitrosoamidine group is readily replaced by a variety of nucleophiles. For example, nucleophilic reagents such as alkoxides, basic amines, and carbanions all effectively replace the nitrosoamidine function in compound **2**. In this manner the facile synthesis of a number of unusual 2-substituted benzodiazepines has been accomplished.

Treatment of the nitrosoamidine **2** with methanol and sodium methoxide at room temperature or with methanol and triethylamine at reflux, led to the imino ether **3a**[2] in nearly quantitative yield. This efficient synthesis of imino ethers under alkaline conditions was especially useful for the preparation of the allylic ether **3b** and the basic ether **3c** (see Scheme I).

Some examples of the use of basic amines as nucleophiles are given by the reaction of hydrazines, hydroxylamines, aziridine, and guanidine with the nitrosoamidine. The reaction with hydrazine proceeded well at room temperature and afforded the known 2-hydrazinobenzodiazepine **4**.[3] Compound **4** was converted by standard techniques into the acetyl derivative **7**. This compound was also obtained together with the triazolobenzodiazepine **10** [4]when the nitrosoamidine **2** was treated with acetylhydrazine. Methylhydrazine attacked the nitrosoamidine **2** predominantly with the more nucleophilic methylated nitrogen and formed compound **5**. The position of the methyl group on the hydrazine was confirmed by the conversion of **5** into the hydrazone **8** on treatment with formaldehyde. The reaction of **2** with ethylenimine at room temperature produced mainly the aziridinobenzodiazepine **6**. Under the more vigorous conditions of refluxing in ethylenimine, the only prodct isolated was compound **9**. The formation of higher "homologs" was not observed under these conditions. It should be pointed out that the aziridine protons of compound **6** appear as a sharp singlet in the nmr spectrum, but in compound **9** where the nitrogen inversion must be quite slow, possibly due to hydrogen bonding, the aziridine protons appear as an A_2B_2 system. The flipping of the diazepine ring seems to be fairly rapid since none of the nmr spectra given in the Experimental Section showed AB systems for the C_3 protons but singlets of varying broadness.

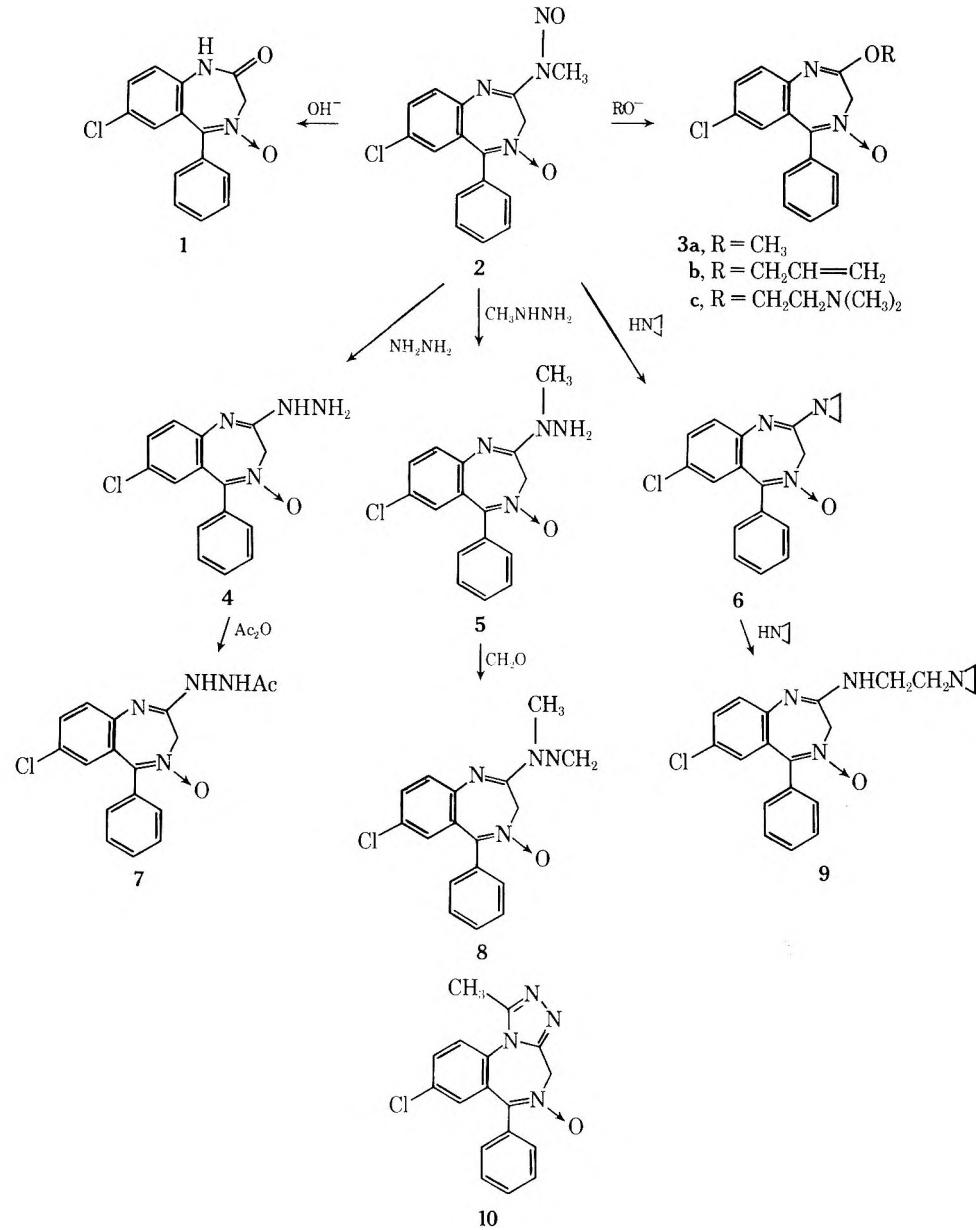
Hydroxylamines also reacted readily with the nitrosoamidine group and led to the formation of compounds **12a** and **12b** (see Scheme II). The spectroscopic data were considered to be more compatible with the assignment of the amidoxime structure rather than with the hydroxyamidine, bearing the double bond in the ring. The 4-deoxy derivative corresponding to **12a** has previously been prepared[5] by reaction of the benzodiazepine-2-thione with hydroxylamine. Since the 2-thione 4-oxide cannot be prepared by the normal route, which would consist of the reaction of **1** with phosphorus pentasulfide, the method *via* the nitrosoamidine obviously has a considerable advantage. The unavailability of the 2-thione 4-oxide was probably also the reason that the thioether **11** has not been described earlier. Compound **11** was obtained by treatment of the nitrosoamidine with potassium ethylthiolate. As expected reaction of **2** with guanidine afforded compound **13**.

The nitrosoamidine also underwent smooth reactions with the carbanions of dimethyl malonate and malononitrile. While the anion of malononitrile reacted at room temperature, the reaction with potassium dimethyl malonate required more vigorous conditions. The spectral data of the products **14a** and **14b** are in agreement with the indicated structures. In the nmr spectra the large chemical shift (11.5 ppm) of the proton on the nitrogen in the 1 position can be explained as being due to hydrogen bonding. The reduction of **14a** and **14b** with phosphorus trichloride led to the corresponding 4-deoxy derivatives **16a** and **16b** while lithium aluminum hydride reduced the nitrosoamidine as expected to the known hydroxylamine **15**.[6]

Experimental Section

Melting points were determined in a capillary melting point apparatus and are not corrected. The uv spectra were measured in 2-propanol on a Cary Model 14 spectrophotometer. Nmr spectra were recorded with a Varian T-60 instrument in deuteriochloroform or deuteriodimethyl sulfoxide with TMS as internal standard. Ir spectra were determined on a Beckman IR-9 spectrometer. Silica gel Merck (70–325 mesh) was used for chromatography.

Scheme I



7-Chloro-2-methoxy-5-phenyl-3*H*-1,4-benzodiazepine 4-Oxide (3a).[2] **A.** Potassium *tert*-butoxide (1 g, 9 mmol) was added to a solution of 10 g (0.03 mol) of 7-chloro-2-(*N*-nitrosomethylamino)-5-phenyl-3*H*-1,4-benzodiazepine 4-oxide (**2**)[1] in 50 ml of ether and 50 ml of methanol. After stirring for 30 min at room temperature, the mixture was partially evaporated. The crystalline material was collected and washed with methanol–water and with methanol to leave 7.9 g of product with mp 186–188°. From the mother liquor another batch of 0.7 g with the same melting point was obtained; yield 8.6 g (94%).

B. A mixture of 3.3 g (0.01 mol) of 7-chloro-2-(*N*-nitrosomethylamino)-5-phenyl-3*H*-1,4-benzodiazepine 4-oxide (**2**), 50 ml of methanol, and 5 ml of triethylamine was refluxed for 10 min. The solvents were evaporated under reduced pressure, and the residue was crystallized from methanol to leave 2.6 g (86%) of product with mp 188–187°.

2-Allyloxy-7-chloro-5-phenyl-3*H*-1,4-benzodiazepine 4-Oxide (3b). A mixture of 3.3 g (0.01 mol) of 7-chloro-2-(*N*-nitrosomethylamino)-5-phenyl-3*H*-1,4-benzodiazepine 4-oxide (**2**), 50 ml of tetrahydrofuran, 5 ml of allyl alcohol, and 0.3 g (2.7 mmol) of potassium *tert*-butoxide was stirred at room temperature for 15 min. The solvents were removed under reduced pressure and the residue was partitioned between saturated aqueous sodium bicarbonate solution and benzene. The benzene layer was separated, dried over sodium sulfate, and evaporated. Crystallization of the residue from ether yielded 1.6 g (49%) of product with mp 118–120°. The analytical sample was recrystallized from acetone–hexane: mp 120–122°; nmr ($CDCl_3$) δ 4.5 (s, 2, C_3–H), 4.8 (d with fine structure, 2, OCH_2), 5.1–6.5 (m, 3, olefinic H), 6.9–7.8 ppm (m, 8, aromatic H); uv λ_{max} 245 mμ (ϵ 25,550), 255 (25,700), 310 (10,400).

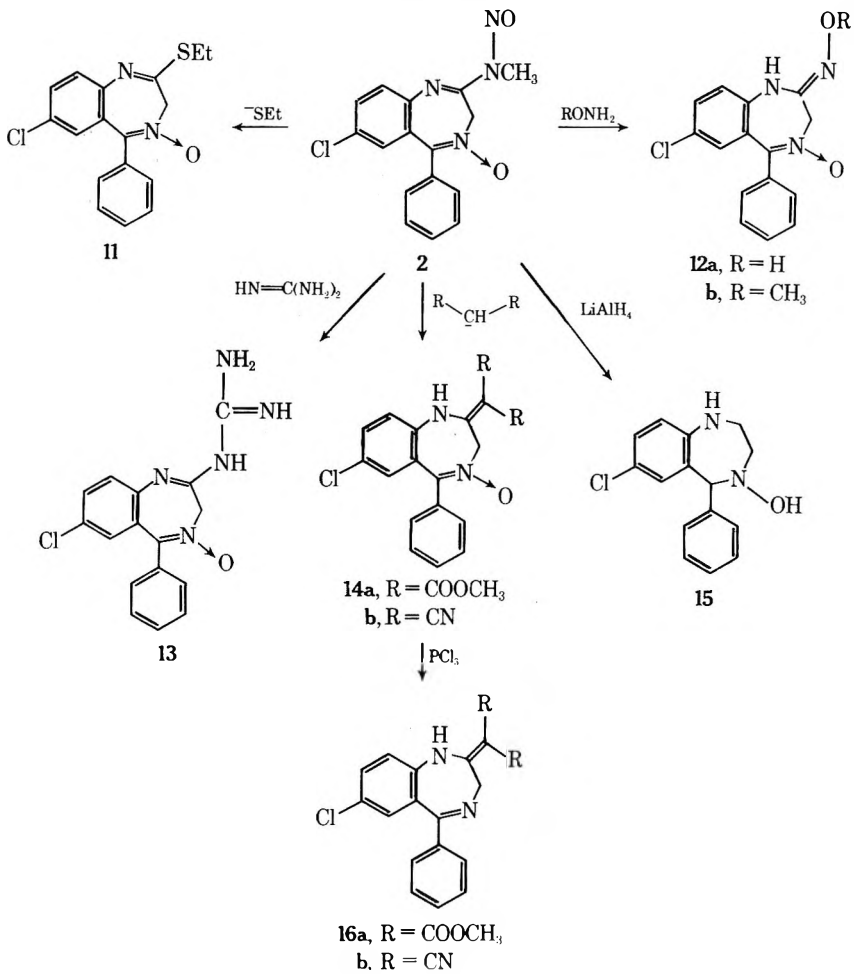
Anal. Calcd for $C_{18}H_{15}ClN_2O_2$: C, 66.16; H, 4.63; N, 8.57 Found: C, 66.16; H, 4.51; N, 8.63.

7-Chloro-2-(2-dimethylaminoethoxy)-5-phenyl-3*H*-1,4-benzodiazepine 4-Oxide (3c). A mixture of 6.6 g (0.02 mol) of 7-chloro-2-(*N*-nitrosomethylamino)-5-phenyl-3*H*-1,4-benzodiazepine 4-oxide, 80 ml of tetrahydrofuran, 10 ml of 2-dimethylaminoethanol, and 0.8 g (7 mmol) of potassium *tert*-butoxide was allowed to stand at room temperature for 16 hr. The solvent was evaporated under reduced pressure and the residue was partitioned between benzene and saturated aqueous sodium bicarbonate solution. The benzene layer was dried over sodium sulfate and evaporated under reduced pressure at the end azeotropically with xylene to remove the rest of 2-dimethylaminoethanol. The residue was chromatographed over 200 g of silica gel which had been treated with 10% (v/v) triethylamine in acetone. The pure fractions eluted with acetone were combined and evaporated. Crystallization from ether–hexane yielded 3 g (42%) of product with mp 105–110°. For analysis it was recrystallized from ether: nmr ($CDCl_3$) δ 2.34 [s, 6, $N(CH_3)_2$], 2.7 (t, 2, J = 6 Hz, N–CH_2–), 4.42 (t, 2, J = 6 Hz, O–CH_2–), 4.53 (s, 2, C_3–H), 7–7.8 ppm (m, 8, aromatic H); uv λ_{max} 245 mμ (ϵ 25,300), 252 (25,400), 310 (10,200).

Anal. Calcd for $C_{19}H_{20}ClN_3O_2$: C, 63.77; H, 5.63; N, 11.74. Found: C, 63.63; H, 5.74; N, 11.75.

7-Chloro-2-hydrazino-5-phenyl-3*H*-1,4-benzodiazepine 4-

Scheme II



Oxide (4).[3] A mixture of 3.3 g (0.01 mol) of 7-chloro-2-(*N*-nitrosomethylamino)-5-phenyl-3*H*-1,4-benzodiazepine 4-oxide (**2**), 30 ml of tetrahydrofuran, 30 ml of methanol, and 3 ml of hydrazine was allowed to sit at room temperature for 1 hr. The solvents were evaporated under reduced pressure and the residue was partitioned between methylene chloride and water. The methylene chloride layer was dried over sodium sulfate and evaporated. Crystallization of the residue from methylene chloride–ether yielded 2.5 g (83%) of yellow product with mp 288–290° (the melting point reported in the literature[3] is considerably lower): nmr (DMSO) δ 4.46 (broad s, 2, C_3–H), 6.78 (m, 1, C_6–H), 7.2–7.7 ppm (m, 7, aromatic H) (the exchangeable protons appear very broad with undefined chemical shift); uv (2-PrOH) λ_{max} 244 mμ (ϵ 52,500), 267 (48,800), infl 310 (20,100), infl 360 (4300); mass spectrum *m/e* 300 (M^+).

Anal. Calcd for $C_{15}H_{13}ClN_4O$: C, 59.91; H, 4.36; N, 18.63. Found: C, 59.85; H, 4.25; N, 18.38.

7-Chloro-2-(1-methylhydrazino)-5-phenyl-3*H*-1,4-benzodiazepine 4-Oxide (5). A mixture of 3.3 g (0.01 mol) of 7-chloro-2-(*N*-nitrosomethylamino)-5-phenyl-3*H*-1,4-benzodiazepine 4-oxide, 30 ml of tetrahydrofuran, 30 ml of methanol, and 3 ml of methylhydrazine was allowed to sit at room temperature for 16 hr.

The solvents were evaporated under reducted pressure and the residue was crystallized from methylene chloride–ether to yield 1.8 g (57%) of light yellow crystals with mp 218–221° dec.

The analytical sample was recrystallized from methylene chloride–2-propanol: mp 220–222° dec; nmr (DMSO-*d*) δ 3.34 (s, 3, NCH_3), 5.05 (broad s, 2, NH_2) (C_3 protons appear as very broad absorption between 4.2 and 5.6 ppm), 6.77 (d, 1, J = 2 Hz, C_6-H), 7.1 (d, 1, J = 8 Hz, C_9-H), 7.35 (q, 1, J_{AB} = 8 Hz, J_{AX} = 2 Hz, C_8-H), 7.45 (s, 5, C_6H_5); uv λ_{max} 246 mμ (ϵ 25,500), 274 (34,200), sh 355 (2700).

Anal. Calcd for $C_{16}H_{15}ClN_4O$: C, 61.05; H, 4.80; N, 17.80. Found: C, 61.08; H, 4.78; N, 17.91.

7-Chloro-2-(2-methylene-1-methylhydrazino)-5-phenyl-3*H*-1,4-benzodiazepine 4-Oxide (8). A mixture of 1 g (3.2 mmol) of 7-chloro-2-(1-methylhydrazino)-5-phenyl-3*H*-1,4-benzodiazepine 4-oxide (**5**), 50 ml of ethanol, and 0.5 ml of aqueous formaldehyde (30%) was heated on the steam bath for 5 min. After concentration down to half of the volume the product crystallized upon cooling. The colorless crystals were collected (0.9 g, 86%) and recrystallized from ethanol for analysis: mp 240–242° dec; nmr ($CDCl_3$) δ 3.44 (s, 3, NCH_3) (C_3 protons appear as very broad signal centered at *ca.* 5.2 ppm), 6.47 (d, 1) and 6.68 (d, 1) (AB system, J = 11 Hz, $=CH_2$). 7–7.9 ppm (m, 8, aromatic H); uv λ_{max} 247 mμ (ϵ23,000), 284 (43,350), infl 360 (2500).

Anal. Calcd for $C_{17}H_{15}ClN_4O$: C, 62.48; H, 4.63; N, 17.15. Found: C, 62.40; H, 4.48; N, 17.06.

2-(2-Acetylhydrazino)-7-chloro-5-phenyl-3*H*-1,4-benzodiazepine 4-Oxide (7). A. Acetic anhydride (1.5 ml) was added to a solution of 2.5 g of 7-chloro-2-hydrazino-5-phenyl-3*H*-1,4-benzodiazepine 4-oxide (**3**) in 50 ml of methylene chloride. After stirring for 15 min at room temperature, the mixture was concentrated and crystallized by addition of ether to yield 2.6 g (91%) of product. The analytical sample was recrystallized from dimethylformanide: mp 272–275°; uv λ_{max} 244–245 mμ (ϵ26,800), 268–269 (30,500), infl 315 (8300), infl 350 (2800).

Anal. Calcd for $C_{17}H_{15}ClN_4O_2$: C, 59.57; H, 4.41; N, 16.35. Found: C, 59.26; H, 4.60; N, 16.34.

B. A mixture of 3.3 g (0.01 mol) of 7-chloro-2-(*N*-nitrosomethylamino)-5-phenyl-3*H*-1,4-benzodiazepine 4-oxide (**2**), 30 ml of ethanol, 3 ml of triethylamine, and 2 g of acetylhydrazine was refluxed for 24 hr. The solvent was evaporated and replaced by 1-butanol and refluxing was continued for another day. The residue obtained after evaporation was crystallized from methylene chloride. The crystals were collected and recrystallized from methylene chloride–ethanol to leave 1.85 g of product with mp 265–270° dec. The filtrate was chromatographed over 70 g of silica gel using 10% ethanol in methylene chloride. Beside an additional amount of 0.11 g of product **7** (total yield 57%), 0.31 g (9.5%) of 8-chloro-1-methyl-6-phenyl-4*H*-*s*-triazolo[4,5-*a*][1,4]benzodiazepine 5-oxide (**10**)[4] was also obtained.

2-(1-Aziridino)-7-chloro-5-phenyl-3*H*-1,4-benzodiazepine 4-Oxide (6). Aziridine (15 ml) was added to a solution of 10 g (0.03

mol) of 7-chloro-2-(*N*-nitrosomethylamino)-5-phenyl-3*H*-1,4-benzodiazepine 4-oxide (**2**) in 100 ml of dry tetrahydrofuran. After stirring for 5 hr at room temperature under a stream of nitrogen, the solvent was removed under reduced pressure and the residue was crystallized from ether–hexane to yield 5.7 g of product with mp 135–140°.

It was further purified by chromatography over 100 g of silica gel using methylene chloride–ethyl acetate 1:1 (v/v). The pure product was crystallized from ether: mp 136–138°; nmr ($CDCl_3$) 2.43 [s, 4, $N(CH_2)_2$], 4.55 (s, 2, C_3-H), 6.9–7.8 ppm (m, 8, aromatic H); uv λ_{max} 239 mμ (ε 27,800), 272 (28,400), infl 310 (9200).

Anal. Calcd for $C_{17}H_{14}ClN_3O$: C, 65.49; H, 4.52; N, 13.47. Found: C, 65.39; H, 4.49; N, 13.44.

2-[2-(1-Aziridino)ethylamino]-7-chloro-5-phenyl-3*H*-1,4-benzodiazepine 4-Oxide (9). A mixture of 10 g (0.03 mol) of 7-chloro-2-(*N*-nitrosomethylamino)-5-phenyl-3*H*-1,4-benzodiazepine 4-oxide (**2**) and 30 ml of aziridine was stirred for 10 min under a stream of nitrogen. The escaping diazomethane was destroyed by bubbling through a solution of acetic acid in ether. After heating to reflux for 5 min, the reaction mixture was partitioned between water and methylene chloride. The organic layer was washed with water, dried over sodium sulfate, and evaporated.

Crystallization of the residue from ether yielded 8.6 g (80%) of product with mp 160–162°. For analysis it was recrystallized from methylene chloride–ether: mp 163–165°; nmr (DMSO-*d*) δ 1.1 (m, 2) and 1.53 [m, 2, A_2B_2 system, $N(CH_2)_2$], 2.32 (t, 2, *J* = 6.5 Hz, $-CH_2-N$), 3.4 (q, 2, *J* = 6 Hz, $-NHCH_2-$), 4.4 (broad s, 2, C_3-H), 6.7 (d, 1, *J* = 2 Hz, C_6-H), 7.05 (d, 1, *J* = 8.5 Hz, C_9-H), 7.1–7.6 (m, 6, C_6H_5 and C_8-H), 8.06 ppm (t, 1, *J* = 5.5 Hz, NH); uv λ_{max} 224 mμ (ε 28,600), 267 (33,150), infl 315 (7300), infl 355 (2900).

Anal. Calcd for $C_{19}H_{19}ClNO_4O$: C, 64.31; H, 5.40; N, 15.79. Found: C, 64.36: H, 5.55; N, 16.00.

7-Chloro-5-phenyl-2-ethylthio-3*H*-1,4-benzodiazepine 4-Oxide (11). A mixture of 16.5 g (0.05 mol) of 7-chloro-2-(*N*-nitrosomethylamino)-5-phenyl-3*H*-1,4-benzodiazepine 4-oxide (**2**), 25 ml of ethanethiol, 150 ml of tetrahydrofuran, and 1 g of potassium *tert*-butoxide was stirred for 20 min with cooling in ice–water. The reaction mixture was partitioned between saturated aqueous sodium bicarbonate solution and benzene. The benzene layer was dried and evaporated. Chromatography of the residue on 250 g of silica gel using 10% ethyl acetate in methylene chloride and crystallization of the clean fractions from methylene chloride–ether–hexane yielded 4.7 g (28%) of product with mp 142–144°: nmr ($CDCl_3$) δ 1.27 (t, 3, *J* = 7 Hz $-CH_3$), 3.14 (q, 2, *J* = 7 Hz, $S-CH_2$), 4.43 (s, 2, C_3-H), 7.03 (m, 1, C_6-H), 7.2–7.9 ppm (m, 7, aromatic H); uv λ infl 224 mμ (ε 18,800), max 246 (21,400), 284 (32,050), infl 320 (9700).

Anal. Calcd for $C_{17}H_{15}ClN_2OS$: C, 61.72; H, 4.57; N, 8.47. Found: C, 61.54; H, 4.63; N, 8.41.

The major product of the reaction (7.5 g) was identified as 7-chloro-2-methylamino-5-phenyl-3H-1,4-benzodiazepine 4-oxide.

7-Chloro-2,3-dihydro-2-hydroxyimino-5-phenyl-1*H*-1,4-benzodiazepine 4-Oxide (12a). A mixture of 3.3 g (0.01 mol) of 7-chloro-2-(*N*-nitrosomethylamino)-5-phenyl-3*H*-1,4-benzodiazepine 4-oxide (**2**), 35 ml of ethanol, 5 ml of triethylamine, and 3 g of hydroxylamine hydrochloride was heated to reflux for 20 min. The product was crystallized by addition of water. It was dissolved in methylene chloride–ethanol. The solution was dried over sodium sulfate and evaporated. Crystallization from methylene chloride–ethanol yielded 2.2 g (73%) of product with mp 250–255° dec: nmr (DMSO-*d*) δ 4.51 (broad s, 2, C_3-H), 6.75 (m, 1, C_6-H), 7.2–7.6 (m, 7, aromatic H), 9.5 (s, 1, OH or NH), 10.2 ppm (s, 1, OH or NH); uv λ_{max} 240 mμ (ε 29,000), infl 279 (17,900), infl 310 (10,000), infl 360 (2800); ir (KBr) 1660 cm^{-1} (C=N–OH).

Anal. Calcd for $C_{15}H_{12}ClN_3O_2$: C, 59.71; H, 4.00; N, 13.93. Found: C, 59.47; H, 4.16; N, 13.80.

7-Chloro-2,3-dihydro-2-methoxyimino-5-phenyl-1*H*-1,4-benzodiazepine 4-Oxide (12b). A mixture of 3.3 g (0.01 mol) of 7-chloro-2-(*N*-nitrosomethylamino)-5-phenyl-2*H*-1,4-benzodiazepine 4-oxide (**2**), 35 ml of triethylamine, and 3 g of methoxyamine hydrochloride was refluxed for 16 hr. The crystals precipitated by addition of water were collected and recrystallized from methylene chloride–ethanol to yield 2.5 g (79%) with mp 232–234°. The analytical sample was recrystallized from the same solvents: nmr (DMSO-*d*) δ 3.77 (s, 3, OCH_3), 4.53 (broad s, 2, C_3-H), 6.75 (m, 1, C_6-H), 7.2–7.6 (m, 7, aromatic H), 9.6 ppm (s, 1, NH); uv λ_{max} 242 mμ (ε 29,600), infl 259 (4400), infl 310 (9600), infl 357 (2600); ir KBr) 1650 cm^{-1} (–C=N–O).

Anal. Calcd for $C_{16}H_{14}ClN_3O_2$: C, 60.86; H, 4.47; N, 13.31. Found: C, 60.84; H, 4.40; N, 13.38.

7-Chloro-2-guanidino-5-phenyl-3*H*-1,4-benzodiazepine 4-Oxide (13). A mixture of 3.3 g (0.01 mol) of 7-chloro-2-(*N*-nitrosomethylamino)-5-phenyl-3*H*-1,4-benzodiazepine 4-oxide (**2**), 30 ml of tetrahydrofuran, 50 ml of *tert*-butyl alcohol, 2 g of guanidine hydrochloride, and 2.3 g of potassium *tert*-butoxide was stirred at room temperature for 3 hr. After evaporation under reduced pressure, the residue was washed with water and dissolved in methylene chloride–ethanol. The solution was dried and evaporated. Crystallization from methylene chloride–ethanol yielded 2 g (61%) of product with mp 245–248° dec. For analysis it was recrystallized from the same solvents: mp 250–252° dec; nmr (DMSO-*d*) δ 4.33 (s, 2, C_3-H), 6.8 (d, 1, *J* = 2 Hz, C_6-H), 7.16 (d, 1, *J* = 8.5 Hz, C_9-4), 7.2–7.6 (m, 6, C_6H_5 and C_8-H), 4 exchangeable protons appear as very broad signal between 7.4 and 10 ppm; uv λ_{max} 245 mμ (ε 17,700) 290 (38,600) infl 300 (3400).

Anal. Calcd for $C_{16}H_{14}ClN_5O$: C, 58.63; H, 4.31; N, 21.37. Found: C, 58.74; H, 4.33; N, 21.38.

7-Chloro-1,3-dihydro-2-(dimethoxymalonylidene)-5-phenyl-2*H*-1,4-benzodiazepine 4-Oxide (14a). A mixture of 3.3 g (0.01 mol) of 7-chloro-2-(*N*-nitrosomethylamino)-5-phenyl-3*H*-1,4-benzodiazepine 4-oxide (**2**), 20 ml of dimethylformamide, 5 ml of dimethyl malonate, and 1.3 g (0.0115 mol) of potassium *tert*-butoxide was heated to 100–120° for 5 min under a stream of nitrogen. After the addition of 2 ml of glacial acetic acid the cool reaction mixture was partitioned between methylene chloride and water. The methylene chloride layer was washed with water, dried over sodium sulfate, and evaporated. Crystallization from ether yielded 2.75 g (69%) of light yellow product with mp 194–195°. For analysis it was recrystallized from methylene chloride–hexane: nmr ($CDCl_3$) δ 3.78 (s, 3, OCH_3), 3.84 (s, 3, OCH_3), 4.92 (broad s, 2, C_3-H), 7–7.8 (m, 8, aromatic H), 11.6 ppm (s, 1, NH); uv λ_{max} 228 mμ (ε 23,500), 304 (38,110), infl 340 (12,500); ir ($CHCl_3$) 3200 (NH), 1720, 1675 cm^{-1} (COOMe).

Anal. Calcd for $C_{20}H_{17}ClN_2O_5$: C, 59.93; H, 4.28; N, 6.98. Found: C, 59.78; H, 4.21; N, 6.90.

7-Chloro-1,3-dihydro-3-(dicyanomethylene)-5-phenyl-2*H*-1,4-benzodiazepine 4-Oxide (14b). A mixture of 3.3 g (0.01 mol) of 7-chloro-2-(*N*-nitrosomethylamino)-5-phenyl-3*H*-1,4-benzodiazepine 4-oxide (**2**), 20 ml of dimethylformamide, 2.3 g (0.035 mol) of malononitrile, and 1.3 g (0.0115 mol) of potassium *tert*-butoxide was stirred at room temperature for 30 min. After the addition of 2 ml of glacial acetic acid the product was crystallized by addition of water. It was collected, washed with water, and recrystallized from methylene chloride–ethanol to leave 2.65 g (79%) with mp 240–242° dec. Nmr indicated these crystals to contain methylene chloride. Other solvents also produced solvates, *e.g.*, 2-propanol and dioxane. A sample recrystallized from dioxane had the same melting point and analyzed well for a hemidioxanate: nmr (DMSO-*d*) 3.57 (s, 4, dioxane), 4.83 (s, 2, C_3-H), 6.95 (m, 1, C_6-H), 7.2–7.7 (m, 7, aromatic H), *ca.* 11.5 ppm (very broad signal N-H); uv λ_{max} 231 mμ (ε 16,750), 303 (35,400), infl 300 (13,700).

Anal. Calcd for $C_{18}H_{11}ClN_4O \cdot \frac{1}{2}C_4H_8O_2$: C, 63.41; H, 3.99; N, 14.79. Found: C, 63.42; H, 3.93; N, 14.65.

7-Chloro-1,3-dihydro-2-(dimethoxymalonylidene)-5-phenyl-2*H*-1,4-benzodiazepine (16a). Phosphorus trichloride (4 ml) was added to a solution of 4 g (0.01 mol) of 7-chloro-1,3-dihydro-2-(dimethoxymalonylidene)-5-phenyl-2*H*-1,4-benzodiazepine 4-oxide in 100 ml of methylene chloride. After sitting at room temperature overnight the solution was washed with 10% aqueous sodium carbonate solution. The methylene chloride layer was dried and evaporated. Crystallization of the residue from 2-propanol and recrystallization from methylene chloride–2-propanol yielded 3.2 g (83%) of product with mp 138–140°. A different crystalline modification with mp 165–166° was also observed: nmr ($CDCl_3$) δ 3.75 (s, 3, OCH_3), 3.85 (s, 3, OCH_3), 4.43 (broad s, 2, C_3-H), 7.05 (d, 1, *J* = 8.5 Hz, C_9-H), 7.1–7.6 (m, 7, aromatic H), 11.5 ppm (s, 1, NH); uv λ sh 277 mμ (ε 14,000), max 310 (31,200); ir ($CHCl_3$) 3150 (NH), 1720, 1670 cm^{-1} ($COOCH_3$).

Anal. Calcd for $C_{20}H_{17}ClN_2O_4$: C, 62.43; H, 4.45; N, 7.28. Found: C, 62.68; H, 4.47; N, 7.11.

7-Chloro-1,3-dihydro-2-(dicyanomethylene)-5-phenyl-2*H*-1,4-benzodiazepine (16b). A mixture of 1 g of 7-chloro-1,3-dihydro-2-(dicyanomethylene)-5-phenyl-2*H*-1,4-benzodiazepine 4-oxide (**14b**), 100 ml of methylene chloride, and 1 ml of phosphorus trichloride was stirred at room temperature for 5 hr. The solution was washed with 10% aqueous sodium carbonate solution, dried over sodium sulfate, and evaporated. Chromatography of the residue over 20 g of silica gel using 10% ethyl acetate in methylene chloride and crystallization from tetrahydrofuran–ethyl acetate yielded 0.55 g (58%) of product with mp 274–276°.

Anal. Calcd for $C_{18}H_{11}ClN_4$: C, 67.82; H, 3.48; N, 17.58. Found:

C, 67.95; H, 3.40; N, 17.33.

7-Chloro-4-hydroxy-5-phenyl-2,3,4,5-tetrahydro-1*H*-1,4-benzodiazepine (15).[6] A solution of 3.3 g (0.01 mol) of 7-chloro-2-(*N*-nitrosomethylamino)-5-phenyl-3*H*-1,4-benzodiazepine 4-oxide (**2**) in 10 ml of tetrahydrofuran was added to a suspension of 2 g (0.05 mol) of lithium aluminum hydride in 50 ml of ether cooled to −20°. The mixture was stirred at −20 to −15° for 15 min and 10 ml of water was added cautiously. The inorganic material was separated by filtration; the filtrate was dried over sodium sulfate and evaporated. Crystallization of the residue from 2-propanol yielded 2.2 g of product with mp and mmp 167–169°.

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Quinoxaline 1,4-Dioxides. Substituent Effects on the Reaction of Benzofurazan 1-Oxides with Carbonyl Compounds[1a]

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Two types of reactions were used to study the effect of substituents (CH_3, OCH_3, and CO_2CH_3) on the condensation of 5(6)-substituted benzofurazan 1-oxides with acetonyl methyl sulfide (BFO reaction, A), and 4-substituted *o*-quinone dioximes with pyruvaldehyde (OQD reaction, B). Each reaction allowed the isolation of only one of the two possible isomers and the study of its nmr properties. The nitrogen atom is an electrophile in reaction A and a nucleophile in reaction B. Thus the same substituent is expected and does favor the formation of opposite ratios of 6:7 isomeric substituted quinoxaline hydroxamic acid esters **4**. The ratios were determined from nmr spectra of these esters where the chemical shifts of the H-5 and H-8 protons, unlike their counterparts in quinoxaline 1,4-dioxides, are assignable. The results are interpreted by assuming that benzofurazan 1-oxides react in their ortho dinitroso tautomeric forms.

A few years ago, an elegant method for the preparation of quinoxaline 1,4-dioxides was reported. It involved a condensation of benzofurazan 1-oxide (BFO) with either enamines or enolate anions.[2,3] Although the exact mechanism was not elucidated, initial attack at either one of the two nitrogen atoms of BFO followed by cyclization with concomitant elimination of amines, in the former, and water, in the latter, would explain the experimental results. Partial support for this mechanism came from the isolation of dihydroquinoxaline 1,4-dioxide which is a suggested intermediate in the above mechanism.[4]

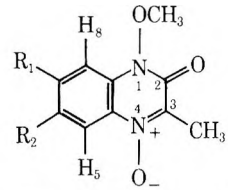
Only one quinoxaline 1,4-dioxide can be obtained when a carbonyl compound, which under the reaction conditions forms one enolic form, is condensed with unsubstituted BFO. However, a mixture of 6- and 7-substituted quinoxaline 1,4-dioxide isomers is expected when 5(6)-substituted BFO's are used. Indeed such a case has been reported when 5(6)-trifluoromethyl BFO was condensed with acetyl acetone.[5]

Contradictory reports concerning reactions of other 5(6)-substituted BFO's with various ketones have also appeared. While Haddadin and coworkers claimed the formation of mixture of isomers when the 5(6)-substituted BFO's (**1a**, **1b**, and **1d**) were condensed with benzoylacetophenone,[6] Mason and Tennant reported the isolation of only the 7-substituted quinoxaline 1,4-dioxide when BFO's (**1b**, **1d**, and **1e**) were allowed to react with benzoylacetonitrile.[7] Later results partially supported the above claims. While the condensation of β-keto esters with 5(6)-chloro-BFO (**1d**) was found to give a mixture of the corresponding 6- and 7-chloroquinoxaline 1,4-dioxides, 5(6)-methoxy-BFO (**1b**) furnished the 7-methoxy isomer only.[8] In the present work a rigorous study of isomer formation was made in which the electronic effects of a 5(6) substituent on the course of BFO reaction with acetonyl methyl sulfide is reported.

Determination of isomer ratios in 6(7)-substituted quinoxaline 1,4-dioxides is not an easy task since both isomers have very similar spectral and chromatographic properties. Their conversion to other derivatives where H-5 and H-8, unlike their counterparts in the parent compounds, are in different chemical environment allows full structural determination by nmr. Such a conversion has been reported earlier when 2-cyano-3-phenyl-7-substituted quinoxaline 1,4-dioxides were treated with sodium ethoxide to furnish the corresponding hydroxamic acids.[7] In the present compounds (**2a**, **2b**, and **2c**) treatment with aqueous potassium hydroxide furnished the highly insoluble hydroxamic acids (**3**) followed by conversion to the esters (**4**) made possible their structural assignment by examining the aromatic region in the nmr spectra (Scheme I). Unlike the earlier method, these ompounds have no other aromatic protons which could complicate spectral analyses.

Scheme I depicts two types of reactions (A and B) used to determine substituent effects; a BFO reaction (A) in which the nitrogen atom is an electrophile, and a condensa-

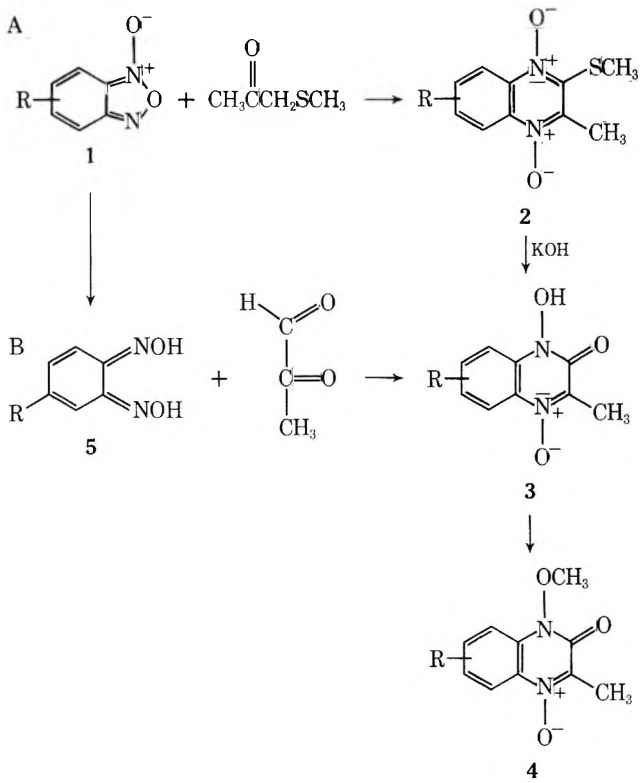
Table I
Chemical Shifts of the Hydroxamic Acid Esters[a]



R_1	R_2	H-5	H-6	H-7	H-8	1-OCH_3	3-CH_3	6 or 7 subs
H	OCH_3	7.9		7.31	7.61	4.18	2.57	3.95
OCH_3	H	8.33	6.98		6.98	4.17	2.53	3.98
H	CH_3	8.23		7.2	7.2	4.16	2.53	2.50
				7.6	7.6			
CH_3	H	8.23	7.2		7.4	4.16	2.53	2.53
H	CO_2CH_3	9.17		8.45	7.8	4.25	2.63	4.06
CO_2CH_3	H	8.61	8.15		8.4	4.26	2.63	4.06

[a] Determined in $CDCl_3$ and expressed in parts per million downfield from TMS. The expected multiplets with the usual ortho, meta, and para coupling constants were observed.

Scheme I



a, R = CH_3
b, R = OCH_3
c, R = CO_2CH_3
d, R = Cl
e, R = Br

tion involving *o*-quinone dioximes (OQD), obtained by reducing BFO's, with pyruvaldehyde[9] (B) in which the nitrogen atom is a nucleophile. Thus, the same substituents would be expected to exert opposite effects on the nitrogen atom involved in the reaction. An electron releasing substituent would reduce the electrophilicity of the nitrogen atom in A while enhancing its nucleophilicity in B. Thus, a major isomer in reaction A, which is obtained pure only by repeated crystallization, would be expected to be a minor one in B. The minor isomer in reaction A becomes a major product in reaction B thus allowing its isolation in pure form. All transformations, except for the BFO condensation reactions (A), have yields ranging from 85 to 90%, minimizing chances of loss of minor isomers.

Table II
Percentages of 7:6 Isomers in the Hydroxamic Acid Methyl Esters (4)

R	BFO reaction A	OQD reaction B
CH_3	71:29	35:65
OCH_3	83:17	20:80
CO_2CH_3	20:80	82:18

The quinoxaline 1,4-dioxides were prepared following earlier procedures in moderate yields.[10] Careful column chromatography of the mother liquors allowed the isolation of all the products formed with overall yields of 50–60%.[11]

A summary of the nmr data used in calculating the various isomer percentages is presented in Table I. The chemical shifts of the aromatic protons in two pure isomers were first determined. Nmr spectra of mixtures of isomers from reactions A and B were then obtained.

Differences in the chemical shifts of the H-5 nuclei, which are doublets with meta coupling constants in one case and ortho in the other, allow the detection of the minor isomer. Its percentage is calculated directly from the integration spectrum as compared to the remainder of the aromatic region. That we are dealing with isomeric mixtures rather than impurities is evidenced by the correct elemental analyses obtained on the compounds whose nmr spectra were used for the calculations.

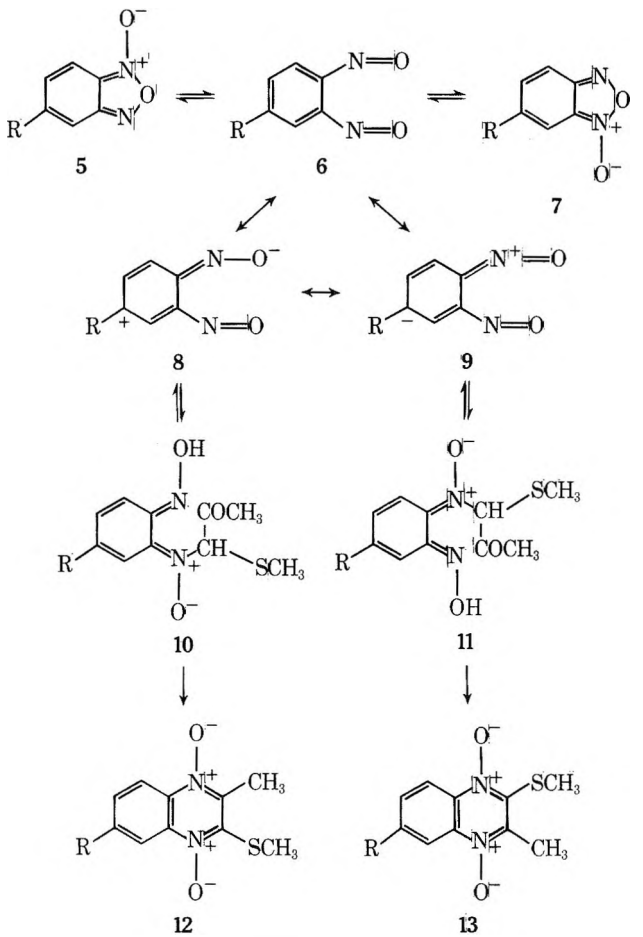
The percentages of 7:6 isomers in the hydroxamic acid methyl esters (4) are shown in Table II. As was predicted earlier, a major isomer in reaction A became the minor one in reaction B.

The experimental results on 5(6)-methoxy-BFO (Table I) confirm the earlier work of Haddadin and coworkers on the formation of isomerides.[6] However, they are in partial agreement with the findings of Mason and Tennant[7] and Duerckheimer[8] in that the major isomer observed corresponds to the *only* product they isolated.

These results are best rationalized by assuming that BFO reacts in its *o*-dinitrosobenzene form. Intermediacy of this compound has been proposed in the rapid interconversions of BFO between forms **5** and **7**.[12]

It can be seen from Scheme II that an electron-releasing substituent would stabilize the resonance form **8** over **9**, while an electron-accepting substitutent would have the

Scheme II



a, R = CH_3
b, R = OCH_3
c, R = CO_2CH_3

opposite effect. Accordingly, the meta nitroso group would suffer initial nucleophilic attack in the former case while the para nitroso group would be more reactive in the latter. Thus 5(6)-methoxy- and 5(6)-methyl-BFO would be expected to furnish the 7-substituted compounds (**12a** and **12b**) as the major isomers while 5(6)-carbomethoxy-BFO leads preferentially to the 6-isomer **13c**. This is in full agreement with the experimental results.

An earlier proposal[7] suggested initial attack at N-3 in the most stable form of BFO, which is **5** for 5(6)-methoxy-BFO and **7** for 5(6)-carbomethoxy BFO,[13] to rationalize the formation of certain isomers. Although such a mechanism explains the results obtained from the reactions of 5(6)-methoxy- and 5(6)-carbomethoxy-BFO, it does not accommodate the data on the 5(6)-methyl compound. A 50:50 mixture of 6- and 7-methylquinoxaline 1,4-dioxide isomers would be expected from the latter BFO since the tautomeric forms **5** and **7** were found to be of equal stability.

Earlier attempts to trap *o*-dinitrosobenzene have not been successful.[14] The present work offers a significant experimental finding to establish the intermediacy of **6** in the rapid equilibrations of benzofuroxans. Similar arguments can be used to explain the results from the OQD reaction with pyruvaldehyde where in each case the opposite isomer to that obtained from the BFO reaction is expected and does predominate.

Experimental Section

Melting points were taken on a Thomas-Hoover capillary melting point apparatus and are uncorrected. The nmr spectra were recorded on a Varian A-60 spectrometer. Microanalyses were performed by Micro-Analysis, Inc., Marshallton, Del.

General Method for the Preparation of Quinoxaline 1,4-Dioxides. Nearly equimolar quantities of BFO and acetonyl methyl sulfide were dissolved in methanol, ammonia gas was bubbled in for a few minutes, and the reaction mixture was allowed to stand at room temperature overnight. The crystalline product was filtered off and washed with methanol and dried. Individual compounds follow.

3,6(7)-Dimethyl-2-methylthioquinoxaline 1,4-Dioxide (2a). 5(6)-Methyl-BFO (**1a**) (4.0 g, 26.7 mmol) and acetonyl methyl sulfide (2.4 g, 23.1 mmol) were dissolved in methanol (100 ml). The product isolated weighed 1.1 g. Evaporation of the mother liquor gave a residue (5.0 g) which was chromatographed on silica gel (150 g). Eluting with chloroform (700 ml) gave an additional amount of the product (1.5 g) bringing the yields up to 45%. Recrystallization from methanol gave the analytical sample: mp 175–177°; nmr ($CDCl_3$) δ 2.6 (s, 3), 2.7 (s, 3), 2.9 (s, 3), 7.6 (q, 1, J = 2 and 9 Hz), 8.3 (d, 1, J = 2 Hz), 8.9 (d, 1, J = 9 Hz).

Anal. Calcd for $C_{11}H_{12}N_2O_2S$: C, 55.92; H, 5.11; N, 11.85. Found: C, 56.04; H, 4.92; N, 11.71.

Further elution of the column with 15% methanol in chloroform (600 ml) furnished 3,6(7)-dimethyl-1-hydroxy-2-iminoquinoxaline 4-oxide (0.22 g), mp 239–240°. The analytical sample was obtained from water.

Anal. Calcd for $C_{10}H_{11}N_3O_2$: C, 58.74; H, 5.37; N, 20.37. Found: C, 58.67; H, 5.38; N, 20.48.

6(7)-Methoxy-3-methyl-2-methylthioquinoxaline 1,4-Dioxide (2b). (5)6-Methoxy-BFO (**1b**) (1.3 g, 7.9 mmol) and acetonyl methyl sulfide (1.0 g, 9.6 mmol) were dissolved in methanol (20 ml). The product obtained after column chromatography (as above) weighed 1.35 g (68%). The analytical sample was obtained from methanol: mp 140–141°; nmr ($CDCl_3$) δ 2.7 (s, 3), 2.9 (s, 3) 4.0 (s, 3) 7.3 (q, 1, J = 3 and 9 Hz), 7.9 (d, 1, J = 3 Hz), 8.5 (d, 1, J = 9 Hz).

Anal. Calcd for $C_{11}H_{12}N_2O_3S$: C, 52.38; H, 4.76; N, 11.11. Found: C, 52.02; H, 4.83; N, 11.11.

The corresponding ammonolysis product 1-hydroxy-2-imino-6(7)-methoxy-3-methylquinoxaline 4-oxide was similarly obtained, mp 253–255°.

Anal. Calcd for $C_{10}H_{11}N_3O_3$: C, 54.29; H, 4.97; N, 19.00. Found: C, 54.51; H, 5.23; N, 18.79.

Methyl-3-methyl-2-methylthioquinoxaline-6(7)-carboxylate 1,4-Dioxide (2c). 5(6)-Carbomethoxy-BFO (**1c**) (5.0 g, 27 mmol) and acetonyl methyl sulfide (2.7 g, 27 mmol) were dissolved in methanol (100 ml); the product weighed 1.9 g (44% based on recovered BFO of 2.0 g). The analytical sample was obtained from methanol–chloroform: mp 181–183°; nmr ($CDCl_3$) δ 2.8 (s, 3), 2.9 (s, 3), 4.1 (s, 3), 8.4 (q, 1, J = 1 and 8 Hz), 8.7 (q, 1, J = 2 and 8 Hz), 9.2 (br s, 1).

Anal. Calcd for $C_{12}H_{12}N_2O_4S$: C, 51.41; H, 4.28; N, 10.00. Found: C, 51.24; H, 4.06; N, 9.80.

3,6-Dimethyl- and 3,7-Dimethyl-1-hydroxyquinoxalin-2-one 4-Oxides (3a). Method A. A suspension of **2a** (1.1 g, 4.58 mmol) in 3% aqueous potassium hydroxide (60 ml) was heated on a steam bath until a solution formed. This was cooled and neutralized with concentrated hydrochloric acid. The precipitate formed weighed 0.65 g (70%). Crystallization from trifluoroacetic acid furnished the analytical sample, mp 228–230°.

Anal. Calcd for $C_{10}H_{10}N_2O_3$: C, 58.26; H, 4.89; N, 13.58. Found: C, 57.95; H, 5.07; N, 13.35.

Method B. To a suspension of **5a** (1.1 g, 7.5 mmol) in water (35 ml) was added 40% pyruvaldehyde (3 ml, 7.5 mmol). The red suspension was warmed up on a steam bath until the color changed to yellow. Upon cooling a precipitate formed (1.4 g). The analytical sample was obtained from trifluoroacetic acid, mp 228–232°.

Anal. Calcd for $C_{10}H_{10}N_2O_3$: C, 58.26; H, 4.89; N, 13.58. Found: C, 58.25; H, 5.04; N, 13.32.

1-Hydroxy-6-methoxy- and 1-Hydroxy-7-methoxy-3-methylquinoxalin-2-one 4-Oxides (3b). Method A. The procedure used for the preparation of **3a** was followed to convert **2b** (2.1 g, 8.4 mmol) to the product (1.7 g, 92%). The analytical sample was obtained from trifluoroacetic acid–methanol, mp 210–212°.

Anal. Calcd for $C_{10}H_{10}N_2O_4$: C, 54.06; H, 4.54; N, 12.61. Found: C, 53.99; H, 4.55; N, 12.48.

Method B. An identical procedure with that mentioned above was applied to **5b** (0.85 g, 5 mmol) and pyruvaldehyde (2 ml of 40% solution) to furnish the product (0.8 g, 80%), mp 252–255°.

Anal. Calcd for $C_{10}H_{10}N_2O_4$: C, 54.06; H, 4.54; N, 12.61. Found: C, 53.78; H, 4.48; N, 12.74.

1-Hydroxy-3-methylquinoxalin-2-one-6- and -7-carboxylic Acid 4-Oxides (3, R = CO_2H). Compound **2c** (0.8 g, 3 mmol) was suspended in a mixture of methanol (5 ml) and 1 *N* potassium hydroxide (50 ml) and was heated on a steam bath for 0.5 hr. The cooled solution was acidified with 6 *N* hydrochloric acid. The precipitate formed 0.6 g (80%) was crystallized from trifluoroacetic acid–methanol, mp above 280°.

Anal. Calcd for $C_{10}H_8N_2O_5$: C, 50.85; H, 3.39; N, 11.86. Found: C, 50.61; H, 3.67; N, 11.56.

Methyl-1-hydroxy-3-methylquinoxalin-2-one-6- and -7-carboxylate 4-Oxides (3c). The dioxime **5c** (0.96 g, 4.9 mmol) was suspended in water (30 ml) and heated on a steam bath. Pyruvaldehyde solution (40%) (1.5 ml) was added to the hot solution and the reaction mixture was allowed to cool down to room temperature. A crystalline precipitate formed (0.84 g, 70%). The analytical sample was obtained by crystallization from trifluoroacetic acid–methanol, mp 235°.

Anal. Calcd for $C_{11}H_{10}N_2O_5$: C, 52.80; H, 4.00; N, 11.20. Found: C, 53.09; H, 4.05; N, 11.28.

3,6-Dimethyl-1-methoxyquinoxalin-2-one 4-Oxide (4a). Crude **3a** (0.9 g, 4.4 mmol), obtained *via* method B was added to previously purified dimethyl sulfate (0.6 ml, 6.2 mmol) dissolved in dry acetone (250 ml). Potassium carbonate (0.75 g) was added and the reaction mixture was refluxed overnight. Acetone was evaporated and the residue was partitioned between chloroform and aqueous potassium carbonate. The organic layer was dried over magnesium sulfate, filtered, and evaporated to dryness to yield a residue (0.74 g). This was crystallized once from chloroform–ether to give the analytical sample, mp 146–148°. The nmr spectrum of this material showed the predominance of the 6-methyl over the 7-methyl isomer.

Anal. Calcd for $C_{11}H_{12}N_2O_3$: C, 60.21; H, 5.46; N, 12.65. Found: C, 60.19; H, 5.56; N, 12.84.

The pure 6 isomer was obtained after three crystallizations, mp 171–173°.

Anal. Calcd for $C_{11}H_{12}N_2O_3$: C, 60.21; H, 5.46; N, 12.65. Found: C, 60.09; H, 5.45; N, 12.93.

3,7-Dimethyl-1-methoxyquinoxalin-2-one 4-Oxide (4a). Crude **3a** (0.65 g, 3.2 mmol), obtained *via* method A, was esterfied in the same manner to give a product (0.6 g, 80%). Crystallization from chloroform–ether gave the analytical sample whose nmr showed the predominance of the 7-methyl over the 6-methyl isomer, mp 149–154°.

Anal. Calcd for $C_{11}H_{12}N_2O_3$: C, 60.21; H, 5.46; N, 12.65. Found: C, 60.12; H, 5.37; N, 12.76.

The pure 7 isomer was obtained after three crystallizations, mp 186–188°.

Anal. Calcd for $C_{11}H_{12}N_2O_3$: C, 60.21; H, 5.46; N, 12.65. Found: C, 60.09; H, 5.88; N, 12.47.

1,6-Dimethoxy-3-methylquinoxalin-2-one 4-Oxide (4b). Crude **3b** (1.1 g, 4.9 mmol), obtained *via* method B, was esterfied with excess diazomethane in ether. The suspension was allowed to stir at room temperature until all the compound went into solution. Excess diazomethane was decomposed with acetic acid followed by evaporation of the solution to dryness. The residue obtained was crystallized once from chloroform–ether (1.0 g, 94%), mp 160°. The nmr spectrum showed the predominance of the 6-methoxy over the 7-methoxy isomer.

Anal. Calcd for $C_{11}H_{12}N_2O_4$: C, 55.92; H, 5.12; N, 11.86. Found: C, 55.87; H, 5.04; N, 11.58.

The pure 6-methoxy isomer was obtained after three crystallizations, mp 183–185°.

Anal. Calcd for $C_{11}H_{12}N_2O_4$: C, 55.92; H, 5.12; N, 11.86. Found: C, 56.07; H, 5.32; N, 11.63.

1,7-Dimethoxy-3-methylquinoxalin-2-one 4-Oxide (4b). Crude **3b** (1.1 g, 4.9 mmol), obtained *via* method A, was esterfied with diazomethane in ether. Usual work-up gave the product (0.92 g, 82%). Crystallization from chloroform–ether gave an analytical sample, mp 180–185°. The nmr spectrum showed the predominance of the 7-methoxy over the 6-methoxy isomer.

Anal. Calcd for $C_{11}H_{12}N_2O_4$: C, 55.92; H, 5.12; N, 11.86. Found: C, 56.02; H, 5.19; N, 11.56.

The pure 7-methoxy isomer was obtained after three crystallizations, mp 191–193°.

Anal. Calcd for $C_{11}H_{12}N_2O_4$: C, 55.92; H, 5.12; N, 11.86. Found: C, 56.16; H, 5.11; N, 11.51.

Methyl-1-methoxy-3-methylquinoxalin-2-one-6-carboxylate 4-Oxide (4c). Crude **3** (R = CO_2H) (0.5 g, 1.7 mmol), obtained *via* method A, was treated with excess diazomethane in ether until complete solution occurred. The usual work-up gave the product (0.55 g). One crystallization from chloroform–ether gave the analytical sample, mp 207–209°. The nmr spectrum showed the predominance of the 6- over the 7-carbomethoxy isomer.

Anal. Calcd for $C_{12}H_{12}N_2O_5$: C, 54.50; H, 4.54; N, 10.60. Found: C, 54.44; H, 4.40; N, 10.40.

The nmr of the pure 6-carbomethoxy isomer was obtained by one further crystallization, mp 210–211°.

Anal. Calcd for $C_{12}H_{12}N_2O_5$: C, 54.50; H, 4.54; N, 10.60. Found: C, 54.77; H, 4.64; N, 10.36.

Methyl-1-methoxy-3-methylquinoxalin-2-one-7-carboxylate 4-Oxide (4c). Crude **3c** (0.6 g, 2.4 mmol) obtained *via* method B was esterified with diazomethane to give the product (0.66 g). One crystallization from chloroform–ether gave the analytical sample, mp 175–178°. The nmr spectrum showed the predominance of the 7- over the 6-carbomethoxy isomer.

Anal. Calcd for $C_{12}H_{12}N_2O_5$: C, 54.50; H, 4.54; N, 10.60. Found: C, 54.29; H, 4.54; N, 10.53.

The nmr spectrum of the pure 7-carbomethoxy isomer was obtained by repeated crystallization, mp 179–181°.

Anal. Calcd for $C_{12}H_{12}N_2O_5$: C, 54.50; H, 4.54; N, 10.60. Found: C, 54.33; H, 4.41; N, 10.46.

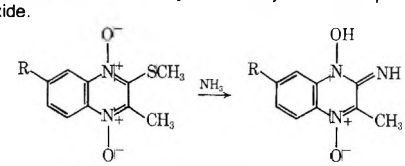
Methyl-*o*-benzoquinone Dioxime 4-carboxylate (5c). 5-Carbomethoxy-BFO (**1c**) (1.0 g, 5 mmol) and di-2,5-*tert*-butylhydroquinone (1.05 g, 5 mmol) were dissolved in tetrahydrofuran (30 ml), and ammonia gas was bubbled in for a few minutes. After standing at room temperature overnight, a dark crystalline precipitate was formed. The tetrahydrofuran solution was decanted. The residue was dissolved in water (20 ml) and filtered. Acidification of filtrate with dilute sulfuric acid precipitated the product, mp 134–135° (0.6 g).

Anal. Calcd for $C_8H_8O_4N_2$: C, 49.00; H, 4.08; N, 14.28. Found: C, 49.09; H, 4.13; N, 14.41.

Registry No.—**1a,** 5 isomer, 19164-41-1; **1a,** 6 isomer, 3524-05-8; **1b,** 5 isomer, 7791-49-3; **1b,** 6 isomer, 3524-06-9; **1c,** 5 isomer, 36389-06-7; **1c,** 6 isomer, 53178-59-9; **2a,** 6 isomer, 53209-82-8; **2a,** 7 isomer, 53209-85-1; **2b,** 6 isomer, 53209-83-9; **2b,** 7 isomer, 53209-86-2; **2c,** 6 isomer, 53209-84-0; **2c,** 7 isomer, 53209-87-3; **3a,** 6 isomer, 53178-64-6; **3a,** 7 isomer, 53178-60-2; **3b,** 6 isomer, 53178-65-7; **3b,** 7 isomer, 53209-90-8; **3c,** 6 isomer, 53178-66-8; **3c,** 7 isomer, 53178-61-3; **3** (R = CO_2H), 6 isomer, 53178-67-9; **3** (R = CO_2H), 7 isomer, 53209-89-5; **4a** 6-isomer, 53178-68-0; **4a,** 7 isomer, 53209-88-4; **4b,** 6 isomer, 53178-69-1; **4b,** 7 isomer, 53178-62-4; **4c,** 6 isomer, 53178-70-4; **4c,** 7 isomer, 53178-63-5; **5a,** 53178-71-5; **5b,** 53178-72-6; **5c,** 53178-73-7; acetonyl methyl sulfide, 14109-72-9; 3,6-dimethyl-1-hydroxy-2-iminoquinoxaline 4-oxide, 53178-74-8; 3,7-dimethyl-1-hydroxy-2-iminoquinoxaline 4-oxide, 53178-75-9; 1-hydroxy-2-imino-6-methoxy-3-methylquinoxalene 4-oxide, 53198-71-3; 1-hydroxy-2-imino-7-methoxy-3-methylquinoxaline 4-oxide, 53198-72-4; pyruvaldehyde, 78-98-8; 2,5-di-*tert*-butylhydroquinone, 88-58-4.

References and Notes

(1) (a) Presented at the 166th National Meeting of the American Chemical Society, Chicago, Ill., Aug 27, 1973. (b) Taken in part from the M.Sc. Thesis of N.D.A., University of Rhode Island, 1974.
(2) C. H. Issidorides and M. J. Haddadin, *Tetrahedron Lett.*, 3253 (1965).
(3) C. H. Issidorides and M. J. Haddadin, *J. Org. Chem.*, **31**, 4067 (1966).
(4) J. W. McFarland, *J. Org. Chem.*, **36**, 1842 (1971).
(5) N. A. Mufarrij, M. H. Haddadin, and C. H. Issidorides, *J. Chem. Soc., Perkin Trans. 1*, 965 (1972).
(6) M. J. Haddadin, G. Agopian, and C. H. issidorides, *J. Org. Chem.*, **36**, 514 (1971).
(7) J. C. Mason and G. Tennant, *Chem. Commun.*, 586 (1971).
(8) W. Duerckheimer, *Justus Liebigs Ann. Chem.*, **756**, 145 (1972).
(9) E. Abushanab, *J. Org. Chem.*, **35**, 4279 (1970).
(10) E. Abushanab, *J. Org. Chem.*, **38**, 3105 (1973).
(11) In addition to the starting BFO and quinoxaline 1,4-dioxides, a polar compound was isolated which proved to be an imino derivative, which was shown to be formed by ammonolysis of the parent quinoxaline 1,4-dioxide.



R = CH_3, OCH_3

(12) F. B. Mallory, S. L. Manatt, and C. S. Wood, *J. Amer. Chem. Soc.*, **87**, 5433 (1965).
(13) A. J. Boulton, A. R. Katritzky, M. J. Sewell, and B. Wallis, *J. Chem. Soc. B*, 914 (1967).
(14) See F. B. Mallory and C. S. Wood, *J. Org. Chem.*, **27**, 4109 (1962), for pertinent references.

Heteroatom Participation during Addition–Rearrangement Reactions of 2-Thia- and 2-Azanorbornenes

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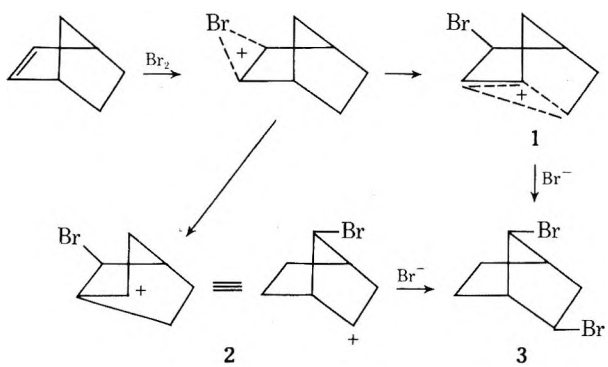
Bromination of a series of substituted 2-thianorbornenes proceeds with sulfur participation to give the rearranged 6,7-dibromides. Addition of bromine to 3-hexafluoroisopropylidene-2-thianorbornene 2,2-dioxide, in which sulfur participation is prevented, results in the formation of the 5,6-dibromide and a thianortricyclene derivative. Sulfenyl halides add to 2-thianorbornenes with rearrangement to form 6-halo-7-(arylthio) derivatives, which indicates that the 1,6-episulfonium intermediate is product directing rather than the 5,6-episulfonium ion. Addition of bromine to 2-oxanorbornenes proceeds without rearrangement. Bromination of 2-azanorbornenes and 2,3-diazanorbornenes takes place with nitrogen participation to form the rearranged 6,7-dibromides. This series reveals the inversion at C-3 that takes place during rearrangement. 2,6 elimination of hydrogen bromide from 6,7-dibromo-2-azanorbornanes having a proton on nitrogen results in azanortricyclenes.

Bromination of norbornene produces five dibromides as well as bromonortricyclene and *exo*-2-bromonorbornane.[2] The principal dibromide, formed in about 32% yield, is the rearranged compound **3**, believed to arise from a nonclassical norbornonium ion **1**, with its three-center electron-deficient bond, rather than the classical carbonium ion **2** (Scheme I). In the case of benzonorbornadiene, where the

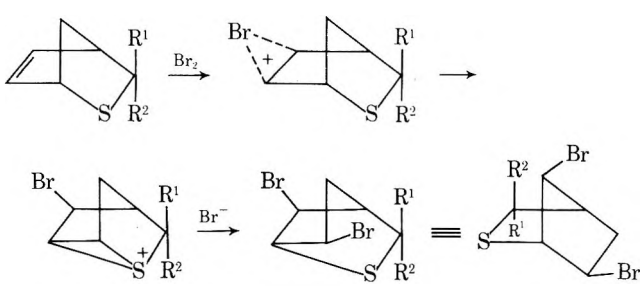
Scheme I



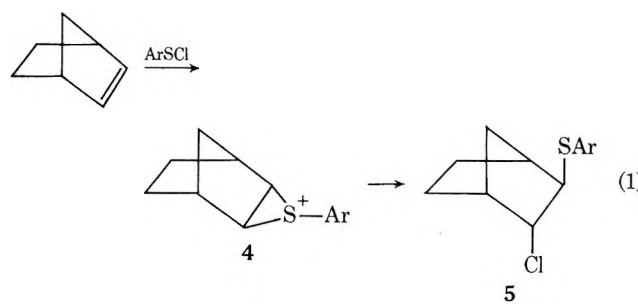
possibility of side reactions is restricted, bromination produces an 87.5% yield of the rearranged dibromide corresponding to **3**.[3,4] Both bromine atoms approach the less hindered exo side in determining the configuration.

I. 2-Thianorbornenes. A. Bromination Results and Discussion. The bromination of 2-thianorbornenes has now been found to proceed with rearrangement also. This course of reaction has not been previously demonstrated. Sulfur participation is believed to provide a product-controlling cation of greater stability than the alternative carbocation in the examples studied, with the result as shown in Scheme II. In this mechanism there is no need to propose the intermediacy of a nonclassical ion.

Scheme II



Postulation of three-membered, cyclic sulfonium salts in reaction mechanisms has precedents, as in the addition of sulfenyl halides to olefins. Addition of benzene- and toluenesulfenyl chlorides to norbornene produces trans adducts, and no Wagner–Meerwein rearrangement products.[5-8]



The sulfur-bridged cation is regarded as product directing and more stable than the carbon-bridged cation required as an intermediate to rearranged product. Further, the tremendous enhancement of solvolysis rate of β-chlorosulfides compared to simply alkyl chlorides is explained on the basis of a bridged sulfonium ion.[9]

B. Preparation and Bromination of 2-Thianorbornenes. The 2-thianorbornenes used as starting materials were prepared by Diels–Alder additions of cyclopentadienes to thiocarbonyl compounds and are listed as compounds **7–10** and **12–16** in Table I. Of these, compounds **10** and **13–16** represent new examples of this synthesis. Compound **11** was made by oxidizing **10**. Their dibromides are listed in Table II. Two of the dibromides, **23** and **24** (Table II), were reported previously but no structures were proposed,[10] though Chemical Abstracts indexed them as 5,6-dibromides. Ionic bromination of the 2-thianorbornenes was indicated by rapid uptake of bromine at 0°, and −78° was used in some cases. Competition from free-radical bromination was not a problem. Brominations were carried out in subdued light as this gave the same result as bromination in the dark. The milder brominating agent, tetramethylammonium tribromide was preferable for use on **12–14** (Table I). The generality of the rearrangement was shown by the fact that 2-thianorbornenes substituted in the 1, 3, 4, and 7 positions were operable. Examination of the crude bromination products of 3,3-bis(trifluoromethyl)-2-thianorbornene and 3-(hexafluoroisopropylidene)-2-thianorbornene by analytical glpc showed a purity of 96.5%.

One 2-thianorbornene, **10** (Table I), was chlorinated with sulfuryl chloride to form a 79:21 mixture of isomers. Preparative glpc did not separate these but did cause the main isomer to crystallize from the mixture. The nmr data (Table II) show it to be the rearranged dichloride.

Table I
2-Thianorbornenes, Nmr Assignments (ppm, CCl_4)[h]

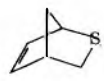
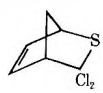
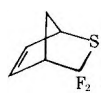
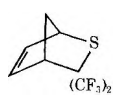
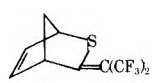
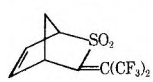
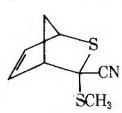
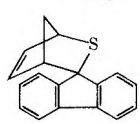
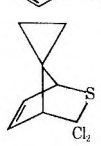
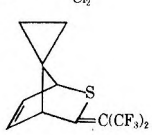
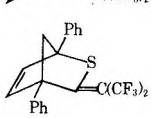
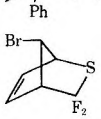
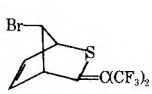
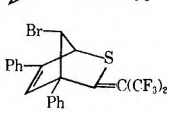
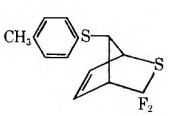
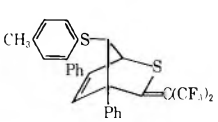
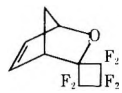
No.	Compd	Position of ring protons 1	4	5	6	7	Other protons
6[a]		3.92 m	3.37 m	5.67 q	6.14 q	1.37 AB, J = 8 Hz	2.09 d, *endo*-3-H 3.08 q, *exo*-3-H J = 9 Hz
7[b]		4.34 m	3.93 m	6.18 m	6.63 q	2.05 AB, J = 10 Hz ttss,[g] J = 2.2 Hz	
8[b]		4.20 m	3.40 split by F	6.13 m	6.72 p	2.14 AB, J = 10 Hz	
9[b]		4.12 s	3.65 m	5.98 septet	6.57 q	1.76 AB, J = 10 Hz	
10[c]		4.45 s	4.55 m	6.15 t	6.47 q	1.91 AB, J = 9.5 Hz	
11[d]		4.12 m	4.25 m	6.50 m	6.50 m	2.72 t	
12[e]		4.40 m	3.82 m	6.02 q	6.48 q	2.00 m	2.32 s, CH_3
13		4.35 m	3.00 m	5.95 q	6.70 q	2.20 AB, J = 10 Hz	7.2–7.8 m, aromatic
14		3.70 m	3.28 m	6.42 m	6.72 q		0.4–1.4 m, CH_2CH_2
15		3.67 s	3.67 m	6.12 m	6.52 q		0.55 m, CH_2CH_2
16				6.83 m	6.83 m	2.57 AB, J = 10 Hz	7.43 m, aromatic
17		4.32 m	3.65 m split by F	6.20 m	6.75 p	4.72 s	
18[c]		4.39 s	4.48 m	6.15 t	6.55 q	4.34 s	
19		4.74 m		6.59 m		4.74 m	7.47 m, aromatic
20[d]		4.24 m	3.54 m 3.67 m	6.18 m	6.72 p	4.07 s	2.30 s, CH_3 7.20 m, aromatic
21[d]		4.79 s		6.64 m		4.02 t, J = 1.2 Hz	2.23 s, CH_3

Table I *(Continued)*

No.	Compd	Position of ring protons 1	4	5	6	7	Other protons
22[f]		5.08 m	3.70 m	6.50 m	6.65 m	1.77 AB	

[a] Reference 49. [b] Reference 10. [c] Run at 220 MHz. [d] In $CDCl_3$. [e] Reference 39. [f] Reference 21. [g] Description of secondary splitting in AB components, reading downfield. [h] Satisfactory analytical data (±0.37%) for C, H, and S were obtained for all new compounds in the table except that **14** was analyzed for Cl and **17**–**19** for Br instead of S.

Table II
2-Thianorbornanes, Nmr Assignments (ppm, CCl_4)[a]

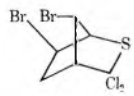
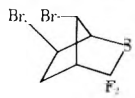
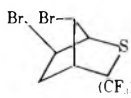
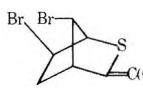
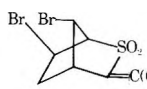
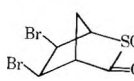
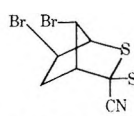
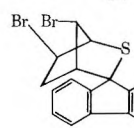
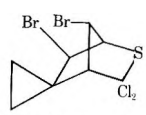
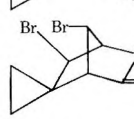
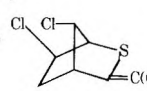
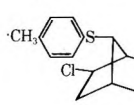
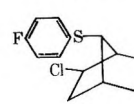
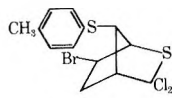
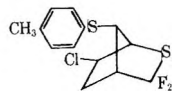
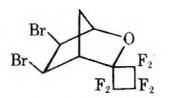
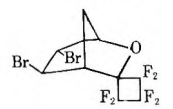
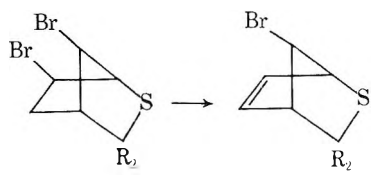
No.	Compd	Position of ring protons 1	4	5	6	7	Other protons
23[a]		3.92 s	3.47 d, J = 5 Hz	3.06 AB, J = 10 Hz, ttdd[b]	4.55 t, J = 7 Hz	5.03 m	
24[a]		3.88 m	3.10 m split by F	2.74 m 2.84 m	4.57 t, J = 6 Hz	4.68 s	
25		3.77 s	3.16 m	2.92 m	4.52 t, J = 6 Hz	4.95 s	
26		3.92 s	3.92 m, narrow	2.78 AB J = 15 Hz, ddtt[b]	4.48 m	4.48 s	
27[c]		3.99 s	3.95 m	2.95 AB J = 15 Hz, ddtt[b]	4.92 t	4.94 s	
28[c]		3.88 m	3.99 m	4.80 AB, J = 7 Hz		2.80 AB, J = 13 Hz	
29		3.82 m, narrow	3.00 m	2.88 m 3.00 m	4.62 t, J = 6 Hz	4.88 m	2.35 s, CH_3
30		3.96 m, narrow	2.88 m	2.47 m 2.88 m	5.00 t, J = 7 Hz	5.52 m	7.22–7.75 m, aromatic
31		4.01 t, J = 1.4 Hz	2.76 t, J = 1.4 Hz		4.62 d, J = 1.4 Hz	5.06 q, J = 1.4 Hz	1.0–1.8 m, CH_2CH_2
32		4.01 s	3.40 m		4.48 s	4.48 s	0.6–1.8 m CH_2CH_2
33		3.74 s	3.84 m	2.64 AB, J = 15 Hz, ddtt[b]	4.37 t, J = 6 Hz	4.37 s	
34[c]		3.72 s	3.22 d	2.80 AB, J = 15 Hz, ttdd[b]	4.45 q	4.35 s	
35[c]		3.74 s	3.32 d	2.83 AB, J = 15 Hz	4.48 t	4.33 s	

Table II (Continued)

No.	Compd	Position of ring protons 1	4	5	6	7	Other protons
36[c]		3.87 s	3.35 d	2.93 AB	4.50 m	4.45	2.35 s, CH_3 7.30 m, C_6H_4
37[c]		3.64 d	2.94 t split by F	2.60 AB, J = 15 Hz, ttdd[b]	4.47 q	4.02 s	2.27 s, CH_3 7.18 m, C_6H_4
38		4.78 s	3.35 s	4.60 AB, J = 13 Hz		2.36 AB, J = 13 Hz	
39		4.58 s	3.19 s	4.30 m, J = 1.4 Hz		2.32 AB, J = 12 Hz	

[a] Reference 10. [b] Description of AB pattern peaks reading downfield. [c] In $CDCl_3$. [d] Satisfactory analytical data (±0.38%) for C, H, and Br were obtained for all new compounds in the table except that **33**, **34**, **35**, and **37** were analyzed for Cl instead of Br, and 20.28% Br (calcd 20.80) was found for **36**.

C. Structure Proof and Nmr Analysis. The fact that rearrangement had occurred during bromination was established by dehydrobrominating **24** and **26** (Table II) with potassium *tert*-butoxide to form the monobromo compounds. The dehydrobromination products have two vinylene protons rather than one (nmr), which would have been the case had vicinal bromination taken place. Spontaneous



dehydrobromination occurred during bromination of 1,4-diphenyl-2-thianorbornene to form 7-bromo-4,6-diphenyl-2-thianorbornene. Other dibromides in Table II were shown to be rearranged by nmr comparisons.

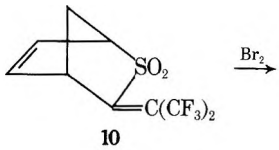
The gross features of the nmr spectra appear in Tables I and II. Peak assignments were made through comparison of spectra. The spectra of norbornenes[11-15] and norbornanes[2,13,16,17] have been extensively studied and this information has been of assistance in interpretation. Comparison of the six dibromides which differ only in the substituents in the 3 position, **23–26**, **29**, and **30** (Table II), shows that the chemical shifts for the proton on one bridgehead fall in the narrow range of 3.77 to 3.96 ppm, suggesting that the adjacent groups are the same. This proton is assigned to the 1 position and its shift is farther downfield than that for the other bridgehead proton as expected since it is near to sulfur. An exception is compound **26** having a hexafluoroisopropylidene group in the 3 position. This group causes the bridgehead proton peaks to overlap. The peaks for the bridgehead protons in the 4 position fall in the range of 2.88–3.92 ppm. The chemical shift varies with the substituent in the 3 position and the shape of the peak is influenced when fluoro groups are in the 3 position because of H–F coupling. As noted for 7-bromonorbornanes,[2b] the peak for the proton in the 7 position is recognizable as a somewhat broadened singlet or narrow multiplet in the range of 4.48–5.52 ppm. The peak for 6-CHBr appears as a triplet, with a spacing of *ca.* 8 Hz, in agreement with its proximity to CH_2, and is in the range of 4.48–5.00 ppm. This triplet has been resolved in some cases into an overlapping pair of doublets by 220 MHz nmr. The 5-CH_2 group appears as a multiplet at 2.5–3.0 ppm. The multiplet has been shown to be an AB pattern for **23** and **24** (Table II) by using 220 MHz nmr.

The splitting of the H-4 peak indicates it is adjacent to CH_2 and this provides evidence that Br is in the 6 position. The H-4 peak for **23** (Table II) is clearly a doublet, from coupling with *exo*-H-5, with further splittings.

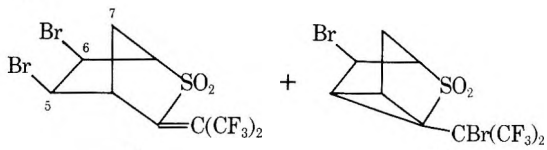
Finally, the stereochemistry of the bromine atoms must be considered to see if it is consonant with mechanistic predictions. The proton in the 6 position must be endo because of its lack of coupling with H-1 (Karplus rule). This is most clearly shown in **31** (Table II) where the triplet for the proton at the 1-bridgehead, which is adjacent to the endo proton, is identical in shape with the peak for the 4-bridgehead proton where there is no proton on the 5 position. All coupling constants in this molecule are about 1.4 Hz. Thus, coupling of H-1 with H-4 and H-7 gives a triplet resulting from two overlapping doublets; coupling of H-4 with H-1 and H-7 forms another such triplet; coupling of H-7 with H-6 produces a doublet for H-6; and coupling of H-7 with H-6, H-1, and H-4 forms a quartet that is the summation of three overlapping doublets. These couplings were established by decoupling experiments. In the other compounds, the H-1 peak is a broadened singlet or narrow multiplet simpler than the H-4 peak.

The above-mentioned coupling between *endo*-H-6 and H-7 indicates that H-7 is toward sulfur. For 2,7-dibromonorbornanes the conclusion was reached that appreciable coupling occurs between *endo*-H-2 and *anti*-H-7 but not between *endo*-H-2 and *syn*-H-7.[2b] For members of the series with a CH_2 group in the 5 position, the components of the triplet for this group have pronounced secondary splitting and this is attributed in part to *endo*-H-5:*syn*-H-7 interaction, syn meaning toward sulfur.

D. Bromination of a 2-Thianorbornene 2,2-Dioxide. In 2-thianorbornene 2,2-dioxides, the sulfur atom is not available for participation in a rearrangement, and bromination of such a compound should lead to a different result according to the proposed mechanism. Thus, bromination of **11** (Table I) was hardly preceptible until irradiation was used to induce a free-radical reaction which proceeded to form a *cis,exo*-5,6-dibromide and the first example of a thianortricyclene.



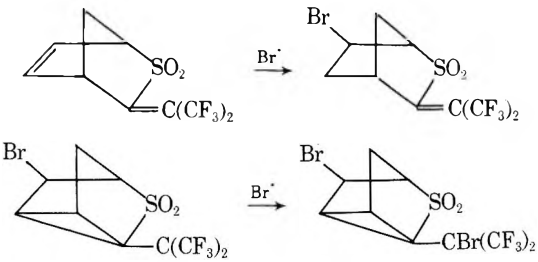
10



28 40

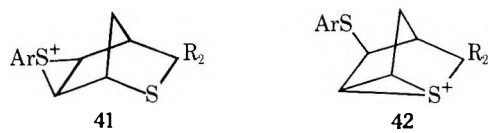
The *cis,exo*-dibromide relationship in **28** is revealed by the AB pattern (J = 7 Hz) in the nmr spectrum and the lack of coupling of the endo protons with the bridgehead protons.[2] Formation of the *cis,exo*-dibromide may be ascribed to steric difficulty in forming a trans dibromide. That this dibromide is not the rearranged 6,7-dibromide was further verified by preparing the 6,7-dibromide 1,1-dioxide by oxidation of **26** (Table II).

The formation of the thianortricyclene can be visualized as follows.



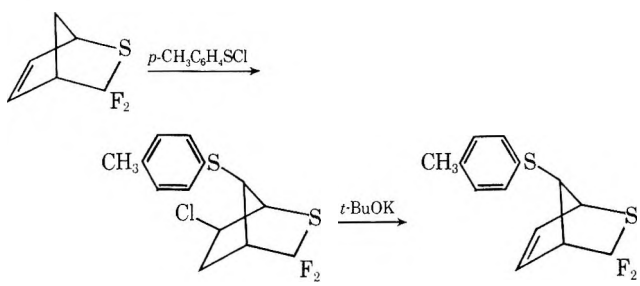
The reaction has precedent in the free-radical addition of carbon tetrachloride, bromotrichloromethane,[18] and benzenethiol[19] to 5-methylenenorbornene and of bromine to 5-(difluoromethylene)-6,6-difluoro-2-norbornene[17e] to form nortricyclene derivatives.

E. Addition of Sulfenyl Halides to 2-Thianorbornenes. As observed earlier, addition of *p*-toluenesulfenyl chloride to norbornene produces the trans adduct **5** and no Wagner–Meerwein rearrangement product (eq 1).[5-8] The 2,3-episulfonium cation **4** is regarded as product directing and more stable than the carbon-bridged cation required as an intermediate to a rearranged product. The addition of *p*-toluenesulfenyl chloride to 2-thianorbornenes raises the interesting question as to which episulfonium intermediate, **41** or **42**, will be product directing.

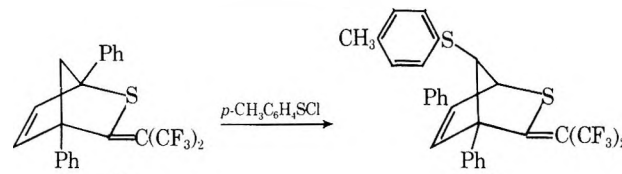


41 42

The addition of sulfenyl halides is analogous to bromination in that rearranged products are obtained. Thus, intermediate **42** is implicated. For example



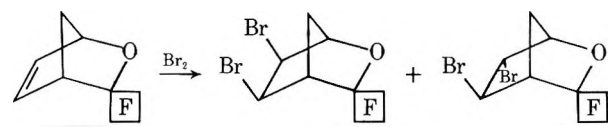
Since norbornene does not give a rearranged product, the result also indicates that the sulfur-bridged cation **42** forms more readily than the carbon-bridged cation. Similarly, rearranged adducts were obtained by addition of *p*-toluenesulfenyl chloride, *p*-fluorobenzenesulfenyl chloride, and *p*-toluenesulfenyl bromide to 3,3-dichloro-2-thianorbornene. Addition of *p*-toluenesulfenyl chloride to 1,4-diphenyl-2-thianorbornene (**16**) occurs with spontaneous loss of hydrogen chloride to form **21.**



16 21

Nmr data for the various compounds are listed in Tables I and II.

II. Bromination of 2-Oxanorbornenes. The behavior of 2-oxanorbornenes toward bromination is of interest. The oxygen atom of ethers tertiizes[20] (*i.e.*, becomes trivalent) less readily than the sulfur atom of sulfides and, thus, a bridged oxonium ion becomes less likely than a bridged sulfonium ion. Bromination of **22** occurs without rearrangement to form **38** and **39** presumably by a free-radical mechanism.

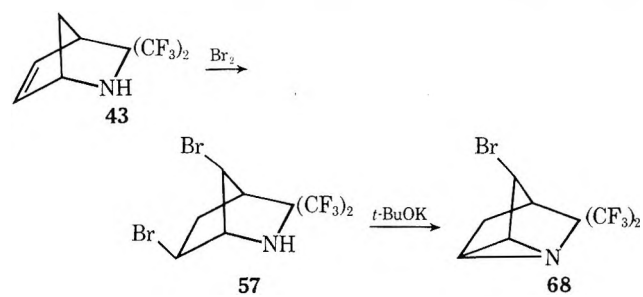


22[21a] 91% 9%

38 39

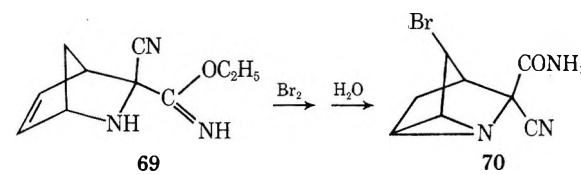
The only other known 2-oxanorbornene, the unstable adduct of cyclopentadiene and hexafluoroacetone, forms only the *cis,exo*-5,6-dibromide[21b] (not indexed by Chemical Abstracts). This result is in direct contrast with the rearranged dibromide obtained from the adduct of cyclopentadiene with hexafluorothioacetone.

III. Bromination of 2-Azanorbornenes. A. Formation of Azanortricyclenes. Finally, among 2-heteronorbornenes, the bromination of 2-azanorbornenes must be considered to determine if a trivalent atom convertible to an onium ion can function in the manner shown for sulfur in Scheme II. Rearrangement seems to have been demonstrated previously only for the case of a 2,3-diazanorbornene (section IV). Bromination of the known 2-azanorbornene[22] **43** gave the rearranged dibromide **57.** Treatment of the dibromide with potassium *tert*-butoxide produced an azanortricyclene **68.** Similarly, bromination of **69,** also



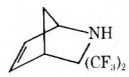
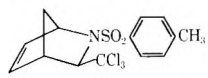
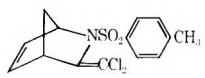
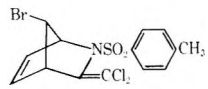
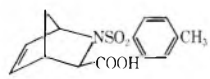
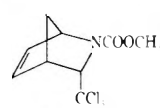
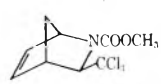
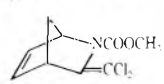
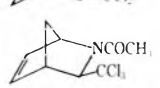
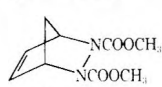
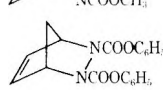
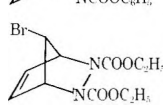
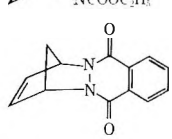
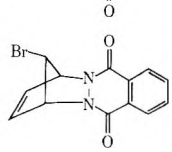
43 57 68

known,[23] gave an azanortricyclene **70** through spontaneous loss of hydrogen bromide. In the nmr spectra of the azanor-



69 70

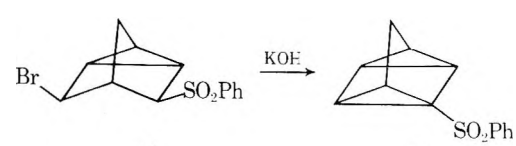
Table III
2-Azanorbornenes, Nmr Assignments (ppm, $CDCl_3$)[e]

No.	Compd	Position of ring protons 1	3	4	5	6	7	Other protons
43[a]		4.12 s		3.52 m	6.27 m	6.50 q	1.78 AB, J = 9 Hz	1.72 m, NH
44[b]		4.92	4.06 s	3.68 m	6.58 m	6.75 q	2.08 AB, J = 9 Hz	2.38 s, CH_3 7.48 m, C_6H_4
45		5.21 m		4.22 m	6.53 m	6.82 q	1.84 AB, J = 9 Hz	2.42 s, CH_3 7.55 m, C_6H_4
46		5.16		4.28 m	6.48 m	6.75 q	4.33	2.41 s, CH_3 7.52 m, C_6H_4
47		4.63 m	3.52 s	3.50 m	6.17 m	6.17 m	1.78 AB, J = 9 Hz	2.46 s, CH_3 7.54 m, C_6H_4 11.9 s, COOH
48		5.07 m	4.87 d, J = 3 Hz	3.72 m	6.40 m	6.50 m	1.67 t	3.74 s, CH_3
49		4.87 m	3.88 s	3.60 m	6.57 m	6.57 m	2.12 AB, J = 9 Hz	3.78 s, CH_3
50		5.00 m		4.15 m	6.53 m	6.53 m	1.82 AB, J = 9 Hz	3.75 s, CH_3
51		4.74 m	4.14 s	3.58 m	6.53 m	6.53 m	2.14 AB, J = 10 Hz	2.17 s, CH_3
52[c]		5.14		5.14	6.51 t		1.71 t	3.75 s, 2 CH_3
53		5.33		5.33	6.65 t		1.72 t	7.20 m, 2 C_6H_5
54		5.13 m		5.13	6.53 t		4.10	1.26 t, CH_3 4.23 q, CH_2
55[d]		5.90		5.90	6.70 t		2.08 AB	7.83 m, 2 H 8.24 m, 2 H
56		5.83		5.83	6.68 t		4.55 m	7.87 m, 2 H 8.22 m, 2 H

[a] Reference 22. [b] Reference 25. [c] Reference 48. [d] Reference 28. [e] Satisfactory analytical data (±0.37%) for C, H, and N were obtained for all new compounds in the table except that 54 and 56 were analyzed for Br instead of N, and 49 was not analyzed except in mixture with 48.

tricyclenes, no protons attached to unsaturated carbon are indicated and the characteristic apparent singlet for bridge CHBr appears at 4.5–4.8 ppm. The only previous examples of this ring system are the unstable parent heterocycle and its methiodide.[50]

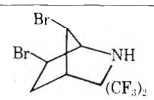
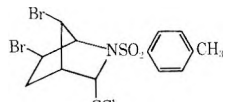
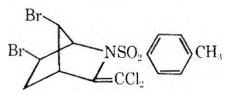
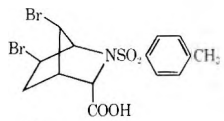
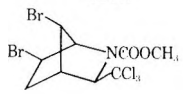
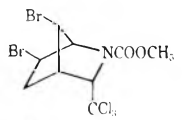
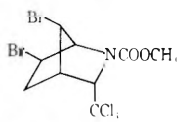
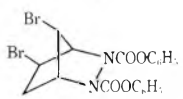
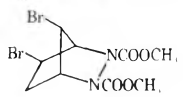
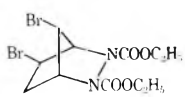
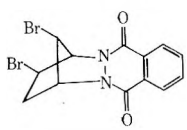
The facile ring closure to an azanortricyclene is evidence that the bromine atom in the 6-position is exo. The nucleophilic attack of the amine anion at C-6 takes place with the expected requirement for inversion at C-6 with loss of bromide ion and formation of the aziridine ring. In the quadricyclene synthesis of Cristol, Harrington, and Singer,[24] **71** was readily ring closed with potassium hydroxide to **72**, whereas the endo bromine analog of **71** could not be ring closed. The reaction presumably involved attack by the phenylsulfonyl carbanion at the brominated position.



71 **72**

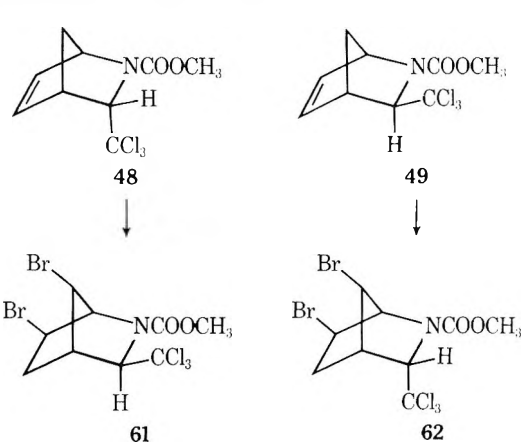
B. Bromination of *N*-Acylated 2-Azanorbornenes. *N*-Acylated 2-azanorbornenes also undergo rearrangement during bromination. Diels–Alder addition of methyl *N*-

Table IV
2-Azanorbornanes. Nmr Assignments in ppm[c]

No.	Compd	Solvent	Position of ring protons 1	3	4	5	6	7	Other protons
57		CCl_4	3.73 s		2.92 m	2.75 AB, J = 15 Hz	4.01 t	4.57 m	2.34 m, NH
58		$CDCl_3$	3.22 m	4.80 d	2.85 m	2.80 AB, ttdd[a]	4.42 t	4.80 m	2.42 s, CH_3 7.54 m, C_6H_4
		C_6D_6	3.67 m	4.40 d, J = 3 Hz	2.32 m	2.45 AB	4.22 t	4.84 m	1.87 s, CH_3 7.10 m, C_6H_4
59		$CDCl_3$	4.33 m		3.56 m	2.57 AB	4.13 t	4.83 m	2.43 s, CH_3 7.54 m, C_6H_4
60		$(CD_3)_2CO$	3.72 m	4.44 d, J = 3 Hz	3.02 m	2.50	4.14 t	4.25 s	2.40 s, CH_3 7.65 m, C_6H_4 11.4 s, COOH
61		$CDCl_3$	4.54 t	4.26 s	3.18 m	2.56 AB, ddtt[a]	3.84 t	5.11 m	3.80 s, CH_3
		$(CD_3)_2CO$	4.54 t	4.43 s	3.27 m	2.73 AB	4.08 t	5.17 m	3.79 s, CH_3
62		$CDCl_3$	4.03 m	4.81 d	3.23 m	2.85 AB	4.48 t	4.80 m	3.80 s, CH_3
		$(CD_3)_2CO$[b]	4.55 m	5.05 d, J = 3.5 Hz	3.34 m	2.82 AB	4.54 t	4.77 m	3.77 s, CH_3
63		$CDCl_3$	3.98 m	4.97 d, J = 3 Hz	3.25 m	2.9 AB	4.50 t	4.50 m	2.22 s, CH_3
64		$CDCl_3$	4.82 m		4.33 m	2.95 AB	4.30 t	5.01 m	7.3 m, 2 C_6H_5
		C_6D_6	4.33 m		3.83 m	2.48 AB	4.10 t	4.87 m	7.13 m, 2 C_6H_5
65		$CDCl_3$	4.53 m		4.04 m	2.72 AB	4.04 t	4.72 m	3.78 s, CH_3
		C_6D_6	4.17 s		3.67 m	2.34 AB	3.87 t	4.61 s	3.37 s, CH_3
66[c]		$CDCl_3$	4.58 m		*ca.* 4.1	2.76 AB	*ca.* 4.1	4.76 m	4.27 q, CH_2 of Et 1.30 t, CH_3 of Et
67		$CDCl_3$	5.34 m		4.45 m	2.98 m	4.26 t	5.44 m	7.75 m, 2H 8.25 m, 2H

[a] Description of secondary splitting in AB components, reading downfield. [b] Positions confirmed by decoupling. [c] References 30 and 31. [d] Satisfactory analytical data (±0.36%) for C, H, and Br were obtained for all new compounds in the table.

(trichloroethylidene)carbamate to cyclopentadiene yields endo (**48**) and exo (**49**) isomers.

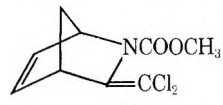


The exo positions of H-3 in **48** is revealed by the sharp doublet which the proton produces in the nmr spectrum because of coupling to H-4. In **49**, on the other hand, *endo*-H-3 produces a sharp singlet because of lack of coupling, a well-established relationship in such skeletal systems. On bromination, the configuration of the H-3 is reversed, as depicted in **61** and **62**. This, in itself, is evidence that the dibromides are rearranged products. This inversion can be visualized by examining Scheme II.

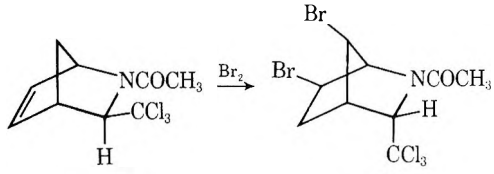
That an acylated nitrogen atom can participate in rearrangement is demonstrated by the acylated 2,3-diazanorbornenes described in section IV. In these, a carbon atom is not available for participation. Nmr data for 2-azanorbornene derivatives and their dibromides are given in Tables III and IV. The data are similar to those for their thia analogs.

Treatment of **48** and **49** with base produced a 3-dichloromethylene-2-azanorbornene (**50**). Reaction of cyclopenta-

diene with $CCl_3CH{=}NCOCH_3$ produced the azanorbornene **51** which formed the rearranged dibromide (**63**).

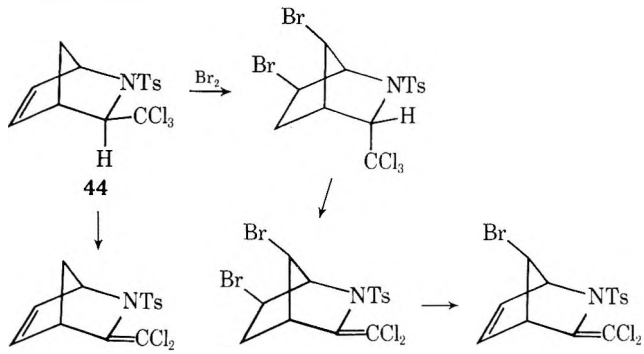


50



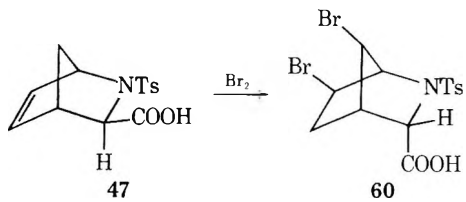
51 **63**

C. Bromination of *N*-Tosylated 2-Azanorbornenes. *N*-Tosylated 2-azanorbornenes also form rearranged dibromides. The known compound[25] **44** undergoes the following transformations.



44

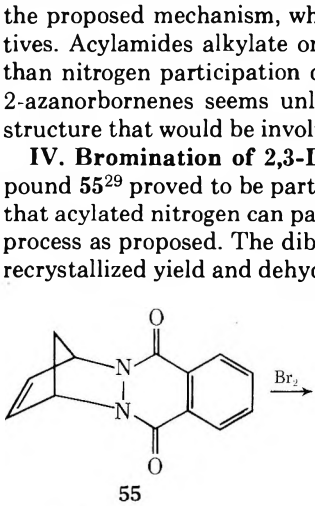
Also, the known butyl ester[26] of **47** has been hydrolyzed and brominated to the rearranged dibromide **60.**



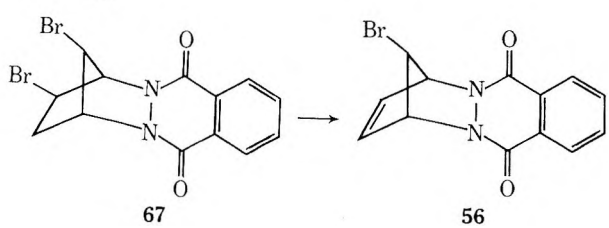
47 **60**

Sulfonamides are known to quaternize,[27] a requirement of the proposed mechanism, when applied to *N*-tosyl derivatives. Acylamides alkylate on oxygen,[28] but oxygen rather than nitrogen participation during bromination of *N*-acyl-2-azanorbornenes seems unlikely because of the strained structure that would be involved.

IV. Bromination of 2,3-Diazanorbornenes. The compound **55**[29] proved to be particularly suitable for indicating that acylated nitrogen can participate in the rearrangement process as proposed. The dibromide **67** was isolated in 84% recrystallized yield and dehydrobrominated to **56.**

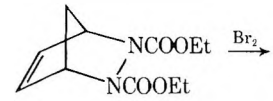


55

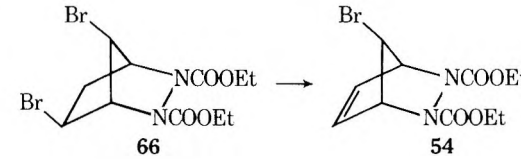


67 **56**

A dibromide of the 2,3-diazanorbornene **68** has been reported to be the 5,6 derivative.[30,31] Actually, it is the rearranged dibromide **66** which has been dehydrobrominated



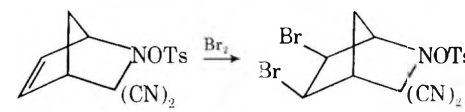
68



66 **54**

to **54.** Recently, the dichloride and dibromide of the dimethyl ester corresponding to **68** were shown to be rearranged by X-ray analysis.[51]

Despite the above data, rearrangement during bromination of 2-azanorbornenes is not universal. The dibromides of **73** and close analogs are reported[23] to be cis–exo (**74**).



73 **74**

Experimental Section

The ^1H nmr spectra were determined on Varian instruments using tetramethylsilane as internal standard. Most of the ^1H nmr data are recorded in the tables. The ^{19}F nmr spectra were measured in a Varian A-56/60 instrument using 1,2-difluoro-1,1,2,2-tetrachloroethane as a standard in a capillary tube placed in the sample tube, and downfield values are recorded as positive. This standard is 3800 Hz (67.4 ppm) upfield from trichlorofluoromethane. Ir spectra were measured in a Perkin-Elmer Model 21 spectrometer. Melting and boiling points are uncorrected.

Anti, as used with 2-heteronorbornenes and norbornanes, applies to the bridge position opposite to the heteroatom. For brevity, hexafluoroisopropylidene is used for $(CF_3)_2C{=}$ instead of the Chemical Abstracts name, 2,2,2-trifluoro-1-(trifluoromethyl)ethylidene.

Because two fatalities have been reported from work with norbornadiene dibromides,[33] the bromine adducts of 2-thianorbornenes and 2-azanorbornenes should be treated with circumspection. However, no unusual toxicity has been noted.

2-Thianorbornenes. A. 3,3-Difluoro-2-thiabicyclo[2.2.1]-hept-5-ene[10] (8). To 33 g (0.4 mol) of thiocarbonyl fluoride in a cold trap in Dry Ice–acetone was added 27 g (0.41 mol) of cyclopentadiene and the mixture was kept in the cold bath for 2 days. Water vacuum was then briefly applied and the solid was placed on a suction funnel. This gave 47 g (79%) which was recrystallized from pentane by cooling in Dry Ice, (mp 47–48°).

B. 3-(Hexafluoroisopropylidene)-2-thiabicyclo[2.2.1]hept-5-ene[34] (10). To 16.5 g (0.25 mol) of freshly prepared cyclopentadiene in 75 ml of dichloromethane was added with stirring, at 15–20°, 48.5 g (0.25 mol) of bis(trifluoromethyl)thioketene.[35] Distillation gave 62.1 g (96%), bp 69° (7 mm), 196° (760 mm): mp 10°; $n^{25}D$ 1.4483; ir 3077 (=CH), 2985, 2941, 2857 (CH), 1616 (exocyclic C=C), 1575 cm^{-1} (ring C=C); Raman 1575 (exocyclic C=C), 1610 cm^{-1} (ring C=C); ^{19}F nmr (neat) 7.64, 11.6 ppm (quadruplets, components of latter split to doublets).

C. Spiro(2-thiabicyclo[2.2.1]hept-5-ene-3,9′-fluorene) (13). 9-Fluorenone (36 g, 0.2 mol) was converted to 9-thiofluorenone as described by Campaigne and Reid.[36] After the thiofluorenone was filtered off and washed, it was not recrystallized but dissolved in 1 l. of hexane and dried ($MgSO_4$). To this was added 14 g (0.21 mol) of cyclopentadiene. The green color was discharged and 34.5 g (70%) of the adduct crystallized out. Concentration of the mother liquor gave 4.5 g (9%) more. The compound was recrystallized from 1,2-dimethoxyethane, filtered, and washed with acetone to remove the yellow color: 30.5 g (58%); mp 126–131°.

D. 3,3-Dichlorospiro(2-thiabicyclo[2.2.1]hept-5-ene-7,1′-cyclopropane) (14). Spiro[2,4]hepta-4,6-diene[37] (5.52 g, 0.06 mol) in 5 ml of dichloromethane was stirred and cooled in ice while 6.90 g (0.06 mol) of thiophosgene was added dropwise. The solvent was

allowed to evaporate and the residue was dissolved in pentane and filtered from polymer. Crystallization from the pentane gave 9.25 g (74%), mp 61°. The compound is unstable to storage at 24°.

E. 3-(Hexafluoroisopropylidene)spiro[2-thiabicyclo[2.2.1]-hept-5-ene-7,1′-cyclopropane][34] (15). To 6.35 g (0.07 mol) of spiro[2,4]hepta-4,6-diene[37] in 20 ml of dichloromethane was added 9.4 g (0.047 mol) of bis(trifluoromethyl)thioketene[35] in 8 ml of dichloromethane with cooling in ice. The solvent was boiled off and about 1.5 g of polymer was filtered off before distillation to give 12.6 g (91%), bp 45° (0.4 mm); n^{25}D 1.4593; ^{19}F nmr (neat) 11.75, 15.9 ppm (quadruplets, latter split to doublets, J = 1.8 Hz).

When an equivalent of the thioketene was used, addition of the last portion caused the entire product to polymerize.

F. 1,4-Diphenyl-3-(hexafluoroisopropylidene)-2-thiabicyclo[2.2.1]hept-5-ene (16). 1,4-Diphenylcyclopentadiene[38] (6.72 g, 0.03 mol), 25 ml of hexane, and 7.56 g (0.04 mol) of bis(trifluoromethyl)thioketene[35] were refluxed for 16 hr. Crystallization from hexane gave 10.7 g (86%) in two crops: ^{19}F nmr ($CDCl_3$) 7.91, 13.6 ppm (quadruplets). The adduct melts when placed in a bath at 101° but soon dissociates to the higher melting 1,4-diphenylcyclopentadiene.

G. 3-(Hexafluoroisopropylidene)-2-thiabicyclo[2.2.1]hept-5-ene 2,2-Dioxide[34] (11). To 26 g (0.1 mol) of **10** in 50 ml of dichloromethane was added 43 g (0.21 mol) of 85% *m*-chloroperbenzoic acid in 450 ml of dichloromethane with cooling in ice. The solution was allowed to stand for 2 days and then washed with 5% aqueous sodium hydroxide and dried (Na_2SO_4). The residue left after evaporation of the solvent was recrystallized from carbon tetrachloride to give 26.4 g (90%) of the dioxide, mp 88°: ir 3077 (=CH), 2985 (CH), 1667 (exocyclic C=C), 1575 cm^{-1} (ring C=C), SO_2 frequently masked by CF absorption.

2-Thianorbornene Dihalides. A. *exo*-6,*anti*-7-Dibromo-3,3-difluoro-2-thiabicyclo[2.2.1]heptane (24). The procedure of Middleton[10] was modified with improvement in yield. A solution of 29.6 g (0.2 mol) of **8** in 50 ml of dichloromethane was stirred and cooled in Dry Ice–acetone while 32 g (0.2 mol) of bromine in 25 ml of dichloromethane was added dropwise. The solvent was allowed to evaporate and the residue was recrystallized from pentane to give 57 g (93%), mp 54–54.5°, in two crops: ^{19}F nmr (CCl_4) AB pattern 4.35, 0.83 (d's, J = 8 Hz), 14.5, 18.0 ppm (m's).

B. *exo*-6,*anti*-7-Dibromo-3,3-bis(trifluoromethyl)-2-thiabicyclo[2.2.1]heptane (25). To a solution of 3.72 g (0.015 mol) of **9**[10] in 3 ml of dichloromethane was added 2.40 g (0.015 mol) of bromine in 3 ml of dichloromethane with stirring and cooling in ice. Evaporation of the solvent gave 6.10 g (100%) of the dibromide: mp 75°; mp 76–77° after recrystallization from hexane; ^{19}F nmr (CCl_4) −1.49, 3.94 ppm (quadruplets, J = 12 Hz).

C. Compound **26**, from the bromination of **10** as described above, was recrystallized from hexane (0.8 ml per g) by cooling in Dry Ice; 86% yield; mp 49–51°; ^{19}F nmr (CCl_4) 8.80, 10.8 ppm (quadruplets).

D. *exo*-6,*anti*-7-Dibromo-*endo*-3-cyano-*exo*-3-(methylthio)-2-thiabicyclo[2.2.1]heptane (29). To 4.0 g (0.022 mol) of **12**[39] in 40 ml of dichloromethane was added, in portions with stirring at 5°, 6.8 g (0.022 mol) of tetramethylammonium tribromide.[40] Tetramethylammonium bromide was filtered off, and the filtrate was decolorized with carbon and allowed to evaporate. The residue (7.14 g, 95%) was recrystallized from carbon tetrachloride to leave 6.65 g (88%) in two crops, mp 115–116°.

E. *exo*-6,*anti*-7-Dibromospiro(2-thiabicyclo[2.2.1]heptane-3,9′-fluorene) (30). **13** (2.62 g, 0.01 mol) was dissolved in 15 ml of dichloromethane, stirred, and cooled in ice, and 3.30 g (0.0105 mol) of tetramethylammonium tribromide[40] was added. The mixture was stirred for 1.5 hr, during which some of the product separated and was then filtered. The filter cake was washed with water to remove tetramethylammonium bromide. The dichloromethane filtrate was evaporated and the residue was rinsed with cold ether to remove some sirupy material. The total yield was 3.54 g (84%). Recrystallization from benzene left 2.77 g (66%) which decomposed when heated.

F. Compound **31**, from the bromination of **14** as described in A, was recrystallized from hexane: 89%; mp 99–100°.

G. *exo*-6,*anti*-7-Dibromo-3-(hexafluoroisopropylidene)-spiro(2-thiabicyclo[2.2.1]heptane-5,1′-cyclopropane) (32). **15** was brominated in pentane and was crystallized out by cooling in Dry Ice: 92% in three crops; mp 73°.

H. *exo*-6,*anti*-7-Dichloro-3-(hexafluoroisopropylidene)-2-thiabicyclo[2.2.1]heptane (33). To 5.2 g (0.02 mol) of **10** in 10 ml of dichloromethane was added 4 g (0.03 mol) of sulfuryl chloride in portions. Sulfur dioxide was evolved. After 30 min the product was distilled to give 5.85 g (88%) of a mixture of dichlorides: bp 60–62° (0.2 mm); n^{25}D 1.4828–4839. Nmr indicated that two isomers were present in a ratio of *ca.* 89:21. The mixture was subjected to preparative glpc over 25% Triton X305 on Chromosorb W at 200° in 55% return. Separation was not achieved, but 1.73 g of the 6,7-dichloro isomer crystallized out. Recrystallization from pentane by cooling in Dry Ice left 1.48 g: mp 38–39°; ^{19}F nmr (CCl_4) 8.63, 11.55 ppm (quadruplets). Chlorination of the thianorbornene with chlorine at 0° also produced a mixture.

I. Bromination of 3-(Hexafluoroisopropylidene)-2-thiabicyclo[2.2.1]hept-5-ene 2,2-Dioxide. A solution of 8.76 g (0.03 mol) of **11** in 30 ml of dichloromethane was stirred and cooled in ice and irradiated with a sun lamp while 4.80 g (0.03 mol) of bromine in 15 ml of dichloromethane was added dropwise. Uptake of bromine was slow, and irradiation was continued for 30 min. The solvent was allowed to evaporate and the crystals that had formed were stirred with cold carbon tetrachloride and filtered to provide 5.51 g (40%) of *exo*-5-bromo-2-[1-bromo-2,2,2-trifluoro-1-(trifluoromethyl)ethyl]-3-thiatricyclo[2.2.1.0^{2,6}]heptane 3,3-dioxide (**40**). Recrystallization from carbon tetrachloride left 4.92 g: mp 148–149°; ir 3086 (CH), 1332, 1174 cm^{-1} (–SO_2–); ^{1}H nmr ($CDCl_3$) 2.66 (t, 1-H + 6-H), 2.83 (AB, J = 5.5 Hz, CH_2), 3.48 (m, 4-H), 4.78 ppm (t, 5-H); ^{19}F nmr 0.31 ppm (s, broadened).

Anal. Calcd for $C_9H_6Br_2F_6O_2S$: C, 23.92; H, 1.34; Br, 35.36. Found: C, 24.11; H, 1.31; Br, 35.52.

The filtrate from the original carbon tetrachloride treatment was evaporated and the residue was recrystallized twice from ethanol to give 1.76 g (13%) of pure (by nmr) *cis,exo*-5,6-dibromo-3-(hexafluoroisopropylidene)-2-thiabicyclo[2.2.1]heptane 2,2-dioxide (**28**): mp 103–104°; ^{19}F nmr ($CDCl_3$) 7.55, 9.01 ppm (quadruplets).

J. *exo*-6,*anti*-7-Dibromo-3-(hexafluoroisopropylidene)-2-thiabicyclo[2.2.1]heptane 2,2-Dioxide (27). A solution of 5.9 g (0.029 mol) of 85% *m*-chloroperbenzoic acid in 60 ml of dichloromethane was added to 5.46 g (0.013 mol) of **26** in 10 ml of dichloromethane. After 2.5 days the precipitated *m*-chlorobenzoic acid was filtered and the filtrate was evaporated. The residue was washed with 5% sodium bicarbonate solution and with water and air dried. Recrystallization from carbon tetrachloride left 4.13 g (70%) of the sulfone, mp 169–171°.

Dehydrobrominations of 2-Thianorbornene Dibromides. A. *anti*-7-Bromo-3,3-difluoro-2-thiabicyclo[2.2.1]hept-5-ene (17). Potassium *tert*-butoxide (8.6 g, 0.077 mol) was added in portions to 21.6 g of **24** in 150 ml of ether stirred and cooled in ice. The mixture was then stirred at 24° for 16 hr. Addition of water caused tar to separate. The ether layer was separated, dried ($MgSO_4$), and distilled. A fraction distilling at 86–90° (10 mm), 4.23 g, crystallized and was recrystallized from pentane to give 3.25 g (20.4%) of the title compound: mp 40–41°; ^{19}F nmr (CCl_4) AB pattern, J = 199 Hz, −3.82, −7.34 (d's), −10.0, −13.5 ppm (quartets).

B. *anti*-7-Bromo-3-(hexafluoroisopropylidene)-2-thiabicyclo[2.2.1]hept-5-ene[34] (18). Potassium *tert*-butoxide (10 g, 0.89 mol) in 150 ml of ether was stirred and cooled in ice while 35 g (0.083 mol) of **26** in 50 ml of ether was added. After 2 hr the mixture was filtered through Celite and distilled at 0.1 mm to give 15 g, bp 43–50°, n^{25}d 1.4900; 5.9 g bp 50–75°, n^{25}d 1.4730, and 7.2 g bp 75–77°, n^{25}d 1.4728. All fractions crystallized. The first was recrystallized from hexane to give 14.1 g (50%) of the title compound in two crops: mp 62–63°; ^{19}F nmr 8.50, 11.8 ppm (quadruplets).

The third cut was recrystallized twice from hexane to yield 4.23 g (12%) of 7-bromo-6-*tert*-butoxy-3-(hexafluoroisopropylidene)-2-thiabicyclo[2.2.1]heptane: mp 56–56.5°; ^{1}H nmr (CCl_4) 1.15 [s, $(CH_3)_3C$], 2.25 (m, CH_2), 3.42 (s, 1-H), 3.74 (4-H, broadened by F), 4.12 (m, 6-H), 4.25 ppm (s, 7-H).

Anal. Calcd for $C_{13}H_{15}BrF_6OS$: C, 37.79; H, 3.66; Br, 19.34. Found: C, 38.14; H, 3.56; Br, 19.27.

C. *anti*-7-Bromo-4,6-diphenyl-3-(hexafluoroisopropylidene)-2-thiabicyclo[2.2.1]hept-5-ene (19). **16** (4.12 g, 0.01 mol) was dissolved in 15 ml of dichloromethane, cooled, and stirred in ice, and 3.30 g (0.0105 mol) of tetramethylammonium tribromide[40] was added in portions. Bromination followed by spontaneous dehydrobromination took place rapidly. The mixture was filtered, the filtrate was evaporated, and the residue was recrystallized twice from hexane: 3.95 g (80%); mp 125–125.5°; ^{19}F nmr (CCl_4) 8.90, 14.2 ppm (quadruplets, J = 9 Hz).

Addition of Sulfenyl Halides to 2-Thianorbornenes. A. 3,3-*exo*-6-Trichloro-7-(*anti*-*p*-tolylthio)-2-thiabicyclo[2.2.1]heptane (34). A solution of 6.0 g (0.033 mol) of **7**[10] in 12 ml of hexane was stirred and cooled in ice while 4.76 g (0.03 mol) of *p*-toluenesulfenyl chloride[41] was added dropwise. The product separated

and was filtered, 8.33 g (82%). Recrystallization from hexane left 7.70 g, mp 83–84°.

B. 3,3,*exo*-6-Trichloro-7-(*anti*-*p*-fluorophenylthio)-2-thiabicyclo[2.2.1]heptane (35). The reaction was run as described above but using *p*-fluorobenzenesulfenyl chloride:[42] 87% yield; mp 89°.

C. *exo*-6-Bromo-3,3-dichloro-7-(*anti*-*p*-tolylthio)-2-thiabicyclo[2.2.1]heptane (36). A composition containing *p*-toluenesulfenyl bromide was made by adding 4.8 g (0.03 mol) of bromine in 25 ml of hexane to 3.72 g (0.03 mol) of *p*-toluenethiol in 25 ml of hexane with stirring and cooling in ice. The solution was then put under vacuum to remove hydrogen bromide and part of the solvent. This solution was added to 5.43 g (0.03 mol) of **7** in 15 ml of hexane. The product gradually precipitated and was filtered from the cooled solution, 4.98 g (43%); mp 103–105° after two recrystallizations from cyclohexane.

D. *exo*-6-Chloro-3,3-difluoro-7-(*anti*-*p*-tolylthio)-2-thiabicyclo[2.2.1]heptane (37). A solution of 4.44 g (0.03 mol) of **8**[10] in 10 ml of pentane was stirred and cooled in ice while 4.76 g (0.03 mol) of *p*-toluenesulfenyl chloride[41] was added. The product was removed in three crops to give 7.90 g (86%), mp 56–57°.

E. Dehydrochlorination of D. A solution of 3.07 g (0.01 mol) of **37** in 10 ml of ether was added to 1.23 g (0.011 mol) of potassium *tert*-butoxide suspended and stirred in 15 ml of ether. The mixture became thick with solid. After it had stood for 16 hr, water was added and the ether layer was separated, dried ($MgSO_4$), and treated with decolorizing charcoal. Evaporation of the filtered solution gave 2.67 g of solid which was recrystallized from hexane to give 3,3-difluoro-7-(*anti*-*p*-tolylthio)-2-thiabicyclo[2.2.1]hept-5-ene (**20**), mp 63–67°.

F. 4,6-Diphenyl-7-(*anti*-*p*-tolylthio)-3-hexafluoroisopropylidene)-2-thiabicyclo[2.2.1]hept-5-ene (21). To 3.09 g (0.0075 mol) of **16** in 10 ml of dichloromethane was added 1.19 g (0.0075 mol) of *p*-toluenesulfenyl chloride.[41] Hydrogen chloride was evolved. The solvent was evaporated, the residue was stirred with cold pentane, and 3.0 g of crystals was filtered off. Recrystallization from hexane gave 2.37 g (59%) of the title compound, mp 130°.

Bromination of a 2-Oxanorbornene. To a solution of 4.88 g (0.02 mol) of 2,2,3,3,4,4-hexafluorospiro(cyclobutane-1,3′-[2]oxabicyclo[2.2.1]hept[5]ene)[21a] (**22**) in 10 ml of dichloromethane was added 3.20 g (0.02 mol) of bromine during 1 hr. Reaction was slow. After decolorization, analytical glpc of the crude product over 20% QF-1 Fluorosilicone on 60/80 Chromosorb P at 168° indicated the mixture was 91% cis dibromide (retention time, 8.6 min) and 9% trans (retention time, 10.9 min). Distillation gave 6.54 g of (81%) the mixed 5′,6′-dibromo-2,2,3,3,4,4-hexafluorospiro(cyclobutane-1,3′-[2]oxabicyclo[2.2.1]heptanes): bp 55–58° (0.2 mm); $n^{25}D$ 1.4635–1.4600.

Preparative glpc was used to obtain nmr samples from the distilled mixture. The cis compound (**38**) is liquid and its nmr spectrum shows an AB pattern, J = 9 Hz, for *cis*-CHBrCHBr whereas the trans isomer (**39**) is solid, mp 58–59°, with an AB pattern, J = 1.4 Hz.

2-Azanorbornenes. A. 3-(Dichloromethylene)-2-(*p*-toluenesulfonyl)-2-azabicyclo[2.2.1]hept-5-ene (45). To 11.0 g (0.03 mol) of 2-(*p*-toluenesulfonyl)-*exo*-3-(trichloromethyl)-2-azabicyclo[2.2.1]hept-5-ene[25] (**44**) in 50 ml of tetrahydrofuran was added 3.70 g (0.033 mol) of potassium *tert*-butoxide in 20 ml of tetrahydrofuran. The mixture was allowed to stand for 16 hr and the solvent was then evaporated. The residue was washed with water, air dried, and recrystallized from carbon tetrachloride to yield 8.84 g (89%): mp 118–120°; ir 2985 (CH), 1653 (exocyclic C=C), 1608, 1572, 1502 (aromatic C=C), 1342, 1163 cm^{-1} ($-NSO_2-$).

B. 2-(*p*-Toluenesulfonyl)-2-azabicyclo[2.2.1]hept-5-ene-*exo*-3-carboxylic Acid (47). The butyl ester[26] of the title compound was hydrolyzed by heating with 1.1 equiv of potassium hydroxide in ethanol for 15 min. The alcohol was evaporated, the residue was dissolved in water, and the acid was precipitated with hydrochloric acid. The precipitate was filtered, washed with water, dried, and recrystallized from chloroform, mp 124–125°. The sharp singlet in the nmr spectrum for H-3 indicates this proton is endo.

C. Methyl 3-(Trichloromethyl)-2-azabicyclo[2.2.1]hept-5-ene-2-carboxylates (48, 49). Methyl *N*-(2,2,2-trichloroethylidene)carbamate[43] (20.5 g, 0.1 mol), 70 ml of benzene, and 18 ml (0.2 mol) of cyclopentadiene were refluxed for 5 hr. The volatiles were removed under vacuum, finally at 0.5 mm and 100°. The residue was crystallized from 25 ml of hexane to give 21.3 g (79%) of the mixed isomers having the correct analysis for C, H, and N and containing about 56% of the *exo*-H-3 isomer. Four recrystallizations from heptane, using 1.5 ml/g and cooling in ice, gave 6.4 g of the *exo*-H-3 isomer (**48**), mp 67–69°. In this isomer, *exo*-H-3 is coupled with H-4 and appears as a sharp doublet (J = 3.2 Hz) in the nmr spectrum. For the ethyl ester, see ref 25c.

Systematic recrystallization from the mother liquor gave more of this product. The more soluble, *endo*-H-3 isomer (**49**) was obtained from the ultimate liquor in about 78% purity. *endo*-H-3 appears as a sharp singlet in the nmr spectrum.

D. Methyl 3-(Dichloromethylene)-2-azabicyclo[2.2.1]hept-5-ene-2-carboxylate (50). To a solution of 2.70 g (0.01 mol) of the mixed isomers of methyl 3-(trichloromethyl)-2-azabicyclo-[2.2.1]hept-5-ene-2-carboxylate in 8 ml of tetrahydrofuran was added 1.23 g (0.011 mol) of potassium *tert*-butoxide in 8 ml of tetrahydrofuran. The mixture was stirred for 15 hr, filtered, and evaporated. The residue was recrystallized from hexane to give 1.67 g (71%) in two crops: mp 50–51°; ir 3049 (=CH), 2985, 2874 (CH), 1745 (C=O), 1658 (exocyclic C=C), 1570 (ring C=C).

E. 2-Acetyl-*exo*-3-(trichloromethyl)-2-azabicyclo[2.2.1]-hept-5-ene (51). *N*-(1,2,2,2-Tetrachloroethyl)acetamide[44] was converted to *N*-(2,2,2-trichloroethylidene)acetamide.[45] A solution containing 7.54 g (0.04 mol) of the latter, 20 ml of benzene, and 6.6 ml (0.08 mol) of cyclopentadiene was refluxed for 4 hr. The volatile ingredients were removed, finally at 100° and 0.5 mm of pressure. Crystallization from cyclohexane gave 5.83 g (57%) of the adduct. A second recrystallization left 4.01 g of the *exo*-trichloromethyl isomer, mp 87–89°.

Bromination of 2-Azanorbornenes. A. *exo*-6,*anti*-7-Dibromo-3,3-bis(trifluoromethyl)-2-azabicyclo[2.2.1]heptane (57). **43**[22] was freed of dicyclopentadiene and a small amount of a fluorinated impurity by preparative glpc over 25% DC-200 Silicone on Chromosorb W at 100°. A solution of 4.62 g (0.02 mol) in 12 ml of dichloromethane was stirred and cooled in ice while 3.20 g (0.02 mol) of bromine in 5 ml of dichloromethane was added dropwise. The bromine was taken up rapidly at first and then slowed down. The solution was allowed to stand for 20 hr and the solvent was removed. Analytical high pressure liquid chromatography on the crude product on a Corasil II column showed a sharp peak with an area per cent of 97.4. Analytical glpc over Triton X-305 on Chromosorb W was unsatisfactory. There was evidence of decomposition and a peak of 69 area per cent was obtained. Crystallization could not be induced and the product was distilled to give 5.93 g, bp 55–65° (0.2 mm), which crystallized. Recrystallization from pentane left 2.98 g (38%) of the 6,7-dibromide, mp 60°.

B. *exo*-6,*anti*-7-Dibromo-2-(*p*-toluenesulfonyl)-*endo*-3-(trichloromethyl)-2-azabicyclo[2.2.1]heptane (58). To a solution of 3.67 g (0.01 mol) of **44**[25] in 12 ml of dichloromethane was added dropwise 1.60 g (0.01 mol) of bromine in 3 ml of dichloromethane. After one hr the solvent was evaporated and the residue was recrystallized from carbon tetrachloride to give 4.6 g (87%), mp 177–178°.

C. Dehydrochlorination of 58. To 2.63 g (0.005 mol) of **58** in 10 ml of tetrahydrofuran was added 1.23 g (0.011 mol) of potassium *tert*-butoxide in 10 ml of tetrahydrofuran. The mixture was stirred for 1 hr and filtered, and the filtrate was evaporated. The residue was stirred with cold ethanol and the crystals (1.7 g) were filtered off. Recrystallization from ethanol gave 1.31 g (54%) of *exo*-6,*anti*-7-dibromo-3-(dichloromethylene)-2-(*p*-toluenesulfonyl)-2-azabicyclo[2.2.1]heptane (**59**), mp 131–132°.

D. Removal of HCl Plus HBr from 58. To a solution of 3.08 g (0.0275 mol) of potassium *tert*-butoxide dissolved in 20 ml of tetrahydrofuran was added 2.63 g (0.005 mol) of **58** in 10 ml of tetrahydrofuran. The mixture became dark and warm. The mixture was stirred for 1 hr and filtered, and the filtrate was evaporated. The residue crystallized when triturated with a little ethanol. The crystals were filtered from the cooled mixture and washed first with cold ethanol and then water. Recrystallization from ethanol gave 0.21 g (10.3%) of *anti*-7-bromo-3-(dichloromethylene)-2-(*p*-toluenesulfonyl)-2-azabicyclo[2.2.1]hept-5-ene (**46**), mp 98–100°.

E. Compound **60** from the bromination of **47**, as described in B, was recrystallized from acetonitrile: 82%; mp 206–207°. Nmr of the crude and recrystallized product indicated that only one isomer formed.

F. Compound **61** from bromination of **48**, as described in B, was recrystallized from hexane: 90%; mp 101–104°.

G. Methyl *exo*-6,*anti*-7-Dibromo-*endo*-3-(trichloromethyl)-2-azabicyclo[2.2.1]heptane-2-carboxylate (62). The mixed isomers of methyl 3-(trichloromethyl)-2-azabicyclo[2.2.1]hept-5-ene-2-carboxylate in dichloromethane were brominated and the product was recrystallized four times from methanol and again from acetone to give the *endo*-trichloromethyl isomer which is the less soluble of the two bromides, mp 147–150°.

H. Compound **63** from the bromination of **51**, as described in B, was recrystallized from ethanol: 57%; mp 177–179°.

Azanortricyclenes. A. *endo*-3-Bromo-7,7-bis(trifluoromethyl)-1-azatricyclo[2.2.1.0^{2,6}]heptane (68). **57** (3.13 g, 0.008 mol) in 5 ml of ether was added to 0.99 g (0.0088 mol) of potassium *tert*-butoxide suspended and stirred in 25 ml of ether. After 3 hr, water was added and the ether layer was separated, dried ($MgSO_4$), and distilled to give 1.75 g (71%) of the 2-azanortricyclene: bp 75° (10 mm); $n^{25}D$ 1.4295; ir 3086, 3049 shoulder (aziridine CH), 2941 cm^{-1} (CH); ^1H nmr (neat) 2.47 (AB, J = 13 Hz, CH_2), 2.85 (m, H-4), 2.94 (s, H-2 + H-6), 4.79 ppm (s, CHBr); ^{19}F nmr 2.77 ppm A_3B_3.

Anal. Calcd for $C_8H_6BrF_6N$: C, 30.99; H, 1.95; N, 4.52. Found: C, 31.03; H, 1.94; N, 4.54.

B. *endo*-3-Bromo-*syn*-7-carbamoyl-1-azatricyclo[2.2.1.-0^{2,6}]heptane-*anti*-7-carbonitrile (70). To 1.15 g (0.006 mol) of ethyl 3-*exo*-cyano-2-azabicyclo[2.2.1]hept-5-ene-3-*endo*-carboximidate[23,32] in 10 ml of dichloromethane was added with stirring 0.96 g (0.006 mol) of bromine in 3 ml of dichloromethane. During the addition of the first half of the bromine, a copious crystalline precipitate formed. This dissolved on addition of the rest of the bromine. The solution was allowed to stand for 16 hr and the solvent was then evaporated. The residue was recrystallized from water to give 0.78 g (55%) of the azanortricyclene. An analytical sample was recrystallized again from nitromethane: mp 167–168°; ir 3279, 3175, 1587 (NH_2), 2242 (CN), 1678 cm^{-1} (C=O); ^1H nmr [$(CD_3)_2SO$] 1.86 (AB, J = 13 Hz, 5-CH_2), 2.8–3.1 (m's, 1-H, 4-H, 6-H), 4.50 (s, CHBr), 7.87 ppm (d, NH_2, removed by D_2O).

Anal. Calcd for $C_8H_8BrN_3O$: C, 39.68; H, 3.33; N, 17.36. Found: C, 39.54; H, 3.21; N, 17.51.

1,4-Methanopyridazine Derivatives. A. *exo*-2,*anti*-13-Dibromo-1,2,3,4-tetrahydro-1,4-methanopyridazine[1,2-*b*]phthalazine-6,11-dione (67). 1,4-Dihydro-1,4-methanopyridazino[1,2-*b*]-phthalazine-6,-11-dione[29] was prepared by the reaction of cyclopentadiene, 1,2-dihydro-1,4-phthalazinedione, and lead tetraacetate in dichloromethane[46] and recrystallized from nitromethane: 78%; mp 238–239°. To a stirred solution of 6.78 g (0.03 mol) of the dione in 170 ml of dichloromethane in a flask wrapped with aluminum foil was added 4.80 g of bromine and the solution was allowed to stand for 16 hr. The solvent was removed and the residue was rinsed with acetone and recrystallized from nitromethane to give 9.7 g (84%) of the dibromide, mp 248–251° dec.

B. *anti*-13-Bromo-1,4-dihydro-1,4-methanopyridazino[1,2-*b*]phthalazine-6,-11-dione (56). A mixture of 4.63 g (0.012 mol) of **67** and 3.17 g (0.02 mol) of 96% 1,5-diazabicyclo[5.4.0]undec-5-ene[47] was heated in a bath at 145° for 15 min. The product was cooled and washed with water, 5% hydrochloric acid, and water again. The yield was 3.38 g (92%). Recrystallization from nitromethane left 3.08 g, mp 194–196° dec.

2,3-Diazabicyclo[2.2.1]hept-5-ene Derivatives. A. Diphenyl 2,3-Diazabicyclo[2.2.1]hept-5-ene-2,3-dicarboxylate (53). A solution of 13.5 g (0.05 mol) of diphenyl diazodicarboxylate[47] dissolved in 50 ml of dichloromethane was stirred and cooled in ice while 3.3 g (0.05 mol) of cyclopentadiene was added. The solution was allowed to stand at 24° for 16 hr and then evaporated. The residue, 15.9 g (95%), was recrystallized from carbon tetrachloride to give 13.8 g (82%), mp 112–114°.

B. Diphenyl *exo*-6,*anti*-7-Dibromo-2,3-diazabicyclo[2.2.1]-heptane-2,3-dicarboxylate (64). To a solution of 3.36 g (0.01 mol) of **53** in 10 ml of dichloromethane was added 1.60 g (0.01 mol) of bromine in 3 ml of dichloromethane. Reaction was slow. After 24 hr the solvent was boiled off. The residue was crystallized from carbon tetrachloride, 2.64 g (53%). A second recrystallization left 2.23 g of the dibromide, mp 133°.

C. Dimethyl *exo*-6,*anti*-7-Dibromo-2,3-diazabicyclo[2.2.1]-heptane-2,3-dicarboxylate (65). Dimethyl 2,3-diazabicyclo-[2.2.1]hept-5-ene-2,3-dicarboxylate[48] (**52**) was brominated as described for the diphenyl ester and recrystallized from methanol, mp 107–108°.

D. Diethyl *anti*-7-Bromo-2,3-diazabicyclo[2.2.1]hept-5-ene-2,3-dicarboxylate (54). A mixture of 4.00 g (0.01 mol) of **66**[30,31] and 3.17 g (0.02 mol) of 96% 1,5-diazabicyclo[5.4.0]undec-5-ene[47] was heated on a steam bath for 15 hr. To the cooled mixture was added 12 ml of 10% sulfuric acid and the product was extracted with ether and dried ($MgSO_4$). Evaporation of the ether gave 2.66 g (83%) of crystals which were recrystallized from methanol by cooling in Dry Ice to give 2.08 g, mp 77–78°.

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Synthesis of 3-Hydroxythienopyrimidine-2,4(1*H*,3*H*)-diones from 2,3- and 3,4-Thiophenedicarboxylic Acids

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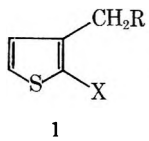
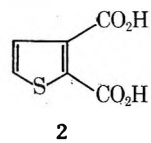
The modified Lossen rearrangement of sodium 2,3-thiophenedicarbohydroxamate with benzenesulfonyl chloride furnished a mixture of 3-benzenesulfonyloxythieno[2,3-*d* and 3,2-*d*]pyrimidine-2,4(1*H*,3*H*)-diones (54%, in the ratio of 1:3). The structure of these isomers was established by means of their proton magnetic resonance spectra. A similar rearrangement of sodium 3,4-thiophenedicarbohydroxamate produced 3-benzensulfonyloxythieno[3,4-*d*]pyrimidine-2,4(1*H*,3*H*)-dione in 67% yield. Each of these sulfonates was hydrolyzed to the corresponding *N*-hydroxy compound.

A number of thienopyrimidines have been reported during the past six years.[1] The majority of these syntheses commenced with vicinal 2- (or 3-) amino-3- (or 2-) thenoic acid derivatives and built up the pyrimidine ring by standard methods. Our approach utilized the partial Lossen degradation of one of the carboxylic acid groups from vicinal thiophenedicarboxylic acids to arrive at the title compounds.

2,3- and 3,4-Thiophenedicarboxylic Acids. The literature preparations for these acids, particularly that for the 2,3 isomer, were unsatisfactory, and reliable large-scale syntheses were developed. Friedel–Crafts acylation of 3-methylthiophene[2] furnished predominantly 2-acetyl-3-methylthiophene (**1**, R = H, X = $COCH_3$; 75%) which was separated from the accompanying 2-acetyl-4-methylthiophene by column (Al_2O_3) or gas chromatography. However, this ideal precursor was oxidized to **2** in poor yield, the major product being 3-methyl-2-thenoic acid.[2,3] Although



1

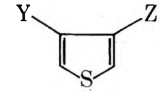


2

2-thenoic acid derivatives have been made with a functionalized 3-methyl substituent (*e.g.*, **1**, R = Br, X = CO_2Et), their preparations were tedious and subsequent oxidation to **2** was not assured.[5]

An attractive route for the synthesis of **2** appeared feasible from 3-thenyl ethers. It was observed that functionalized 3-thenyl derivatives [*e.g.*, **1**, R = OCH_3 or $N(CH_3)_2$, X = H] were lithiated exclusively at the 2 position. Subsequent exposure of these lithio intermediates to electrophilic substrates, such as D_2O, DMF, C_6H_5CN, or $(C_6H_5)_2CO$, furnished 2,3-disubstituted thiophenes in excellent yields.[6,7] Thus, 3-thenyl methyl ether was lithiated and carbonated and furnished 3-methoxymethyl-2-thenoic acid (**1**, R = OCH_3, X = CO_2H). Permanganate oxidation of this acid completed the sequence to produce **2** in 86% yield.

Another synthesis of **2** was based on 2,3-dilithiothiophene.[8] Lithiation of 2,3-dibromothiophene[9] followed by carbonation gave **2** and 3-bromo-2-thenoic acid in 37 and 38% yields, respectively. A similar transformation converted 3,4-dibromothiophene (**3**) into the dicarboxylic acid (**4**). Sicé[4] had reacted 3,4-diiodothiophene with butyllithium and carbonated acid to obtain **4** in 74% yield. We planned to use the more accessible 3,4-dibromothiophene (**3**). Although two methods were explored for the synthesis of **3**,

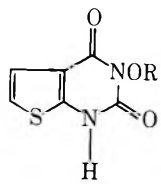


3, Y = Z = Br
4, Y = Z = CO_2H
5, Y = Br; Z = CO_2H

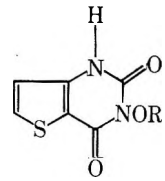
the first one of these was preferred, although it involved larger quantities of bromine. Thiophene was brominated in carbon tetrachloride to tetrabromothiophene, which was reduced with zinc and acetic acid to **3** in good overall yields.[10] The alternate method started with bromination of thiophene in benzene which furnished 2,5-dibromothiophene in excellent yield (80%).[11] However, the rearrangement of the 2,5 isomer to **3** by sodamide proceeded in considerably lower yield (42%) than had been reported (73%).[12] Lithiation of **3**, followed by Dry Ice produced **4** (40%) and

3-bromo-4-thenoic acid (**5**) (17%). These methods of converting **3** into **4** do not greatly improve on (yieldwise) a method published while this work was in progress. That procedure converted **3** first into the bis-nitrile, which was then hydrolyzed to **4** in 59% yield.[13a]

Rearrangement. Conversion of **2** into the ethyl ester and then to the corresponding bis-hydroxamate was accomplished in the usual way.[14] Treatment of this hydroxamate with benzenesulfonyl chloride under conditions developed in this laboratory resulted in a mixture of **6** and **8** in the ratio of 1:3. Separation of these two isomers was achieved when it was found that **8** precipitated first at pH 8, while the isomer **6** was recovered at a lower pH. Mild hydrolysis of **6** or **8** provided the isomeric *N*-hydroxy compounds **7** and **9**, respectively.



6, R = $C_6H_5SO_2$
7, R = H

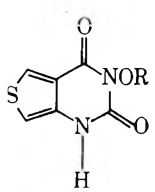


8, R = $C_6H_5SO_2$
9, R = H

To prove the structure of **7** and **9**, we resorted to pmr spectral analysis. There were extensive pmr data available on both the thieno[3,2-*d*]- and -[2,3-*d*]pyrimidine systems. The close resemblance of the chemical shift and coupling constants of the two thiophene ring protons in **7** and **9** with those found in related ring systems permitted structure assignments.[1c,d,f,i]

In DMSO-d_6, a number of thieno[3,2-*d*]pyrimidine-4(3*H*)-ones showed resonances of the two thiophene ring protons as two doublets consistently between δ 8.23–8.26 for H-6 and 7.43–7.50 for H-7 for that ring system.[1c] Isomers in the [2,3-*d*] system presented the thiophene ring proton resonances (in DMSO-d_6) further upfield either as an AB pattern between δ 7.40 and 7.55 or as a singlet in that region. When an AB pattern was observed, these authors could not assign the chemical shifts of H-5 and H-6 in the thieno[2,3-*d*]pyrimidine-4(3*H*)-one system. As members of the thieno[2,3,-*d*]pyrimidine system, **6** and **7** both showed singlets for H-5 and H-6 around δ 7.15 in DMSO-d_6. On the other hand, the proton magnetic resonances spectra clearly revealed two doublets assignable to the thiophene ring protons: H-6 and H-7 at δ 8.20 and 6.95, 8.05 and 6.94 for **8** and **9**, respectively. The coupling constant, $J_{6,7}$ = 5.2 Hz, was of similar magnitude as had been reported for the [3,2-*d*] system.[1c] It was found that for the [2,3-*d*] system, coupling constants were usually a little larger (J = 5.6–5.9 Hz). Therefore, on the basis of the chemical shift data, **8** and **9** were assigned structures in the thieno[3,2-*d*]pyrimidine system, while **6** and **7** belong to the isomeric [2,3-*d*] system.[1c]

In a similar series of reactions, 3,4-thiophenedicarboxylic acid was converted into the thieno[3,4-*d*]pyrimidine derivatives **10** and **11**.



10, R = $C_6H_5SO_2$
11, R = H

There was no problem in proving the structure of **10** or **11**. The aromatic nature of these compounds is attested to by the chemical shift of the ring protons. It is reasonable to assign the furthest downfield proton δ 8.40 to the thiophene ring proton flanked by the C=O.[1c] Furthermore, both **10** and **11** showed a coupling constant expected for "meta" type of coupling through sulfur, J = 3.2 Hz. This coupling resembles that reported for a number of unsymmetrical 3,4-disubstituted thiophenes[13b] and a number of thieno[3,4-*d*]pyrimidines.[1k]

Experimental Section

All melting points are uncorrected and were determined in capillary tubes on a Thomas Hoover Unimelt up to 300° and over 300° on a Mel-Temp melting point apparatus. Nitrogen analyses were determined by means of a Coleman Nitrogen Analyzer, Model D-29, and those for other elements by Micro-Tech Labs, Skokie, Ill. Ir spectra were obtained on a Perkin-Elmer 337 recording infrared spectrophotometer. Pmr spectra were recorded by means of a Varian A-60 spectrometer in ppm (δ), downfield from $(CH_3)_4Si$. Mass spectra were obtained by R. Dvorak at 70 eV using a Hitachi Perkin-Elmer RMU-6D single focusing mass spectrometer and substantiated the proposed structures. Thin layer chromatographs (tlc) were developed over 15 min on 7.2-cm slides coated with silica gel and a fluorescent indicator (Eastman Chromagram Sheet 6060) using ethyl acetate. Spots were detected by uv light.

Methyl 3-Thenyl Ether. Details for the preparation of this ether have not been reported.[15] The reaction of thenyl bromide[16] and sodium methoxide in methanol gave considerably lower yield due to the azeotropic distillation of the product with methanol. The following procedure gave reproducible results.

Sodium (18.4 g, 0.8 g-atom) was dissolved in absolute methanol (150 ml) and the solution evaporated to dryness, *in vacuo*. The last traces of methanol were removed by azeotropic distillation with benzene (twice with 200 ml). Residual sodium methoxide was suspended in anhydrous ether (250 ml), and thenyl bromide[16] (129 g, 0.73 mol) was added with occasional swirling (20 min). The vigorous exothermic reaction was controlled by immersing the reaction flask in an ice–water bath so as to maintain gentle reflux. After the exothermic reaction ceased, the mixture was boiled for 2 hr. The mixture was filtered and after removal of the ether, the product (82 g, 89%) boiled at 78° (10 Torr) [lit.[15] bp 65–67° (17 Torr)]: pmr ($CDCl_3$) δ 3.34 (s, CH_3), 4.40 (s, CH_2), 6.95–7.40 (m, thiophene protons).

3-Methoxymethyl-2-thenoic Acid. To a suspension of freshly prepared ethereal solution of butyllithium (0.4 mol)[17] in a 300-ml pressure bottle was added cautiously methyl 3-thenyl ether (38.4 g, 0.3 mol) in a stream of nitrogen. The flask was then filled up with anhydrous ether, stoppered, and kept at 25° for 10 hr. The mixture was poured slowly into a slurry of Dry Ice in anhydrous ether under a blanket of nitrogen. The mixture was permitted to stand at 25° for 3 hr and was then mixed with water (375 ml). The ether layer was separated and was washed with water (2 × 50 ml). The combined aqueous phase was extracted with ether (2 × 50 ml) and then heated on the steam bath to expel dissolved ether. After cooling to 25°, the solution was acidified with concentrated HCl to pH < 2. After 3 hr at 5°, the acid (46 g, 89%) was collected and washed with water and dried; mp 115–120°. The product was recrystallized from water (charcoal): mp 126–127°; ir (Nujol) 3300–2200 (broad, COOH), 1675 (CO) cm^{-1}; pmr ($CDCl_3$) δ 3.46 (s, CH_3), 4.86 (s, CH_2), 7.31, 7.64 (AB pattern, H-4, H-5, $J_{4,5}$ = 5.2 Hz), 10.8 (broad, s, exchangeable with D_2O).

Anal. Calcd for $C_7H_8O_3S$: C, 48.84; H, 4.68. Found: C, 48.73; H, 4.59.

2,3-Thiophenedicarboxylic Acid. Method A. To a stirred solution of 3-methoxymethyl-2-thenoic acid (16 g, 0.1 mol) in 10% NaOH solution (500 ml) was added potassium permanganate (30 g, 0.2 mol). After stirring at 50° for 1 hr, manganese dioxide was filtered off, and the filter cake was washed with boiling water (2 × 50 ml). The combined filtrate was acidified and cooled to 5° to afford **2** (12 g, 75%), mp 264°; recrystallization from water raised the melting point to 270° (lit.[3,18] mp 270°, 271–272°,[19] 277–278°).[4] An additional batch (1.7 g) was obtained by evaporating the mother liquor to half-volume (total yield, 86%). The acid was identical to a sample prepared by a literature method.[3]

Method B. To a stirred suspension of ethereal butyllithium (0.4 mol) at −70° was added 2,3-dibromothiophene[9] (26.3 g, 0.1 mol) over 5 min. The mixture was stirred at −70° for 0.5 hr and then

poured slowly into a slurry of Dry Ice in anhydrous ether. After 3 hr, water (200 ml) was added to the ethereal suspension. The aqueous layer was separated and the ether layer was extracted several times with water (3 × 200 ml). The combined aqueous phase was washed with ether (2 × 100 ml) and then warmed to remove dissolved ether. After cooling to 25°, a small amount of a solid was filtered off. The filtrate was acidified to pH 1 with concentrated HCl and immersed in an ice–water bath. Several hours later the solid was filtered and recrystallized from water (charcoal) to give 3-bromo-2-thenoic acid (7.8 g, 38%), mp 190–193° (lit.[20] mp 195–197°); its ir spectrum was identical with the one reported in the literature.[20]

The combined mother liquors were concentrated *in vacuo*, to about 350 ml. After several hours, at 5°, **2** was isolated (6.9 g, 37%), which was identical with the sample prepared in method A. Attempts to increase the yield of **2** by increasing the reaction time or the ratio of butyllithium to 2,3-dibromothiophene were unsuccessful.

Esterification of **2** was achieved by refluxing the *acid* (4.9 g) with ethanol (200 ml), toluene (100 ml), and concentrated sulfuric acid (1 ml) (Dean–Stark apparatus attached). During the first 5 hr, 50 ml were withdrawn every hour and replenished by an equal volume of the ethanol–toluene mixture. The solution was then concentrated *in vacuo*, to 10 ml and neutralized with cold saturated $NaHCO_3$, and the organic phase was extracted into benzene (4 × 30 ml). The extract was dried ($MgSO_4$) and distilled to yield the ester (5.6 g, 86%): bp 109° (0.015 Torr); ir (neat) 3120, 3000, 1720 cm^{-1}; pmr (CCl_4) δ 1.34 (t, CH_3's), 4.34 (q, CH_2's), 7.24, 7.45 (AB pattern, H-4, H-5, $J_{4,5}$ = 5.2 Hz).

Anal. Calcd for $C_{10}H_{12}O_4S$: C, 52.63; H, 5.30. Found: C, 52.67; H, 5.30.

3,4-Thiophenedicarboxylic Acid. A sample of 3,4-dibromothiophene[10,12] (30.5 g, 0.126 mol) was lithiated and then carbonated as described in method B for **2.** The aqueous extract was acidified and the first precipitate proved to be 4-bromo-3-thenoic acid (4.5 g, 17%) which was recrystallized from water, mp 153–156° (lit.[21] mp 157–159°). Its ir spectrum was identical to the published one.

The aqueous mother liquors were concentrated to 200 ml *in vacuo*, and the hot solution was charcoaled to give **4** (8.5 g, 40%); mp 225–229° (lit.[22] mp 223–225°, 230–231°,[4] 225–226°[13a]).

Esterification of **4** (8.5 g) was achieved as described under method B above, producing the ethyl ester (6.8 g, 77%): bp 136–142° (1 Torr) [lit.[23] bp 156–157° (8 Torr)]; ir (neat) 3150, 3020, 1720 (CO) cm^{-1}; pmr ($CDCl_3$) δ 1.32 (t, CH_3's), 4.33 (q, CH_2's), 7.81 (s, thiophene protons).

Sodium 2,3-Thiophenedicarbohydroxamate. An ethanolic solution of hydroxylamine was prepared by stirring a suspension of finely powdered dry hydroxylammonium chloride in absolute ethanol (14.6 g in 400 ml) with a solution of sodium ethoxide in absolute ethanol (4.8 g in 200 ml) at temperatures below 25°, until neutral to wet litmus. Sodium chloride was filtered off and ethyl 2,3-thiophenedicarboxylate (24 g, see method B, above) was added in one portion to the alcoholic hydroxylamine solution, followed by more sodium ethoxide solution (4.8 g in 200 ml of absolute ethanol) after the mixture had been stirred for 0.5 hr. The yellow suspension was then stirred for 18 hr. The mixture was cooled to 5° and the hydroxamate (17.6 g) was filtered off, washed with small amounts of absolute ethanol and dry ether, and dried *in vacuo* at 25° (over sulfuric acid) for 4 hr. It was used immediately without further purification.

3-Benzenesulfonyloxythieno[2,3-*d* and 3,2-*d*]pyrimidine-2,4(1*H*,3*H*)-diones, 6 and 8, Respectively. To a stirred suspension of the finely powdered hydroxamate (19 g) prepared as described above, in tetrahydrofuran (650 ml) was added dropwise a solution of benzenesulfonyl chloride (32 g, 0.18 mol) in tetrahydrofuran (150 ml) over 1 hr. The temperature was maintained between 10 and 13° by submersing the flask occasionally in an ice–water bath. After 0.5 hr, sodium acetate trihydrate (18 g) was added and stirring continued for 8 hr at 25°. The solids were filtered and washed several times with tetrahydrofuran. The tetrahydrofuran filtrates were concentrated *in vacuo*, to produce an oily residue.

This residue was partitioned between water (800 ml) and petroleum ether (bp 30–60°, 900 ml) and the mixture stirred vigorously until the oil solidified. The solid was filtered and washed with water and ether. It weighed 15.8 g (54% yield based on original ester) and proved to be a mixture of **6** and **8** in the ratio of 1:3 (pmr).

When the following procedure was used, reproducible results were obtained in the separation of the isomers. It was critical to adhere closely to the pH VALUES USED HERE/[24] It was also found that adjustment of the pH of the original alkaline solution (~10) to pH 8 relatively quickly gave the cleanest separation. Fractions were examined by tlc to ensure their purity.

The crude mixture of **6** and **8** (2 g) was dissolved in 80 ml of dilute ammonium hydroxide solution (1:7, aqueous solution) at 5°. A very small amount of an insoluble substance was filtered off. To the filtrate at 5° was added of 10% aqueous acetic acid (~80 ml) until pH 8 was reached. This neutralization was accomplished quickly (~2 min). After several minutes at 5°, **8** (1 g) precipitated. Its purity was checked by tlc and, if contaminated by **6**, this operation had to be repeated. Recrystallization of **8** from absolute ethanol (charcoal) furnished colorless crystals (0.9 g): mp 222–224° dec; tlc R_f 0.48; ir (Nujol) 3190 (NH), 1755, 1720, 1695 (CO) cm^{-1}; pmr (DMSO-d_6) δ 6.95 (d, H-7), 7.40–8.08 (5, m, benzene ring protons), 8.20 (d, H-6, $J_{6,7}$ = 5.2 Hz).

Anal. Calcd for $C_{12}H_8N_2O_5S_2$: C, 44.46; H, 2.49; N, 8.64. Found: C, 44.30; H, 2.39; N, 8.87.

The filtrate from **8**, above, was acidified further to pH 5 with 10% aqueous acetic acid to give **6** (0.5 g). This sulfonate was recrystallized from methanol (charcoal) to afford colorless needles (0.4 g): mp 250–252° dec; tlc R_f 0.24; ir (Nujol) 3200 (NH), 1745, 1690 (CO) cm^{-1}; pmr (DMSO-d_6) δ 7.15 (2, s) (thiophene protons), 7.45–8.12 (5, m, benzene ring protons).

Anal. Calcd for $C_{12}H_8N_2O_5S_2$: C, 44.46; H, 2.49; N, 8.64. Found: C, 44.31; H, 2.44; N, 8.86.

3-Hydroxythieno[3,2-*d*]pyrimidine-2,4(1*H*,3*H*)-dione. A solution of **8** (1.9 g) in 20 ml of 10% sodium hydroxide solution was heated at 95° for 10 min. After dilution with water (10 ml) the solution was acidified with concentrated hydrochloric acid to pH 5. After 10 min at 5°, **9** (1.0 g, 93%) was collected. It was recrystallized from water (with 80% recovery): mp 305–308° dec; ir (Nujol) 3145 (broad, NH and OH), 1700, 1650 (CO) cm^{-1}; pmr (DMSO-d_6) δ 6.94 (d, H-7), 8.05 (d, H-6, $J_{6,7}$ = 5.2 Hz), 11.32 (broad, NH and OH); uv max (ethanol) 207 nm (log ϵ 4.19), 257 (3.96), 289 (3.75).

Anal. Calcd for $C_6H_4N_2O_3S$: C, 39.14; H, 2.19; N, 15.22. Found: C, 39.01; H, 2.04; N, 15.19.

3-Hydroxythieno[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (7). The hydrolysis of **6** (0.5 g) was carried out as described for **8** to yield **7** (0.3 g, 100%): mp 275–277° dec; ir (Nujol) 3260, 3120, (NH and OH), 1700, 1670, 1630 (CO) cm^{-1}; pmr (DMSO-d_6) δ 7.16 (s, H-5 and H-6); uv max (ethanol) nm (log ϵ) 205 sh (4.08), 224 (4.41), 250 sh (3.76), 275 sh (3.53).

Anal. Calcd for $C_6H_4N_2O_3S$: C, 39.14; H, 2.19; N, 15.22. Found: C, 39.06; H, 2.12; N, 15.31.

3-Benzenesulfonyloxythieno[3,4-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (10). The 3,4-bishydroxamate (6.1 g, prepared as for the 2,3 isomer, above) reacted with benzenesulfonyl chloride (10.6 g) as described for the synthesis of **6** and **8** to furnish **10** (6.5 g, 67%, based on the ester used). The sulfonate was recrystallized from ethanol (charcoal): mp 232–233° dec; tlc R_f 0.52; ir (Nujol) 3250 (NH), 1750, 1710 (CO) cm^{-1}; pmr (DMSO-d_6) δ 6.95 (d, H-7), 7.48–8.20 (5, m, benzene ring protons), 8.54 (d, H-5, $J_{5,7}$ = 3.2 Hz).

Anal. Calcd for $C_{12}H_8N_2O_5S_2$: C, 44.46; H, 2.49; N, 8.64. Found: C, 44.21; H, 2.44; N, 8.65.

3-Hydroxythieno[3,4-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (11). The hydrolysis of **10** (1.6 g) was carried out as described for **8.** After adjusting the pH of the resultant solution to 1, **11** was collected. The product was recrystallized from water to brown needles (0.75 g, 83%); mp 306° dec; ir (Nujol) 3130 (NH and OH), 1720, 1700, 1665 (CO) cm^{-1}, pmr (DMSO-d_6) δ 6.89 (d, H-7), 8.40 (d, H-5, $J_{5,7}$ = 3.2 Hz), 10.40, 11.32 (broad, NH and OH); uv max (ethanol) 211 nm (log ϵ 4.51), 259 (3.96), 302 (3.69).

Anal. Calcd for $C_6H_4N_2O_3S \cdot 0.25\ H_2O$: C, 38.21; H, 2.40; N, 14.85. Found: C, 38.46; H, 2.27; N, 14.85.

Acknowledgments. We thank Dr. W. J. Tuman for the exploratory work in this project. Useful discussions with Dr. S. Gronowitz on thiophene conversions are also gratefully acknowledged.

Registry No.—1 (R = OCH_3, X = H), 53229-44-0; **1** (R = Br, X = H), 34846-44-1; **1** (R = OCH_3, X = CO_2H, 53229-45-1; **2**, 1451-95-2; **2** diethyl ester, 53229-46-2; **3**, 3141-26-2; **4**, 4282-29-5; **4** diethyl ester, 53229-47-3; **5**, 16694-17-0; **6**, 53229-48-4; **7**, 53229-49-5; **8**, 53229-50-8; **9**, 53229-51-9; **10**, 53229-52-0; **11**, 53229-53-1; sodium methoxide, 12441-4; 2,3-dibromothiophene, 3140-93-0; 3-bromo-2-thenoic acid, 7311-64-0; sodium 2,3-thiophenecarbohy-

droxamate, 53229-54-2; hydroxylamine, 7803-49-8; benzenesulfonyl chloride, 98-09-9; sodium 3,4-thiophenecarbohydroxamate, 53229-55-3.

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Photochromic Aziridines. On the Photochemical Valence Tautomerization and Cycloaddition Reactions of a Substituted Indano[1,2-*b*]aziridine[1]

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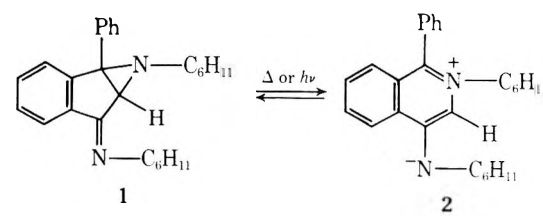
Heat or ultraviolet light partially converts 1-cyclohexyl-6-(cyclohexylimino)-1a-phenylindano[1,2-*b*]aziridine to an aromatic valence tautomer, the red isoquinolinium imine. The red color associated with the 1,3 dipole is rapidly discharged upon exposure to visible light, oxygen, or acetylenic dipolarophiles. The regiochemistry of the initial 1,3-dipolar adducts obtained with acetylenic dipolarophiles is discussed in light of some earlier results published in the literature. The initial cycloadducts were found to undergo a novel rearrangement to a benzazocine derivative whose structure was determined by X-ray crystallography. The details of each reaction are described and evidence is presented demonstrating the existence of transient intermediates in some of the irradiation experiments.

During the past decade, systematic studies of molecules or complexes which undergo reversible photoinduced color changes have contributed greatly to the basic understanding of the factors which govern the behavior of a photochromic system.[2,3] Although these systems have been the subject of valuable and penetrating mechanistic investigations, there are still many gaps in our understanding of this phenomenon.[4] Irradiation of solutions of acyclic[5,6] or bicyclic[7-9] aziridines with ultraviolet light is known to produce red colors which fade spontaneously in the dark. The colored species produced in these photoinduced reversible reactions were assigned as 1,3 dipoles (azomethine ylides).[9] Reactions involving the thermal and photochemical cleavage of aziridines to azomethine ylides and their subsequent 1,3-dipolar additions to reactive carbon–carbon multiple bonds have been studied by several groups of investigators.[10-14] Huisgen and coworkers have firmly established that the thermal ring cleavage of aziridines involves stereospecific, conrotatory ring opening. A disrotatory course has been found to occur from the excited state. Lown and Matsumoto[15] have recently pointed out that when the aziridine ring is constrained in a bicyclic structure of medium size, disrotatory photochemical ring opening is allowed, but thermal conrotatory ring opening is not permitted by the geometry of the system.[16,17] These workers reported, however, that 1-cyclohexyl-6-(cyclohexylimino)-1a-phenylindano[1,2-*b*]aziridine (1) undergoes thermal conversion to the tautomeric isoquinolinium imine (2), despite the geometrical restrictions imposed by the molecule. The driving

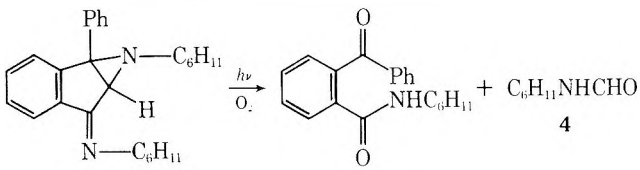


1 2

force for the thermally disallowed valence tautomerization in this system was attributed to the relief of ring strain in 1 and to the gain in resonance energy in 2. Our interest in 1,3-dipolar cycloaddition reactions also led us to study independently the thermal and photochemical behavior of the phenylindano[1,2-*b*]aziridine ring system.[18] The present paper reports on the photochemical valence tautomerization and cycloaddition reactions of the indano[1,2-*b*]aziridine ring, as well as some of the interesting ground-state chemistry encountered with this system which differs, in

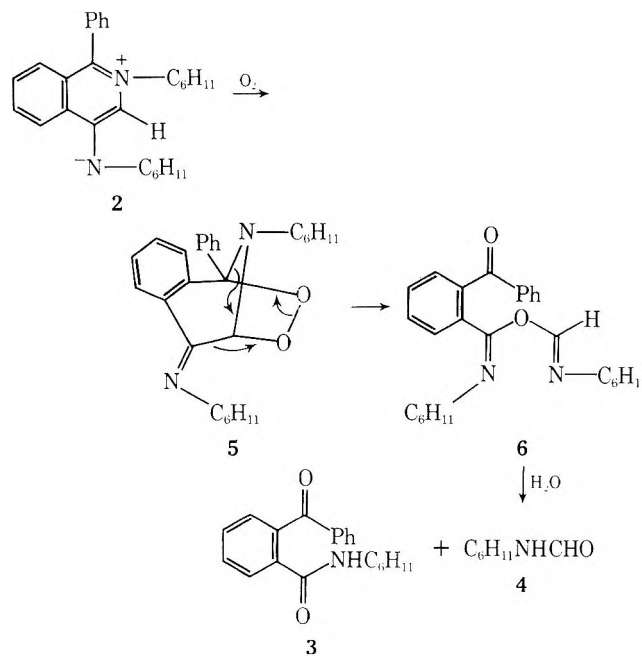
part, from the results described by Lown and Matsumoto.[15]

Upon brief irradiation of solutions of 1 with ultraviolet light, the red isoquinolinium imine 2 was formed. Intensely colored solutions could also be developed by rapid heating of 1 in toluene or xylene to 135°. The intense red color faded upon cooling or on exposure to visible light. The red color was also sensitive to oxygen and electron deficient olefins or acetylenes. Addition of trace quantities of acid or base also resulted in the rapid bleaching of the color. Two products were obtained when indano[1,2-*b*]aziridine 1 was exposed to ultraviolet irradiation in the presence of oxygen. These were identified as 2-benzoyl-*N*-cyclohexylbenzamide (3) and *N*-cyclohexylformamide (4) by comparison with authentic samples. Structure 3 was independently



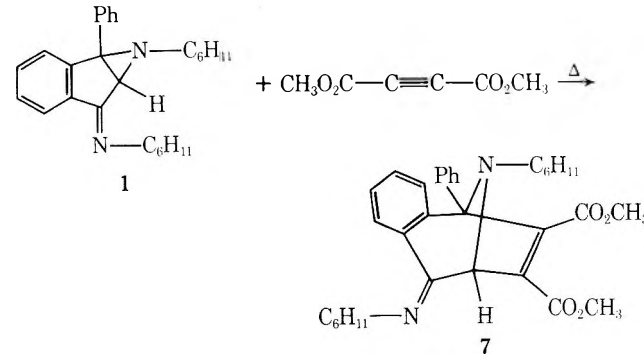
1 3 4

synthesized by treating *o*-benzoylbenzoic acid with thionyl chloride and cyclohexylamine. The formation of these products can be rationalized by assuming that oxygen adds to the initially generated isoquinolinium imine (2) by analogy to the known dipolar additions of reactive olefins and acetylenes to this compound.[15,18] Other six-membered, heteroaromatic betaines have been found to undergo similar cycloadditions with oxygen and provide reasonable chemical precedent for this step.[19-21] The transient peroxide (5) formed undergoes a subsequent Baeyer–Villiger-like rearrangement to a dimine anhydride (6) which readily hydrolyses to the observed products on work-up. The conversion



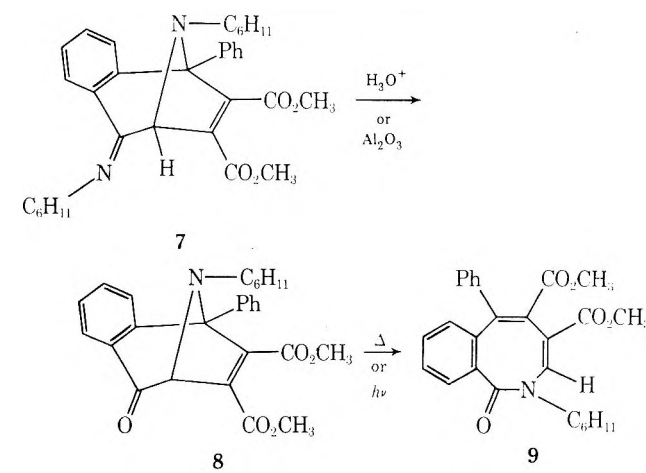
of the ozonide-like structure 5 into 6 parallels findings in the reaction of certain oxazoles with singlet oxygen in which the initial 4 + 2 cycloadduct undergoes a subsequent rearrangement to produce a triamide.[22]

Heating a degassed solution of 1 with an equimolar quantity of dimethyl acetylenedicarboxylate in xylene for 36 hr afforded a crystalline adduct (7), mp 177–179°, in 71% yield, whose structure is assigned as dimethyl 10-cyclohexyl-8,9-dihydro-9-(cyclohexylimino)-5-phenyl-5*H*-



benzocyclohepten-5,8-imine-6,7-dicarboxylate on the basis of the physical and chemical data outlined below. This structure corresponds to the 1,3-dipolar cycloaddition of dimethyl acetylenedicarboxylate across the azomethine ylide system. The elemental analysis obtained for this adduct was consistent with the empirical formula $C_{33}H_{38}N_2O_4$. The nmr spectrum showed multiplets at δ 0.6–2.20 (21 H) and 3.8–4.10 (1 H), singlets at 3.70 (6 H) and 5.50 (1 H) in addition to the aromatic protons at 6.6–8.3 (9 H). The adduct that we have obtained differs from that isolated by Lown and Matsumoto in its melting point (reported[15] mp 68–70°) and nmr spectrum. The nmr spectrum reported by these authors had two distinct singlets for the bridgehead protons at δ 4.90 and 5.55 and two sets of signals for the ester methyl groups at δ 3.57 and 3.78. These authors rationalized their nmr spectrum by assuming the existence of syn–anti stereoisomerism about the 6-cyclohexylimino group. In our hands, the above cycloaddition reaction produced a homogeneous adduct which displayed single absorptions for the carbomethoxy and bridgehead protons in the crude reaction mixture. It is conceivable that under our reaction conditions we have isolated the more stable anti isomer.

Mild acid hydrolysis of cycloadduct 7 using Lown's conditions gave a sharp melting keto compound (8), mp 143–145°. The nmr spectrum showed singlets at δ 3.76 (6 H) and 4.84 (1 H). This compound was assigned the structure of dimethyl 10-cyclohexyl-8,9-dihydro-9-oxo-5-phenyl-5*H*-benzocyclohepten-5,8-imine-6,7-dicarboxylate (8). This same compound could also be obtained by passing the initial cycloadduct (7) through an acid-washed alumina column. It is interesting to note the similarity of the nmr spec-



tra of our hydrolyzed product with that reported by Lown but the difference in melting point (lit.[15] mp 134–135°). We are unable to account for this discrepancy.

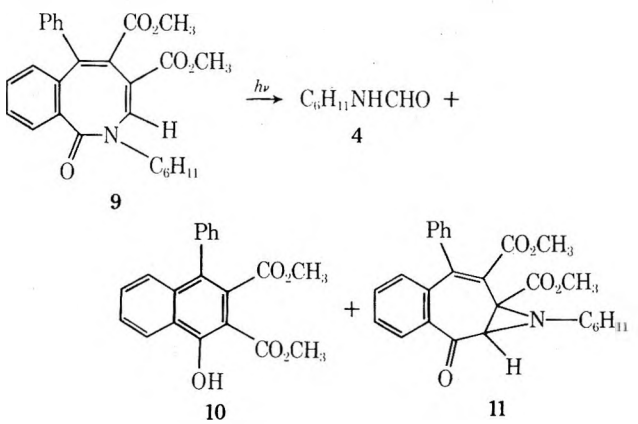
Ketone 8 was found to undergo a novel rearrangement to dimethyl 2-cyclohexyl-1,2-dihydro-1-oxo-6-phenyl-2-benzazocine-4,5-dicarboxylate (9) when heated in toluene or

irradiated with a 450-W Hanovia lamp through a Pyrex filter. The mass spectrum of **9** showed the molecular ion at *m/e* 445 and had an elemental analysis consistent with the empirical formula $C_{27}H_{27}NO_5$. The infrared spectrum showed two different ester carbonyls at 5.80 and 5.85 μ and an amide band at 6.00 μ. The nmr spectrum contained two sets of carbomethoxy protons at δ 3.46 and 3.7 in addition to the cyclohexyl and aromatic protons.

The structure of **9** was unequivocably established by an X-ray single-crystal structure analysis. The three-dimensional intensity data were measured by the stationary–counter-stationary crystal method, using Cu K radiation and balanced filters (Ni *vs.* Co) on a GE-XRD-6 diffractometer equipped with single-crystal orientators. In the range of intensity measurements (0 to 100 in 2θ) 1721 unique reflections of the 2418 unique ones examined for the space group $P2_1/C$ had peak counts significantly greater than their respective background. The structure was derived from Patterson and Fourier synthesis and refined by least squares to an R value of 0.0514, for all the data. The overall geometry of the molecule is shown in Figure 1.

The formation of benzazocine **9** can be postulated to arise by attack of the lone pair of electrons on nitrogen onto the carbonyl group followed by C_8–C_9 and C_5–N_{10} bond cleavage. Alternatively, the thermolysis could proceed *via* diradical intermediates formed by homolytic rupture of the benzoyl carbon–carbon bond. The fact that the thermal rearrangement proceeds at a much faster rate when *n*-amyl alcohol was used as the solvent would tend to support a mechanism where ionic charges are being developed along the reaction coordinate.

The rearranged benzazocine adduct **9** was also found to exhibit interesting photochemistry. Irradiation of a solution of **9** in benzene through a Corex filter for 4 hr gave a mixture of *N*-cyclohexylformamide (**4**, 14%), 1-hydroxy-2,3-dicarbomethoxy-4-phenylnaphthalene (**10**, 23%), and dimethyl-1-cyclohept[1,2-*b*]azirine-8,8a-(1*H*)-dicarboxylate (**11**, 43%). The structure of naphthol **10** was based on a



parent peak at *m/e* 336 in the mass spectrum: infrared absorptions at 5.73 and 6.00 μ; nmr singlets at δ 3.48 (3 H), 3.90 (3 H), 12.18 (1 H–D_2O exchanged), aromatic multiplet at 6.80–8.48 (9 H); elemental analysis ($C_{20}H_{16}O_5$); and its characteristic ultraviolet absorption spectrum which showed bands at 230 (ϵ 30,400), 240 (ϵ 36,100), and 345 nm (ϵ 6200). Structure **11** showed a parent peak at *m/e* 445 in the mass spectrum, infrared bands at 5.75 and 5.88 μ, nmr singlets at δ 3.16 (3 H), 3.80 (3 H), 4.58 (1 H), multiplets at 0.6–2.0 (10 H), 3.4–3.76 (1 H), 7.0–7.9 (9 H), and an elemental analysis which revealed that structure **11** was isomeric with starting material. Treatment of **11** with hydrochloric acid transformed it into anhydride **12**. The structure of **12** was based on its mass spectrum M^+ 431 and $M^+ - CO_2$ at 387 (base); anhydride and ester absorptions at

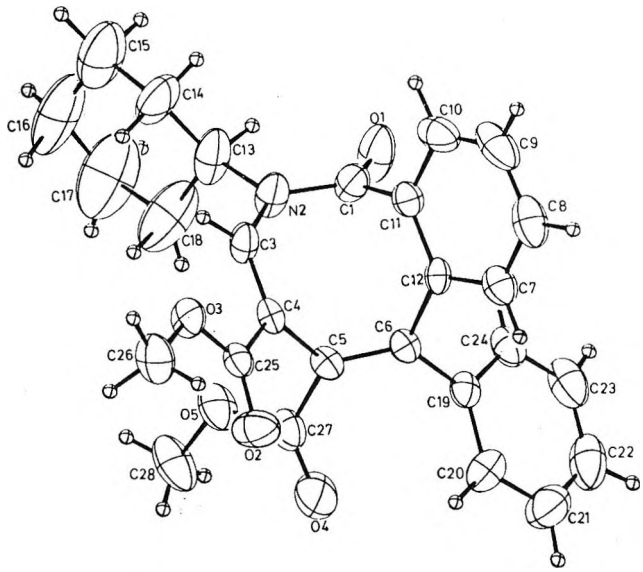
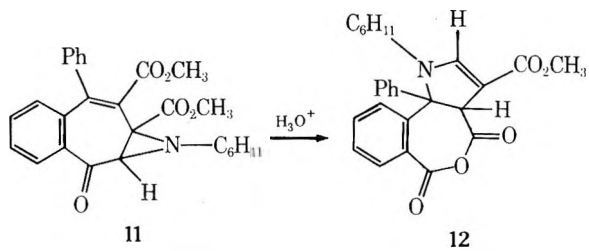
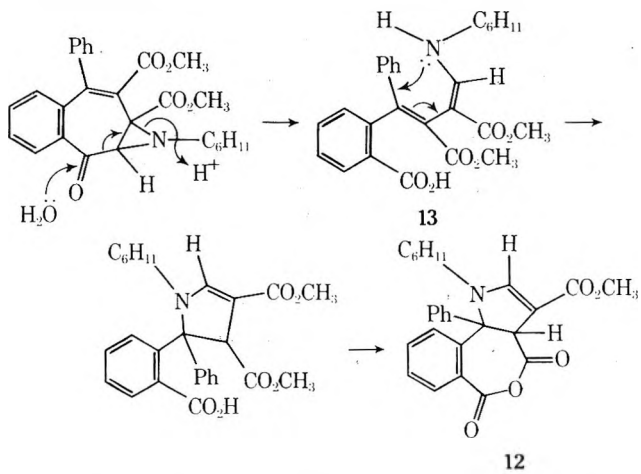


Figure 1. A general view of dimethyl 2-cyclohexyl-1,2-dihydro-1-oxo-6-phenyl-2-benzazocine-4,5-dicarboxylate (**9**).

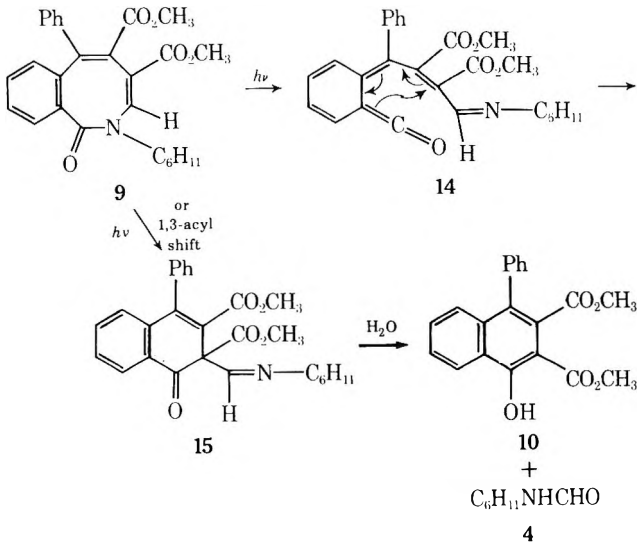


5.60, 5.75, and 5.85 μ in the infrared; nmr singlets at δ 3.04 (3 H), 4.76 (1 H), 6.25 (1 H) in addition to the cyclohexyl and aromatic protons, and an elemental analysis which indicated the molecular formula $C_{26}H_{25}NO_5$.

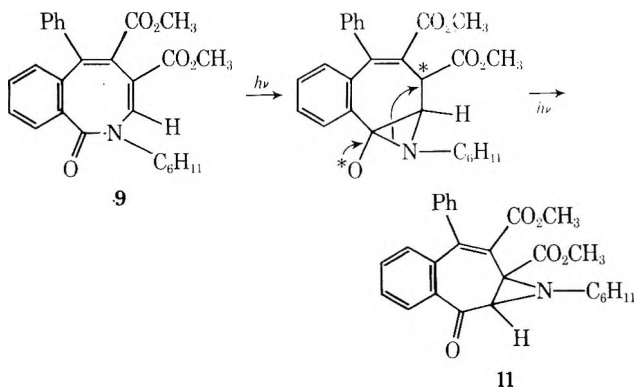
The formation of anhydride **12** is envisaged to occur by protonation of the aziridine ring followed by addition of water to the carbonyl group to produce intermediate **13** which undergoes subsequent ring closure and cyclization.



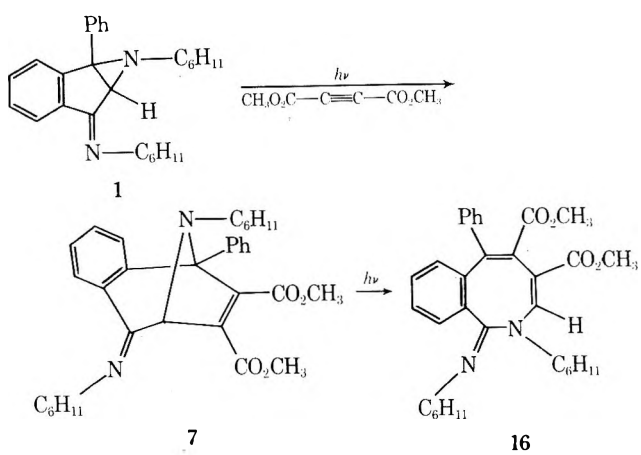
A possible mechanistic rationalization of the photochemistry of benzazocine **9** would involve a photoinduced ring opening to ketene **14** followed by ring cyclization and hydrolysis to *N*-cyclohexylformamide and naphthol **10**. Alternatively, the reaction may be rationalized by a 1,3-acyl shift to generate intermediate **15** which is subsequently converted to **4** and **10** on work-up. This latter process would be analogous to that involved in the photochemical rearrangment of a number of *N*-vinylamides,[23-25] for which evidence has been presented in support of a Norrish Type I cleavage and recombination path.



The formation of aziridine **11** may be considered to be derived from a competing 1,2-acyl shift. This latter process is reminiscent of the formation of substituted cyclopropanes from the irradiation of a β,γ-unsaturated ketones (*i.e.*, oxadi-π-methane rearrangement).[26]

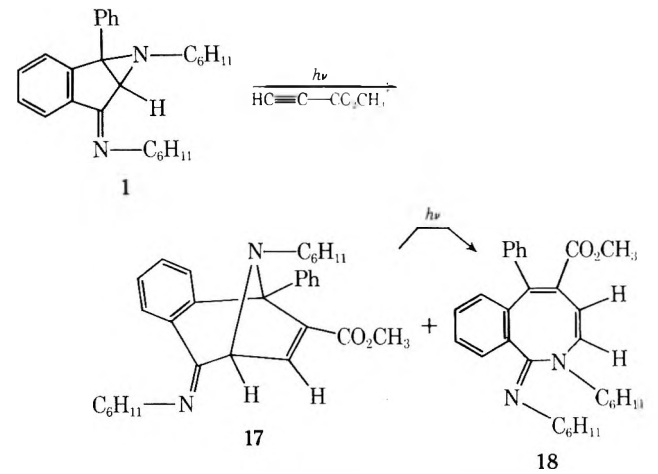


When the irradiation of indano[1,2-*b*]aziridine (**1**) was carried out for 5 hr in a benzene solution containing an equimolar quantity of dimethyl acetylenedicarboxylate, only a trace amount of cycloadduct **7** was isolated. Instead, the major product obtained was identified as dimethyl 2-cyclohexyl-1,2-dihydro-1-(cyclohexylimino)-6-phenyl-2-benzazocine-4,5-dicarboxylate (**16**). The structure of **16** was based on the similarity of its spectral properties with that of benzazocine **9** (see Experimental Section).



A study of product distribution *vs.* extent of irradiation established that the ratio of **7**:**16** varied as a function of time. With short exposures, significant quantities of cycloadduct **7** were found in the reaction mixture by nmr analysis. At longer exposures, owing to a secondary photoreaction of **7**, the amount of **16** increased. This was independently demonstrated by the quantitative conversion of an authentic sample of **7** to **16** in benzene under comparable photolytic conditions.

A similar set of cycloaddition reactions was carried out with indano[1,2-*b*]aziridine (**1**) and methyl propiolate. Irradiation of an equimolar mixture of **1** and methyl propiolate in benzene for 4 hr produced a mixture of two adducts (**17** and **18**) which were readily separated by column chromatography. Examination of the photoreaction as a function

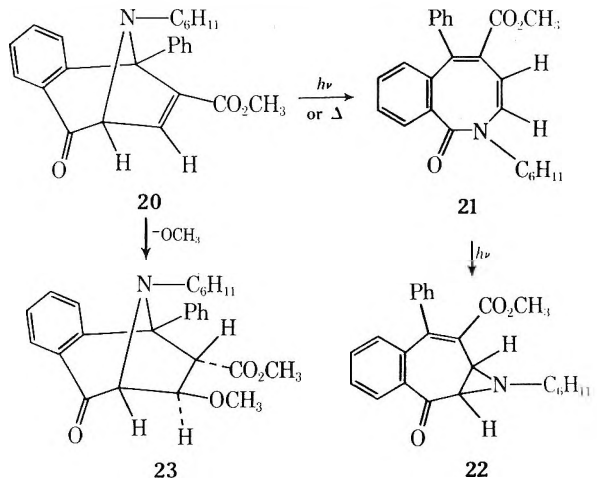


of time clearly showed that **18** was a secondary photoproduct derived from **17**. The structure of **17** was based on its elemental analysis ($C_{31}H_{32}N_2O_2$), mass spectrum (M^+ 468), infrared (5.80 and 6.10μ), and nmr spectrum which showed a singlet at δ 3.60 (3 H) and doublets at 5.16 (1 H, J = 2.5 Hz) and 6.07 (1 H, J = 2.5 Hz) in addition to the cyclohexyl and aromatic protons. This same adduct, mp 147–149°, could also be independently prepared by refluxing a mixture of **1** and methyl propiolate in xylene for 2 days.

It should be noted that our assignment for structure **17** differs from that made by Lown and Matsumoto.[15] These authors claimed that the reaction of **1** with methyl propiolate produced a different stereoisomer in which the bridgehead and vinyl protons were separated by the carbomethoxy group. Moreover, these workers claim that their adduct (mp 73°) exists as a syn–anti stereoisomeric mixture. This was postulated in order to rationalize the set of doublets (δ 4.46 (0.5 H) and 5.08 (0.5 H)) for the bridgehead protons in the nmr. We were unable to detect these signals in our crude reaction mixture. The magnitude of the vicinal coupling constant corresponds to that reported for norbornadiene in which J_{AB} = 2.9 Hz.[27] Allylic coupling in the model compound has been reported to have a value less than 1.0 Hz (*i.e.*, J_{AC} = 0.95 Hz).[27] Consequently, we believe that the nmr data support our assignment and exclude the alternate structure (which was previously postulated[15]) in which the dipolarophile added to the azomethine ylide in the alternative orientation. We are unable to account for the discrepancy in the melting points and nmr data. It should be pointed out that treatment of cycloadduct **17** with sodium methoxide in methanol resulted in Michael addition of methanol across the double bond and gave a product (**19**), the structure of which is perfectly consistent with our new assignment (see Experimental Section).

The rearrangement of cycloadduct **17** to benzazocine **18** is completely analogous to that observed with the related cycloadduct **7** (*i.e.*, **7** → **16**). It is especially interesting to note that benzazocine **18** contains two doublets in the nmr

for the two vinyl protons (δ 5.52 and 6.00). These hydrogens show a coupling constant of 8.0 Hz. This observation adds further support to our assignment for cycloadduct **17** and strongly argues against the stereochemical assignment made by Lown and Matsumoto.[15] Moreover, hydrolysis of cycloadduct **17** gave the analogous methyl 10-cyclohexyl-8,9-dihydro-9-oxo-5-phenyl-5*H*-benzocyclohepten-5,8-imine-6-carboxylate (**20**) which was smoothly converted to benzazocine **21** on thermolysis or photolysis. The AB quartet observed in the nmr spectrum of **21** (δ 6.0–6.20 (J = 8.0 Hz)) also demands that the bridgehead and vinyl protons of adduct **20** be adjacent to each other.



If the irradiation of **20** was carried out for an extended period of time, aziridine **22** was obtained as the major photoproduct. The formation of **22** was shown to arise from a subsequent photoreaction of benzazocine **21** and probably proceeded *via* a 1,2-acyl shift as had been previously observed with benzazocine **9**. Treatment of **20** with sodium methoxide in methanol gave a product (**23**) which also corresponds to Michael addition across the carbon–carbon double bond.

In summary, these experiments demonstrate that heat or ultraviolet light partially converts the indano[1,2-*b*]aziridine ring system into the red isoquinolinium imine. This reactive 1,3 dipole can be trapped with oxygen or with acetylenic dipolarophiles to give cycloadducts which undergo mechanistically intriguing transformations on further excitation.

Experimental Section

All melting points are corrected and boiling points uncorrected. Elemental analyses were performed by Scandinavian Microanalytical Laboratory, Herlev, Denmark, and Alfred Bernhardt Laboratories, Hohenweg, Germany. The infrared absorption spectra were determined on a Perkin-Elmer Infracord spectrophotometer, Model 137. The ultraviolet absorption spectra were measured with a Cary recording spectrophotometer, using 1-cm matched cells. The nuclear magnetic resonance spectra were determined at 100 MHz using a Jeolco-MH-100 spectrometer.

Irradiation of 1-Cyclohexyl-6-(cyclohexylimino)-1,1a,6,6a-tetrahydro-1a-phenylindeno[1,2-*b*]azirine (1). A solution containing 500 mg of **1**[28] in 500 ml of cyclohexane was irradiated through a Vycor filter sleeve under a nitrogen atmosphere for 20 min. At the end of this time an intense bright red color had developed. The red solution faded when exposed to visible light. Removal of the solvent under reduced pressure led to the recovery of unreacted starting material.

Different results were obtained when aziridine **1** was irradiated under an oxygen atmosphere. A solution containing 183 mg of **1** in 200 ml of benzene was irradiated with a Hanovia 450-W lamp through a Vycor filter for 3 hr. The solvent was removed under reduced pressure and the residue was subjected to preparative thick layer chromatography. The plate was developed using a 1:1 pentane–ether mixture. Extraction of the lower band with methylene chloride followed by evaporation of the solvent gave 9.0 mg (15%) of *N*-cyclohexylformamide (**4**). This structure was verified by comparison with an authentic sample.

The second band isolated from the thick layer plate amounted to 15 mg (10%) of a compound whose structure is assigned as 2-benzoyl-*N*-cyclohexylbenzamide (**3**): mp 203–205°; ir (KBr) 3.10, 6.02, and 8.30 μ; nmr ($CDCl_3$) δ 0.7–2.80 (m, 10 H), 3.2–3.5 (m, 1 H), 6.8–7.7 (m, 9 H), and 8.50 (s, 1 H); uv (methanol) λ_{max} 285 (ε 1560) and 258 nm (ε 4230); *m/e* 307 (parent), 209 (base), 105, and 98. The structure of this compound was verified by an independent synthesis described below.

A solution containing 2.26 g of 2-benzoylbenzoic acid and 4 ml of thionyl chloride was heated for 30 min at 50°. Removal of the excess thionyl chloride under reduced pressure gave a crystalline compound which was characterized by a major band at 5.60 μ in its infrared spectrum. This material was dissolved in 5 ml of benzene and the above solution was added dropwise to a stirred solution of 2 g of cyclohexylamine in 5 ml of benzene. The mixture was allowed to stand at room temperature overnight. The cyclohexylamine hydrochloride that formed was filtered and the solvent removed under reduced pressure to leave a solid, mp 203–205°, whose infrared and nmr spectra were identical with 2-benzoyl-*N*-cyclohexylbenzamide prepared from the irradiation of **1**. No other characterizable compounds could be obtained from the thick layer plate.

Thermal Cycloaddition of 1-Cyclohexyl-6-(cyclohexylimino)-1a-phenylindano[1,2-*b*]aziridine with Dimethyl Acetylenedicarboxylate. A solution of 0.5 g of **1** and 0.2 g of dimethyl acetylenedicarboxylate was refluxed in 100 ml of xylene for 36 hr. The solvent was removed under reduced pressure and the residue was triturated with hexane to give 500 mg of a crystalline product which was recrystallized from hexane to give a white solid, mp 177–179°. This material was characterized as dimethyl 10-cyclohexyl-8,9-dihydro-9-(cyclohexylimino)-5*H*-benzocyclohepten-5,8-imine-6,7-dicarboxylate (**7**) on the basis of the following data: ir (KBr) 5.80, 6.10, 8.00, 8.83, 10.21, 10.70, 11.20, 13.02, 13.47, and 14.17 μ; uv (95% ethanol) 245 nm (ε 19,400); nmr ($CDCl_3$) δ 0.6–2.20 (m, 21 H), 3.70 (s, 6 H), 3.8–4.10 (m, 1 H), 5.50 (s, 1 H), 6.6–8.30 (m, 9 H); *m/e* 526 (parent) and 344 (base).

Anal. Calcd for $C_{33}H_{38}N_2O_4$: C, 75.25; H, 7.27; N, 5.32. Found: C, 75.26; H, 7.25; N, 5.26.

Photochemical Cycloaddition of 1-Cyclohexyl-6-(cyclohexylimino)-1a-phenylindano[1,2-*b*]aziridine with Dimethyl Acetylenedicarboxylate. A solution containing 0.5 g of **1** and 0.2 g of dimethyl acetylenedicarboxylate in 500 ml of benzene was irradiated for 5 hr using a 450-W Hanovia Mercury arc fitted with a Corex filter sleeve. Removal of the solvent under reduced pressure followed by trituration of the residue with hexane gave 470 mg (73%) of dimethyl 2-cyclohexyl-1,2-dihydro-1-(cyclohexylimino)-6-phenyl-2-benzazocine-4,5-dicarboxylate (**16**): mp 222–224°; ir (KBr) 5.73, 5.90, 6.00, 6.35 (s), 6.92, 7.02, 7.50, 8.12, 8.25, 8.90, 9.45, 9.55, 11.12, 11.90, 12.65, 13.00, 13.75, and 14.15 μ; uv (95% ethanol) 245 (ε 14,500) and 310 nm (ε 9600); nmr ($CDCl_3$) δ 1.8–2.3 (m, 21 H), 2.87 (s, 3 H), 3.60 (s, 3 H), 3.82–4.20 (m, 1 H), 7.0–8.2 (m, 10 H); *m/e* 526 (parent) and 344 (base).

Anal. Calcd for $C_{33}H_{38}N_2O_4$: C, 75.25; H, 7.27; N, 5.32. Found: C, 75.27; H, 7.29; N, 5.30.

This same product could be obtained in quantitative yield from the irradiation of **7** in benzene for 1 hr using a 450-W Hanovia lamp equipped with a Corex filter.

Acid Hydrolysis of Dimethyl 10-Cyclohexyl-8,9-dihydro-9-(cyclohexylimino)-5-phenyl-5*H*-benzocyclohepten-5,8-imine-6,7-dicarboxylate (7). A solution containing 550 mg of **7** in 2 ml of benzene was chromatographed through a column containing 30 g of alumina (acid washed, Merck) using benzene as the eluent. The main fraction was collected, the solvent was removed under reduced pressure, and the residue was triturated with pentane to give 300 mg (68%) of dimethyl 10-cyclohexyl-8,9-dihydro-9-oxo-5-phenyl-5*H*-benzocyclohepten-5,8-imine-6,7-dicarboxylate (**8**): mp 143–145°; ir (KBr) 3.45, 5.80, 5.85, 6.07, 7.57, 7.70, 7.93, 8.02, 8.20, 12.50, 12.70, 12.90, and 14.00 μ; uv (methanol) 240 (ε 15,100) and 305 nm (ε 1600); nmr ($CDCl_3$) δ 0.6–2.20 (m, 11 H), 3.76 (s, 6 H), 4.84 (s, 1 H), and 6.80–8.00 (m, 9 H); *m/e* 445 (parent), 414, 320, 304, 289, and 276 (base).

Anal. Calcd for $C_{27}H_{27}NO_5$: C, 72.79; H, 6.11; N, 3.14. Found: C, 72.58; H, 6.03; N, 3.11.

This same product could also be formed by treating **7** with aqueous hydrochloric acid (2 *N*) in 10 ml of methanol at room temperature for 5 hr.

Thermal Rearrangement of Dimethyl 10-Cyclohexyl-8,9-

dihydro-9-oxo-5-phenyl-5*H*-benzocyclohepten-5,8-imine-6,7-dicarboxylate (8). A solution containing 70 mg of **8** in 15 ml of toluene was heated at reflux for 4 hr. Removal of the solvent under reduced pressure gave 66 mg (93%) of a crystalline solid, mp 189–191°, whose structure is assigned as dimethyl 2-cyclohexyl-1,2-dihydro-1-oxo-6-phenyl-2-benzazocine-4,5-dicarboxylate (**9**) on the basis of the following data: ir (KBr) 5.80, 5.85, 6.00, 7.80, and 8.20 μ; uv (methanol) 245 nm (ϵ 14,500); nmr ($CDCl_3$) δ 1.0–2.0 (m, 10 H), 3.46 (s, 3 H), 3.70 (s, 3 H), 4.4–4.80 (m, 1 H), 6.8–7.4 (m, 10 H); *m/e* 445 (parent), 320, 305, 289, and 276 (base).

Anal. Calcd for $C_{27}H_{27}NO_5$: C, 72.79; H, 6.11; N, 3.14. Found: C, 72.69; H, 6.10; N, 3.16.

This same compound could also be formed (73%) by irradiating **8** in 100 ml of benzene through a Pyrex filter sleeve for 1 hr.

X-Ray Crystal Structure Analysis of Dimethyl 2-Cyclohexyl-1,2-dihydro-1-oxo-6-phenyl-2-benzazocine-4,5-dicarboxylate (9). The molecular structure of dimethyl 2-cyclohexyl-1,2-dihydro-1-oxo-6-phenyl-2-benzazocine-4,5-dicarboxylate (**9**) was unequivocally determined by an X-ray crystal structure analysis. The crystals used in the structure determination were obtained from methanol as needles. The crystal data obtained are a = 7.855 ± 0.002, b = 18.816 ± 0.002 Å, and c = 17.629 ± 0.002 Å, space group P_{21}/C, d_m = 1.268 g/cm^3, d_c = 1.252 g/cm^3, and Z = 4 molecules. The intensities were measured by the stationary technique using balanced Ni Co filters. A General Electric XRD diffractometer was utilized for this purpose. In the range of measurement (0–100 in 2θ), 1721 unique reflections out of a possible number of 2413 had intensities significantly greater than their background counts. These data were corrected for Lorentz and polarization factors of α_1–α_2 splitting. An adjustment for the anisotropy of transmission of X-rays as a function of the angle φ was made as a means of correcting for absorption. The crystal used to collect the data was approximately 0.5 mm along a (which in turn was parallel to the φ axis) and with a 0.1 mm i.d. The $|F$'s$|$ were put on an absolute scale by use of Wilson statistics[29] and then converted to their respective normalized structure factors, $|E$'s$|$. The phases of 236 normalized structure factors, all having values of E greater than 1.6, were determined using the Sayre equation[30] which is the same as the Σ_2 formula of Hauptman and Karle.[31] A program written by Long was utilized for this purpose.[32] An E-Fourier map was calculated from the solution with the highest consistency index (0.69). The whole molecule was recognized from this map. The positional and thermal parameters were refined by least squares using a block-diagonal approximation to the thermal equations. After anisotropic temperature factors were introduced, the usual reliability index (R value) was found to be 0.149. The positions of the hydrogen atoms were found from a three-dimensional Fourier difference synthesis. These atoms were included in the final cycles of least squares and were refined to a final R value of 0.0514. The positional and thermal parameters obtained from the least-squares refinement are given in Tables I and II. (See paragraph at end of paper regarding supplementary material.) A view of the molecule along with the atomic labeling used is shown in Figure 1. There are no intermolecular contacts that suggest forces stronger than normal van der Waals are operative in the crystal.

Irradiation of Dimethyl 2-Cyclohexyl-1,2-dihydro-1-oxo-6-phenyl-2-benzazocine-4,5-dicarboxylate (9). A solution containing 580 mg of **9** in 500 ml of benzene was irradiated through a 450-W Hanovia lamp fitted with a Corex filter sleeve for 4 hr. The solvent was removed under reduced pressure and the residue was subjected to preparative thick layer chromatography using a 1:1 pentane–ether mixture as the eluent. The slowest moving band was identified as *N*-cyclohexylformamide (14%) by comparison with an authentic sample. The band with the second lowest R_f contained 247 mg (43%) of a crystalline solid, mp 155–157°, whose structure is assigned as dimethyl 1-cyclohexyl-1a-2-dihydro-2-oxo-7-phenylbenzo[4,5]cyclohept[1,2-*b*]azirine-8,8*a*(1*H*)-dicarboxylate (**11**) on the basis of the following data: ir (KBr) 3.43, 5.75, 5.88, 6.98, 7.50, 8.20, 8.60, 8.90, 9.40, 9.70, 11.20, 11.90, 12.40, 13.10, 14.00, and 14.35; uv (methanol) 235 nm (ϵ 3500); *m/e* 445 (parent), 387, 386, 292, and 276 (base); nmr ($CDCl_3$) δ 0.6–2.0 (m, 10 H), 3.16 (s, 3 H), 3.4–3.76 (m, 1 H), 3.8 (s, 3 H), 4.58 (s, 1 H), and 7.0–7.9 (m, 9 H).

Anal. Calcd for $C_{27}H_{27}NO_5$: C, 72.79; H, 6.11; N, 3.40. Found: C, 72.54; H, 6.21; N, 3.40.

The fastest moving band on the thick layer plate contained 100 mg (23%) of a crystalline solid, mp 146–148°, whose structure is assigned as dimethyl 4-phenyl-1-naphthol-2,3-dicarboxylate (**10**) on the basis of the following data: ir (KBr) 5.73, 6.00, 6.93, 7.13, 7.23, 7.43, 8.03, 9.08, 9.63, 10.16, 12.80, 13.83, and 14.26 μ; uv (methanol) 230 (ϵ 30,400), 240 (36,100) and 345 nm (ϵ 6200); *m/e* 305 (base), 218, and 189; nmr ($CDCl_3$) δ 3.48 (s, 3 H), 3.90 (s, 3 H), 6.8–8.5 (m, 9 H), and 12.18 (s, 1 H).

Anal. Calcd for $C_{20}H_{16}O_5$: C, 71.42; H, 4.80. Found: C, 71.26; H, 4.86.

Acid-Induced Rearrangement of Dimethyl 1-cyclohexyl-1a,2-dihydro-2-oxo-7-phenylbenzo[4.5]cyclohept[1,2-*b*]azirine-8,8*a*(1*H*)-dicarboxylate (11). A solution containing 208 mg of **11**, 25 ml of a 2 *N* hydrochloric acid solution, and 25 ml of methanol was refluxed for 2 days. After removal of the solvent under reduced pressure, the crude reaction mixture was extracted with ether and washed with water. Removal of the solvent gave 168 mg (84%) of a colorless solid, mp 206–208°, which was assigned as anhydride **12** on the basis of the following data: ir (KBr) 5.60, 5.75, 5.85, 7.03, 8.02, 8.60, 8.72, 9.20, 9.63, 10.10, 10.43, 10.90, 11.13, 13.43, and 14.35 μ; uv (methanol) 273 nm (ϵ 540); *m/e* 431, 400, 387 (base), 350, 262, 250, and 218; nmr ($CDCl_3$) δ 1.0–2.0 (m, 10 H), 3.04 (s, 3 H), 3.76–4.20 (m, 1 H), 4.76 (s, 1 H), 6.25 (s, 1 H), and 6.80–7.60 (m, 9 H).

Anal. Calcd for $C_{26}H_{25}NO_5$: C, 72.37; H, 5.84; N, 3.25. Found: C, 72.08; H, 5.88; N, 3.29.

Thermal Cycloaddition of 1-Cyclohexyl-6-(cyclohexylimino)-1a-phenylindano[1,2-*b*]aziridine with Methyl Propiolate. A solution of 0.5 g of **1** and 1.0 g of methyl propiolate was refluxed in 100 ml of xylene for 2 days. The solvent was removed under reduced pressure and the residue was triturated with cold methanol to give 400 mg (67%) of methyl 10-cyclohexyl-8,9-dihydro-9-(cyclohexylimino)-5-phenyl-5*H*-benzocyclohepten-5,8-imine-6-carboxylate (**17**) on the basis of the following data: mp 147–149°; ir (KBr) 3.43, 3.55, 5.80, 6.10, 7.70, 8.20, 9.10, 10.40, 11.62, 12.70, 12.98, 13.10, 13.40, and 14.20 μ; uv (methanol) 240 nm (ϵ 17,400); nmr ($CDCl_3$) δ 0.6–2.2 (m, 21 H), 3.60 (s, 3 H), 3.60–3.80 (m, 1 H), 5.18 (d, 1 H, J = 2.5 Hz), 6.06 (d, 1 H, J = 2.5 Hz), 7.0–8.20 (m, 9 H); *m/e* 468 (parent), 435, 371, and 359 (base).

Anal. Calcd for $C_{31}H_{32}N_2O_2$: C, 79.45; H, 7.74; N, 5.98. Found: C, 79.25; H, 7.76; N, 5.98.

Photochemical Cycloaddition of 1-Cyclohexyl-6-(cyclohexylimino)-1a-phenylindano[1,2-*b*]aziridine with Methyl Propiolate. A solution containing 500 mg of **1** and 2 ml of methyl propiolate in 500 ml of benzene was irradiated through a Corex filter sleeve for 4 hr. The solvent was removed under reduced pressure and the crude product was chromatographed over 30 g of neutral alumina. The column was eluted with 100 ml of dry hexane followed by a mixture of 5% ethyl acetate–benzene. The first 100-ml fraction contained 100 mg of methyl 10-cyclohexyl-8,9-dihydro-9-(cyclohexylimino)-5-phenyl-5*H*-benzocyclohepten-5,8-imine-6-carboxylate (**17**), mp 147–149°. The later fractions contained 50 mg (9%) of a solid material, mp 164–166°, whose structure is assigned as methyl 2-cyclohexyl-1,2-dihydro-1-(cyclohexylimino)-6-phenyl-2-benzazocine-5-carboxylate (**18**) on the basis of the following data: ir (KBr) 3.50, 3.55, 5.85, 6.15, 6.96, 9.15, 11.22, 13.40, and 14.30 μ; uv (methanol) 235 nm (ϵ 22,200); nmr ($CDCl_3$) δ 0.8–2.10 (m, 20 H), 2.4–2.7 (m, 1 H), 3.44 (s, 3 H), 4.16–4.50 (m, 1 H), 5.52 (d, 1 H, J = 8.0 Hz), 6.0 (d, 1 H, J = 8.0 Hz), 6.70–7.30 (m, 9 H); *m/e* 468 (parent), 359 (base), 284, 245, and 217.

Anal. Calcd for $C_{31}H_{31}N_2O_2$: C, 79.45; H, 7.74; N, 5.98. Found: C, 79.41; H, 7.86; N, 6.00.

This same product could be obtained in high yield (62%) from the irradiation of **17** in benzene for 1.5 hr using a 450-W Hanovia lamp equipped with a Corex filter sleeve.

Reaction of Methyl 10-Cyclohexyl-8,9-dihydro-9-(cyclohexylimino)-5-phenyl-5*H*-benzocyclohepten-5,8-imine-6-carboxylate with Sodium Methoxide. A solution containing 218 mg of **17** and 100 mg of sodium in 20 ml of anhydrous methanol was stirred at room temperature for 17 hr. The solvent was removed under reduced pressure and the residue was dissolved in ether and washed with water. Removal of the ethereal layer followed by trituration of the residue with pentane gave 154 mg (66%) of a white crystalline solid, mp 136–138°, whose structure is assigned as the Michael adduct **19**: ir (KBr) 5.80, 6.10, 6.90, 7.50, 10.80, 11.20, 12.70, 13.23, 14.15 μ; uv (cyclohexane) 247 nm (ϵ 17,300); nmr ($CDCl_3$) δ 0.6–2.40 (m, 21 H), 3.30 (s, 3 H), 3.36 (s, 3 H), 3.88 (d, 1 H, J = 4.0 Hz), 4.22 (d, 1 H, J = 4.0 Hz), 3.6–4.0 (m, 1 H), 4.68 (s, 1 H), and 6.44–8.24 (m, 9 H); *m/e* 468, 372, 302, 116, and 85 (base).

Anal. Calcd for $C_{32}H_{40}N_2O_3$: C, 76.76; H, 8.05; N, 5.60. Found: C, 76.63; H, 8.03; N, 5.65.

Acid Hydrolysis of Methyl 10-Cyclohexyl-8,9-dihydro-9-(cyclohexylimino)-5-phenyl-5H-benzocyclohept-5,8-imine-6-carboxylate. A solution containing 312 mg of **17** in 2 ml of benzene was chromatographed through a column containing 30 g of

alumina (acid-washed Merck) using benzene as the eluent. The main fraction contained 200 mg (78%) of methyl 10-cyclohexyl-8,9-dihydro-9-oxo-5-phenyl-5*H*-benzocyclohepten-5,8-imine-6-carboxylate (**20**) as white needles: mp 129–131°; ir (KBr) 3.45, 3.53, 5.80, 5.88, 6.20, 6.92, 7.75, 8.03, 8.28, and 9.12 μ; uv (methanol) 235 nm (ϵ 14,500); nmr ($CDCl_3$) δ 0.6–2.0 (m, 11 H), 3.64 (s, 3 H), 4.56 (d, 1 H, J = 2.5 Hz), 7.08 (d, 1 H, J = 2.5 Hz), and 7.10–8.0 (m, 9 H); *m/e* 387 (parent), 328, 305, 278, and 246 (base).

Anal. Calcd for $C_{25}H_{25}NO_3$: C, 77.49; H, 6.50; N, 3.62. Found: C, 77.40; H, 6.56; N, 3.59.

This same product could also be formed by treating **17** with aqueous hydrochloric acid in methanol.

Reaction of Methyl 10-Cyclohexyl-8,9-dihydro-9-oxo-5-phenyl-5*H*-benzocyclohepten-5,8-imine-6-carboxylate with Sodium Methoxide. A solution containing 178 mg of **20** and 60 mg of sodium in 100 ml of anhydrous methanol was stirred at room temperature for 4.5 hr. The solution was diluted with water and extracted with ether. After removal of the dried ethereal solution, the residue was triturated with pentane to give 137 mg (71%) of a yellow crystalline solid, mp 123–125°, whose structure is assigned as Michael adduct **23** on the basis of the following data: ir (KBr) 5.75, 5.85, 6.25, 7.95, 8.50, 9.90, 10.40, 12.55, and 14.10 μ; uv (methanol) 245 (ϵ 13,400) and 290 nm (ϵ 200); nmr ($CDCl_3$) δ 0.64–1.68 (m, 10 H), 2.04–2.24 (m, 1 H), 3.32 (s, 3H), 3.36 (s, 3 H), 3.92 (d, 1 H, J = 5.0 Hz), 4.08 (s, 1 H), 4.27 (d, 1 H, J = 5.0 Hz) and 6.52–8.04 (m, 9 H); *m/e* 116, 101, 87, and 85.

Anal. Calcd for $C_{26}H_{29}NO_4$: C, 74.44; H, 6.97; N, 3.34. Found: C, 74.24; H, 6.96; N, 3.29.

Thermal Rearrangement of Methyl 10-Cyclohexyl-8,9-dihydro-9-oxo-5-phenyl-5*H*-benzocyclohepten-5,8-imine-6-carboxylate. A solution containing 170 mg of **20** in 40 ml of toluene was refluxed for 3.5 hr. The solvent was removed under reduced pressure and the residue was triturated with pentane to give a nearly quantitative yield of methyl 2-cyclohexyl-1,2-dihydro-1-oxo-6-phenyl-2-benzazocine-5-carboxylate (**21**): mp 146–149°; ir (KBr) 5.85, 6.10, 6.95, 7.10, 7.55, 8.65, 9.20, 11.15, 13.32, and 14.15 μ; uv (95% ethanol) 275 nm (ϵ 8500); nmr ($CDCl_3$) δ 0.7–2.00 (m, 10 H), 3.44 (s, 3 H), 4.3–4.6 (m, 1 H), 6.0–6.2 (AB q, 2 H, J = 8.0 Hz), and 7.0–7.3 (m, 9 H); *m/e* 387, 328, 305, 278, 250, and 246 (base).

Anal. Calcd for $C_{25}H_{25}NO_3$: C, 77.49; H, 6.50; N, 3.62. Found: C, 77.62; H, 6.56; N, 3.45.

This same product was also formed in high yield (73%) by irradiating a benzene solution of **20** through a Pyrex filter sleeve with a 450-W Hanovia lamp.

Irradiation of Methyl 2-Cyclohexyl-1,2-dihydro-1-oxo-6-phenyl-2-benzazocine-5-carboxylate. A solution containing 95 mg of **21** in 120 ml of benzene was irradiated through a Corex filter using a 450-W Hanovia lamp for 1.5 hr. The solvent was removed under reduced pressure and the residue was subjected to thick layer chromatography. The plate was developed using a 1:1 mixture of pentane and ether. The slowest moving band on the thick layer plate was extracted with ether to give 57 mg (61%) of a white crystalline solid, mp 161–163°. The structure of this material is assigned as methyl 1-cyclohexyl-1*a*,2-dihydro-2-oxo-7-phenylbenzo[4.5]cyclohept[1,2-*b*]azirine-8(1*H*)-carboxylate (**22**) on the basis of the following information: ir (KBr) 3.40, 5.73, 5.93, 6.90, 7.12, 8.05, 9.80, 10.65, 12.55, 12.85, 13.12, and 14.25; uv (methanol) 275 nm (ϵ 570); nmr ($CDCl_3$) δ 0.6–2.0 (m, 10 H), 3.24 (s, 3 H), 3.40–3.76 (m, 1 H), 3.42 (d, 1 H, J = 6.0 Hz), 3.98 (d, 1 H, J = 6.0 Hz), 6.8–7.6 (m, 9 H); *m/e* 387 (parent), 328, 262 (base), and 250.

Anal. Calcd for $C_{25}H_{25}NO_3$: C, 77.49; H, 6.50; N, 3.62. Found: C, 77.19; H, 6.58; N, 3.65.

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Supplementary Material Available. The positional and thermal parameters obtained from the least-squares refinement (Tables I and II) will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 m, 24× reduction; negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 16th Street, N.W., Washington, D. C. 20036. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche, referring to code number JOC-75-175.

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Ring-Opening Reactions of Certain 2-Carbonyl-Substituted Cyclopropylamines[1]

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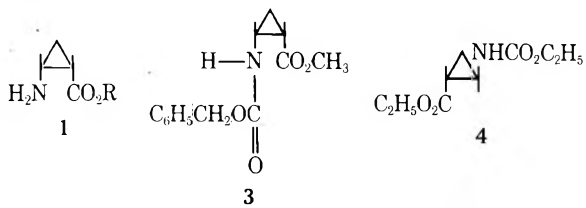
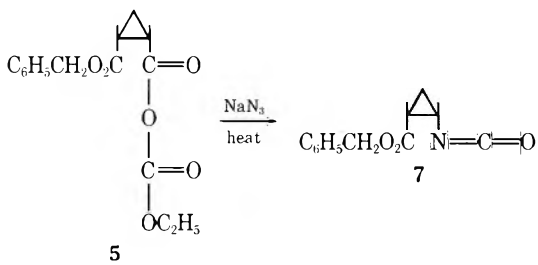
Aqueous acid treatment of *cis*- or *trans*-2-carbalkoxycyclopropyl isocyanates gives rise to the same ring-opened product, a β-formylpropionate ester corresponding to the ester group in the starting system. Experimental data and literature precedent are consistent with a reaction pathway involving initial hydration of the isocyanate group to a carbamate moiety, followed by decarboxylation of the carbamate group and ring opening to an immonium function which is immediately hydrolyzed to an aldehyde. This explanation can be invoked to rationalize literature reports of failures to achieve normal Hofmann hypohalite reactions on 2-carbalkoxy- and 2-carboxycyclopropanecarboxamides.

In the course of a continuing study of 1,2-difunctionalized cyclopropane systems, it was desired to obtain esters of *cis*-2-aminocyclopropanecarboxylic acid **1**. A Curtius reaction on *cis*-2-carbomethoxycyclopropanecarbonyl chloride (**2**) and treatment of the isocyanate product with benzyl alcohol permitted isolation of the carbamate **3** in 45% overall yield. Attempts to remove the *N*-benzyl group from **3** by hydrogenolysis failed; no identifiable organic nitrogen product could be isolated. Schroff, *et al.*,[2] reported that attempted acid-catalyzed hydrolysis of **4** gave polymeric material.



1 **3** **4**

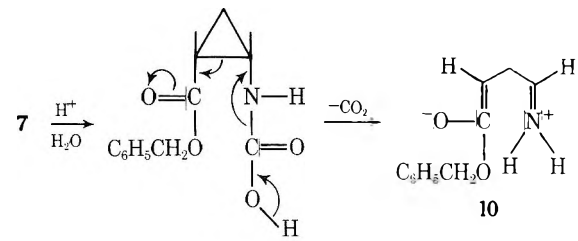
As an alternate approach, the mixed anhydride **5** was subjected to a modification[3] of the Curtius reaction to form **7**. Attempts to hydrolyze the isocyanate group of **7** and of



5 **7**

its trans isomer (**17**) with dilute hydrochloric acid led to the formation of the same distillable oil, which formed a 2,4-dinitrophenylhydrazone. The identity of this material (**8**) as benzyl β-formylpropionate was established by spectral and analytical data and was verified by conversion into a known compound, benzyl hydrogen succinate.

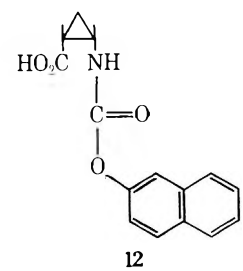
Walborsky and Ronman[4] have described a facile, base-catalyzed ring opening of 1-methyl-2,2-diphenylcyclopropylamine to a single product, 4,4-diphenyl-2-butanone. It was proposed by these workers that this ring opening may be expected of all primary cyclopropylamines, but that tertiary amines and salts are stable. In the present work, it is suggested that in an acidic aqueous environment, initial hydration of the isocyanate group is followed by decarboxylation and ring opening, analogous to a mechanism proposed by Rynbrandt and Dutton[5] for aminocyclopropyl sulfones.



9 **10**

A similar pathway may be proposed for the catalytic debenzylation of **3**. Further hydrolysis of **10** converts the immonium group into the aldehyde. This interpretation is consistent with our finding that hydrolysis of **7** with DCl in D_2O indicated that it had undergone deuteration of three succinate protons, but that it had retained the protons on the benzyl and the formyl groups. It is concluded that primary cyclopropylamines bearing a carbonyl substituent at position 2 and with a mobile electron pair on the nitrogen are highly prone to ring-opening processes, leading to replacement of the amino function by carbonyl. Kuehne and King[6] stated that protonation of the nitrogen of a cyclopropylamine prevents its assistance in ring opening and inhibits its cyclopropane fission. In the case of **7**, acid treatment did not permit isolation of 2-carbobenzyloxycyclopropylamine. Failures to achieve normal Hofmann hypohalite reactions on 2-carboxy- or 2-carbalkoxycyclopropanecarboxamides[2,7] may be explainable on the basis of this type of ring opening.

Treatment of **7** with 2-naphthol gave a 2-naphthyl carbamate (**11**); hydrogenolysis of this product gave a carboxylic acid **12**, with no indication of ring opening.



12

Experimental Section[8]

***cis*-2-Carbomethoxycyclopropanecarbonyl Chloride (2).** *cis*-2-Carbomethoxycyclopropanecarboxylic acid[2] (13 g, 0.09 mol) and 20 ml of $SOCl_2$ were stirred at room temperature for 4 hr. Excess $SOCl_2$ was removed by distillation and residual portions were azeotroped with anhydrous benzene. Distillation of the residue gave 12.2 g (85%) of product: bp 52–53° (0.35 mm); ir (film) 1790 (acyl chloride C=O), 1730 cm^{-1} (ester C=O); nmr (CCl_4) δ 1.20–2.80 (m, 4 H, ring H), 3.73 (s, 3 H, OCH_3).

Anal. Calcd for $C_6H_7ClO_3$: C, 44.32; H, 4.33; Cl, 21.80. Found: C,

44.53; H, 4.32; Cl, 21.59.

***cis*-2-Carbomethoxy-(*N*-carbobenzyloxy)cyclopropylamine (3).** A mixture of 5.4 g (0.0375 mol) of 2, 2.7 g (0.0415 mol) of NaN_3, and 100 ml of Na-dried, redistilled toluene was refluxed for 8 hr, or until the ir spectrum of the reaction solution revealed no carbonyl chloride band at 1790 cm^{-1} and the presence of a strong isocyanate band at 2365 cm^{-1}. Benzyl alcohol (4.1 g, 0.039 mol) was added and the solution was refluxed for 1 hr. Removal of the toluene under reduced pressure gave a residue which was treated with excess Et_2O. The resulting solid was removed by filtration and the filtrate was evaporated to afford a solid which was recrystallized from hexane to give 3.7 g (45%) of 3: mp 78.5–80°; ir (KBr) 3320 (NH), 1720 (ester C=O), 1690 cm^{-1} (carbamate C=O); nmr (CCl_4) δ 1.17 (t, 2 H, ring CH_2), 1.83 (q, 1 H, $CHCO_2R$), 3.36 (t, 1 H, CHN), 3.63 (s, 3 H, OCH_3), 5.03 (s, 2 H, CH_2Ph), 5.57 (broad, 1 H, NH), 7.25 (s, 5 H, ArH).

Anal. Calcd for $C_{13}H_{15}NO_4$: C, 62.63; H, 6.07; N, 5.62. Found: C, 62.32; H, 5.92; N, 5.85.

***cis*-2-Carbobenzyloxycyclopropanecarboxylic Acid (6).** *cis*-Cyclopropane-1,2-dicarboxylic acid anhydride[9] (33.6 g, 0.3 mol) and 35 g (0.322 mol) of benzaldehyde-free benzyl alcohol were stirred at 50–60° for 3 hr. Et_2O (15 ml) was added and the resulting mixture was cooled overnight. The resulting solid was recrystallized from Et_2O to give 60 g (90%) of product: mp 80–81.5°; ir (KBr) 3300–2500 (acid OH), 1730 (ester C=O), 1710 cm^{-1} (acid C=O); nmr ($CDCl_3$) δ 1.10–2.27 (m, 4 H, ring H), 5.14 (s, 2 H, CH_2Ph), 7.35 (s, 5 H, ArH), 10.40 (s, 1 H, CO_2H).

Anal. Calcd for $C_{12}H_{12}O_4$: C, 65.44; H, 5.49. Found: C, 65.64; H, 5.65.

***cis*-2-Carbobenzyloxycyclopropyl Isocyanate (7).** A procedure of Weinstock[3] was used. Compound 6 (33 g, 0.15 mol), 50 ml of H_2O, and 150 ml of Me_2CO were cooled to 0° and 16.1 g (0.16 mol) of triethylamine was added with stirring. Ethyl chloroformate (17.4 g, 0.16 mol) was added dropwise at 0° over 0.2 hr, and the resulting mixture was stirred for 1 hr. NaN_3 (16.2 g, 0.25 mol) in a minimum volume of H_2O was added dropwise with stirring at 0°. After 1 hr, 250 ml of ice–H_2O was added dropwise, and the resulting solution was extracted repeatedly with Et_2O. The combined extracts were washed with ice–H_2O and were dried ($MgSO_4$). Removal of volatiles under reduced pressure left the oily azide, to which was added 100 ml of Na-dried toluene, and the mixture was carefully refluxed for 3 hr. Removal of the toluene under reduced pressure left an orange oil which was distilled at 117–119° (0.1 mm) to give 21.8 g (75%) of product: ir (film) 2280 (NCO), 1730 cm^{-1} (ester C=O); nmr ($CDCl_3$) δ 1.05–1.67 (m, 2 H, ring CH_2), 1.90 (q, 1 H, $CHCO_2R$), 2.97 (q, 1 H, CHNCO), 5.24 (s, 2 H, CH_2Ph), 7.37 (s, 5 H, ArH).

Anal. Calcd for $C_{12}H_{11}NO_3$: C, 66.35; H, 5.10;, N, 6.44. Found: C, 66.26; H, 5.30; N, 6.38.

***trans*-Cyclopropane-1,2-dicarbonyl Chloride (13).** This was prepared from *trans*-cyclopropane-1,2-dicarboxylic acid[9] by the method of Gruen,[10] bp 50–60° (0.05 mm).

Dibenzyl *trans*-Cyclopropane-1,2-dicarboxylate (14). Benzyl alcohol (42 g, 0.39 mol) was added dropwise to a vigorously refluxing solution of 32.1 g (0.192 mol) of 13 in 400 ml of anhydrous Et_2O, and this mixture was refluxed for 8 hr. After repeated washing with 10% $NaHCO_3$, the organic layer was dried ($MgSO_4$), and the volatiles were removed. The residue was distilled at 177–180° (0.02 mm) to yield 46.3 g (78%) of product: ir (film) 1735 cm^{-1} (C=O); nmr ($CDCl_3$) δ 1.41 and 2.21 (sym t, 4 H, ring H), 5.10 (s, 4 H, CH_2Ph), 7.35 (s, 10 H, ArH).

Anal. Calcd for $C_{19}H_{18}O_4$: C, 73.53; H, 5.84. Found: C, 73.68; H, 5.85.

***trans*-2-Carbobenzyloxycyclopropanecarboxylic Acid (15).** A mixture of 13 g (0.1 mol) of *trans*-cyclopropane-1,2-dicarboxylic acid,[9] 15.6 g (0.05 mol) of 14, 23 g (0.22 mol) of benzyl alcohol, and 5.2 ml of concentrated HCl was stirred and heated at 120–130° for 3 hr. An additional 5.2 ml of concentrated HCl was added and stirring was continued for 9 hr. The cooled reaction mixture was dissolved in 200 ml of Et_2O and was extracted with 10% $NaHCO_3$ until the washings were basic to litmus. The aqueous solution was acidified with 6 *N* HCl and was extracted with five 75-ml portions of Et_2O. The ethereal extract was dried ($MgSO_4$) and filtered, and the volatiles were removed to leave an oil which was treated with 10 ml of methylene chloride and cooled overnight. Crystals of *trans*-cyclopropane-1,2-dicarboxylic acid which separated were collected on a filter. The filtrate was evaporated to leave a viscous oil which was distilled at 158–160° (0.09 mm) to yield 7.9 g (36%) of 15: ir (film) 3600–2350 (acid OH), 1735 (ester C=O), 1700 cm^{-1} (acid C=O); nmr ($CDCl_3$) δ 1.42 and 2.23 (2 m, 4 H, ring H), 5.10 (s, 2 H, CH_2Ph), 7.35 (s, 5 H, ArH), 10.86 (s, 1 H, CO_2H, exchanged with D_2O).

Anal. Calcd for $C_{12}H_{12}O_4$: C, 65.44; H, 5.49. Found: C, 65.27; H, 5.53.

***trans*-2-Carbobenzyloxycyclopropanecarbonyl Chloride (16).** Compound 15 (5.5 g, 0.025 mol) was stirred with 40 ml of $SOCl_2$ at room temperature for 5 hr. Excess $SOCl_2$ was removed by azeotroping with benzene under reduced pressure. The residue was distilled at 128–130° (0.3 mm) to give 4.9 g (83%) of product: ir (film) 1888 cm^{-1} (acyl chloride C=O); nmr ($CDCl_3$) δ 1.66 (m, 2 H, ring H), 2.52 (m, 2 H, ring H), 5.17 (s, 2 H, CH_2Ph), 7.40 (s, 5 H, ArH).

Anal. Calcd for $C_{12}H_{11}ClO_3$: C, 60.38; H, 4.64; Cl, 14.85. Found: C, 60.16; H, 4.46; Cl, 15.11.

***trans*-2-Carbobenzyloxycyclopropyl Isocyanate (17).** NaN_3 (6.5 g, 0.1 mol) in 30 ml of H_2O was added dropwise to a cooled (0°) solution of 23.8 g (0.1 mol) of 16 in 200 ml of anhydrous diglyme. After stirring for 0.5 hr, the reaction mixture was extracted with Et_2O and the organic layer was washed with H_2O and dried ($MgSO_4$). Removal of the volatiles under reduced pressure left an oil which was refluxed with 100 ml of Na-dried toluene for 2 hr. Evaporation of the toluene left an oil: bp 116–119° (0.3 mm); yield 16.8 g (78%); ir (film) 2280 (NCO), 1728 cm^{-1} (C=O); nmr ($CDCl_3$) δ 1.00–1.60 (m, 2 H, ring H), 1.73–2.08 (m, 1 H, $CHCO_2R$), 3.13–3.40 (m, 1 H, CHNCO), 5.13 (s, 2 H, CH_2Ph), 7.39 (s, 5 H, ArH).

Anal. Calcd for $C_{12}H_{11}NO_3$: C, 66.35; H, 5.10; N, 6.44. Found: C, 66.02; H, 5.14; N, 6.70.

Benzyl β-Formylpropionate (8). The hydrolysis procedure of Weinstock[3] was used. Compound 7 or 17 (2.7 g, 0.0125 mol) was added with vigorous stirring to 10 ml of 20% HCl (0.0125 mol), and the resulting solution was stirred for 10 hr. The reaction mixture was extracted with four 50-ml portions of Et_2O. The combined extracts were dried ($MgSO_4$), and filtered, and the Et_2O was removed to leave an oil which distilled at 89–92° (0.05 mm) to yield 1.15 g (48%) of product: ir (film) 2730 (CHO), 1730–10 cm^{-1} (ester, aldehyde C=O); nmr ($CDCl_3$) δ 2.72 (t, 4 H, CH_2 CH_2), 5.13 (s, 2 H, CH_2Ph), 7.37 (s, 5 H, ArH), 9.78 (s, 1 H, CHO, no D_2O exchange).

Anal. Calcd for $C_{11}H_{12}O_3$: C, 68.73; H, 6.29. Found: C, 68.56; H, 6.29.

Concentration of the aqueous solution from the Et_2O extraction and addition of anhydrous EtOH to the residue afforded 0.55 g (78%) of a white solid which gave a positive test for chloride with $AgNO_3$ and which liberated NH_3 upon addition of NaOH; nmr (D_2O) revealed no C–H signals.

Benzyl Hydrogen Succinate (18). Compound 8 (1 g, 0.0052 mol) was allowed to stand exposed to the air with periodic agitation for 30 days. Distillation gave 0.2 g of unchanged 8, bp 89–95° (0.05 mm), followed by 0.55 g (52%) of 18, bp 131–133° (0.05 mm), which crystallized on standing, mp 117–119°. An authentic sample[11] of 18 (mp 117–119°) gave an identical nmr spectrum to that of the product of the reaction described.

***cis*-2-Carbobenzyloxy(*N*-carbo-2-naphthyloxy)cyclopropylamine (11).** The method used for 7 was repeated, utilizing 19 g (0.086 mol) of 6, 50 ml of H_2O, 80 ml of Me_2CO, 8.8 g (0.088 mol) of triethylamine, 12.6 g (0.11 mol) of ethyl chloroformate, and 8.0 g (0.125 mol) of NaN_3 in a minimum amount of H_2O. The azide thermolysis was conducted in refluxing toluene for 2 hr; then 12 g (0.0832 mol) of 2-naphthol was added and refluxing was continued for 2 hr. The reaction mixture was permitted to stand at room temperature overnight, and the volatiles were removed under reduced pressure to leave a brown solid. This was taken up in $CHCl_3$ and was washed with three 50-ml portions of 5% NaOH and then repeatedly with H_2O until the washings were neutral to litmus. The organic solution was dried ($MgSO_4$) and the solvent was removed to give a solid which was recrystallized from toluene to yield 22 g (70%) of a white powder: mp 178–179.5°; ir (KBr) 3280 (NH), 1728 (ester C=O), 1710 cm^{-1} (carbamate C=O); nmr ($CDCl_3$) δ 1.35 (t, 2 H, ring CH_2), 2.04 (q, 1 H, $CHCO_2R$), 3.55 (m, 1 H, CHN), 5.23 (s, 2 H, CH_2Ph), 5.92 (m, 1 H, NH), 7.38 (s, 5 H, ArH), 7.15–8.00 (m, 7 H, 2-naphthyl).

Anal. Calcd for $C_{22}H_{19}NO_4$: C, 73.11; H, 5.29; N, 3.87. Found: C, 73.26; H, 5.39; N, 4.02.

***cis*-[2-(*N*-Carbo-2-naphthyloxy)amino]cyclopropanecarboxylic Acid (12).** Compound 11 (9 g, 0.025 mol) in 100 ml of EtOAc was hydrogenated in a Parr shaker apparatus in the presence of 1 g of 5% Pd/C at 75° and an initial pressure of 55 psig. The reaction was complete in 3 hr. The hot reaction mixture was filtered through a Celite pad and upon removal of the solvent from the filtrate, a solid was formed which was recrystallized from tolu-

ene to afford 5.3 g (78%) of **12**: mp 169–172° (dec); ir (KBr) 3320 (NH), 1710 (carbamate C=O), 1685 cm^{-1} (acid C=O); nmr (DMSO-d_6) δ1.32 (t, 2 H, ring CH_2), 1.85 (q, 1 H, $CHCO_2R$), 3.10 (m, 1 H, CHN), 7.10–8.10 (m, 7 H, 2-naphthyl).

Anal. Calcd for $C_{15}H_{13}NO_4$: C, 66.41; H, 4.83; N, 5.16. Found: C, 66.71; H, 4.95; N, 4.90.

Registry No.—2, 53229-56-4; **3,** 53229-57-5; **6,** 53229-58-6; **7,** 53229-59-7; **8,** 53229-60-0; **11,** 53403-91-1; **12,** 53229-62-2; **13,** 6860-35-1; **14,** 53229-63-3; **15,** 53229-64-4; **16,** 53229-65-5; **17,** 53229-66-6; **18,** 103-40-2; $SOCl_2$, 7719-09-7; *cis*-2-carbomethoxycyclopropanecarboxylic acid, 31420-47-0; *cis*-cyclopropane-1,2-dicarboxylic acid anhydride, 5617-74-3; benzyl alcohol, 100-51-6; *trans*-cyclopropanedicarboxylic acid, 696-75-3.

References and Notes

(1) This investigation was supported by Grant No. NS-06100, National Institute of Neurological Diseases and Stroke. Abstracted from a portion of a thesis submitted by J.E.G. in partial fulfillment of the requirements for the Ph.D. degree, University of Iowa, 1974.
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Carbon-13 Nuclear Magnetic Resonance Spectroscopy Quantitative Correlations of the Carbon Chemical Shifts of Simple Epoxides[1]

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Fourier transform carbon-13 nuclear magnetic resonance spectra have been obtained for 42 simple epoxides. A set of additivity parameters have been developed which allow the calculation of the expected chemical shift of the carbon atoms of the epoxide functional group. The effect of adjacent unsaturation is also discussed.

Carbon-13 nuclear magnetic resonance (^{13}C nmr) spectroscopy has become an extremely important research tool in the structural elucidation of organic compounds.[4] To interpret the ^{13}C nmr spectra of any particular compound it is usually required to examine the ^{13}C nmr spectra of closely related compounds containing similarly substituted carbons. A number of methods have been developed to aid in the assignment of the carbon resonances. One method in particular has proved to be quite useful for the assignment of carbon resonances. Using least-squares analyses, a system of substituent parameters has been developed for a number of compound types. These parameters are then used to predict the carbon chemical shifts of related compounds. This method has been most successfully applied by Grant,[5] Roberts,[6] and Djerassi.[7] We have extended this method to aliphatic epoxides and obtained a series of empirical substituent parameters which should prove very useful in the assignment of structure to molecules containing the epoxide functionality.

Experimental Section

A. Preparation of the Epoxides. The epoxides were either obtained commercially or synthesized by peracetic acid oxidation of the appropriate olefin. The structures of the epoxides were confirmed by proton magnetic resonance spectroscopy.

B. ^{13}C Spectra. The carbon-13 chemical shifts were obtained on a Bruker HX-90-E instrument equiped with a Bruker-Nicolet Data System, Model B-NC-12. The spectra were recorded at 22.6 MHz with 5-μsec pulse widths applied at 1-sec intervals. All of the chemical shifts were measured relative to 10% internal TMS using 45% $CDCl_3$ as solvent. At these concentrations 1000 pulses were used to obtain a reasonable signal-to-noise ratio. Complete proton decoupling was used to obtain the chemical shifts and single-frequency-off-resonance decoupled spectra were used to assign the resonances of the epoxy carbons in questionable cases. No attempts were made to assign the other carbons in the molecules.

C. Least-Squares Solutions. The least-squares solutions were obtained by using a modification of the BMD03R[8] regression analysis program for the CDC 3151 computer at California State University, Los Angeles. The program computed the least-squares empirical value for the substituent parameter, the 96% confidence limits for the parameters, the deviation between each calculated and experimental chemical shift, the standard error of prediction, and the multiple correlation coefficient.[9]

Results and Discussion

Recently several papers have appeared on the subject of the ^{13}C spectra of epoxides. Tori and Komeno[10] have studies the conformational effects in steroidal epoxides. Anet and Servis have investigated the conformational analysis of cycloheptane oxide by ^{13}C spectroscopy[11] and Anet has also studied the ^{13}C spectra of a series of di-, tri-, and tetraepoxides[12] and assigned additivity parameters to these classes of polyepoxides. However, there has not been a detailed study of simple epoxides. We now wish to report such a study.

In calculating the chemical shifts of the epoxy carbon atoms, substituent effects shown in Chart Ia were used. These are defined in the same manner as those defined by Roberts in his study of acyclic alkenes.[6] Using this method, the substituent effects for carbon 3 of *trans*-3,4-epoxy-5-methylheptane are given as $\alpha + \beta + \alpha' + 2\beta' + \gamma'$ (Chart Ib). In addition to the substituent parameters α, β, γ, α', β', and γ', it was found that better results were obtained if a cis correction factor was included when α and α' were located cis to one another. Finally a gem correction factor was also included when a system contained two α parameters. Thus the substituent effects of carbon 4 of *cis*-4,5-epoxy-4-methyloctane are given as $2\alpha + \beta + \gamma + \alpha' + \beta' + \gamma' +$ gem factor + cis factor (Chart Ic). The ^{13}C nmr shift of any epoxide can be calculated by addition of the appropriate substituent parameters to the chemical shift of ethylene oxide. The values obtained for the substituent parameters are given in Table I.

Table I
Substituent Parameters for Epoxide Carbons

α (48)[a]	8.3 ± 0.5[b]
β (32)	4.4 ± 0.2
γ (19)	−0.9 ± 0.2
α' (48)	7.1 ± 0.3
β' (32)	−0.9 ± 0.2
γ' (19)	0.2 ± 0.2
cis factor (15)	−2.7 ± 0.4
gem factor (9)	−4.3 ± 0.6
Standard error of estimate 0.85	
Multiple correlation coefficient 0.99	

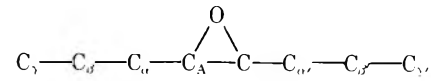
[a] The numbers in parentheses represent the number of occurrences of that parameter. [b] Values are given in parts per million (ppm).

In Table II the observed chemical shifts are given for 10 of the 30 simple epoxides used to generate the parameters shown in Table I. The calculated chemical shifts for each of these 10 epoxides are also given in Table II along with the residuals. The complete carbon nuclear magnetic resonance spectra of all 30 compounds are available as supplementary material. See paragraph on supplementary material at the end of this paper.

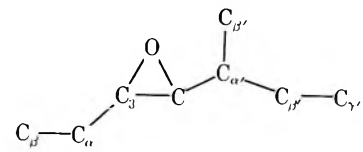
These substituent parameters generally parallel but are somewhat lower in magnitude than the parameters found by Roberts in his study of acyclic alkenes.[6] The α and β substituent parameters are deshielding as they are for the alkanes studied by Grant.[5] The α' parameter is deshielding as expected since the substituent is actually β to the carbon atom in question. However, this contrasts with the alkene series where the α' parameter was found to be shielding.[6] The γ and β' parameters are all shielding. They are small in magnitude and may be of only minor significance. The γ' parameter is the same value as the error in the γ' parameter and thus this parameter can be excluded.

Chart I

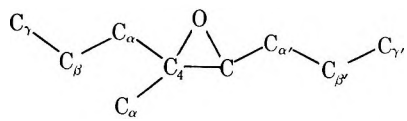
A. Definition of the Substituent Effects Used in Calculation of the Chemical Shift of Carbon A



B. Substituent Effects of Carbon 3 of *trans*-3,4-Epoxy-5-methylheptane

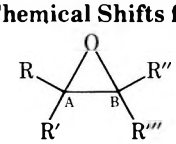


C. Substituent Effects of Carbon 4 of *cis*-4,5-Epoxy-4-methyloctane



The cis and gem parameters point up the great importance of steric factors in these systems. They are probably due to the so-called "steric compression shift" introduced by Grant.[13] This steric effect is shielding in nature and is directly related to the force component along the H–^{13}C bond associated with nonbonded hydrogen–hydrogen interactions. It is apparently due to an induced polarization of charge along the H–^{13}C bond. One could also rationalize the γ and β' parameters as steric compression shifts. It should also be pointed out that compounds which contain the gem factor give the largest deviation between calculated and observed chemical shift values. This could be due to either the smaller number of examples which contain the gem factor or to a nonlinear nature of steric effects.

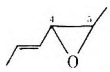
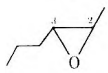
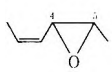
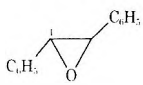
Table II
Calculated and Observed ^{13}C Chemical Shifts for a Series of Simple Epoxides[a,b]



Compd	R	R'	R''	R'''	Carbon	Obsd	Calcd	Residual
1	H	H	H	H	A	40.6		
2	CH_3	H	H	H	A	47.5	48.4	−0.9
					B	47.2	47.1	0.1
3	n-C_3H_7	H	H	H	A	51.9	51.9	0.0
					B	46.7	46.5	0.2
4	i-C_4H_9	H	H	H	A	51.1	51.0	0.1
					B	47.0	46.8	0.2
5	sec-C_5H_{11}	H	H	H	A	57.0	56.3	0.7
					B	46.7	45.7	1.0
6	n-C_3H_7	CH_3	H	H	A	56.5	55.9	0.6
					B	53.5	53.6	−0.1
7	C_2H_5	C_2H_5	H	H	A	60.6	61.2	−0.6
					B	51.5	52.5	−1.0
8	C_2H_5	H	H	CH_3	A	60.7	59.8	0.9
					B	54.1	54.6	−0.5
9	C_2H_5	H	CH_3	H	A	58.1	57.2	0.9
					B	52.4	51.9	0.5
10	C_2H_5	C_2H_5	CH_3	H	A	64.4	65.7	0.3
					B	58.5	58.2	0.3
11	CH_3	CH_3	CH_3	CH_3	A	61.2	61.2	0.0

[a] The chemical shift data are relative to internal TMS and are given in ppm. [b] The complete ^{13}C nmr data for these and other similar compounds are given in the supplementary material.

Table III
Effect on Unsaturation on ^{13}C Chemical Shift of Epoxides[a,b]

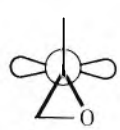
Compound	Carbon	Obsd	Calcd
	4	59.3	59.2
	5	55.8	54.4
	3	59.6	59.2
	2	54.3	54.4
	4	53.7	56.0
	5	52.4	52.2
	1	62.6	61.5

[a] The chemical shift data are relative to internal TMS and are given in ppm. [b] The complete carbon magnetic resonance spectra for these and similar compounds are included in the supplementary material.

The effect of adjacent unsaturation on the ^{13}C chemical shift of the epoxy carbons is minimal as is shown in Table III. Even the effect of an aromatic ring can be approximated by our additivity parameters. This has also been observed with alkenes. Allylic carbons usually have a chemical shift very close to the analogous saturated molecule. Cycloheptatriene is a striking example of the insensitivity of ^{13}C chemical shift to the hybridization of the adjacent carbons.[14] The lone sp^3 hydridized carbon appears at 28.8 ppm downfield from TMS while the chemical shift for cycloheptane is 28.5 ppm.

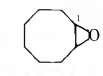
Table IV presents evidence that adjacent unsaturation can have a pronounced effect if the epoxy group and the olefinic group are oriented properly. The saturated cyclopentyl and cyclooctyl epoxides come very close to the calculated value using our additivity parameters for acyclic epoxides. The cyclohexyl system deviates significantly from the calculated value. This may be due to a steric compression shift caused by interaction between the epoxy group and the proton on carbon 4 of the ring. The approximately 4-ppm upfield shift from the calculated value in cyclohexene oxide is consistent with this argument. The conjugated alicyclic epoxides show a pronounced upfield shift for the epoxy carbon atom adjacent to the unsaturation as compared to the other epoxy carbon atom. This effect is largest in the 3,4-epoxycyclohexene system where the difference in chemical shift between the two epoxy carbons is 7.8 ppm.

The largest conjugative interaction between the epoxy group and the olefinic π bond would be expected in the bisected conformation shown below. This prediction is based



on a comparison with the corresponding cyclopropyl system.[15] In this conformation the overlap between the darkened σ orbitals of the epoxy group and the π system would be the greatest. Models indicate that the cyclohexenyl system most closely approximates this bisected geometry, and thus one would expect a significant conjugative interaction in this case. Such an interaction would lead to an electron deficiency at the carbon in question and give the observed upfield shift. The geometry in the other cases is much different from the bisected geometry needed for maximum overlap and a smaller effect would be expected.

Table IV
Unsaturated Cyclic Epoxides[a,b]

Compound	Carbon	Obsd	Δδ
	1	56.6	
	3	55.8	2.4
	4	58.2	
	1	51.3	
	3	46.2	7.8
	4	54.0	
	1	55.1	
	3	52.8	
	4	57.2	4.4

[a] The chemical shift data are relative to internal TMS and are given in ppm. [b] Complete ^{13}C data for these and similar compounds are found in the supplementary material.

Acknowledgment. The authors wish to express their appreciation to Mr. T. Murillo and Mr. R. Perrigan for their valuable assistance in obtaining the ^{13}C spectra.

Registry No.—**1**, 75-21-8; **2**, 75-56-9; **3**, 1003-14-1; **4**, 23850-78-4; **5**, 53229-39-3; **6**, 3657-41-8; **7**, 1192-17-2; **8**, 3203-98-3; **9**, 3203-99-4; **10**, 53229-40-6; **11**, 5076-20-0; **12**, 1436-34-6; **13**, 2984-50-1; **14**, 2855-19-8; **15**, 53229-41-7; **16**, 53229-42-8; **17**, 15359-10-1; **18**, 53229-43-9; **19**, 2390-95-6; **20**, 6124-91-0; **21**, 17612-35-0; **22**, 1192-22-9; **23**, 2245-30-9; **24**, 1758-33-4; **25**, 21490-63-1; **26**, 106-88-7; **27**, 2245-29-6; **28**, 5076-19-7; **29**, 16262-93-4; **30**, 10353-53-4; **31**, 286-62-4; **32**, 286-20-4; **33**, 285-67-6; **34**, 31598-71-7; **35**, 6690-12-6; **36**, 6253-27-6; **37**, 6705-51-7; **38**, 7129-41-1; **39**, 36808-01-2; **40**, 36808-00-1; **41**, 34485-82-0; **42**, 1439-07-2.

Supplementary Material Available. Full ^{13}C nmr data for all of the compounds used in this study (42 compounds) appear following this article in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 24× reduction, negatives) containing all the supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 16th Street, N.W., Washington, D.C. 20036. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche, referring to code number JOC-75-184.

References and Notes

(1) Supported by a grant from the California State University Foundation, Los Angeles, Calif.
(2) National Science Foundation Undergraduate Research Program, Summer 1973.
(3) American Chemical Society, Project Catalyst Program, Summer 1973.
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Alkyl Nitrate Nitration of Active Methylene Compounds. Nitration of Toluenes.[1] A Facile Preparation of Stilbenes

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The alkyl nitrate nitration of toluenes substituted in the ortho or para position with an electron-withdrawing group gives the corresponding α-nitrotoluenes in yields of about 40–55%. The reaction is successful with o- and p-tolunitriles, *N,N*-dimethyl-*p*-toluenesulfonamide, phenyl *p*-tolyl sulfone, 4-methylbenzophenone, and even such a weak acid as diphenylmethane. The reaction is unsuccessful with o- and *p*-*N,N*-dimethyltoluamides, which are converted into the corresponding *o*- and *p*-toluamides in the alkali amide–liquid ammonia system. The para-substituted α-nitrotoluenes are readily converted in good yield into the corresponding para-substituted stilbenes on treatment with catalytic amounts of potassium acetate in refluxing ethanol. However, the reaction with *o*-cyano-α-nitrotoluene leads to 3-oximinophthalimide.

In continuation of our studies of the alkyl nitrate nitration[2] in the alkali amide–liquid ammonia system, we now report on its application to the preparation of α-nitrotoluenes substituted in the ortho or para position with an electron-withdrawing group such as cyano, *N,N*-dimethylsulfonamido, phenylsulfonyl, and benzoyl (eq 1).

$$\underset{\mathbf{1}}{RC_6H_4CH_3} \xrightarrow[2.\ H^+]{1.\ MNH_2\text{-liquid } NH_3\text{-}R'ONO_2\ (M = K, Na)} \underset{\mathbf{2}}{RC_6H_4CH_2NO_2} \quad (1)$$

a, R = *p*-CN

b, R = *o*-CN

c, R = *p*-$(CH_3)_2NSO_2$

d, R = *p*-$C_6H_5SO_2$

e, R = *p*-C_6H_5CO

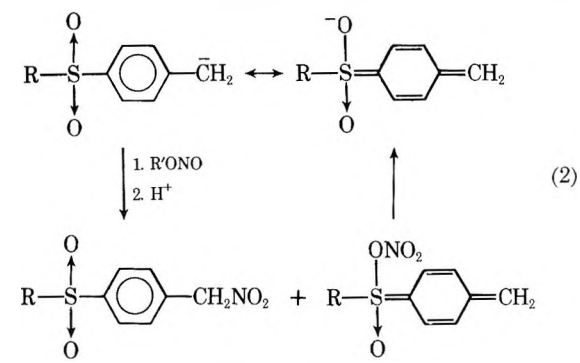
A search of the literature indicated that the only α-nitrotoluene reported bearing an electron-withdrawing group in the ortho or para position is α-*p*-dinitrotoluene (**3**). It was prepared by Kornblum, *et al.*,[3] in 75% yield from *p*-nitrobenzyl bromide by the Victor Meyer reaction.

In order to determine optimum reaction conditions, various reaction parameters were studied with *p*-tolunitrile (**1a**). *p*-Cyano-α-nitrotoluene (**2a**) was obtained in 46% yield and 42% of **1a** was recovered when nitrations were carried out in systems A (potassium amide–liquid ammonia) or B (sodium amide–liquid ammonia), and when the molar ratio of **1a** to base and alkyl nitrate was 1:1.5:2. Anion formation was carried out at −33° for 15 min, and the crude nitronate salt was generally isolated and then acidified with acetic acid in absolute ether or in water.

However in the case of *o*-tolunitrile (**1b**), pure *o*-cyano-α-nitrotoluene (**2b**) (38%) was obtained only when the potassium salt of **2b** was recrystallized from 95% ethanol prior to acidification with acetic acid and the crude **2b** was thoroughly washed with water to remove all traces of potassium acetate. The recrystallization of **2b**, contaminated with traces of potassium acetate, with 95% ethanol led exclusively to 3-oximinophthalimide (*vide infra*).

Nitrations of *N,N*-dimethyl-*p*-toluenesulfonamide (**1c**) and phenyl *p*-tolyl sulfone (**1d**) did not proceed equally well in systems A and B. In system B, **1c** and **1d** were converted into the corresponding nitro compounds **2c** and **2d** in yields of 39.5 and 54%, respectively, while in system A the yields were only 15 and 4%. These results are contrary to what one would expect on the basis of base strength. They were not due to side reactions because the material balances were about 80–88%. The results could be explained by the ambident nature of the anions of **1c** and **1d**.

In one of the resonance structures of these anions the negative charge resides on the oxygen, and it is conceivable that the electrophilic attack of the nitrate ester would be directed toward the oxygen rather than carbon. The product of such O-nitration would probably be unstable and revert to starting material (eq 2). According to the well-



(2)

R = $(CH_3)_2N$, C_6H_5

known cation effect[4] O-nitration would predominate in system A and as a consequence the yields in the nitration of **1c** and **1d** would be lower than in system B and C-nitration would be favored.

4-Methylbenzophenone (**1e**) underwent nitration only in system A. *p*-Benzoyl-α-nitrotoluene (**2e**) was obtained in 16% yield and 64% of **1e** was recovered. Nitration in system B led to a quantitative recovery of **1e**. Attempts to increase the yield of **2e** by carrying out the anion formation with potassium amide in refluxing ether were unsuccessful. Compound **1e** was cleaved in a Haller–Bauer-type reaction[5] to *p*-toluamide (**4**) in 58% yield. The other cleavage product benzamide (**5**) was hydrolyzed during work-up to benzoic acid (42% yield) (eq 3).

$$\mathbf{1e} \xrightarrow[\text{reflux; 5 min}]{KNH_2\text{-}Et_2O} \underset{\mathbf{4}}{p\text{-}CH_3C_6H_4CONH_2} + \underset{\mathbf{5}}{C_6H_5CONH_2} \quad (3)$$

Diphenylmethane was converted into diphenylnitromethane[6] (**6**) in 40% yield. Compound **6** was found to be unstable, and even a spectroscopically pure sample decomposed to benzophenone[6b] (**7**) when stored at 0° (eq 4). Di-

$$(C_6H_5)_2C{=}NO_2^-K^+ \xrightarrow[0\text{–}5^\circ]{dil\ H_2SO_4} \underset{\mathbf{6}}{(C_6H_5)_2CHNO_2} \longrightarrow \underset{\mathbf{7}}{(C_6H_5)_2CO}$$

$$\xrightarrow[H_2O]{KOBr,\ 0^\circ} \underset{\mathbf{8}}{(C_6H_5)_2CBrNO_2} \quad (4)$$

phenylbromonitromethane[6b] (8), however, was found to be unchanged even after 3 years, when stored at 0°. Compound 8 was obtained in 68% yield when the bromination of 6 was performed at 0° with aqueous potassium hypobromite or with bromine in absolute ether (eq 4).

It should be mentioned that the nitration was unsuccessful with *o*-*N*,*N*-dimethyltoluamide (9), its para isomer (10), 2-methylbenzophenone (11), and *p*-nitrotoluene (12). As shown in eq 5, compounds 9 and 10 were converted in a

$$CH_3C_6H_4CON(CH_3)_2 \xrightarrow[n\text{-}C_3H_7ONO_2]{KNH_2\text{-liquid } NH_3} CH_3C_6H_4CONH_2 \quad (5)$$

transamidation reaction into *o*- and *p*-toluamides, respectively.

The failure of compound 11 to undergo nitration is believed to be due to the lack of anion formation in systems A or B. No deuterium was incorporated when 11 was treated with potassium amide in refluxing ether and the reaction mixture quenched with deuterium oxide. Hauser[7] reported that 11 did not undergo alkylation in system B.

Nitration of compound 12 at the usual conditions in system A did not give the expected 3 but rather led to the formation of *p*,*p*′-dinitrobibenzyl (13). The conversion of compound 12 into compound 13 in basic media has been well established.[8]

The substituted α-nitrotoluenes were identified by infrared and nmr spectral data, and by conversion into the corresponding α-halo-α-nitrotoluenes.

Dihalo derivatives of the α-nitrotoluenes were obtained when their nitronate salts were treated with aqueous solutions of potassium hypohalite (eq 6).

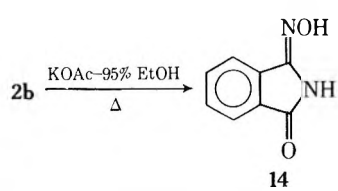
$$\underset{\mathbf{2}}{RC_6H_4CH{=}NO_2^-M^+} \xrightarrow[H_2O]{KOX} RC_6H_4CX_2NO_2 \quad (6)$$

M = Na, K; X = Br, Cl

Treatment of the potassium salt of **2a** with a stoichiometric amount of bromine in carbon tetrachloride afforded *p*-cyano-α-bromo-α-nitrotoluene (eq 7).

$$p\text{-}CNC_6H_4CH{=}NO_2^-K^+ \xrightarrow[CCl_4]{Br_2} p\text{-}CNC_6H_4CHBrNO_2 \quad (7)$$

As already mentioned *o*-cyano-α-nitrotoluene (**2b**) was converted into 3-oximinophthalimide (**14**) in 92% yield in the presence of potassium acetate (eq 8).



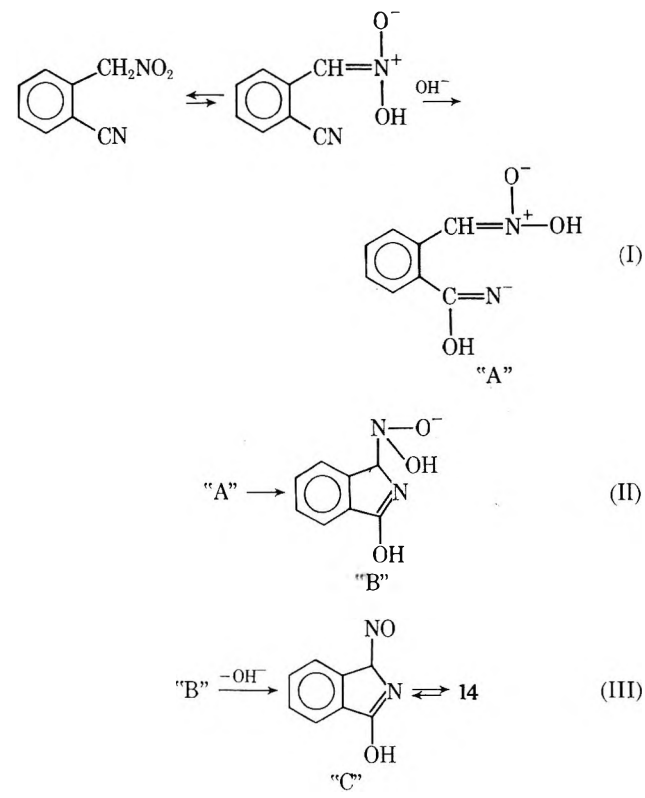
14 (8)

The transformation might occur by the pathway shown in Scheme I. It would account for the fact that only a catalytic amount of base is required. In step I nucleophilic attack of hydroxide ion on the nitrile group[9] of **2b** which would be expected to exist to some extent in the aci form,[10] gives the enol form of amide "A." Cyclization of "A" by intramolecular nucleophilic attack in step II leads to intermediate "B." Loss of hydroxide ion in step III gives rise to nitroso compound "C" which tautomerizes to 14.

Conversion of α-Nitrotoluenes into Stilbenes. The facile conversion of o-cyano-α-nitrotoluene (**2b**) to 3-oximinophthalimide (**14**) prompted the investigation of the reaction of the α-nitrotoluenes **2** with base.

A survey of the literature revealed that Wislicenus and coworkers[11] had found that **2g** and its *o*- and *p*-bromo de-

Scheme I



rivatives were converted into the corresponding stilbenes in yields of 85, 30, and 60% respectively, on refluxing with aqueous sodium hydroxide for several hours. Our investigation showed that even such a weak base as potassium acetate in refluxing 95% ethanol converts compounds **2** into the corresponding stilbenes **15** (eq 9). Under these mild

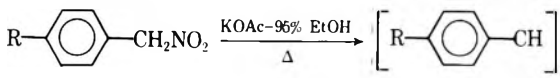
$$\underset{\mathbf{2}}{p\text{-}RC_6H_4CH_2NO_2} \xrightarrow[\Delta]{KOAc\text{–}95\%\ EtOH} \underset{\mathbf{15}}{(p\text{-}RC_6H_4CH)_2} \quad (9)$$

a, R = *p*-CN
c, R = $SO_2N(CH_3)_2$
d, R = $C_6H_5SO_2$
e, R = C_6H_5CO
f, R = NO_2
g, R = H

conditions, groups sensitive to strong base such as sulfonamido, nitrile, and nitro were not affected during stilbene formation. It was established that only a catalytic amount of potassium acetate was required to convert **2c** into stilbene **15c** in 64% yield after a reaction time of 21 hr. In the absence of potassium acetate **2c** was recovered unchanged after refluxing in 95% ethanol.

The results which are summarized in Table I show that the stilbenes were obtained in yields which varied from 36 to 100% and that the material balances amounted to about 80%. The low yield (36%) in the case of **2f** was apparently due to a Nef reaction which gave rise to the formation of *p*-nitrobenzoic acid (**16**) in 10% yield. It is of interest that although no **16** was obtained after a reaction time of 2 hr the yield of **15f** had not changed but 35% of **2f** was recovered. Moreover, it should be emphasized that an electron-withdrawing group is not essential for the transformation, since α-nitrotoluene itself was converted into stilbene in high yield.

Table I
Conversion of α-Nitrotoluenes into Stilbenes[a]



R	Stilbene yield, %	Mp, °C	α-Nitrotoluene recovery, %
CN	76[b]	275–277[c]	9.5
Me_2NSO_2	67[d]	254–255	7.0
$C_6H_5SO_2$	55.3[b]	324–325	26.6
C_6H_5CO	100	233–235[e]	
NO_2	35.7[b]	306–307[f]	*g,h*
H	81	123–124[i]	0

[a] Unless stated otherwise, equimolar amounts of potassium acetate were employed and the reaction time was 21 hr. [b] The yield was the same when the reaction time was 2 hr. [c] C. D. Weiss, *Helv. Chim. Acta*, 49, 234 (1965), reports mp 272–274°. [d] The yield was 64% when a catalytic amount of potassium acetate was used. [e] G. Wittig and W. Wiener, *Justus Liebigs Ann. Chem.*, 483, 144 (1930), report mp 234–235°. [f] C. M. Anderson, L. G. Cole, and E. C. Gilbert, *J. Amer. Chem. Soc.*, 74, 6313 (1952), report mp 302–304°. [g] *p*-Nitrobenzoic acid was obtained in 10.5% yield. [h] After a reaction time of 2 hr, no *p*-nitrobenzoic acid was formed; however, 35% of starting material was recovered. [i] Lit.[11a] mp 124–125°.

Experimental Section

All melting points are uncorrected. All infrared spectra were taken with Perkin-Elmer recording spectrophotometer, Models 21 and 421. Nuclear magnetic resonance spectra were determined on a Varian Model A-60 analytical nmr spectrometer using tetramethylsilane as an internal standard. Gas chromatographic analyses were performed on an Aerograph A-700 using a 4-ft SF-96 on Chromosorb W column and a 6-ft SE-30 on Chromosorb P column. Solvents were evaporated on a Buchler flash-evaporator.

Reagents. Amyl nitrate was a generous gift from Ethyl Corp.; propyl nitrate, *N,N*-dimethyl-*p*-toluenesulfonamide, and *o*- and *p*-tolunitriles were of Eastman White Label grade; *o*-toluoyl chloride and diphenylmethane were obtained from Aldrich Chemical Co., 4-methylbenzophenone and *p*-nitrotoluene from J. T. Baker Chemical Co., and *p*-toluenesulfonyl chloride from Matheson Coleman and Bell. All of these compounds were used as received.

***p*-Cyano-α-nitrotoluene (2a).** The following experiment is typical of the procedure employed for the preparation of α-nitrotoluenes. Into an oven-dried 500-ml round-bottom four-necked flask equipped with Dry Ice condenser, thermometer, mechanical stirrer, and addition funnel were placed, at −33°, 250 ml of liquid ammonia, a crystal of ferric nitrate nonahydrate, and 2.95 g (0.075 g-atom) of potassium. After potassium amide had formed, a solution of 5.9 g (0.05 mol) of *p*-tolunitrile (**1a**) in 15 ml of ether was added dropwise within 2 min. The mixture was stirred 15 min at −33° and then 10.51 g (0.1 mol) of propyl nitrate was added in 5 min [*CAUTION!* The first drops of alkyl nitrate should be added slowly because a considerable exotherm might develop], while the temperature was kept at −33° with a Dry Ice–$CHCl_3$–CCl_4 bath. The mixture was stirred for an additional 30 min at −33°, and the ammonia was allowed to evaporate while replacing it with anhydrous ether. Filtering and drying the solid at 25° (0.7 mm) gave 17.8 g of crude potassium *p*-cyanophenylmethanenitronate.

To a suspension of the crude salt in 150 ml of anhydrous ether at −40° was added 15 g (0.25 mol) of glacial acetic acid. The mixture was stirred overnight in an ice–salt bath, filtered and concentrated *in vacuo* to afford 3.78 g (46.6%, based on **1a**) of *p*-cyano-α-nitrotoluene, mp 94–96°. The analytically pure sample, obtained after recrystallizing the crude material from 95% ethanol and subliming at 60° (0.25 mm), gave mp 95–96°: ir (KBr) 2230 (CN) and 1558 and 1375 cm^{-1} (NO_2); nmr ($CDCl_3$) δ 5.57 (s, 2, CH_2) and 7.72 (q, 4, C_6H_4).

Anal. Calcd for $C_8H_6N_2O_2$: C, 59.27; H, 3.73; N, 17.28. Found: C, 59.03; H, 3.54; N, 17.44.

Concentrating the filtrate from the nitration gave 2.44 g (41.5%) of recovered **1a** as determined by glpc analysis.

***o*-Cyano-α-nitrotoluene (2b).** The general procedure was followed up to the isolation of the nitronate salt. From 5.9 g (0.15 mol) of potassium amide, 11.8 g (0.1 mol) of o-tolunitrile (**1b**), and 21.2 g (0.2 mol) of propyl nitrate was obtained 19.3 of potassium o-cyanophenylmethanenitronate. One recrystallization from 95% ethanol gave 12.8 g of nitronate salt, mp 220° dec. The salt was dissolved in 250 ml of water, acidified with 9 g (0.15 mol) of glacial acetic acid at room temperature, and filtered to give 6.2 g (38.3%) of *o*-cyano-α-nitrotoluene, mp 52–55°. One recrystallization from 95% ethanol gave mp 58–59°: ir (KBr) 2230 (CN) and 1555 and 1378 cm^{-1} (NO_2); nmr ($CDCl_3$) δ 5.57 (s, 2 CH_2) and 7.75 (m, 4, C_6H_4).

Anal. Calcd for $C_8H_6N_2O_2$: C, 59.26; H, 3.73; N, 17.28. Found: C, 58.99; H, 3.78; N, 17.15.

Compound **1b** (4.1 g, 35%) was recovered as determined by glpc analysis.

***p*-*N,N*-Dimethylsulfonamido-α-nitrotoluene (2c).** The general procedure was followed up to the isolation of the nitronate salt. From 3.46 g (0.15 mol) of sodium amide, 19.9 g (0.1 mol) of *N,N*-dimethyl-*p*-toluenesulfonamide (**1c**), and 21.2 g (0.2 mol) of propyl nitrate there was obtained 22.4 g of salt. It was dissolved in 400 ml of water; the solution was filtered and acidified with 9 g (0.15 mol) of glacial acetic acid to give 9.6 g (39.4%) of *p*-*N,N*-dimethylsulfonamido-α-nitrotoluene, mp 110–114°. Two sublimations at 95–100° (0.45 mm) gave mp 113–114°: ir (KBr) 1550 (NO_2) and 1340 and 1162 cm^{-1} (SO_2); nmr ($CDCl_3$) δ 2.72 (s, 6, NCH_3), 5.50 (s, 2, CH_2), and 7.65 (q, 4, C_6H_4); mass spectrum (75 eV) *m/e* (rel intensity) 244 (30) and 198 (100).

Anal. Calcd for $C_9H_{12}N_2O_4S$: C, 44.26; H, 4.92; N, 11.48; S, 13.11. Found: C, 44.51; H, 5.07; N, 11.30; S, 13.36.

Compound **1c** (5.4 g, 27.1%) was recovered.

When the reaction was carried out in system A, a small amount of material remained when the crude nitronate salt was dissolved in water. It was identified as *p,p*-bis(*N,N*-dimethylsulfonamido)-stilbene (*vide infra*).

***p*-Phenylsulfonyl-α-nitrotoluene (2d).** From 3.46 g (0.15 mol) of sodium amide, 23.2 g (0.1 mol) of phenyl *p*-tolyl sulfone (**1d**), 21.2 g (0.2 mol) of propyl nitrate, and 9 g (0.15 mol) of glacial acetic acid there was obtained 7.05 g (54.7%) of *p*-phenylsulfonyl-α-nitrotoluene, mp 65–70°. Three recrystallizations from 95% ethanol gave mp 94–95°: ir (KBr) 1560 and 1380 (NO_2) and 1308 and 1160 cm^{-1} (SO_2); nmr ($CDCl_3$) δ 5.4 (s, 2, CH_2) and 7.6 (m, 9, C_6H_5 and C_6H_4).

Anal. Calcd for $C_{13}H_{11}NO_4S$: C, 56.32; H, 3.97; N, 5.05; S, 11.55. Found: C, 56.40; H, 3.97; N, 5.06; S, 11.51.

Compound **1d** (9.1 g, 39.2%) was recovered.

***p*-Benzoyl-α-nitrotoluene (2e).** From 5.9 g (0.15 mol) of potassium amide, 19.6 g (0.1 mol) of 4-methybenzophenone (**1e**), 26.6 g (0.2 mol) of amyl nitrate, and 9.9 g (0.165 mol) of glacial acetic acid there was obtained 2.09 g (16%) of *p*-benzoyl-α-nitrotoluene, mp 88–89°. One sublimation at 65° (0.7 mm) gave mp 89–89.5°: ir (KBr) 1660 (CO), 1550 and 1372 cm^{-1} (NO_2); nmr ($CDCl_3$) δ 5.70 (s, 2, CH_2NO_2) and 7.92 (m, 9, C_6H_5 and C_6H_4).

Anal. Calcd for $C_{14}H_{11}NO_3$: C, 69.70; H, 4.59; N, 5.80. Found: C, 69.46; H, 4.58; N, 5.75.

Compound **1e** (12.49 g, 64%) was recovered as determined by glpc analysis.

Diphenylnitromethane (6). The general procedure was employed up to the isolation of the nitronate salt; 5.9 g (0.15 mol) of potassium amide, 16.8 g (0.1 mol) of diphenylmethane, and 21.2 g (0.2 mol) of propyl nitrate were used.

The reaction mixture was filtered and a solution of 7.2 g (0.0286 mol) of crude nitronate salt in 150 ml of water was acidified to pH 5 with 4 *M* sulfuric acid. Filtering and drying the pink solid *in vacuo* gave 2.4 g (39.5%) of diphenylnitromethane, mp 85–90° dec. One recrystallization of the crude compound from ether gave mp 90–91° dec (lit.[6b] mp 90–91° dec): ir (KBr) 1557 and 1358 cm^{-1} (NO_2); nmr ($CDCl_3$) δ 6.8 (s, 1, $CHNO_2$) and 7.41 (m, 10, C_6H_5).

Diphenylmethane (4.91 g, 29.2%) was recovered.

***p*-Cyano-α,α-dibromo-α-nitrotoluene.** The following experiment is typical of the procedure employed for the preparation of α,α-dihalo-α-nitrotoluenes. Into a 300-ml round-bottom flask equipped with a magnetic stirring bar and thermometer were placed 26.4 g (0.47 mol) of potassium hydroxide dissolved in 100 ml of water and 26.4 g (0.165 mol) of bromine. Then a solution of 6 g (0.03 mol) of crude potassium *p*-cyanophenylmethanenitronate in 80 ml of water was added all at once by keeping the temperature at 5°. After room temperature was attained, the mixture was extracted with 6 × 50 ml portions of ether. Drying the extracts (sodium sulfate) and concentrating *in vacuo* gave 3.0 g (31.5%) of *p*-cyano-α,α-dibromo-α-nitrotoluene, mp 80–90°. Three sublimations at 50° (0.1 mm) gave mp 86–87°: ir (KBr) 2240 (CN) and 1585 cm^{-1} (NO_2); nmr ($CDCl_3$) δ 7.89 (q, 4, C_6H_4).

Anal. Calcd for $C_8H_4N_2O_2Br_2$: C, 30.03; H, 1.26; N, 8.75; Br, 49.95. Found: C, 30.23; H, 1.29; N, 8.82; Br, 49.72.

p-Cyano-α,α-dichloro-α-nitrotoluene. A suspension of 7.5 g (0.375 mol) of crude potassium p-cyanophenylmethanenitronate in 50 ml of water at 25° was added to 58 ml of a 1.3 *M* potassium hypochlorite solution.[12]

The reaction mixture was extracted with 6 × 50 ml portions of ether and dried (sodium sulfate), and the extracts were concentrated *in vacuo* to give 3.4 g (39.6%) of p-cyano-α,α-dichloro-α-nitrotoluene, mp 72–75°. Three sublimations at 65° (3 mm) gave mp 81–82°: ir (KBr) 2240 (CN) and 1600 cm^{-1} (NO_2); nmr ($CDCl_3$) δ 7.83 (q, 4, C_6H_4).

Anal. Calcd for $C_8H_4N_2O_2Cl_2$: C, 41.60; H, 1.75; N, 12.13; Cl, 30.73. Found: C, 41.63; H, 1.88; N, 11.94; Cl, 30.57.

o-Cyano-α,α-dibromo-α-nitrotoluene. Crude potassium o-cyanophenylmethanenitronate (10.1 g, 0.0505 mol) gave 4.34 g (27%) of yellowish o-cyano-α,α-dibromo-α-nitrotoluene, mp 100–101°. One sublimation at 50–55° (0.05 mm) gave mp 101–102°: ir (KBr) 2225 (CN) and 1570 cm^{-1} (NO_2); nmr ($CDCl_3$) δ 7.85 (m, 4, C_6H_4).

Anal. Calcd for $C_8H_4N_2O_2Br_2$: C, 30.03; H, 1.26; N, 8.75; Br, 49.95. Found: C, 30.32; H, 1.50; N, 8.45; Br, 50.16.

p-N,N-Dimethylsulfonamido-α,α-dibromo-α-nitrotoluene. Crude sodium p-N,N-dimethylsulfonamidophenylmethanenitronate (7.3 g, 0.0274 mol) gave 8.6 g (78.2%) of p-N,N-dimethylsulfonamido-α,α-dibromo-α-nitrotoluene, mp 158–160°. One recrystallization from 95% ethanol gave mp 163–164°: ir (KBr) 1572 (NO_2) and 1325 and 1162 cm^{-1} (SO_2); nmr ($CDCl_3$) δ 2.72 (s, 6, NCH_3) and 7.80 (q, 4, C_6H_4); mass spectrum (75 eV) *m/e* (rel intensity) 356 (100).

Anal. Calcd for $C_9H_{10}N_2O_4Br_2S$: C, 26.87; H, 2.47; N, 6.97; Br, 39.80; S, 7.96. Found: C, 26.62; H, 2.45; N, 6.75; Br, 39.57; S, 8.24.

p-Phenylsulfonyl-α,α-dibromo-α-nitrotoluene. Crude sodium p-phenylsulfonylphenylmethanenitronate (8.65 g, 0.0289 mol) gave 11.27 g (90%) of p-phenylsulfonyl-α,α-dibromo-α-nitrotoluene, mp 121–124°. Recrystallizing three times from 95% ethanol gave mp 130–131°: ir (KBr) 1580 (NO_2) and 1310 and 1151 cm^{-1} (SO_2); nmr ($CDCl_3$) δ 7.64 (m, 9, C_6H_5 and C_6H_4).

Anal. Calcd for $C_{13}H_9NO_4Br_2S$: C, 35.86; H, 2.07; N, 3.22; Br, 36.78; S, 7.38. Found: C, 36.03; H, 2.20; N, 3.20; Br, 36.00; S, 7.80.

p-Benzoyl-α,α-dibromo-α-nitrotoluene. Crude potassium p-benzoylphenylmethanenitronate (7 g, 0.025 mol) gave 2.5 g (54%) of p-benzoyl-α,α-dibromo-α-nitrotoluene, mp 90–93°. One recrystallization from absolute ethanol gave mp 99–99.5°: ir (KBr) 1668 (CO) and 1580 cm^{-1} (NO_2); nmr ($CDCl_3$) δ 7.78 (m, 9, C_6H_5 and C_6H_4).

Anal. Calcd for $C_{14}H_9NO_3Br_2$: C, 42.15; H, 2.27; N, 3.51; Br, 40.04. Found: C, 42.28; H, 2.42; N, 3.46; Br, 40.05.

α-Bromo-α-nitro-α-phenyltoluene. Crude potassium diphenylmethanenitronate (7.6 g, 0.0303 mol) gave, after one recrystallization from 95% ethanol, 6.8 g (67.5%) of α-bromo-α-nitro-α-phenyltoluene: mp 47–49° (lit.[6b] mp 44°); ir (KBr) 1562 and 1331 cm^{-1} (NO_2); nmr ($CDCl_3$) δ 7.44 (s, 10, C_6H_5).

Anal. Calcd for $C_{13}H_{10}NO_2Br$: C, 55.44; H, 3.45; N, 4.80. Found: C, 53.51; H, 3.43; N, 4.55.

p-Cyano-α-bromo-α-nitrotoluene. Into a 300-ml round-bottom flask equipped with a magnetic stirring bar, dropping funnel, and thermometer were placed 150 ml of dry carbon tetrachloride and thermometer were placed 150 ml of dry carbon tetrachloride and 10.0 g (0.05 mol) of crude potassium p-cyanophenylmethanenitronate. The suspension was cooled to 0–5°, a solution of 8 g (0.05 mol) of bromine in 10 ml of carbon tetrachloride added, and the mixture stirred an additional 1.25 hr at 0–5°. The filtrate was concentrated *in vacuo* to give a yellow oil which deposited white crystals upon storage in the freezer. Two recrystallizations from 95% ethanol gave 3.0 g (32%) of p-cyano-α-bromo-α-nitrotoluene: mp 44–45°; ir (KBr) 2250 (CN) and 1562 cm^{-1} (NO_2); nmr ($CDCl_3$) δ 5.58 (s, 1, $CHNO_2Br$) and 7.82 (m, 4, C_6H_4).

Anal. Calcd for $C_8H_5N_2O_2Br$: C, 39.85; H, 2.09; N, 11.62; Br, 33.14. Found: C, 40.02; H, 2.33; N, 11.62; Br, 33.13.

p,p′-Bis(N,N-dimethysulfonamido)stilbene (15c). The following experiment is typical of the procedure employed for preparing disubstituted stilbenes. Into a 50-ml round-bottom flask equipped with a magnetic stirring bar and reflux condenser were placed 0.267 g (1.09 mmol) of p-(N,N-dimethylsulfonamido)-α-nitrotoluene (**2c**), 0.107 g (1.09 mmol) of potassium acetate, and 20 ml of 95% ethanol. The mixture was refluxed for 21 hr, cooled, and filtered to give 0.1431 g (67.5%) of p,p′-bis(N,N-dimethylsulfonamido)stilbene, mp 245–250°. One recrystallization from trifluoroacetic acid and water (1:1) gave mp 254–255°; ir (KBr) 1600 (C=C) and 1340 and 1162 cm^{-1} (SO_2); nmr (CF_3CO_2H) δ 2.83 [s, 12, $N(CH_3)_2$], 7.30 (s, 2, CH), and 7.78 (s, 8, C_6H_4).

Anal. Calcd for $C_{18}H_{22}N_2O_4S_2$: C, 54.82; H, 5.58; N, 7.16; S, 16.24. Found: C, 54.67; H, 5.77; N, 7.31; S, 16.19.

Concentrating the filtrate *in vacuo* gave 0.019 g (7%) of unreacted **2c**.

p,p′-Diphenylsulfonylstilbene (15d). Similarly, 0.84 g (3.06 mmol) of p-phenylsulfonyl-α-nitrotoluene (**2d**) gave 0.36 g (52%) of p,p′-diphenylsulfonylstilbene: mp 324–325° [CF_3CO_2H–H_2O (1:1)]; ir (KBr) 1600 (C=C) and 1308 and 1158 cm^{-1} (SO_2); mass spectrum (75 eV) *m/e* (rel intensity) 460 (100).

Anal. Calcd for $C_{26}H_{20}O_4S_2$: C, 67.83; H, 4.35; S, 13.91. Found: C, 67.85; H, 4.13; S, 13.65.

3-Oximinophthalimide (14). o-Cyano-α-nitrotoluene (**2b**) (0.54 g, 2.1 mmol), potassium acetate (0.023 g, 0.2 mmol) and 25 ml of 95% ethanol were refluxed 3 hr. The solution was placed in the freezer to give 0.495 g (92%) of 3-oximinophthalimide, mp 220–225°. Two recrystallizations from 95% ethanol gave mp 255–256° (lit.[13] mp 256.5°); ir (KBr) 2800–3500 (NH and OH), 1715 (CO), and 1695 cm^{-1} (C=N); nmr (DMSO-d_6) δ 7.68 (s, 4, C_6H_4), and 11.12 (s, 2, NH and OH); mass spectrum (75 eV) *m/e* (rel intensity) 162 (100).

Registry No.—**1a,** 104-85-8; **1b,** 529-19-1; **1c,** 599-69-9; **1d,** 640-57-3; **1e,** 643-65-2; **2a,** 42157-95-9; **2a** K salt, 53178-76-0; **2b,** 53178-77-1; **2b** K salt, 53178-78-2; **2c,** 53178-79-3; **2c** Na salt, 53178-80-6; **2d,** 53178-81-7; **2d** Na salt, 53178-82-8; **2e,** 53178-83-9; **2e** K salt, 53178-84-0; **2f,** 1610-26-0; **2g,** 622-42-4; **6,** 42138-78-3; **6** K salt, 53178-85-1; **8,** 53178-86-2; **14,** 29833-90-7; **15a,** 6292-62-2; **15c,** 53178-87-3; **15d,** 13333-14-7; **15e,** 53178-88-4; **15f,** 2501-02-2; **15g,** 588-59-0; potassium amide, 17242-52-3; sodium amide, 7782-92-5; diphenylmethane, 101-81-5; propyl nitrate, 627-13-4; p-cyano-α,α-dibromo-α-nitrotoluene, 53178-89-5; p-cyano-α,α-dichloro-α-nitrotoluene, 53178-90-8; o-cyano-α,α-dibromo-α-nitrotoluene, 53178-91-9; p-N,N-dimethylsulfonamido-α,α-dibromo-α-nitrotoluene, 53178-92-0; p-phenylsulfonyl-α,α-dibromo-α-nitrotoluene, 53178-93-1; p-benzoyl-α,α-dibromo-α-nitrotoluene, 53178-94-2; p-cyano-α-bromo-α-nitrotoluene, 53178-95-3.

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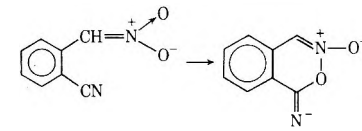

when the potassium salt of **2b** was recrystallized from 95% ethanol does not support this suggestion.

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6α-Substituted Penicillins

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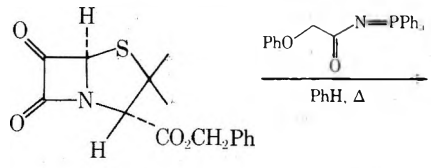
Syntheses of 6α-methoxy-6β-phenoxyacetamidopenicillanic acid and 6α-cyano-6β-phenoxyacetamidopenicillanic acid from benzyl 6-oxopenicillanate are reported. Both compounds showed weak antibacterial activities.

Syntheses of 6-methoxypenicillin have been reported[1-3] from a number of laboratories. In addition, alkyl,[4] hydroxyalkyl,[4] thioalkyl,[5] hydroxy,[1c] formyloxy,[1c] fluoro,[1c] azido,[1c] and cyano[1c] derivatives have been reported. Many of these syntheses depend on addition of the proper nucleophile to the *N*-acylimine **2** generated by halogenation and elimination.

This intermediate has been synthesized from 6-OPA (6-oxopenicillanic acid) benzyl ester **1** by a route analogous to the synthesis of the 6β-carbon analog of penicillin.[6]



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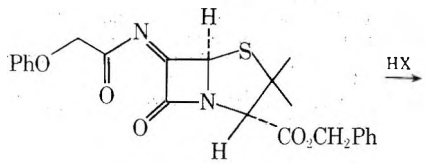

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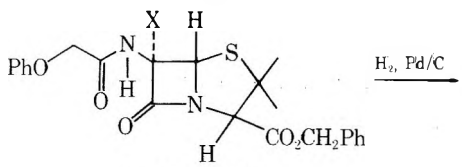
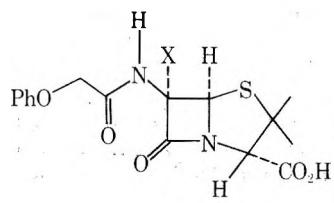
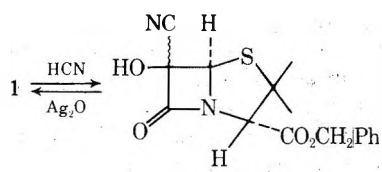


3a, X = OCH_3
b, X = CN



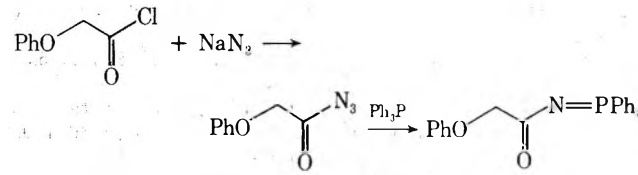
4

Impure 6-OPA benzyl ester is satisfactory for the syntheses of 6-carbon[6] and 6-oxygen[7] analogs of penicillins. However, condensation with a nitrogen Wittig requires a relatively pure sample of 6-OPA benzyl ester due to the high reactivity of the intermediate *N*-acylimine **2** toward nucleophiles. Purification of **1** was accomplished by forming the crystalline cyanohydrin derivative **5**. Treatment of



5

5 with silver oxide gives pure **1**. *N*-Phenoxyacetyliminotriphenylphosphorane was prepared from the azide.



Condensation of the phosphorane with **1** gave the *N*-acylimine **2** as a thermally stable compound. Comparison of the ir and nmr spectra of the reaction product mixture containing **2** with those of starting materials allowed the following signals to be assigned for the acylimine: ir (film), 1785 (β-lactam), 1735 (ester), 1715 (C=O of acylimine), 1695 cm^{-1} (imine); nmr ($DCCl_3$) δ 5.75 (s, H-5), 4.65 (s, H-3), 4.75 ppm (s, CH_2 of acylimine group).

Addition of methanol or liquid hydrogen cyanide to the cooled reaction mixture containing **2** gave the substituted penicillins **3**. In both cases, addition occurred from the less-hindered side of **2** to give the α-substituted penicillins **3**.

Both 6α-methoxy-6β-phenoxyacetamidopenicillanic acid (**4a**) and 6α-cyano-6β-phenoxyacetamidopenicillanic acid (**4b**) showed weak antibacterial activities.

Experimental Section

Melting points were determined on a Fisher-Johns melting point apparatus. Elemental analyses were performed by Galbraith Microanalytical Laboratories, Knoxville, Tenn. Ir spectra were recorded on a Perkin-Elmer 237 spectrophotometer. Nmr spectra were taken on a Varian T-60 spectrometer and are reported in parts per million downfield from TMS.

Benzyl 6-Cyano-6-hydroxypenicillanate (5). Liquid hydrogen cyanide was made according to the method of Vogel.[9] It was transferred to a flask containing the oily benzyl 6-oxopenicillanate (2.04 g) and a few crystals of sodium cyanide. A solid was formed rapidly. The mixture was left at 0° for 0.5 hr and then at room temperature to evaporate excess hydrogen cyanide. Final residual hydrogen cyanide was removed at reduced pressure. The solid was collected and washed with benzene to give 1.10 g product (54% from the crude starting material). After recrystallization from methylene chloride, a white, shiny crystalline compound was obtained: mp 148–160° dec; $[\alpha]^{25}D$ +185° (c 0.545, $CHCl_3$); ir (KBr) 3300, 1790, 1730 cm^{-1}; nmr ($DCCl_3$) 7.50 (s, 5 H), 5.90 (s, 1 H), 5.35 (s, 2 H), 4.70 (s, 1 H), 3.10 (s, 1 H), 1.63 (s, 3 H), 1.50 ppm (s, 3 H).

Anal. Calcd for $C_{16}H_{16}O_4N_2S$: C, 58.00; H, 4.83; N, 8.48; S, 9.64. Found: C, 58.09; H, 4.79; N, 8.47; S, 9.59.

Benzyl 6-Oxopenicillanate (1). Benzyl 6-cyano-6-hydroxypenicillanate (3.3 g) was dissolved in 350 ml of CH_2Cl_2. Sodium sulfate (3.5 g) and silver oxide (5 g) were added with stirring at 20°. After 24 hr, charcoal was added and stirred 1 hr. Filtration and evaporation gave a brown oil which was redissolved in 300 ml of benzene and treated with charcoal for 2 hr. Filtration and evaporation gave a yellow oil: 2.89 g, 95% yield; ir (film) 1830, 1780, 1735 cm^{-1}; nmr ($DCCl_3$) 7.40 (s, 5 H), 5.85 (s, 1 H), 5.30 (s, 2 H), 4.87 (s, 1 H), 1.55 (s, 3 H), 1.48 ppm (s, 3 H).

***N*-Phenoxyacetyliminotriphenylphosphorane.** Phenoxyacetyl chloride (8.5 g) was dissolved in acetone (15 ml) and cooled. Sodium azide (4 g) in water (25 ml) was added dropwise with stirring over 45 min. Stirring was continued for an additional 30 min. A white precipitate was formed during addition. Ice–water was added to bring out more precipitate which was collected by filtration and dried in a desiccator, 8.2 g.

The dry product (5 g) in benzene (20 ml) was added dropwise to a heated, stirred solution of triphenylphosphine (9 g) in benzene (50 ml) over 20 min followed by refluxing for 30 min. After cooling,

filtering, and evaporation, a white solid was obtained which was recrystallized from benzene–petroleum ether: 11 g; mp 121–122°; ir (KBr) 3040, 1580, 1485, 1435, 1360, 1220, 1110, 820 cm^{-1}; nmr ($DCCl_3$) 7.80–6.65 (m, 20 H), 4.70 ppm (s, 2 H).

Condensation and Subsequent Addition of HX. Pure benzyl 6-oxopenicillanate and 3 equiv of *N*-phenoxyacetyliminophosphorane were refluxed in benzene for 44 hr. To the cool mixture an excess amount of HX was added rapidly. The solvent was removed to give a brown syrup which was purified by chromatography.

Benzyl 6α-methoxy-6β-phenoxyacetamidopenicillanate: 42% yield; R_f 0.41 (1:20 Et_2O–CH_2Cl_2); ir (film) 3330, 1780, 1745, 1695, 1600, 1500, 1325, 1215 cm^{-1} nmr ($DCCl_3$) 7.62 (s, br, 1 H), 7.35–6.85 (m, 10 H), 5.62 (s, 1 H), 5.17 (s, 2 H), 4.52 (s, 2 H), 4.45 (s, 1 H), 3.48 (s, 3 H), 1.40 (s, 3 H), 1.36 ppm (s, 3 H); $[\alpha]^{25}D$ +213° (c 0.92, $CHCl_3$).

Anal. Calcd for $C_{24}H_{26}N_2SO_6$ (470.54): C, 61.26; H, 5.57; N, 5.95; S, 6.81. Found: C, 61.44; H, 5.70; N, 6.04; S, 6.77.

Benzyl 6α-cyano-6β-phenoxyacetamidopenicillanate: 36% yield; R_f 0.43 (1:30 Et_2O–CH_2Cl_2); ir (film) 3300, 1795, 1740, 1695, 1600, 1500, 1315, 1215 cm^{-1}; nmr ($DCCl_3$) 7.62 (s, 1 H), 7.40–6.85 (m, 10 H), 5.88 (s, 1 H), 5.21 (s, 2 H), 4.60 (s, 2 H), 4.52 (s, 1 H), 1.38 ppm (s, 6 H); $[\alpha]^{25}D$ +179° (c 0.94, $CHCl_3$).

Anal. Calcd for $C_{24}H_{23}N_3SO_5$ (461.51): C, 61.92; H, 4.98; N, 9.03; S, 6.89. Found: C, 61.79; H, 5.04; N, 8.89; S, 6.76.

Hydrogenolysis of Benzyl Esters. The benzyl ester was hydrogenated in ethyl acetate over 10% palladium on charcoal for 4 hr at room temperature and 1 atm pressure. The resulting mixture was filtered and the filtrate was extracted twice with cold 1*N* potassium bicarbonate solution. The combined aqueous extracts were washed once with ether and cooled to 0°. Ether was added and the stirred mixture was acidified to pH 2 by slow addition of 12*N* hydrochloric acid. The ether layer was separated and the aqueous layer extracted three times with ether. The organic phase was washed with distilled water, dried (Na_2SO_4), and evaporated to yield an oil. This oil, after freeze-drying from benzene, gave a white solid as the product.

6α-Methoxy-6β-phenoxyacetamidopenicillanic acid: 68% yield; ir ($CHCl_3$) 3380, 1780, 1725, 1695, 1600, 1495, 1205 cm^{-1}; nmr ($DCCl_3$) 8.20 (s, br, 1 H), 7.68 (s, 1 H), 7.36–6.86 (m, 5 H), 5.60 (s, 1 H), 4.58 (s, 2 H), 4.45 (s, 1 H), 3.53 (s, 3 H), 1.55 (s, 3 H), 1.50 ppm (s, 3 H).

6α-Cyano-6β-phenoxyacetamidopenicillanic acid: 58% yield; ir ($CHCl_3$) 3380, 1795, 1725, 1695, 1600, 1490, 1235 cm^{-1}; nmr ($DCCl_3$) 8.40 (s, br, 1 H), 7.60 (s, 1 H), 7.38–6.86 (m, 5 H), 5.88 (s, 1 H), 4.62 (s, 2 H), 4.52 (s, 1 H), 1.57 (s, 3 H), 1.42 ppm (s, 3 H).

Acknowledgment. This work was assisted financially by the Sloan Basic Research Fund.

Registry No. —1, 39126-59-5; **2**, 53198-76-8; **3a**, 35353-37-8; **3b**, 53198-77-9; **4a**, 35353-34-5; **4b**, 53198-78-0; **5**, 39486-17-4; *N*-phenoxyacetyliminotriphenylphosphorane, 53229-99-5, phenoxyacetyl chloride, 4461-31-8; sodium azide, 26628-22-8; triphenylphosphine, 603-35-0.

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Ligantrol and Ligantrol Monoacetate, Two New Linear Polyoxygenated Diterpenes from *Liatris elegans*[1]

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The geranylnerol derivative ligantrol (**1a**) and its monoacetate (**1b**) have been isolated from *Liatris elegans* (Walt.) Michx. and their structures established. The absolute stereochemistry assigned to C-11 and C-14 (11*R*, 14*S*) was deduced by degradation to a known lactone **16** of established absolute configuration.

As part of our study of the genus *Liatris* (tribe Eupatoriae, Compositae)[1a,2] which elaborates various cytotoxic and antitumor sesquiterpene lactones[3-5] we have examined *Liatris elegans* (Walt.) Michx.,[6] a species widely distributed in the Southern U.S. In the present communication we report isolation and structure determination of ligantrol (**1a**) and ligantrol monoacetate (**1b**), two highly oxygenated linear diterpenes, which are derivatives of geranylnerol. Future reports will deal with sesquiterpene lactones of this and other *Liatris* species.

Ligantrol, $C_{20}H_{36}O_5$, was obtained as a gum, $[\alpha]^{25}D$ +5.1°, and attempts to crystallize it were unsuccessful. It had ir bands at 3400, 1600, 1085, and 960 cm^{-1} and only end absorption in the uv. Ligantrol and the naturally occurring ligantrol monoacetate (**1b**), $[\alpha]^{25}D$ +25°, on acetylation with acetic anhydride–pyridine furnished the same triacetate (**1d**), $[\alpha]^{25}D$ −4.3°, which had ir bands at 3500, 1735, 1660, 1240, 1060, and 900 cm^{-1}. It was clear from these results that ligantrol had three acylable hydroxyl groups; as the ir spectrum of the triacetate still exhibited hydroxyl absorption, the other two oxygens had to be two tertiary hydroxyls or one tertiary hydroxyl and one ethereal oxygen. Since **1d** was not attacked by $CrO_3 \cdot 2Py$, the possibility of a hindered secondary hydroxyl group was ruled out.

The cmr spectrum of ligantrol (Figure 1) proved to be very helpful at this stage. The noise-decoupled spectrum accounted for all 20 carbon atoms and was also indicative of purity, as the decoupled spectrum of a mixture would have given rise to extra signals. The off-resonance decoupled spectrum displayed, in addition to ten difficult-to-disentangle signals, apparently all multiplets, in the range 23.3–32.3 ppm[9] downfield from TMS, two doublets (125.3 and 127.7) and two singlets (138.4 and 139.1 ppm)

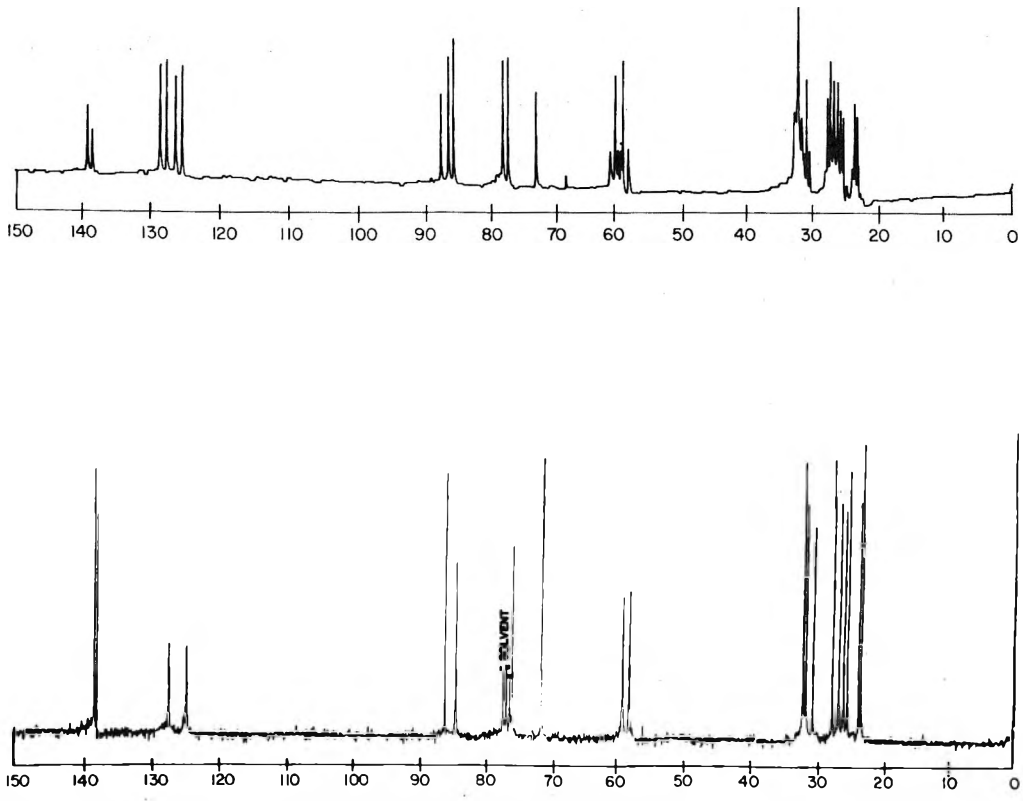
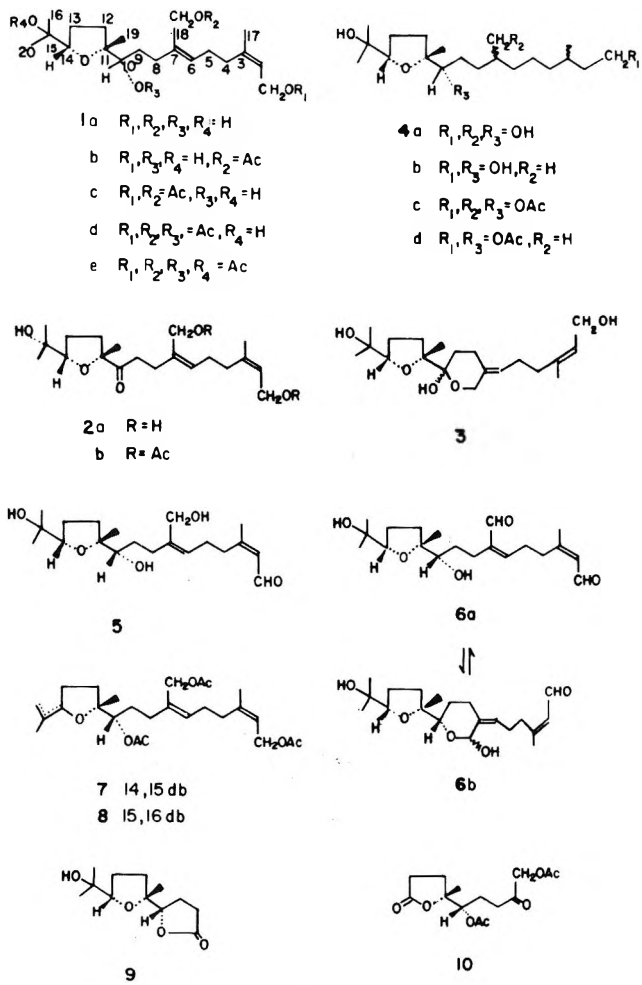
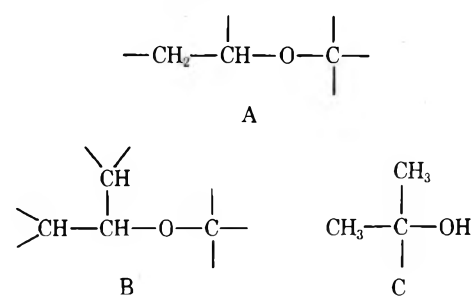


Figure 1. Top, off-resonance decoupled cmr spectrum of ligantrol. Bottom, noise-decoupled cmr spectrum of ligantrol.



which clearly indicated the presence of two trisubstituted double bonds. Six signals in the range 58.6–86.3 revealed that the five oxygen atoms of ligantrol are attached to six carbon atoms which is only possible if one of the oxygens is present as an ether function. The off-resonance spectrum further classified these carbons as two primary (triplets at 58.5 and 59.6), two secondary (doublets at 76.3 and 84.7), and two tertiary (singlets at 71.8 and 86.3 ppm).

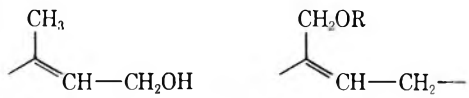
The pmr spectrum of ligantrol (Table I) indicated that the two trisubstituted and unconjugated (because of the lack of uv absorption) double bonds were of the type $>C{=}CHCH_2$ because of the presence of two slightly broadened vinyl triplets near 5.4 ppm. One of these carried a vinyl methyl group as evidenced by a narrowly split multiplet at 1.72 ppm. Comparison of the pmr spectra of **1a, 1b,** and **1d** (Table I) further demonstrated that the three acetylable hydroxyl groups were of the type $>CHCH_2OH$, $>CCH_2OH$, the latter acetylated in ligantrol monoacetate and both giving rise to the cmr triplets at 58.7 and 59.8 ppm, and $>CHCH(OH)CH<$ or $>CCH(OH)CH_2$, this giving rise to the cmr doublet at 76.4 ppm.[10] The chemical shift of a sharp triplet near 3.8 ppm which was unaffected by acylation and oxidation suggested the presence of a cyclic or acyclic ether of type A or B rather than an oxirane.[12] Presumably, this function was also responsible for the cmr doublet at 84.8 and the singlet at 86.3.[10]



Lastly the observation of three methyl singlets gave rise to the suspicion that the tertiary hydroxyl group was included in partial structure C which would be responsible for the remaining carbon signal in the C–O region, the sin-

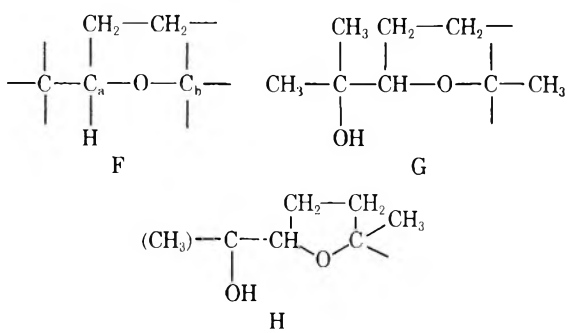
glet at 71.8 ppm.[10] Indeed, acetylation under stringent conditions (BF_3–Ac_2O) produced a tetraacetate **1e**[13] whose pmr spectrum (Table I) displayed two of the three methyl signals at considerably lower field consonant with this hypothesis; simultaneously, the ethereal proton had experienced a paramagnetic shift of 0.2 ppm, an observation which indicated its proximity to the tertiary hydroxyl group.

Decoupling experiments on ligantrol monoacetate **1b** revealed that the two primary alcohol functions were attached to the olefinic systems as in D and E. Thus, irradia-



D E, R = H or Ac

tion at the frequency of the superimposed vinyl protons collapsed the two-proton signal at 4.11 ppm (D) to an AB quartet and the two-proton signal at 4.60 ppm (E) to a singlet, while also effecting some changes in the region of the allylic methylenes. Conversely, irradiation at 4.11 ppm collapsed one of the vinyl triplets, the other remaining undisturbed, while irradiation at 3.53 (CHOH) only caused some changes in the methylene region. In addition, irradiation at the frequency of the ethereal proton (3.79 ppm) changed a two-proton multiplet at 1.88 to a triplet while irradiation in the reverse sense, *i.e.*, at 1.88 ppm, collapsed the triplet at 3.79 ppm to a singlet and affected the methylene region as well. Thus part structure A, not B, was correct and could be expanded to F where C_a most likely represented the point of attachment of partial structure C. If this were so, the remaining tertiary methyl group had to be located on C_b as in G.

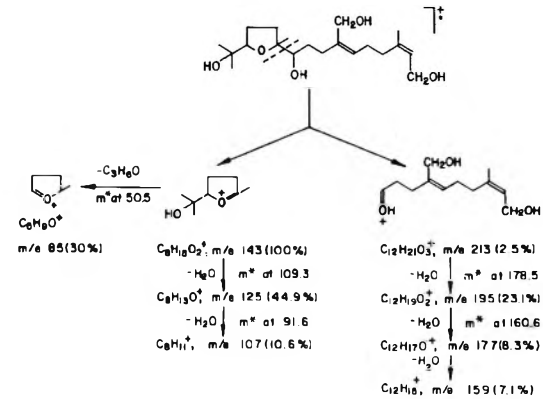


F G H

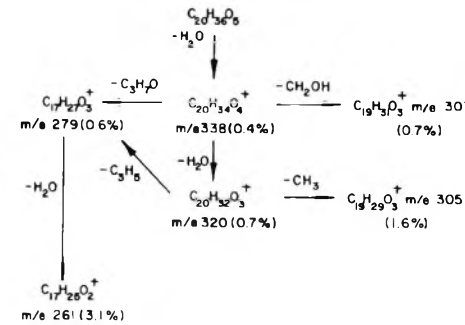
Formulas **1a** and **1b** (exclusive of stereochemistry) were biogenetically plausible structures for ligantrol and its monoacetate which incorporated the various partial structures and satisfied all other requirements. Their correctness was demonstrated unambiguously by the following transformations.

Catalytic hydrogenation of ligantrol furnished two products, **4a** by saturation of both double bonds and **4b**, a minor product, by concomitant hydrogenolysis of partial structure E. Comparison of the high-resolution mass spectra of **1a**, **4a**, and **4b** (see Schemes I–IV which are supported by metastable ions where indicated) revealed the following facts. While each substance gave rise to the same base peak at *m/e* 143 representing the ion $C_8H_{15}O_2$ which underwent loss of H_2O to $C_8H_{13}O$ or decomposition to C_5H_9O (*m/e* 85), another series of transitions in the mass spectrum of ligantrol, $C_{12}H_{21}O_3 \rightarrow C_{12}H_{19}O_2 \rightarrow C_{12}H_{17}O \rightarrow C_{12}H_{15}$, was shifted 4 mass units higher in the mass spectrum of **4a** and 12 mass units lower in the mass spectrum of **4b** and was much reduced in intensity. Thus, the most prominent re ult of electron impact on ligantrol appeared to be fragmentation into two "halves," one, the

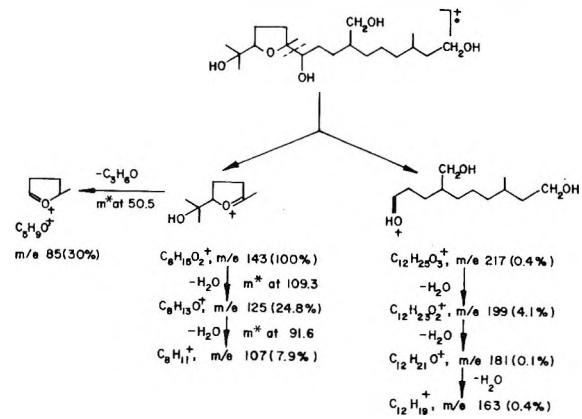
Scheme I
Mass Spectral Fragmentation of Ligantrol (A)



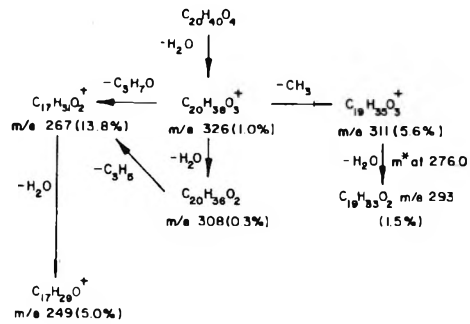
Scheme II
Mass Spectral Fragmentation of Ligantrol (B)



Scheme III
Mass Spectral Fragmentation of Tetrahydroligantrol



Scheme IV
Mass Spectral Fragmentation of 4b



$C_{12}H_{21}O_3$ portion, including partial structures D and E in some combination with C_4H_8O, the second, $C_8H_{15}O_2$, accounting for all the atoms of partial structure G. Ring closure of G to H provided an obvious rationalization of this

Table I
Pmr Spectra of Ligantrol and Derivatives[a]

Compd	H-1	H-2	H-6	H-10	H-14	H-17[b]	H-18	Me[b]	Ac[b]
1a	4.06[c]	5.38 t br (7)	5.38 t br (7)	3.56 dd (10, 3)	3.78 t (6.5)	1.72 m	4.11 br[d]	1.11, 1.14 1.25	
1b	4.11[c]	5.45 t br (7)	5.45 t br (7)	3.53 dd (10, 3)	3.79 t (6.5)	1.71 m	4.60 br[d]	1.13, 1.13 1.25	2.06
1c	4.54[c]	5.40 t br (7)	5.40 t br (7)	3.52 dd (10, 3)	3.80 t (6.5)	1.75 m	4.58 br[d]	1.13, 1.15 1.26	2.05 2.05
1d	4.52[c]	5.38 t br (7)	5.38 t br (7)	4.90 dd (10, 3)	3.74 t (6.5)	1.73 m	4.57 br[d]	1.09, 1.17 1.17	2.01, 2.03 2.05
1e	4.52[c]	5.36 t br (7)	5.36 t br (7)	4.90 dd (10, 3)	4.00 t (6.5)	1.73 m	4.56 br[d]	1.16, 1.40 1.44	1.96, 2.02 2.04
2b	4.51	5.38 t br (7)	5.38 t br (7)		3.88 t (6.5)	1.71 m	4.56 br[d]	1.08, 1.27 1.37	2.01 2.03
4c	4.10 t (6.5)[d]			4.89 dd (8, 2)	3.74 t (6.5)	0.90 d (6)	3.95 d (6)	1.12, 1.20 1.20	2.05, 2.05 2.07
4d	4.09 t (6.5)[d]			4.90 dd (8, 2)	3.74 t (6.5)	0.90 d (6)	0.85 d[b] (6)	1.12, 1.18 1.18	2.04 2.07
5	9.85 d (8)	5.88 d br (8)	5.27 t br (7)	3.47 dd (6.5)	3.74 t (1)	1.90[d]	4.05[c]	1.03, 1.06 1.19	
6a	9.88 d (8)	5.98 d br (8)	6.50 t br (7)	3.40 dd (10, 3)	3.77 t (6.5)	1.98 d (1.5)	10.06	1.08, 1.10 1.25	
6b	9.86 d (8)	5.80 d (8)	5.17 t br (7)	4.14 dd (10, 3)	3.79 t (6.5)	1.94 d (1.5)	5.77 br	1.08, 1.14 1.25	
7	4.52[c]	5.36 t br (7)	5.36 t br (7)	4.88 dd (10, 3)		1.73 m	4.56 br[d]	1.22 1.66 br, 1.66 br	2.02, 2.03 2.04
9				4.40 t (7)	3.80 t (6.5)			1.07, 1.10 1.10	
10				4.91 dd (10, 3)			4.58 br[d]	1.34	2.01, 2.08

[a] Run at 90 or 270 MHz in $CDCl_3$ solution using TMS as internal standard. Values are in parts per million. Multiplicities are indicated by the usual symbols: d, doublet; t, triplet; br, broadened singlet; m, multiplet whose center is given. Unmarked signals are singlets. Figures in parentheses are line separations or coupling constants in hertz. [b] Intensity three protons. [c] Intensity two protons. Center of AB part of ABX system. [d] Intensity two protons.

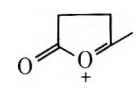
behavior in terms of the characteristic α fission of α-substituted tetrahydrofurans[14] depicted in Schemes I and III.

Selective acetylation of **1b** to **1c** (room temperature, 10 min), followed by oxidation with Collins reagent gave an unconjugated ketodiacetate **2b** which did not react with periodic acid. The oxidation also resulted in a significant downfield shift of one of the methyl signals (Table I), an observation which suggested that the new carbonyl group was attached to the one still available position of partial structure H. Hydrolysis of **2b** gave a substance whose ir and pmr spectrum (Table I) indicated its existence mainly in the hemiketal form 3 rather than in the ketodiol form **2a**. This facile formation of a hemiketal required interposition of four or five carbon atoms between the primary hydroxyl group of E and the secondary hydroxyl.

The same conclusion was reached by oxidation of ligantrol with activated MnO_2. This gave the terminal α,β-unsaturated aldehyde **5** and a second product whose pmr spectrum (Table I) showed that it was an equilibrium mixture of the bis-α,β-unsaturated dialdehyde **6a** and the aldehydic hemiacetal **6b**, as the result of interaction between the secondary hydroxyl group and the aldehyde formed by oxidation of partial structure E.

Ozonolysis of ligantrol followed by cleavage of the intermediate ketol with sodium metaperiodate resulted in formation of a γ-lactone $C_{12}H_{20}O_4$, $[\alpha]^{25}D$ +37.5°, whose pmr and high-resolution mass spectrum (α fission to *m/e* 143) retained all the features previously attributed to partial structure H. In addition, the lactone hydrogen now appeared as a sharp triplet at 4.40 ppm (Table I). The only structure compatible with these properties was **9**, a formula also fully consonant with the cmr spectrum.[15] The formation of **9** by loss of eight carbon atoms requires presence of the sequence C-1 through C-7 in the ligantrol formula and leads unequivocally to gross structure **1a**.

Confirmation for the substitution on the tetrahydrofuran ring of ligantrol was provided as follows. Dehydration of **1d** with thionyl chloride–pyridine gave a mixture of **7** and **8** (pmr spectrum). Ozonolysis of the mixture and chromatography permitted isolation and characterization of the diacetate **10** of a ten carbon γ-lactone whose pmr spectrum exhibited only one methyl resonance (singlet) and lacked the characteristic triplet of H-14. Moreover, the base peak in the high-resolution mass spectrum now corresponded to ion L (*m/e* 99, $C_5H_7O_2$) arising from α fission in **10**.



L

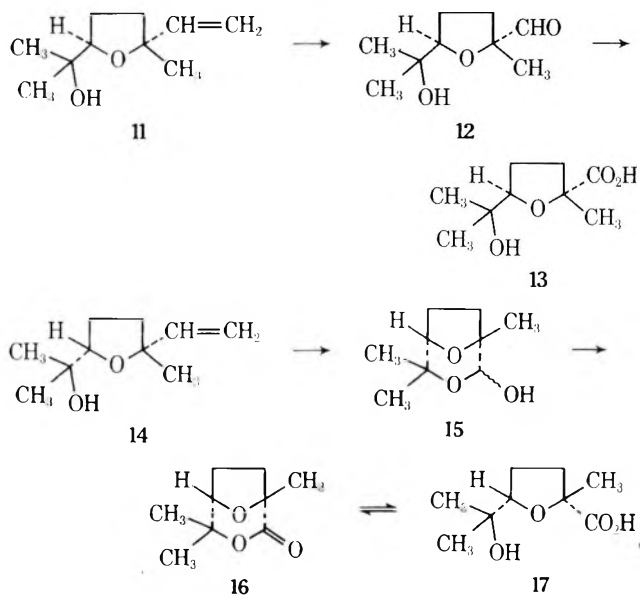
The stereochemistry attributed to ligantrol is based on the following observations. (1) The *Z* or nerol configuration around C-2–C-3 is evident because (a) the resonance of the methyl group on C-3 in **1a–e, 2b,** and **7** is in the range 1.71–1.75 ppm as in *cis,trans*-farnesol rather than near 1.64 ppm as in geraniol and *trans,trans*-farnesol;[16] (b) in the nmr spectra of the aldehydes **5, 6a,** and **6b,** the narrowly split vinylic methyl signal is found in the range 1.90–1.98 ppm, characteristic of the *Z* configuration, rather than at 2.15–2.18 ppm appropriate for the *E* configuration;[17] (c) in the cmr spectra of **1a** and **1b,** the absence of signals upfield from 23.3 ppm and from the region near 40 ppm indicates a

cis relationship of H-2 and the C-3 methyl group.[18]

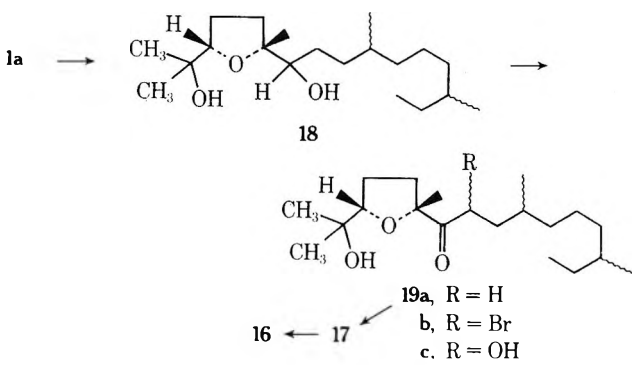
(2) The *Z* configuration around the C-6–C-7 double bond is evident from the pmr spectrum of **6a.** The chemical shift of the aldehyde proton on C-18 (10.06 ppm) is indicative of a trans relationship between the aldehyde function and the vinylic hydrogen, *cis*-aldehydes of this substitution pattern giving rise to signals in the range 9.26–9.4 ppm.[19]

(3) The absolute configuration of C-10 as *S* was established by applying Horeau's method[21] to **1c.** The optical yield of the recovered (*R*)-(−)-α-phenylbutyric acid was 8%.

(4) Kovàts and coworkers[22] differentiated between *cis*-(2*R*,5*S*)-and *trans*-(2*R*,5*R*)-2-methyl-2-vinyl-5-(α-hydroxyisopropyl)tetrahydrofuran as follows. Osmium tetroxide–periodate oxidation of the trans isomer **11** gave the aldehyde **12** and thence the acid **13,** whereas oxidation of the cis isomer **14** afforded a substance which was entirely in the hemiacetal form **15.** This could be oxidized to a lactone **16** which was interconvertible with an acid **17.** Since the hydroxyketodiacetate **2b** which is a homolog of either **12** or **14** exists entirely in the ketol, not the hemiketal, form, since the corresponding ketotriol is mainly in the hemiacetal form **3** and since treatment of **1d** or **4c** with BF_3–acetic anhydride results in acetylation rather than cyclic ether formation, we originally inferred that the two side chains on the tetrahydrofuran ring of ligantrol were trans (*i.e.* 11*R*,14*R* or 11*S*,14*S*) rather than cis.[23] However, eventual degradation of ligantrol to **16** demonstrated that it had the cis (11*R*,14*S*) absolute stereochemistry depicted in the formulas. This was accomplished as follows.

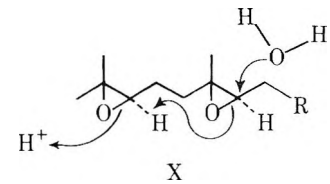


Catalytic hydrogenation of ligantrol (Pt, acetic acid) resulted in hydrogenolysis to **4b** and a mixture of isomers **18.**



Oxidation of **18** to **19a,** followed by bromination to **19b,** hydrolysis to **19c,** and subsequent cleavage with periodate gave a solid acid, presumably identical with **17.**[24] On heating, this was converted to a lactone whose physical properties and rotation corresponded to those reported[22] for **16.** Direct comparison established identity.

The functionalization of ligantrol at C-10, C-11, C-14, and C-15 is such that a biogenetic pathway involving at some stage the hydration of a 10,14-diepoxide or its biological analog appears plausible (see structure X below). If the diepoxide is derived from an all-trans or a cis,trans,trans precursor, as seems logical, *S* stereochemistry at C-10 and C-14 and *R* stereochemistry at C-11 of the eventual product coupled with mechanistic considerations (enzymatic trans hydration of a C-10,C-11 epoxide and inversion at C-14)[25,26] indicates that the hypothetical precursor diepoxide should possess the stereochemistry shown in structure X.[27]



Although tetrahydrofurans derived from farnesol are common, ligantrol appears to be the first diterpene of this genre. Moreover, the few linear diterpene alcohols so far known are derivatives of geranylgeraniol rather than geranylnerol.

Experimental Section[27]

Isolation of Ligantrol (1a) and Ligantrol Monoacetate (1b). *Liatris elegans* (Walt.) Michx., wt 21.9 kg, collected by Mr. R. L. Lazor on Sept 23, 1971 on the Sinkola plantation 4 miles west of the junction of U.S. 319 and State Road 755, Thomas Co., Georgia (Lazor no. 5586, voucher on deposit in herbarium of Florida State University), was extracted with chloroform and worked up in the usual manner.[28] The crude gum (80 g) was chromatographed over 1 kg of silicic acid (Mallinckrodt 100 mesh), 1-l. fractions being collected in the following order: 1–10 (benzene), 11–20 (benzene–$CHCl_3$, 5:1), 21–30 (benzene–$CHCl_3$, 1:1), 30–40 (benzene–$CHCl_3$, 1:5), 41–50 ($CHCl_3$), 51–60 ($CHCl_3$–MeOH, 20:1), 61–70 ($CHCl_3$–MeOH, 10:1), 71–80 ($CHCl_3$–MeOH, 5:1). All fractions were monitored by tlc. Fractions 12–18 yielded a crystalline sesquiterpene lactone whose constitution will be discussed elsewhere.

Fractions 52–59 on evaporation gave a gum which showed one major spot on tlc and was further purified by chromatography over silica gel. $CHCl_3$–MeOH (20:1) eluted 5 g of pure **1b:** $[\alpha]^{25}D$ +25° (*c* 1.2); ir bands at 3400 (OH), 1735, 1240 (acetate), 1660 (C=C), 1085, 1030 (C—O stretching), 960, 845 cm^{-1}. The low-resolution mass spectrum exhibited a weak molecular ion peak at *m/e* 398 and others at *m/e* 380 (M − H_2O), *m/e* 365, 362, and 338 (M − CH_3CO_2H). The high-resolution did not show the molecular ion but peaks at *m/e* (per cent, composition measured at high resolution) 365 (M − H_2O − CH_3) (0.3, $C_{21}H_{33}O_5$), 362 (M − H_2O − H_2O) (0.4, $C_{22}H_{34}O_4$), 338 (M − CH_3CO_2H) ($C_{20}H_{32}O_5$), 261 (2.4, $C_{17}H_{25}O_2$), 195 (0.3, $C_{12}H_{19}O_2$), 177 (1.8, $C_{12}H_{17}O$), 159 (4.6, $C_{12}H_{15}$), 143 (100, $C_8H_{15}O_2$), 125 (25.6, C_8H_3O), 107 (7. C_8H_{11}), 85 (17.4, C_5H_9O), 71 (18.9, C_4H_7O).

Anal. Calcd for $C_{22}H_{38}O_6$: C, 66.30; H, 9.61; O, 24.09. Found: C, 65.64; H, 9.69; O, 24.40.

Fractions 61–68 gave a gum which showed one major spot on tlc and was purified by chromatography over silica gel to give **1a** (10 g): homogeneous on tlc; $[\alpha]^{25}D$ +5.1° (*c* 0.6); ir bands at 3400 (hydroxyl), 1660 (double bond), 1085, 1020, 960, and 845 cm^{-1}. The elemental analysis was unsatisfactory. The high-resolution mass spectrum, whose main features are displayed in Schemes I and II, did not exhibit the molecular ion; the peak of highest mass number corresponded to $M^+ + 1$.

Anal. Calcd for $C_{20}H_{36}O_5$ (M + 1): mol wt, 357.2640. Found: mol wt (ms), 357.2642.

Acetylations of Ligantrol and Ligantrol Monoacetate. (A) Acetylation of 0.1 g of **1a** or 0.1 g of **1b** with 1 ml of acetic anhy-

dride and 0.5 ml of pyridine at room temperature for 24 hr followed by the usual work-up gave 0.1 g of **1d** as a gum: $[\alpha]^{25}D$ −4.3° (c 0.7); ir bands at 3500 (hydroxyl), 1735, 1240 (acetates), 1660 (C=C), 1060, 1030 (C—O stretching), 960, 900, and 850 cm^{-1}. The cmr spectrum exhibited signals due to 24 carbon atoms, 170.7 (two superimposed singlets, C=O) and 170.5 (singlet, C=O), 141.5 (C-7), 133.9 (C-3), 130.4 d (C-2), 120.0 d (C-6), 85.1 d (C-14), 84.1 (C-11), 77.2 d (C-10), 70.9 (C-15), 61.6 t and 60.9 t (C-1 and C-18), and 13 multiplets in the range 20.8–34.5 ppm downfield from TMS.

Anal. Calcd for $C_{26}H_{42}O_8$: C, 64.71; H, 8.77; O, 26.52. Found: C, 64.23; H, 8.63; O, 26.51.

When 0.1 g of **1d** was placed on a silica gel column (50 g) and eluted with methanol, hydrolysis to **1a** took place in quantitative yield.

(B) Exposure of **1a** or **1b** to acetic anhydride–pyridine at room temperature for 10 min followed by the usual work-up gave diacetate **1c** in 80% yield, together with triacetate **1d** (10%) and unreacted starting material (**1a** or **1b**, 10%). The diacetate **1c** was separated as an oil by preparative tlc on silica gel $PF_{254-355}$ (solvent benzene–ethyl acetate, 1:1). It had $[\alpha]^{25}D$ +9.0° (c 0.5); ir bands at 3420 (hydroxyl), 1725, 1240 (acetates), 1080, 1030 (C–O stretching), 955, 900, and 840 cm^{-1}.

Anal. Calcd for $C_{24}H_{40}O_7$: C, 65.43; H, 9.15; O, 25.47. Found: C, 65.25; H, 9.15; O, 25.52.

A solution of 0.360 g of α-phenylbutyric anhydride (1.16×10^{-3} mol) and 50 mg of **1c** (1.14×10^{-4} mol) in 2 ml was kept at room temperature for 48 hr. Excess anhydride was destroyed by addition of 5 ml of water. After 12 hr, the solution was extracted with ether which was washed with water and 5% $NaHCO_3$ solution. The combined aqueous layers were washed with chloroform, acidified with 1 *M* H_2SO_4, and extracted with chloroform. The washed and dried chloroform extracts were evaporated; the residue, wt 0.330 g, was pure α-phenylbutyric acid, $[\alpha]D$ −0.40°, which corresponded to an optical yield of 8%.

(C) A solution of 0.1 g of the triacetate **1d** in 3 ml of dry ether was cooled to 0°, mixed with 2 ml of freshly distilled acetic anhydride and 1.5 ml of freshly distilled BF_3–etherate, kept at 0° for 24 hr, poured into ice water, and extracted with $CHCl_3$. The washed and dried extract on evaporation gave a gum which showed two spots on tlc. It was separated by preparative tlc on silica gel $PF_{254-355}$ (solvent benzene–ethyl acetate, 2:1). The major component (0.07 g) was unreacted starting meterial **1d**; the minor component (0.01 g) was the tetraacetate **1e**: ir bands at 1730, 1235 (very strong, acetates), 1030 (C–O stretching), 950, and 880 cm^{-1}; mass spectrum *m/e* 524 (M^+, $C_{28}H_{44}O_9$), 464 (M − CH_3CO_2H), 422 (M − CH_3CO_2H − C_2H_2O), 404 (M − $2CH_3CO_2H$), 344 (M − $3CH_3CO_2H$), 284 (M − $4CH_3CO_2H$), 185 (80%, $C_{10}H_{17}O_3$ usual base peak, but acetylated), 125 ($C_8H_{13}O$), 43 (base peak, C_2H_3O).

Oxidation of 1c. To a solution of 0.1 g of the diacetate **1c** in 15 ml of methylene chloride was added dropwise, with magnetic stirring, 50 mg of CrO_3–2Py complex, the reaction being followed by tlc. All starting material had disappeared after 6 hr. The reaction mixture was diluted with methylene chloride, washed, dried, and evaporated. The residual gum was purified by preparative tlc (solvent benzene–ethyl acetate, 2:1) to give 70 mg of **2b**: $[\alpha]^{25}D$ +8.6° (c 0.7); CD curve λ_{max} 285 nm ([θ] +1890); ir bands at 3420 (hydroxyl), 1735, 1725, 1260 (acetates), 1710 (ketone), 1030, 960, 920, 900, and 850 cm^{-1}. Low-resolution mass spectrometry revealed the molecular ion peak at *m/e* 438; other major peaks were at *m/e* 420 (M − H_2O), 410 (M − CO), 392 (M − H_2O − CO), 379 (M − $C_2H_3O_2$), 320 (M − H_2O − $C_2H_4O_2$), 303, 285, 259, 143 (base peak), 125, 107, and 85.

Anal. Calcd for $C_{24}H_{38}O_7$: C, 65.73; H, 8.73; O, 25.54. Found: C, 65.55; H, 8.67; O, 25.76.

The material was hydrolyzed by allowing 0.1 g of **2b** to stand in a 10% solution of KOH in ethanol for 2 hr. Acidification followed by the usual work-up gave 75 mg of **2a** whose ir and pmr spectra showed that it was predominantly in the hemiketal form **3**: ir bands at 3400, 1705 (very weak), 1050, 1030, 900, and 840 cm^{-1}; pmr signals at 4.09 (2 p, AB of ABX, H-1), 5.38 t br (2 p, H-2 and H-6), 3.88 t (6.5, H-14), 1.73 m (30, H-17), 4.25 br (2 p, H-18), 1.20, 1.17, 1.03 (three tertiary methyls); mass spectrum *m/e* 354 (M^+, $C_{20}H_{34}O_5$). Other major peaks were at *m/e* 336 (M − H_2O), 318 (M − $2H_2O$), 305 (M − H_2O − CH_2OH), 143 (usual base peak), 125, 107, and 85.

Hydrogenation of Ligantrol. A solution of 0.2 g of ligantrol in 15 ml of ethyl acetate was hydrogenated at atmospheric pressure in the presence of 50 mg of PtO_2. After 5 hr the catalyst was filtered and washed with ethyl actetate. Evaporation of the combined filtrate and washings gave a gum which showed two spots on tlc and was separated by preparative tlc on silica gel $PF_{254-355}$ (solvent $CHCl_3$–MeOH, 9:1). The major component (R_f slightly less than starting material) was **4a**: $[\alpha]^{25}D$ −12.2° (c 0.8); ir bands at 3350, 1085, and 1060 cm^{-1}. The high-resolution mass spectrum did not exhibit the molecular ion; significant peaks (in addition to those shown in Scheme III), which paralleled peaks shown in Scheme II for **1a**, were at *m/e* 342 (0.2, $C_{20}H_{38}O_4$), 327 (0.2, $C_{19}H_{35}O_4$), 283 (0.7, $C_{17}H_{31}O_3$), 265 (1.3, $C_{17}H_{29}O$). Acetylation of **4a** in the usual manner gave **4c**, ir bands at 3450, 1735, 1240, and 1035 cm^{-1}.

Anal. Calcd for $C_{26}H_{46}O_8$: C, 64.17; H, 9.53; O, 26.30. Found: C, 64.12; H, 9.51; O, 26.45.

The minor component (R_f 0.8) was characterized as **4b**: $[\alpha]^{25}D$ +10.2° (c 0.22); ir bands at 3350, 1080, and 1060 cm^{-1}. The high-resolution mass spectrum did not exhibit the molecular ion. Significant peaks (in addition to those in Scheme IV) which paralleled those in Schemes I and III were at *m/e* 201 (5, $C_{12}H_{25}O_2$), 183 (0.3, $C_{12}H_{23}O$), 165 (0.5, $C_{12}H_{21}$), 143 (100, $C_8H_{15}O_2$), 125 (36.2, $C_8H_{13}O$), 107 (6.4, C_8H_{11}). Acetylation of **4b** in the usual manner gave **4d**: $[\alpha]^{25}D$ −7.5° (c 0.6); ir bands at 3450, 1735, 1240, 1060, and 1030 cm^{-1}.

Anal. Calcd for $C_{24}H_{44}O_6$: C, 67.26; H, 10.35; O, 22.40. Found: C, 67.22; H, 10.30; O, 22.73.

MnO_2 Oxidation of Ligantrol. A solution of 0.1 g of **1a** in 15 ml of spectral grade chloroform was stirred with 0.2 g of active MnO_2, the reaction being monitored by tlc. After 24 hr, the mixture was filtered and the MnO_2 washed repeatedly with chloroform. The combined filtrate and washings were evaporated and the residue separated by preparative tlc on silica gel $PF_{254-355}$ (solvent benzene–ethyl acetate, 1:2). The more polar material, R_f 0.3, yield 53 mg, was characterized as the trihydroxy aldehyde **5**: $[\alpha]^{25}D$ −9.7° (c 1.0); ir bands at 3500 (hydroxyl), 1650 (conjugated aldehyde), 108, 1040, 960, 900, 845, and 800 cm^{-1}; uv λ_{max} 240 nm (ϵ 10,500); low-resolution mass spectrum *m/e* 354 (M^+, $C_{20}H_{34}O_5$). Other major peaks were at *m/e* 336 (M − H_2O), 321 (M − H_2O − CH_3), 305 (M − H_2O − CH_2OH), 143 (base peak, $C_8H_{15}O_2$), 125 ($C_8H_{13}O$), 107 (C_8H_{11}), and 85 (C_5H_9O).

The pmr spectrum of the less polar material, R_f 0.6, which was obtained only in small yield (15 mg) showed it to be an equilibrium mixture of **6a** and **6b** (Table I). Treatment of a purified sample of the trihydroxyaldehyde **5a** with active MnO_2 gave a quantitative yield of the equilibrium mixture after 1 hr:[30] ir bands at 3400, 1650, and 1080 cm^{-1}; pmr spectrum in Table I, low-resolution mass spectrum *m/e* 352 (M^+, $C_{20}H_{32}O_5$). Other significant peaks were at *m/e* 334 (M − H_2O), 321 (M − CH_2OH), 143 (base peak), 125, 107, and 85.

Ozonolysis of Ligantrol. A solution of 0.4 g of **1a** in 50 ml of chloroform (Anal-R grade) was ozonized at −30° for 15 min. The solvent was removed at 40° on a rotary evaporator. The residue was dissolved in 15 ml of MeOH, allowed to stand with 0.5 g of sodium metaperiodate in 2 ml of water overnight, diluted with water, and extracted with $CHCl_3$. The washed and dried extracts were evaporated and the residue purified by preparative tlc (solvent $CHCl_3$–MeOH, 19:1) to give 0.1 g of **9**: $[\alpha]^{25}D$ +37.5° (c 1.1); ir bands at 3500 (hydroxyl), 1750 (γ-lactone), and 1060 cm^{-1}. The low-resolution mass spectrum gave the correct molecular ion peak at *m/e* 228; other major peaks were at *m/e* 213 (M − CH_3), 195 (M − CH_3 − H_2O), 169 (M − CO_2), 152, 143, 125, and 107, the last three typical of the "left" side of the molecule.

Anal. Calcd for $C_{12}H_{20}O_4$: mol wt, 228.1361. Found: mol wt (ms), 228.1348.

Degradation of 1c to 10. A solution of 0.2 g of **1c** in 3 ml of dry pyridine was cooled to 0° and mixed with 0.2 ml of thionyl chloride with efficient stirring, the reaction being followed by tlc. After 30 min starting material had disappeared. The mixture was decomposed with ice water and extracted with chloroform. The washed and dried extracts were evaporated; the residual gum showed one major spot on tlc. However, preparative tlc (solvent benzene–ethyl acetate, 2:1) and pmr analysis showed that the major spot corresponded to a mixture of **7** and **8**. The low-resolution mass spectrum exhibited significant peaks at *m/e* 464 (M^+, $C_{26}H_{40}O_7$), 284 (M − $3CH_3CO_2H$), 125, and 43. The mixture (100 mg) was dissolved in 40 ml of Anal-R chloroform and ozonized at −30° for 15 min. After addition of 5 ml of dimethyl sulfide to decompose the ozonide, the mixture was stirred at room temperature overnight. Removal of solvent gave a residue which was separated by preparative tlc (solvent benzene–ethyl acetate, 1:1) to give 10 mg of **10** as a pure substance (pmr spectrum). The low-resolution mass spectrum exhibited the molecular ion at *m/e* 300; other major peaks were at *m/e* 258 (M − C_2H_2O), 240 (M − CH_3CO_2H), 227 (M −

$C_2H_2O - C_2H_3O$), 201 (M − 99), 185 (M − $2C_2H_2O - C_2H_3O$), 167 (M − $CH_3CO_2H - C_2H_2O - C_2H_3O$), 99 (base peak).

Anal. Calcd for $C_{14}H_{20}O_7$: mol wt, 300.1209. Found: mol wt (ms), 300.1204.

Degradation of 1a to 16. A solution of 0.3 g of **1a** in 20 ml of acetic acid was hydrogenated at atmospheric pressure in the presence of 0.25 g of PtO_2. After 4 hr, the catalyst was filtered and washed with ethyl acetate. Evaporation of solvent furnished a gum which showed two spots on tlc and was separated by preparative tlc on silica gel (benzene–ethyl acetate, 2:1) into **4b** (0.1 g) and **18** (0.15 g). The latter had pmr signals at 3.80 t (J = 6.5 Hz, H-14), 3.5 m (H-10), 1.25, 1.15, 1.13 (3 methyl singlets), and 0.85–0.95 ppm (two methyl doublets and one methyl triplet).

Oxidation of 0.15 g in 5 ml of CH_2Cl_2 with 0.2 g of $CrO_3 \cdot 2Py$ complex for 24 hr with stirring, dilution with 50 ml of $CHCl_3$, washing, drying, and evaporation at reduced pressure gave, after preparative tlc over silica gel (benzene–ethyl acetate, 3:1), 0.105 g of **19a** which had pmr signals at 3.90 t (J = 6.5 Hz, H-14), 1.40, 1.33, 1.14 (three methyl singlets), and 0.85–0.95 ppm (two methyl doublets and one triplet).

To a solution of 0.1 g of **19a** in 2 ml of acetic acid was added dropwise a solution of 50 mg of bromine in 0.2 ml of acetic acid containing a trace of HBr. The bromine color was discharged quickly; after 5 min the mixture was diluted with water and extracted with $CHCl_3$. The washed and dried extract was evaporated and the gummy residue (**19b**) was purified by preparative tlc on silica gel (benzene–acetate, 3:1): yield 0.105 g; pmr signals at 5.0 m (H-9), 3.91 t (J = 6.5 Hz, H-14), 1.50, 1.34, 1.16 (three methyl singlets), and 0.85–0.95 ppm (two methyl doublets and one triplet).

A solution of 0.095 g of the bromoketone **19b** in 5 ml of ethanol was stirred at room temperature in a nitrogen atmosphere with 0.5 ml of a 5% ethanol potassium hydroxide solution, the reaction being monitored by tlc. After 25 min, when all of the starting material had disappeared, the mixture was diluted with water and extracted with $CHCl_3$. The washed and dried extract was evaporated and the residue purified by preparative tlc over silica gel (benzene–ethyl acetate, 2:1) to give 0.065 g of **19c** which had pmr signals at 4.5 m (H-9), 3.90 t (J = 6.5 Hz, H-14), 1.40, 1.34, 1.16 (three methyl singlets), and 0.85–0.95 ppm (two methyl doublets and one triplet).

A solution of hydroxy ketone **19c** in 3 ml of methanol was oxidized with 0.25 g of $NaIO_4$ in 1 ml of water at room temperature for 5 hr, diluted with water, and extracted with $CHCl_3$. Evaporation of the solvent gave a gum which was separated by tlc on silica gel (MeOH–$CHCl_3$, 4:1). The most polar component which exhibited streaking on the plate (carboxylic acid) was a solid (**17**): yield 25 mg; mp 104–105° (lit. 96–97°,[22a] 108–109°[22b]); pmr spectrum (270 MHz) 5.2–5.7 (2 H, OH), 3.98 m (H-14), 1.7–2.6 (4 H), 1.53, 1.36, 1.15 ppm (three methyl singlets).

Acid **17** was kept at 150° for 15 min. On cooling, the solid deposited on the neck of the flask (mixture of **16** and **17**) was washed out with $CHCl_3$ and separated by preparative tlc. The less polar material was **16**: yield 5 mg; mp 80–81° (lit. 83–84°[22a,b]); $[\alpha]^{22}D$ +35° ($CHCl_3$, c 0.5) [lit. $[\alpha]D$ +40° ($CHCl_3$, c 1)];[22b] pmr signals (270 MHz) at 4.1 dbr (J = 7 Hz, H-14), 1.6–2.25 (four protons), 1.58, 1.55, and 1.33 ppm (three methyl singlets). Tlc behavior and pmr spectrum of authentic material[22b] were identical.

Registry No.—**1a,** 53198-13-3; **1b,** 53198-14-4; **1c,** 53198-15-5; **1d,** 53198-16-6; **1e,** 53198-17-7; **2a,** 53198-18-8; **2b,** 53198-19-9; **3,** 53198-20-2; **4a,** 53198-21-3; **4b,** 53198-22-4; **4c,** 53198-23-5; **4d,** 53198-24-6; **5,** 53198-25-7; **6a,** 53198-26-8; **6b,** 53198-27-9; **7,** 53198-28-0; **8,** 53198-29-1; **9,** 53198-30-4; **10,** 53198-31-5; **16,** 53274-44-5; **17,** 53198-32-6; **18,** 53198-33-7; **19a,** 53198-34-8; **19b,** 53198-35-9; **19c,** 53198-36-0.

References and Notes

(1) (a) Part V in the series "Constituents of *Liatris* Species." For Part IV, see H. Wagner, M. A. Iyengar, and W. Herz, *Phytochemistry*, **12**, 2063 (1973). (b) This work was supported in part by U. S. Public Health Service Research Grant No. CA-13121 from the National Cancer Institute.

(2) W. Herz and I. Wahlberg, *Phytochemistry*, **12**, 429 (1973).

(3) W. Herz and I. Wahlberg, *Phytochemistry*, **13**, 1421 (1973); *errata*, **14**, 315 (1974).

(4) W. Herz and I. Wahlberg, *J. Org. Chem.*, **38**, 2485 (1973).

(5) S. M. Kupchan, V. H. Davis, T. Fujita, M. R. Cox, and R. F. Bryan, *J. Amer. Chem. Soc.*, **93**, 4916 (1971).

(6) In our earlier report on flavone glycosides of *Liatris* species,[1a] this species was erroneously referred to as *L. elegans* (Walt.) Kuntze, due to confusion with an earlier name *Lacinaria elegans* (Walt.) Kuntze[7] with which it is synonymous. The analysis of the volatile constituents of our collection of *L. elegans* by glc–mass spectrometry has been reported elsewhere.[8]

(7) (a) J. K. Small, "Manual of the Southeastern Flora," University of North Carolina Press, Chapel Hill, N. C., 1933; (b) L. O. Gaiser, *Rhodora*, **48**, 165, 216, 273, 331 (1946).

(8) K. Karlsson, I. Wahlberg, and C. R. Enzell, *Acta Chem. Scand.*, **27**, 1613 (1973).

(9) In the noise-decoupled spectrum (bottom of Figure 1), the ten singlets in this range were clearly visible, although the two lowest field signals at 32.3 and 32.0 ppm were almost superimposed.

(10) Assignments are based on predicted cmr shifts,[11] comparison of the chemical shifts in the cmr spectra of **1a, 1b,** and **9,** and selective single frequency decoupling of C-10 and C-14.

(11) G. C. Levy and G. L. Nelson, "Carbon-13 Nuclear Magnetic Resonance for Organic Chemistry," Wiley-Interscience, New York, N. Y., 1972.

(12) L. M. Jackman and S. Sternhell, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," 2nd ed, Pergamon Press, Elmsford, N. Y., 1969, p 199.

(13) The yield was only 15%, the remaining material being unchanged.

(14) H. Budzikiewicz, C. Djerassi, and D. H. Williams, "Structure Elucidation of Natural Products by Mass Spectrometry," Vol. II, Holden-Day, San Francisco, Calif., 1964, p 270.

(15) Aside from the signal of the carbonyl carbon at 176.6 ppm downfield from TMS, the low-field signals could be identified easily as arising from C-11 (singlet at 86.3), C-14 (doublet at 84.0), C-15 (singlet at 71.8)—all three essentially unchanged—and C-10 (doublet at 83.4, shifted downfield ~7 ppm from 1a). The remaining seven signals were in the range 21.8–33.9 ppm.

(16) R. B. Bates and D. M. Gale *J. Amer. Chem. Soc.*, **82,** 5749 (1960); R. B. Bates, D. M. Gale, and B. J. Gruner, *J. Org. Chem.*, **28,** 1086 (1963). For more recent examples, see G. Stork, M. Gregson, and P. A. Grieco, *Tetrahedron Lett.*, 1391 (1969); J. Meinwald, W. R. Thompson, T. Eisner, and D. F. Owen, *ibid.*, 3485 (1971).

(17) L. M. Jackman and R. H. Wiley, *J. Chem. Soc.*, 2886 (1960); P. B. Venuto and A. R. Day, *J. Org. Chem.*, **29,** 2735 (1964); K. T. Suzuki, N. Suzuki, and S. Nozoe, *Chem. Commun.*, 527 (1971); J. Meinwald, K. Opheim, and T. Eisner, *Proc. Nat. Acad. Sci. U. S.* **69,** 1208 (1972).

(18) M. Jautelat, J. B. Grutzner, and J. D. Roberts, *Proc. Nat. Acad. Sci. U. S.*, **65,** 288 (1970); D. E. Dorman, M. Jautelat, and J. D. Roberts, *J. Org. Chem.*, **36,** 2757 (1971). In the cmr spectra of geraniol and *trans,trans*-farnesol, the C-3 methyl frequency is 16.2–16.3 and the C-4 frequency is 40.0–40.1 ppm downfield from TMS.

(19) R. E. Klinck and J. B. Stothers, *Can. J. Chem.*, **44,** 45 (1966); E. Bertele and P. Schuedel, *Helv. Chim. Acta*, **50,** 2445 (1967); K. C. Chan, R. A. Jewell, W. H. Nutting, and H. Rapoport, *J. Org. Chem.*, **33,** 3382 (1968); A. F. Thomas and M. Ozainne, *Chem. Commun.*, **47** (1969); U. Schwieter and S. Liaaen-Jensen, *Acta Chem. Scand.*, **23,** 1057 (1969). In rigid systems, the aldehydic proton appears at slightly lower fields (9.45–9.6 ppm).[20]

(20) C. S. Barnes and J. W. Lodger, *Aust. J. Chem.*, **15,** 322 (1962); C. J. W. Brooks and G. H. Draffan, *Tetrahedron*, **25,** 2887 (1969); T. Kato, T. Suzuki, M. Tanemura, A. S. Kumanireng, N. Otoani, and Y. Kitahara, *Tetrahedron Lett.*, 1961 (1971).

(21) A. Horeau, *Tetrahedron Lett.*, 506 (1961); 965 (1962); A. Horeau and H. B. Kagan, *Tetrahedron*, **20,** 2431 (1964); W. Herz and H. B. Kagan, *J. Org. Chem.*, **32,** 216 (1967).

(22) (a) D. Felix, A. Melera, J. Seibl, and E. sz. Kovàts, *Helv. Chim. Acta*, **46,** 1513 (1973); (b) F. Klein, H. Farnow, and W. Rojahn, *Justus Liebigs Ann. Chem.*, **675,** 73 (1964); E. Klein and W. Rojahn, *Tetrahedron*, **21,** 2353 (1965). We wish to thank Dr. Klein for an authentic sample of compound **16.**

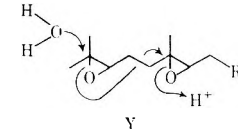
(23) Although in theory, this conclusion should have been verifiable by demonstrating the existence of NOE's between certain groups attached to the tetrahydrofuran ring, for example between H-16 and H-19, attempts to do so were frustrated by superposition or proximity of signals. No NOE was observed between H-10 and H-14, in accordance with expectations derived from inspection of models of cis and trans isomers.

(24) Due to the small scale on which the degradation was carried out, no attempt was made to purify **17,** especially since the literature values for the mp of **17** differ (see Experimental Section).

(25) D. M. Jerina, J. W. Daly, B. Witkop, P. Z. Nirenberg, and S. Udenfriend, *J. Amer. Chem. Soc.*, **90,** 6525 (1968); W. G. Niehaus, Jr., A. Kisic, A. Torkelson, D. J. Bedrarczyk, and G. J. Schroepfer, Jr., *J. Biol. Chem.*, **245,** 3802 (1970).

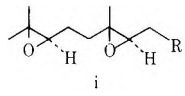
(26) Y. Suzuki, K. Imai, and S. Marumo, *J. Amer. Chem. Soc.*, 96, 3703 (1974). The demonstration by these workers that fungal predominantly trans hydration of racemic 10,11-epoxyfarnesol is accompanied by a small amount of overall cis opening of the epoxide ring is not considered to invalidate this argument.

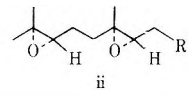
(27) The suggested scheme involves precominant nucleophilic attack on C-10 of the hypothetical precursor followed by intramolecular displacement at C-14 rather than initial nucleophilic attack on the tertiary center C-15 followed by displacement at C-11 (structure Y), in analogy with the



Y

observation of predominant nucleophilic attack on C-10 during the fungal hydration of 10,11-epoxyfarnesol.[26] Diepoxide i and diepoxide ii


i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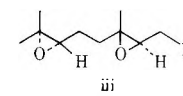
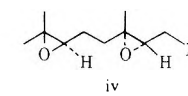

iii


iv

form the same 11*R*,14*S* cis isomer *via* structures X and Y, respectively. Trans isomer 11*R*,14*R* would be formed by operation of scheme X from diepoxide iii or by scheme Y from diepoxide iv. Formation of the 11*S*,14*S* trans isomer could not occur by a concerted reaction.

(28) For experimental details, see previous articles of this series.
(29) W. Herz and G. Högenauer, *J. Org. Chem.*, **27**, 905 (1962).
(30) Apparently initial oxidation of one of the hydroxyl groups results in deactivation of MnO_2.

New Guaianolides from *Liatris* Species[1]

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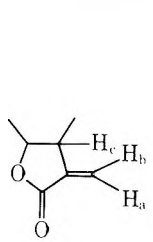
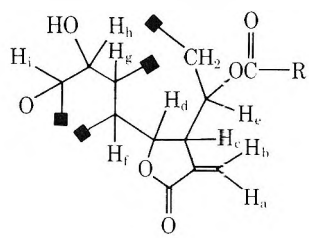
Five closely related guaianolides have been isolated from three *Liatris* species. *L. graminifolia* (Walt.) Kuntze gave graminiliatrin (**1a**), deoxygraminil atrin (**2a**), and graminichlorin (**3**). *L. spicata* (L.) Kuntze yielded spicatin (**2b**) and *L. pycnostachya* (Michx.) Kuntze furnished spicatin and epoxyspicatin (**1c**). Euparin was also found. Structures and stereochemistries of the new lactones were determined by chemical transformations, correlations, and physical techniques.

Since previously investigated representatives of the genus *Liatris* (tribe Eupatorieae, Compositae) have been found to elaborate cytotoxic and antileukemic sesquiterpene lactones of the germacranolide type,[2-4] it was of interest to examine other accessible *Liatris* species. In the present article, we report isolation and structure determination of five new closely related guaianolides from *Liatris graminifolia* (Walt.) Kuntze, *L. pycnostachya* (Michx.) Kuntze, and *L. spicata* (L.) Kuntze. Three of these, graminiliatrin (**1a**), deoxygraminiliatrin (**2a**), and graminichlorin (**3**), were isolated from *L. graminifolia;* two others, spicatin and epoxyspicatin, for which structures **2b** and **1c** are preferred to structures **2d** and **1d**, came from *L. pycnostachya*. Spicatin was also the main lactone constituent of *L. spicata*. In addition the benzofuran derivative euparin (**14**) was isolated from *L. graminifolia* and *L. spicata*.[5]

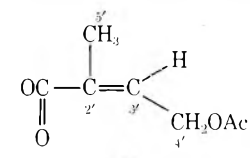
Since none of the new lactones could be induced to crystallize, purification had to depend on chromatography monitored by spectroscopic techniques. Graminiliatrin (**1a**), $C_{22}H_{26}O_9$ (high-resolution mass spectrum, $[\alpha]^{22}D$ −48.6°, the major lactone constituent of *L. graminifolia*, was, like the other four lactones, a conjugated γ-lactone (ir bands at 1770 and 1660 cm^{-1}) of the type represented by partial formula A because of the presence in the nmr spectrum of the characteristic signals of H_a and H_b at 6.31 and 5.53 ppm. Expansion of A to partial structure B, where the symbol ■ represents quaternary carbon, was made possible


A


B

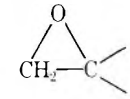
by spin-decoupling experiments.[8] Thus, H_c (multiplet near 3.6 ppm) was coupled to H_d (doublet of doublets near 4.7 ppm) and H_e (d of d of d near 5.6 ppm) as well as to H_a and H_b; the relative shifts of H_d and H_e indicated that H_d represented the proton under the lactone ether oxygen,[9] whereas H_e was attached to a carbon atom carrying one of the two ester functions whose presence was suggested by ir bands at 1740 and 1725 cm^{-1}. The two other protons responsible for the appearance of the H_e signal were visible in the 270-MHz spectrum as the AB part of an ABX system, geminally coupled ($|J|$ = 15 Hz) and apparently adjacent to fully substituted carbon. H_d was also coupled to H_f (d of d at 2.50 ppm); H_f was in turn coupled to H_g (d of d at 1.76 ppm) which was coupled to a broad doublet at 4.35 ppm (H_h). That H_h was geminal to the hydroxyl group evidenced in the ir spectrum of graminiliatrin was demonstrated by the sharpening of its signal of D_2O exchange and by the paramagnetic shift to 5.36 ppm which accompanied acetylation of graminiliatrin to **1b**. Lastly, the additional broadening of the H_h signal could be traced to coupling to H_i at 3.33 ppm; the chemical shift of the latter suggested that it represented a proton on carbon carrying an ethereal oxygen atom.

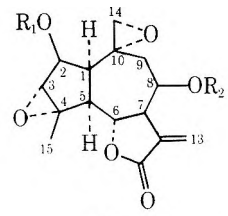
The pmr spectrum of graminiliatrin also revealed the presence of a vinyl methyl multiplet at 1.84 ppm, a vinyl proton multiplet at 6.02 ppm, a two-proton multiplet at 4.88 ppm, and an acetate methyl at 2.07 ppm. Irradiation at 6.02 ppm simplified the multiplets at1.84 and 4.88 ppm, thus indicating the presence of partial structure C^{10} which

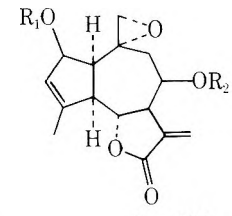

C

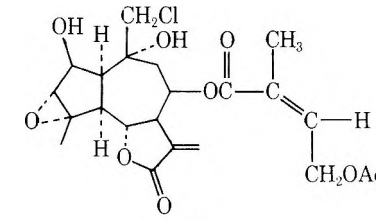
would represent the ester function geminal to H_e and would account for the ir bands at 1740 and 1725 cm^{-1}. This deduction was strengthened by the presence in the high-resolution mass spectrum of peaks at *m/e* 158 ($C_7H_{10}O_4$), 140 ($C_7H_8O_3$), and 99 ($C_5H_7O_2$).

Two additional features of the pmr spectrum remain to be mentioned. One was a three-proton singlet at 1.67 ppm ascribable to a methyl group on carbon carrying oxygen. The second was a two-proton AB system centered at 2.68 ppm characteristic of the grouping



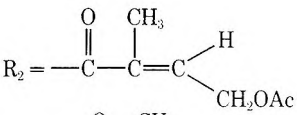




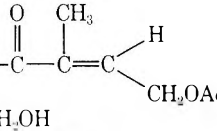


3

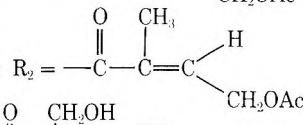
1a, R_1 = H; R_2 =



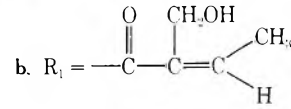
2a, R_1 = H; R_2 =



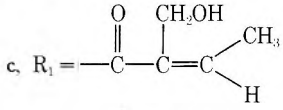
b, R_1 = Ac; R_2 =



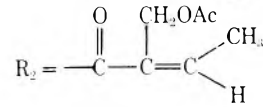
b, R_1 =



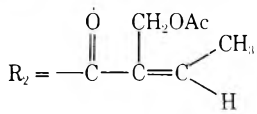
c, R_1 =



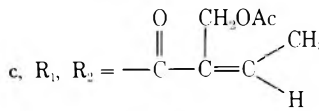
R_2 =

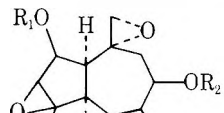


d, R_1, R_2 reverse of 1c

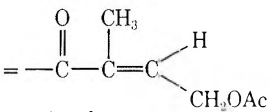


d, R_1, R_2 reverse of 2b



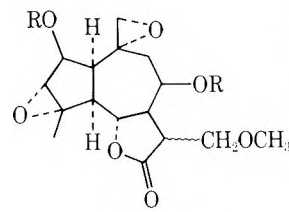


4a, R_1 = H; R_2 =



b, R_1, R_2 same as in 2b

5a, R = H
b, R = Ac



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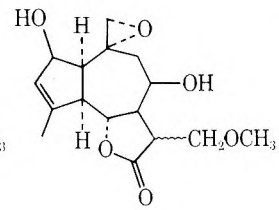

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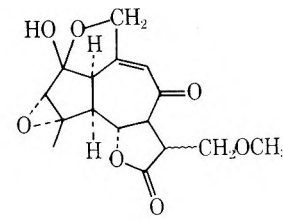

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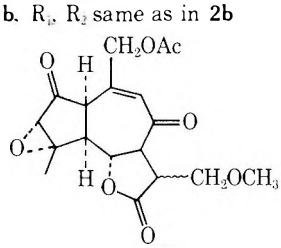
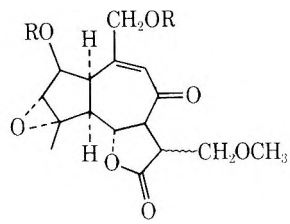


9a, R = H
b, R = Ac



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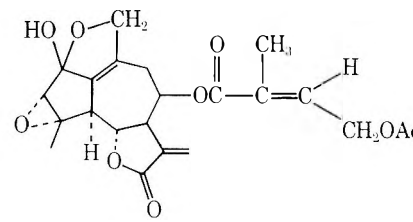
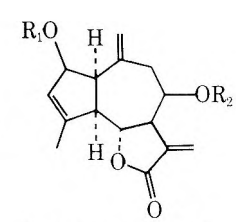
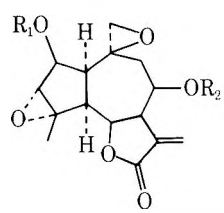


11, R_1, R_2 same as in 2b



12, R_1, R_2 same as in 2b



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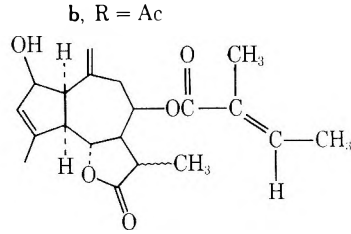

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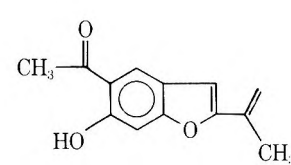

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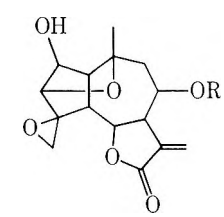
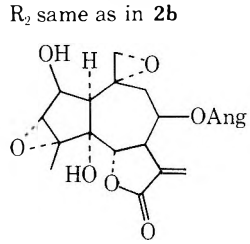
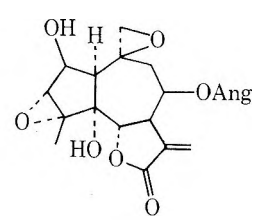


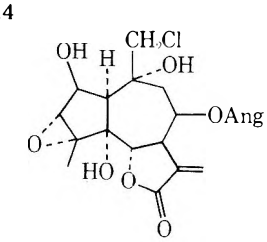
16



17



18



These features can be combined with partial structure B in two and only two ways, **1a** (exclusive of stereochemistry) or **15**, to satisfy the empirical formula and the spectral data. Either formula is biogenetically plausible, but only **1a** is compatible with the transformations and correlations which will be described in the sequel.

Treatment of **1a** with K_2CO_3–MeOH at room temperature resulted in conversion to crystalline **5a** by loss of the

seven-carbon ester function and addition of the elements of methanol to the conjugated exocyclic methylene function, as evidenced in the pmr spectrum (Table I) and by mass spectrometry. Acetylation of **5a** gave the diacetate **5b**; comparison of the chemical shifts of H_d and H_e in the course of the transformation **1a** → **5a** → **5b** confirmed the correctness of the original assignment of H_d to H-6 and H_e to H-8 and demonstrated that hydrolysis had occurred without lactone ring reorientation.

Jones oxidation of **5a** afforded a mixture which was separated chromatographically. The major component, $C_{16}H_{18}O_7$, was the α,β-unsaturated ketone **7** (λ_{max} 235 nm, new ir band at 1670 cm^{-1}) whose pmr spectrum (Table I) no longer contained the signal of H-2 and the ABX system of H-8, H-9a, and H-9b, but exhibited instead a new ABX system involving H-8 as a vinyl multiplet 6.06 ppm, clearly part of the conjugated ketone chromophore, coupled to two protons at 4.94 and 4.59 ppm assignable to H-14a and H-14b. Formation of this system as the result of β elimination definitely ruled out formula **15** for graminiliatrin. Since the ir spectrum of the oxidation product exhibited only a very weak cyclopentanone frequency at 1735 cm^{-1}, preponderance of the hemiketal structure **7** was assumed, but conversion to the acetate resulted in regeneration of the ketone structure **8** (new ir bands at 1750 and 1735 cm^{-1}, downfield shift of H-3).

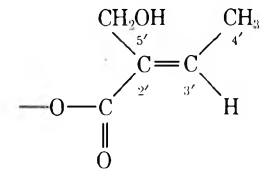
The minor component of the oxidation mixture, $C_{16}H_{20}O_7$, was recognized as **9a** on the basis of its spectral properties and could be converted to the diacetate **9b** whose ir, pmr, and mass spectra were in complete agreement with the assigned structure. Lastly, Jones oxidation of graminiliatrin itself gave a substance **10** by β elimination toward C-1, a transformation which confirms the relationship of the functional groups on C-14, C-10, and C-2 deduced previously. The pmr spectrum of **10** (Table I) was similar to that of **1a** except for the shift of H-14a and H-14b to lower field, the disappearance of H-1 and H-2, and some simplification in the signals of H-7 and H-8. Apparently the introduction of the 1,10 double bond has the result of reducing $J_{7,8}$ to a very small value. Molecular models based on the stereochemistry deduced for graminiliatrin (*vide infra*) demonstrate that this should actually be the case.

The second sesquiterpene lactone from *L. graminifolia*, deoxygraminiliatrin, $C_{22}H_{26}O_8$, had one less oxygen atom than graminiliatrin and appeared to possess an isolated double bond (ir band at 1610 cm^{-1}). Comparison of its pmr spectrum with that of **1a** showed the following differences (Table I). The H-3 singlet of **1a** at 3.33 ppm was replaced by a multiplet at 5.68 ppm which was coupled to a broad vinyl methyl singlet at 1.94 ppm, the latter having replaced the sharp three-proton singlet of **1a** at 1.67 ppm, and the H-2 signal had experienced a downfield shift to 4.6 ppm.

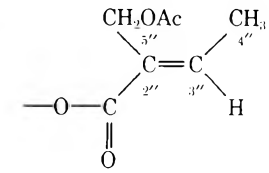
On this basis it appeared obvious that deoxygraminiliatrin had a 3,4-double bond instead of a 3,4-epoxide. Confirmation for its formation as **2a** was provided by treatment of deoxygraminiliatrin with *m*-chloroperbenzoic acid which resulted in formation of two products with opposite stereochemistry at C-3, C-4. The major isomer was identical with graminiliatrin. The pmr spectrum of the minor product **4a** (Table I) differed from that of **1a** only in the value of $J_{2,3}$ and in the chemical shifts of H-14.

The third lactone from *L. graminifolia* was named graminichlorin because of its molecular formula which suggested that it was an HCl adduct of **1a**.[11] The pmr spectrum (Table I) was in complete agreement with its formulation as **3**, apart from the stereochemistry. Treatment of graminichlorin with acid-washed alumina or silica gel resulted in essentially quantitative conversion to **1a**, thus confirming this conclusion.

Spicatin, $C_{27}H_{32}O_{10}$, $[\alpha]^{22}$ −146°, the main lactone constituent of *L. spicata* and *L. pycnostachya*, contained the *cis*-sarracinoyl and *cis*-acetylsarracinoyl residues D and E. This was evident from the pmr spectrum which exhibited two sets of quartets near 7 ppm characteristic of H-3′ and H-3″ in a *cis*-sarracenoyl unit,[4,15] each coupled to a separate vinyl methyl doublet near 1.9 ppm (H-4′ and H-4″), a broadened two-proton singlet (H-5″) at 4.2, a two-proton AB system centered near 4.8 ppm (H-5′), and an acetate singlet. High-resolution mass spectra which contained diagnostic peaks corresponding to $C_7H_9O_3$, $C_5H_7O_2$, and C_5H_5O or to ions resulting from loss of such fragments supported this assignment, as did conversion of spicatin to its monoacetate **2c** which sported two identical ester side chains.



D



E

While analysis of the pmr spectra of spicatin, which was isolated prior to the discovery of graminiliatrin, and its derivatives (Table I) independently led to its formulation as **2b**, the procedure, because of the superposition of signals, was very involved and will not be detailed here. Instead we describe the eventual correlation of spicatin with deoxygraminiliatrin (**2a**) which achieved the same result. Hydrolysis of **2a** with K_2CO_3–MeOH gave a gummy diol lactone **6** without reorientation of the lactone ring (pmr spectrum, Table I), which was converted for characterization purposes to the previously described crystalline epoxide **5a** and its acetate **5b**.[16] Hydrolysis of spicin under identical conditions was more complicated; the material formed in largest amount, again without reorientation of the lactone ring, was identical with **6** and was again converted to **5a** and **5b** identical with authentic samples.

Epoxidation of spicatin gave epoxyspicatin (**1c**), identical with a minor constituent of *L. pycnostachya*. The pmr spectrum of this material (Table I) was very similar to that of acetylgraminiliatrin (**1b**), except for the difference in ester functions on C-2 and C-8; hence the epoxide ring of **1c** has the same stereochemistry as that of graminiliatrin (**1a**).

There remained the problem of deciding between structure **2b** for spicatin and the alternative **2d** in which the location of the two ester side chains is reversed. Numerous attempts to hydrolyze one of the two ester functions selectively in order to settle this question were abortive; however, a tentative solution to the problem was provided in the course of work aimed at deoxygenation of spicatin.

Treatment of spicatin with zinc–copper couple in ethanol gave, as expected,[12,17] a substance **11** whose pmr spectrum (Table I), by exhibiting the H-1 signal as a deshielded doublet of doublets at 3.47 ppm, was useful in deducing the carbon skeleton of spicatin by pmr spectrometry. Epoxidation of **11** gave two isomers, the first of which was identical with **1c** which had been obtained earlier by direct epoxidation of spicatin. The second product was provisionally assigned formula **12** rather than **4b** because of the appearance and chemical shift of the H-3 and H-14 signals (*vide supra*).

When the reduction of spicatin with zinc–copper couple

Table I
Pmr Spectra of Graminiliatrin and Derivatives[a]

Compd	H-1	H-2	H-3	H-5	H-6	H-7	H-8	H-9	H-13	H-14[b]	H-15[c]	Miscellaneous
1a[d]	1.76 dd (4.5, 7.4)	4.35 d br (4.5)	3.33 br	2.50 dd (7.4, 11)	4.83 dd (11, 8)	3.55 dddd (8, 4, 3.5, 3.2)	5.60 ddd (4, 8.5, 7)	2.13 d (15, 7) 2.90 dd (15, 8.5)	6.31 d (3.5) 5.53 d (3.2)	2.70[e]	1.67	6.02 m (H − 3′), 4.88 m (H − 4′)[e], 1.84 m (H − 5′),[c] 2.07 (Ac)
1b	*f*	5.36 d br (4.5)	3.38 br	*f*	4.72 dd (11, 8)	3.56 m	5.59	*f*	6.37 d (3.5) 5.56 d (3.2)	2.69[e]	1.68	6.02 m (H − 3′), 4.89 m (H − 4′),[e] 1.83 m (H − 5′),[c] 2.06, 2.10 (Ac)
1c	*f, g*	5.37 d br (4.5)	3.40 br	2.58 dd (8, 11)	4.74 dd (11, 8)	3.56 dddd (8, 3.9, 3.6, 3.2)	5.63 td (8, 8, 3.9)	2.23 dd[h] (15, 8)	6.31 d (3.6) 5.58 d (3.1)	2.68[e]	1.68	6.90 q (7, H − 3′), 1.92 d (7, H − 4′),[c] 4.33 br (H − 5′),[e] 7.08 q (7, H − 3″), 1.97 d (7, H − 4″),[c] 4.89 (H − 5″),[e] 2.11 (Ac)
2a	*f*	4.60 d br (4.5)	5.68 m	*f*	4.70 dd (11, 8)	3.50 m	5.53 m	*f*	6.27 d (3.5) 5.50 d (3.2)	2.73[e]	1.94 br	5.93 m (H − 3′), 4.89 m (H − 4′),[e] 1.83 m (H − 5′),[c] 2.02 (Ac)
2b[i]	~1.58	*j*	*j*	2.19 dd (9, 11)	4.60 dd (11, 8)	3.56 dddd (8, 3.9, 3.6, 3.2)	5.51 td (8, 8, 3.9)	2.18[k]	6.23 d (3.6) 5.21 d (3.1)	2.22[e]	1.68 br	6.81 q (7, H − 3′), 1.39 d (7, H − 4′),[c] 4.25 br (H − 5′),[e] 6.94 q (7, H − 3″), 1.50 d (7, H − 4′),[c] 4.76 (H − 5″),[e] 1.83 (Ac)
2c	*f*	*l*	*l*	2.82 dd (9, 11)	4.64 dd (11, 8)	3.60 m	*e*	2.26 m	6.21 d (3.6) 5.21 d[e] (3.1)	2.74[e]	2.02 br	7.06 q (7, H − 3′, H − 3″),[b] 1.93 d (7, H − 4′, H − 4″),[m] 4.85 (H − 5′, H − 5″),[e] 2.02, 2.02 (Ac)
3	*f*	4.29 d br (4.5)	3.31 br	*f*	4.81 dd (11, 8)	4.03 m	5.62	*f*	6.27 d (3.5) 5.45 d (3.2)	3.61 d (12) 3.78 d (12)	1.71	6.03 m (H − 3′), 4.88 m (H − 4′),[e] 1.85 m (H − 5′),[c] 2.08 (Ac)
4a	*f*	4.50 dd (4.5, 1.5)	3.49 d (1.5)	*f*	4.91 dd (11, 8)	3.33 m	5.61	*f*	6.35 d (3.5) 5.59 d (3.2)	3.36 d (4.5) 2.77 d (4.5)	1.60	6.06 m (H − 3′), 4.91 m (H − 4′),[e] 1.87 m (H − 5′),[c] 2.09 (Ac)
5a[o]	*f*	4.13 t (4.5)[p]	3.22 br	*f*	4.55 dd (11, 8.5)	*f*	3.77 m	*f*	3.55 m	2.60[e]	1.44	3.25 (OMe), 4.96 d (OH) 5.46 d (OH)
5[b]	*f*	5.30 d (4.5)	3.30	*f*	4.61 dd (11, 8.5)	*f*	5.18 m	*f*	3.61 m	2.60[e]	1.55	3.33 (OMe), 2.08, 2.03 (Ac)
7	*f*		3.47	*f*	4.26 dd (11, 8.5)	*f*		6.06 br[q]	3.58 m	4.94[r] 4.59[r]	1.55	3.33 (OMe)
8	*f*		3.93	*f*	4.27 dd (11, 8.5)	*f*		6.08 br[q]	3.60 m	4.99[r] 4.69[r]	1.54	3.33 (OMe), 2.10 (Ac)
9a[n]	*f*	4.22 t (4.5)[p]	3.47 br	*f*	4.55 t (10)	*f*		6.27 br[q]	3.55 m	4.05 m[e]	1.55	3.22 (OMe), 5.38 d, 5.33 m (OH)

9b	*f*	5.49 d (4.5)	*f*	*f*	4.36 t (10)	*f*		6.27 br[a]	3.55 m	4.60 m[g]	1.70	3.33 (OMe), 2.13, 1.95 (Ac)	
10			3.42	*f*	4.17 t (10)	3.16 m	5.72 d br (6)	*f*	6.22 d (3.5) 5.47 d (3.0)	4.66 br 4.25 br	1.80	6.04 m (H − 3′), 4.81 m (H − 4′),[e] 1.80 m (H − 5′),[c] 2.04 (Ac)	
11	3.47 dd (6.8, 9)	*l*	*l*	*f*	4.63 dd (10.5, 8.5)	3.23 m	*l*	2.39 m	6.26 d (3.6) 5.54 d (3.1)	5.03 br	1.97 br	6.89 q (7, H − 3′), 1.93 d (H − 4′),[c] 4.33 br (H − 5′),[c] 7.09 q (7, H − 3′′), 1.99[d] (7, H − 4′′),[c] 4.90 (H − 5′′),[e] 2.02 (Ac)	
12	*f*	5.42 d br (5)	3.47 br	*f*	4.76 dd (11, 8)	3.62 m	5.63 m	*f*	6.32 d (3.6) 5.60 d (3.1)	2.70[g]	1.71	6.88 q (7, H − 3′), 1.95 d (7, H − 4′),[c] 4.35 br (H − 5′),[e] 7.09 q (7, H − 3′′), 1.93 d (7, H − 4′′),[c] 4.87 (H − 5′′),[e] 2.15 (Ac)	
13	3.15 dd (5.5, 8)	4.74 d br (5.5)	5.74 m	*f*	4.54 dd (9.5, 10)	2.14 ddd (10, 3.2, 12)	5.22 dt (3.2, 8, 8)	2.7 m[e]	1.24 d (7)[c]	5.08 m	1.97 br	2.53 q[d] (7, 12, H − 11), 6.85 m (H − 3′), 1.83 m,[c] 1.97 m (H − 4′, H − 5′)[c]	

[a] Run at 90 MHz in $CDCl_3$ solution except where indicated, using TMS as internal standard. Values are in parts per million. Multiplicities are indicated by the usual symbols: d, doublet; t, triplet; q, quartet; br, broadened singlet; m, multiplet whose center is given. Unmarked signals are singlets. Figures in parentheses are line separations or coupling constants in hertz. [b] Intensity two protons. [c] Intensity three protons. [d] Run at 270 MHz, spin decoupled. [e] Center of AB, frequently broad singlet. [f] Obscured by superposition of signals. [g] Visible in C_6D_6 solution (decoupled) as 1.73 dd (5, 9). [h] Second proton obscured. In C_6D_6, center of AB part of ABX, superimposed on H-5 signal at 2.13 ppm. [i] In C_6D_6, spin decoupled. [j] In two-proton multiplet at 5.44 ppm. [k] Center of AB part of ABX, $J_{AX} \pm J_{BX} = 9$, $J_{AB} = 15$ Hz. [l] In four-proton multiplet near 5.6 ppm. [m] Intensity six protons. [n] Intensity four protons. [o] In DMSO-d_6. [p] Collapses to doublet on D_2O exchange. [q] X of ABX ($J_{AX} = 2$; $J_{BX} = 1.5$; $J_{AB} = 14$ Hz). [r] A and B of ABX.

was carried out in the presence of hydrochloric acid, the only product which could be characterized satisfactorily was the monoester **13.** That reduction of the conjugated lactone system had accompanied deoxygenation of the epoxide function was evident from the pmr spectrum (Table I), as was the hydrolytic loss of the ester side chain on C-2. The remaining ester side chain on C-8 had suffered hydrogenolysis to a tigloyl residue (H-3′ multiplet at 6.85, two vinyl methyl multiplets at 1.83 and 1.97 ppm), a conclusion confirmed by the mass spectrum which exhibited the base peak at *m/e* 83.0436 (C_5H_7O). Since acetate is a much better leaving group than OH, we suggest that the formation of **13** favors formula **2b** for spicatin rather than formula **2d.** Nevertheless, further evidence on this point is clearly desirable and is currently being sought.

The stereochemistry of the substances described in this report has been deduced as follows. If the usual assumption is made that the C-7 side chain is β and equatorial as in all sesquiterpene lactones of authenticated stereochemistry, the values of $J_{5,6}$ and $J_{6,7}$ given in Table I (generally 11 and 8 Hz, respectively) require that H-5 be trans to H-6 and α and that H-6 be trans to H-7 and β, *i.e.*, that the lactone ring be trans fused. This conclusion is reinforced by the magnitude of $J_{7,13a}$ and $J_{7,13b}$ (>3 Hz) which according to Samek's rule[18] indicates presence of a *trans*-lactone.[19] The relatively small value of $J_{7,8}$ (~4 Hz) then requires that H-8 be equatorial and α.

The relative stereochemistry in the five-membered ring was established as follows. H-3 appears as a slightly broadened singlet in the pmr spectra of all epoxides except **4a** which is stereoisomeric at C-3 and C-4. The molecular models show that with the epoxide α and the 2-hydroxyl group β as in **1a,** the dihedral angle subtended by H-2 and H-3 is 90°, whereas with the epoxide β and the hydroxyl β, as suggested for **4a,** the dihedral angle is 60°, thus accounting for the differences in the coupling constants actually observed. The values of $J_{1,2}$ (4.5 Hz) and $J_{1,5}$ (7.4 Hz) then require α orientation for H-1 and H-5; the latter conclusion has been reached independently (see previous paragraph) by considering the coupling constants in the seven-membered ring. Hence the two rings are cis fused.

The stereochemistry at C-10 then follows from the effect of the β-oriented epoxide function of **4a** on the chemical shift of H-14. The observed downfield shift (see Table I) can be rationalized only if the methylene group attached to C-10 is β oriented. A similar conclusion is reached when the appearance and chemical shifts of H-1, H-9, and H-14 in the pmr spectrum of **1a** are compared with the corresponding signals in the pmr spectra of eupatoroxin (**16**) and 10-epieupatoroxin (**17**)[12] whose relative and absolute stereochemistry is known. Lastly, comparison of the pmr spectra of graminichlorin (**3**) and eupachloroxin (**18**) shows that the C-10 substituents of both compounds are similarly oriented. In both instances, H-7 exhibits a downfield shift of about 0.5 ppm. This indicates that the hydroxyl group on C-10 is in close proximity to H-7 which is possible only if the hydroxyl group of **3** (like that of **18**) and hence the epoxide function of **1a** are α-oriented.[23]

A consequence of the cis-1,5,trans-6,7 stereochemistry deduced for the new lactones is the proximity, apparent from models, of H-6 to one of the protons on H-9 which should be reflected in a relatively strong NOE. Indeed, irradiation at a frequency corresponding to the center of the H-9 AB system in spicatin (C_6D_6 solution) produced a 27.1% enhancement in the integrated intensity of H-6. As expected on the basis of the model, there were no NOE's between H-1 on the one hand and H-2, H-5, and H-7 on the other.

Experimental Section[24]

Extraction of *Liatris graminifolia*. Above ground parts of *Liatris graminifolia* (Walt.) Kuntze, wt 16.2 kg, collected by R. Lazor on Sept 22, 1971, 12 km east of the junction of U.S. 319 and State Road 155, Thomas Co., Georgia (Lazor no. 5585 on deposit in herbarium of Florida State University) was extracted with chloroform and worked up in the usual manner.[25] The crude gum, wt 120 g, was chromatographed over 1.25 kg of silicic acid (Mallinckrodt 10 mesh), 1-l. fractions being collected. Fractions 1–2 (benzene) gave 100 mg of a yellow solid which melted at 120–121° after recrystallization from isopropyl ether–hexane and was identified as euparin by comparison of its ir and nmr spectra with those of an authentic sample, mmp 120–121°.[26]

Fractions 3–10 (benzene) gave 1.2 g of gummy graminichlorin (**3**) which was homogeneous on tlc: $[\alpha]^{22}D$ −36.0° (c 1.25, $CHCl_3$); uv end absorption; ir bands at 3460 (hydroxyl), 1770 (γ-lactone), 1740 (acetate), 1725 (conjugated ester), 1650 (C=C), 1250, 1030, 980, 950, and 830 cm^{-1}; low-resolution mass spectrum *m/e* 470 and 472 (3:1, M^+, $C_{22}H_{27}O_9Cl$), 452 and 454 (3:1, M −18, $C_{22}H_{25}O_8Cl$); other major peaks were at 392 (M − 18 − 60), 375, 278, 277, 276, 275, 259, 258, 257, 150, 140, and 99 (base peak).

Anal. Calcd for $C_{22}H_{27}ClO_9$: C, 56.17; H, 5.75; Cl, 7.45. Found: C, 56.18; H, 5.84; Cl, 7.19.

Fractions 11–15 (benzene) gave 2 g of crude gummy deoxygraminiliatrin (**2a**) which was purified by preparative tlc on silica gel (solvent benzene–ethyl acetate, 2:1): $[\alpha]^{22}D$ −48.5° (c 0.735, $CHCl_3$); ir bands at 3460 (hydroxyl), 1770, 1660 (conjugated γ-lactone), 1725 (conjugated ester), 1610, 1240, 1020, 925, and 860 cm^{-1}; low-resolution mass spectrum *m/e* 418 (M^+), 358 (M − 60), 277, 276 (M − $C_7H_{10}O_3$), 261, 260 (M − $C_7H_{10}O_4$), 259, 243, 242 (M − $C_7H_{10}O_4$ − H_2O), and 99 (base peak).

Anal. Calcd for $C_{22}H_{26}O_8$: C, 63.15; H, 6.26; O, 30.59. Found: C, 63.43; H, 6.20; O, 30.67.

Elution with benzene–$CHCl_3$ (10:1 and 1:1, fractions 16–41) gave the major component which was further purified by chromatography over 600 g of silica gel to give 40 g of colorless graminiliatrin (**1a**) which could not be induced to crystallize: $[\alpha]^{22}D$ −48.6° (c 1.0, $CHCl_3$); CD curve λ_{max} 260 nm; $[\theta]$ −545; uv λ_{max} 212 (ε 15,600); ir bands at 3460 (hydroxyl), 1770, 1660 (conjugated γ-lactone), 1740 (acetate), 1725 (conjugated ester), 1250, 1020, 970, 920, and 835 cm^{-1}; high-resolution mass spectrum *m/e* (composition, per cent) 434 (M^+, $C_{22}H_{26}O_9$, 0.2), 392 (M − 42, $C_{20}H_{24}O_8$, 1.2), 374 (M − 60, $C_{20}H_{22}O_7$, 0.4), 277 (M − $C_7H_9O_4$, $C_{15}H_{17}O_5$, 2.8), 276 (M − $C_7H_1O_4$, $C_{15}H_{16}O_5$, 2.0), 275 (M − $C_7H_{11}O_4$, $C_{15}H_{15}O5$, 0.9), 259 (M − 157 − 18, $C_{15}H_{15}O_4$, 5.4), 258 (M − 158 − 18, $C_{15}H_{14}O_4$, 4.8), 158 ($C_7H_{10}O_4$, 5.6), 140 ($C_7H_8O_3$, 8.7), 99 ($C_5H_7O_2$, 100).

Anal. Calcd for $C_{22}H_{26}O_9$: mol wt, 434.1575. Found: mol wt (ms), 434.1546.

Acetylation of 0.1 g of **1a** with 1 ml of acetic anhydride in 0.5 ml of pyridine at room temperature overnight gave, after the usual work-up, the acetate **1b** as a gum: yield 0.095 g; $[\alpha]^{22}D$ −55.3° (c 0.11, $CHCl_3$); ir bands at 1760, 1740, 1725, 1650, 1240, 1025, 970, 920, 870, and 830 cm^{-1}; high-resolution mass spectrum *m/e* (composition, per cent) 476 (M^+, $C_{24}H_{28}O_{10}$, 2–3), 433 (M − 43, $C_{22}H_{25}O_9$, 1.2), 417 (M − 59, $C_{22}H_{25}O_8$, 37.5), 375 (M − 59 − 42, $C_{20}H_{23}O_7$, 1.4), 374 (M − 59 − 43, $C_{20}H_{22}O_7$, 4.8), 373 (M − 60 − 43, $C_{20}H_{21}O_7$, 4.3), 357 ($C_{20}H_{21}O_6$, 2.4), 356 ($C_{20}H_{20}O_6$, 3), 277 ($C_{15}H_{17}O_5$, 8.5), 276 ($C_{15}H_{16}O_5$, 10), 259 ($C_{15}H_{15}O_4$, 6.1), 258 ($C_{15}H_{14}O_4$, 44.5), 159 ($C_7H_{11}O_4$, 0.9), 158 ($C_7H_{10}O_4$, 3.4), 141 ($C_7H_9O_{31}$, 3.6), 140 ($C_7H_8O_3$, 16.3), 99 ($C_5H_7O_2$, 100).

Anal. Calcd for $C_{24}H_{28}O_{10}$: mol wt, 476.1680. Found: mol wt (ms), 476.1673.

Extraction of *Liatris spicata*. Above ground parts of *Liatris spicata* (L.) Kuntze, wt 22.2 kg, collected by Dr. R. K. Godfrey on Sept 18, 1971 in the vicinity of Tallahassee (Godfrey no. 70894) was extracted with $CHCl_3$ and worked up as usual. The crude gum, wt 70 g, was chromatographed over 1 kg of silicic acid, 1-l. fractions being collected in the following order: 1–28 (benzene), 29–40 (benzene–$CHCl_3$, 4:1), 41–55 (benzene–$CHCl_3$, 1.4), 71–100 ($CHCl_3$), 101–110 ($CHCl_3$–MeOH, 99:1), 111–120 ($CHCl_3$–MeOH, 19:1), 121–125 (MeOH). Fractions 2 and 3, wt 4.2 g, were combined and recrystallized to give euparin, mp 120°, identical with an authentic sample. Fractions 4–54, total wt 4.5 g, contained mixtures. Fractions 55–80, wt 20 g, which showed a major spot on tlc were combined and rechromatographed over 1.3 kg of silica gel (Grace 60–200 mesh), using initially petroleum ether–acetone–ether saturated with water (4:1:1) and then increasing polarity of the solvent system. The central fractions which showed single spots on tlc were combined to give 8.48 g of spicatin (**2b**) as a resin which could not be induced to crystallize. It was further purified by rechromatography over 80 g of cellulose (Whatman standard grade), using the previous solvent system and then had $[\alpha]^{22}Hg$ −146° (c 0.20, $CHCl_3$); CD curve λ_{max} 265 nm ($[\theta]$ −900); ir bands at 3510 (OH), 1778, 1652 (conjugated γ-lactone), 1715 (strong, conjugated esters); chemical ionization mass spectrum *m/e* 517 (MH^+, 0.5), 499 (MH^+ − 18, 0.2), 439 (MH^+ − 18 − 60, 2.3), 399 (MH^+ − 118, 7); high-resolution mass spectrum *m/e* (composition, per cent) 516 (M^+, 0.2), 498 ($C_{27}H_{30}O_9$, 0.05), 456 ($C_{25}H_{28}O_8$, 0.2), 420 ($C_{25}H_{24}O_6$, 0.7), 359 ($C_{20}H_{23}O_6$, 0.9), 342 ($C_{20}H_{22}O_5$, 1.0), 312 ($C_{19}H_{20}O_4$, 1.4), 99 ($C_5H_7O_2$, 100), and 81 (C_5H_5O, 48).

Anal. Calcd for $C_{27}H_{32}O_{10}$: C, 62.78; H, 6.24; O, 30.97; mol wt, 516.1992. Found: C, 62.41; H, 6.65; O, 30.40; mol wt (ms), 516.2009.

Acetylation of 0.1 g of spicatin with 1 ml of acetic anhydride in 1 ml of pyridine for 12 hr at 0° followed by the usual work-up gave 0.095 g of a gum (**2c**) which was purified by preparative tlc (solvent petroleum ether–acetone–ether saturated with water, 4:1:1); ir bands at 1770, 720 (very strong), 1655 cm^{-1}; high-resolution mass spectrum *m/e* (composition, per cent) 558 (M^+, $C_{29}H_{34}O_{11}$, very weak), 438 ($C_{25}H_{26}O_7$, 2.5), 340 ($C_{20}H_{21}O_7$, 3.6), 259 ($C_{15}H_{15}O_4$, 5.1), 242 ($C_{15}H_{14}O_3$, 23.6), 141 ($C_7H_9O_3$, 41), and 81 (C_5H_5O, 100).

Fractions 81–112, total wt 13.8 g, contained mixtures; fractions 113 and 114, wt 11.5 g, although exhibiting a single spot on tlc, actually contained two substances which are still under investigation.

Extraction of *Liatris pycnostachya*. Above ground parts of *Liatris pycnostachya* (Michx.) Kuntze, wt 9.9 kg, colleced by Dr. N. C. Henderson in late August, 1972 in the vicinity of Belton, Mo., was extracted with $CHCl_3$ and worked up as usual. The crude gum, wt 80 g, was chromatographed over 1 kg of silicic acid, 600-ml fractions being collected. Fractions 1–40 (benzene) gave 30 g of crude spicatin. Fractions 41–50 (benzene–$CHCl_3$, 1:1) gave 5 g of a gum which was purified by preparative tlc, and was shown to be identical with synthetic **1c**, prepared from spicatin (*vide infra*), by ir and nmr spectroscopy and by mixed tlc. Further elution of the column with $CHCl_3$ and $CHCl_3$–MeOH (10:1) gave mixtures.

Conversion of Graminichlorin (3) to Graminiliatrin (1a). A solution of 0.1 g of **3** in a few milliliters of $CHCl_3$ was placed on a 50-g column of acid-washed alumina or silica gel. Elution with 5% methanol in $CHCl_3$ gave 0.080 g of **1a**, characterized by ir, nmr, and tlc comparison with authentic material.

Conversion of Deoxograminiliatrin (2a) to 1a. A solution of 0.1 g of **2a** in 5 ml of $CHCl_3$ was oxidized with 0.1 g of *m*-chloroperbenzoic acid at 0° for 2 hr with stirring. The mixture was diluted with chloroform, washed with sodium metabisulfite and water, dried, and evaporated. The residual gum exhibited two spots on tlc. It was separated by preparative tlc on silica gel (solvent benzene–ethyl acetate 2:1). The substance with R_f 0.6 (0.06 g) was identical with graminiliatrin (**1a**) in all respects. The substance with R_f 0.55 (0.030 g) could not be induced to crystallize and was characterized as **4a**: ir bands at 3450, 1770, 1740, 1725, 1655, 1250, 1030, 960, and 880 cm^{-1}.

Anal. Calcd for $C_{22}H_{26}O_9$: C, 60.82; H, 6.03; O, 33.14. Found: C, 60.61; H, 5.98; O, 33.40.

Epoxidation of Spicatin. Epoxidation of 0.1 g of **2b** at 0° for 5 days in the manner described in the previous paragraph furnished a gum which exhibited two spots on tlc. Preparative tlc on silica gel gave starting material and 0.036 g of noncrystalline **1c**, identical with material isolated from *L. pycnostachya*: $[\alpha]^{22}Hg$ −80° (c 0.20, $CHCl_3$); uv strong end absorption (ϵ_{210} 14,900); ir bands at 3502, 1770, 1715, and 1650 cm^{-1}; high-resolution mass spectrum *m/e* (composition, per cent) 532 (M^+, $C_{27}H_{32}O_{11}$, 0.5), 514 ($C_{27}H_{30}O_{10}$, 1.8), 435 ($C_{22}H_{27}O_9$, 2.6), 417 ($C_{22}H_{25}O_8$, 3.5), 357 ($C_{20}H_{21}O_6$, 1.6), 337 ($C_{17}H_{21}O_7$, 0.9), 319 ($C_{17}H_{19}O_6$, 1.7), 259 ($C_{15}H_{15}O$, 14.6), 179 ($C_{10}H_{11}O_3$, 8.4), 141 ($C_7H_9O_3$, 18.6), 99 ($C_5H_7O_2$, 81.4), and 81 (C_5H_5O, 38.4).

Anal. Calcd for $C_{27}H_{32}O_{11}$: C, 60.89; H, 6.06; O, 33.05; mol wt, 532.1942. Found: C, 59.99; H, 6.22; O, 33.56; mol wt (ms), 532.1921.

Hydrolysis of Graminiliatrin to 5a. A solution of 0.3 g of **1a** in 15 ml of methanol containing 0.5 g of K_2CO_3 in 2 ml of water was stirred in a nitrogen atmosphere. After 30 min the mixture was diluted with water and extracted with ethyl acetate. The washed and dried extract was evaporated and the solid residue was recrystallized from ethyl acetate–methanol to provide 0.1 g of **5a**: mp 197°; $[\alpha]^{22}D$ −110.3° (c 0.17, MeOH); ir bands at 3400, 1760, 1230, 1055, 1020, 1015, 950, 920, and 810 cm^{-1}; significant peaks in the low-resolution mass spectrum at *m/e* 326 (M^+), 311 (M − CH_3), and 295 (M − CH_2OH).

Anal. Calcd for $C_{16}H_{22}O_7$: C, 58.89; H, 6.79; O, 34.32. Found: C, 58.96; H, 6.75; O, 34.52.

Acetylation of 0.040 g of **5a** at room temperature for 24 hr gave a solid which was recrystallized from methanol: yield of **5b** 0.040 g; mp 99°, $[\alpha]^{22}D$ −112.5° (c 0.5, $CHCl_3$); ir bands at 1780, 1740 (strong), 1250, 1040, 1030, 950, and 820 cm^{-1}; low-resolution mass spectrum *m/e* 410 (M^+), 395 (M − CH_3), 379 (M − CH_2OH), 368 (M − C_2H_2O), 351 (M − $C_2H_3O_2$), 309 (M − C_2H_2O − $C_2H_3O_2$), 290 (M − $2CH_3CO_2H$).

Anal. Calcd for $C_{20}H_{26}O_9$: C, 58.53; H, 6.39; O, 35.08. Found: C, 58.33; H, 6.35; O, 35.24.

Correlation of Spicatin with 1a and 2a. Hydrolysis of 0.3 g of **2a** with K_2CO_3 in aqueous methanol as described in the previous section followed by preparative tlc on silica gel gave **6**, wt 0.1 g, as the major product which could not be induced to crystallize and had clearly visible pmr signals at 4.65 d br (4.5, H-2), 5.64 br (H-3), 4.60 dd (11, 8), 4.1 m (H-8), 3.65 m (H-13), 3.35 (OMe), 2.75 (AB, H-14), 1.92 br (H-15), but was not further characterized. Epoxidation with *m*-chloroperbenzoic acid gave a mixture of two isomers, the major isomer having the same R_f as **5a**. Isolation by preparative tlc followed by acetylation in the usual fashion afforded **5b**, identical with authentic material by melting point, mixture melting point, and spectral comparison (ir, pmr).

Hydrolysis of 0.4 g of spicatin with K_2CO_3 in aqueous methanol under identical conditions gave a mixture of four products. The material with the same R_f as **6** was isolated by preparative tlc on silica gel (solvent benzene–ethyl acetate, 1:5), yield 0.115 g, ir and nmr spectrum superimposable on that of **6** as prepared in the previous paragraph. Epoxidation again gave a mixture of two products; the major isomer (**5a**) was isolated by preparative tlc and converted to the diacetate **5b**, identical with material from **1a** and **2a** by melting point, mixture melting point, and spectral comparison (ir, pmr).

Oxidation of 5a. A solution of 0.1 g of **5a** in 50 ml of acetone (Anal-R grade) was oxidized at 0° by dropwise addition of 1 ml of Jones' reagent with vigorous stirring. After 0.5 hr excess reagent was destroyed with isopropyl alcohol and the reaction mixture was diluted with water and extracted with ethyl acetate. Evaporation of the washed and dried extract gave a gum which showed two spots on tlc. Separation by preparative tlc on silica gel (solvent benzene–ethyl acetate, 1:1) gave **7** (major product, R_f 0.7) and **9a** (minor product, R_f 0.5). Crystallization of **7** from ethyl acetate afforded colorless prisms: yield 0.04 g; mp 173–175°, $[\alpha]^{22}D$ +65.6° (c 0.80, $CHCl_3$); uv λ_{max} 235 nm (ε 10,500); ir bands at 3500, 1775 (γ-lactone), 1725 (very weak, cyclopentanone), 1670 (enone), 1080, 1030, 930, and 870 cm^{-1}; low-resolution mass spectrum *m/e* 322 (M^+), 304 (M − H_2O).

Anal. Calcd for $C_{16}H_{18}O_7$: C, 59.62; H, 5.63; O, 34.75. Found: C, 59.58; H, 5.58; O, 34.61.

Acetylation of 0.02 g of **7** in the usual manner gave **8** as a gum (0.02 g): $[\alpha]^{22}D$ +45.5° (c 0.66, $CHCl_3$); ir bands at 1780 (γ-lactone), 1750 (cyclopentanone), 1735 (acetate), 1670 (enone), 1240, 1030, 920, 860, and 835 cm^{-1}; high-resolution mass spectrum did not exhibit the molecular ion, but had significant peaks at *m/e* (composition, per cent) 322.1040 (M^+ − C_2H_2O, $C_{16}H_{18}O_7$, 100), calcd 322.1051; 304.0944 (M^+ − $C_2H_4O_2$, $C_{16}H_{16}O_6$, 46.8), calcd 304.0946.

Recrystallization of the minor oxidation product from methanol furnished 10 mg of **9a**: mp 173°; $[\alpha]D$ +8.7° (c 0.86, MeOH); λ_{max} 238 nm (ε 11,000); ir bands at 3400, 1760 (γ-lactone), 1665 (enone), 1220, 1060, 980, 930, and 850 cm^{-1}; significant peaks in the low-resolution mass spectrum *m/e* 324 (M^+), 306 (M − 18), 293 (M − CH_2OH), 278 (M − 18 − 28).

Anal. Calcd for $C_{16}H_{20}O_7$: C, 59.25; H, 6.22; O, 34.53. Found: C, 59.16; H, 6.26; O, 34.72.

Acetylation of 20 mg of **9a** gave the diacetate **9b** as a gum: yield 18 mg; $[\alpha]^{22}D$ −8.5° (c 0.1, $CHCl_3$); ir bands at 1775 (γ-lactone), 1750 (acetates), 1675 (enone), 1240, and 1030 cm^{-1}. The high-resolution mass spectrum had significant peaks at *m/e* (composition, per cent) 408 (M^+, $C_{20}H_{24}O_9$, 1.3), 366 (M − 42, $C_{18}H_{22}O_8$, 8.1), 348 (M − 60, $C_{18}H_{20}O_7$, 28.8), 324 (M − 2 × 42, $C_{16}H_{20}O_7$, 2), 306 (M − 42 − 60, $C_{16}H_{18}O_6$, 5.6).

Anal. Calcd for $C_{20}H_{24}O_9$: mol wt, 408.14.19. Found: mol wt (ms), 408.1394.

Oxidation of Graminiliatrin. Oxidation of 0.15 g of **1a** in 40 ml of acetone with 1 ml of Jones' reagent in the manner described for **5a** and purification of the crude product by preparative tlc on silica gel (solvent benzene–ethyl acetate 2:1) gave **10** as a gum: wt 0.11; ir bands at 3500, 1720, and 1620 (conjugated ester), 1240 and 1030 cm^{-1}. The low-resolution mass spectrum exhibited significant peaks at *m/e* 432 (M^+), 275 (M^+ − 157), 274 (M − 158), 256 (M − 158 − 18). Because **10** decomposed on standing, elementary analysis was not attempted.

Deoxygenations of Spicatin. (A) A mixture of 0.125 g of spicatin, 4 g of zinc–copper couple, and 40 ml of absolute ethanol was refluxed for 4 days, cooled, and filtered through Celite. Evaporation of the filtrate gave a gum which was separated into starting material (0.030 g) and deoxospicatin (**11**, 0.037 g) by preparative tlc on silica gel (solvent ether–$CHCl_3$–MeOH, 60:60:1). Substance **11** exhibited ir bands at 3510, 1770, and 1655 (conjugated γ-lactone), and 1715 cm^{-1} (strong conjugated esters). The high-resolution mass spectrum had significant peaks *m/e* (composition, per cent) 500 (M^+, $C_{27}H_{32}O_9$, 0.06), 440 ($C_{25}H_{28}O_7$, 3.4), 342 ($C_{20}H_{22}O_5$, 2.9), 326 ($C_{20}H_{22}O_4$, 8.4), 244 ($C_{15}H_{16}O_3$, 18.6), 228 ($C_{15}H_{16}O_2$, 42.4), 197 ($C_{10}H_{13}O_4$, 28.8), 141 ($C_7H_9O_3$, 25.4), 99 ($C_5H_7O_2$, 100), 81 (C_5H_5O, 72.8).

Anal. Calcd for $C_{27}H_{32}O_9$: C, 64.79; H, 6.44; O, 28.77. Found: C, 64.23; H, 6.46; O, 28.59.

Oxidation of 0.08 g of **11** with 0.1 g of *m*-chloroperbenzoic acid at 0° for 6 days and work-up of the reaction mixture as described previously gave a gum (0.05 g) which gave two spots on tlc. Preparative tlc on silica gel (solvent $CHCl_3$–ether–methanol, 15:15:1) afforded two noncrystalline products. The first, 18 mg, was identical (tlc, ir, nmr) with **1c**. The second, 12 mg, was assigned formula **12** rather than **4b** because of the H-14 frequencies (see Table I). The low-resolution mass spectrum exhibited significant peaks at 532 (M^+), 514 (M − H_2O), 435 (M − $C_5H_5O_2$), 417 (M − $C_5H_7O_3$), 357 (M − $C_7H_{11}O_5$), 277, 259, 141, and 99 (base peak).

Anal. Calcd for $C_{27}H_{32}O_{11}$: mol wt, 532. Found: 532.

(B) A mixture of 0.5 g of spicatin, 16 g of Zn–Cu couple, 100 ml of absolute ethanol, and 2 ml of HCl was refluxed for 5 days, cooled, filtered through Celite, and evaporated at reduced pressure. The residual gum showed three spots on tlc. Repeated preparative tlc on silica gel (solvent $CHCl_3$–ether–methanol, 30:30:1) permitted isolation of **13** as the middle fraction: wt 0.045 g; ir bands at 3480, 1775, 1710, and 1650 cm^{-1}. The high-resolution mass spectrum exhibited significant peaks *m/e* (composition, per cent) 346 (M^+, $C_{20}H_{26}O_5$, 0.2), 328 ($C_{20}H_{24}O_4$, 0.4), 263 ($C_{15}H_{19}O_4$, 1.7), 246 ($C_{15}H_{18}O_3$, 3.2), 228 ($C_{15}H_{16}O_2$, 4.9), 215 ($C_{15}H_{15}O_2$, 6.9), 83 (C_5H_2O, 100).

Anal. Calcd for $C_{20}H_{26}O_5$: mol wt, 346.1779. Found: mol wt (ms), 246.1806.

Registry No.—**1a**, 53142-34-0; **1b**, 53142-35-1; **1c**, 53177-31-4; **2a**, 53142-47-5; **2b**, 53142-46-4; **2c**, 53142-45-3; **3**, 53142-40-8; **4a**, 53177-32-5; **5a**, 53142-43-1; **5b**, 53142-44-2; **7**, 53142-41-9; **8**, 53142-42-0; **9a**, 53142-48-6; **9b**, 53142-49-7; **10**, 53142-36-2; **11**, 53142-37-3; **12**, 53142-38-4; **13**, 53142-39-5.

References and Notes

(1) (a) Part VI in a series "Constituents of *Liatris* Species." For Part V, see W. Herz and R. P. Sharma, *J. Org. Chem.*, **40**, 192 (1975). (b) This work was supported in part by U. S. Public Health Service Research Grant No. CA-13121 from the National Cancer Institute.

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(5) The flavone glycoside content of these collections and the analysis of the volatile constituents of our collection of *L. spicata* have been reported.[6,7]

(6) H. Wagner, M. A. Iyengar, and W. Herz, *Phytochemistry*, **12**, 2063 (1973).

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(8) Decoupling was carried out on **1a**, **1b**, or **3** depending on which spectrum exhibited the best separation of signals.

(9) Evidence for the correctness of this assumption will be presented subsequently.

(10) Just as in the case of the tiglic acid–angelic acid isomer pair, the H-3′ signal of the *Z* isomer C would be expected to occur near 6.1 ppm, whereas the H-3′ signal of the *E* isomer would be expected at considerably lower field.

(11) Graminichlorin is an addition to the small number of know chlorine-containing guianolides.[12-14]

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(16) A small amount of an isomeric 3,4-epoxide which was not further characterized was also formed.
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(18) Z. Samek, *Tetrahedron Lett.*, 671 (1970). Although some exceptions to the rule have been found,[4] it seems to be generally applicable to guaianolides.
(19) If the absolute configuration is as postulated, the observation that the CD curves of graminiliatrin and spicatin display negative Cotton effects near 260 nm could be interpreted as providing additional support for the trans fusion of the lactone ring.[20] However, the presence of one or two additional inherently symmetric but asymmetrically perturbed unsaturated ester chromophores in **1b** and **2b** could conceivably affect the CD curve so that the argument is not without pitfalls. A summary of X-ray results for several sesquiterpene lactones of established absolute configuration indicates that a C-6,C-7 trans lactone fusion gives rise to left-handed chirality (*i.e.*, the C=C—C=O torsion angle is negative).[21] Whether there is a direct connection between the chirality of the C=C—C=O grouping and the sign of the Cotton effect is still moot.[22]
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(23) The coupling constants involving H-1, H-2, H-3, H-6, H-7, and H-8 of **1a** and **3** are very similar to those reported for **16** and **18**, respectively, thus providing additional evidence for the stereochemistry assigned to **1a**.
(24) For experimental details see previous papers of this series.
(25) W. Herz and G. Hogenauer, *J. Org. Chem.*, **27**, 905 (1962).
(26) We wish to thank Dr. Thorleif Anthonsen, Institute for Organisk Kjem, Norges Tekniske Hogskole, Trondheim, for the authentic sample.

Total Synthesis of *dl*-9-Deoxyprostaglandin E_1

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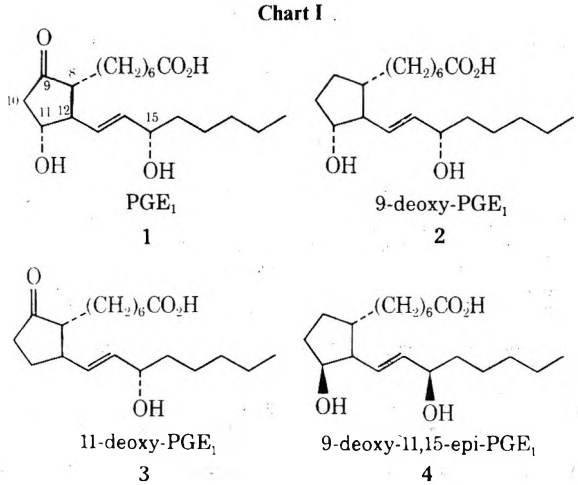
dl-9-Deoxyprostaglandin E_1 (PGE_1) **2** has been synthesized in nine steps from 2-carbomethoxy-3-oxo-1-cyclopenteneheptanoic acid methyl ester **36**. Details are provided of model studies and development of a synthetic procedure for preparation of one of the simplest PGE_1 model compounds **35** which contains all but one of the stereochemical features of PGE_1 **1**.

Extensive work has been carried out for several years with 11-deoxyprostaglandins **3**,[1,2] but only recently have accounts appeared of work with the 9-deoxyprostaglandins **2**.[3-5] These reports have prompted us to describe our synthesis of this type, which was disclosed previously in the patent literature[6] (Chart I).

Chart I

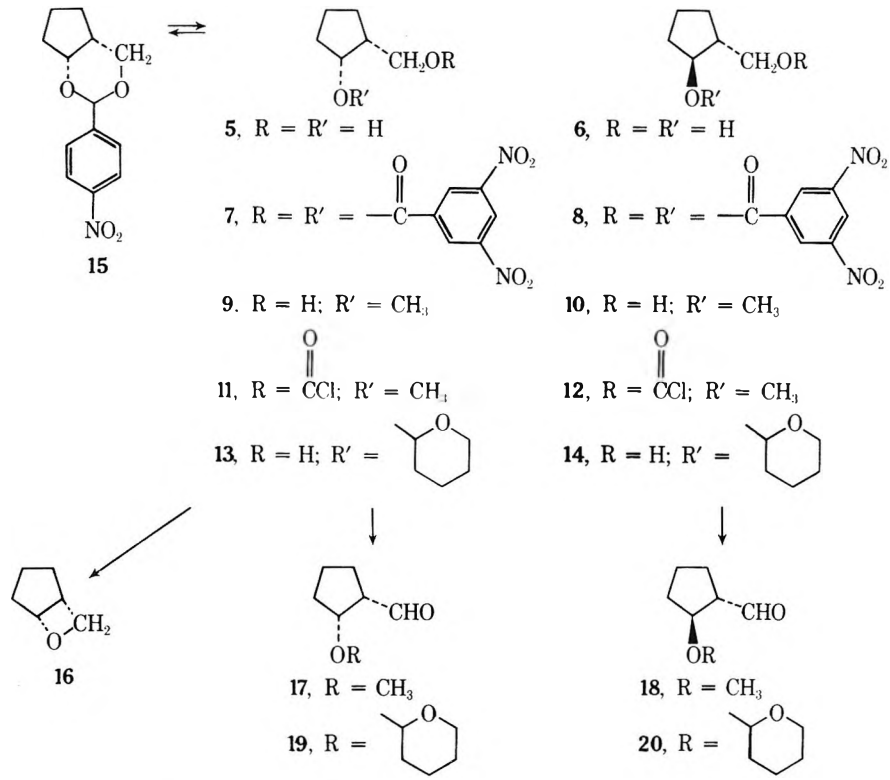


We also now describe the model experiments which were carried out to establish the stereochemical assignments in this synthetic sequence and that used for the synthesis of prostaglandin E_1 **1** itself.[7]

Reaction of a mixture of the carbinols **5** and **6**, obtained by $LiAlH_4$ reduction of a mixture of *cis*- and *trans*-2-carbomethoxycyclopentanols, with *p*-nitrobenzaldehyde dimethyl acetal[8] and acid catalysis yielded only one *p*-nitrobenzylidene cyclic acetal **15**. This was shown to be derived from the cis hydroxycarbinol **5** by cleavage back to this compound, which had been obtained also by $LiAlH_4$ reduction of the low-boiling *cis*-2-carbomethoxycyclopentanol. Separation of the *cis*- and *trans*-2-carbomethoxycyclopentanols could be achieved conveniently by fractional distillation using a spinning band column.[9] The cis assignment to the crystalline 2-hydroxymethylcyclopentanol **5** was rigorously proved by conversion into the oxetane **16** by Kovács *et al.*[10] (Chart II). This selective acetalization was used for assignment of stereochemistry to intermediates **44** and **46** in the 9-deoxyprostaglandin synthesis.

One important synthetic operation we had to accomplish for synthesis of either PGE_1 **1** or 9-deoxy-PGE_1 **2** was attachment of the *trans*-allylic alcohol side chain to the cyclopentane ring. The most attractive route seemed to be reaction of an appropriate cyclopentane aldehyde with a Wittig reagent and then metal hydride reduction of the resultant enone. The snag with this route was that the Wittig reagent could function as base as well as nucleophile and cause at least epimerization of the aldehyde, if not elimination. To explore the viability of this route for use in a prostaglandin synthesis, we therefore decided to attempt synthesis of cis and trans 2-methoxycyclopentane aldehyde **17** and **18**. The mixture of 2-carbomethoxy- and carboethoxycyclopentanols was O-methylated.[11,12] The cis and trans mixture of methoxy carbinols **9** and **10**, obtained by $LiAlH_4$ reduction of the mixture of O-methylated esters, was separated by fractional distillation through a spinning band column. The lower boiling fraction was assigned the cis configuration **9** by correlation with material obtained directly from the pure *cis*-2-carbomethoxycyclopentanol. A similar correlation was carried out for the high-boiling trans isomer **10**. The oxidation of the *trans*-2-hydroxymethyl-1-methoxycyclopentane **10** to the *trans*-2-methoxycyclopentane aldehyde **18** proceeded well with Jones reagent. Unfortunately, Jones reagent did not work for the preparation of the *cis*-2-methoxycyclopentane aldehyde **17** from the cis carbinol **9**. Instead a little used procedure due to Barton[13] was tried on the carbinols **9** and **10** and worked extremely well, providing both cis and trans 2-methoxycyclopentane aldehydes **17** and **18** free of each other. Not surprisingly, the trans aldehyde **18** was more stable and yielded normal

Chart II



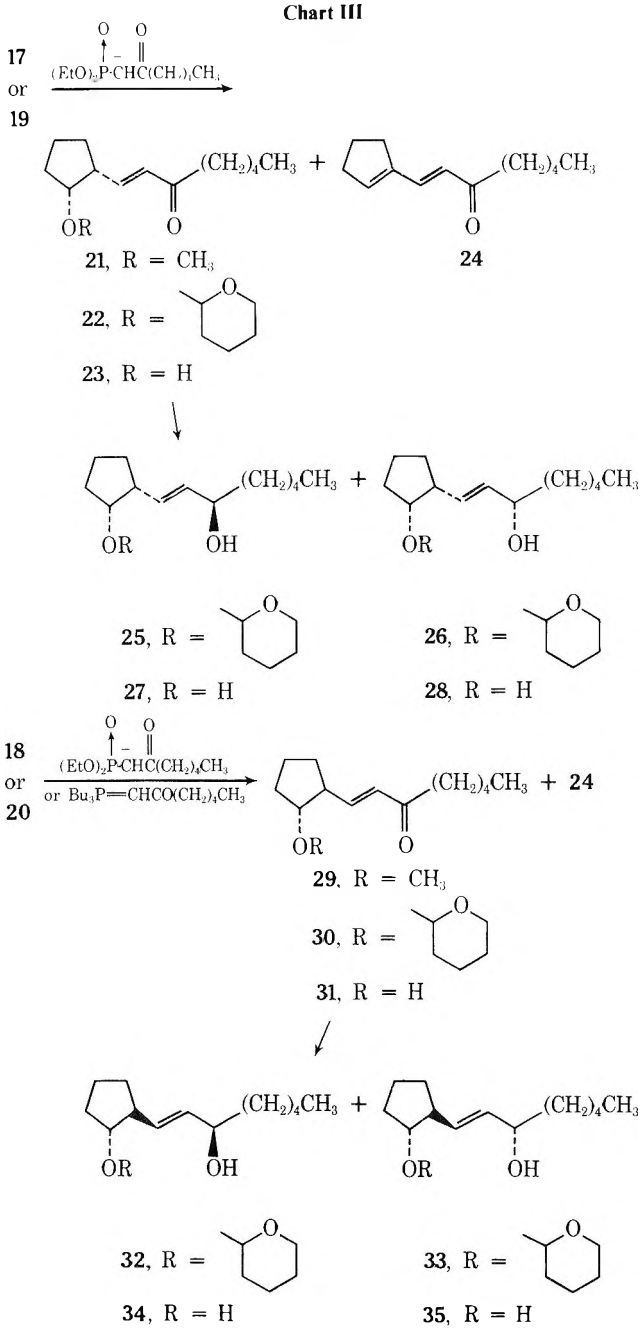
derivatives, *e.g.*, a semicarbazone, whereas cis aldehyde **17** underwent rapid elimination and yielded only derivatives of cyclopentene aldehyde.

Addition of the side chain was achieved by reaction of the aldehydes **17** and **18** with the sodio derivative of diethyl (2-oxoheptyl)phosphonate[14,25] (Chart III).

To our satisfaction, the cis methoxy aldehyde **17** gave exclusively the cis methoxy enone **21**, and the trans methoxy aldehyde **18** the trans enone **29**. Thus, while in both cases, some elimination to the dienone **24** was observed, in neither case did epimerization take place. This was especially evident in the nmr spectra of the enones **21** and **29** as the $-OCH_3$ signal was at different positions (δ 3.26 and 3.30, respectively) and the presence of one in the other would have been obvious. More interestingly though, the position and splitting of the β vinyl H was also quite distinctive, and was obviously to be of value in stereochemical assignments to the allylic alcohol side chain in the more complex molecules we intended to prepare.

Use of the 2-methoxycyclopentane aldehydes **17** and **18** was predicated on their ease of preparation and the utility of a methoxy group as an nmr marker. To be of use as intermediates for a prostaglandin synthesis, it was obviously necessary to explore the sequence with a group which could be more easily converted into a free hydroxyl group. For this purpose tetrahydropyranyloxy was chosen. Preparation of the cis and trans tetrahydropyranyloxy carbinols **13** and **14** proceeded uneventfully. Unfortunately, they did not stand up to the phosgene treatment necessary for the Barton oxidation.[13] Instead the Moffat oxidation[15] was employed, modified by the use of the water-soluble 1-cyclohexyl-3-(2-morpholinoethyl)carbodiimide metho-*p*-toluenesulfonate.[26] Using this variant, excellent yields of the cis and trans 2-tetrahydropyranyloxycyclopentane aldehydes **19** and **20** could be obtained from the carbinols **13** and **14**. This modified Moffat oxidation was subsequently used in our synthesis of PGE_1.[7] Reaction of the *cis*-2-tetrahydropyranyloxycyclopentanecarboxaldehyde (**19**) with the sodio derivative of diethyl (2-oxoheptyl)phosphonate yielded the desired enone **22**, plus some dienone **24**. At this point it was decided to investigate alternative "side-chain addition reagents," which would not cause material loss *via* elimination. One criterion to be met would be reduced basicity. The preformed redistilled ylid 1-tributylphosphoranylidene-2-heptanone met this criterion. This variant of the usual Wittig reagent gave an excellent yield of the desired enone **30** from the trans 2-tetrahydropyranyloxycyclopentane aldehyde **20**. The tetrahydropyranyl group was readily removed from both enones to give the hydroxy enones **23** and **31**. The inspection of the β vinyl H in the nmr spectra, which was less complex than in the tetrahydropyranyl derivatives **22** and **30**, as these were epimeric mixtures at the tetrahydropyranyl group, could now be made and the absence of epimerization α to the aldehyde in either side-chain addition process be assured. We now encountered a further problem in that sodium borohydride reduction of the hydroxy enones **23** and **31** gave substantial amounts of products derived from conjugate addition of hydride, based on a substantial reduction in the integrated area of the vinyl region in the nmr spectra of the products. This presumably occurs *via* intramolecular hydride addition from the alkoxyborane formed from the free alcohol. This was very simply resolved by carrying out the sodium borohydride reduction on the tetrahydropyranyloxy enones **22** and **30**, and cleaving the tetrahydropyranyl ether after reduction. Only a cursory investigation of these last two steps was made with the *cis*-tetrahydropyranyloxy enone **22** and the final diols **27** and **28** were not characterized. Attention was directed to the natural PGE_1 trans stereochemistry. Sodium borohydride reduction of the *trans*-2-tetrahydropyranyloxy enone **30** gave a complex mixture of epimers **32** and **33**. On removal of the tetrahydropyranyl group, the trans diols **34** and **35** were readily separable by silica gel column chromatography. Although stereochemical assignments could not rigorously be made, based on their chromatographic behavior, one could conjecture that the slower moving epimer **35** had the stereochemistry of PGE_1 at the allylic alcohol. Thus, the diol **35** had the stere-

Chart III



ochemistry of PGE_1 at three of its four asymetric centers and also the trans arrangement of the olefin. The stereochemistry of the olefin followed from the method of synthesis *via* a stabilized phosphorus ylid. This had also been confirmed by the coupling constant between the α and β protons in the nmr spectrum of the enone precursor **30.**

Thus, having developed a satisfactory process for conversion of 2-alkoxy cyclopentane aldehydes into compounds such as the diol **35,** which had almost all of the stereochemical features of PGE_1, it seemed appropriate to consider application of the process to a cyclopentane aldehyde with the heptanoic acid side chain of PGE_1 attached.

The choice of starting material for the synthesis of such a cyclopentane aldehyde was the readily available 2-carbomethoxy-3-oxo-1-cyclopenteneheptanoic acid methyl ester[16] **36** (Chart IV). Sodium borohydride reduction of this diester **36** yielded a mixture of two hydroxy diesters **38** and **39,** along with varying amounts of carbinols **42** and **43,** resulting from overreduction. The same two diesters **38** and **39** were also obtained from the cyclopentanone diester **37** by sodium borohydride reduction; therefore, we may presume that they differ only in the stereochemistry of the cyclopentanol carbon C_{11}. The assignment of the faster moving epimer **38** as having the cis arrangement of cyclopentanol hydroxyl and carbomethoxy groups was assured by an infrared study of the OH stretching region as a function of concentration, as was done for the simpler case of the *cis*- and *trans*-2-carbomethoxycyclopentanols.[17] This was confirmed by the rapid selective reduction of the hydroxy diester **38** to the diol ester **42** by sodium borohydride. This diol ester **42** was characterized as the *p*-nitrobenzylidine acid **46,** a process shown in the unsubstituted cyclopentane case to be specific for a cis arrangement of the hydroxy and ester groups (*i.e.*, diol **5** → *p*-nitrobenzylidine acetal **15**). The most convenient synthesis of the trans hydroxy diester **39** took advantage of the more rapid reduction of the cis hydroxy diester **38.** The cyclopentenone diester **36** reacted with excess sodium borohydride at room temperature, rather than 4°. This converted all the *cis*-hydroxy diester **38** formed into the carbinol **42,** enabling the trans hydroxy diester to be isolated by a filtration through silica gel rather than careful chromatography.

In order to strengthen further the stereochemical assignments, the hydroxy diesters **38** and **39** were hydrolyzed to the crystalline diacids **40** and **41** under conditions known to epimerize such an arrangement on a cyclopentane ring, if it were all cis.[7,18]

Reesterification of the hydroxy diacids **40** and **41** with diazomethane regenerated the same hydroxy diesters **38** and **39.**

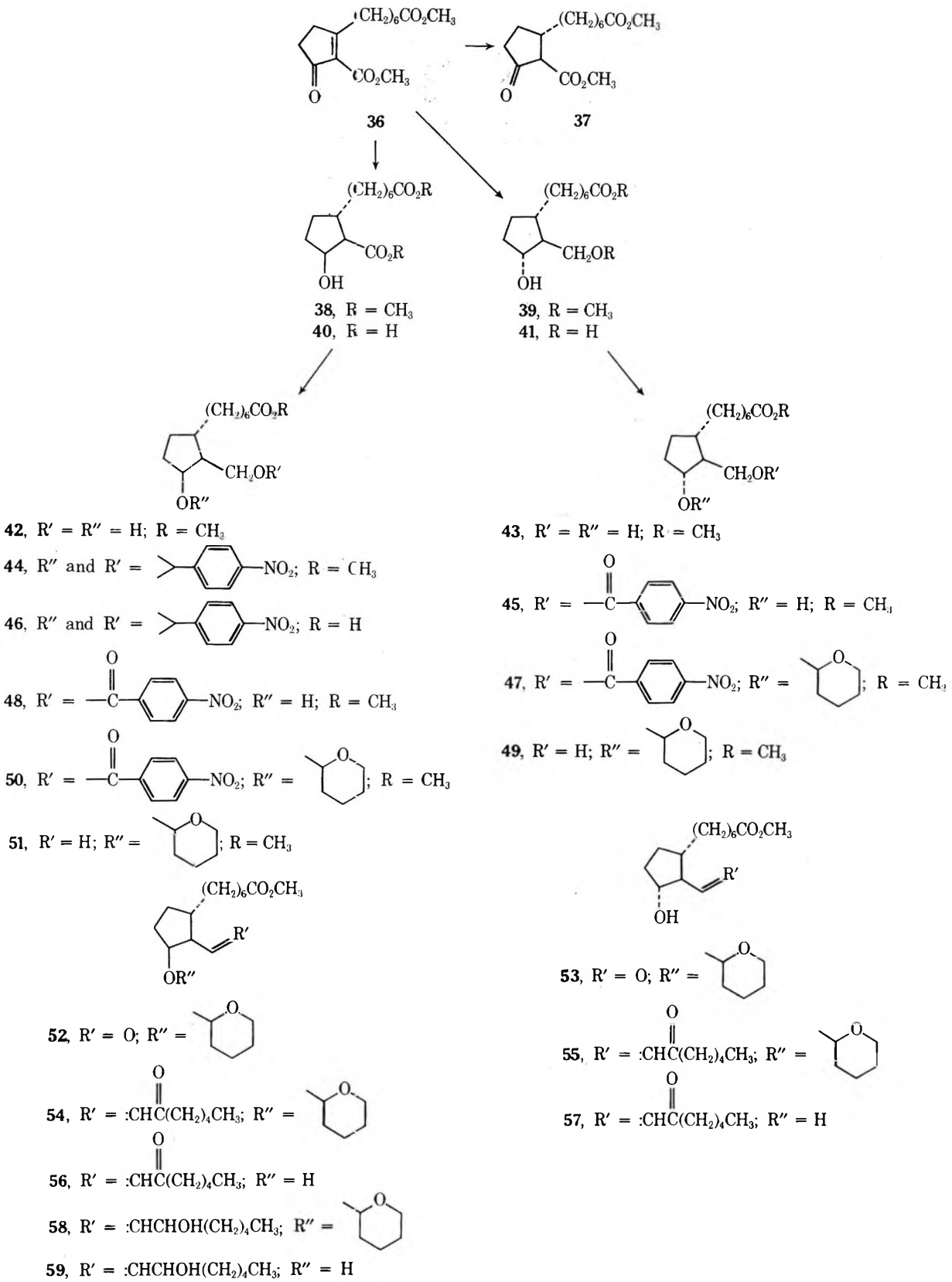
Conversion of the hydroxy diesters **38** and **39** into the tetrahydropyranyloxy aldehydes **52** and **53** was performed slightly differently from that done in the unsubstituted cyclopentane cases, where the *cis*- and *trans*-2-carbomethoxycyclopentanols were converted into the tetrahydropyranyloxy aldehydes **19** and **20.** This was necessitated by the presence of two ester groups in the hydroxy diesters **38** and **39.** Fortunately, with these compounds, access to the diol esters **42** and **43** from the hydroxy diesters **38** and **39** was easier than in the analogous case in the PGE_1 synthesis.[7] Reduction of the cis hydroxy ester **38** to the diol ester **42** did occur faster than reduction of the trans hydroxy ester **39** to the diol ester **43.** However, reduction by sodium borohydride of the carbomethoxy group on the cyclopentane ring, even with the trans hydroxy ester **39,** was substantially faster than reduction of the heptanoic ester. Thus, the diol esters **42** and **43** were best prepared directly from the cyclopentenone diester **36,** by permitting extensive overreduction. The mixture of diol esters **42** and **43,** obtained from a rough column chromatography, was para-nitrobenzoylated. The pure cis *p*-nitrobenzoate **48** and trans *p*-nitrobenzoate **45** could be isolated by preparative thick layer chromatography. The assignment of structure was assured by preparation of the cis *p*-nitrobenzoate **48** from the purified diol ester **42.**

Reaction of these cis and trans *p*-nitrobenzoates **48** and **45** with dihydropyran gave the tetrahydropyranyl ethers **50** and **47.** Methanolysis of these compounds gave the desired tetrahydropyranyloxy carbinol esters **51** and **49,** which could be oxidized to the tetrahydropyranyloxy aldehydes **52** and **53** by either the modified Moffat procedure as used for the cyclopentane derivatives **13** and **14,** or by the use of Collins' reagent.[19]

The cis tetrahydropyranyloxy aldehyde **52** underwent very facile elimination to the cyclopentene aldehyde which was characterized as the semicarbazone.

Reaction of the cis and trans tetrahydropyranyloxy aldehydes **52** and **53** with 1-tributylphosphoranylidine-2-

Chart IV



heptanone gave the enones **54** and **55.** These were reduced with sodium borohydride and the tetrahydropyranyloxy group cleaved with acid. However, an alternative procedure using zinc borohydride,[20] which gives less conjugate reduction, also enabled the hydroxy enones **56** and **57** to be utilized. This was helpful, as comparison of the nmr spectra of **56** and **57** with those of the model compounds **23** and **31** reassured us of the stereochemical assignments, which had been made to these compounds. Reduction with zinc borohydride gave in each case a 1:1 mixture of allylic alcohols epimeric at C_{15}. These were separated by preparative thick layer chromatography. By analogy with the PGE_1 case, the slower moving band from the reduction of the trans hydroxy enone **57** was assigned the PGE_1 configuration. Hydrolysis of the ester gave the beautifully crystalline acid, mp 76–78°, *dl*-9-deoxy-PGE_1 **2.** The C_{15} epimer was not

crystalline; however this is analogous to the situation with *dl*-PGE_1 and *dl*-15-epi-PGE_1.[21]

The slower moving band from the preparative tlc plate of the zinc borohydride reduction of the cis hydroxy enone **56** also yielded a crystalline acid, mp 71–72°, on hydrolysis, which was assigned the 11,15-epi configuration **4**. The C_{15} epimer, obtained by hydrolysis of the faster moving band, was a waxy solid which could not be satisfactorily recrystallized.

All four compounds from the synthesis showed prostaglandin-like effects in various biological tests.[22] These effects were more pronounced, with a given dose, from the crystalline acids 9-deoxy-PGE_1 **2** and 9-deoxy-11,15-epi-PGE_1 **4**, thus providing support for the stereochemical assignments.

Experimental Section[23]

Preparation of *cis*- and *trans*-2-Carbomethoxycyclopentanols. Commercial 2-carboethoxycyclopentanone (190 g), as a mixture of methyl and ethyl esters, was hydrogenated in ethanol (200 ml) at 55 psi over PtO_2 (10 g) until a negative $FeCl_3$ test was obtained (several hours). The catalyst and solvent were removed and the residue was distilled to give 167 g, bp 71–87° (1.5 mm).

A portion (33 g, 0.2 mol) of this material was stirred at room temperature with 10% aqueous KOH (250 ml) until a clear solution was obtained (4 hr). This solution was extracted with ether, acidified with concentrated HCl, saturated with NaCl, and extracted with ether. The extracts were dried ($MgSO_4$) and the ether was removed. The viscous oil (26.5 g) was redissolved in ether and treated with excess ethereal diazomethane. The ethereal solution was washed with 10% $KHCO_3$ and dried ($MgSO_4$) and the ether removed. The resulting oil (33.0 g) was distilled through a Nester Faust spinning band column using a water aspirator. Two principal fractions were collected: the cis isomer, bp 95–97° (15.3 g); and the trans isomer, bp 110–112° (13.3 g). The homogeneity was checked by tlc (silica gel eluted by HCO_2H–$CHCl_3$ 5:95).

***trans*-2-Hydroxymethylcyclopentanol 6 and the *p*-Nitrobenzylidine Derivative of *cis*-2-Hydroxymethylcyclopentanol 15.** The mixture of hydroxy esters from PtO_2 hydrogenation of commercial 2-carboethoxycyclopentanone (5.01 g, 0.032 mol) was refluxed in ether (200 ml) overnight with excess $LiAlH_4$. The excess $LiAlH_4$ was decomposed with saturated Na_2SO_4 solution and the ether separated. The aqueous solution was made strongly acid (10 *N* H_2SO_4) to dissolve the precipitated solids and was continuously extracted overnight with ether. The combined ethereal extracts were dried ($MgSO_4$), and the ether was removed to yield an amber oil (**5** + **6**), 3.3 g (90%).

This amber oil (506 mg, 4.35 mmol) was dissolved in benzene (15 ml), and *p*-nitrobenzaldehyde dimethyl acetal[8] (426 mg, 2.16 mmol) and a few crystals of *p*-toluenesulfonic acid were added. The mixture was refluxed for 2.5 hr; the benzene was concentrated to half-volume and added directly to an alumina column (13 g, neutral I) made up in benzene. Elution by benzene yielded **15** as an oil (467 mg, 1.87 mmol 43%) which crystallized, mp 86–88°. Recrystallization from hexane yielded colorless needles; mp 88–89°; ir (Nujol) 1610 (m), 1525 (s), 1328 (s), 1100 (s) cm; uv λ_{max} (MeOH) 263 mμ (ε 11,780); nmr ($CDCl_3$) δ 7.99 (m,4), 5.54 (s,1), 4.37 (m,1), 4.21 (broad singlet, 2).

Anal. Calcd for $C_{13}H_{15}O_4N$: C, 62.64: H, 6.07; N, 5.62. Found: C, 62.45; H, 6.20; N, 5.04.

Elution of the column with ethyl acetate gave an amber-colored oil (260 mg, 2.24 mmol, 51%). Several such column strippings were combined and distilled. A main fraction was collected of *trans*-2-hydroxycyclopentanol **6**: bp 82–83° (0.1 mm); ir (film) 3320 (s), 1430 (m), 1335 (m), 1020 (s) cm^{-1}; nmr ($CDCl_3$) δ 4.00 (m, 1), 3.62 (complex multiplet, 2).

Anal. Calcd for $C_6H_{12}O_2$: C, 62.04; H, 10.41. Found: C, 61.77; H, 10.29.

$LiAlH_4$ reduction in ether of the *trans*-2-hydroxycyclopentanecarboxylic acid methyl ester obtained by fractional distillation yielded an oil identical (tlc,[24] ir, nmr) with that obtained from the above column strippings.

***cis*-2-Hydroxymethylcyclopentanol 5 *via* the *p*-Nitrobenzylidine Acetal 15.** The *p*-nitrobenzylidine acetal **15** (1 g, 4.02 mmol) was stirred in methanol (25 ml), and Brady's reagent (0.8 g of 2,4-dinitrophenylhydrazine, 1.6 ml of concentrated H_2SO_4, 12 ml of MeOH, and 4 ml of water) was added dropwise during 30 min. The mixture was stirred overnight at room temperature. The yellow precipitate was collected (1.19 g, 3.59 mmol, 89%), mp 321–323° dec (lit value for *p*-nitrobenzaldehyde 2,4-dinitrophenylhydrazone, mp 320°). The filtrate was diluted with saturated $(NH_4)_2SO_4$ solution and continuously extracted overnight with ether. The ether was dried ($MgSO_4$) and removed. The residue (500 mg) was distilled in a short path apparatus to give a colorless oil, bp 81–83° (0.5 mm) (300 mg, 2.58 mmol, 64%), which crystallized on standing, mp 31–34°. Recrystallized from ether–pentane to give *cis*-2-hydroxymethylcyclopentanol **5**: mp 33–34°; ir (film) 3295–3345 (broad, s), 1005 (s), 930 (m) cm^{-1}; nmr ($CDCl_3$) δ 4.34 (m, 1), 3.73 (doublet, 2).

Anal. Calcd for $C_6H_{12}O_2$; C, 62.04; H, 10.41. Found: C, 62.03; H, 10.39.

$LiAlH_4$ reduction in ether of the *cis*-2-hydroxycyclopentanecarboxylic acid methyl ester obtained by fractional distillation yielded a crystalline diol, mp 33–34°, identical (tlc,[24] melting point, mixture melting point, ir, nmr) with that obtained by regeneration from the cyclic acetal.

The Bis-3,5-dinitrobenzoate of *trans*-2-Hydroxymethylcyclopentanol (8). *trans*-2-Hydroxymethylcyclopentanol (**6**) (0.9 g, 7.76 mmol) was dissolved in dry pyridine (25 ml) and with stirring 3,5-dinitrobenzoyl chloride (4.31 g, 18.66 mmol) was added slowly. The mixture was stirred at room temperature overnight. The pyridine was removed *in vacuo*. The residue was dissolved in CH_2Cl_2 and passed through an alumina column (neutral I) made up in and eluted by CH_2Cl_2. The eluted solids (2.79 g, 4.72 mmol, 61%) were recrystallized from CH_2Cl_2–hexane to give the trans bis-3,5-dinitrobenzoate (**8**): mp 152–154°; ir (Nujol) 1720 (s), 1630 (m), 1545 (s), 720 (s) cm^{-1}; nmr (DMSO) δ 8.89 (m, 6), 5.49 (m, 1), 4.51 (m, 2).

Anal. Calcd for $C_{20}H_{16}N_4O_{12}$: C, 47.62; H, 3.20. Found: C, 47.85; H, 3.62.

The Bis-3,5-dinitrobenzoate of *cis*-2-Hydroxymethylcyclopentanol (7). *cis*-2-Hydroxymethylcyclopentanol (**5**) (438 mg, 3.77 mmol) reacted with 3,5-dinitrobenzoyl chloride in pyridine in an analogous manner. The CH_2Cl_2 eluted solids (1.52 g, 3.01 mmol, 80%) were crystallized from CH_2Cl_2–hexane to the cis bis-3,5-dinitrobenzoate **7**: mp 172–174°; ir (Nujol) 1725 (s), 1625 (m), 1545 (s), 718 (s), cm^{-1}; nmr (DMSO) δ 8.91 (m, 6), 5.67 (m, 1), 4.56 (doublet, 2).

Anal. Calcd for $C_{20}H_{16}N_4O_{12}$: C, 47.62; H, 3.20. Found: C, 47.63; H, 3.36.

Preparation of *cis*- and *trans*-2-Hydroxymethylcyclopentanol Methyl Ether 9 and 10. The mixture of hydroxy esters from PtO_2 hydrogenation of commercial 2-carboethoxycyclopentanone (45 g, 0.312 mol) was dissolved in acetonitrile (200 ml) and methyl iodide (160 ml). Ag_2O (80 g) was added. The mixture was refluxed and stirred overnight. The solids were removed by filtration and the solvents removed. The residue was distilled at the aspirator. The main fraction, bp 81–86° (34.6 g, 0.219 mol, 70%), was used for reduction directly.

The mixture of methoxy esters (52 g, 0.329 mol) was refluxed with $LiAlH_4$ (35 g) in dry 1,2-dimethoxyethane (350 ml) overnight. The excess $LiAlH_4$ was decomposed with saturated Na_2SO_4 solution and ether extracted. Removal of the ether gave an oil (35 g, 0.269 mol, 82%) which was distilled through a Nester Faust spinning band column at the aspirator. Two main fractions were collected.

cis-2-Hydroxymethylcyclopentanol methyl ether **9**: bp 75–76°; ir (film) 3400 (broad, s), 1080 (s), 1035 (m) cm^{-1}; nmr ($CDCl_3$) δ 3.72 (m, 3), 3.30 (s, 3).

Anal. Calcd for $C_7H_{14}O_2$: C, 64.58; H, 10.84. Found: C, 64.43; H, 10.68.

trans-2-Hydroxymethylcyclopentanol methyl ether **10**: bp 84–85°; ir (film) 3410 (s), 1470 (m), 1372 (m), 1080 (s) cm^{-1}; nmr ($CDCl_3$) δ 3.58 (m, 3), 3.29 (s, 3).

Anal. Calcd for $C_7H_{14}O_2$: C, 64.58; H, 10.84. Found: C, 64.77; H, 11.05.

The stereochemical assignments were checked by a CCl_4 dilution ir study which showed evidence of strong intramolecular hydrogen bonding in the cis isomer **9** and only intermolecular hydrogen bonding in the trans **10**.

***cis*-2-Methoxycyclopentanecarboxylic Acid Methyl Ester.** *cis*-2-Hydroxycyclopentanecarboxylic acid methyl ester (2 g, 0.0139 mol) was dissolved in CH_3CN (15 ml) and CH_3I (15 ml). The mixture was stirred at reflux overnight with Ag_2O (5 g). Methylation was complete based on tlc (silica gel–$CHCl_3$). The solids were removed by filtration and the filtrate concentrated to dry-

ness, and the residue (2.16 g) was distilled at the aspirator, to give *cis*-2-methoxycyclopentanecarboxylic acid methyl ester: bp 80° (1.5 g, 0.00948 mol, 68%); nmr ($CDCl_3$) δ 3.99 (m, 1), 3.70 (s, 3), 3.29 (s, 3), 2.83 (m, 1).

***cis*-2-Hydroxymethylcyclopentanol Methyl Ether 9.** *cis*-2-Methoxycyclopentanecarboxylic acid methyl ester (800 mg, 5.06 mmol) was dissolved in dry 1,2-dimethoxyethane. $LiAlH_4$ (2 g) was added and the mixture refluxed overnight. The excess reagent was decomposed with saturated Na_2SO_4 solution and made acidic (HCl) and ether extracted. The ether was dried and removed and the residue (1 g) distilled in a short path apparatus at the aspirator. The main fraction, bp 85–86°, was identical (tlc, ir, nmr) with the lower-boiling fraction compound **9** from the spinning band distillation of the cis/trans mixture of 2-methoxycyclopentanols.

***trans*-2-Hydroxymethylcyclopentanol Methyl Ether 10.** *trans*-2-Hydroxycyclopentanecarboxylic acid methyl ester was O-methylated and reduced by $LiAlH_4$ analogously to the cis ester. The main fraction had bp 77° (aspirator) and was identical (tlc, ir, nmr) with the higher-boiling fraction compound **10** from the spinning band distillation of the cis/trans mixture of 2-methoxycyclopentanols.

***trans*-2-Methoxycyclopentanecarboxaldehyde (18) *via* Jones Oxidation.** *trans*-2-Hydroxymethylcyclopentanol methyl ether **10** (1 g, 7.68 mmol) was dissolved in acetone (10 ml). The solution was cooled to 0° (ice–salt bath) and treated dropwise with Jones reagent (1 ml). On completing the addition, the mixture was diluted with ice-cold salt solution and ether extracted. The ethereal extract was washed with ice-cold 10% $KHCO_3$ and the ether removed. The residue (800 mg, 6.24 mmol, 81%) contained only a trace of the starting alcohol **10** by the tlc (silica gel–$CHCl_3$) and consisted of a single faster moving material. Attempts to distil this material to obtain an analysis were not successful. The spectra were satisfactory for *trans*-2-methoxycyclopentanecarboxaldehyde (18): ir (film) 1721, 1092 cm^{-1}; nmr ($CDCl_3$) δ 9.72 (m, 1), 4.02 (m, 1), 3.30 (s, 3), 2.79 (m, 1).

The aldehyde was characterized as the semicarbazone; mp 178° (methanol); ir (Nujol) 3450 (m), 3210 (m), 3150 (m), 1692 (s), 1573 (m) cm^{-1}; uv λ_{max} (MeOH) 228 mμ (ϵ 14,010).

Anal. Calcd for $C_8H_{15}N_3O_2$: C, 51.87; H, 8.16; N, 22.69. Found: C, 51.78; H, 8.18; N, 22.83.

***trans*-2-Methoxycyclopentanecarboxaldehyde (18) *via* Barton Oxidation.** *trans*-2-Hydroxymethylcyclopentanol methyl ether **10** (11.1 g, 0.0852 mol) was dissolved in a 12.5% benzene solution of phosgene (150 ml). The solution was stirred overnight at room temperature, and the solvents were removed at the aspirator. The residue was distilled and the main fraction was the chloroformate **12**: bp 72–3° (1.5 mm) (14.03 g, 0.0728 mol, 85%); ir (film) 1770–1790 (broad, s), 1150 (s) cm^{-1}; nmr ($CDCl_3$) δ 4.27 (doublet, 2), 3.52 (m, 1), 3.28 (s, 3).

Anal. Calcd for $C_8H_{13}ClO_3$: C, 49.88; H, 6.80; Cl, 18.41. Found: C, 49.90; H, 6.89; Cl, 18.53.

The trans 2-methoxychloroformate **12** (8.62 g, 0.0451 mol) was cooled to ~5° and dry DMSO (25 ml) added slowly. The temperature rose (30°) and gas evolution was evident. The solution was stirred at room temperature for 25 min. Dry triethylamine (6.4 ml) was added dropwise; again the reaction was slightly exothermic and a precipitate developed. The mixture was stirred at room temperature for 25 min and then poured onto ice–water and ether extracted. The ethereal extract was dried ($MgSO_4$) and evaporated. The residue (5.5 g, 0.0429 mol, 95%) contained only traces of *trans*-2-hydroxymethylcyclopentanol methyl ether **10** by tlc (silica gel–$CHCl_3$). This was distilled and the main fraction (3.5 g, 0.0273 mol, 60%), bp 41–46° (2.5 mm), was identical (tlc, ir, nmr) with the trans 2-methoxycyclopentane aldehyde **18** prepared by the Jones oxidation.

***cis*-2-Methoxycyclopentanecarboxaldehyde (17) *via* the Barton Oxidation.** *cis*-2-Hydroxymethylcyclopentanol methyl ether **9** (5.47 g, 0.042 mol) was converted into the chloroformate **11** in a manner analogous to the trans compound **12**. This was treated with DMSO and in turn with triethylamine. The resulting oil (5.0 g, 0.039 mol, 93%) was distilled. The main fraction was cis 2-methoxycyclopentane aldehyde **17** (3.63 g, 0.028 mol, 67%): bp 44–51° (1.8 mm); ir (film) 2740 (w), 1723 (s), 1035 (s) cm^{-1}; nmr ($CDCl_3$) δ 9.79 (m, 1), 4.17 (m, 1), 3.28 (s, 3). Satisfactory analysis could not be obtained although the material contained only traces of impurities (cyclopentene aldehyde and the starting alcohol) by tlc (silica gel–$CHCl_3$). Also, attempts to obtain derivatives were unsuccessful. Reaction with thiosemicarbazide gave the thiosemicarbazone of cyclopentene aldehyde, mp 175° (aqueous acetic acid).

Anal. Calcd for $C_7H_{11}N_3S$: C, 49.61; H, 6.55; N, 24.83. Found: C, 49.29; H, 6.42; N, 24.80.

Wadsworth–Emmons Reaction with *trans*-2-Methoxycyclopentanecarboxaldehyde (18). Diethyl (2-oxoheptyl)phosphonate[25] (10.97 g, 0.0438 mol) was dissolved in dry DMSO (60 ml) and treated with NaH (0.957 g, 0.0399 mol) for 1 hr at room temperature. Then *trans*-2-methoxycyclopentanecarboxaldehyde (**18**) (5.1 g, 0.0398 mol) in dry DMSO (25 ml) was added dropwise with stirring at room temperature. The mixture was stirred overnight and poured into ice–water and ether extracted. The ether was dried ($MgSO_4$) and removed *in vacuo*. The residue, an amber oil (10.5 g), was chromatographed over silica gel (215 g) eluted by CH_2Cl_2. The early eluates contained artefacts, but a main fraction was collected (1.35 g, 0.007 mol, 18%) which was distilled. The bulk distilled at 99–101° (0.35 mm) to give the dienone **24** as a clear oil (951 mg, 4.95 mmol, 12%): ir (film) 1685 (m), 1660 (s), 1610 (s), 1590 (m) cm^{-1}; nmr ($CDCl_3$) δ 7.37 (d, 1), 6.21 (m, 1), 5.98 (d, 1), 2.50 (m, 6), 0.89 (m, 3); uv λ_{max} (MeOH) 222 mμ (ϵ 3,430), 284 (22,260).

Anal. Calcd for $C_{13}H_{20}O$: C, 81.20; H, 10.48. Found: C, 80.63; H, 10.46.

The principal fraction was eluted by 5–10% ethyl acetate–CH_2Cl_2 (4.51 g, 0.0201 mol, 50%). This was distilled and the center fraction (2.656 g, 0.0118 mol, 29%), bp 110–111° (0.3 mm), was the trans methoxy enone **29**: ir (film) 1690 (m), 1670 (s), 1625 (s) 1100 (s) cm^{-1}; nmr ($CDCl_3$) δ 6.80 (pair of doublets, 1), 6.10 (d, 1), 3.56 (m, 1), 3.30 (s, 3), 0.90 (m, 3); uv λ_{max} (MeOH), 228 mμ (ϵ 12,700).

Anal. Calcd for $C_{14}H_{24}O_2$: C, 74.95; H, 10.78. Found: C, 74.83; H, 10.52.

Wadsworth–Emmons Reaction with Cis 2-Methoxycyclopentane Aldehyde 17. The cis 2-methoxycyclopentane aldehyde **17** (2.7 g, 21.1 mmol) reacted with diethyl (2-oxoheptyl)phosphonate[25] (5.8 g, 23.2 mmol) in an analogous manner. The principal chromatographic fraction (3.31 g, 14.8 mmol, 70%) was eluted by 5% ethyl acetate in CH_2Cl_2 from silica gel. This was distilled and the main fraction (2.59 g, 11.5 mmol, 55%), bp 91–5° (0.02 mm), was the cis methoxy enone **21**: ir (film) 1700 (m), 1675 (s), 1630 (s), 1090 (s) cm^{-1}; nmr ($CDCl_3$) δ 6.96 (pair doublets, 1), 6.05 (d, 1), 3.64 (m, 1), 3.26 (s, 3), 0.89 (m, 3); uv λ_{max} (MeOH) 228 mμ (ϵ 12,450).

Anal. Calcd for $C_{14}H_{24}O_2$: C, 74.95; H, 10.78. Found: C, 74.73; H, 10.72.

***trans*-2-Tetrahydropyranyloxycyclopentanecarboxylic Acid Methyl Ester.** *trans*-2-Hydroxycyclopentanecarboxylic acid methyl ester (4.583 g, 0.0318 mol) was dissolved in CH_2Cl_2 (15 ml). 2,3-Dihydro-γ-pyran (3.21 g, 0.0382 mol) and concentrated HCl (3 drops) were added and the mixture was shaken. After standing at room temperature for 1 hr, the reaction was checked by tlc (silica gel–benzene), then washed (10% aqueous $KHCO_3$), dried ($MgSO_4$), and concentrated *in vacuo*. The residue was distilled and the main fraction was the trans THP ether methyl ester (5.785 g, 0.0253 mol, 80%): bp 98–100° (0.1 mm); ir (film) 1730 (s), 1200 (s), 1032 (s) cm^{-1}; nmr ($CDCl_3$) δ 4.65 (m, 1), 441 (m, 1), 3.66 (s, 3), 3.22–4.15 (complex multiplet, 2).

Anal. Calcd for $C_{12}H_{20}O_4$: C, 63.13; H, 8.83. Found: C, 62.94; H, 8.99.

***cis*-2-Tetrahydropyranyloxycyclopentanecarboxylic Acid Methyl Ester.** *cis*-2-Hydroxycyclopentanecarboxylic acid methyl ester reacted in an exactly analogous way to give an 80% yield of the *cis*-THP ether methyl ester: bp 100–105° (0.1 mm); ir (film) 1745 (s), 1250 (s), 1025 (s) cm^{-1}; nmr ($CDCl_3$) δ 4.71 (m, 1), 4.45 (m, 1), 3.71 (s, 3), 3.28–4.10 (complex multiplet, 2).

Anal. Calcd for $C_{12}H_{20}O_4$: C, 63.13; H, 8.83. Found: C, 63.24; H, 8.87.

***trans*-2-Hydroxymethylcyclopentanol THP Ether (14).** The trans THP methyl ester (23.89 g, 0.105 mol) was added to $LiBH_4$ (6 g) in ether (250 ml). The mixture was refuxed for 3 hr, allowed to stand overnight at room temperature, and then washed with water. The ether was removed to give an oil (19.2 g). This was distilled and the main fraction was the trans THP carbinol **14** (17.17 g, 0.086 mol, 82%): bp 90–96° (0.01 mm); ir (film) 3432 (s), 1135 (m), 1075 (m), 1025 (s) cm^{-1}; nmr ($CDCl_3$) δ 4.64 (m, 1), 3.90 (m, 2), 3.56 (m, 2).

Anal. Calcd for $C_{11}H_{20}O_3$: C, 65.97; H, 10.07. Found: C, 65.99; H, 9.89.

***cis*-2-Hydroxymethylcyclopentanol THP Ether (13).** The cis THP ester (23.4 g, 0.102 mol) was reduced by $LiBH_4$ in ether and worked up as previously described to give a principal fraction: bp 110° (0.1 mm) which was the cis THP carbinol **13** (16.43 g, 0.082 mol, 80%); ir (film) 3450 (s), 1350 (m), 1025 (s) cm^{-1}; nmr

($CDCl_3$) δ 4.63 (m, 1), 4.27 (m, 1), 3.35–4.17 (complex multiplet, 4).

Anal. Calcd for $C_{11}H_{20}O_3$: C, 65.97; H, 10.07. Found: C, 65.87; H, 10.06.

***trans*-2-Tetrahydropyranyloxycyclopentanecarboxaldehyde (20).** The *trans*-2-tetrahydropyranyloxycyclopentylcarbinol (14) (6.25 g, 0.0312 mol) was dissolved in a mixture of dry benzene (250 ml) and dry DMSO (250 ml) and cooled to 4° in ice. Dry pyridine (4.5 ml), trifluoroacetic acid (3.4 ml), and 1-cyclohexyl-3-(2-morpholinoethyl)carbodiimide metho-*p*-toluenesulfonate[26] (60 g, 0.142 mol) were added and the mixture stirred for 5 days at 0–4°. The reaction was diluted with ice–water and extracted with ether. Removal of the ether gave an oil which was distilled. The main fraction, bp 77–82° (0.06 mm) (4.97 g, 0.0251 mol, 80%), did not give a satisfactory elemental analysis, but was principally the trans aldehyde **20** based on ir (film) 2710 (w), 1722 (s), 1035 (s) cm^{-1}; nmr ($CDCl_3$) δ 10.55 (m, 1), 4.63 (m, 1), 4.42 (m, 1).

***cis*-2-Tetrahydropyranyloxycyclopentanecarboxaldehyde (19).** The *cis*-2-tetrahydropyranyloxycyclopentylcarbinol (13) (10 g, 0.0499 mol) was oxidized analogously to give after distillation a main fraction, bp 80–83° (0.05 mm) (8.49 g, 0.0428 mol, 86%), which was the cis aldehyde **19** based on ir (film) 2720 (w), 1720 (s), 1130 (s), 1020 (s) cm^{-1}; nmr ($CDCl_3$) δ 9.93 (m, 1), 4.68 (m, 1), 4.41 (m, 1).

Wadsworth–Emmons Reaction with *cis*-2-Tetrahydropyranyloxycyclopentanecarboxaldehyde (19). *cis*-2-Tetrahydropyranyloxycyclopentanecarboxaldehyde (19) (897 mg, 4.52 mmol) was dissolved in dry DMSO (5 ml) and added dropwise to a solution of diethyl (2-oxoheptyl)phosphonate[25] (1.515 g, 6.05 mmol) in DMSO (10 ml) which had been treated with 1 equiv of NaH for 1 hr. The mixture was stirred overnight at room temperature, diluted with water, and extracted with ether. The ether was removed and the residue chromatographed on silica gel made up in CH_2Cl_2 and eluted by ethyl acetate–CH_2Cl_2 (1:19 and 1:9). The main fraction was the cis tetrahydropyranyloxy enone **22** (856 mg, 2.91 mmol, 64%) which was characterized spectrally: ir (film) 1742 (s), 1725 (m), 1700 (m), 1680 (s), 1635 (m) cm^{-1}; nmr ($CDCl_3$) δ 6.58–7.08 (complex multiplet, 1), 6.12 (d, 1), 4.67 (m, 1), 4.25 (m, 1), 0.89 (m, 3); uv λ_{max} (MeOH) 228 mμ (ε 9751). Forerun material from the column chromatography was characterized as the 2,4-dinitrophenylhydrazone of the dienone **24**: mp 126–128° (aq MeOH): ir (Nujol) 3310 (w), 1615 (s), 1595 (s), 1310 (s) cm^{-1}; nmr ($CDCl_3$) δ 9.05 (d, 1), 8.10 (m, 2), 6.98 (m, 1), 6.27 (m, 2), 0.91 (m, 3); uv λ_{max} (MeOH) 225 mμ (ε 16,720), 265 (17,470), 301 (13,770), 387 (29,560).

Anal. Calcd for $C_{19}H_{24}N_4O_4$: C, 61.27; H, 6.48. Found: C, 60.93; H, 6.71.

Wittig Reaction with *trans*-2-Tetrahydropyranyloxycyclopentanecarboxaldehyde (20). *trans*-2-Tetrahydropyranyloxycyclopentanecarboxaldehyde (**20**) (6.7 g, 0.0338 mol) was dissolved in ether (150 ml), and 1-tributylphosphoranylidene-2-heptanone[7] (10.15 g, 0.033 mol) was added. The mixture was stirred overnight at room temperature. The ether was removed; the residue was dissolved in CH_2Cl_2 and filtered through a silica gel column (450 g) made up in CH_2Cl_2. A main fraction (8.4 g, 0.0285 mol, 84%) was eluted by ethyl acetate–CH_2Cl_2 (1:9) which based on spectra [ir (film) 1725 (m), 1695 (m), 1675 (s), 1630 (m), 1135 (s), 1020 (s) cm^{-1}; nmr ($CDCl_3$) δ 6.70–7.21 (complex multiplet, 1) 6.07 (d, 1), 4.61 (m, 1), 4.23 (m, 1), 0.88 (m, 3)] was the desired trans tetrahydropyranyloxy enone **30.** Attempts to distil this product gave a main fraction, bp 135° (0.05 mm), but some decomposition occurs and a satisfactory elemental analysis could not be obtained. The material was used for the next step directly from the chromatography.

The Trans 2-Hydroxy Enone 31. The trans tetrahydropyranyloxy enone **30** (2.76 g, 9.37 mmol) was dissolved in 10% methanolic oxalic acid (30 ml) and allowed to stand at room temperature for 5 hr. The methanol was removed. The residue was dissolved in excess 10% aqueous $KHCO_3$ solution and ether. The ether was separated, dried, and removed. The residue was chromatographed on silica gel (60 g) made up in ethyl acetate–CH_2Cl_2 (1:9). Elution yielded 218 mg, principally starting material. Elution with a 1:4 mixture yielded the principal fraction (1.713 g, 8.15 mmol, 87%), which was distilled in a short path apparatus. The main fraction, bp 118–119° (0.03 mm) (1.192 g, 5.67 mmol, 60%), was the hydroxy enone **31**: ir ($CHCl_3$) 3620 (w), 3465 (w), 1690 (s), 1665 (s), 1625 (s) cm^{-1}; nmr ($CDCl_3$) δ 6.83 (pair doublets, 1), 6.17 (d, 1), 4.02 (m, 1), 2.55 (m, 2), 0.89 (m, 3); uv λ_{max} (MeOH) 230 mμ (ε 14,070).

Anal. Calcd for $C_{13}H_{22}O_2$: C, 74.24; H, 10.54. Found: C, 74.48; H, 10.78.

Borohydride Reduction of the Trans 2-Tetrahydropyranyloxy Enone 30. The trans tetrahydropyranyloxy enone **30** (3.558 g, 0.0121 mol) was dissolved in methanol (20 ml) and cooled to −5°. $NaBH_4$ (2 g) was added portionwise with stirring and cooling, making sure that the temperature did not rise above 5°; reaction time was 1 hr. Completion of the reaction was checked by tlc (silica gel–$CHCl_3$). The methanol was removed *in vacuo*. The residue was dissolved in salt solution and extracted with ether. The ether was removed and the residue (3.64 g) chromatographed on silica gel (100 g). The main fraction was eluted by ethyl acetate–CH_2Cl_2 (1:9) (2.79 g, 0.0094 mol, 78%), which was distilled to give a mixture of the alcohols **32** and **33**: bp 130–134° (0.03 mm); ir (film) 3460 (m), 1450 (m), 1350 (m), 1130 (s), 1030 (s) cm^{-1}; nmr ($CDCl_3$) δ 5.58 (m, 2), 4.64 (m, 1), 3.92 (m, 3), 0.92 (m, 3).

Anal. Calcd for $C_{18}H_{32}O_3$: C, 72.92; H, 10.88. Found: C, 72.81; H, 11.13.

The PGE_1 Model Compounds 34 and 35. The trans tetrahydropyranyloxy alcohol mixture **32** and **33** (3 g, 0.0101 mol) was dissolved in methanol (300 ml), and 1.0 *N* HCl (4 ml) was added. The mixture was stirred at room temperature for 1 hr. Based on tlc (silica gel eluted by ethyl acetate–chloroform 1:4) the reaction was completed. It was diluted with salt solution and extracted by ether. The ethereal extracts were dried ($MgSO_4$) and the ether removed. The residue (1.99 g, 0.0094 mol, 93%) was chromatographed on silica gel (60 g) made up in ethyl acetate–CH_2Cl_2 (1:9). The progress of the chromatography was followed by tlc fractions were combined on the basis of the tlc data. Three main fractions were obtained by elution with ethyl acetate–CH_2Cl_2 (1:4). The first fraction (640 mg, 0.00301 mol, 30%) was exclusively the faster moving epimer **34.** This was distilled, bp 120–125° (0.05 mm); nmr ($CDCl_3$) δ 5.58 (m, 2), 3.91 (m, 2), 0.88 (m, 3).

Anal. Calcd for $C_{13}H_{24}O_2$: C, 73.53; H, 11.39. Found: C, 73.32; H, 11.29.

The second fraction (385 mg, 0.00181 mol, 18%) was a mixture of both epimers **42** and **43.**

The third fraction (665 mg, 0.00313 mol, 31%) was exclusively the slower moving epimer **35.** This was also distilled, bp 120–128° (0.05 mm); nmr ($CDCl_3$) δ 5.51 (m, 2), 3.82 (m, 2) 0.88 (m, 3).

Anal. Calcd for $C_{13}H_{24}O_2$: C, 73.53; H, 11.39. Found: C, 73.67; H, 11.22.

Borohydride Reduction of the Cyclopentenone Diester 36 to the Cyclopentanol Diester 38. The cyclopentanone diester[16] **36** (12.5 g, 0.0442 mol) was dissolved in methanol (250 ml) and cooled in an ice bath. With stirring $NaBH_4$ (6.5 g) was added portionwise during 1.5 hr such that the temperature remained around 5°. Stirring was continued for a further 30 min. The methanol was removed *in vacuo*. The residue was shaken with ice–saturated NaCl solution and ether. The ether was separated, dried ($MgSO_4$), and removed. The residue (12.9 g) was chromatographed on alumina (580 g of neutral III) made up in CH_2Cl_2. Elution by CH_2Cl_2 gave a colorless oil **38** (6.23 g, 0.0217 mol, 49%) which was homogeneous based on tlc (silica gel–ethyl acetate) This diester **38** was characterized by hydrolysis to the crystalline diacid **40.**

Hydrolysis of the Cyclopentanol Diester 38 to the Diacid 40. The cyclopentanol diester **38** (104 mg, 0.363 mmol) was dissolved in methanol (3 ml), and 10% aqueous K_2CO_3 (3 ml) was added. The mixture was refluxed for 1 hr, concentrated *in vacuo*, and diluted with water; ether was extracted. The aqueous part was acidified and reextracted with ether. Removal of the ether gave a colorless oil (107 mg) which crystallized slowly. This was recrystallized from ether–petroleum ether to give the cyclopentanol diacid **40** (74 mg, 0.286 mmol, 79%): mp 100–101°; ir (Nujol) 3425 (m), 1705 (broad, s) 1300 (m) cm^{-1}.

Anal. Calcd for $C_{13}H_{22}O_5$: C, 60.44; H, 8.59. Found: C, 60.20; H, 8.49.

In a repeat experiment, the crude diacid **40** instead of being recrystallized was redissolved in ether and treated with excess diazomethane. Removal of the ether gave an oil **38** which was identical (ir, tlc) with original diester **38.**

Borohydride Reduction of the Cyclopentanol Diester 38 to the Diol Ester 42. The cyclopentanol diester **38** (2.6 g, 9.08 mmol) was dissolved in methanol (75 ml) and cooled to 4° in ice. $NaBH_4$ (1.7 g) was added with stirring and the reaction allowed to warm to room temperature. By tlc (silica gel–ethyl acetate–chloroform 1:4) the reaction was half-complete. Further $NaBH_4$ (250 mg) was added and the mixture stirred overnight at room temperature. The reaction was diluted with water and extracted with ether. The ether was removed and the residue chromatographed on silica gel (60 g) made up in ethyl acetate–CH_2Cl_2 (2:3). Elution with this mixture yielded a forerun (460 mg) which was principally the starting diester **38** (ir, tlc). The principal fraction was the diol ester

42 eluted by ethyl acetate–CH_2Cl_2 (4:1) (1.8 g, 6.97 mmol, 76%): ir (film) 3380 (broad, s), 1735 (s), 1440 (m) cm^{-1}; nmr ($CDCl_3$) δ 4.38 (m, 1), 3.68 (s, 3), 3.62 (m, 2), 2.33 (t, 2).

This material was characterized as the *p*-nitrobenzylidene acetal. The diol ester **42** (390 mg, 1.51 mmol) was dissolved in benzene (35 ml). *p*-Nitrobenzaldehyde dimethyl acetal[8] (300 mg, 1.52 mmol) and *p*-toluenesulfonic acid (a few crystals) were added. The mixture was refluxed overnight, then filtered through alumina (20 g, neutral III) made up in benzene and eluted by benzene. The eluates were concentrated to dryness to give a pale yellow waxy solid **44** (534 mg, 1.36 mmol, 90%); ir (film) 1732 (s), 1610 (m), 1525 (s), 1350 (s), 850 (m) cm^{-1}; nmr ($CDCl_3$) δ 7.90 (m, 4), 5.53 (m, 1), 4.38 (m, 1), 4.20 (m, 2), 3.66 (s, 3).

A portion (225 mg, 0.575 mmol) of this ester **44** was hydrolyzed by reflux for 30 min in methanol (10 ml) and aqueous 10% K_2CO_3 (10 ml) to yield a crystalline acid **46** (185 mg, 0.49 mmol, 85%), mp 115–117°, which was recrystallized from ether–pentane to give the analytical sample: mp 115–117°; ir (Nujol) 1700 (s), 1610 (w), 1520 (s), 840 (m) cm^{-1}; nmr ($CDCl_3$) δ 7.91 (m, 4), 5.52 (m, 1), 4.38 (m, 1), 4.19 (m, 2), 2.35 (t, 2).

Anal. Calcd for $C_{20}H_{27}NO_6$: C, 63.64; H, 7.21; N, 3.71. Found: C, 63.32; H, 7.12; N, 3.54.

Borohydride Reduction of the Cyclopentenone Diester 36 to the Trans Cyclopentanol Diester 39. The cyclopentenone diester[16] **36** (3.14 g, 11.1 mmol) was dissolved in methanol (90 ml) and cooled in a cold water bath. $NaBH_4$ (3.14 g) was added portionwise during 2.5 hr such that the temperature did not rise above room temperature. The bath was removed and the reaction stirred at room temperature for a further 2.5 hr. The methanol was removed *in vacuo*. The residue was shaken with water and ether. The ethereal layer was separated and the ether removed. The residue was chromatographed over silica gel, made up in CH_2Cl_2. Only traces of material were eluted with CH_2Cl_2. A major fraction was eluted by ethyl acetate–CH_2Cl_2 (2:3) which was the trans hydroxy ester **39** (1.04 g, 3.63 mmol, 33%); ir (film) 3465 (m), 1735 (s) cm^{-1}; nmr ($CDCl_3$) δ 4.37 (m, 1), 3.72 (m, 2), 3.65 (s, 3), 2.30 (t, 2).

Elution of the column by ethyl acetate gave a mixture of diols **42** and **43** which were utilized later [1.27 g, 4.92 mmol, 44%); ir (film) 3390 (s), 1738 (s) cm^{-1}].

The trans hydroxy diester **39** was hydrolyzed by refluxing aqueous 10% K_2CO_3 as for the cis isomer **38**, to yield the diacid **41**: mp 70–71° (ether); ir (Nujol) 3365 (m), 1700 (broad, s), 1200 (s) cm^{-1}.

Anal. Calcd for $C_{13}H_{22}O_5$: C, 60.44; H, 8.59. Found: C, 60.75; H, 8.75.

A portion of the diacid **41** was redissolved in ether and reesterified with the diazomethane. The hydroxy diester **39** thus obtained was identical (tlc, ir, nmr) with that obtained from the original column chromatography of the borohydride reduction of **36**.

Borohydride Reduction of the Cyclopentanone Diester 37. The cyclopentanone diester[16] **37** (460 mg, 1.62 mmol) was dissolved in methanol (25 ml) and cooled in an ice bath to 4°. $NaBH_4$ (230 mg) was added portionwise during 15 min so that no appreciable temperature rise was noted. The reaction was stirred for a further 45 min, diluted with NaCl solution, and extracted with ether. The ether was removed and the residue (415 mg) was compared on tlc (silica gel–ethyl acetate–chloroform 1:4) with the reaction products obtained from $NaBH_4$ reductions of the cyclopentenone diester **36** and the purified cis and trans hydroxy diesters **38** and **39**. No new products were evident. The composition of the reaction mixtures varied only as to the extent of reduction. The residue was chromatographed on silica gel (15 g), made up in ethyl acetate–CH_2Cl_2 (1:19), and eluted with this mixture. The first major fraction was the cis hydroxy ester **38** (300 mg, 1.047 mmol, 65%) identical (ir, tlc, nmr) with that prepared directly from the cyclopentenone diester **36**. Subsequent elution by ethyl acetate–CH_2Cl_2 (2:3) yielded the trans hydroxy ester **39** (86 mg, 0.30 mmol, 18%) identical (ir, tlc, nmr) with that obtained from the cyclopentenone diester **36**.

Mono-para-nitrobenzoylation of the Cis Diol Ester 42. The cis diol ester **42** (4.87 g, 0.0188 mol) was dissolved in dry pyridine (125 ml), and *p*-nitrobenzoyl chloride (4 g, 0.0215 m mol) was added. The mixture was stirred overnight at room temperature. The pyridine was removed *in vacuo*. The residue was shaken with water and ether. The ether was separated and removed. The residue (8 g) was chromatographed on silica gel (240 g) made up in ethyl acetate–CH_2Cl_2 (1:19) and eluted with this mixture. The first fractions consisted of bis-*p*-nitrobenzoate (2.037 g, 0.00366 mol, 19%). The major fraction eluted by ethyl acetate–CH_2Cl_2 (1:9) and (3:17) was the desired mono-*p*-nitrobenzoate **48** (5.26 g, 0.0129 mol, 69%): ir (film) 3490 (m), 1720 (s), 1610 (m), 1539 (s), 720 (s), cm^{-1}; nmr ($CDCl_3$) δ 8.18 (s, 4), 4.41 (complex multiplet, 3), 4.65 (s, 3), 2.30 (t, 2).

Mono-*p*-nitrobenzoates of the Cis and Trans Diol Esters 42 and 43. The ethyl acetate column strippings from the borohydride reduction of the cyclopentenone diester **36** to the trans hydroxy ester **39** (1.53 g, 5.92 mmol) (see above) were dissolved in dry pyridine (40 ml) and *p*-nitrobenzoyl chloride (1.2 g, 6.45 mmol) in pyridine (10 ml) added dropwise. The reaction mixture stood overnight at room temperature. The pyridine was removed *in vacuo*. The residue was shaken with water and ether. The ether layer was washed, dried ($MgSO_4$), and concentrated to dryness. The residue (2.54 g) was chromatographed on six preparative silica gel plates eluted twice with ethyl acetate–chloroform (1:9). Some starting diols were still evident, as were the bis-*p*-nitrobenzoates close to the solvent front. The two central bands were removed and eluted. The faster moving band (R_f 0.61) (1.38 g, 3.39 mmol, 57%) was the cis mono-*p*-nitrobenzoate **48** identical (ir, nmr, tlc) with that obtained directly from the purified cis diol ester **42**. The slower moving band (R_f 0.48) (433 mg, 1.06 mmol, 18%) was the trans mono-*p*-nitrobenzoate **45**: ir (film) 3430 (m), 1725 (s), 1605 (m), 1550 (s), 730 (s) cm^{-1}; nmr ($CDCl_3$) δ 8.25 (s, 4), 4.20 (complex multiplet, 3), 3.64 (s, 3), 2.31 (t, 2).

THP Ether of the Cis Mono-*p*-nitrobenzoate (50). The cis mono-*p*-nitrobenzoate **48** (1.10 g, 2.70 mmol) was dissolved in methylene chloride (70 ml). 2,3-Dihydro-γ-pyran (0.75 ml, 8.1 mmol) and picric acid (50 mg) were added and mixture stirred for 18 hr at room temperature. The solvent was removed *in vacuo*. The residue was dissolved in ether and washed (10% aqueous $KHCO_3$ and H_2O). The ether was removed. The residue (1.36 g, 2.7 mmol) which was free of starting alcohol based on tlc (silica gel–ethyl acetate–chloroform 1:9) was characterized spectrally as the tetrahydropyranyl ether **50**: ir (film) 1735 (s), 1723 (s), 1612 (m), 1278 (s), 720 (s), cm^{-1}; nmr ($CDCl_3$) δ 8.25 (s, 4), 4.47 (m, 4), 3.66 (s, 3), 3.55 (m, 3), 2.28 (t, 2). It was then utilized for the next step.

The trans mono-*p*-nitrobenzoate **45** (320 mg, 0.785 mmol) in an exactly analogous process yielded the tetrahydropyranyl ether **47** [400 mg; nmr ($CDCl_3$) δ 8.23 (s, 4), 4.45 (m, 4), 3.65 (s, 3), 3.60 (m, 3), 2.26 (t, 2)] homogeneous on tlc (silica gel–ethyl acetate–chloroform 1:9).

The Cis THP Carbinol 51. The cis tetrahydropyranyloxy *p*-nitrobenzoate **50** (1.48 g, 3.01 mmol) was dissolved in methanol (75 ml), and aqueous 10% K_2CO_3 solution (22 ml) was added. The mixture was stirred at room temperature for 40 min, diluted with water, and extracted with ether. The ether extract was washed (H_2O), dried ($MgSO_4$), and concentrated to dryness to yield the cis tetrahydropyranyl carbinol **51** [(1.05 g, 3.06 mmol; ir (film) 3450 (m), 1735 (s), 1025 (s) cm^{-1}; nmr ($CDCl_3$) δ 3.67 (s, 3), 2.31 (t, 2)] which was homogeneous on tlc (silica gel–CH_2Cl_2–ethyl acetate 4:1).

The Trans THP Carbinol 49. The trans tetrahydropyranyloxy *p*-nitrobenzoate **47** (445 mg, 0.90 mmol) was hydrolyzed in an analogous way to give the trans tetrahydropyranyl carbinol **49** (300 mg, 0.88 mmol) homogeneous on tlc.

The Cis THP Aldehyde 52. *Via* Moffat Oxidation. The cis THP carbinol **51** (365 mg, 1.06 mmol) was dissolved in dry benzene (15 ml) and dry DMSO (15 ml) and cooled to 4° in an ice bath. Dry pyridine (0.15 ml), trifluoroacetic acid (0.1 ml), and 1-cyclohexyl-3-(2-morpholinoethyl)carbodiimide metho-*p*-toluenesulfonate[26] (2.2 g, 5.3 mmol) were added and the mixture stirred at 4° for 4 days. The reaction was diluted with ice–water and ether extracted. The ethereal extract was washed (ice–water), dried ($MgSO_4$), and concentrated to dryness. The residue (360 mg, 1.05 mmol 98%) was the cis tetrahydropyranyloxy aldehyde **52** [ir (film), 2700 (w), 1740 (s), 1710 (s), 1440 (m), 1030 (m), 1020 (m) cm^{-1}; nmr ($CDCl_3$) δ 9.75 (m, 1), 3.63 (s, 3), 2.38 (complex multiplet, 3)] homogeneous by tlc (silica gel–CH_2Cl_2–ethyl acetate 9:1).

***Via* Collins Oxidation.** The cis THP carbinol **51** (545 mg, 1.6 mmol) was dissolved in dry CH_2Cl_2 (150 ml). A solution of pyridine dichromate (2.5 g, 9.6 mmol) in dry CH_2Cl_2 (50 ml) was added in one portion with stirring. The mixture was stirred for 15 min at room temperature. Then the CH_2Cl_2 was decanted, washed with water, and removed *in vacuo*. The residue (505 mg, 1.48 mmol, 92%) was identical (tlc, ir, nmr) with the aldehyde **52** prepared *via* the modified Moffatt procedure as described above.

The trans THP carbinol **49** (332 mg, 0.97 mmol) was oxidized *via* the pyridine dichromate procedure to yield the trans THP aldehyde **53** (330 mg, 100%) homogeneous on tlc (silica gel–CH_2Cl_2–ethyl acetate 9:1).

Elimination to the Cyclopentene Aldehyde of the Cis THP

Aldehyde 52. The cis THP aldehyde **52** (236 mg, 0.69 mmol) was dissolved in benzene (10 ml). Piperidine (2 drops) and acetic acid (1 drop) were added and the mixture was warmed in a steam bath for 30 min. The entire mixture was added to an alumina column (15 g, neutral III) made up in CH_2Cl_2–ethyl acetate (1:19) and eluted by that mixture. The material first eluted was the cyclopentene aldehyde. This crude cyclopentene aldehyde was characterized as the semicarbazone, mp 115–116° (aq MeOH); ir (Nujol) 3445 (m), 3150 (m), 1725 (m), 1680 (s), 1590 (m) cm^{-1}; uv λ_{max} (EtOH) 267 mμ (ε 28,560).

Anal. Calcd for $C_{15}H_{25}N_3O_3$: C, 60.99; H, 8.53; N, 14.23. Found: C, 60.84; H, 8.92; N, 14.58.

Wittig Reaction on the Cis THP Aldehyde 52 to the Enone 54. The cis tetrahydropyranyloxy aldehyde **52** (500 mg, 1.47 mmol) and 1-tributylphosphoranylidene-2-heptanone[7] (900 mg, 2.87 mmol) were dissolved in dry THF (30 ml) and refluxed for 3 days. The THF was removed and the residue chromatographed on preparative silica gel plates eluted by ethyl acetate–CH_2Cl_2 (1:19). The main band (R_f 0.71) was removed and eluted to give the cis tetrahydropyranyloxy enone **54** (390 mg, 0.89 mmol 61%); ir (film) 1738 (s), 1675 (m), 1630 (m), 1445 (m), 1027 (s), cm^{-1}; nmr ($CDCl_3$) δ 6.73 (m, 1), 6.02 (m, 1), 3.63 (s, 3), 2.35 (m, 5), 0.89 (m, 3).

Wittig Reaction on the Trans THP Aldehyde 53 to the Enone 55. The trans tetrahydropyranyloxy aldehyde **53** (330 mg, 0.97 mmol) reacted with 1-tributylphosphoranylidene-2-heptanone[7] (608 mg, 1.94 mmol) in THF, and worked up analogously to yield a principal fraction from the plate at R_f 0.62 of the trans tetrahydropyranyloxy enone **55** (212 mg, 0.485 mmol, 50%): nmr ($CDCl_3$) δ 6.75 (m, 1), 6.11 (m, 1), 3.65 (s, 3), 2.40 (m, 5), 0.90 (m, 3).

The Cis Hydroxy Enone 56. The cis tetrahydropyranyloxy enone **54** (380 mg, 0.87 mmol) was dissolved in methanol (30 ml) and 2*N* HCl (0.5 ml) was added. The mixture stood at room temperature for 18 hr. The methanol was removed *in vacuo*. The residue was dissolved in ether and washed with water twice. The ether was removed and the residue chromatographed on preparative silica gel plates eluted by ethyl acetate–CH_2Cl_2 (4:1). The central band (R_f 0.54) was removed and eluted to give the cis hydroxy enone **56** (105 mg, 34%): nmr ($CDCl_3$) δ 6.80 (m, 1), 6.20 (m, 1), 4.28 (m, 1), 3.67 (3), 2.35 (m, 5), 0.91 (m, 3).

The Trans Hydroxy Enone 57. Trans tetrahydropyranyloxy enone **55** (210 mg, 0.48 mmol) reacted in an analogous manner with methanolic HCl to give the trans hydroxy enone **57** (160 mg, 0.45 mmol, 95%), homogeneous on tlc (silica gel–ethyl acetate–CH_2Cl_2 4:1): nmr ($CDCl_3$) δ 6.75 (m, 1), 4.15 (m, 1), 4.05 (m, 1), 3.65 (s, 3), 2.39 (m, 5), 0.89 (s, 3).

9-Deoxy-PGE$_1$ 2. The trans hydroxy enone **57** (160 mg, 0.45 mmol was dissolved in ether (25 ml), and an ethereal solution of $Zn(BH_4)_2$ (20 ml) was added. The mixture was stirred at room temperature for 1.5 hr. Water was added and acetic acid added dropwise until the emulsion broke. The ether was separated and removed. The residue was chromatographed on preparative silica gel plates eluted by ethyl acetate–CH_2Cl_2 (1:1).

The faster moving band (R_f 0.46) (52 mg, 32%) was eluted and dissolved in methanol (5.5 ml) and 10% aqueous K_2CO_3 (5.5 ml). The mixture was refluxed for 2 hr and then concentrated *in vacuo*. The residue was diluted with water, extracted with ether, acidified (2 HCl), and reextracted with ether. Removal of the ether gave the *dl*-9-deoxy-15-epi-PGE$_1$ as a viscous oil (43 mg, 90%) homogeneous by tlc (silica gel–benzene–dioxane–acetic acid 10:10:05, R_f 0.48): ir ($CHCl_3$), 3610 (w), 3400 (m), 1710 (s), 1600 (w), cm^{-1}; mass spectrum, *m/e* 322 (M − H_2O), 304 (M − $2H_2O$). 278 (M − H_2O, CO_2).

The slower moving band (R_f 0.22) (42 mg, 26%) was eluted and hydrolyzed in an analogous manner with methanolic K_2CO_3 solution. Removal of the final ether gave a colorless oil which crystallized (30 mg, 81%). This was homogeneous by tlc (silica gel–benzene–dioxane–acetic acid 10:10:05, R_f 0.46). Recrystallization from ether–hexane gave *dl*-9-deoxy-PGE$_1$ **2**: mp 76–78°; mass spectrum *m/e* 322 (M − H_2O), 304 (M − $2H_2O$), 278 (M − H_2O, CO_2).

Anal. Calcd for $C_{20}H_{36}O_4$: C, 70.54; H, 10.66. Found: C, 70.64; H, 10.51.

9-Deoxy-11,15-epi-PGE$_1$ 4. The cis hydroxy enone **56** (360 mg, 1.02 mmol) was reduced in ether with ethereal $Zn(BH_4)_2$ in an analogous manner and worked up by preparative tlc.

The faster moving band (R_f 0.49) (81 mg, 22%) was hydrolyzed by methanolic K_2CO_3 solution as described above to give *dl*-9-deoxy-11-epi-PGE$_1$ as a wax (71 mg, 90%) homogeneous on tlc (silica gel–benzene–dioxane–acetic acid 10:10:05, R_f 0.55): nmr ($CDCl_3$) δ 5.61 (m, 2), 4.16 (m, 2), 0.93 (m, 3); mass spectrum *m/e* 322 (M − H_2O), 304 (M − $2H_2O$), 278 (M − H_2O, CO_2).

The slower moving band (R_f 0.33) (93 mg, 26%) was hydrolyzed by methanolic K_2CO_3 solution as described above to give *dl*-9-deoxy-11,15-epi-PGE$_1$ **4** (81 mg, 91%) which crystallized and was homogeneous on tlc (silica gel–benzene–dioxane–acetic acid 10:10:0.5, R_f 0.50). Recrystallization from ethyl acetate gave the analytical sample: mp 71–72°; nmr ($CDCl_3$) δ 5.58 (m, 2), 4.12 (m, 2), 0.92 (m, 3); mass spectrum *m/e* 322 (M − H_2O), 304 (m − $2H_2O$), 278 (M − H_2O, CO_2).

Anal. Calcd for $C_{20}H_{36}O_4$: C, 70.54; H, 10.66. Found: C, 70.73; H, 10.76.

9-Deoxy-11,15-epi-PGE$_1$ 4 *via* $NaBH_4$ Reduction. The cis tetrahydropyranyloxy enone **54** (2.75 g, 6.4 mmol) was dissolved in 95% ethanol (150 ml). To the well-stirred solution at room temperature was added $NaBH_4$ (5.5 g). After 30 min, the reaction was diluted with water, and ether was extracted. Removal of the ether gave a residue which was chromatographed on silica gel (75 g) made up in CH_2Cl_2. The main fraction, the mixture of allylic alcohols **58** (2.09 g, 4.76 mmol, 74%), was eluted by ethyl acetate–CH_2Cl_2 (1:6): ir (film) 3440 (m), 1733 (s), 1017 (s) cm^{-1}; nmr ($CDCl_3$) δ 5.54 (m, 2), 4.61 (m, 1), 3.67 (s, 3), 0.91 (m, 3).

The mixture of allylic alcohols **58** (2.05 g, 4.67 mmol) was dissolved in methanol (125 ml) and 1 *N* HCl (3 ml) added. The mixture was stirred at room temperature for 2.5 hr and diluted with water, and ether was extracted. The ether was removed and the residue **59** (1.62 g, 4.57 mmol, 98%) was chromatographed on silica gel (60 g). Two chromatographically pure fractions (tlc) were eluted. The faster one eluted by ethyl acetate–CH_2Cl_2 (1:4) (0.518 g, 1.46 mmol, 31%) was identical (ir, nmr, tlc) with *dl*-9-deoxy-11-epi-PGE$_1$ methyl ester from the preparative tlc plates. The slower fraction (0.530 g, 1.49 mmol, 32%) eluted by ethyl acetate–CH_2Cl_2 (2:3) was identical (ir, nmr, tlc) with the *dl*-9-deoxy-11,15-epi-PGE$_1$ methyl ester from the preparative tlc plates.

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Registry No.—**2**, 53317-71-8; **4**, 53317-72-9; **5**, 53229-67-7; **6**, 53229-68-8; **7**, 53229-69-9; **8**, 53293-20-2; **9**, 53229-70-2; **10**, 53229-71-3; **11**, 53229-72-4; **12**, 53229-73-5; **13** (or **14**), 53229-74-6; **15**, 53229-75-7; **17**, 53229-76-8; **18**, 53229-77-9; 18 semicarbazone, 53229-78-0; **19** (or **20**), 53229-79-1; **21**, 53229-80-4; **22**, 53229-81-5; **24**, 53229-82-6; **24** 2,4-DNPH, 53229-83-7; **29**, 53275-01-7; **31**, 53229-84-8; **32** (or **33**), 53229-85-9; **34**, 53229-89-3; **35**, 53275-05-1; **36**, 39493-34-0; **37**, 53229-86-0; **38**, 53229-87-1; **39**, 53275-02-8; **40**, 53229-88-2; **41**, 53275-03-9; **42**, 53275-04-0; **43**, 53275-06-2; **44**, 53229-90-6; **45**, 53275-07-3; **46**, 53229-91-7; **47** (or **50**), 39493-38-4; **48**, 53275-08-4; **49** (or **51**), 39493-39-5; **52** (or **53**), 38460-69-4; **54**, 53275-09-5; **55**, 53275-10-8; **56**, 53317-73-0; **57**, 53275-11-9; **58** 15α-OH, 53275-12-0; **58** 15β-OH, 53275-13-1; 2-carboethoxycyclopentanone, 53229-92-8; 2-carbomethoxycyclopentanone, 53229-93-9; *cis*-2-carbomethoxycyclopentanol, 53229-94-0; *trans*-2-carbomethoxycyclopentanol, 53229-95-1; *p*-nitrobenzaldehyde dimethyl acetal, 881-67-4; 3,5-dinitrobenzoyl chloride, 99-33-2; 1-cyclopentene-1-carboxaldehydethiosemicarbazone, 53229-96-2; diethyl (2-oxoheptyl)phosphonite, 3450-65-5; 2,3-dihydro-γ-pyran, 110-87-2; 2-tetrahydropyranyloxycyclopentanecarboxylic acid methyl ester, 53229-97-3; 1-tributylphosphoranylidene-2-heptanone, 35563-52-1; *p*-nitrobenzoyl chloride, 122-04-3; 2-formyl-2-cyclopentene-1-heptanoic acid methyl ester semicarbazone, 53229-98-4; *dl*-9-dioxy-15-epi-PGE$_1$, 53317-74-1; *dl*-9-dioxy-11-epi-PGE$_1$, 53317-75-2.

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(23) Melting points were obtained in a Thomas-Hoover melting point apparatus and are uncorrected. Nmr were obtained on a Varian A-60 unless otherwise stated. Mass spectra were obtained on an MS9 instrument at 70 eV.
(24) Homogeneity of the *cis*- and *trans*-2-hydroxymethylcyclopentanols was most conveniently checked by tlc using Silica Gel GF eluted by benzene–chloroform–formic acid–isopropyl alcohol (2:8:2:1).
(25) Dimethyl (2-oxoheptyl)phosphonate is now available from Aldrich Chemical Co.
(26) Available from the Aldrich Chemical Co.

Intramolecular Friedel–Crafts Reaction of 3-Cyclohexen-1-acetyl Chloride and Its 4-Methyl Analog[1]

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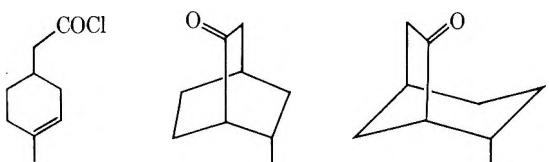
Stannic chloride catalyzed cyclization of 3-cyclohexen-1-acetyl chloride (1) yielded a mixture of 6-chlorobicyclo[2.2.2]octan-2-one (**3b**) and 2-chlorobicyclo[3.2.1]octan-7-one (**4b**). Reductive fragmentation of **3b** and **4b** with lithum aluminum hydride gave 2-(3-cyclohexenyl)ethanol. Treatment of the keto chloride mixture with DBN–HMPA gave bicyclo[3.2.1]oct-3-en-6-one (**9**) as the only elimination product. Cyclization of 4-methyl-3-cyclohexen-1-acetyl chloride (**2**) followed by DBN–HMPA elimination furnished 4-methylbicyclo[3.2.1]oct-3-en-6-one (**15**) in good yield. These intramolecular Friedel–Crafts acylations provide a regioselective synthetic route to bicyclo[3.2.1]octane systems containing differentiated functionality in two bridges.

The intramolecular Friedel–Crafts acylation of aliphatic substrates to give fused-ring products is well documented.[2,3] This method also provides an attractive synthetic route to bicyclic derivatives characterized by differentiated functionality in two bridges.[4] An investigation of the Lewis acid catalyzed cyclization of 3-cyclohexen-1-acetyl chloride (**1**) and its 4-methyl analog **2** was undertaken to evaluate further this approach to functionalized bicyclooctane skeletons.

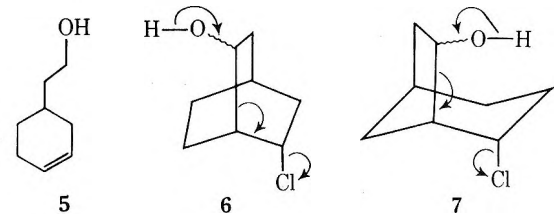
Treatment of acid chloride **1** with stannic chloride in carbon disulfide (−15°, 1 hr) yielded a mixture of three bicyclic keto chlorides (ratio 11:6:6) in 90% yield. Reduction of this mixture with tri-*n*-butyltin hydride gave two ketones which were identified as bicyclo[2.2.2]octan-2-one (**3a**) and bicyclo[3.2.1]octan-6-one (**4a**) by comparison with authentic materials. Separation of the keto chloride mixture and reduction of the individual components revealed that the major isomer furnished **3a**, one minor isomer gave **4a**, and the other minor isomer was not reduced under these conditions. Assignment of structure **3b** to the major keto chloride component and structure **4b** to one of the minor isomers was based on the observation that treatment of the keto chloride mixture with lithium aluminum hydride gave alcohol **5** in 75% yield. A reductive fragmentation[4a] of **3b** and **4b** (see arrows in **6** and **7**) readily accounts for the formation of **5** and suggests the anti disposition of the carbonyl group and the chlorine atom shown in **3b** and **4b**.



1, R = H
2, R = Me

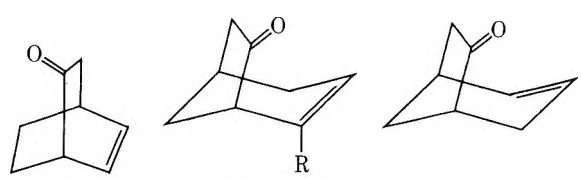
3a, R = H
b, R = Cl

4a, R = H
b, R = Cl



5 6 7

When the initial keto chloride mixture was heated with 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) in hexamethylphosphortriamide (HMPA) solution (115°, 5 hr) a *single* bicyclic keto olefin was isolated together with recovered keto chloride(s). Vpc comparison of this new material with known samples of the possible elimination products, 8[5] and a mixture[6] of **9** and **10**, indicated that it was one of the bicyclo[3.2.1]octenes **9** or **10**. Initial structural assignment as

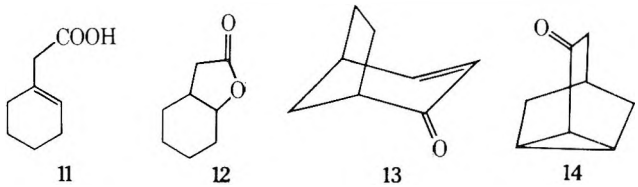


8 9, R = H 15, R = CH_3 10

9 was made on the basis of the lanthanide shift nmr analysis method of Willcott and Davis[7] (see Experimental Section for details) and was confirmed by comparion with authentic **9**.[8] The reluctance of keto chloride **3a** to undergo

dehydrochlorination under these conditions to give the bicyclo[2.2.2]octene 8 certainly reflects the steric strain associated with elimination in this system.[9] The favored trans, antiparallel elimination geometry is easily achieved in the chlorobicyclo[3.2.1]octane skeleton **4b.**

In two recent related studies, cyclohexene acid **11**[10] and and lactone **12**[11] were treated with polyphosphoric acid to give α,β-unsaturated ketone **13** and cyclopropyl ketone **14**



11 **12** **13** **14**

as major products. Closure of the monocyclic precursor 3-cyclohexene-1-acetic acid (**1**, Cl = OH) to either a bicyclo[2.2.2]- or a bicyclo[3.2.1]octyl cation, followed by subsequent rearrangement to **13** and **14**, was proposed in both cases. The same bicyclic cations may be generated when acid chloride **1** is treated with $SnCl_4$ but, in contrast to the PPA solutions, a good nucleophile is present to trap these cations before rearrangement occurs.

Cyclization of acid chloride **2** was examined next with the expectation that the vinyl methyl substituent would direct ring closure to give regioselective formation of the bicyclo[3.2.1]octane skeleton (*e.g.*, **15**). Treatment of **2** with $SnCl_4$ gave a mixture of two bicyclic keto chlorides which underwent smooth elimination (DBN–HMPA) to give 4-methylbicyclo[3.2.1]oct-3-en-6-one (**15**) in 51% overall yield from the starting acid **2**, Cl = OH. The nmr spectrum of **15** showed a vinyl methyl signal at δ 1.73 and a one-proton vinyl absorption at δ 5.4 ppm which confirm initial ring closure to give the bicyclo[3.2.1]octane skeleton.

Experimental Section

General. Melting points were determined on a Mel-Temp apparatus and are uncorrected. Infrared spectra were obtained on a Perkin-Elmer Model 237B grating infrared spectrometer. Nmr spectra were measured on a Varian Associates A-60 or a Perkin-Elmer R-12 spectrometer and chemical shifts are reported in ppm downfield (δ) from internal TMS. Gas chromatographic analysis were performed on a Varian Aerograph 1200 instrument. Combustion analyses were done by Chemalytics, Inc., Tempe, Ariz.

6-Chlorobicyclo[2.2.2]octan-2-one (3b) and 2-Chlorobicyclo[3.2.1]octan-7-one (4b). A solution of acid chloride[12] **1** (1.00 g, 6.3 mmol), prepared from the corresponding acid[13] ($SOCl_2$ in benzene), in carbon disulfide (5 ml) was added to a mixture of $SnCl_4$ (1.64 g, 6.3 mmol) in carbon disulfide (5 ml) at −15° under a nitrogen atmosphere. This mixture was stirred for 1 hr, water (15 ml) was added, the organic phase was separated, and the aqueous phase was extracted with ether. The combined organic phases were dried ($MgSO_4$) and evaporated *in vacuo* to give 0.90 g (90%) of products which could be purified by chromatography in silica gel or by sublimation: mp 120–128°; ir ($CHCl_3$) 1740 cm^{-1}; nmr ($CDCl_3$) δ 4.3 (m, 1) and 2.8–1.5 ppm (m, 10); vpc analysis (15% QF-1 on Chrom W, 180°) revealed three components in the ratio of 11:6:6 in order of increasing retention times.

Anal. Calcd for $C_8H_{11}ClO$: C, 60.57; H, 6.99. Found: C, 60.16; H, 6.63.

Tri-*n*-Butyltin Hydride Reduction of 3b and 4b. A. The above keto chloride mixture (0.30 g, 1.9 mmol) and tri-*n*-butyltin hydride[14] (0.55 g, 1.9 mmol) were mixed under a nitrogen atmosphere. After the initial exotherm, this mixture was heated at 50° for a total of 16 hr at which time vpc analysis showed complete disappearance of the two keto chlorides with the shortest retention times and the appearance of **3a**[15] and **4a**[16] (ratio of *ca.* 8:5) as judged by comparison to authentic samples.

B. Preparative vpc separation of the above keto chloride mixture and reduction of the individual components as described in A indicated that the shortest retention time keto chloride **3b** yielded **3a**, the second, **4b**, gave **4a** and the longest retention time keto chloride was recovered unchanged. The structure of the latter remains unknown.

Lithium Aluminum Hydride Reduction of 3b and 4b. The above keto chloride mixture (0.80 g, 5.0 mmol) and $LiAlH_4$ (0.26 g, 7.0 mmol) in THF (10 ml) were heated at reflux under a nitrogen atmosphere for 6 hr. The mixture was cooled, dilute HCl was added dropwise, the layers were separated after removal of solid precipitate by filtration, and the aqueous phase was extracted twice with ether. The combined organic phases were dried ($MgSO_4$) and evaporated *in vacuo* to give 490 mg of residue (75%). Distillation gave pure **5**: bp 107–112° (23 mm) [lit.[12] bp 110–112° (23 mm)]. The ir and nmr spectra and vpc retention time of **5** were identical with authentic material prepared by hydroboration–oxidation of 4-vinylcyclohexene with diisoamylborane.[17]

Bicyclo[3.2.1]oct-3-en-6-one (9). The above keto chloride mixture (1.0 g, 6.3 mmol) and DBN (2.4 g, 6.3 mmol) in HMPA (10 ml) were heated at 115° for 5 hr under a nitrogen atmosphere. Water (10 ml) was added, and the mixture was extracted with ether. After drying ($MgSO_4$) the organic phase was evaporated to give 325 mg of crude product (42%). Vpc analysis indicated the presence of **9** (68%) and recovered keto chlorides (32%). A pure sample of **9** was obtained by evaporative distillation: bp 110° (bath temperature) (1.7 mm); ir ($CHCl_3$) 1740 cm^{-1}; nmr ($CDCl_3$) δ 5.7 (broad d, 2), and 3.0–1.5 ppm (m, 8). Vpc analysis (15% QF-1, 140°) showed a single peak with retention time of 3.0 min; authentic[5] **8** showed retention time of 2.6 min and a mixture[6] of **9** and **10** showed retention times of 2.4 and 3.0 min; authentic[8] **9** showed retention time of 3.0 min.

Lanthanide Shift Nmr Analysis of 9. Nmr spectra of **9** were obtained with 12 increasing concentrations of $Yb(fod)_3$[7b] using an internal TMS standard. Using a set of relative shifts for eight distinguishable proton groups, minimum values of R[7a] of 6.90% for **9** and 11.96% for **10** were obtained. The calculated ratio for the two vinyl proton relative shifts of 2.23 for **9** agrees quite well with the experimentally observed value of 2.04; the calculated ratio for **10** is 1.21. These data establish structure **9**.[18]

4-Methyl-3-cyclohexen-1-ylmethanol. Ethyl 4-methyl-3-cyclohexene-1-carboxylate[19] (74.0 g, 0.48 mol) and $LiAlH_4$ (19.0 g, 0.50 mol) in ether (150 ml) were stirred for 1 hr at room temperature under a nitrogen atmosphere. Dilute HCl was added carefully, the layers were separated, and the aqueous phase was extracted with ether. The combined organic phases were dried ($MgSO_4$) and evaporated *in vacuo*, and the residue was distilled to give 50.0 g (84%) of product: bp 108–109° (20 mm); nmr (CCl_4) δ 5.31 (broad s, 1), 3.88 (s, 1), 3.40 (d, 2, J = 6 Hz), 1.62 (s, 3), and 2.2–1.1 ppm (m, 7).

Anal. Calcd for $C_8H_{14}O$: C, 76.14; H, 11.18. Found: C, 76.52; H, 11.54.

4-Methyl-3-cyclohexene-1-acetonitrile. The above alcohol (16.0 g, 0.13 mol) and *p*-toluenesulfonyl chloride (28.6 g, 0.15 mol) in pyridine (120 ml) were stirred at 0° for 3 hr. Ice was added, the layers were separated, and the organic phase was extracted with ether. The combined organic phases were washed with 6 *N* HCl and then water and finally were dried ($MgSO_4$). The solvent was removed *in vacuo* and the crude tosylate was used in the next step.

Crude tosylate (from 0.4 mol of alcohol) in DMSO (150 ml) was added dropwise to a stirred slurry of NaCN (56.1 g, 1.14 mol) in DMSO (600 ml) at 90°. The resulting solution was stirred for 2 hr, cooled to room temperature, diluted with water (450 ml), and extracted with ether. The organic phase was washed with water, dried ($MgSO_4$), and evaporated to give a residue which was distilled to yield 41.2 g (85%) of product: bp 117–118° (17 mm); nmr ($CDCl_3$) δ 5.35 (broad s, 1), 2.32 (d, 2, J = 7 Hz), 1.68 (s, 3), 2.3–1.6 ppm (m, 7).

Anal. Calcd for $C_9H_{13}N$: C, 79.95; H, 9.69; N, 10.36. Found: C, 79.96; H, 9.89; N, 10.47.

4-Methyl-3-cyclohexene-1-acetic Acid. The above nitrile (12.2 g, 0.09 mol) and NaOH (14.4 g, 0.36 mol) in water (150 ml) were heated at reflux for 24 hr. After cooling to 0° the solution was neutralized with 6 *N* HCl and then extracted with a mixture of ether–benzene. The organic phase was dried ($MgSO_4$) and evaporated *in vacuo* to give 13.0 g (94%) of product: mp 58–60°; nmr ($CDCl_3$) δ 11.8 (s, 1), 1.64 (s, 3), and 2.5–1.5 ppm (m, 10).

Anal. Calcd for $C_9H_{14}O_2$: C, 70.10; H, 9.15. Found: C, 70.14; H, 9.42.

4-Methylbicyclo[3.2.1]oct-3-en-6-one (15). A solution of thionyl chloride (5.0 g, 0.04 mol) in benzene (60 ml) was added to a suspension of the sodium salt of 4-methyl-3-cyclohexene-1-acetic acid (5.4 g, 0.03 mol) in benzene (60 ml). After stirring for 17 hr at room temperature the solution was evaporated *in vacuo* and the

crude acid chloride was dissolved in carbon disulfide (30 ml). To this solution was added stannic chloride (7.9 g, 0.03 mol) in carbon disulfide (30 ml) at 0°. This mixture was stirred for 0.5 hr at 0°, and then 4 hr at room temperature. After cooling to 0°, water (20 ml) was added, the layers were separated, and the aqueous phase was washed with ether. The combined organic phases were washed with 10% Na_2CO_3 solution, dried ($MgSO_4$), and evaporated to give 3.2 g (61%) of crude keto chlorides. Vpc analysis showed two components. Using the procedure described for **9**, the crude keto chlorides (1.7 g, 9.5 mmol) and DBN (3.7 g, 30 mmol) yielded 1.1 g (82%) of **15** which was purified by chromatography on silica gel or by evaporative distillation: bp 160° (bath temp) (19 mm); ir ($CHCl_3$) 1740 cm^{-1}; nmr ($CDCl_3$) δ 5.4 (broad s, 1), 1.73 (broadened s, 3), and 2.8–1.6 ppm (m, 8).

Anal. Calcd for $C_9H_{12}O$: C, 79.37; H, 8.88. Found: C, 79.24; H, 8.96.

Registry No.—**1**, 7086-71-7; **3a**, 2716-23-6; **3b**, 53216-65-2; **4a**, 6553-12-4; **4b**, 53216-66-3; **5**, 18240-10-3; **9**, 31444-32-3; **15**, 53216-75-4; DBN, 3001-72-7; 4-methyl-3-cyclohexen-1-ylmethanol, 39155-38-9; ethyl 4-methyl-3-cyclohexene-1-carboxylate, 20292-15-3; 4-methyl-3-cyclohexene-1-acetonitrile, 53216-76-5; 4-methyl-3-cyclohexene-1-acetic acid, 7086-66-0; 4-methyl-3-cyclohexene-1-acetic acid sodium salt, 53216-77-6.

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Stereochemistry of the Thermal Addition of β-Pinene to Methyl Pyruvate[1]

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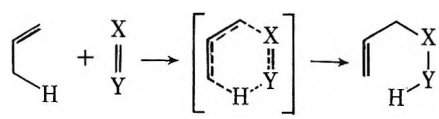
An nmr investigation of the adduct **2** formed in the ene reaction between β-pinene and methyl pyruvate has shown it to be a 1:1 mixture of diastereomers, not a single stereoisomer as originally believed. The pure adducts have been separated and their absolute configurations determined by degradation to citramalic acid. It is concluded that steric and stereoelectronic factors play little part in creating the new asymmetric center.

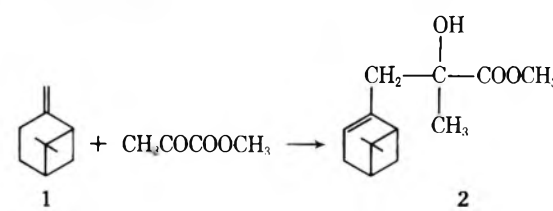
Many olefins react thermally with compounds containing reactive double bonds (C=C, C=O, N=N, etc.) to form 1:1 adducts in a process believed usually to involve a cyclic transition state[2] and broadly classified as the "ene" reaction[3] (eq 1). Consistent with its description as a concerted



(1)

1,5-sigmatropic hydrogen transfer, the ene reaction exhibits several facets of stereospecificity. (1) The new C–C and C–H bonds are generated cis to each other.[4] (2) Asymmetric induction may be observed when the α carbon of the olefin is chiral, transferring chirality to the new asymmetric center in the enophile.[5] (3) In an olefin with multiple asymmetric centers, one of the diastereotopic allylic hydrogens is selectively transferred; in β-pinene (**1**), *e.g.*, only the endo hydrogen is involved in ene reactions.[6,7] It is not yet clear whether this is due to simple steric factors or to a stereoelectronic preference for breaking that C–H bond parallel to the π orbitals of the double bond. (4) In the cases so far investigated, endo orientation of the addends predominates over exo.[7,8]

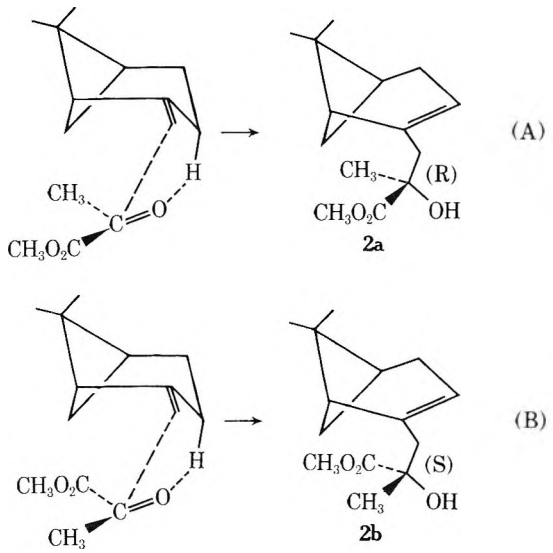
During the course of our studies[5,7] on the stereospecificity of the ene reaction, we were attracted by the report of Arnold and Veeravagu[9] that the thermal addition of β-pinene to methyl pyruvate (eq 2) furnishes adduct **2** as a single stereoisomer. Most ene adducts of β-pinene, such as those with maleic anhydride, methyl maleate, and methyl fumarate,[10] as well as the maleic anhydride adducts of cyclopentene and *cis*- and *trans*-2-butene,[8] are mixtures of stereoisomers resulting from competing endo and exo addition, and it is surprising that this simple keto ester should exhibit such pronounced stereospecificity.[11] Arnold and Veeravagu suggested that the favored transition state should be that with minimum nonbonded repulsions, in which the pyruvate approaches the olefin from the methylene bridge side with the carbomethoxyl group oriented away from the hydrocarbon moiety.[9] As depicted in Chart IA, this would result in an *R* configuration at the new asymmetric center. On the other hand, were stereoelectronic considerations to favor endo orientation (Chart IB) as is the case with other ene additions of β-pinene,[7] then the



(2)

1 2

Chart I
Possible Stereochemical Courses of Addition of β-Pinene to Methyl Pyruvate



other diastereoisomer with the *S* configuration at the new asymmetric center would predominate.

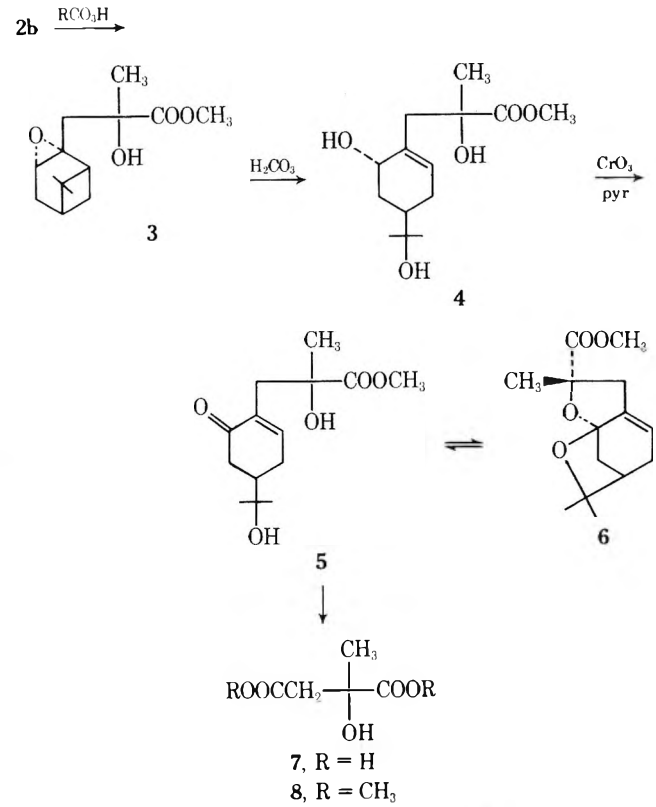
These considerations made clear the importance of determining the absolute configuration at the new asymmetric center in adduct **2**, for the identification of which diastereomer is formed would reveal whether simple steric or stereoelectronic factors were responsible for the unexpected stereospecificity. We undertook a study of this adduct with this aim in mind, but soon found that adduct **2** is not a single stereoisomer but rather a 1:1 mixture of the two possible diastereomers.

Demonstration of Adduct Inhomogeneity. Adduct **2** was prepared from methyl pyruvate and (−)-β-pinene as described and had properties similar to those reported. Arnold and Veeravagu reported that glc analysis on a polyester column showed a single peak, and we obtained a single peak on a Carbowax column as well. Moreover, nmr spectra in chloroform, benzene, carbon tetrachloride, or pyridine showed no doubling of peaks indicative of a mixture. Addition of the nmr shift reagent Eu(fod)$_3$ to a carbon tetrachloride solution of **2**, however, caused the methoxyl singlet at δ 3.66 to split into two singlets of equal intensity at 3.80 and 3.85, and the side-chain methyl signal at δ 1.29 also to split into two signals of equal intensity at 1.57 and 1.68. None of the other peaks, though shifted, showed any doubling. The shift reagent undoubtedly complexes with the ester and/or hydroxyl oxygens and affects only those substituents in the immediate vicinity.

Confirming evidence was obtained from the proton-decoupled ^{13}C nmr spectrum of adduct **2**. The signals due to the carbinol carbon, the three carbons attached to it (carbonyl, methyl, and methylene), and the two olefinic carbons all appeared as doublets of comparable intensity, again showing the presence of diastereomers.[12]

With this evidence that adduct **2** is a mixture of diastereomers, efforts were made to separate them. Arnold and Veeravagu had found that saponification of the adduct and recrystallization of the potassium salt gave a pure isomer, and we were able to confirm this, obtaining a less soluble salt as shiny platelets, mp 105–107°, by recrystallization from ethyl acetate. From the mother liquors, in addition, we could isolate a more soluble salt which crystallized as prisms, mp 204–206°, from ethyl acetate. Each of the potassium salts was converted into a pure diastereomer of **2** by acidification and esterification with diazomethane. Isomer **2a**, from the high-melting salt, had $[\alpha]_D$ −33.4°, while isomer **2b**, from the low-melting salt, had $[\alpha]_D$ −12.5°. The homogeneity of each was confirmed in two ways. The methoxyl and side-chain methyl singlets in the nmr spectra of both remained as singlets upon the addition of Eu(fod)$_3$, and the proton-decoupled ^{13}C nmr spectra of both showed each carbon signal as a sharp singlet.

Scheme I
Degradation of Adduct 2b to Methyl Citramalate



These results demonstrate that the β-pinene–methyl pyruvate adduct is not a single stereoisomer, but that diastereomers **2a** and **2b** are formed in approximately equal amounts. Several control experiments were run to see whether this 1:1 ratio is kinetically or thermodynamically controlled.

(1) Each of the pure diastereomers **2a** and **2b** was heated separately with β-pinene for 89–96 hr, under the conditions of the original ene reaction. Reisolation of the adduct and nmr analysis with added Eu(fod)$_3$ showed that the starting material in each case was recovered stereochemically pure and with unchanged optical rotation. Thus the adducts do not equilibrate under the conditions of their formation.

(2) The reaction between β-pinene and methyl pyruvate was interrupted after various periods. After 6, 24, 48, and 96 hr the yields of adduct were 9, 19, 34, and 57%, respectively. The adduct isolated in each case had the same optical rotation, however, and nmr analysis with added Eu(fod)$_3$ showed the same 1:1 ratio of diastereomers in each run. The product ratio does not change with time and appears to be kinetically controlled, *i.e.*, **2a** and **2b** are formed at about equal rates. This of course means that the transition states leading to **2a** and **2b** are of approximately equal energy; neither steric nor stereoelectronic factors play a decisive role in orienting the pyruvate in the transition state.

Determination of Absolute Configuration. It was still of interest to determine which adduct corresponds to **2a** and which to **2b**, *i.e.*, to assign absolute configurations at the new asymmetric center. An efficient degradative se-

quence was devised to destroy the chiral pinene moiety and relate the remaining asymmetric center to that of citramalic acid (Scheme I). Isomer **2b** was oxidized with peroxytrifluoroacetic acid to give epoxide **3**; the oxide is assigned the α configuration by analogy with the epoxidation of α-pinene.[13] Following the procedure used to convert α-pinene oxide into *trans*-sobrerol,[14] the oxide was treated with a mixture of Dry Ice and water to afford triol **4**. Collins oxidation led to ketone **5**; however, if the crude oxidation product was distilled, a different substance, lacking hydroxyl and ketone absorption in the infrared, was isolated. Infrared and nmr spectra were consistent with the ketal structure **6**. Aqueous acid hydrolysis gave **5**, which could be distilled unchanged after washing with dilute alkali. Finally, ruthenium tetroxide oxidation of **5** destroyed the cyclohexenone ring; esterification of the acidic products with diazomethane, distillation, and purification by glc afforded (*S*)-(+)-methyl citramalate (**8**), $[\alpha]_D$ +26.4°, identical with a sample prepared from (*S*)-(+)-citramalic acid (**7**).

This correlation establishes that adduct **2b** has the *S* configuration at the new asymmetric center, and isomer **2a** accordingly has the *R* configuration at this site.

Experimental Section

Melting points were determined in a Hoover melting point apparatus and are uncorrected. Nuclear magnetic resonance spectra were recorded on Varian HA-100, Hitachi R-20, and Varian T-60 instruments. Chemical shifts are reported as δ units, with tetramethylsilane as an internal standard. Carbon-13 nuclear magnetic resonance spectra were recorded on a JEOL PFT-100 instrument. Infrared spectra were recorded on a Perkin-Elmer Model 257 infrared spectrophotometer. Ultraviolet spectra were recorded on a Perkin-Elmer Model 202 spectrophotometer. A 1-dm cell was used to determine optical rotations in a Perkin-Elmer Model 141 polarimeter; *c* is expressed as grams per 100 milliliter solution. Elemental analyses of liquid samples were performed at Galbraith Laboratories in Knoxville, Tenn., and elemental analyses of solid samples were performed at the University of Georgia.

Methyl 2'-Hydroxy-2'-methyl-3'-(6,6-dimethyl)bicyclo[3.1.1]hept-2-en-2-yl propionate (2). (1*S*,5*S*)-(−)-β-Pinene (Aldrich Chemical Co.) was purified by fractional distillation at reduced pressure; bp 66° (28 mm), $[\alpha]^{25}D$ −22.1° (neat).

Following the procedure of Arnold and Veeravagu,[9] a solution of methyl pyruvate (30.6 g), hydroquinone (0.1 g), and β-pinene (408 g) was refluxed gently for 96 hr. The excess reagents were removed by distillation up to 60° (8 mm). The resulting viscous liquid was fractionated, collecting the adduct at 79–89° (0.2 mm): 40.82 g, 57.1%; ir (neat) 3550, 2950, 1740, and 1210 cm^{-1}; nmr (CCl_4) 5.20 (m, 1 H), 3.66 (s, 3 H), 2.91 (s, hydroxyl, 1 H), 2.19 (m, 8 H), 1.29 (s, 3 H), 1.21 (s, 3 H), and 0.79 (s, 3 H); mass spectrum M^+ 238; R_f 29 on 12 ft 10% Carbowax column, 150°, as single peak; d_{25} 1.0119. Several runs gave $[\alpha]^{26}D$ −21.0° (neat), $[\alpha]^{30}D$ −22.6° (neat), $[\alpha]^{28}D$ −20.4° (ethanol, *c* 16.3); reported[9] bp 88–89° (0.5 mm), $[\alpha]^{26}D$ −30.2°.

Addition of the nmr shift reagent Eu(fod)$_3$ to a carbon tetrachloride solution of the adduct caused the methoxyl singlet at δ 3.66 to split into two singlets of equal intensity at 3.80 and 3.85, and the methyl singlet at δ 1.29 to split into two signals of equal intensity at 1.57 and 1.68.

Saponification of 2 and Separation of Potassium Salts. A mixture of adduct 2 (17.71 g, 74.3 mmol) and 4.17 g (74.3 mmol) of potassium hydroxide in 60 ml of water and 20 ml of ethanol was refluxed for 2 hr and stirred overnight. After extracting with ether, the aqueous solution was reduced to dryness. The dark residue was taken up in 150 ml of hot ethyl acetate and on cooling, scratching induced crystallization. Recrystallization twice from ethyl acetate gave 6.30 g of one pure potassium salt: mp 105–107°; ir (KBr) 3450, 2920, 1590, and 1120 cm^{-1}; $[\alpha]^{25.5}D$ −18.4° (abs EtOH, *c* 1.67).

The washings and mother liquors were combined and concentrated to a volume of 150 ml. Crystallization occurred on standing. Recrystallization from ethyl acetate–ethanol gave 5.49 g of the diastereomeric potassium salt, mp 204–209°; $[\alpha]^{25.5}D$ −12.1° (abs EtOH, c 1.70). A mixture of the two salts melted at 105–210°.

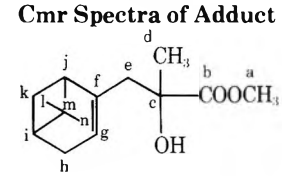
Diastereomeric Adducts 2a and 2b. A solution of 15.75 g of the potassium salt of mp 105–106° was neutralized with 6.50 g of 36% hydrochloric acid. The acidic solution was extracted with three 200-ml portions of chloroform. The extracts were combined, dried, and concentrated to give 13.5 g of crude acid. The acid was treated with excess ethereal diazomethane and the solvents were removed *in vacuo*. Ester **2b** was isolated by distillation as a low-melting solid: bp 72–80° (0.20 mm); 13.90 g, 96.5%; ir (neat) 3510, 2950, 1740, and 1201 cm^{-1}; nmr (CCl_4) 5.29 (m, 1 H), 3.71 (s, 3 H), 2.89 (s, hydroxyl, 1 H), 2.26 (m, 8 H), 1.35 (s, 3 H), 1.29 (s, 3 H), and 0.82 (s, 3 H); mass spectrum M^+ 238; $[\alpha]^{25}D$ −12.5° (abs EtOH, *c* 4.93); lit.[9] $[\alpha]^{26}D$ −29.42°.

The potassium salt of mp 204–207°, 9.49 g, was converted into the ester in the same manner to give 9.56 g, 95%, of the low-melting methyl ester **2a**: bp 74–80° (0.15 mm); ir (neat) 3540, 2940, 1739, and 1199 cm^{-1}; nmr (CCl_4) 5.10 (m, 1 H), 3.64 (s, 3 H), 2.85 (s, hydroxyl, 1 H), 2.15 (m, 8 H), 1.31 (s, 3 H), 1.25 (s, 3 H), and 0.81 (s, 3 H); $[\alpha]^{23}D$ −33.4° (abs EtOH, c 1.95).

Addition of Eu(fod)$_3$ to each diastereomer **2a** and **2b** caused no detectable splitting of the methoxyl or methyl singlets in the nmr, demonstrating that each was a pure isomer.

The natural abundance cmr spectra of the adduct mixture and the pure diastereomer **2a** are tabulated in Table I. Assignment of signals was based on coupling and on the published assignment to the spectrum of α-pinene.[15]

Table I
Cmr Spectra of Adduct



Adduct mixture 2	Isomer 2a	Carbon	Coupling
177.177, 177.016	176.922	b	s
144.888, 144.399	144.694	f	s
121.924, 121.392	121.198	g	d
75.768, 75.088	75.574	c	s
52.177	52.080	a	q
48.391, 48.197	48.003	e	t
47.566	47.323	j	d
41.110	40.916	i	d
33.198	37.955	m	s
32.180	31.986	h	t
32.034	31.986	k	t
26.646, 26.404	26.549	d	q
26.161	26.307	l	q
21.453	21.307	n	q
0	0	TMS	

Control Experiments. A. A solution of adduct **2a** (500 mg, $[\alpha]^{22}D$ −33.4°) and 5 mg of hydroquinone in 12 ml of β-pinene was refluxed for 96 hr. Removal of solvent gave a residue which was distilled in a Kugelrohr apparatus to give the unchanged adduct (331 mg), $[\alpha]^{25*}D$ −33.1° (abs EtOH, c 2.12). The ir and nmr spectra were identical with starting material, and addition of Eu(fod)$_3$ caused no splitting of nmr signals.

B. A solution of adduct **2b** (700 mg, $[\alpha]^{25}D$ −12.5°) and 7 mg of hydroquinone in 12 ml of β-pinene was refluxed for 89 hr. Removal of solvent gave a residue which was distilled in a Kugelrohr apparatus to give unchanged **2b** (484 mg), bp 56–60° (0.18 mm), $[\alpha]^{24}D$ −12.9° (abs EtOH, *c* 4.60). The ir and nmr spectra were unchanged, and addition of Eu(fod)$_3$ caused no splitting of the nmr signals.

C. In three separate experiments, a solution of 68.0 g of β-pinene, 0.0166 g of hydroquinone, and 5.1 g of methyl pyruvate was gently refluxed for 6, 24, and 48 hr, respectively. Excess β-pinene and methyl pyruvate were removed at reduced pressure. The residue was distilled in a Kugelrohr apparatus to afford adduct, 2, bp 60–70° (0.19 mm), in 8.9, 19.1, and 34.4% yields, respectively. The respective optical rotations were −18.9, −18.1, and −18.6° (abs EtOH, *c* 5.3–5.9). Examination of the nmr spectrum of each product with added Eu(fod)$_3$ showed that an approximately 1:1 mixture of diastereomers was formed in each case.

Preparation of Epoxide 3. To a solution of 4.737 g of acetic anhydride (46.4 mmol), 30 ml of ethylene chloride, and 1.338 g of 80% hydrogen peroxide (31.5 mmol) was added 0.15 g of trifluoroacetic acid. After stirring for 2 hr, the peracid solution was added dropwise to a mixture of 4.8710 g of diastereomer **2b** (20.4 mmol), 9.9652 g of anhydrous sodium carbonate (94.1 mmol), and 0.2 g of anhydrous sodium acetate in 120 ml of dry methylene chloride. After stirring 12 hr, the salts were filtered and the solution concentrated to an oil. The epoxide was purified by distillation at 96–102° (0.15 mm) to give a colorless liquid: 4.53 g, 87.5%; ir (neat) 3510, 2960, 1745, and 1225 cm^{-1}; nmr (CCl_4) 3.70 (s, 3 H), 3.40 (s, hydroxyl, 1 H), 3.29 (m, 1 H), 1.95 (m, 8 H), 1.29 (s, 3 H), 1.25 (s, 3 H) and 0.95 (s, 3 H); R_f 0.72, hexane–ethyl acetate (9:1) on silica gel: mass spectrum M^+ 254; $[\alpha]^{24}D$ −69.9° (abs EtOH, *c* 3.63). *Anal.* Calcd for $C_{14}H_{22}O_4$: C, 66.12; H, 8.72. Found: C, 66.36; H, 8.82.

Preparation of Triol 4. Dry Ice, 0.5 g, was added to 20 ml of water at 0°. Rapidly, 750 mg of epoxide **3** was added. the flask stoppered, and the solution mixed. After stirring 30 min, the solution was extracted with chloroform. The extracts were combined, dried, and concentrated to afford an oil. The triol was chromatographed on 15 g of 60–200 mesh silica gel, the product appearing in the 1800–1900 ml volume of eluent using hexane–ethyl acete (9:1), and characterized as an oil: 0.486 g, 60.5%; ir (neat) 3350, 2940, 1739, and 1208 cm^{-1}; nmr (acetone-d_6) 5.62 (m, 1 H), 4.4 (br s, hydroxyl, 3 H), 4.15 (br s, 1 H), 3.80 (s, 3 H), 2.25 (m, 7 H), 1.40 (s, 3 H), and 1.19 (s, 6 H); mass spectrum M^+ 254; R_f 0.1 using hexane–ethyl acetate (9:1) on silica gel; $[\alpha]^{23}D$ −94.0° (abs EtOH, *c* 15.8).

The same procedure, beginning with the adduct mixture 2, gave an oil, which was crystallized from benzene–hexane to a white solid (40%): mp 133–135°; ir (KBr) 3350, 2960, 1730, and 1199 cm^{-1}; nmr (acetone-d_6) 5.65 (m, 1 H), 4.4 (br s, hydroxyl, 3 H), 4.10 (br s, 1 H) 3.70 (s, 3 H), 2.0 (m, 7 H), 1.38 (s, 3 H), and 1.10 (s, 6 H); nmr ($CDCl_3$) 5.68 (m, 1 H), 4.60 (br s, hydroxyl, 3 H), 4.18 (m, 1 H), 3.80 (s, 3 H), 2.20 (m, 7 H), 1.40 (s, 3 H), 1.22 (s, 3 H), and 1.19 (s, 3 H); $[\alpha]^{25}D$ −91.0° (abs EtOH, *c* 0.95). *Anal.* Calcd for $C_{14}H_{24}O_5$: C, 61.74; H, 8.88. Found: C, 61.98; H, 8.97.

Preparation of Ketone 5. To a solution of 125 ml of methylene chloride and 15.70 g of pyridine (198.3 mmol) was added 9.92 g of chromium trioxide (99.2 mmol) in the usual manner. The triol 4 (4.4519 g) in 20 ml of methylene chloride was added and stirring continued for 30 min. Ether was added and the mixture filtered. The ethereal solution was washed with dilute acid, base, and saturated salt solution and dried. Removal of the solvent gave crude ketone which was purified by distillation: 3.15 g, 73.6%; bp 145–150° (0.1 mm); ir (neat) 3465, 2980, 1740, 1670, and 1110 cm^{-1}; nmr (acetone-d_6) 7.0 (m, 1 H), 3.70 (s, 3 H), 3.35 (s, hydroxyl, 2 H), 2.4 (m, 7 H), 1.39 (s, 3 H), and 1.35 (s, 6 H); λ_{max} (EtOH) 239 nm (ϵ 9500); mass spectrum M^+ 252; $[\alpha]^{23}D$ −17.4° (abs EtOH, c 2.5).

Preparation of Ketal 6. The crude enone 5 from the Collins oxidation above was freed of inorganic salts by filtration, concentrated, and distilled to give the ketal 6 as a colorless liquid: 3.39 g, 82.5%; bp 110–120° (0.1 mm); ir (neat) 2980, 1741, 1050, and 1010 cm^{-1}; nmr ($CDCl_3$) 5.1 (m, 1 H) 3.58 (s, 3 H), 2.3 (m, 7 H), 1.49 (s, 3 H), 1.20 (s, 3 H), and 1.15 (s, 3 H); mass spectrum M^+ 234; R_f 0.82 using hexane–ethyl acetate (9:1) on silica gel; $[\alpha]^{23}D$ −1.31° (abs EtOH, c 2.82). *Anal.* Calcd for $C_{14}H_{20}O_4$: C, 66.65; H, 7.99. Found: C, 66.55; H, 7.87. A solution of the ketal (1.50 g) in 10 ml of dioxane and 110 ml of water was treated with 6 drops of concentrated hydrochloric acid. After stirring at 40° for 3 hr, the solution was extracted with chloroform. The extracts were combined, washed with bicarbonate, and dried. Concentration of the chloroform solution gave an oil which was distilled in a Kugelrohr apparatus, yielding the ketone **5**, bp 160–170° (0.1 mm). The ir and nmr spectra, as well as the optical rotation, were identical with those of the ketone described above.

Ruthenium Tetroxide Oxidation. A solution of ketone 5 (1.55 g, 5.75 mmol) in 50 ml of acetone was added to a solution of ruthenium tetroxide. The tetroxide was freshly prepared by adding 1.00 g of sodium periodate (4.67 mmol) in 20 ml of water to 173.7 mg of 52.7% ruthenium dioxide (0.69 mmol) in 50 ml of acetone. As the reaction progressed, 5.0 g of sodium periodate (23.4 mmol) in a solution of 50 ml of water–20 ml of acetone was added portionwise.

After stirring the mixture 5 hr at room temperature, 20 ml of 2-propanol was added and the mixture was filtered. The solvents were removed *in vacuo*, and the residue was esterified with excess diazomethane. The ether was removed and the product distilled in a Kugelrohr apparatus to give 0.865 g (85.6%) of ester: bp 80–110° (2.0 mm), $[\alpha]^{21}D$ +15.5° (chloroform, c 9.42). The sample was further purified by glc to give (*S*)-(+)-dimethyl citramalate,[16,17] purity 95% by glc; ir (neat) 3510, 2960, 1740, and 1195 cm^{-1}; nmr ($CDCl_3$) 3.80 (s, hydroxyl, 1 H), 3.71 (s, 3 H), 3.61 (s, 3 H), 2.90 and 2.60 (AB quartet, 2 H, J = 15 Hz), and 1.40 (s, 3 H); $[\alpha]^{21}D$ +26.4° (chloroform, *c* 4.22) [lit.[17] $[\alpha]^{20}D$ +30.6° (chloroform, c 3.24)]. The mass spectrum and glc retention time were identical with those of a sample of dimethyl citramalate prepared from racemic citramalic acid.[18]

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Registry No.—**1**, 18172-67-3; **2a**, 53216-67-4; **2a** K salt, 53216-68-5; **2b**, 53216-69-6; **2b** K salt, 53216-70-9; **3**, 53216-71-0; **4**, 53216-72-1; **5**, 53216-73-2; **6**, 53216-74-3; 8, 38574-61-7; methyl pyruvate, 600-22-6.

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Ethylenic Compounds Reactivity: Bromination. XXXVII. Comparison of Alkenes and β-Substituted Styrenes

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The bromination reactivities of *trans*-styrenes $C_6H_5C_\alpha H{=}C_\beta HR$ (R = alkyl or heteropolar) are related to those of the corresponding alkenes $C_\alpha H_2{=}C_\beta HR$ by a linear equation with a slope of 0.75. The styrene–ethylene pair lies off this regression. These results imply that the distribution of charge in the transition state is different for both these families. Consideration of log *k* *vs.* σ* correlations for styrenes favors a transition state polarity corresponding to that of a carbonium ion with the charge located on C_α.

While the hypothesis that the intermediate in the bromination of ring-substituted styrenes is a carbonium ion (with or without weak Br–C^+ interaction) is well supported by data on the reaction products and on the sensitivity of the reaction to substituents on the ring, the case of styrenes with substituents on the double bond is less clear and, in particular, a bromonium ion intermediate or a competition between two carbonium ions has been considered for β,β-dimethylstyrene.[1] Moreover, whereas until now it was generally accepted[2] that the transition state was similar in structure to the intermediate, Yates and Mac Donald[3] propose in a recent study a bromonium-like transition state followed by a carbonium ion intermediate for arylethylenes. The need is thus felt for a direct investigation, therefore based on kinetic measurement, of the nature of the transition state for such compounds. To this end we had studied polar effects on the reactivity of a series of β-substituted styrenes *trans*-$C_6H_5CH{=}CHR$; we now wish to report these results and to compare them with those obtained previously for a set of analogous alkenes $CH_2{=}CHR$.

Results

To be comparable with previous work[4] the kinetic measurements were performed in methanol. Bromination rate constants follow[5] eq 1 in which *k* is the rate constant at a

$$k(1 + K[Br^-]) = k_{Br_2} + \beta[Br^-] \quad (1)$$

bromide ion concentration $[Br^-]$; *K* is the equilibrium constant for the formation of tribromide ion $Br_2^- + Br^- \rightleftarrows Br_3^-$; k_{Br_2} is the rate constant for the addition of molecular bromine; β is a term whose mechanistic interpretation is controversial[6] but is often equated with $Kk_{Br_3^-}$, where $k_{Br_3^-}$ is the rate constant for the addition of Br_3^-.

Values of k_{Br_2} and $k_{Br_3^-}$ for different substituents R are listed in Table I. The values of $Q = k_{Br_2}/k_{Br_3^-}$ are much greater than unity and are consistent with the idea that Br_2 and Br_3^- react simultaneously, the latter being less electrophilic. The value of *Q* varies very little, so that the following equation is obeyed

$$\log k_{Br_3^-} = +0.96 \log k_{Br_2} - 1.48 \quad (2)$$

(correlation coefficient *R* = 0.995; standard deviation on the slope = 0.04). Thus any reactivity–structure relationship applicable to the reactivity of one of those electrophiles can readily be transposed to the other. It is therefore enough to discuss one series of constants only, and we have chosen k_{Br_2} whose meaning is unambiguous. It should be noted that constancy of *Q* has already been observed for aliphatic olefins in methanol.[6,7] The *Q* values, albeit slightly greater for styrenes than for alkenes, are of the same order of magnitude. Rolston and Yates[1] have, on the other hand, obtained totally different results (*Q* variable and even less than unity) for the addition of bromine to ring-substituted styrenes in acetic acid. This remark confirms that there is no analogy between *Q* values measured in different solvents; this disparity was noted previously in a study of the reactivity of aliphatic olefins in methanol and in water.[8]

Discussion

Comparison of Styrenes and Alkenes. Rather than attempt to compare the styrene reactivities directly with a scale of substituent effects, we prefer first of all to relate these data to those of a reference family $CH_2{=}CHR$, very close to the family in question. In this way the most possible of the extrastructural parameters (nature of the reaction, solvent, temperature) are held constant; thus errors due to faults in external scales of substituent constants are avoided and it is possible to exploit directly mechanistic information available for the reference family. In the present case, studies of the kinetics[9] and the products[10] of the reaction in methanol confirm that a mechanism with a bromonium ion intermediate is of general validity for the $CH_2{=}CHR$ series.

With the exception of the particular case of the styrene–ethylene pair which we shall discuss later, the reactivities of the styrenes and the alkenes are linearly related by

$$\log k_{Br_2}(trans\text{-}C_6H_5CH{=}CHR) = 0.75 \log k_{Br_2}(CH_2{=}CHR) + 1.62 \quad (3)$$

(*R* = 0.997; standard deviation on the slope = 0.025). Since the alkenes follow a single reaction mechanism the linearity of the correlation implies that the nature of the effect of *R* is identical for both families. It has been shown in the case of alkenes that, for the substituents chosen, only their polar effects are involved; steric effects are excluded.[9b] As the value of the slope in (3) expresses the ratio of the sensitivities of each family to the substituent effect, the charge in the case of styrenes must be either lower or further from the substituent R than in the case of alkenes.

We can suggest a bromonium-like transition state with part of the charge delocalized on the carbons for alkenes and for styrenes a carbonium ion-like transition state where the charge is on C_α. In the second case charge is further from the substituent R than in the case of alkenes. To the extent to which the results obtained by Olah, *et al.*, for stable ions in superacid media can be transposed to methanolic media, they support the existence of such structures. According to those authors the alkylethylene bromonium ions are stabilized[11,12] by the resonance forms $-C^+R^1-CBrR^2-$ and $-CBrR^1-C^+R^2-$. The interpretation of the ^{13}C nmr data regarding bromine participation in benzylic structures is, however, rather delicate; having found that the bromine atom clearly took part in the stabilization of

Table I
Reactivity of β-Substituted Styrenes, *trans*-C_6H_5CH=CHR in Methanol at 25°

Compd	R	k_{Br_2}[a]	$k_{Br_3^-}$[a]	Q[b]
1	$-C_2H_5$	4.29×10^3	1.22×10^2	35
2	$-CH_3$[c]	3.26×10^3	8.27×10^1	39
3	$-H$[d]	1.53×10^3	4.40×10^1	35
4	$-CH_2OH$	1.01×10^3	1.93×10^1	52
5	$-CH_2OCH_3$	2.68×10^2	6.36	42
6	$-CH_2OCOCH_3$	5.59×10	1.28	44
7	$-CH_2Cl$	1.17×10	4.55×10^{-1}	26
8	$-CH(OCOCH_3)_2$	1.41		

[a] k_{Br_2} and $k_{Br_3^-}$ (in M^{-1} sec^{-1}) are calculated by (1) from the rate constants measured at different NaBr concentrations (see Experimental Section). [b] $Q = k_{Br_2}/k_{Br_3^-}$. [c] J.-E. Dubois and M. de Ficquelmont-Loïzos, unpublished results. [d] M. de Ficquelmont-Loïzos, Doctoral Thesis No. AO 8355, Paris, 1973.

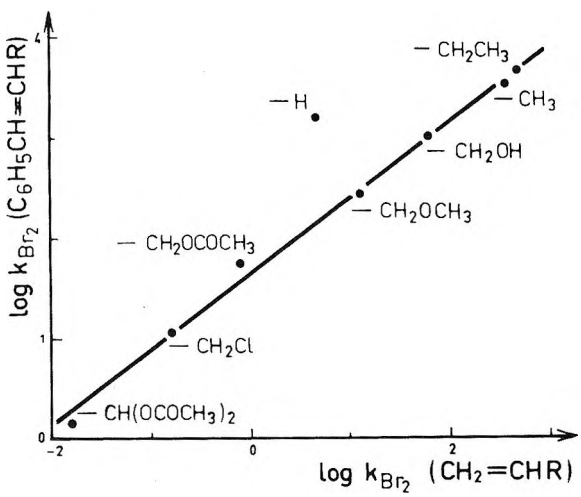

Figure 1. Styrene–alkene correlation. Each point corresponds to a substituent R indicated on the graph. Styrene data are from Table I; alkene data are from Table II and ref 6 and 17.

the ions $ArC^+(CH_3)CH_2Br$,[13] Olah, *et al.*, now conclude that bromine bridging plays only a minor role.[14] We shall now show that our hypothesis is substantiated by consideration of reactivity *vs.* polar effect correlation.

Reactivity *vs.* Polar Effect Correlation. Reactivity must be related to the polar effect of the substituent *directly* attached to the atom bearing charge in the transition state. In our hypothesis this atom is C_β for alkenes and C_α for styrenes; thus log k_{Br_2} is to be plotted *vs.* σ_R^* for alkenes and *vs.* σ_{CHBrR}^* (or more simply $\sigma_{CH_2R}^*$)[15] for styrenes. Our preceding results[9b] show that in the case of alkenes a linear relationship is observed between log k_{Br_2} and σ_R^*.

$$\log k_{Br_2} = -3.10\sigma_R^* + 8.80 \quad (4)$$

In the case of the styrene family, if we plot reactivity against σ_R^*, styrene (R = H) lies 1.5 log units above the regression line;[16] if we plot reactivity against $\sigma_{CH_2R}^*$, a satisfactory linear relationship including styrene itself is obtained.

$$\log k_{Br_2} = -4.80\sigma_{CH_2R}^* + 3.23 \quad (5)$$

$$(R = 0.982)$$

σ^* values are taken from ref 15a; when necessary a transmission coefficient of 0.43[17] has been applied for heteropolar substituents. If σ_R^* was linearly related to $\sigma_{CH_2R}^*$ for all substituents, the two regressions for styrenes would be equivalent. But the attenuation coefficient of the polar effect for heteropolar substituents is not valid for alkyl ones.[18] This fact can explain why the point corresponding to R = H fits one regression and not the other and consequently why the couple styrene–ethylene lies off correlation 3.

The expected sequence[19] is $|\rho^*|$ (carbonium intermediate) > $|\rho^*|$ (bridged intermediate), since in the second case the charge is dispersed over the atoms making up the bridged ion. This sequence is observed here. The ρ^* value of −4.80 for styrenes is close to the values of ρ and ρ^+ determined for addition reactions with carbonium ion intermediates implying structures XC_6H_4CH=CH_2 or XC_6H_4CH=CHC_6H_4Y very similar to that which we are studying. For the bromination of styrenes[20] and stilbenes,[21] and for the hydration of styrenes,[22] the values of ρ^+ (bromination) and of ρ (hydration) are −4.3, −5.0, and −4.0, respectively. These comparisons confirm the proposal that the polarity of the bromination transition state for β-substituted styrenes is analogous to that of a carbonium ion and not a bromonium ion.

Resonance Contribution of Phenyl Rings. One can compare the β-substituted styrenes with α-methylstyrene, where the methyl substituent is directly attached to the C_α and can only favor the arylcarbonium intermediate, and with *trans*-stilbene, for which carbonium and bromonium ion pathways are of similar importance.[21b] In the case of α-methylstyrene, the benzene ring is no longer in the plane of the C=C double bond[23,24] and this compound can be expected to be of diminished reactivity. The experimentally observed reactivity (log k_{Br_2} = 5.21) is indeed slightly less than the value calculated from eq 5.[25] This difference (0.51 kcal mol^{-1}) is consistent with the angle of rotation given by Suzuki.[23] The resonance contribution to the reactivity of styrene[26] is about 2.2 kcal mol^{-1}. Following a rotation of the benzene ring out of the plane of the double bond through an angle Φ, this contribution is multiplied by the factor[27] $\cos^2 \Phi$. The corresponding energy decrease is 0.65 kcal mol^{-1} which is to be compared with the value of 0.51 kcal mol^{-1} observed. In the case of *trans*-stilbene two identical carbonium ion intermediates are possible but the statistical correction is counterbalanced by the correction due to the presence of a bromonium ion path which is about as important as the carbonium path.[21b] The reactivity of *trans*-stilbene by carbonium ion path is 1.2 log units less than that calculated from eq 5. Both for styrenes and *trans*-stilbene resonance between the ring attached to C_α and the double bond is replaced in the transition state by a greater resonance energy between the ring and the electron deficient C_α. However, in the case of *trans*-stilbene the additional resonance energy existing in the ground state between the double bond and the ring attached to C_β is considerably decreased in the transition state. According to Wheland,[28] comparison of the resonance energies of benzene, styrene, and stilbene suggests that a value of 3–4 kcal mol^{-1} can be attributed to the resonance energy of the double bond with one of the benzene rings. This energy corresponds to 2.2–2.9 log units when expressed in terms of log

Table II
Rate Constants at Different NaBr Concentrations at 25° in MeOH (M^{-1} sec^{-1})

R	NaBr 0.05	NaBr 0.10	NaBr 0.20
	A. β-R-Substituted Styrenes		
$-C_2H_5$	5.46×10^2	3.45×10^2	2.37×10^2
$-CH_2OH$	1.18×10^2	7.33×10^1	4.62×10^1
$-CH_2OCH_3$	3.28×10^1	2.04×10^1	1.35×10^1
$-CH_2OCOCH_3$	6.78	4.22	2.77
$-CH_2Cl$	1.58	1.06	7.62×10^{-1}

	0.05	0.10	0.20	k_{Br_2}	$k_{Br_3^-}$
	B. Others				
$C_6H_5C(CH_3)=CH_2$[a]	1.85×10^4	1.09×10^4	6.77×10^3	1.62×10^5	2.39×10^3
$CH_2=CHCH_2OCH_3$[b]	1.98	1.38	1.06	1.31 × 10	7.17×10^{-1}
$CH_2=CH_2$[c]				4.65	

Registry no. [a] 98-83-9. [b] 627-40-7. [c] 74-85-1.

k, and this is compatible with the deviation observed, since this energy is not reduced completely to zero in the transition state.

In a recent study on the bromination of 1,2-disubstituted ethylenes, Yates and Mac Donald[3] find that steric constraints in cis isomers are increased in the transition state. They propose, therefore, for all the compounds studied including those with a phenyl substituent that the transition state is bromonium ion like. A similar dichotomy between steric and polar data has already been noted in a related addition reaction, the Prins reaction of β-methyl styrenes.[29] It seems that in order to reconcile the two sets of data it is necessary to abandon pure carbonium and bromonium ions as transition state models and to adopt a more flexible representation. Currently available results on the bromination of α-arylethylenes suggest that the transition state has the following characteristics: polarity analogous to that of an α-aryl α-bromocarbonium ion, but spatial layout analogous to that of the CTCE[30] which precedes the transition state along the reaction coordinate, without free rotation about the BrC–C$^+$ bond.

Experimental Section

Chemicals. Compounds **5**, **6**, and **8** were prepared as described previously.[31-33] Other compounds were obtained commercially. Compounds were purified by vapor-phase chromatography on $AgNO_3$ or DEGS columns except for ethylene which was used without further purification, compounds **4** and **7** which were distilled at reduced pressure, and compound **8** which was recristallized from petroleum ether. Methanol was dried by distillation over Mg and was then twice distilled over Br_2.

Kinetic Measurements. Except for α-methylstyrene where the couloamperometric method[34] was used the rate constants were determined by potentiometry[35,36] at different Br^- concentrations (Table II). The variation of the potential E of the electrode Pt, $Br_2|Br^-$ relative to a calomel reference electrode is measured as a function of time. Bromine is produced in the medium by electrolysis of NaBr. Initial Br_2 concentrations are in the range 2×10^{-5}–1×10^{-4} M. Pseudo-first-order conditions are obtained by using an olefin/bromine ratio greater than 20. The rate constants are calculated by the expression $k_2 = -78.2\, dE/[(a - b)dt]$, where a and b are the initial concentrations of olefin and bromine and E is the emf in millivolts. The standard deviation (between different determinations and the mean value) is in all cases less than 2.5%. The rate constants k_{Br_2} and $k_{Br_3^-}$ are calculated from eq 1 by the least-squares method applied to all the experimental data (not mean values). The standard deviation is about 2% on k_{Br_2} and about 3% on $k_{Br_3^-}$.

The rate constant k_{Br_2} is particularly small for ethylene and compound **8** and was determined directly in the absence of NaBr by titration. The bromine is neutralized by a buffered As_2O_3 solution and the back titration by electrolytically generated I_2 is performed amperometrically. The measurements can in this case be falsified by the production of Br^- during the reaction (formation of solvent incorporated product). In view of the concentrations used the amount of Br^- produced on the end of the reaction could be as much as 4×10^{-4} M. This would correspond to a rate constant at most 7% less than k_{Br_2}. However, no indication of any regular curvature can be seen in the log $[(a - x)/(b - x)]$ *vs.* time plots and the systematic error of the experimental value relative to k_{Br_2} is very probably much less than 7%. These two rate constants are slightly less reproducible than those measured by potentiometry: the standard deviation is 3.6 and 4.8% respectively for ethylene and compound **8**. The constants are, however, obtained without extrapolation. Whereas in all other cases the initial olefin concentration is determined by weighing, the ethylene concentration is determined indirectly. If there is excess Br_2 the initial ethylene concentration is reckoned to be the difference between the initial and final Br_2 concentrations; if there is excess ethylene a methanolic ethylene solution is titrated against Br_2.

Acknowledgment. We wish to thank Mrs. C. Boussu for technical assistance and Dr. J. S. Lomas for critical reading of the manuscript.

Registry No.—**1**, 1005-64-7; **2**, 873-66-5; **3**, 100-42-5; **4**, 4407-36-7; **5**, 22688-03-5; **6**, 21040-45-9; **7**, 21087-29-6; **8**, 37973-54-9.

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Reaction of Carbethoxynitrene with Allenes[1]

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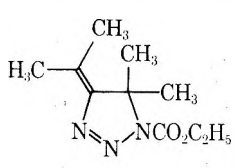
Carbethoxynitrene, from base-catalyzed α elimination of *N*-(*p*-nitrobenzenesulfonoxy)urethane (**9**), reacts with allene and 1,1-dimethylallene to produce 1,2-cycloaddition products. Tetramethylallene fails to produce an adduct with the nitrene. The results appear to be most consistent with a cycloaddition mechanism in which the initial step is reaction of triplet nitrene with a terminal carbon atom of the allenic moiety. The thermal isomerization of 2-isopropylidene-*N*-carbethoxyaziridine (**14**) to 2-ethoxy-5,5-dimethyl-4-methylene-2-oxazoline (**5b**) is described.

The reaction of various types of carbenes or carbenoids with allenes has been investigated and proceeds in an unexceptional fashion to yield methylenecyclopropanes regardless of whether the divalent carbon species is in a singlet or triplet spin state.[2,3] In view of the recent interest in the chemistry of nitrenes,[5] isoelectronic analogs of carbenes, it is somewhat surprising that the corresponding reaction of this species with allenes has received only cursory examination. Thus, the sole reported investigation of this type of reaction is that of Bleiholder and Shechter in which they studied the thermally induced reaction of ethyl azidoformate (**1**) with tetramethylallene (**2**) and the photochemically initiated reaction of **1** with 1,1-dimethylallene (**3**).[6] The thermal process afforded the triazoline **4** (38%) and the isopropylideneoxazoline **5a** (29%) as addition products; the photochemical reaction produced the methyleneoxazoline **5b** (47%) as the only reported product. The *N*-carbethoxyaziridines, **6**, products that might have been anticipated if allenes were to behave toward nitrenes as do carbenes, were not observed in either experiment.



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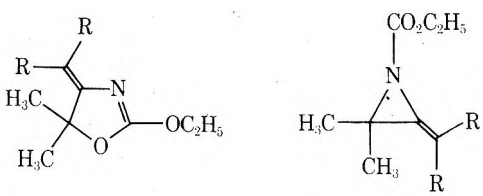
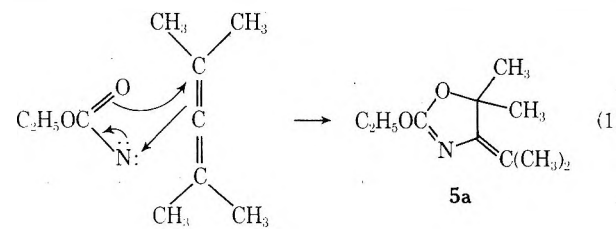


5 **6**

a, R = CH_3
b, R = H

Whereas photolysis of **4** was found to yield **5a** (43%), thermolysis did not promote this transformation; thus **5a** potentially represented a primary product of reaction of carbethoxynitrene with tetramethylallene. Two mechanistic pathways for formation of **5a** appeared to be reasonable, *viz.*, 1,3-dipolar cycloaddition of the nitrene to tetramethylallene to generate **5a** directly (eq 1) or 1,2 cycloaddition

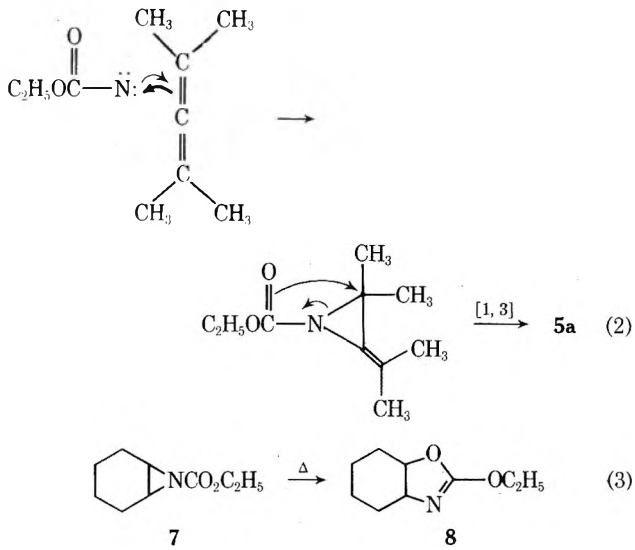


(1)

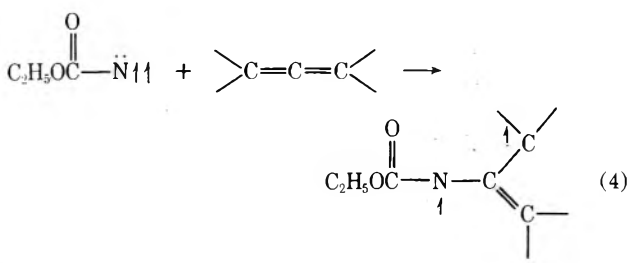
5a

between the nitrene and the allene to produce **6a**, which in turn underwent a [1,3]-sigmatropic isomerization to **5a** (eq 2). Since the pathway involving 1,3-dipolar cycloaddition was without precedent in nitrene chemistry, Bleiholder and Shechter favored the second alternative (eq 2), a suitable analogy for the rearrangement of **6a** being the reported thermal conversion of the aziridine **7** to the oxazoline **8** (eq 3).[7]

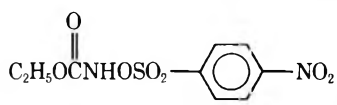
We have reinvestigated the reaction of carbethoxynitrene with allenes under conditions more conducive not only to isolation of alkylideneaziridines, should they be formed, but also to the extension of such studies to triplet



nitrenes. The latter aspect is of interest in that triplet carbethoxynitrene is radical-like in character and its addition to C-2 of the allenic moiety would potentially provide an entry into triplet heterotrimethylenemethanes (eq 4).[8]



Thus we chose to generate carbethoxynitrene by treatment with base of *N*-(*p*-nitrobenzenesulfonoxy)urethane (**9**), a

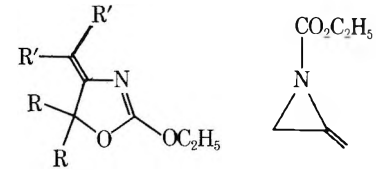


9

procedure known to yield singlet and/or triplet nitrenes depending on the reaction conditions employed.[7,10]

Results

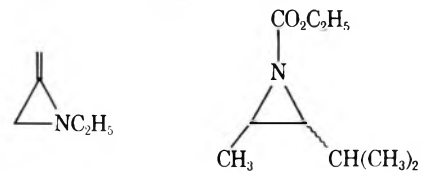
Triethylamine-catalyzed decomposition of **9** at room temperature in a 2.6 mol % solution of allene in dichloromethane afforded, upon careful work-up (see Experimental Section), a 6% yield of a colorless oil as the only isolable volatile product. The oil was isolated by vacuum transfer and polymerized with ease at 0°. It analyzed as $C_6H_9NO_2$ (high resolution mass spectroscopy), a molecular formula consistent with a 1:1 adduct of carbethoxynitrene and allene. The 100 MHz nuclear magnetic resonance (nmr) spectrum of the oil revealed broad singlet resonances at δ 2.73 (2 H, ring protons), 4.74 (1 H, vinyl proton), and 4.92 ppm (1 H, vinyl proton) in addition to absorptions at δ 1.32 [t (3 H)] and 4.16 ppm [q (2 H)] attributable to the ethoxy group. An intense absorption at 1730 cm^{-1} indicated that the product retained the carbonyl function.[11] These spectral data exclude the oxazoline **10a** as the structure of the reaction product; this substance, for example, would be expected to exhibit resonances in its nmr spectrum in the region of δ 4–4.5 ppm for its vinylic protons[6] and would not have absorptions in its ir spectrum in the range of 1730–1740 cm^{-1}.



10 **11**

a, R = R′ = H
b, R = H; R′ = CH_3

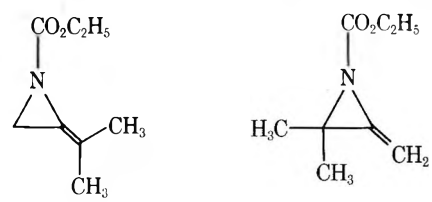
The data are, however, consistent with 2-methylene-*N*-carbethoxyaziridine (**11**). Although the resonance at δ 2.73 ppm that is assigned to the ring hydrogens may appear to be at unexpectedly low field, reference to model compounds supports the assignment. Thus the ring protons of the methyleneaziridine **12** appear at about δ 2.0[13] and those of the *N*-carbethoxyaziridine **13** occur in the range of δ 1.7–2.6 ppm.[10] The addition to allene of carbethoxynitrene generated by α elimination therefore occurs in the 1,2-cycloaddition mode common to the reaction of carbenes and allenes, albeit in low yields.



12 **13**

The generation as above of carbethoxynitrene in the presence of 1,1-dimethylallene and dichloromethane again afforded an unstable colorless oil, isolable by preparative thin layer chromatography (tlc) in yields of 3–8%. High resolution mass spectroscopy was consistent with formulation of the product as a 1:1 adduct of the nitrene and allene, and observation of a strong ir band at 1730 cm^{-1} allowed exclusion of the oxazolines **5b** and **10b** as structural possibilities.

Two alkylideneaziridines, **14** and **15**, are possible adducts from this reaction, and the nmr spectrum of the isolated



14 **15**

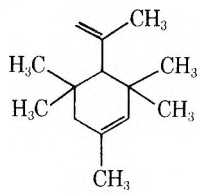
product allows differentiation between them as follows. The spectrum reveals an ethoxy moiety as a triplet at δ 1.30 and a quartet at 4.12 ppm, in addition to a two-proton singlet at 2.65 and two separate three-proton singlets at 1.75 and 1.80 ppm, respectively. The chemical shift of the lowest field singlet is that expected for the ring protons of an alkylidene-*N*-carbethoxyaziridine, *cf.* **11**, whereas the two singlets at higher fields are consistent with the presence of allylic methyl groups. The spectral evidence thus confirms structure **14**.

To test the premise that isomer **15** might have been formed during the reaction and subsequently either decomposed or underwent a rearrangement of the methylenecyclopropane type during work-up to produce the observed **14**, an attempt was made to detect transient formation of **15** by nmr spectroscopy. Monitoring of the reaction was achieved by removal of aliquots over the course of 4 hr and analyzing them by nmr spectroscopy. Although formation of **14** could be detected within 60 min of initiation of the reaction, characteristic resonances for **15** which were expected to occur at about δ 5 and 1 ppm never appeared. Be-

cause it seems unlikely that **15** would be rapidly rearranging to **14** at room temperature and that **15** would be more labile toward decomposition than the unsubstituted methyleneaziridine **11**, it is reasonable to conclude not only that **14** is a primary product of the reaction of carbethoxynitrene with 1,1-dimethylallene but also that **15** is not formed in the process.

It was discovered that the urethane **9** which is the precursor of the nitrene contained trace amounts of acid (see below). To assess the possible effect the acid might have on the course of the reaction, 1,1-dimethylallene and carbethoxynitrene were allowed to react in the presence of 2,6-di-*tert*-butylpyridine, a proton scavenger. This modification had no effect on the course of the reaction, and **14** was isolable in 8% yield.

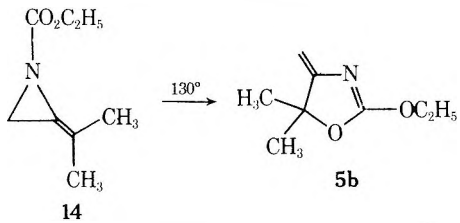
Initial attempts to extend the investigation to the reaction of carbethoxynitrene with tetramethylallene resulted in isolation in high yield of a colorless oil analyzing as $C_{14}H_{24}$ (high resolution mass spectroscopy). The nmr spectrum of this oil agrees with that reported by Poutsma for the dimer obtained by treatment of tetramethylallene with acids and to which structure **16** has been assigned.[14] The source of the acid catalyst in our experiment proved to be contaminants in the urethane **9.**



16

Repetition of the reaction of the nitrene with tetramethylallene under conditions such that acid-catalyzed dimerization of the allene was completely suppressed by the addition of 2,6-di-*tert*-butylpyridine failed to afford any of the expected alkylideneaziridine in the dichloromethane-soluble portion of the reaction mixture. As adjudged by nmr analysis, only unchanged allene and the pyridine were present.

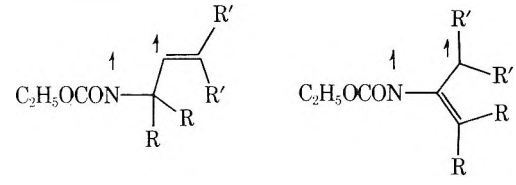
Thermolysis at 130° of a dilute degassed solution of **14** in carbon tetrachloride for 0.7 hr caused essentially complete disappearance of starting material and produced a substance having nmr resonances at δ 1.37 [t (3 H)], 1.42 [s (6 H)], 3.95 [s (1 H)], 4.32 [q (2 H)], and 4.50 ppm [s (1 H)]. This is the same nmr spectrum obtained by Bleiholder and Shechter for the adduct formed by photolysis of ethyl azidoformate in the presence of 1,1-dimethylallene and for which they assigned the structure of 2-ethoxy-5,5-dimethyl-4-methylene-2-oxazoline (**5b**) (eq 5).[6]



14 **5b** (5)

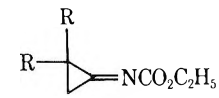
Discussion

The characterization of 2-methylene-*N*-carbethoxyaziridine (**11**) as the adduct between carbethoxynitrene and allene itself demonstrates for the first time that nitrenes can undergo net 1,2-cycloaddition reactions with allenes. Mechanism of the reaction is unclear, however. Even though the conditions chosen for generation of carbethoxynitrene in the presence of the allenes were such as to favor formation of triplet nitrene,[10] in hopes that products resulting from attack at C-2 of the allenic moiety might be discerned, the presence of the singlet species cannot be eliminated. The formation of **11**, therefore, could be rationalized mechanistically as the result either of a concerted addition of a singlet nitrene to allene or of a stepwise addition of triplet nitrene to produce diradicals **17a** or **18a** followed by spin relaxation and collapse to product.



17 **18**

a, R = R′ = H
b, R = H; R′ = CH_3



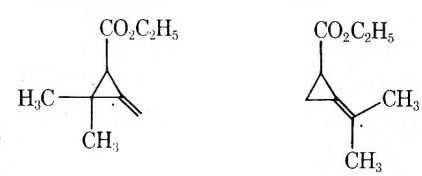
19

a, R = H
b, R = CH_3

Two products, the methyleneaziridine (**11**) and the imine **19a**, are possible from diradical **18a**, but resonances attributable to **19a** could not be detected in the volatile fraction obtained by vacuum line techniques. Because **19a** would be anticipated to be extremely susceptible to nucleophilic attack, its absence can in no way be taken as evidence against the possible intermediacy of **18a** in the reaction. Moreover, the low yield of product coupled with the paucity of detailed information regarding the relative rates of reaction of singlet and triplet nitrenes with π systems discourages attempts to designate the species responsible for product **11**.[15]

Extension of the reaction of carbethoxynitrene to 1,1-dimethylallene was attempted because this system provided a different type of test of the possibility that triplet nitrenes might add initially at C-2 of an allenic function. The diradical **18b** resulting from such a process could ultimately form both of the methyleneaziridines **14** and **15** as well as the imine **19b.** Once again the low yields of the adduct **14** thwart the drawing of definitive conclusions regarding reaction mechanism, but the results do merit the development of some tentative proposals.

If formation of **14** is in fact a consequence of reaction of singlet nitrene with the allene, attack has occurred at the less nucleophilic of the two possible double bonds, a regioselectivity that is rarely observed for reactions of divalent carbon with π systems. For example, carbethoxy carbenoid, generated by copper-catalyzed decomposition of ethyl diazoacetate, adds to 1,1-dimethylallene to produce mainly **20** (96%) and little **21** (4%).[16] There is little reason to believe



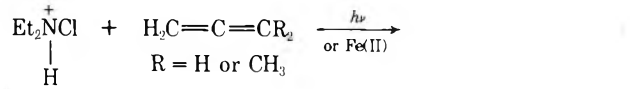
20 **21**

that the steric requirements for addition of carbethoxynitrene are greater than those of the corresponding copper carbenoid—in fact, just the reverse is more likely; so an alternative explanation for the exclusive formation of **14** seems desirable.

Such an explanation is found in the proposal that triplet

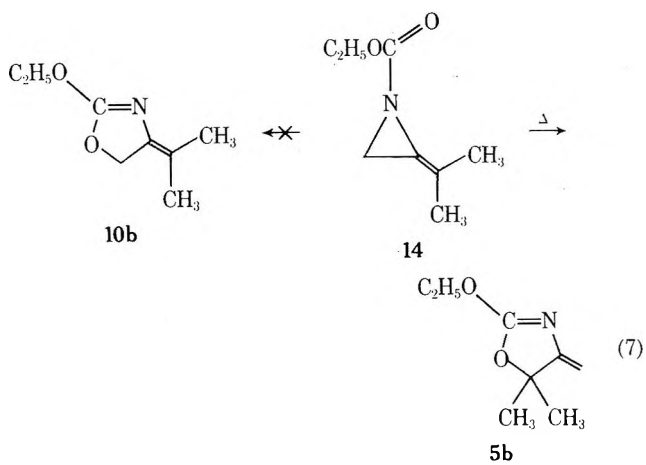
rather than singlet nitrene is the entity responsible for the cycloaddition product. If this be true, the absence in the reaction mixture of **15** can be taken as evidence that diradical **18b** is not being generated in significant quantities and that attack of the triplet nitrene has occurred preferentially at the sterically less encumbered terminal position of the allenic moiety to produce diradical **17b**, the precursor to **14**. Support for the hypothesis that steric factors are of importance in the reaction of carbethoxynitrene with allenes is derived from the observation that none of the 1,2-cycloaddition product **6a** is formed if tetramethylallene is used as a trap for the nitrene.

Thus our experimental results seem most compatible with the intervention of triplet diradicals of type **17** in the addition of triplet carbethoxynitrene with allenes.[17] It is to be noted that this orientation of attack has analogy in the report that diethylaminium radical adds exclusively to a terminal carbon atom of either allene or 1,1-dimethylallene (eq 6).[18]



$$Et_2NCH_2C(Cl)=CR_2 \quad (6)$$

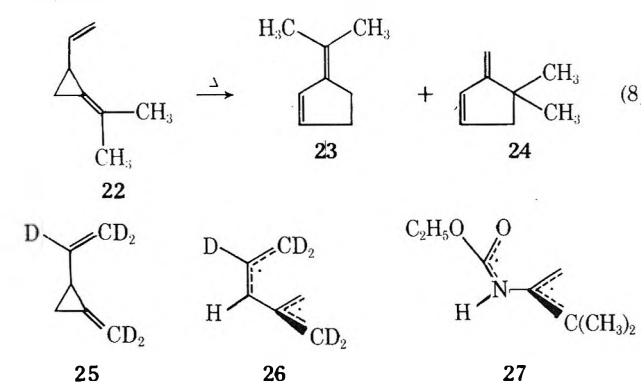
The thermolysis of 2-isopropylidene-*N*-carbethoxyaziridine (**14**) was of interest because of the proposal by Schechter and Bleiholder that alkylidene-*N*-carbethoxyaziridines may have been precursors to the oxazolines observed in their work.[6] The fact that **14** does rearrange to **5b** (eq 7) offers support of their hypothesis, but the absence of



(7)

10b as a product raises some questions regarding the detailed mechanism of the isomerization.

There is a clear structural analogy between **14** and 2-vinyl-1-isopropylidenecyclopropane (**22**), and the latter substrate is known thermally to rearrange to a *mixture* of 3-isopropylidenecyclopentene (**23**) and 4,4-dimethyl-3-methylenecyclopent-1-ene (**24**, eq 8).[19] Studies of the fate



(8)

of the deuterium label upon isomerization of the labeled vinylmethylenecyclopropane **25** to the methylenecyclopentenes indicated that the diradical **26** was a crucial reaction intermediate.[20] Had the analogous species **27** been formed from **14**, then, in analogy to the results illustrated in eq 8, both **5b** and **10b** would have been expected as products. That only **5b** was observed suggests that the mechanism for thermal isomerization of **14** is best represented as a concerted [3,3]-sigmatropic process as opposed to a stepwise reaction involving **27**.[21] The basis for the difference in mechanistic pathways for **14** as compared to **22** and **25** most likely resides in the lack of conjugative stabilization afforded radicals by carbonyl groups, thereby making **27** unstable relative to the all-carbon analog.

Experimental Section

Infrared (ir) spectra were obtained with a Beckman Model IR-5A or a Perkin Elmer Model 237-B spectrometer. Nmr spectra were recorded on either a Varian A-60, a Perkin-Elmer R-12, or a Varian HA-100 spectrometer. Unless specified otherwise, carbon tetrachloride was the solvent used for all ir as well as nmr spectra. Tetramethylsilane (TMS) was used as an internal standard for the nmr spectra, and all the chemical shifts are reported as δ values in parts per million (ppm) downfield from the TMS signal.

High resolution mass spectra were obtained with a Du Pont (CEC) Model 21-110 mass spectrometer.

A Varian Aerograph A-90-P3 was used in all gas-liquid phase chromatography (glpc) analyses. Wtih few exceptions, the flow rate of helium, the carrier gas, was ~60 ml/min. The following columns were used: column A, 3 ft. × ¼ in., 15% FFAP on 60/80 Chromosorb P (acid-washed); column B, 4 m × ¼ in., 15% FFAP on 60/80 Chromosorb P (acid-washed); column C, 2 ft. × ¼ in., 20% dinonyl phthalate on 60/80 Chromosorb P (acid-washed).

Microanalyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn.

Unless stated otherwise, all reactions involving the generation of nitrenes were run under nitrogen, and the resulting products were stored at −78°. All solvents and substrates involved in this series of reactions were purified before use.

2-Methylene-*N*-carbethoxyaziridine (11). A 500-ml three-neck round-bottomed flask was equipped with a magnetic stirring bar, a dropping funnel, a Dry Ice–methanol condenser connected to a nitrogen source, and a gas inlet. While a continuous blanket of dry nitrogen was maintained in the system, the reaction flask was immersed in a Dry Ice–methanol bath and was charged with *N*-(*p*-nitrobenzenesulfonoxy)urethane (**9**)[12] (4.4 g, 15 mmol) and 350 ml of purified anhydrous dichloromethane. A tenfold excess of allene (6.0 g, 150 mmol) was then condensed into the reaction flask to produce a solution containing 2.5 mol % of allene. The reaction flask was removed from the cooling bath, and a solution of triethylamine (1.7 g, 17 mmol) in dichloromethane (10–15 ml) was slowly added from the dropping funnel with good stirring. The reaction mixture was then stirred for 6.5 hr at room temperature, with a nitrogen atmosphere being maintained at all times. Pentane was added to precipitate salts, the organic solution was decanted, and then the solvents were removed with the aid of a rotary evaporator. Vacuum line transfer of the residue that resulted gave 0.25 g of a sample containing ~50% dichloromethane and 50% a compound whose spectral characteristics were consistent with 2-methylene-*N*-carbethoxyaziridine (**11**) (see Results). On this basis, the actual yield of aziridine is 6%. Pure **11** was obtained by removal of residual solvent under vacuum: calculated mass for $C_6H_9NO_2$ 127.0633, found *m/e* 127.0638.

The compound polymerized when kept under nitrogen and at 0°. When the product was stored at −78° and under an inert atmosphere, polymerization was significantly inhibited. Nevertheless, microanalytical data for a sample kept at this temperature at all times were not completely satisfactory. The data are summarized as follows. *Anal.* Calcd for $C_6H_9NO_2$: C, 56.60; H, 7.08; N, 11.00. Found: C, 55.76; H, 7.21; N, 10.69.

2-Isopropylidene-*N*-carbethoxyaziridine (14). A 500-ml round-bottom three-neck flask immersed in an ice–water bath was fitted with a dropping funnel and an ice–water-cooled condenser which was connected to the nitrogen source. A tenfold excess of 1,1-dimethylallene (10.2 g, 150 mmol) was added in one portion to a rapidly stirred solution of 4.4 g (15 mmol) of the urethane **9** which had been dissolved in ~350 ml of dichloromethane. A solu-

tion of 1.7 g (17 mmol) of freshly purified triethylamine in 15 ml of anhydrous dichloromethane was then added dropwise over 1.5 hr to the rapidly stirred reaction mixture. After addition was complete, the ice-water bath was removed, and the reaction mixture was allowed to stir at room temperature for ~7 hr. After addition of pentane, the precipitated triethylammonium salts were removed from the reaction mixture by filtration. This salt was obtained in 87% yield. The solution was concentrated *in vacuo* to give a yellow liquid weighing 3.0 g.

Attempts at purification of crude product by vacuum transfer using pot temperatures up to 40° did not effect separation of the reaction mixture. Even at these low temperatures, significant decomposition was observed.

Glpc (columns A, B, C) using either carbon tetrachloride solutions or neat samples of the product mixture were also ineffective in product purification. Column temperatures between 50 and 160° were tried. For the most part, the products polymerized on the columns. At 160° (column A) a product was collected which was initially clear but decomposed immediately to a light brown liquid.

Thin layer chromatography (tlc) on silica gel H using a 5:5:1 mixture of benzene–hexane–methanol for development proved effective in the isolation of pure product. Two product bands were observed under uv light. Extraction with carbon tetrachloride of the band having the lower mobility followed by removal of solvent afforded a yellowish viscous liquid of a polymeric nature; similar treatment of the band of higher mobility provided 72 mg (~3% yield) of a compound assigned as the 2-isopropylidene-*N*-carbethoxyaziridine (**14**): the nmr and ir spectral data are consistent with **14** (see Results); calculated mass for $C_8H_{13}O_2N$ 155.0946, found *m/e* 155.0951.

To detect the possible transient formation of **15** during the course of the reaction, product formation was monitored by nmr spectroscopy at short reaction times. The reaction was carried out by a procedure analogous to that described above except that the three-neck reaction flask was fitted with a rubber septum to permit the removal of aliquots at appropriate intervals. Aliquots of 20 ml were removed after 30, 60, 120, 180 and 240 min. Detection of **14** by nmr was possible after 60 min. At this point, and in all subsequent aliquots, no resonances characteristic of **15** could be detected, however. Examination by nmr analysis of the crude product following completion of the reaction also failed to reveal measurable quantities of **15**.

The reaction of 1,1-dimethylallene with carbethoxynitrene was repeated under conditions designed to inhibit any acid-catalyzed reactions that might be occurring as the result of the presence of traces of acid.[14] All glassware with which the reaction mixture or product mixture was to come in contact was rinsed with concentrated ammonium hydroxide and dried in an oven at 110°. In addition, 2,6-di-*tert*-butylpyridine was added as a proton scavenger to the solution of **9** in dichloromethane. The rest of the procedure remained unchanged. After concentration of the reaction mixture *in vacuo*, a crude product (2.20 g), which was ~50% di-*tert*-butylpyridine, was obtained. Again the spectrum of the crude product mixture contained no evidence for the presence of **15**. Purification of the reaction mixture by tlc as described above afforded **14** (8% yield) as the second most mobile band; the pyridine was the most mobile under our conditions of development.

Reaction of Carbethoxynitrene and Tetramethylallene. All glassware was rinsed with ammonium hydroxide solution and dried in an oven at 110° prior to use and 2,6-di-*tert*-butylpyridine was added to the reaction mixture to suppress acid-catalyzed dimerization of tetramethylallene.[14]

Small-scale reactions at ambient temperature and at 42° were performed maintaining the same molar ratios as in the previous experiments. *N*-(*p*-Nitrobenzenesulfonoxy)urethane (**9**, 0.3 g, 1 mmol) was dissolved in a minimum amount of dichloromethane, 2,6-di-*tert*-butylpyridine (~5 drops) was added, and the solution was tested with litmus to assure neutrality. After 1.0 g (10 mmol) of tetramethylallene had been added to the reaction flask, addition of triethylamine (0.12 g, 1.2 mmol) was commenced. After a reaction time of ~6 hr, the precipitated salts were removed as before, and the reaction mixture was concentrated *in vacuo*. The nmr spectrum of the recovered material indicated the presence of only di-*tert*-butylpyridine and tetramethylallene. No evidence of any product formation was found.

Thermolysis of 2-Isopropylidene-*N*-carbethoxyaziridine (14). A 20 (v/v) % solution of a pure sample of **14** in carbon tetrachloride was placed in a thick-walled nmr tube, the solution was degassed, and the tube was sealed. This solution was then heated at 130°. Monitoring (R-12) of the solution showed that essentially all of the aziridine had rearranged to 2-ethoxy-5,5-dimethyl-4-methylene-2-oxazoline (**5b**) and small amounts of decomposition products within 40 min. The 100-MHz spectrum of this sample was consistent with oxazoline **5b** (see Results).

Acknowledgments. Partial support of this research by the Robert A. Welch Foundation (Grant F-204) is gratefully acknowledged. Mr. Charles Fletcher performed some of the preliminary experiments on which this work was based.

Registry No.—**5b**, 53336-56-4; **9**, 2955-74-0; **11**, 53336-57-5; **14**, 53336-58-6; carbethoxynitrene, 2655-26-7; allene, 463-49-0; 1,1-dimethylallene, 598-25-4; tetramethylallene, 1000-87-9.

References and Notes

(1) This work taken in part from the M.A. Thesis of E.M.B, UT—Austin, 1972.
(2) M. Jones, Jr., *et al.*, *J. Amer. Chem. Soc.*, **94**, 7469 (1972), and references therein cited.
(3) The reaction with allenes of carbenes in the latter spin state is of particular interest because attack at C-2 of the allene moiety would produce triplet trimethylenemethanes.[4]
(4) For a review on trimethylenemethanes, see P. Dowd, *Accounts Chem. Res.*, **5**, 247 (1972), and references therein cited.
(5) (a) W. Lwowski, "Nitrenes," Interscience, New York, N.Y., 1970; (b) T. L. Gilchrist and C. W. Rees, "Carbenes, Nitrenes, and Arynes," Thomas Nelson and Sons, London, 1969.
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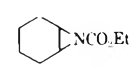
(7) W. Lwowski and T. J. Maricich, *J. Amer. Chem. Soc.*, **87**, 3630 (1965).
(8) Although the location of attack of a free radical on an allene is a function both of the nature of the attacking radical and of the substituents on the substrate allene,[9a] some analogy for the possible attack of triplet nitrene at C-2 is available from the reported exclusive attack of ethylthiyl radical on this position of 1,1-dimethylallene.[9b]
(9) (a) D. R. Taylor, *Chem. Rev.*, **67**, 317 (1967); (b) T. L. Jacobs and G. E. Illingworth, *J. Org. Chem.*, **28**, 2692 (1963).
(10) J. S. McConaghy, Jr., and W. Lwowski, *J. Amer. Chem. Soc.*, **89**, 2357 (1967).
(11) *Cf.* the strong absorption noted for i at 1720 cm^{-1} assigned to the carbonyl function.[12]



i

(12) W. Lwowski and T. W. Mattingly, *J. Amer. Chem. Soc.*, **87**, 1947 (1965).
(13) A. T. Bottini and J. D. Roberts, *J. Amer. Chem. Soc.*, **79**, 1462 (1957); J. D. Roberts and A. T. Bottini, *J. Amer. Chem. Soc.*, **80**, 5203 (1958).
(14) M. L. Poutsma, *J. Org. Chem.*, **33**, 4080 (1968).
(15) It is to be noted that performance of the reaction under conditions favorable to the singlet reaction, *viz.*, 33 mol % allene in dichloromethane, also affords **11** as the only isolable ether-soluble product (C. Fletcher, unpublished results).
(16) P. Battioni, L. Vo-Quang, and Y. Vo-Quang, *Bull. Soc. Chim. Fr.*, 3938 (1970).
(17) Jones, *et al.*, have reached the analogous conclusion with regard to the reaction of triplet carbenes and allene.[2]
(18) R. S. Neale, *J. Amer. Chem. Soc.*, **86**, 5340 (1964).
(19) A. S. Kende and E. E. Riecke, *J. Amer. Chem. Soc.*, **94**, 1397 (1972).
(20) J. C. Gilbert and D. P. Higley, *Tetrahedron Lett.*, 2075 (1973).
(21) The possibility that the reaction involves a prior isomerization of **14** to *N*-carbethoxy-3,3-dimethyl-2-methyleneaziridine (**15**) followed by a [1,3]-sigmatropic rearrangement cannot rigorously be excluded but seems less likely on steric grounds.

Copyrolysis of 1,1-Dimethyl-2-phenyl-1-silacyclobutane and Acrolein

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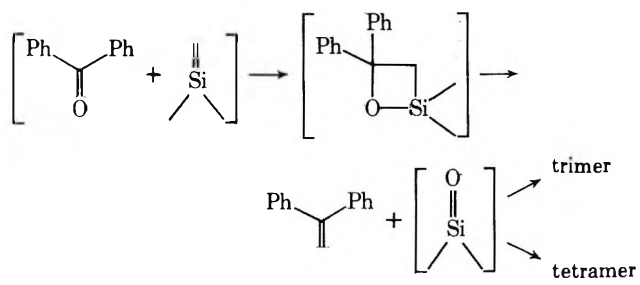
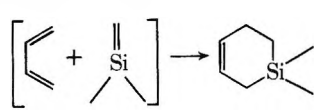
Copyrolysis at 500° in the gas phase of 1,1-dimethyl-2-phenyl-1-silacyclobutane and acrolein yields hexamethylcyclotrisiloxane, octamethylcyclotetrasiloxane, 1,2-dihydronaphthalene, naphthalene, and 1,1-dimethyl-1-sila-2-oxa-6-phenyl-3-cyclohexene. 1,2-Dihydronaphthalene was shown to be formed from *trans*-1-phenyl-1,3-butadiene under the reaction conditions. Formation of these products can be accounted for in terms of competing [2 + 2] and [2 + 4] cycloaddition reactions between acrolein and a reactive intermediate [$(CH_3)_2Si{=}HC_6H_5$] possessing a carbon–silicon double bond.

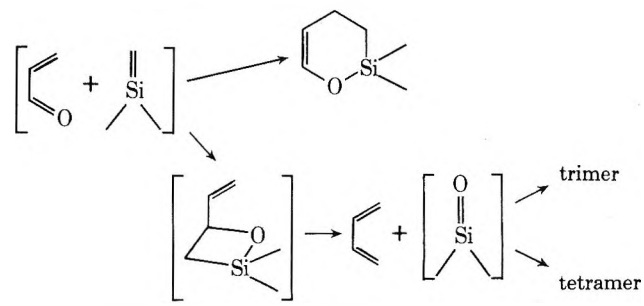
There has been considerable recent interest in the chemical reactions of intermediates possessing a formal carbon–silicon double bond.[1-6] These intermediates may be generated by pyrolysis of silacyclobutanes.[7-10] Photolysis of 1,1-diphenyl-1-silacyclobutane[11] or pentaphenylmethyldisilane[12] also leads to reactive intermediates possessing a formal carbon–silicon double bond. Several pieces of evidence suggest that carbon–silicon double bonded intermediates have significant zwitterionic or ylide character in which the silyl center is positively charged while the carbon is negatively charged. Thus pyrolytic fragmentation of 1,1-dimethyl-1-silacyclobutane (I) in the gas phase yields ethylene and 1,1,3,3-tetramethyl-1,3-disilacyclobutane, the head-to-tail dimer of two silicon–carbon double bonded intermediates.[7-9] This exclusive formation of head-to-tail dimer can be economically rationalized in terms of the polar nature of the intermediates. Copyrolysis of I in the presence of the nonenolizable ketone benzophenone leads to 1,1-diphenylethylene and hexamethylcyclotrisiloxane (trimer) and octamethylcyclotetrasiloxane (tetramer).[2,5] Formation of these products has been explained by the following reaction sequence. A [2 + 2] cycloaddition reaction between the carbon–silicon double bonded intermediate and the ketone yields an unstable silaoxetane which thermally decomposes to yield an olefin and a silanone [$(CH_3)_2Si{=}O$] which undergoes cyclic oligomerization to yield the stable trimer and tetramer observed.[4] Analogous [2 + 2] cycloaddition reactions between carbon–silicon double bonded intermediates and added alkenes to yield new silacyclobutanes[9,13] as well as with imines to yield alkenes and cyclodisilazane[6] have been observed.



On the other hand, copyrolysis of I with dienes such as 1,3-butadiene yields 1,1-dimethyl-1-sila-3-cyclohexene and ethylene. Formation of this product can be explained by a [2 + 4] cycloaddition reaction between a carbon–silicon double bonded intermediate and the diene.[14,15] Similar [2 + 4] cycloaddition reactions have been observed with isoprene and 2,3-dimethyl-1,3-butadiene.



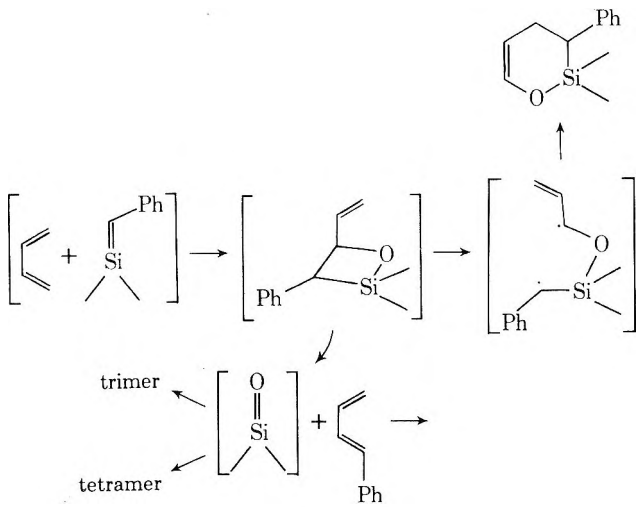
We were interested in the reaction of carbon–silicon double bonded intermediates with nonenolizable α,β-unsaturated aldehydes since both [2 + 2] and [2 + 4] cycloaddition pathways are possible. Only a few cycloaddition reactions are known in which [2 + 2] and [2 + 4] cycloaddition pathways are competitive.[16-20]



The following products were isolated from the copyrolysis of 1,1-dimethyl-2-phenyl-1-silacyclobutane and a tenfold excess of acrolein at 500° and atmospheric pressure in a flow pyrolysis system with purified nitrogen as the carrier gas: 1,2-dihydronaphthalene, naphthalene, trimer, tetramer, and 1,1-dimethyl-1-sila-2-oxa-6-phenyl-3-cyclohexene. Formation of these products may be rationalized in terms of competing [2 + 2] and [2 + 4] cycloaddition reactions between a phenyl-substituted carbon–silicon double bonded intermediate[21] and acrolein. 1,2-Dihydronaphthalene, naphthalene, trimer, and tetramer may be formed *via* an initial [2 + 2] cycloaddition reaction. Thus 1,2-dihydronaphthalene was shown in control experiments to be formed under the reaction conditions from *trans*-1-phenyl-1,3-butadiene, an expected [2 + 2] cycloaddition product. Naphthalene has been shown to be the major pyrolysis product of *trans*-1-phenyl-1,3-butadiene under slightly more stringent conditions (550°),[22] while 1,2-dihydronaphthalene has been converted into naphthalene under more vigorous conditions.[23] On the other hand, formation of 1,1-dimethyl-1-sila-2-oxa-6-phenyl-3-cyclohexene may be economically accounted for by a direct [2 + 4] cycloaddition reaction. However, an alternative possibility exists, namely that the initial silaoxetane adduct formed by [2 + 2] cycloaddition may undergo scission of a carbon–carbon bond to yield an allylic and a benzylic radical pair which recombine to yield 1,1-dimethyl-1-sila-2-oxa-6-phenyl-3-cyclohexene in competition with fragmentation of the siloxetane to yield *trans*-1-phenyl-1,3-butadiene and dimethylsilanone.

The ratio of 1,1-dimethyl-1-sila-2-oxa-6-phenyl-3-cyclohexene to 1,2-dihydronaphthalene and naphthalene is roughly 1:4.

While the system is intriguing, a decision between the two possible mechanisms is not at this time possible.



1,2-dihydronaphthalene ⟶ naphthalene

Experimental Section

Infrared spectra were obtained on a Perkin-Elmer 337 spectrometer and were calibrated against known bands in a polystyrene film. Nmr spectra were recorded on a Varian T-60 spectrometer with methylene chloride (δ 5.28) as internal standard. Mass spectra were obtained on a Hitachi Perkin-Elmer RMU-6E spectrometer. Conditions used in determination of mass spectra were source temperature 150°; solid inlet 50°; ionizing voltage 70 eV; filament emission 70 μA; target current 50 μA. Vapor phase chromatography was carried out on a Hewlett-Packard F&M 700. Microanalysis was performed by Elek Microanalytical Laboratories. Melting points are uncorrected.

1,1-Dimethyl-2-phenyl-1-silacyclobutane was prepared from allylbenzene and dimethylchlorosilane in 50% yield by the method of Valkovich, *et al.*[21]

Copyrolysis of 1,1-Dimethyl-2-phenyl-1-silacyclobutane (II) and Acrolein. The pyrolysis was performed using a vertical tube oven. The pyrolysis tube consisted of a 30-cm long Pyrex glass tube (12.5 mm o.d., 9 mm i.d.) packed with 1-cm long pieces of 3-mm Pyrex tubing. Due to a premature reaction upon standing at room temperature of acrolein and II leading to polymeric material, it was necessary to mix the two together immediately prior to pyrolysis. This was accomplished by use of the following apparatus. A 25-ml, three-neck, pear-shaped flask was adapted by placing a stopcock at the bottom, the exit of which was connected to the top of the pyrolysis tube. In two of the three necks of the flask were placed pressure equalizing addition funnels. A nitrogen inlet was placed in the third neck. Nitrogen also entered the pyrolysis tube just before the oven, so that there was a continuous flow of nitrogen in the pyrolysis tube even when the stopcock of the mixing flask was closed. The exit of the pyrolysis tube was connected to a 50-ml two-neck flask which was immersed in a Dry Ice–acetone bath. The second neck of the flask was connected to another Dry Ice–acetone trap. The nitrogen flow rate was adjusted to 0.5 ml/sec. The column was allowed to reach a temperature of 500°. The entire apparatus was flame dried. At this point 6.38 g of freshly distilled acrolein was placed in one addition funnel, while 2.0 g of II was placed in the other. The pyrolysis was carried out as follows. One drop of II was added to 3–4 drops of acrolein in the mixing flask. This mixture was added all at once to the pyrolysis tube. This procedure was repeated. The addition was complete within 0.5 hr. The apparatus was allowed to cool, and the pyrolysis tube was rinsed with 1 ml of benzene. The material collected in the two traps was purified as follows. Benzene and excess acrolein were removed by distillation at atmospheric pressure. The residue, 2.63 g was purified by bulb-to-bulb distillation at 0.1 mm. This material (2.43 g) was separated by preparative glpc on a ¼ in. × 4 ft 20% SE-30 on Chromosorb P column at 120°. The following compounds were isolated and identified. A number of additional components were present in very small amounts. All yields are based on recovered starting material generally about 40%.

Hexamethylcyclotrisiloxane: 49.9% yield; properties (mp 64°; ir, and glpc retention time) identical with those of an authentic sample.[24]

Octamethylcyclotetrasiloxane: 7.7% yield; properties (ir and glpc retention time) identical with those of an authentic sample.[24]

A mixture of 1,2-dihydronaphthalene and naphthalene was next collected. This mixture was separated on a ¼ in. × 10 ft 20% DC-QF-1 on Chromosorb W column at 110°. The ratio of 1,2-dihydronaphthalene to naphthalene was 14:1.

Naphthalene: 4% yield, mp 80–81° (lit. mp 80.5°);[25] its nmr was identical with that of an authentic sample.

1,2-Dihydronaphthalene: 58% yield; its ir was identical with that of authentic 1,2-dihydronaphthalene;[26] nmr δ 2.66 (m, 4 H), 6.03 (m, 1 H), 6.51 (m, 1 H), 7.12 (m, 4 H).

1,1-Dimethyl-1-sila-2-oxa-6-phenyl-3-cyclohexene. Final purification was accomplished by preparative glpc on a ¼ in. × 10 ft Silar 5 CP on Gas-Chrom Q column at 110°: 16.6% yield; mp 40–41°; nmr (CCl_4) δ 0.16 (s, 3 H), 0.32 (s, 3 H), 2.60 (m, 3 H), 4.82 (m, 1 H), 6.42 (d, 1 H, J = 6.2 Hz), 7.27 (m, 5 H). The following decoupling experiments were performed. Irradiation at δ 2.6 caused the multiplet at δ 4.82 to collapse to a doublet, J = 6 Hz, while irradiation at δ 4.82 caused the doublet at 6.42 to collapse to a singlet: ir (film) 1254 (Si–CH_3), 1071, 1081, and 1125 (Si–O and C–O, and 1635 cm^{-1} (C = C); mass spectrum parent at m/e 204 (44.6%).

Anal. Calcd for $C_{12}H_{16}SiO$: C, 70.53; H, 7.83. Found C, 70.45; H, 7.89.

***trans*-1-Phenyl-1,3-butadiene** was prepared by the method of Grummitt and Becker.[27] It was pyrolyzed at 500° using the apparatus previously described. 1,2-Dihydronaphthalene and naphthalene were obtained in 81% yield in a ratio of 8:1.

Acknowledgment. This work was supported by the Air Force Office of Scientific Research Grant No. 73-2424.

Registry No.—II, 52500-06-8; acrolein, 107-02-8; hexamethylcyclotrisiloxane, 541-05-9; octamethylcyclotetrasiloxane, 556-67-2; naphthalene, 91-20-3; 1,2-dihydronaphthalene, 447-53-0; 1,1-dimethyl-1-sila-2-oxa-6-phenyl-3-cyclohexene, 53210-17-6; *trans*-1-phenyl-1,3-butadiene, 16939-57-4.

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Generation and Synthetic Applications of 2-Lithio-1,3-dithianes

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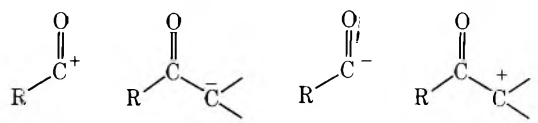
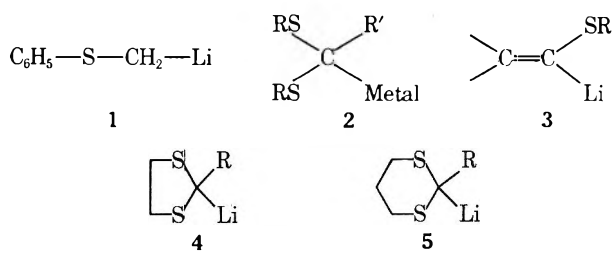
The preparation and metalation of 1,3-dithianes leads to protected acyllithium derivatives which are synthetically equivalent to acyl anions. Experimental procedures and a number of examples are given for the reactions of 2-lithio-1,3-dithianes with common electrophiles such as alkyl, allyl, and benzyl halides, aldehydes, ketones, and carboxylic acid derivates, as well as 1,2-and 1,3-oxides. The examples given demonstrate the high nucleophilicity of 2-lithio-1,3-dithianes and the value of these reagents in synthesis.

One of the major objectives of modern organic synthesis is the broadening of techniques for assembling collections of carbon atoms and functional groups. In order to increase the probability of developing simple routes for the synthesis of complex molecules, it is desirable to have reagents of opposite polarity for the introduction of a given fragment or synthon.[1] Thus, the nucleophilic cyanide, CN^-, or the electrophilic carbon dioxide, CO_2, can be used for incorporating the synthon COX into a molecule. We consider the design of new reagents which are the *equivalents* of inaccessible nucleophiles or electrophiles an effective strategy for the extension of the general methodology of organic synthesis.[1-5] Among the most commonly encountered reactive sites are carbonyl groups which, in their normal reactivity, provide acyl cation and enolate anion equivalents A and B, respectively. At the outset[2] of our work to be described here in detail,[6] there were no general methods supplying the counterparts, acyl anions C or enolate cations D.



A B C D

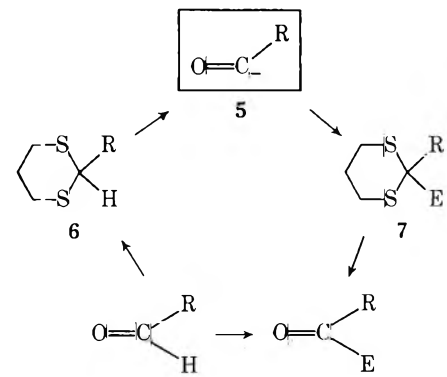
We thought that sulfur-stabilized anions might be suitable as masked nucleophilic acylating equivalents. Alkali metal derivatives of such anions had been generated previously by Gilman and Webb[7] and by Arens and Fröling[8] who showed that thioanisole could be metalated to give **1** and that certain thioacetals could be converted to compounds of type **2**. However, the yields were low, the experimental procedures unsatisfactory, and the structural limitations severe. In attempts to improve these reactions, we found[9] that solutions of **1** and **2**, R = C_6H_5, R′ = H, metal = Li, can be obtained quantitatively by metalation of corresponding precursors with butyllithium in tetrahydrofuran (THF). Likewise, a derivative **3** could be made under these conditions for the first time.[9] Both **2** and **3** are nucleophilic acylating reagents C, because by hydrolysis of their products with electrophiles, carbonyl compounds are formed in which a formerly electrophilic atom has been attached to the carbonyl carbon. While examining the scope and limitations of creating Li derivatives **2** and **3**[10] for this



1 **2** **3**

4 **5**

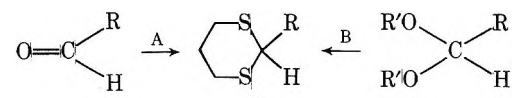
Scheme I



purpose, we also investigated the cyclic 2-lithio-1,3-dithiolanes (**4**) and -dithianes (**5**). The former underwent facile elimination to form ethylene and dithiocarbonate; the latter turned out to be most generally available and satisfactory. As indicated in Scheme I, these sulfur-stabilized anionic reagents are equivalent to acyl anions which implies that they can be used effectively to reverse the characteristic electrophilicity of a carbonyl carbon (symmetrization of reactivity,[1] reversible umpolung[5]). In the following sections we will discuss the preparation of 1,3-dithianes **6** from carbonyl derivatives, their metalation to give **5**, and the reactions of lithiodithianes **5** with various electrophiles to form products **7**. We have previously supplied full accounts of our work on the use of **5** for the preparation of silyl ketones[11a] and of cyclic ketones.[11b] Our contributions to the methods of hydrolysis of thioacetals have been published elsewhere.[11] We have also extensively summarized[3-5] actual examples of the synthesis of carbonyl compounds by the dithiane route and have reviewed[3,5] the many alternative reagents for nucleophilic acylation developed since our early preliminary publication.[2]

Preparation of 1,3-Dithianes and Conversion to 2-Lithio-1,3-dithianes (5)

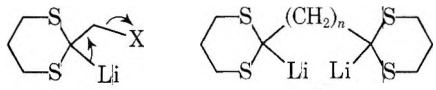
Dithianes **6** are readily produced from aldehydes (method A) or acetals (method B) by standard methods.[12,13] We



6

found the use of chloroform as a solvent and hydrogen chloride as catalyst most convenient in both cases. The products can be readily distilled or recrystallized. Their nmr spectra may show a very complex pattern from the protons in the 4, 5, and 6 positions of the ring.[4] The conversion of dithianes **6** into 2-lithiodithianes **5** is most conveniently achieved by adding an equimolar amount of *n*-

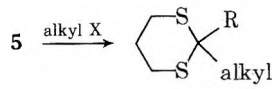
butyllithium to a THF solution of a dithiane at −20°. The reaction time varies with the steric and electronic character of the group R in the 2 position. Thus, with R = C_6H_5 metalation occurs within a few minutes, while the *tert*-butyl derivative requires about 5 hr for complete metalation. The progress of the reaction can be followed by sampling aliquots from the solution which are deuterated. The degree of deuterium incorporation is determined by nmr spectroscopy (see Experimental Section). Li derivatives of type 8 with a leaving group X (OR, SR, halogen, CN)[11b,14-16] cannot be generated under these conditions, dilithio compounds **9** are accessible if $n > 3$.



8 **9**

Alkylation of 2-Lithio-1,3-dithianes

This reaction converts the formaldehyde derivative **5**, R = H, into thioacetals of higher aldehydes, or thioacetals **5**, R ≠ H, into thioketals **10**. It proceeds extremely rapidly

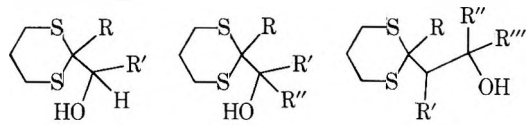


10

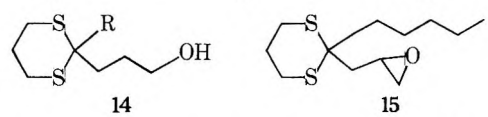
with primary alkyl iodides (15 min at −78°) and with allylic acid and benzylic halides. In other cases, longer periods of time are required (see Table II). In order to obtain good yields, the main side reaction, *i.e.*, elimination of HX from the halide, must be suppressed by carrying out the alkylations at low temperature. Work-up of samples from the reaction mixture, which sometimes precipitates lithium halide, is recommended to follow the progress of C–C formation. Tertiary and cyclic halides (cyclohexyl iodide), secondary chlorides, and primary and secondary tosylates could not be used successfully in these intermolecular alkylations.

Hydroxyalkylations of 5 with Aldehydes, Ketones, Oxiranes, and Oxetanes

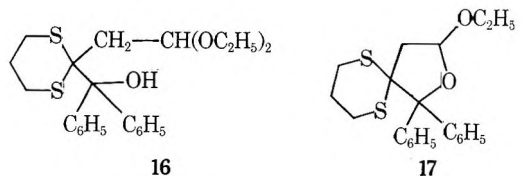
Carbonyl compounds and small-ring ethers react readily with lithiodithianes to give derivatives of α-, β-, and γ-hydroxy aldehydes or ketones of the general structures **11–14**.



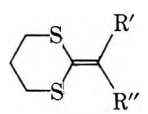
11 **12** **13**



14 **15**



16 **17**

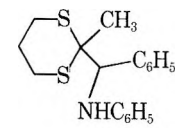


18

Aldehydes or ketones should be added to the solutions of **5** at −78° which minimizes possible enolization. Under these conditions, readily enolized ketones, such as cyclopentanone and cyclohexanone, give the products of carbonyl addition in high yields. This demonstrates the very effective nucleophilicity of the sulfur-substituted lithium reagents **5**. Epoxides and oxiranes are opened very slowly. However, high yields of derivatives **13** and **14** are obtained if the reaction mixtures are stored under an inert atmosphere in a refrigerator (0°) or freezer (−20°) for up to a week. (At higher temperatures, solutions of lithiodithianes in THF are not sufficiently stable.) Epichlorohydrin can be used for epoxyalkylations; *cf.* **5** → **15**.

The adduct **16** of 2-lithio-2-(β,β-diethoxyethyl)-1,3-dithiane to benzophenone could not be isolated; instead the product was the cyclic acetal **17**. Other ketone and aldehyde adducts **11** and **12** with R = H can be dehydrated directly or through the chlorides derived from these alcohols to give ketene thioketals **18**.[17]

(Table III in the Experimental Section lists a number of products **11–14** obtained, together with the yields and physical and spectroscopic data.) The carbonyl addition of lithiodithianes **5** is, of course, also applicable to carbonyl analogs. For instance, the amino ketone derivative **19** is formed quantitatively from methyldithiane and benzalanilide.



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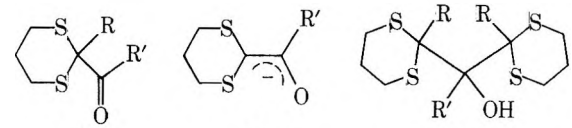
Acylations of Lithiodithianes

This reaction leads to derivatives of 1,2-dicarbonyl compound (**20**) in which one of the carbonyl groups is protected



20 **21** **22**

as a thioacetal. Of the potential acylating reagents, enolizable tertiary carboxamides and nitriles cannot be used since they are converted to enolates.[18] Esters and acid chlorides can be employed with the following limitations: (a) if unsubstituted lithiodithiane is to be acylated, the primary product **20**, R = H, contains a relatively acidic proton in the dithiane 2 position which is abstracted by excess lithium reagent to give **21**, resulting in a 2:1 stoichiometry of the acylation; (b) if R in **20** is not hydrogen, a second mole of lithiodithiane can attack as a nucleophile to give the diadduct **22**. Therefore, the lithiodithiane should be added to a large excess of acylating reagent. Finally, those nonenolizable acylating derivatives which do not lead to free carbonyl compounds **20** until the aqueous work-up of the original reaction mixture, such as carbon dioxide (RCOOLi → **20**, R′ = OH), dimethylformamide (RCH[$N(CH_3)_2$]OLi → **20**, R′ = H), and aromatic nitriles ($R_2C{=}NLi$ → **20**, R′ = aryl) furnish acyldithianes in excellent yields. Examples for each of these different types of acylations are given in the Experimental Section.

Experimental Section

Flasks and stirring bars used for the generation and reactions of lithiodithianes were dried for *ca.* 12 hr at 120° and allowed to cool in a desiccator over P_4O_{10}. Distillations were carried out under nitrogen. Anhydrous THF was obtained by distillation from LAH. The yields listed in the tables were determined by concentration of aliquots and nmr analysis.

Most boiling points given correspond to bath temperatures measured during short-path evaporative distillation. Melting points are uncorrected. Chemical shifts are given in τ values relative to

Table I
Rates of Metalation of 1,3-Dithianes at −20°

R in 2 position of 1,3-dithiane	Reaction time with *n*-butyllithium before hydrolysis with D_2O, hr	Recovery of dithiane, %	Deuteration, %
H	1.3	95	>95
CH_3	0.6	77 (volatile)	80
	1.2	69	>95
n-C_5H_{11}	0.8	80	85
$CH_2CH(OC_2H_5)_2$	1.7	86	>95
i-C_3H_7	1.6	96	>95
t-C_4H_9	1.3	90	80
	15.0	85	>95

internal tetramethylsilane. Infrared absorption data are given in microns and do not include the band at 11.00 ± 0.05 μ typical of 1,3-dithianes.

A. **General Procedure for the Preparation of 1,3-Dithianes (6) from Aldehydes or Their Acetals (Method A and B).** A 0.1–1 *M* solution of an aldehyde or acetal in chloroform is combined with an equimolar amount of propane-1,3-dithiol at room temperature. With aldehydes, the solution is kept for 1 hr prior to cooling to −20°; with acetals, the solution is cooled in an ice bath immediately after mixing the components. Dry HCl gas is slowly passed through the solution for 5–10 min, or alternatively, a 0.05–0.10 *M* amount of BF_3 etherate or $ZnCl_2$ can be added. The solutions are allowed to warm to room temperature. Reaction mixtures from aldehydes are worked up after 1–15 hr by successively washing three times each with water, 10% aqueous KOH, and water and drying over K_2CO_3. Evaporation of the solvent furnishes crude products which are distilled or recrystallized. The forerun of distillations is often yellow and, although seemingly pure by nmr analysis, is not satisfactory for conversion to lithiodithianes.

Ketones or ketals can be converted to disubstituted dithianes similarly. We have previously given specific procedures for the preparation of 1,3-dithiane,[19] 2-methyl-,[11c] 2-chloromethyl-,[20] 2-(β-chloroethyl)-,[11b] 2-*sec*-butyl-,[21] 2-phenyl-1,3-dithiane,[22] and of the bis(1,3-propylene)dithioacetals of malonaldehyde and succinaldehyde.[11b] Five more examples are described below.

2-Ethyl-1,3-dithiane (6, R = C_2H_5). From 0.3 mol of propionaldehyde an 87% yield of distilled dithiane was obtained: bp 91° (10 mm) (lit.[12] 85° (5 mm), 112° (21 mm)); $n^{25}D$ 1.5501; ir (neat) 3.4, 6.88, 7.04, 7.85, 8.42, 9.10, 12.0, 12.4, 13.1, and 14.6 μ; nmr (CCl_4) 8.96 (t, *J* = 6.3 Hz, CH_3), 6.08 (t, *J* = 6.7 Hz, 2-dithiane H). *Anal.* Calcd for $C_6H_{12}S_2$: C, 48.64; H, 8.16; S, 43.20. Found: C, 48.63; H, 7.99; S, 43.43.

2-*n*-Pentyl-1,3-dithiane (6, R = *n*-C_5H_{11}). On a 0.125 molar scale a 68% yield was obtained from hexanal: bp 85° (0.35 mm); $n^{30}D$ 1.5247; ir (neat) 3.86, 6.85, 7.04, 7.85, and 8.5 μ; nmr (CCl_4) 6.04 (degenerate t, *J* = 6.5 Hz, 2-dithiane H). *Anal.* Calcd for $C_9H_{18}S_2$: C, 56.82; H, 9.54; S, 33.64. Found: C, 56.90; H, 9.42; S, 33.63.

2-*tert*-Butyl-1,3-dithiane (6, R = *t*-C_4H_9). From 0.016 mol of pivalaldehyde an 82% yield of dithiane was obtained: bp 61° (0.4 mm) (lit.[12] 129° (22 mm)); mp 35.5–36.0° (methanol); ir (CCl_4) 3.32, 3.40, 6.78, 6.83, 7.04, 7.18, 7.31, 7.82, 8.04, 8.10, 8.67, 9.71, 10.81, 11.53, and 14.6 μ; nmr (CCl_4) 8.93 (s, *t*-C_4H_9), 6.12 (s, 2-dithiane H). *Anal.* Calcd for $C_8H_{16}S_2$: C, 54.53; H, 9.15; S, 36.32. Found: C, 54.46; H, 9.05; S, 36.14.

Bis(1,3-propylene)dithioacetal of Methyl Glyoxal. 2-Formyl-2-methyl-1,3-dithiane (see below, acylation products) was converted in 77% yield to the bis(dithiane) derivative: mp 115.2–115.7° (methanol); ir ($CHCl_3$) 3.28, 3.37, 3.47, 6.93, 7.05, 7.27, 7.83, 8.50, and 11.50 μ; nmr ($CDCl_3$) 8.20 (s,CH_3), 5.26 (s, 2-dithiane H). *Anal.* Calcd for $C_9H_{16}S_4$: C, 42.86; H, 6.39; S, 50.75. Found: C, 42.86; H, 6.31; S, 50.74.

2-(Cyclohexen-1-yl-4)-1,3-dithiane. Using $ZnCl_2$ as catalyst 100 mmol of the aldehyde gave 6.3 g (31%) of dithiane: bp 104° (0.19 mm); nmr (CCl_4) 7.7–8.5 (9 H multiplet), 5.95 (d, 2-dithiane H), 4.4 (2 H multiplets).

B. **General Procedure for the Preparation of 2-Lithio-1,3-dithiane (5) Solutions in THF.** A round-bottomed flask with ST neck and side arm is equipped with a magnetic spin bar, a three-way stopcock, and a serum cap. Solid dithianes are weighed into the flask prior to subsequent flushing with nitrogen or argon. The reaction vessel is kept under positive inert gas pressure until work-up. Solvents, liquid reagents, and solutions of reagents are introduced, and samples are withdrawn through the serum cap by hypodermic syringes. To avoid loss of pressure, pierced caps are sealed with parafilm tape.

The amount of freshly distilled THF necessary to obtain a 0.1–0.5 *M* solution of dithiane is added. A 5% excess of *n*-butyllithium in *n*-hexane (1.5–2.5 *M*) is added at a rate of 3–5 ml/min to the solution stirred at −40°. After 1.5–2.5 hr at −25 to −15°, most dithianes are metalated quantitatively (Table I) as determined by deuteration of an aliquot of the solution containing 50–100 mg of dithiane. This is done by injecting the withdrawn solution into 1–3 ml of D_2O in a small separatory funnel and extracting with ether, methylene chloride, or pentane; the organic layer is dried for a few minutes with K_2CO_3 and concentrated evaporatively. Integration of the dithiane C_2-proton nmr signal *vs.* any other well-defined and separated peak of the particular dithiane thus provides the extent of deuteration with an accuracy of ±5% within 15 min. Examples of large scale deuteration for the preparation of deuterioaldehydes have been described in detail.[22,23]

The anion solutions are clear and colorless if R is H or alkyl, orange if R is phenyl. The solution of dithiane **5**, R = H, can be stored for a few hours at room temperature without decomposition. After 2 weeks at −25° the solutions of **5**, R = H, CH_3, C_2H_5, showed no decomposition; with R = *t*-C_4H_9, however, 5% decomposition was detected after 17 hr under these conditions.

Instead of *n*-butyllithium, the *tert*-butyl derivative can be used to metalate dithianes at lower temperatures or within shorter periods of time.

Detailed procedures for the preparation of lithiodithianes have been published previously: **5**, R = H,[24] R = CH_3,[25] R = C_6H_5.[22]

C. **General Procedure for the Alkylation of 2-Lithio-1,3-dithianes with Primary and Secondary Halides to Give 10.** At −60 to −78° an equivalent of neat halide is added to a stirred solution of 2-lithio-1,3-dithiane. With primary iodides, allylic, and benzylic halides the reaction takes place within a few hours at this temperature. In the case of secondary iodides and especially bromides and primary chlorides, the reaction mixture should be kept between −20 to −60° for up to 5 days, because too rapid warming leads to appriciable elimination. The progress of the reactions should be checked by withdrawing small samples, hydrolyzing, and analyzing by nmr. Nonactivated secondary chlorides and primary and secondary tosylates are not useful alkylating reagents.

Before work-up the solutions from which lithium halide or products may crystallize are allowed to slowly warm to 0° and are kept in a refrigerator for up to 3 days. The mixture is poured into three volumes of water; large-scale preparations are concentrated evaporatively prior to hydrolysis to avoid inconvenient manipulation with large separatory funnels. Several extractions with chloroform or pentane furnish an organic solution which is washed twice each with water, 7% aqueous KOH, and again water and dried over K_2CO_3. The residue obtained after solvent removal is distilled *in vacuo* or recrystallized. Specific procedures have been given by us[2,11,17,21,22,24,26] previously, including cases in which two identical or two different alkyl groups have been introduced by sequential one-pot alkylations starting from unsubstituted dithiane. Table II lists some of the reactions carried out.

D. **Hydroxyalkylations with Carbonyl Derivatives, Oxiranes, and Oxetane. (a) (1) General Procedure for the Reaction of 5 with Carbonyl Compounds to Give Alcohols 11 and 12.** A neat liquid carbonyl compound or the THF solution of a solid carbonyl compound is added to the vigorously stirred solution of the anion at −70°. In large-scale reactions the addition rate should be adjusted so that the temperature of the reaction mixture does not exceed −50°. Many reactions of this type can also be carried out at higher temperatures (up to −20°); however, the tendency of the highly nucleophilic lithiodithianes to abstract protons from enolizable carbonyls decreases with decreasing temperature. With aldehydes the reaction is completed instantaneously. With highly hindered or otherwise unreactive ketones, *e.g.*, benzophenone, and/or with lithiodithianes bearing bulky 2 substituents, subsequent storage of the reaction mixture at −20° (enolizable ketones) or at 0° (benzophenone) for 12–24 hr is favorable. The work-up method described in the general alkylation procedure is followed using methylene chloride or chloroform as solvent.

For examples, see Table III; a detailed procedure for the reaction of **5**, R = CH_3, with cyclohexanone has been published.[25]

Table II
Products 10 of Alkylation of 2-Lithio-1,3-dithianes 5

5, R	Registry No.	Halide, R'–X	Registry No.	Product, –1,3-dithiane [a]	Registry No.	Reaction times, hr (°C)	Yield, %	mp (°C), bp (°C (mm)), n_D °C
H	36049-90-8	CH_3I	74-88-4	2-Methyl-	6007-26-7	3 (0)	86	94 (21), 1.5573^{25}
H		C_2H_5I	75-03-6	2-Ethyl-	6007-23-4	4 (0)	85	116 (22), 1.5480^{25}
H		n-$C_5H_{11}Br$	110-53-2	2-n-Pentyl-	21777-32-2	13 (0)	92	1.5209^{28}
H		CH_3CHICH_3	75-30-9	2-Isopropyl-	6007-25-6	14 (0)	82	52 (0.9) (lit. [13] 134 (35)),
		$CH_3CHBrCH_3$	75-26-3			19 (0)	68	1.5410^{28}
H		p-tol-$O(CH_2)_5Br$	53178-42-0	2-[(ω-p-Tolyloxy)-n-pentyl]-	53178-43-1	1 (–30) 12 (0)	88	65.1–65.7
H		$ClCH_2\overset{CH_3}{\overset{\vert}{C}}HCH_2Br$	6974-77-2	2-(3-Chloro-2-methylpropyl-1)-	53198-70-2	1 (–50) 12 (–20)	81	105 (0.08), 1.5555^{20}
H			53188-14-0	2-(*cis*-4-Chloromethylcyclohexylmethyl)-	53178-44-2	24 (–20) 23 (0)	73	136 (0.07), 1.5622^{25}
H		$(C_2H_5O)_2CHCH_2Br$	2032-35-1	2-(2,2-Diethoxyethyl-1)-	5849-13-8	46 (0)	87	115 (0.3), 1.5099^{26}
H		$\frac{1}{2}Br(CH_2)_3Br$	109-64-8	Bis(1,3-propylene)dithioacetal of glutaraldehyde	4883-05-0	2 (–30) 22 (0)	93	101.5–102.0 (CH_3OH)
H		$\frac{1}{2}Br(CH_2)_4Br$	110-52-1	Bis(1,3-propylene)dithioacetal of adipaldehyde	4883-04-9	0.5 (–50) 21 (0)	96	102.5–103.5 (pentane–cyclohexane)
CH_3	27969-97-7	CH_3CHICH_3		2-Methyl-2-isopropyl-	5849-02-5	0.5 (–60) 8 (0)	83	60 (0.3), 1.5403^{25}
CH_3		$C_6H_5CH_2Br$	100-39-0	2-Methyl-2-benzyl-	5849-03-6	0.5 (–70) 75 (0)	98	113 (0.08), 1.5966^{28}
CH_3		$\frac{1}{2}Br(CH_2)_4Br$		Bis(1,3-propylene)dithioacetal of octane-2,7-dione	5012-00-0	0.5 (–70) 76 (0)	89	108.5–109.0 (pentane–cyclohexane)
C_2H_5	53178-38-4	$(CH_3)_2C{=}CHCH_2Br$	870-63-3	2-Ethyl-2-(3',3'-dimethylpropen-2'-yl-1')-	53178-45-3	0.5 (–60) 12 (0)	71	85 (0.03), 1.5438^{25}
$CH(CH_3)_2$	53178-39-5	CH_3CHICH_3		2,2-Diisopropyl-	5849-29-6	0.5 (–5) 14 (0)	80	95 (0.5), 1.5392^{25}
t-C_4H_9	53178-40-8	CH_3CHICH_3		2-Isopropyl-2-*tert*-butyl-	5849-05-8	40 (0)	50	
n-C_5H_{11}	21777-36-6	CH_3CHICH_3		2-n-Pentyl-2-isopropyl-	5849-10-5	12 (0)	85	84 (0.03), 1.5245^{24}
n-C_5H_{11}		n-$C_5H_{11}Br$		2,2-Di-n-pentyl-	5849-09-2	45 (0)	83	118 (0.35), 1.5117^{25}
C_6H_5	53178-41-9	CH_3CHICH_3		2-Isopropyl-2-phenyl-	5849-12-7	14 (0)	97	50.5–51.5 (CH_3OH)

[a] Satisfactory C, H, and S analyses were obtained.

Table III
α-, β-, and γ-Hydroxyalkylated Dithianes 11–14 from 5 and Aldehyde, Ketones, Epoxides, and Oxetane (See General Procedures Da1 and Db1)

5, R	Electrophile	Registry No.	Product, –1,3–dithiane[a]	Registry No.	Yield, %	mp (°C) bp (°C (mm)), n_D °C
H	Benzaldehyde	100-52-7	2-(Phenylhydroxymethyl)- (11)	5849-19-4	99	71.3–72.1 (pentane–cyclohexane–benzene)
H	Cyclopentanone	120-92-3	2-(1′-Hydroxycyclopentyl-1′)- (12)	5849-20-7	70	113 (0.02), 1.5755^{25}
H	Cyclohexanone	108-94-1	2-(1′-Hydroxycyclohexyl-1′)- (12)	5849-22-9	95	
CH_3	Cyclohexanone		2-Methyl-2-(1′-hydroxycyclohexyl-1′)- (12)	5849-24-1	86	165 (1.2), 1.5723^{23}
H	Cyclohexanone		2-(1′-hydroxycyclohexen-2′-yl-1′)- (12)	53178-46-4	77	Oil, chromatography over silica–gel
H	Benzophenone	119-61-9	2-(Diphenylhydroxymethyl)- (12)	5849-23-0	98	136.0–136.5 (pentane–cyclohexane, 1:3)
CH_3	Benzophenone		2-Methyl-2-(diphenylhydroxymethyl)- (12)	5849-25-2	98	136.5–137.5 (methanol)
C_2H_5	Benzophenone		2-Ethyl-2-(diphenylhydroxymethyl)- (12)	53178-51-1	99	97.5–98.0 (methanol)
$CH(CH_3)_2$	Benzophenone		2-Isopropyl-2-(diphenylhydroxymethyl)- (12)	5849-27-4	70	152.5–153.0 (methanol)
n-C_5H_{11}	Benzophenone		2-n-Pentyl-2-(diphenylhydroxymethyl)- (12)	5849-26-3	98	94.5–95.5 (methanol)
n-C_5H_{11}	Propylene oxide	75-56-9	2-n-Pentyl-2-(β-hydroxypropyl)- (13)	53178-52-2	95	140 (0.15), 1.5300^{20}
H	Styrene oxide	96-09-3	2-(β-hydroxy-β-phenylethyl)- (13)	53178-47-5	87	Oil
CH_3	Styrene oxide		2-Methyl-2-(β-hydroxy-β-phenylethyl)- (13)	5849-17-2	78[b]	Oil
H	Oxetane	503-30-0	2-(3′-Hydroxypropyl)- (14)	53178-48-6	80[c]	120 (0.03), 1.5660^{20}

[a] Satisfactory C, H, and S analyses were obtained. [b] The product was hydrolyzed under neutral conditions ($HgCl_2$–HgO–CH_3OH), and the crude hydroxyaldehyde isolated was added to a sulfuric acid–ethanol 2,4-dinitrophenylhydrazine reagent solution. The DNP of cinnamaldehyde precipitated in 76% yield and had the melting point given in the literature, 253–254° (from acetic acid). [c] Hydrolysis as described in footnote *b* gave 55% of the DNP of benzylidene acetone, mp 156.0–156.5° (ethanol).

For the conversion of the adducts of unsubstituted dithiane to benzaldehyde, benzophenone, and cyclohexanone into ketene thioacetals **18**, see sections a2 and a3; the preparation of the products **17** and **19** is described in sections a4 and a5, respectively.

(2) 1,3-Propylenedithioketals of the Ketenes of Phenyl- and Diphenylacetic Acid (18, R′ = C_6H_5, R″ = H, and 18, R′ = R″ = C_6H_5). In a round-bottomed flask, equipped with a water separatory head, a solution in benzene which is 0.05 *M* in carbinol and 0.0005–0.005 *M* in *p*-toluenesulfonic acid monohydrate is stirred and heated at reflux. (In large-scale reactions the concentrations can be increased.) Depending on the particular carbinol and on the scale used, the water separation is over in 3–20 min. The solution is allowed to cool to room temperature, washed with 10% KOH and with water, and dried over K_2CO_3. Evaporation of the solvent furnishes the dehydrated product in nearly quantitative yield.

18, R′ = C_6H_5, R″ = H: yield 93%; bp 150° (0.14 mm); ir (neat) 3.25, 3.40, 3.50, 6.30, 6.53, 6.73, 7.11, 7.72, 11.53, 12.35, 13.4, and 14.4 μ; nmr (CCl_4) 4.00 (s, vinylic H), 2.75 (m, C_6H_5). *Anal.* Calcd for $C_{11}H_{12}S_2$: C, 63.45; H, 5.81; S, 30.74. Found: C, 63.36; H, 5.79; S, 30.40. **18**, R′ = R″ = C_6H_5: yield 97%; mp 134.5–135.0 (pentane); ir ($CHCl_3$) 3.20, 3.25, 3.35, 6.25, 6.70, 6.93, 7.05, 7.68, 9.39, 9.68, 11.6, and 14.24 μ; nmr ($CDCl_3$) 2.75 (broad s, C_6H_5). *Anal.* Calcd for $C_{17}H_{16}S_2$: C, 71.82; H, 5.67; S, 22.51. Found: C, 71.66; H, 5.64; S, 22.43.

(3) 2-Cyclohexylidene-1,3-dithiane (18, R′–R″ = $(CH_2)_5$). Pure 2-(1-hydroxycyclohexyl-1)-1,3-dithiane (5.64 mmol, 1.230 g) and 5.2 g of pyridine were dissolved in 100 ml of CH_2Cl_2 and stirred in an ice bath. Thionyl chloride (24.8 mmol, 2.95 g) was added all at once. The solution turned yellow, was stirred for 25 min at 0° and for an additional 10 min after removal of the bath, and was poured on ice. The aqueous layer was extracted twice with CH_2Cl_2, and the combined organic layers were washed successively three times each with water, saturated $CuSO_4$, and water. Drying over Na_2SO_4 and evaporating the solvent gave 1.161 g (86.5%) of colorless crystals of 2-(1-chlorocyclohexyl-1)-1,3-dithiane, mp 95.6–96.5° (methanol): molecular ion in mass spectrum at 236; ir ($CHCl_3$) 3.40, 6.95, 7.10, and 7.90 μ; nmr ($CDCl_3$) 5.66 (s, 2-dithiane H). *Anal.* Calcd for $C_{10}H_{17}ClS_2$: C, 50.77; H, 7.24; S, 27.08. Found: C, 50.72; H, 7.15; S, 27.36.

A solution of 1.774 g of the chloride in 40 ml of dry THF was added within 5 min to a suspension of 1.105 g of potassium *tert*-butoxide (9.75 mmol) in 5 ml of THF stirred in an ice bath. The mixture turned orange, the temperature was allowed to rise to 20° within 1 hr, and stirring was continued at room temperature for 14 hr to give a brown, pale solution. Work-up with chloroform led to the isolation of 1.398 g (93%) of light brown crystals of **18**, R′–R″ = $(CH_2)_5$: mp 93.6–94.0° (methanol); ir ($CHCl_3$) 3.35, 3.45, 6.32, 6.91, 7.02, 7.83, 10.05, 11.50, and 12.22 μ; *Anal.* Calcd for $C_{10}H_{16}S_2$; C, 59.98; H, 8.05; S, 31.96. Found: C, 60.14; H, 8.01; S, 32.05.

(4) 1,3-Propylenedithioketal of 2-Ethoxy-4-oxo-5,5-diphenyltetrahydrofuran (17). The solution of 10 mmol of 2-lithio-2-(β,β-diethoxyethyl)-1,3-dithiane is combined at −78° with an equimolar amount of benzophenone in THF. The temperature is allowed to rise to 0° within 3 hr, and the flask is sealed and stored in a refrigerator for 18 hr. Work-up with chloroform gives 95% of almost pure product which is recrystallized from a 6:2:1 mixture of pentane–cyclohexane–benzene to give 83% of analytically pure massive prisms: mp 144.0–145.2°; ir ($CHCl_3$) 6.72, 6.93, 8.9, 9.8,

10.0, and 11.29 μ; nmr ($CDCl_3$) 8.63 (t, J = 7.0 Hz, ethyl CH_3), 4.39 (d of d, J = 7.0 and 5.0 Hz, CH), 2.76 and 2.15 (aromatic protons as two multiplets), ratio 3:1:10. *Anal.* Calcd for $C_{21}H_{24}O_2S_2$: C, 67.73; H, 6.50; S, 17.18. Found: C, 67.49; H, 6.54; S, 17.03.

(5) *N*-Phenyl-2-phenylaminomethyl-2-methyl-1,3-dithiane (19) from 5, R = CH_3, and Benzalanilide. After combining equimolar amounts of the reactants, both dissolved in THF, at 0° on a 5 m*M* scale, the cooling bath was removed. After 1.5 hr the solution was poured into three times its volume of water. Extraction with chloroform yielded 98% of amine: mp 102.5–103.8° (methanol); ir ($CHCl_3$) 2.90, 2.95, 3.25, 3.30, 3.40, 3.50, 6.23, 6.68, 6.91, 7.04, 7.53, 7.92, 14.25, and 14.45 μ; nmr ($CDCl_3$) 8.46 (s, CH_3), 5.47 (s, CH), 5.10 (broad s, NH). *Anal.* Calcd for $C_{18}H_{21}NS_2$: C, 68.55; H, 6.71; N, 4.44; S, 20.29. Found: C, 68.19; H, 6.78; N, 4.49; S, 20.63.

(b) (1) General Procedure for Reactions of 5 with Oxiranes and Oxetanes. The neat three- or four-membered cyclic ether is added to the lithiodithiane solution stirred at −20°. The reaction vessel is closed under positive inert gas pressure and stored for up to 1 week in a refrigerator (0–5°) or a freezer (−20 to −30°). The work-up procedure is the same as described for the reactions with ketones (see above, Da1).

The reactions of 2-lithio-1,3-dithiane with ethylene, propylene, and cyclohexene oxide have been described in detail.[11b] Further applications of this general reaction are listed in Table III.

(2) Epoxide of 2-*n*-pentyl-2-(propen-2′-yl-1′)-1,3-dithiane Oxide (15) from 5, R = *n*-C_5H_{11}, and Epichlorohydrin. A solution of 2.506 g (27.1 mmol) of epichlorohydrin in 14 ml of THF was added to 26.9 mmol of 2-lithio-2-*n*-pentyl-1,3-dithiane at −70°. After storage at 0° for 24 hr, the mixture was worked up with water and CH_2Cl_2. Crude yield 94%, after distillation through a 10-cm column 3.50 g (64%) of a colorless oil was obtained: bp 123–125° (0.1 mm); n^{20}D 1.5326; ir (neat) 7.87, 11.80, 13.10 μ; nmr (CCl_4) typical terminal epoxide hydrogens as doublet of doublets at τ 7.63 (J = 4.2 and 5.7 Hz). *Anal.* Calcd for $C_{12}H_{22}OS_2$: C, 58.51; H, 9.00; O, 6.49; S, 26.00. Found: C, 58.49; H, 8.78; O, 6.52; S, 26.03.

E. **Reactions of 5 with Acylating Reagents. (a) Carboxylations, Preparation of 1,3-Dithiane-2-carboxylic Acids, 20, R′ = OH.** In a separatory funnel freshly chopped Dry Ice is added to 10 ml of THF and treated with a solution containing 5–10 mmol of a lithiodithiane which is injected by syringe. After warming to room temperature 50 ml of ether and 10 ml of 10% KOH are added. The organic layer is extracted twice with 5 ml of the KOH solution, and the combined alkaline layers are washed three times each with ether and chloroform, cooled in an ice bath, and acidified with stirring by dropwise addition of concentrated HCl. The acids are extracted into chloroform. Drying over Na_2SO_4 and solvent removal furnishes the crude products.

The yields of acids given below for three specific examples can be increased to nearly 100% by working under anhydrous conditions.

(1) 1,3-Dithiane-2-carboxylic Acid (20, R = H, R′ = OH). From 5 mmol of anion solution a 32% yield of acid was obtained: mp 114.5–116.0° (pentane–benzene) (lit.[27] 115–116°); ir ($CHCl_3$) broad absorption between 2.7 and 4.5 μ, 5.84, 7.08, 7.73, 8.04, 8.49, 9.90, 11.29, 12.20, and 14.53 μ; nmr ($CDCl_3$) 5.85 (s, 2-dithiane H), −0.42 (broad s, COOH).

(2) 2-Methyl-1,3-dithiane-2-carboxylic Acid (20, R = CH_3, R′ = OH). On a 3.4 m*M* scale a 70% yield was achieved: mp 133.5–135.0° (water); ir ($CHCl_3$) 2.7–4.4, 5.87, 6.89, 7.28, 7.85, 8.98, 9.25, 11.55, 12.4, and 14.3 μ; nmr ($CDCl_3$) 8.34 (s, CH_3); −1.86 (s, COOH). *Anal.* Calcd for $C_6H_{10}O_2S_2$: C, 40.91; H, 5.48; O, 18.17; S, 36.34. Found: C, 40.43; H, 5.67; O. 18.24; S, 36.16.

(3) 2-*tert*-Butyl-1,3-dithiane-2-carboxylic Acid (20, R = *t*-C_4H_9, R′ = OH). From 25 mmol of **5**, R = *t*-C_4H_9, 76% of the acid was isolated: mp 98.5–99.3° (pentane); ir ($CHCl_3$) 2.7–4.2, 5.70, 5.89, 7.05, 7.16, 7.31, 7.96, 12.25, and 14.3 μ; nmr ($CDCl_3$) 8.72 (s, CH_3), −0.83 (s, COOH). *Anal.* Calcd for $C_9H_{16}O_2S_2$: C, 49.08; H, 7.32; S, 29.06. Found: C, 49.02; H, 7.36; S, 28.85.

(b) Bis(1,3-propylenedithioacetals) 22 of 2-Hydroxy-1,3-dicarbonyl Compounds, 2-Formyl- (20, R′ = H) and 2-Acyl-1,3-dithianes 20, R′ ≠ H, by Reaction of 5 with Esters, Acid Chlorides, and Dimethylformamide.[28] (1) Ethyl-1,3-dithiane-2-carboxylate (20, R = H, R′ = OC_2H_5) from 5, R = H, and Ethyl Chloroformate. A solution of 29.1 mmol of 2-lithio-1,3-dithiane is stirred at −78° and combined with 1.64 g (15.2 mmol) of neat ethyl chloroformate. After raising the temperature to +20° within 2 hr the mixture was stirred for 4 hr and poured into water. Extraction with ether gave an organic layer which was washed with 10% KOH and dried over Na_2SO_4. Solvent evaporation furnished 4.23 g of crude product consisting of a 1:1 molar mixture of 1,3-dithiane and the desired ester, by nmr analysis. The former was removed evaporatively at 60° (0.6 mm), the ester distilled at 96° (0.4 mm): yield 2.22 g (76% calcd from chloroformate); n^{25}D 1.5385; ir (neat) 3.38, 5.77, 7.06, 7.36, 7.80, 8.78, and 9.74 μ; nmr (CCl_4) 5.98 (s, 2-dithiane H), 5.84 (q, J = 7.0 Hz, ethyl CH_2), 8.71 (t, J = 7.0 Hz, ethyl CH_3). *Anal.* Calcd for $C_7H_{12}O_2S_2$: C, 43.75; H, 6.29. Found: C, 43.99; H, 6.37.

(2) 2-Cinnamoyl-1,3-dithiane (20, R = H, R′ = Styryl) and Bis(1,3-propylenedithioacetal) of 2-Hydroxy-2-ω-styrylmalonaldehyde (22, R = H, R′ = Styryl) from 5, R = H, and Ethyl Cinnamate. The anion solution obtained from 1.0 g (8.3 mmol) of 1,3-dithiane was added within 5 min to 0.76 g (4.3 mmol) of ethyl cinnamate dissolved in 5 ml of THF and stirred at −78°. Warming up and working up as described above (b1) give 1.30 g of a yellow oil which contains according to its nmr spectrum 42% of 1,3-dithiane, 42% of the ketone, and 16% of the alcohol. The alcohol is separated by adding 5 ml of ether and allowing the mixture to crystallize overnight; the ketone is recovered from the mother liquor by evaporation of the solvent and of 1.3-dithiane.

Alcohol (**22**): mp 176.6–177.4° (colorless, short, heavy prisms from methanol); ir ($CHCl_3$) 2.87, 3.27, 3.38, 3.99, 7.02, 7.83, 9.04, 9.34, 10.30, and 14.44 μ; nmr ($CDCl_3$) 5.38 (s, 2-dithiane H), 6.82 (s, OH), 3.12 and 3.77 (d, J = 16.0 Hz, vinylic hydrogens), 2.66 (m, C_6H_5). *Anal.* Calcd for $C_{17}H_{22}OS_4$: C, 55.13, H, 5.99; O, 4.32; S, 34.56. Found: C, 55.05; H, 6.03; O, 4.34; S, 34.45. Ketone (**20**): mp 99.5–100.0° (yellow, flat clustered needles from pentane–hexane–benzene 5:2:1); ir ($CHCl_3$) 3.28, 3.40, 3.50, 5.92, 6.01, 6.20, 6.33, 6.92, 7.03, 7.52, 9.33, 10.20, 11.14, 11.25, and 14.55 μ; nmr ($CDCl_3$) 5.46 (s, 2-dithiane H), 2.49 and 3.13 (d, J = 16.2 Hz, vinylic hydrogens), 2.6 (m, C_6H_5). *Anal.* Calcd for $C_{13}H_{14}OS_2$: C, 62.39; H, 5.64; O, 6.39; S, 25.58. Found: C, 62.70; H, 5.72; O, 6.23; S, 25.11.

(3) 2-Formyl-2-methyl-1,3-dithiane (20, R = CH_3, R′ = H) from 5, R = CH_3, and DMF. A 5% solution of DMF (0.81 g, 11.0 mmol) in THF was stirred at −5°; 10 mmol of the lithiodithiane were added and allowed to react for 15 hr in a refrigerator (−2°). Work-up with ether gave 1.12 g of a colorless liquid which contained 80% of the aldehyde (corresponding to 57% yield). The yield can be increased considerably using excess DMF freshly distilled from CaH_2 and lower temperatures: bp 63° (0.06 mm); n^{26}D 1.5612; ir (neat) 3.35, 3.30, 3.66, 5.79, 6.92, 7.01, 7.32, 7.80, 9.28, and 11.45 μ; nmr (CCl_4) 8.56 (s, CH_3), 1.00 (s, formyl H). *Anal.* Calcd for $C_6H_{10}OS_2$: C, 44.44; H, 6.22; O, 9.87; S, 39.47. Found: C, 44.48; H, 6.32; O, 10.15; S, 39.45. 2,4-Dinitrophenylhydrazone: mp 167.5–168.5 (yellow needles from ethanol); *Anal.* Calcd for $C_{12}H_{14}N_4O_4S_2$: C, 42.11; H, 4.12; N, 16.37. Found: C, 42.26; H, 4.24; N, 16.24. Conversion into bis(1,3-propylenedithioacetal) of methylglyoxal, see section A.

(4) Ethyl 2-Methyl-1,3-dithiane-2-carboxylate (20, R = CH_3, R′ = OC_2H_5) from 5, R = CH_3, and Ethyl Chloroformate. To a 1:1 (v/v) mixture of THF and the chlorformate (0.2 mol) was added with stirring in a −73° bath within 20 min a solution of 10 mmol of the anion in 40 ml of THF–hexane. After 2 hr the mixture had reached −5°. The flask was connected through a large cold trap kept at −78° to remove solvents and most of the excess acid chloride under *ca.* 5 mm. The residue was dissolved in water and ether. From the organic layer a 60% yield of dithiane ester was isolated: bp 95° (0.3 mm); n^{28}D 1.5182; ir (neat) 3.34, 3.40, 5.78, 6.90, 7.80, 8.12, 8.62, 9.04, 9.76, and 11.51 μ; nmr (CCl_4) 8.69 (t, J = 7.2 Hz, ethyl CH_3), 5.83 (q, J = 7.2 Hz, ethyl CH_2), 8.43 (s, CH_3). *Anal.* Calcd for $C_8H_{14}O_2S_2$: C, 46.60; H, 6.84; O, 15.52; S, 31.04. Found: C, 46.67; H, 6.90; O, 15.64; S, 30.92.

(5) 2-Acetyl-2-methyl-1,3-dithiane (20, R = R′ = CH_3) and Bis(1,3-propylenedithioacetal) of 3-Hydroxy-3-methylpentane-2,4-dione (22, R = R′ = CH_3) from 5, R = CH_3, and Acetyl Chloride. Using exactly the procedure described for the reaction with ethyl chloroformate, section b4, a 30-fold excess of acetyl chloride was combined at −78° with the anion solution (17.15 mmol) within 50 min with rapid stirring. Yield of ketone, 1.50 g (50%): bp 72° (0.2 mm); n^{24}D 1.5455; ir (neat) 3.39, 5.86, 6.93, 7.05, 7.54, 8.32, 9.26, 10.45, and 11.50 μ; nmr (CCl_4) 7.74 (s, $COCH_3$), 8.23 (s, CH_3). *Anal.* Calcd for $C_7H_{12}OS_2$: C, 47.72; H, 6.87; O, 9.08; S, 36.33. Found: C, 47.76; H, 6.67; O, 9.24; S, 36.19. 2,4-Dinitrophenylhydrazone: mp 183.5–184.2° (yellow needles, clustered to plates, from ethanol). *Anal.* Calcd for $C_{13}H_{16}N_4O_4S_2$: C, 43.81; H, 4.52; N, 15.72; O, 17.96; S, 17.99; Found: C, 44.37; H, 4.52; N, 15.41; O, 17.95; S, 17.95. Adding the anion solution within 20 min at −20° to excess acetyl chloride and within 15 min at −5° to excess ethyl acetate furnished 30 and 51%, respectively, of the 2:1 alcohol adduct under otherwise identical conditions. The alcohol can be re-

crystallized from methanol: mp 99.5–100.0°; ir ($CHCl_3$) 2.80, 3.29, 3.35, 3.50, 6.93, 7.07, 7.28, 7.83, 8.08, 8.72, and 9.25 μ; nmr ($CDCl_3$) 7.95 (s, 2-dithiane CH_3), 8.21 (s, CH_3), 6.6 (s, OH). *Anal.* Calcd for $C_{12}H_{22}OS_4$: C, 46.45; H, 7.17; O, 5.16; S, 41.25. Found: C, 46.51; H, 6.93; O, 5.31; S, 41.11.

(6) 2-Hexahydrobenzoyl-2-methyl-1,3-dithiane (20, R = CH_3, R′ = C_6H_{11}) from 5, R = CH_3, and Cyclohexane Carboxylic Ester. A solution of 17.0 mmol of the lithium compound was added dropwise within 12 min at −60° to 1.37 g (8.8 mmol) of the ethyl ester in 15 ml of THF. The bath temperature was allowed to warm to −10° within 70 min and the mixture was kept 1 day in a refrigerator. The usual work-up with chloroform and distillation (200° (0.1 mm)) gave 60% of a colorless oil: ir (neat) 3.35, 5.87, 6.92, 7.33, 9.36, and 10.13 μ; nmr (CCl_4) 2.25 (s, 2-dithiane CH_3).

(7) Bis(1,3-propylenedithioacetal) of 3-hydroxy-3-phenylpentane-2,4-dione (22, R = CH_3, R′ = C_6H_5) from 5, R = CH_3, and Ethyl Benzoate. Neat ester (388 mg, 2.58 mmol) was added to a solution of 5.64 mmol of metalated 2-methyl-1,3-dithiane at 0°. After removing the ice bath stirring was continued for 1 hr. Work-up with chloroform–water gave rise to 931 mg (96.6%) of product **22** as colorless crystals, mp 151–155°. The analytical sample was prepared by recrystallization from CH_3OH–$CHCl_3$ 3:1: mp 156.5–158.0°; ir ($CHCl_3$) 2.84, 3.20, 3.28, 3.35, 3.49, 6.70, 6.92, 7.07, 7.28, 7.83, 8.60, 9.31, 9.74, and 14.2 μ; nmr ($CDCl_3$) 7.85 (s, CH_3), 5.58 (s, OH), 2.0 (broad m, C_6H_5), and 2.7 (narrow m, C_6H_5). *Anal.* Calcd for $C_{17}H_{24}OS_4$: C, 54.83; H, 6.50; O, 4.29; S, 34.38. Found: C, 54.72; H, 6.55; O, 4.41; S, 34.12.

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Registry No.—**5** (R = $(C_2H_5O)_2CHCH_2$), 53178-53-3; **6** (R = *t*-C_4H_9), 6007-21-2; **6** (R = cyclohexen-1-yl-4), 53178-49-7; **6** (R = H), 505-23-7; **6** (R = 1-chlorocyclohexyl-1), 53178-50-0; **15**, 53178-54-4; **17**, 53209-81-7; **18** (R′ = C_6H_5, R″ = H), 17590-58-8; **18** (R′ = R″ = C_6H_5), 36998-40-0; **18** (R′ = R″ = $(CH_2)_5$), 37891-71-7; **19**, 5849-28-5; **20** (R = H, R′= OH), 20461-89-6; **20** (R = CH_3, R′ = OH), 4901-19-3; **20** (R = *t*-C_4H_9, R′ = OH), 4882-94-4; **20** (R = H, R′ = OC_2H_5), 20462-00-4; **20** (R = H, R′ = styryl), 4883-02-7; **20** (R = CH_3, R′ = H), 4882-97-7; **20** (R = CH_3, R′ = H) DNPH, 5849-01-4; **20** (R = CH_3, R′ = OEt), 4882-95-5; **20** (R = R′ = CH_3), 5011-99-4; **20** (R = R′ = CH_3) DNPH, 53178-55-5; **20** (R = CH_3, R′ = C_6H_{11}), 4882-98-8; **22** (R = H, R′ = styryl), 4883-03-8; **22** (R = R′ = CH_3), 4882-99-9; **22** (R = CH_3, R′ = C_6H_5), 4883-00-5; propane-1,3-dithiol, 109-80-8; propionaldehyde, 123-38-6; hexanal, 66-25-1; pivalaldehyde, 630-19-3; methyl glyoxal bis(1,3-propylene)dithioacetal, 53178-56-6; cyclohexene-1-carboxyaldehyde-4, 100-50-5; benzalanilide, 93-98-1; ethyl chloroformate, 541-41-3; ethyl cinnamate, 103-36-6; dimethylformamide, 68-12-2; epichlorohydrin, 106-89-8; acetyl chloride, 75-36-5; ethyl cyclohexanecarboxylate, 3289-28-9; ethyl benzoate, 93-89-0.

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Transfer Hydrogenation and Transfer Hydrogenolysis. V. Hydrogen Transfer from Amines, Ethers, Alcohols, and Hydroaromatic Compounds to Olefins Catalyzed by Chlorotris(triphenylphosphine)rhodium(I)

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In the hydrogen transfer from organic compounds to olefins catalyzed by $RhCl(PPh_3)_3$, some cyclic amines were found much more reactive than oxygenated and hydroaromatic compounds such as primary and secondary alcohols, tetralin, etc. Reactivity decreased in the order indoline > pyrrolidine > tetrahydroquinoline > piperidine > 2,3-butanediol > dioxane > cyclohexanol > isopropyl alcohol. Indoline and tetrahydroquinoline gave stoichiometrically indole and quinoline, respectively.

The transfer of hydrogen to olefins from hydroaromatic compounds and primary and secondary alcohols[2] is heterogeneously catalyzed. Alcohols,[3] arylaldehydes,[4] *N*-methylformamide,[4] formic acid,[4] and dioxane[5] have been reported as hydrogen sources in homogeneous reactions.

This paper reports on investigation of the hydrogen-donating ability of various organic compounds catalyzed by chlorotris(triphenylphosphine)rhodium(I), which has high catalytic activity in the reduction of olefins by molecular hydrogen.[6] It was found that some cyclic amines such as

Table I
Transfer Hydrogenation of Cycloheptene[a]

Hydrogen donor and solvent	Registry No.	Yield of cycloheptane, %	Dehydrogenation product
Tetralin	119-64-2	60	Naphthalene
Cyclohexene[b]	110-83-8	2	
Tetradecane[d]	629-59-4	2	
Cyclohexanol	108-93-0	100	Cyclohexanone
2,3-Butanediol	513-85-9	100	
Isopropyl alcohol	67-63-0	92	Acetone
sec-Butyl alcohol	78-92-2	72	2-Butanone
1,3-Butanediol[c]	107-88-0	37	
Benzyl alcohol[c]	100-51-6	12	
Isobutyl alcohol[c]	78-83-1	7	
Ethyl alcohol[c]	64-17-5	6	
Propyl alcohol[c]	71-23-8	6	
Butyl alcohol[c]	71-36-3	6	
Ethylene glycol[c]	107-21-1	5	
tert-Butyl alcohol[d]	75-65-0	3	
Dioxane	123-91-1	72	Dioxene
Tetrahydrofuran	109-99-9	22	
Tetrahydropyran[c]	142-68-7	8	
Isopropyl ether[d]	108-20-3	4	
2,3-Dihydrofuran	1191-99-7	2	
2,3-Dihydropyran[c]	110-87-2	2	
Propyl ether[d]	111-43-3	1	
Propionic acid butyl ester	590-01-2	7	
Acetone	67-64-1	7	
Acetic acid[c]	64-19-7	3	
Acetic acid benzyl ester	140-11-4	3	
2-Butanone	78-93-3	3	
Tetrahydrothiophene	110-01-0	3	

[a] Cycloheptene (0.50 *M*) and $RhCl(PPh_3)_3$ (0.02 *M*) were heated at 190° for 1 hr in the designated organic compound which was used as a hydrogen donor and solvent. [b] Cyclopentene was used instead of cycloheptene. [c] The formation of $RhCl(CO)(PPh_3)_2$ was observed. [d] The catalyst did not dissolve completely even at 190°.

pyrrolidine, piperidine, indoline, and tetrahydroquinoline were much better donors than hydrocarbons, ethers, carbonyl compounds, and most alcohols studied.

Results and Discussion

Hydrogen-Donating Ability of Hydrocarbons and Oxygen Compounds. The hydrogen-donating ability of some hydrocarbons and oxygen compounds was evaluated by heating them with cycloheptene and $RhCl(PPh_3)_3$. The dehydrogenation products identified and the yields of cycloheptane are shown in Table I. It has been reported that cyclohexene hydrogenates several olefins in the presence of palladium.[1a] However, cyclohexene hardly reduced cycloheptene in this system, and the hydrogen-donating ability of tetralin was found much higher than that of cyclohexene.

Secondary alcohols and dioxane had high hydrogen-donating ability and stoichiometrically gave the corresponding ketones and dioxene, respectively. For example, when an isopropyl alcohol solution of cycloheptene (0.50 *M*) and $RhCl(PPh_3)_3$ (0.02 *M*) was heated at 170° for 1 hr, the formation of 0.34 *M* acetone and 0.36 *M* cycloheptane in addition to the survival of 0.14 *M* cycloheptene was shown by the glc analysis of the reaction mixture. Also a dioxane solution of cycloheptene (0.50 *M*) and the catalyst, which had been heated at 190° for 1 hr, contained 0.35 *M* dioxene and 0.35 *M* cycloheptane as well as 0.14 *M* cycloheptene. The

Table II
Hydrogen Transfer from Amines to Cycloheptene[a]

Hydrogen donor and solvent		Yield of cycloheptane %
Indoline	496-15-1	100
Pyrrolidine	123-75-1	100
Tetrahydroquinoline	635-46-1	98
Piperidine	110-89-4	94
Morpholine	110-91-8	44
N-Methylmorpholine	109-02-4	40
Benzylamine	100-46-9	26
Piperazine	110-85-0	23
Isopropylamine	75-31-0	18
N-Methylpiperazine	109-01-3	17
N-Methylpyrrolidine	120-94-5	12
Propylamine	107-10-8	8
N-Methylpiperidine	626-67-5	7
N,N'-Dimethylpiperazine	106-58-1	6
Dipropylamine[b]	142-84-7	3
Tripropylamine[b,c]	102-69-2	2

[a] Cycloheptene (0.50 *M*) and $RhCl(PPh_3)_3$ (0.02 *M*) were heated at 190° for 1 hr in the designated amine which was used as a hydrogen donor and solvent. [b] Cyclopentene was used instead of cycloheptene. [c] The catalyst did not dissolve completely even at 190°.

Table III
Quantitative Relation in Transfer Hydrogenation[a]

Hydrogen donor	Donor concn, *M*	Temp, °C	Time, hr	Composition of reaction mixture, *M*: Cycloheptane	Cycloheptene	Dehydrogenation product	Survived donor
Indoline[b]	0.50	170	1	0.34	0.16	0.34[c]	0.15
Tetrahydroquinoline	0.50	190	2	0.46	0.05	0.23[d]	0.26
Piperidine[e]	0.25	180	2	0.15	0.34	*f*	0.10
Pyrrolidine[e]	0.25	180	1	0.22	0.29	*g*	*h*

[a] Cycloheptene (0.50 *M*), $RhCl(PPh_3)_3$ (0.02 *M*), and the designated hydrogen donor were heated in toluene. [b] The concentration of the catalyst was 0.01 *M*. [c] Indole was formed. [d] Quinoline was formed. [e] o-Dichlorobenzene was used as a solvent. [f] Pyridine was not detected. [g] Neither pyrrole nor 3-pyrroline was detected. [h] Pyrrolidine was detected, but the amount could not be measured.

cyclic ether, tetrahydrofuran which contains one oxygen atom, also reduced the olefin. When primary alcohols, tetrahydropyran, and 2,3-dihydropyran were used, reduction of the olefin hardly occurred and $RhCl(CO)(PPh_3)_2$ was obtained as yellow crystals. This carbonyl complex does not catalyze the transfer hydrogenation of cyclopentene to cyclopentane by dioxane.[5] Therefore, $RhCl(PPh_3)_3$ is inferred to be deactivated by carbonyl abstraction from primary alcohols or pyrans. Moreover, the inference is supported by the fact that primary alcohols reduce olefins effectively to form the corresponding aldehydes in the presence of $RhH(PPh_3)_4$,[3e] and $RhCl(PPh_3)_3$ abstracts carbon monoxide from aldehydes to give $RhCl(CO)(PPh_3)_2$.[6,7] When *N*-methylformamide or formic acid was used, facile formation of the carbonyl complex was observed.

Hydrogen scarcely transferred from tetrahydrothiophene.

Hydrogen-Donating Ability of Amines. Amines cannot poison $RhCl(PPh_3)_3$ by carbonylation and also coordinate well. So they were expected to be excellent hydrogen donors and the results are shown in Table II. N-Unsubstituted cyclic amines such as pyrrolidine, piperidine, indoline, and tetrahydroquinoline had greater hydrogen-donating ability than dioxane and most alcohols but alicyclic

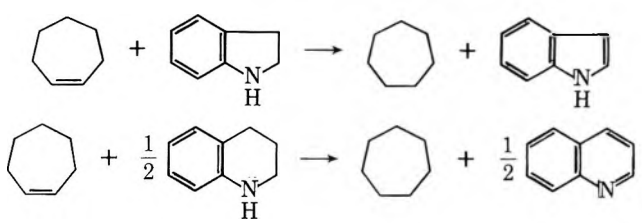
Table IV
Solvent Effect in Transfer Hydrogenation[a]

Solvent	Registry No.	Initial rate, mol $l.^{-1}$ min^{-1}
Chlorobenzene	108-90-7	6.3×10^{-3}
o-Dichlorobenzene	95-50-1	5.1×10^{-3}
Aniline	62-53-3	4.0×10^{-3}
Anisole	100-66-3	3.4×10^{-3}
Toluene	108-88-3	2.9×10^{-3}
Benzene	71-43-2	2.7×10^{-3}
2-Butanone		2.3×10^{-3}
Dimethyl sulfoxide	67-68-5	1.1×10^{-3}
Pyridine	110-86-1	1.6×10^{-4}
Propionitrile	107-12-0	1.1×10^{-4}

[a] Cyclopentene (0.50 *M*), indoline (0.50 *M*), and $RhCl(PPh_3)_3$ (0.006 *M*) were heated at 160° in the designated solvent.

amines were less effective. For example, the conversions of cyclopentene to cyclopentane were 100% in the reaction in pyrrolidine at 150° for 1 hr and 29% at 120°, while the corresponding values for dioxane were 22 and 1%, respectively. N-Substituted cyclic amines such as *N*-methylpyrrolidine and *N*-methylpiperidine showed much smaller hydrogen-donating ability than the corresponding N-unsubstituted ones. However, morpholine and *N*-methylmorpholine showed comparable ability.

Analyses of the dehydrogenation products are summarized in Table III. It is clearly shown from the observations described below that indoline and tetrahydroquinoline donated hydrogen to cycloheptene stoichiometrically, to form indole and quinoline, respectively, as follows.



(1) The amount of indole was equal to that of cycloheptane and the amount of quinoline was equal to one-half the amount of cycloheptane. (2) The total amount of the survived hydrogen donor and the dehydrogenated donor equaled that of the charged hydrogen donor. (3) The total amount of cycloheptane and cyclohetene was equal to that of the charged cycloheptene. (4) In the absence of the hydrogen sources, cycloheptene was not reduced in toluene. (5) Cycloheptadienes which are the products of the disproportionation of the olefin, were negligibly detected.

The amount of piperidine consumed was almost equal to that of the cyclopentane formed but no low-boiling dehydrogenation products such as pyridine were detected. This suggests that the dehydrogenation intermediates from piperidine formed products of higher molecular weight. The amount of the survived pyrrolidine could not be measured precisely and anticipated five-membered dehydrogenation products such as pyrrole and 3-pyrroline were not detected. It has been reported that 1-piperideine and 1-pyrroline are so unstable as to undergo rapid trimerization in the absence of amines[8] or addition reaction in the presence of amines.[9] Therefore, it is inferred that dehydrogenation intermediates might react further to give products of high-boiling points which could not be detected by glc analysis.

The driving force for piperidine and pyrrolidine to donate hydrogen may not be due to aromatization, because aromatization products, such as pyridine and pyrrole, were not detected in the reaction mixtures.

Table V
Rate of Transfer Hydrogenation of Cycloolefins[a]

Cycloolefin (0.30*M*)	Registry No.	Initial rate, mol $l.^{-1}$ $min^{-1} \times 10^3$
Cyclopentene	142-29-0	2.6
Cyclohexene	110-83-8	2.8
Cycloheptene	628-92-2	2.8
Cyclooctene	931-88-4	1.8
1,3-Cyclooctadiene	1700-10-3	0
1,5-Cyclooctadiene	111-78-4	0[b]

[a] Cycloolefin, indoline (0.25 *M*), and $RhCl(PPh_3)_3$ (0.006 *M*) were heated at 160° in xylene. [b] 1,5-Cyclooctadiene was partly isomerized to 1,3- and 1,4-dienes.

Table VI
Ability to Donate Hydrogen[a]

Hydrogen donor	Initial rate, mol $l.^{-1}$ min^{-1}
None	0
Indoline	4.8×10^{-3}
Pyrrolidine	1.9×10^{-3}
Tetrahydroquinoline	1.4×10^{-3}
Piperidine	2.8×10^{-4}
2,3-Butanediol	1.5×10^{-4}
Dioxane	6.1×10^{-5}
Cyclohexanol	5.7×10^{-5}
Isopropyl alcohol	3.5×10^{-5}

[a] Cyclopentene (0.50 *M*), a hydrogen donor (0.50 *M*), and $RhCl(PPh_3)_3$ (0.006 *M*) were heated in toluene at 160°.

Measurement of Reaction Rates. The initial rates of the reduction of several olefins were measured in several solvents. The conversion of cyclomonoenes to cycloparaffins was proportional to reaction time over the ranges up to 20–25% conversion. Initial rates were derived from the linear parts.

Initial rates of the reaction of cyclopentene with indoline were measured in several solvents, and the results are summarized in Table IV. Some solvents which have high polarity and strong coordinating power, such as dimethyl sulfoxide, pyridine, and propionitrile, dissolved the catalyst easily, but reduction in these solvents was slow. Possibly strongly coordinating solvents block coordination of reactants. In most aromatic solvents such as halogenated benzenes and toluene, the catalyst dissolved well at reaction temperatures and the reaction proceeded rapidly. Toluene or xylene was employed in the reactions described hereafter because of the convenience of the glc analysis.

The initial rates of transfer hydrogenation of several cycloolefins by indoline are shown in Table V. There is little difference among the rates of the cyclomonoenes except for cyclooctene. Although partial isomerization of 1,5-cyclooctadiene to 1,3-cyclooctadiene occurred, the cyclooctadienes were not reduced. Inertness of the cyclooctadienes toward reduction by molecular hydrogen has also been reported[10] and may be rationalized by their strong coordination power[11] which like in the case of excess triphenylphosphine saturates the catalyst.[6] The reason why cyclooctene was reduced more slowly than other cyclomonoenes may be that it was contaminated with 0.5% of 1,5-cyclooctadiene.

The rates of the reduction of cyclopentene in toluene were measured in the presence of several hydrogen donors. From the results summarized in Table VI, it was found that the hydrogen-donating ability decreased in the order: indoline > pyrrolidine > tetrahydroquinoline > piperidine > 2,3-butanediol > dioxane > cyclohexanol > isopropyl alcohol.

Experimental Section

Materials. $RhCl(PPh_3)_3$[6] and dioxene[12] were prepared by the methods previously reported. Olefins and ethers were purified by distillation over metallic sodium. Alcohols were dried with molecular sieves after distillation. Amines, except for piperadine, were distilled. Piperadine was recrystallized from benzene. Tetralin and all solvents were purified by distillation and dried by usual methods. The compounds corresponding to the dehydrogenation products, excluding dioxene, were purchased and purified by distillation.

Transfer Hydrogenation in Excess Hydrogen Donor. Cycloheptene (48.1 mg, 0.50 mmol) or cyclopentene (34.1 mg, 0.50 mmol) and $RhCl(PPh_3)_3$ (18.5 mg, 0.02 mmol) were put into a Pyrex glass tube which had been sealed at one end. Into the mixture, an organic compound, which serves both as a hydrogen donor and a solvent, was added, and the total volume of the solution was made 1.0 ml. The tube was sealed under vacuum after two freeze–pump–thaw cycles at 10^{-2} Torr on a vacuum line with liquid nitrogen. The sealed tube was heated for 1 hr in the silicone-oil bath kept at 190 ± 1°. The reaction mixture was submitted to glc analysis which was performed at 90° for cycloheptene or at 50° for cyclopentene with Hitachi K 53 equipped with a flame-ionization detector, using 25 μl of cyclohexane as an internal standard. A 2 m × 6 mm stainless steel column packed with 25% of 1,2,3-tris(2′-cyanoethoxy)propane on Celite 545 was used. The detection and identification of dehydrogenation products were tried using various columns.

An Example of Stoichiometric Transfer Hydrogenation in a Solvent. Cycloheptene (48.1 mg, 0.50 mmol), indoline (59.5 mg, 0.50 mmol), and $RhCl(PPh_3)_3$ (9.3 mg, 0.01 mmol) were put into a Pyrex glass tube sealed at one end and the total volume of the solution was made 1.0 ml by the addition of toluene as a solvent. The tube, sealed by the method described above, was heated in a silicone-oil bath kept at 170 ± 1° for 1 hr. Though the catalyst dissolved slowly at room temperature, it dissolved at once at the elevated temperature. The reaction mixture was submitted to glc analysis. The amounts of cycloheptane and cycloheptene were measured using the column described above, and the amounts of indole and indoline were measured using a 1 m × 6 mm stainless steel column packed with 25% of Silicone GE SE-30 on Celite 545. In the latter, *n*-tetradecane was used as an internal standard.

Other transfer hydrogenations were carried out in a similar way.

An Example of Kinetic Runs. Six reaction samples, prepared by the method described above, were heated in the silicone-oil bath kept at 150 ± 1° for 10, 20, 30, 40, 50, and 60 min. The reaction mixtures were submitted to glc analysis.

Registry No.—$RhCl(PPh_3)_3$, 14694-95-2.

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Transfer Hydrogenation and Transfer Hydrogenolysis. VI. The Mechanism of Hydrogen Transfer from Indoline to Cycloheptene Catalyzed by Chlorotris(triphenylphosphine)rhodium(I)

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The mechanism of hydrogen transfer from indoline to cycloheptene in toluene catalyzed by $RhCl(PPh_3)_3$ has been studied. The rate data of the reaction can be accommodated by the rate expression of the form, rate = $a[D][C]_0/(b + [L])$ where $[C]_0$, [D], and [L] are the concentration of the catalyst, indoline, and triphenylphosphine, respectively. The rate-determining step of the reaction is inferred to be the dehydrogenation of indoline, that is, the hydrogen transfer from the amine to a Rh(I) complex to form a hydride complex by oxidative addition.

In the previous paper,[1] we have reported that in hydrogen transfer from organic compounds to olefins catalyzed by $RhCl(PPh_3)_3$, some cyclic amines, such as indoline, pyrrolidine, tetrahydroquinoline, and piperidine, have much higher hydrogen-donating ability than ethers, hydroaromatic compounds, and most alcohols. This study was undertaken to investigate the mechanism of the hydrogen transfer from amines to olefins catalyzed by $RhCl(PPh_3)_3$.

Results and Discussion

Indoline was used as a hydrogen donor because the amine had the highest hydrogen-donating ability and gave the dehydrogenation product, indole, stoichiometrically. Cycloheptene and toluene were used as a hydrogen acceptor and a solvent, respectively.

Dependence on the Catalyst Concentration. It has been reported that $RhCl(PPh_3)_3$ dimerizes to the inactive species, $[RhCl(PPh_3)_2]_2$, during the reduction by molecular hydrogen in benzene and that the rate is expressed in the form: $R = \alpha'[RhCl(PPh_3)_3] - \beta'[RhCl(PPh_3)_3]_2$ in which α' and β' are constants and the second term is due to the deactivation of the catalyst by dimerization.[2] However, in the region where the catalyst concentration was higher than 1.0×10^{-3} *M*, the initial rate of the transfer hydrogenation had first-order dependence on the catalyst concentration and was expressed in the form: $R =$

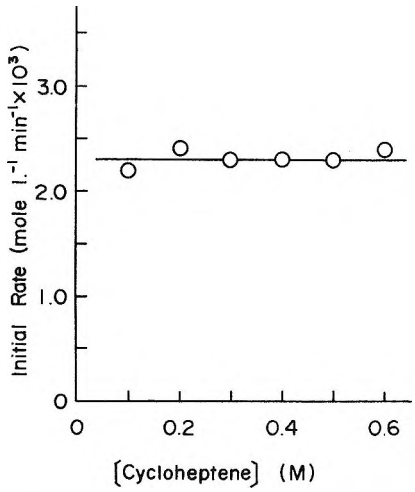


Figure 1. Dependence of the initial rate on the concentration of cycloheptene. Cycloheptene, indoline (0.25 *M*), and $RhCl(PPh_3)_3$ (0.01 *M*) in toluene were heated at 160°.

Table I
Dependence of the Initial Rate on the Concentration of Catalysts[a]

[Rh],[b] l. mol^{-1} x 10^3	Rate, l. mol^{-1} min x 10^3	
	$RhCl(PPh_3)_3$	$[RhCl(PPh_3)_2]_2$
1.0	0.3	
1.5	0.7	
2.0	1.0	1.3
4.0	1.9	2.8
6.0	2.9	3.9
8.0	3.7	5.0

[a] Cycloheptene (0.30 *M*), indoline (0.25 *M*), and a catalyst in toluene were heated at 160°. [b] In the case of $[RhCl(PPh_3)_2]_2$, [Rh] is twice the concentration of $[RhCl(PPh_3)_2]_2$.

$\alpha[RhCl(PPh_3)_3]$, in which α is a constant, as shown in Table I. This suggests the absence of the deactivation of the catalyst by the dimerization and may be rationalized by the assumption that in the presence of indoline, the chloro bridges of the binuclear complex are cleaved by the amine. This assumption is supported by the fact that in this transfer hydrogenation, the catalytic activity of $[RhCl(PPh_3)_2]_2$ is higher than that of $RhCl(PPh_3)_3$ even at the same concentration of rhodium atom in the solution, as shown in Table I.

Dependence of the Olefin Concentration. It has been reported that the influence of the olefin concentration on the rate is rather complicated in the reduction by molecular hydrogen in which the rate-limiting step is the coordination of an olefin to the dihydride complex, $RhH_2Cl(PPh_3)_2$ (solvent), by replacing a solvent molecule.[2,3] However, as seen from Figure 1, the initial rate of the transfer hydrogenation was independent on the olefin concentration, as in the transfer hydrogenation in dioxane.[4] This may correspond to the fact that the rate of this reaction system is hardly influenced by the kind of cyclic monoenes whose coordinating power differs a little.[1] The zero-order dependence may be interpreted either by the assumption that the olefin coordinates to the metal of the catalyst after the rate-determining step or by the assumption that the olefin coordinates so completely as to show a leveling effect as it does before the rate-limiting step. The former assumption seems to be more plausible, because the complexing power of internal monoenes on the phosphine catalyst is weak,[2,3] no olefin complex was detected in this system, and the results in the transfer hydrogenation in dioxane accorded with the former assumption.[4]

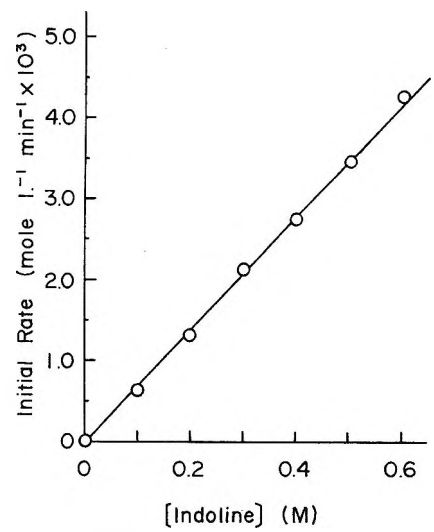


Figure 2. Dependence of the initial rate upon the concentration of indoline. Cycloheptene (0.30 *M*), indoline, and $RhCl(PPh_3)_3$ (0.006 *M*) in toluene were heated at 160°.

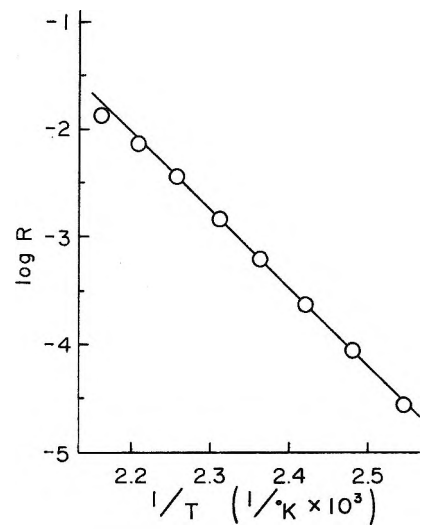


Figure 3. Arrhenius plot of the transfer hydrogenation at 120, 130, 140, 150, 160, 170, 180, and 190°. Cycloheptene (0.30 *M*), indoline (0.25 *M*), and $RhCl(PPh_3)_3$ (0.006 *M*) were heated in toluene.

Dependence on the Donor Concentration. As shown in Figure 2, the initial rate of the reduction has first-order dependence upon the concentration of indoline. Upon this result, it may be guessed that the coordination of indoline occurs before the rate-determining step and the coordinating power is not so strong as to show a leveling effect. The supposition is supported by the fact that no indoline complexes were isolated even from indoline solution.

Dependence on Temperature. Initial rates were measured at the temperatures ranging from 120 to 190° and a plot of log *R* against $1/T$ is shown in Figure 3. A good linear plot is obtained, indicating that the kinetics of the system are not so complicated. From Figure 3, a value for the activation energy, E_a, of 33.2 kcal mol^{-1} is obtained; ΔH^* is 32.0 kcal mol^{-1} and ΔS^* is 10.2 eu.

Effect of Added Phosphine. The reduction rate was decreased by the addition of excess triphenylphosphine to the reaction system, as in the case of the reduction by molecular hydrogen,[2,3] although such addition effect of the phosphine was not observed in the transfer hydrogenation in dioxane.[4] The plot of the reciprocal of the rate against the

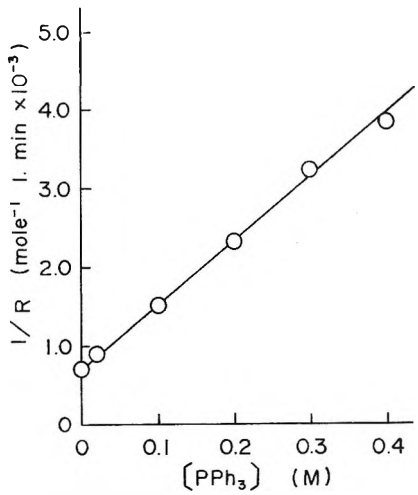


Figure 4. Dependence of the initial rate on the added triphenylphosphine. Cycloheptene (0.30 *M*), indoline (0.25 *M*), $RhCl(PPh_3)_3$ (0.005 *M*), and triphenylphosphine were heated in toluene at 160°.

Table II
Dependence of Initial Rates on Ratio of Phosphine to Rhodium[a]

PPh_3/Rh	Initial rate, mol $l.^{-1}$ min^{-1} × 10^4
0	180[b]
1	22
2	37
3	31
4	22
5	21

[a] Cyclopentene (0.50 *M*), indoline (0.50 *M*), $[RhCl(cyclooctene)_2]_2$ (0.0025 *M*), and triphenylphosphine were heated at 160° in toluene. [b] A metallic mirror was formed.

added phosphine concentration is linear with a positive intercept on the *y* axis, as shown in Figure 4. The relation is expressed in the form $1/R = a[PPh_3] + b$, in which *a* and *b* are constants. From Figure 4, 8×10^3 mol^{-2} $l.^2$ min and 7×10^2 mol^{-1} l. min were obtained as the values of *a* and *b*, respectively. From these values the dissociation constant of the catalyst was derived as described later.

Further, we examined the catalytic activity of $[RhCl(cyclooctene)_2]_2$ to which various amounts of triphenylphosphine were added, and the result summarized in Table II shows that the maximum rate appeared when the ratio of the phosphine to rhodium was equal to two. It is inferred from the appearance of the maximum rate and the depressing effect of the added phosphine that the coordinating power of indoline which is a sterically hindered aromatic amine is not so strong and the amine competes with triphenylphosphine for a vacant coordination site of an intermediate which is formed by the release of a triphenylphosphine from $RhCl(PPh_3)_3$ and has two triphenylphosphines. The inference is supported by the fact that no indoline complex was isolated even by heating the catalyst in indoline.

Effect of Added Indole. As seen from Figure 5 the addition of the dehydrogenation product, indole, made the rate increase. It may be explained either by the assumption that indole has the ability to donate hydrogen or by the one that indole shows such solvent effect as increases the reaction rate by the appropriate coordinating ability as the halogenated benzenes. The former assumption is denied by the fact

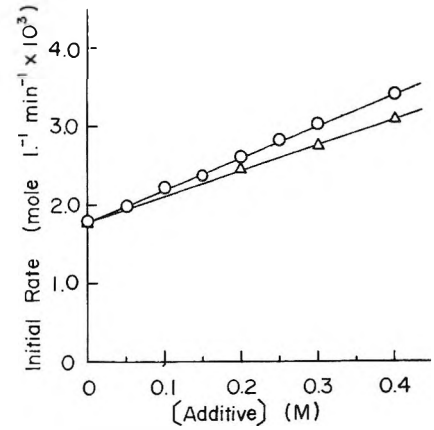


Figure 5. Effect of the added indole and chlorobenzene. Cycloheptene (0.30 *M*), indoline (0.25 *M*), and $RhCl(PPh_3)_3$ (0.005 *M*) in toluene were heated at 160° along with indole (○) or chlorobenzene (△).

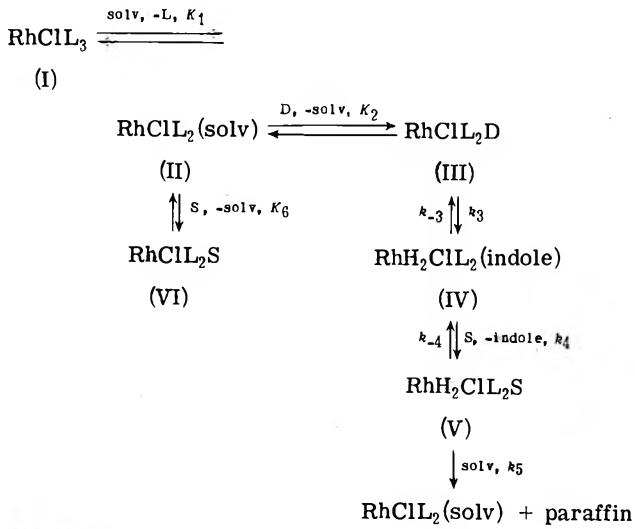
that the transfer hydrogenation never proceeded when indole was used as a hydrogen source. The latter one seems to be supported by the result that the effect of the added chlorobenzene was similar to that of indole, as shown in Figure 5. The promoting effect of indole seems to show also that the aromatized amine is no longer hydrogenated to indoline, so it does not compete with the olefin.

Catalytic Activity of $[RhCl(PPh_3)_2]_2$. Though the dimerization of $RhCl(PPh_3)_3$ inhibits the reduction by molecular hydrogen,[2] in this transfer hydrogenation using indoline the catalytic activity of $[RhCl(PPh_3)_2]_2$ was greater than that of $RhCl(PPh_3)_3$ even in the same rhodium concentration, as shown in Table I. This may be compatible with the observation that the transfer hydrogenation was faster at the phosphine–rhodium ratio of 2 than at the ratio of 3, as seen in Table II.[5] The results suggest that in the presence of indoline, the dimer decomposes at the reaction temperature to give $RhCl(PPh_3)_2L'$, in which L′ represents a solvent, a hydrogen donor, or an olefin molecule.

Attempt to Isolate Reaction Intermediates. Complexes coordinated by indoline were obtained neither from the reaction mixtures nor from the indoline solution which was heated at 80° and cooled. The complex obtained in both cases contained no nitrogen and showed the elemental analysis and the ir and the nmr spectrum which may be due to the mixture of $RhCl(PPh_3)_3$ and $[RhCl(PPh_3)_2]_2$. In the reactions in which $[RhCl(PPh_3)_2]_2$ was used, the original binuclear complex was recovered and no indoline complex was obtained. These results may be interpreted by the assumption that the coordinating ability of indoline is not so great because the aromatic amine does not have as strong basicity as alkyl amines and has rather large steric hindrance. However, yellow needles were obtained from $RhCl(PPh_3)_3$ or $[RhCl(PPh_3)_2]_2$ in pyrrolidine, which has greater basicity and lesser steric hindrance, and gave the elemental analysis and the ir and the nmr spectrum explainable by $RhCl(PPh_3)_2$(pyrrolidine). Perhaps this complex may be a reaction intermediate in the transfer hydrogenation by pyrrolidine.

Kinetic Discussion

The reduction,[2,3,6] the isomerization,[7] and the hydrogen–deuterium exchange[8] of olefins under hydrogen atmosphere catalyzed by $RhCl(PPh_3)_3$ have been studied in detail by many researchers. Based on the studies of these reactions, the transfer hydrogenation in dioxane,[4] and the results described earlier, we should like to propose the following reaction scheme for the transfer hydrogenation.



L = PPh_3, D = indoline, S = olefin, solv = solvent

In spite of the report that $RhCl(PPh_3)_3$ scarcely releases a triphenylphosphine at room temperature in rigorously oxygen-free benzene although even a trace of oxygen intensely promotes the dissociation,[9] we introduced the species, $RhClL_2$(solvent), based on the following grounds: (1) the kinetic expressions derived from the schemes which do not involve the intermediate cannot explain the experimental results obtained;[10] (2) the fact that $RhCl(PPh_3)_2$(solvent) is isolated from dioxane,[4] acetonitrile,[2] or pyridine[2] solution suggests that $RhCl(PPh_3)_2$(toluene) also exists in toluene solution; (3) the dissociation of $RhCl(PPh_3)_3$ may be considered to be easier at the elevated temperatures at which the transfer hydrogenation was carried out than at room temperature.

Based on the proposed reaction scheme and the assumptions described later, the rate, R, is expressed as follows

$$R = \frac{k_3K_1K_2[D][C]_0}{[L] + K_1 + K_1K_2[D] + K_1K_6[S]} \quad (1)$$

where k_3 is a rate constant, K_1, K_2, and K_6 are equilibrium constants, $[C]_0$ is the total concentration of rhodium species, and [D], [L], and [S] are the concentration of the hydrogen donor, triphenylphosphine, and the olefin, respectively. The assumptions used are (1) the intermediates, IV and V, are so unstable and exist in so small a concentration that the steady state treatment is applicable to them, and (2) indole is not hydrogenated, that is, k_{-3} is zero. The former assumption is supported by the fact that hydride olefin complexes are intermediates in the hydrogenation by molecular hydrogen which occurs under milder conditions; so the hydrogen transfer to olefins in the intermediates is considered to be fast. The latter assumption also seems to be not so unreasonable by the fact that indole is an aromatized product and the addition of indole to the reaction system did not show the decrement of the reaction rate which suggests the competition of indole with the olefin for the reduction.

We rearranged eq 1 as follows

$$1/R = \frac{K_6}{k_3K_2[D][C]_0}[S] + \frac{K_1 + [L] + K_1K_2[D]}{K_1K_2[D][C]_0} \quad (2)$$

As the rate was independent on the olefin concentration, $K_6/k_3K_2[D][C]_0$ must be so small as to be negligible. Perhaps this means K_6 is negligibly small, that is, the concentration of VI is small.[11] This reasoning may be partly supported by the fact that no olefin complex was detected in this system and by the reports that the coordinating power of internal olefins to the catalyst is weak[2] and the concentration of the Rh(I)–olefin complex is small in the transfer hydrogenation in dioxane.[4] Then the rate expression is reduced to

$$R = \frac{k_3K_1K_2[D][C]_0}{K_1 + [L] + K_1K_2[D]} \quad (3)$$

As described earlier, the rate had the first-order dependence on the concentration of indoline. This fact may require $K_1 + [L] \gg K_1K_2[D]$, that is, [I] + [II] $\gg$ [III]. This supposition seems to be reasonable because no indoline complex was isolated even from indoline solution of the catalyst. Then the rate expression becomes

$$R = k_3K_1K_2[D][C]_0/(K_1 + [L]) \quad (4)$$

This expression is found to accommodate reasonably all the experimental observations described earlier. (1) The dependence of the rate on the catalyst concentration should be linear. This agrees with the result that the initial rate of the transfer hydrogenation was proportional to the charged catalyst concentration. (2) When triphenylphosphine is added to the reaction system catalyzed by $RhCl(PPh_3)_3$, the concentration of the added phosphine may approximately be regarded as the phosphine concentration. The dependence of the rate on the phosphine concentration is

$$1/R = \frac{1}{k_3K_1K_2[D][C]_0}[L] + \frac{1}{k_3K_2[D][C]_0}$$

which is identical in form with that obtained previously with

$$a = 1/k_3K_1K_2[D][C]_0$$
$$b = 1/k_3K_2[D][C]_0$$

From Figure 5, the value for the gradient, a, and the one for the intercept, b, 8×10^3 l.^{2} min mol^{-2} and 7×10^2 l. min mol^{-1} were obtained, respectively. By using these values, $K_1 = b/a = 9 \times 10^{-2}$ mol l.$^{-1}$ and $k_3K_2 = 1$ l. mol^{-1} min^{-1} were obtained, as the values at 160°. As the reaction was carried out at the much higher temperature, the K_1 value, which suggests about 25% of $RhCl(PPh_3)_3$ replaced a molecule of the phosphine by a molecule of the solvent, seems to be not so unreasonable, in spite of the report that only 1.2% of the complex dissociates in oxygen-free benzene at 25°.[12] Then the overall rate expression at 160° may be formulated as $R = 9 \times 10^{-2}[D][C]_0/(9 \times 10^{-2} + [L])$ (3) As the reduction,[2,3,6] the isomerization,[7] and the hydrogen-deuterium exchange[8] of olefins under hydrogen gas occur under milder conditions than the transfer hydrogenation, the steps which can correspond to the steps in the former reactions may not be rate determining in the latter. In eq 4, k_3 is the only rate constant; so the dehydrogenation step, III → IV, may be the rate limiting in the transfer hydrogenation. This is supported by the fact that the reactions under hydrogen involve no dehydrogenation step.

Experimental Section

All the transfer hydrogenations and kinetic measurements were carried out by the method reported previously.[1]

Materials. $RhCl(PPh_3)_3$,[2] $[RhCl(PPh_3)_2]_2$,[2] and $[RhCl(cyclooctene)_2]_2$[13] were prepared according to the literature. Other reagents were treated as reported previously.[1]

An Attempt to Isolate Reaction Intermediates. To a mixture of $RhCl(PPh_3)_3$ (93 mg, 0.1 mmol), indoline (238 mg, 2.0 mmol), and cyclopentene (68 mg, 1.0 mmol), toluene was added, and the total volume of the solution was made up to 1.0 ml. Three samples prepared by the method described above were heated at 80° for 2 hr, at 110° for 1 hr, and at 140° for 30 min, respectively, and

cooled. The precipitated crystals were separated by filtration, washed with ether, and dried *in vacuo*. The ir and nmr spectra of all the complexes obtained were identical with one another, similar to the mixture of $RhCl(PPh_3)_3$ and $[RhCl(PPh_3)_2]_2$, and showed no peaks assignable to indoline. The elemental analysis of the complex isolated in the reaction at 140° was also explainable by the mixture.

Anal. Calcd for the mixture of $C_{54}H_{45}ClP_3Rh$ and $C_{72}H_{60}Cl_2P_4Rh_2$ (1:3): C, 66.44; H, 4.65; N, 0.0. Found: C, 66.46; H, 4.82; N, 0.0.

A similar mixture was obtained also when $RhCl(PPh_3)_3$ (0.03 mmol) was heated in indoline (2.0 mmol) at 80° for 5 hr.

Anal. Found: C, 67.99; H, 4.84; N, 0.0.

When $[RhCl(PPh_3)_2]_2$ (0.03 mmol) was heated in indoline (2.0 mmol) at 80° for 5 hr, the dimer was recovered.

Isolation of $RhCl(PPh_3)_2$(pyrrolidine). $RhCl(PPh_3)_3$ (27.8 mg, 0.03 mmol) and pyrrolidine (142 mg, 2.0 mmol) were sealed in a Pyrex glass tube *in vacuo* and heated at 80° for 30 min. The yellow crystals isolated melted at 105–106°. The nmr spectrum of them showed three multiplets centered at τ 8.2, 6.8, and 2.7, with 1:1:8 area (in $CDCl_3$ with TMS as the internal standard). The ir spectrum showed bands at 2930, 2860, and 886 cm^{-1} which are assignable to pyrrolidine.

Anal. Calcd for $C_{40}H_{39}ClNP_2Rh$: C, 65.45; H, 5.37; N, 1.91. Found: C, 65.11; H, 5.48; N, 1.83.

The same complex which was identified by elemental analysis, ir spectrum, and melting point was obtained in the similar reaction between $(RhCl(PPh_3)_2)_2$ and pyrrolidine.

Registry No.—$RhCl(PPh_3)_3$, 14694-95-2; $[RhCl(PPh_3)_2]_2$, 25966-16-9; $[RhCl(cyclooctene)_2]_2$, 12279-09-3; $RhCl(PPh_3)_2$(pyrrolidine), 53166-29-3; indoline, 496-15-1; cycloheptene, 628-92-2; pyrrolidine, 123-75-1.

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(3) (a) F. H. Jardine, J. A. Osborn, and G. Wilkinson, *J. Chem. Soc. A*, 1574 (1967); (b) S. Montelatici, A. Ent, J. A. Osborn, and G. Wilkinson, *ibid.*, 1054 (1968).
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(5) When $[RhCl(cyclooctene)_2]_2$ was added to the toluene solution of triphenylphosphine at the phosphine–rhodium ratio of 2, $[RhCl(PPh_3)_2]_2$ was isolated.
(6) (a) H. D. Kaesz and R. B. Saillant, *Chem. Rev.*, **72**, 231 (1972); (b) C. A. Tolman, *Chem. Soc. Rev.*, **11**, 337 (1972); (c) G. N. Schruzer, "Transition Metals in Homogeneous Catalysis," Mercer Dekker, New York, N.Y., 1971, pp 33 and 41.
(7) (a) J. F. Biellmann and M. J. Jung, *J. Amer. Chem. Soc.*, **90**, 1673 (1968); (b) A. S. Hussey and Y. Takeuchi, *ibid.*, **91**, 672 (1969); (c) G. C. Bond and R. A. Hillyare, *Discuss. Faraday Soc.*, **46**, 20 (1968); (d) C. H. Heathcock and S. R. Poulter, *Tetrahedron Lett.*, 2755 (1969); (e) R. L. Augustine and J. F. V. Peppen, *J. Amer. Oil Chem. Soc.*, **47**, 478 (1970).
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(9) (a) D. R. Eaton and S. R. Suart, *J. Amer. Chem. Soc.*, **90**, 4170 (1968); (b) P. Meakin, J. P. Jesson, and C. A. Tolman, *ibid.*, **94**, 3240 (1972); (c) D. D. Lehman, D. F. Shriver, and I. Wharf, *Chem. Commun.*, 1486 (1970); (d) H. Arai and J. Halpern, *ibid.*, 1571 (1971).
(10) For example, the kinetic expression derived from the fact shown in Figure 1, and the scheme which is formed by removing $RhCl(PPh_3)_2$(solvent) from the scheme in the text, is the type $R = a'[D][C]_0/(b'[L] + c'[D])$. This cannot explain the facts shown in Figures 2 and 4 without contradiction.
(11) Because $[VI] = K_6[II][S]$.
(12) It has been reported[9d] that the dissociation constant, K, equals 1.4×10^{-4} mol $l.^{-1}$.
(13) L. Porri, A. Lionetti, G. Alleegra, and A. Immirzi, *Chem. Commun.*, 336 (1965).

Catalytic Hydrogenolysis–Reduction of Aryl Phosphate Esters[1]

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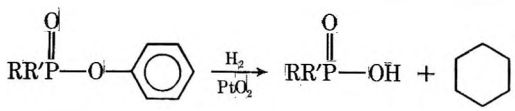
The platinum-catalyzed hydrogenolysis–reduction of aryl phosphate esters has been investigated with a view toward the determination of the sequence of reaction steps. The aromatic hydrocarbons related to the ester functions have been isolated and identified as intermediates; these arenes, when subjected to facilitated reaction conditions, yield reduction products in the same proportions as observed in the hydrogenolysis reaction systems. The course of intermediate formation and decay has been followed and the stereoregularity of the reduction process has also been investigated.

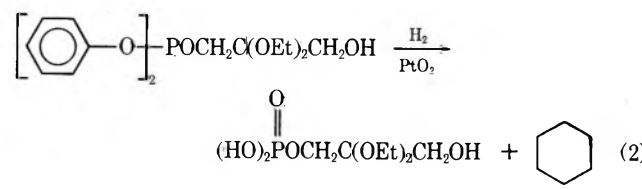
The hydrogenolysis–reduction of aryl esters of phosphorus-containing acids over platinum catalysts (eq 1) is a



(1)

reaction which has been of significant utility in the synthesis of numerous organophosphorus compounds; the phenyl ester linkage is cleaved yielding the free acid while the original aromatic ring is reduced to cyclohexane. Its utility arises as it allows the protection of a phosphorus acid function with an ester linkage at an early stage in a synthetic sequence and at a later stage allows the generation of the free acid without resorting to hydrolytic conditions.

One example of this utility is shown in the synthesis of dihydroxyacetone phosphate.[2] At an early stage of the synthetic route the critical phosphate linkage is introduced by the reaction of diphenyl phosphorochloridate with an aliphatic alcohol. The alkyl position is then properly functionalized and at a latter stage the phenyl groups are removed by hydrogenolysis generating the free acid (eq 2).



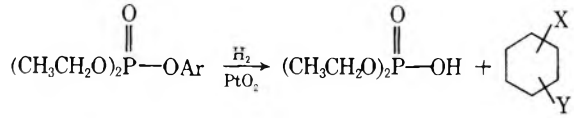
(2)

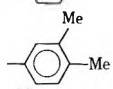
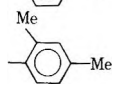
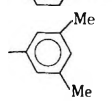
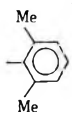
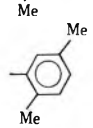
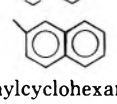
The hydrolytic removal of either aryl or alkyl protecting ester linkages is not feasible as the critical phosphate linkage in the desired product would also be cleaved.

A most interesting aspect of this reaction is the overall reduction of the phenyl ring to cyclohexane under the relatively mild reaction conditions. Thereby it is rather surprising that so little attention has been given to this point. No efforts have been reported to elucidate the course of this overall reaction, and it appears that, aside from phenyl esters themselves, only *p*-nitrophenyl esters have been used in this reaction;[3] in this latter work it was presumed that hydrogenolysis–reduction yielded cyclohexylamine although this was not shown definitively.

As it is known that aromatic hydrocarbons undergo com-

Table I



Ar	Compd	Rel % *cis*-HC[a] 1 atm H_2	Rel % *cis*-HC[a] 4 atm H_2	Rel % *trans*-HC[a] 1 atm H_2	Rel % *trans*-HC[a] 4 atm H_2	Overall hydrocarbon yield,[b] % 1 atm H_2	Overall hydrocarbon yield,[b] % 4 atm H_2
	I	84.2	90.5	15.8	9.5	71.8	36.2
	II	83.2	90.0	16.8	10.0	75.2	27.8
	III	73.0	78.4	27.0	21.6	90.1	31.9
	IV	75.6	79.3	24.4	20.7	93.8	68.3
	V	75.9	81.0	24.1	19.0	57.8	24.3
	VI	69.2	72.7	30.8	27.3	76.3	67.4
	VII	83.6	87.8	16.4	12.2	89.0	65.0
	VIII	82.3	85.0	17.7	15.0	76.6	65.3

[a] Dimethylcyclohexane for xylene reactions and decalin for naphthalene reactions. [b] Average value for a reaction time of 24 hr under reaction conditions described in the Experimental Section.

plete reduction over platinum catalysts at low hydrogen pressure if an acidic solvent is used or there is present a strong acid (provided the accompanying anion is not inhibitory),[4,5] a reasonable possibility for the sequence in aryl phosphate hydrogenolysis appears to be (a) initial cleavage of the aryl ester linkage yielding arene and the phosphorus-containing acid, followed by (b) the acid-facilitated reduction of the arene. To investigate this hypothesis the complete series of diethyl xylyl phosphate esters were prepared and subjected to hydrogenolysis, the amounts of *cis*- and *trans*-dimethylcyclohexanes formed being measured. Similarly, the two naphthyl diethyl phosphate esters were prepared and subjected to hydrogenolysis, and the amounts of decalins formed were measured.

Two comparisons were to be made using the data thus obtained. First, the cis:trans ratios for the dimethylcyclohexanes (and the decalin) were to be compared with those from the facilitated reduction of the corresponding xylene (or naphthalene) which were the proposed intermediates. Second, the product ratios for the two xylyl esters with methyl groups in an ortho relationship were to be compared with each other as were the product ratios for the three xylyl esters with methyl groups in a meta relationship. The latter comparison would provide information concerning the possibility of a common intermediate in each of the two sets of reactions as is necessitated by the postulated route.

Finally, direct evidence (detection, isolation) for the structure of any intermediate involved was to be obtained.

Results and Discussion

The diethyl xylyl phosphates (I–VI), which have not been reported previously, and the diethyl naphthyl phosphates[6] (VII, VIII) were prepared using a modification of a standard method.[7] These were subjected to hydrogenolysis–reduction over Adams catalyst in absolute ethanol solution at 1 and 4 atm pressure of hydrogen. The reaction solutions contained an internal reference of cyclohexane for gas–liquid chromatographic (glc) analysis. The overall yield and hydrocarbon product distribution data for these reactions are summarized in Table I.

Similarly, the xylenes and naphthalene were subjected to catalytic hydrogenation over Adams catalyst in absolute ethanol solution with diethyl phosphoric acid added for facilitation of reaction.[4] Again, cyclohexane was used as an internal reference for glc analysis of the reduction products. The data for these reactions are summarized in Table II.

First should be noted the close correlation of product distribution under both sets of reaction conditions for the two compounds (I and II) containing methyl groups in an ortho relationship, for the three compounds (III–V) containing methyl groups in a meta relationship, and finally for the two naphthyl compounds (VII, VIII). This serves as as preliminary evidence of a common intermediae within each set. Moreover, the close correspondence with product distribution data for the xylene and naphthalene reductions is indicative of the intermediacy in each case of the free arene. It should also be noted that these relative yields are in good agreement with the work of Schuetz and Caswell[5] on xylene reductions over Adams catalyst and the distribution trends with changing pressure are in accord with those observed by Siegel, *et al.*[8]

While the previously mentioned data are *indicative* of the intermediacy of free arene, they by no means serve as *definitive proof;* this is best attained by detection and iso-

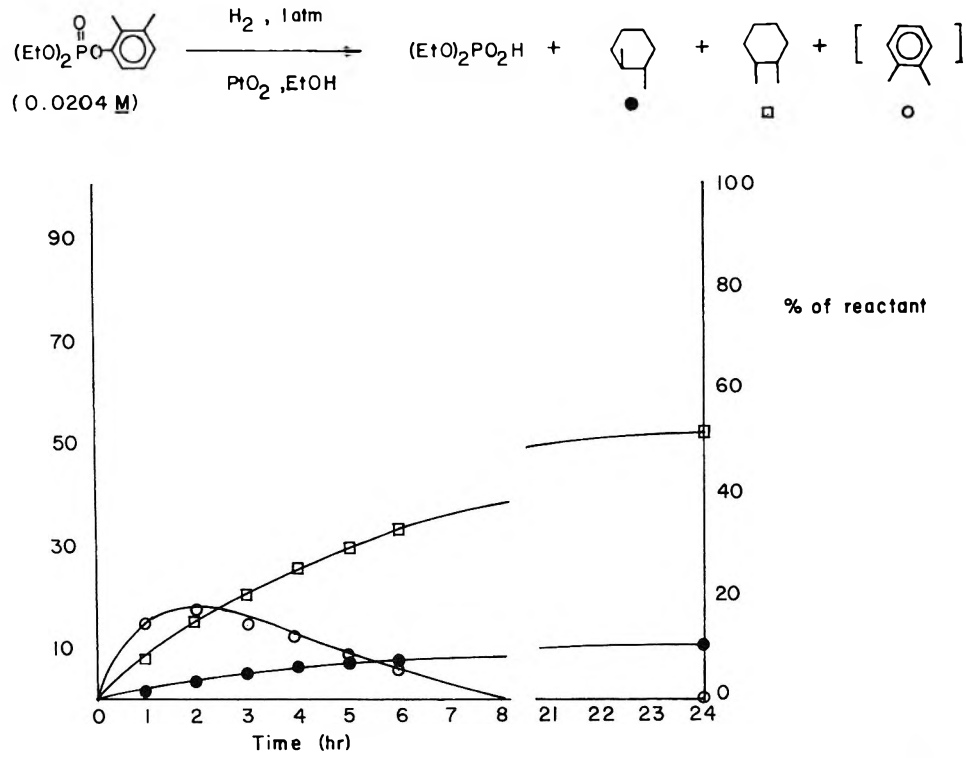


Figure 1.

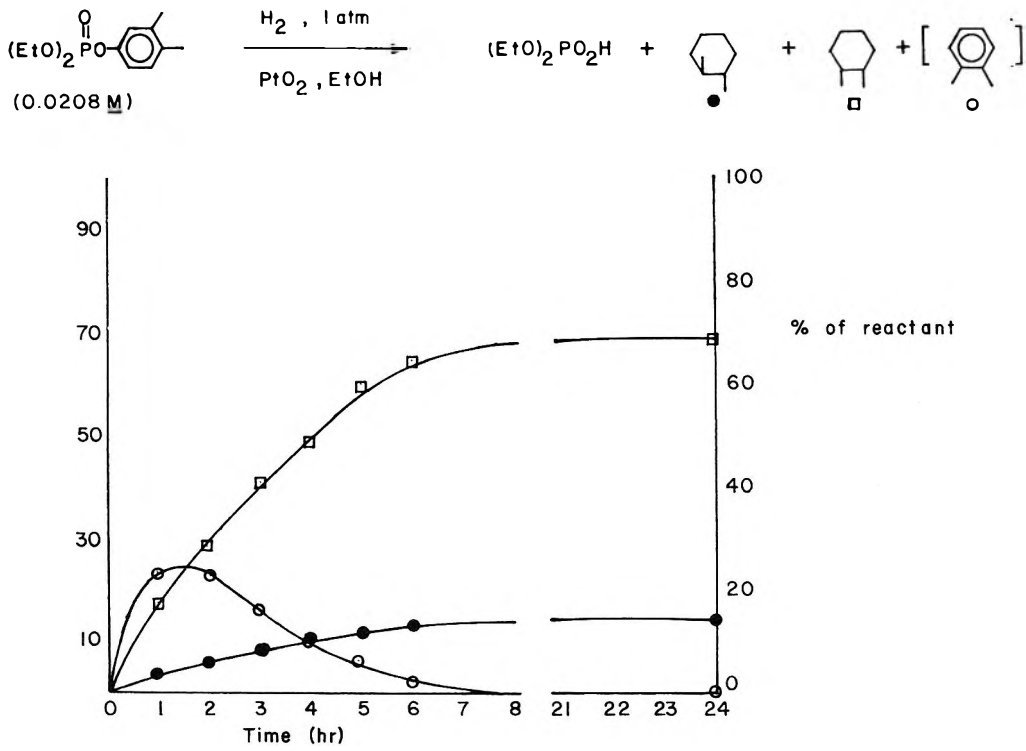


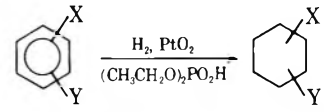
Figure 2.

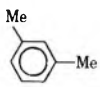
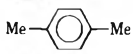
lation of the intermediates themselves. This situation was realized for all aryl ester reactants with the exception of compound V. (This reaction system will be discussed more fully in a succeeding paragraph.) The arenes could be intercepted during the reaction using glc and were identified by comparison of their spectral and physical properties with those of authentic samples.

For all reaction systems (with the exception of compound V) the formation and disappearance of intermediate arene, at atmospheric reaction conditions, was followed by glc analysis. Two examples of the data obtained are shown graphically in Figures 1 and 2. Similar plots are obtained for the five other compounds from which intermediate arene may be isolated. Maxima in arene concentration for these systems (compounds I–IV, VI–VIII) were attained within 1–2 hr after reaction initiation. For the xylyl esters these maxima ranged between 8 and 30% of the concentration of the initial reactant whereas for the naphthyl esters they were about 40% of the initial reactant concentration.

As mentioned above, the diethyl 2,6-dimethylphenyl phosphate, compound V, appeared anomolous as no *m*-xylene could be detected although its intermediacy was indicated by the stereochemical data. This result may be rationalized in the following way. The hydrogenolysis of the

Table II



Compd	Registry no.	Rel % *cis*-HC[a]		Rel % *trans*-HC[a]		Overall yield, %	
		1 atm H_2	4 atm H_2	1 atm H_2	4 atm H_2	1 atm H_2	4 atm H_2
	95-47-6	87.4	89.1	12.6	10.9	100.0	98.4
	108-38-3	75.2	79.8	24.8	20.2	97.4	89.3
	106-42-3	67.4	74.9	32.6	25.1	100.0	100.0
	91-20-3		86.4		13.6		100.0

[a] Dimethylcyclohexane for xylene reactions and decalin for naphthalene reactions. [b] Average value for a reaction time of 24 hr.

Table III

Compd	Elemental analyses,[a,b] %		Yield, %	Mass spectra,[c] *m/e*		Bp, °C (*P*, mm)
	Carbon	Hydrogen		Parent	Base	
I	55.65	7.44	54	258	104	104 (0.12)
II	55.48	7.58	75	258	122	109 (0.17)
III	55.41	7.47	27	258	132	101 (0.10)
IV	55.89	7.50	38	258	122	97 (0.14)
V	55.99	7.25	43	258	104	107 (0.45)
VI	56.12	7.66	81	258	201	99 (0.05)

[a] All analyses were performed by Schwarzkopf Microanalytical Laboratories, Woodside, N.Y. [b] Calcd for $C_{12}H_{19}O_4P$: C, 55.81; H, 7.36. [c] All mass spectra were measured using a Varian MAT CH-7 instrument operating at 70 eV and 100-μA trap current.

ester linkage is presumed to be slow relative to the other esters investigated due to steric interference by the two methyl groups, *both* of which are adjacent to the position where cleavage reaction occurs. The *m*-xylene once formed, however, reacts at the same rate as if derived from any other source. Whereas for all other reaction systems investigated the rate-limiting step in saturated hydrocarbon production is arene reduction, for compound V the opposite situation attains and *cleavage is rate limiting*. Thus a *detectable* concentration of *m*-xylene is never present.

This rationalization is also in accord with the relatively low overall yield of saturated hydrocarbon isolated from reaction of compound V. After generation of sufficient diethylphosphoric acid for activation of the catalyst, the rate of ester cleavage remains slow; however, reduction of the aromatic ring *of the ester* may occur yielding a substituted cyclohexyl ester which does not cleave.[9] Evidence for the presence of these reduced esters in the reaction mixture has been found although detailed structural characterizations have not been made.

However, when the reaction is conducted in cyclohexane solution, *m-xylene is obtained in significant quantity from compound V,* as are the arenes from the other aromatic esters investigated. This provides an interesting and possibly useful reaction medium; in cyclohexane hydrogenolysis proceeds smoothly but reduction of the arene is retarded.

Observation of the catalyst during the two processes provides a clue to understanding this behavior. Using alcohol solvents the catalyst, upon initial reduction, begins to coagulate slightly as arene is formed; upon complete reduction of arene the finely dispersed catalyst is regenerated. In contrast, with cyclohexane as the reaction medium, upon reaction initiation, the catalyst clumps and later congeals to an oil which adheres to the glass walls of the reactor; the normal finely dispersed catalyst is *not* regenerated. This oil retains activity for hydrogenolysis of the aryl phosphate linkage but *not* for arene reduction. As such it bears potential utility for selective isolation of arenes.

Experimental Section

Reagents. All reagents used in the preparation of the phosphate esters were purchased from Aldrich Chemical Co. and used without further purification. Solvents in the preparative work were dried over sodium metal prior to use. Absolute ethanol was purchased from Commercial Solvents Corp. and used without further purification. The platinum oxide catalyst (83 ± 0.5%) was purchased from Engelhard Minerals and Chemicals Corp.

General Synthesis of Diethyl Aryl Phosphates. To a solution of 0.10 mol of the substituted phenol in 400 ml of sodium-dried benzene was added 0.13 mol of sodium hydride with constant mechanical stirring. The reaction medium was stirred overnight as hydrogen was evolved. To the stirred slurry of phenolic salt was added dropwise 0.10 mol of diethyl phosphorochloridate. Upon dissolution of the salt yielding a clear solution, the reaction mixture was washed with 500 ml of water. The organic layer was separated and dried over anhydrous magnesium sulfate, and the benzene was removed by distillation at reduced pressure. The residue was then vacuum distilled to yield the diethyl aryl phosphate. Yield and analytical data are shown in Table III. Satisfactory elemental analyses and ir, nmr, and mass spectra were obtained for all compounds.

General Procedure for Atmospheric Pressure Hydrogen Reactions. The reactor used was of standard design[10] operated with manual adjustment to maintain atmospheric pressure of hydrogen in the reaction vessel. The reaction mixture was stirred throughout the reaction period using a magnetic stirrer. A reaction flask bearing a side arm fitted with a serum cap was used that samples could be removed for analysis during the course of the reaction. For the analytical experiments the reaction flask was charged with 25 ml of an absolute ethanol solution *ca.* 0.020 *M* in the compound to be investigated and *ca.* 0.020 *M* in cyclohexane which was used as the reference for glc analysis. To this was added 25 mg of PtO_2. For the xylene reactions the reaction solution was also prepared *ca.* 0.010 *M* in diethyl phosphoric acid. For studies involving the isolation of intermediates and products the concentra-

tion of reactant was increased to *ca.* 1 *M*. Reactions of phosphates in cyclohexane were performed at the same concentrations with the same amount of catalyst. Control experiments were performed to ensure that isomerization of initial products did not occur.

General Procedure for 4-Atm Hydrogen Reactions. All reactions were performed using a standard Parr apparatus with shaker. The pressure was adjusted manually to maintain 4 atm pressure in the reaction portion. The reaction solutions used were as described above for atmospheric pressure investigations. All systems were removed from the reactor and filtered through Celite to remove the catalyst prior to glc analysis.

Analysis. Gas–liquid chromatographic analyses (and preparative-scale glc) were performed using a 5 ft × ¼ in. column of 20% Apiezon L on Chromsorb W at column temperatures of 70–120°, varying with the compounds to be observed. For analytical data all products and intermediates were compared for relative response factors; chart areas were measured using a compensating planimeter. Control experiments were made to ensure that product interconversion was not occurring during analysis.

All ir spectra were measured using a Perkin-Elmer Model 237 B spectrophotometer, nmr spectra were measured using a Varian EM 360 spectrometer, and mass spectra were measured using a Varian MAT CH-7 instrument.

Summary

The hydrogenolysis–reduction of aryl phosphate esters has been found to proceed by initial hydrogenolysis yielding the free phosphorus-containing acid and the free arene followed by reduction of the arene. The reaction may be intercepted at the arene stage by conducting it in cyclohexane solvent; here the catalyst activity for reduction is retarded by the strong acid which is formed in the initial step.

Registry No.—I, 53336-80-4; II, 14143-06-7; III, 53336-81-5; IV, 53336-82-6; V, 39604-15-4; VI, 53336-83-7; VII, 33650-14-5; VIII, 16519-26-9.

References and Notes

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A Nuclear Magnetic Resonance Investigation of the Iodination of 1,2-Disubstituted Ethylenes. Evidence for a Trans Addition–Cis Elimination

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Iodine was allowed to react with olefins, in the dark, for periods of up to 10 days and their nmr spectra were periodically recorded. All of the olefins showed extensive conversion to their respective diiodides. The reaction was monitored by the disappearance of the olefin peak and the appearance of an iodinated methine proton peak. In the case of cis olefins, between the second and third days, a second halogenated methine band was observed at higher field. Its chemical shift corresponded to that of the iodinated trans olefin. Based on this evidence and supported by glc experiments, a trans addition–cis elimination mechanism is postulated for the "dark" reaction.

In spite of a gradually increasing number of papers dealing with the iodination of olefins,[1-10] most texts either ignore the reaction or state that it does not occur. In actuality certain olefins have been shown to add iodine easily, though more slowly than either bromine or chlorine. The iodinated products however are relatively unstable and can eliminate iodine on heating.

Various investigators have demonstrated that the reaction is extremely complex. Robertson[2] and others studied what they believed was the ionic reaction and found that the reaction was homogeneous in polar solvents and heterogeneous in nonpolar solvents. They were also able to show that the reaction was catalyzed by light.[1] This finding led to additional work on the free-radical iodination of olefins. Most of the recent work has concentrated on the light-catalyzed process and its kinetics and stereochemistry.[5,7] Sumrell[6] showed that the reaction of lower olefins was exothermic in the absence of solvent and was able to utilize the products to make iodohydrins in good yield.

As a result of other investigations in this laboratory it became of interest to look at the "dark" reaction, especially of unsaturated fatty acids. The reversibility of the iodination of olefins suggests itself as a possible mechanism for the biotransport of iodine in living systems. A study was therefore undertaken to follow this reaction using nuclear magnetic resonance as a probe to determine the course and stereochemistry of the reaction.

Results

A variety of unsaturated compounds with emphasis on fatty acids, their esters, and phospholipids were mixed with an equimolar quantity of iodine in an inert solvent in the absence of light and the reaction followed in an nmr instrument. Comparable saturated fatty acids and their derivatives were similarly treated as controls. In addition several related dibromo adducts were also prepared as model compounds whose stereochemistry is well known. Since the original olefinic protons and the newly halogenated ones comprised but a small proportion of the total proton content of the compounds studied, the double-resonance technique was employed to enhance the sensitivity of the nmr measurements and to give accurate chemical shifts. None of the decoupled spectra were corrected for the Bloch–Siegert shift,[11] but it is estimated that the error in the observed chemical shift is less than 0.05 ppm. The results are summarized in Table I.

Table I
Chemical Shift (δ) Data for the Halogenated Ethylenes

Compd	Halogen	Olefin type	X–C–H shift, ppm
4-Octene	Br_2	Trans	4.16
4-Octene	I_2	Trans	4.18
Oleic acid	Br_2	Cis	4.22
Oleic acid	I_2	Cis	4.5, 4.15
Methyl oleate	I_2	Cis	4.5, 4.15
Elaidic acid	Br_2	Trans	4.16
Methyl elaidate	I_2	Trans	4.17
Nervonic acid	Br_2	Cis	4.20
Nervonic acid	I_2	Cis	4.5, 4.18
Methyl nervonate	I_2	Cis	4.5, 4.18
Olive oil	I_2	Cis	4.5
Cottonseed oil	I_2	Cis	4.5
Dioleyl lecithin	I_2	Cis	4.5
Egg lecithin	I_2	Cis	4.5
Beef heart lecithin	I_2	Cis	4.5
	Controls		
Arichidic acid	I_2	Satd	
Behenic acid	I_2	Satd	
Ethyl myristate	I_2	Satd	
Tristearin	I_2	Satd	
Dipalmitoyl lecithin	I_2	Satd	

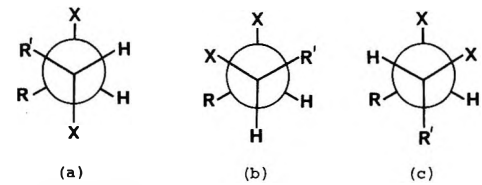

Figure 1. Threo rotamers.

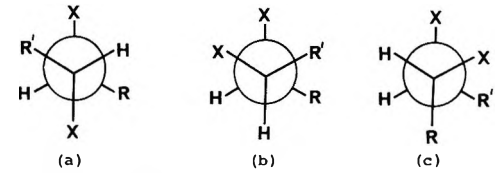

Figure 2. Erythro rotamers.

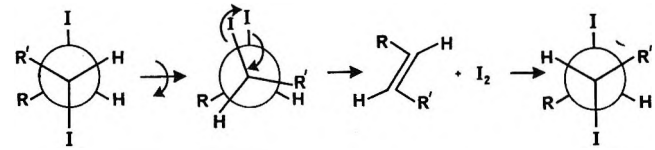

Figure 3. Cis elimination mechanism.

The iodine was allowed to react at 20° with the olefins for periods up to 10 days with periodic spectra of the samples being recorded. All of the olefins showed extensive conversion to their respective diiodides but the trans isomers reacted noticeably slower than the cis isomers. The cis compounds showed immediate formation of diiodide compound with 50% conversion occurring in as little as 60 min. Under these conditions the final conversion to diiodide ranged from 70 to 90% for periods up to 10 days. Loss of solvent prevented measurements of longer duration.

The reaction was followed by the disappearance of the olefin peak (5.4 ppm) and by the simultaneous appearance of a halogenated methine proton (4.1–4.5 ppm). Without decoupling, these bands appeared as weak, diffuse triplets. Since the methylene protons vicinal to both the olefinic and halogenated methine protons have chemical shifts in the 1.7–2.0-ppm range, a single H_2 frequency (1.9 ppm) was sufficient simultaneously to decouple both of the protons being studied. The total integral for the olefinic and methine protons remained constant.

As Table I shows, the iodinated methine proton resulting from the cis isomers gave similar chemical shifts regardless of the compound employed. The trans compounds also gave consistent but different shifts for the methine proton. The saturated compounds showed no changes in their nmr spectra over a period of many days. The dibromo compounds gave similar but smaller differences between the cis and trans adducts.

During the course of the iodination of the cis olefins, an unusual phenomenon occurred. Between the second and third days of the iodination, a second halogenated methine band was observed at higher field than the original band. Between the second and tenth days, this band continued to grow at the expense of both the olefinc and initial methine peaks. Again the total integral of the three peaks remained constant. Eventually, most of the original methine band was lost and the new peak predominated. The chemical shift of this new peak (4.16 ppm) was coincidental with that observed for the iodinated trans olefins and was tentatively assigned as such. A similar interconversion of the *trans*-diiodo compound was not observed.

To verify this apparent isomerization, parallel experiments were run using gas chromatography. A column was found which could separate methyl oleate (cis) from methyl elaidate (trans). The methyl oleate was partially iodinated for several hours and checked by nmr to verify that no rearrangement had occurred. This sample was then analyzed by glc; only one peak was observed, indicating that the diiodo compound was thermally degraded to oleate without rearrangement. Samples of diiodide containing varying amounts of isomeride were then subjected to simultaneous thermal degradation and glc analysis and in every case the nmr ratio of oleate to elaidate was the same by both methods.

Discussion

It is apparent from the chemical shifts of the *cis*- and *trans*-diiodo adducts that the addition must be occurring stereospecifically. That the addition is probably trans is inferred by analogy with bromine[5] and chlorine addition reactions. Anet[12] and Bothner-By[13] used nmr to study the dibromobutanes. They demonstrated that a proton gauche to a methyl group and a bromine atom will resonate at higher field than will a proton gauche to a hydrogen and a bromine. In Figure 1 the relevant conformers for the trans addition product of iodine to a cis olefin are shown. Conformer **1a** probably makes the greatest contribution since in this form the iodines are anti to each other. In this conformer, the methine proton is gauche to a proton and an iodine and the result should be a deshielded proton. That this isomer gives the most deshielded methine proton permits its assignment as the threo compound.

Figure 2 depicts the conformers which would result from the trans addition of iodine to a trans olefin. In this case conformer **2a** fits the observed spectrum best. The chemical shift (at high field) correlates well with those seen for the other dihalides and this conformer is obviously the most stable since it again has the iodine atoms anti to each other as well as the alkyl groups. It then follows that iodination of trans olefins leads to erythro isomers.

In the observed isomerization reaction, the threo diiodo compound is slowly converted into its erythro isomer. Assuming trans addition, the conversion must be occurring via cis elimination followed by a second trans iodination as shown in Figure 3. This trans addition–cis elimination mechanism accounts for the isomerization of cis olefins to

trans olefins. Further support for this mechanism comes from the observation that the olefin isomerization seems to occur only from cis to trans and not the reverse. If conformers **1a** and **2a** (the two most stable for the threo and erythro compounds) are compared, it is apparent that **2a**, the erythro compound, is more stable than **1a**, the threo compound. Thus the isomerization would be most likely to proceed in the direction leading to the more stable compound.

The obvious differences between the "dark" reaction studied here and the light-catalyzed reaction studied by others argues for two fundamentally different mechanisms, namely, ionic and free radical. Although none of the work reported here unambiguously indicates an ionic reaction course, it seems reasonable to so assign it until such time as it can be more definitely established.

As a result of these studies and earlier ones, it now appears that the addition of iodine to double bonds occurs trans regardless of whether the mechanism is free radical or ionic. In the reverse reaction, however, elimination of halogen can occur either trans (free radical) or cis (ionic).

Experimental Section

Materials. *trans*-2-Pentene was prepared by the dehydration of 2-pentanol; the product was fractionated and analyzed by gas chromatography. *trans*-4-Octene (99%) was obtained from the Aldrich Chemical Co. Oleic, nervonic, and elaidic acids were obtained from Applied Science Laboratories, Inc. All other esters were secured from Supelco Inc. All compounds were checked by nmr.

The dibromo adducts were all prepared by the slow addition of a bromine solution (in $CHCl_3$) to the olefins in $CHCl_3$ in the absence of light. The products were solvent stripped to remove the slight excess of bromine and the residues were analyzed by nmr without further purification.

Iodination Reactions. Oleic acid was initially iodinated according to the method of Sumrell, *et al.*[6] All other iodination reactions were carried out in chloroform or deuteriochloroform solutions A Perkin-Elmer R-12 nmr spectrometer equipped with a double-resonance accessory was used for the analyses. Tetramethylsilane (TMS) was used as the internal reference standard from which all chemical shifts were measured.

Gas–Liquid Chromatography. Gas–liquid chromatography was performed using a Packard Model 846 with an 8 ft long glass column packed with 10% SP-2340 on 100 mesh Supelco support. Argon at 25 lb pressure was used as the carrier gas. Temperature programming was carried out from 140 to 180° at 0.5°/hin. Standards obtained from various sources were used to establish the correct retention time for the methyl esters of oleic and elaidic acids. The mixture was dissolved in 5 ml of ether and 5–10 μl was injected directly.

Registry No.—Iodine, 7553-56-2; bromine, 7726-95-6; oleic acid, 112-80-1; methyl oleate, 112-62-9; elaidic acid, 112-79-8; methyl elaidate, 1937-62-8; nervonic acid, 506-37-6; methyl nervonate, 2733-88-2; *trans*-4-octene, 14850-23-8.

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Notes

Analogs of Sparteine. I. A Reexamination of the Reaction of *N*-Methyl-4-piperidone with Formaldehyde and Methylamine. A Revised Synthesis of *N,N'*-Dimethylbispidinone

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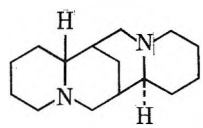
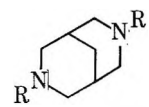
In a study of uterotropic agents related to sparteine (**1**) it was desired to prepare *N,N'*-dimethylbispidine (3,7-dimethyl-3,7-diazabicyclo[3.3.1]nonane) (**2a**). Bispidine (**2b**) had been prepared previously,[3,4] but all attempts to convert it into **2a** produced derivatives of diazadamantane.[5]

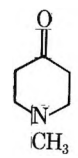


1



2a, R = CH_3
b, R = H

The synthesis of various *N,N'*-dialkylbispidines was reported in 1968.[6] Douglass and Ratliff utilized a double-Mannich condensation of *N*-methyl-4-piperidone (**3**) with methylamine and formaldehyde to give **4**. The amino ketone **4** was subjected to Wolff–Kishner reduction conditions to give **2a**. In this laboratory the published procedure[6] did not give the results described but a mixture of products.



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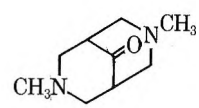
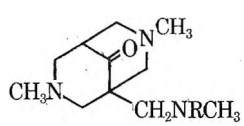
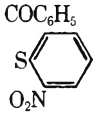


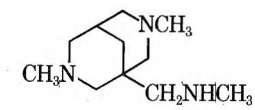
4

The mixture obtained consisted of 58% of **4** and 42% of a by-product which was shown to have the structure **5a**. The product composition was determined by gas–liquid chromatography—mass spectrometry (glc-ms). Distillation, *in vacuo*, of the mixture resulted in the enrichment of **5a** in the distillate (20% **4**, 80% **5a**). This enrichment was not due to conversion of **4** into **5a** during distillation. Complete spectroanalytic characterization of **5a** was made through its benzamide derivative **5b**.



5a, R = H
b, R = COC_6H_5
c, R = 

It was found that separation of **4** and **5a** could best be conducted by conversion of **5a** into **5c** by treatment of the mixture with *o*-nitrophenylsulfenyl chloride.[7] After separation, **5c** could be converted into **5a** by treatment with dry



6

hydrogen chloride. From the Huang-Minlon modified Wolff–Kishner reduction of **5a**, **6** was obtained in low yield.

The conditions of the double-Mannich condensation were altered (see Experimental Section) to give predominantly the desired product **4**, in the absence of **5a**. This amino ketone was readily reduced to **2a** *via* the published procedure.[6]

Experimental Section

General. Analytical glc was performed with a F&M 810 gas chromatograph using dual column flame ionization detection, and with a Varian Aerograph in glc–eims experiments. The carrier gas was helium (55 ml/min) and the detector gases were hydrogen (55 ml/min) and compressed air (250 ml/min). Columns: 6 ft × ⅛ in. stainless steel containing Dowfax 9N9/KOH supported on 80-100x A/W DMCS-treated HP Chrom G. Instrument temperatures: injection port, 210°; oven, 170° isothermal; detector, 225°. Melting points were taken on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were taken on Beckman IR 10 and IR 33 spectrophotometers. Nuclear magnetic resonance spectra were obtained using Varian A-60A and T-60 spectrometers using tetramethylsilane as the internal standard. Electron impact mass spectra (eims) were recorded at 70 eV using Finnegan 1015 and Varian CH 5 spectrometers. Chemical ionization mass spectra (cims) were obtained from the Finnegan instrument using isobutane as the ionizing gas. Elemental analysis were obtained using a F&M 185 CHN analyzer, and from Midwest Microlab, Inc., Indianapolis, Ind.

Synthesis of *N,N'*-Dimethylbispidinone (4) and 1-(*N*-Methylamino)methyl-3,7-dimethyl-3,7-diazabicyclo[3.3.1]nonan-9-one (5a). The initial procedure utilized was that of Douglass and Ratliff.[6] A modification was developed in which the two products were separated by treating 1.0 g of a 1:4 mixture of **4** and **5a** (3.9 mmol of **5a**) with 1.0 g (5.3 mmol) of *o*-nitrophenylsulfenyl chloride in 10 ml of chloroform. After standing at 25° for 18 hr, the solution was poured into 10 ml of water, and the mixture was shaken. The aqueous phase was separated and adjusted to pH 9 with 1.5 ml of 10% aqueous sodium hydroxide and extracted with three successive 20-ml portions of chloroform. The combined dried (sodium sulfate) extracts were filtered and concentrated to give 0.9 g of a red oil, **5c**: nmr ($CDCl_3$) δ 2.30 (s, 6, NCH_3), 3.10 (s, 3, $NHCH_3$), 2.30–3.50 (m, 10, NCH_2 and bridgehead CH), 7.20–8.50 (m, 4, C_6H_5). This was dissolved in 15 ml of chloroform and treated with excess ethereal hydrogen chloride. After stirring for 24 hr at room temperature, the suspension was filtered and washed with ether. The gummy yellow solid was partitioned between 10 ml of cold chloroform and 10 ml of 10% aqueous sodium hydroxide. Concentration of the dried (sodium sulfate) layer gave **5a** as a clear colorless liquid, 0.5 g (60%): bp (bath) 76–78° (0.1 mm); glc >98% purity, retention time 10.25 min; ir (neat) 3.41, 3.62, 5.83 μ (C=O); nmr ($CDCl_3$) δ 2.25 (s, 6, NCH_3), 2.40 (s, 3, $NHCH_3$), 2.50–3.0 (m, 12, remaining protons); eims *m/e* 212 (QM), 210 (M − 1), 193 (B, M − 18).

Anal. Calcd for $C_{11}H_{21}N_3O$: C, 62.52; H, 10.02; N, 19.89. Found: C, 62.48; H, 9.74; N, 19.94.

The pH 9 aqueous phase, after removal of **5c** by chloroform extraction was made strongly basic by addition of 10% aqueous sodium hydroxide and extracted with four 10-ml portions of cold chloroform. The combined extracts were dried (sodium sulfate), filtered, and concentrated to give 0.1 g (59%) of **4** as a colorless oil which solidified on cooling: bp (bath) 130–135° (0.25 mm); mp 51–52°; glc >98% purity, retention time 4.25 min; nmr ($CDCl_3$) δ 2.35 (s, 6, NCH_3), 2.10–3.20 (m, 10, remaining protons); eims *m/e* 168 (M), 58 (B). Treatment of an ethereal solution of **4** with an equivalent amount of aqueous ethanolic perchloric acid gave the

monoperchlorate salt as white needles from ethanol, mp 218–220° dec.

Anal. Calcd for $C_9H_{17}ClN_2O_5$: C, 40.23; H, 6.38; N, 10.42. Found: C, 39.92; H, 6.42; N, 10.08.

1-(*N*-Methylbenzamido)methyl-3,7-dimethyl-3,7-diazabicyclo[3.3.1]nonan-9-one (5b). To an enriched mixture of **5a** (1.33 g, 6.3 mmol) in 10 ml of chloroform was added 1.4 g (10 mmol) of benzoyl chloride. After stirring for 4 hr at room temperature, the solution was poured into 10 ml of water. The chloroform was separated and discarded. The aqueous phase was washed once with 10 ml of chloroform. The aqueous layer was adjusted to pH 12 with 10% aqueous sodium hydroxide and extracted with two 15-ml portions of chloroform. The combined, dried (sodium sulfate), and filtered extracts were concentrated *in vacuo* leaving a yellow oil. This was dissolved in ether and treated with excess aqueous ethanolic perchloric acid. The dried precipitate was triturated with 5 ml of water, filtered, and washed with water to give the monoperchlorate of **5b** as a white solid, 0.5 g (50%): mp 224–226° dec; ir (KBr) 3.18 (w, C_6H_5), 5.78 (s, C=O), 6.14 (s, N-C=O), 9.26 μ (s, ClO_4^-).

Anal. Calcd for $C_{18}H_{26}N_3O_6Cl$: C, 51.98; H, 6.30; N, 10.10. Found: C, 52.24; H, 6.30; N, 9.89.

The monoperchlorate salt (149 mg, 0.36 mmol) was partitioned between 5 ml of 10% aqueous sodium hydroxide and 6 ml of chloroform. The combined, dried extracts were filtered and concentrated *in vacuo* to give 110 mg of a colorless, semicrystalline oil: nmr (CCl_4) δ 2.30 (s, 6, amine NCH_3), 3.05 (s, 3, amide NCH_3), 3.60 (s, 2, amide NCH_2), 7.35 (s, 5, aromatic), 2.30–3.30 (m, 8, amine NCH_2 and bridgehead CH); eims *m/e* 315 (M), 58 (B).

1-(*N*-Methylamino)methyl-3,7-dimethyl-3,7-diazabicyclo-[3.3.1]nonane (6). Crude amino ketone **5a** (4 g) was reduced by the literature procedure.[6] The distillate that collected was saturated with sodium chloride and extracted with 25 ml of ether; the ether extracts contained 50 mg of **4**: nmr (identical with the published spectrum[6]); eims *m/e* 154 (M), 58 (B). Amino ketone **6** was recovered from the reaction solution by steam distillation as a white solid (0.85 g, 25%): mp 45–46°; ir (neat) 3.41 (s), 3.61 (s), 6.90, 6.99, 7.94 μ; nmr (C_6H_6) δ 1.30 (d, J = 3 Hz, 2, CH_2 bridge), 1.80 (m, 1, bridgehead CH), 2.20 (s, 6, NCH_3), 2.30 (s, 3, $NHCH_3$), 2.10–2.70 (m, 10, NCH_2); eims *m/e* 197 (M), 58 (B). The base was converted into the diperchlorate by treatment with excess perchloric acid. It crystallized from ethanol as white needles, mp 227–230° dec.

Anal. Calcd for $C_{11}H_{25}Cl_2N_3O_8$: C, 33.18; H, 6.33; Cl, 17.81; N, 10.55. Found: C, 33.32; H, 6.63; Cl, 18.00; N, 10.82.

Revised Synthesis of *N,N'*-Dimethylbispidinone (4). In a 2000-ml round-bottomed flask were placed 44.3 g of paraformaldehyde, 18.7 g (0.2 mol) of methylamine acetate, and 1000 ml of methanol. To this magnetically stirred suspension was added a solution of 36 g (0.2 mol) of *N*-methyl-4-piperidone acetate in 100 ml of methanol in increments over a period of 14 days. The paraformaldehyde slowly dissolved during this time. After completion of addition, the solution was stirred at room temperature for an additional 32 days. Then the solvent was removed *in vacuo*, and the residual oil, dissolved in 150 ml of water, was extracted twice with 75-ml portions of chloroform. These extracts were discarded. To the aqueous phase was cautiously added 20 g of anhydrous sodium carbonate. The resulting suspension was filtered and extracted with five successive 200-ml portions of chloroform. The pH of the aqueous phase was maintained at 8.5–9.0 with 10% aqueous sodium carbonate. The chloroform extracts, containing starting materials and polymeric products, were discarded. The aqueous phase was concentrated at an oil pump to a volume of 50 ml, filtered, and made strongly alkaline with 10% aqueous sodium hydroxide. This suspension was extracted with five successive 90-ml portions of chloroform. Work-up of the combined extracts left 24.7 g of an amber oil. Distillation of this crude product gave 6.82 g (10%) of 4 which crystallized upon cooling; analytical data were identical with those of the extraction-purified sample (see above).

Registry No.—**3** acetate, 53210-06-3; **4**, 14789-54-9; **4** $HClO_4$, 53210-07-4; **5a**, 53210-08-5; **5b**, 53210-09-6; **5b** $HClO_4$, 53210-10-9; **5c**, 53210-11-0; **6**, 53230-02-7; **6** $2HClO_4$, 53230-03-8; *o*-nitrophenylsulfinyl chloride, 7669-54-7; methylamine acetate, 6998-30-7.

References and Notes

(1) Deceased July 14, 1974.
(2) NIH predoctoral trainee, University of Kansas, 1971–1974. Correspondence should be addressed to School of Pharmacy, University of Georgia, Athens, Ga. 30602.
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2-(2-Imidazolyl)acetophenones. Preparation and Some Reactions

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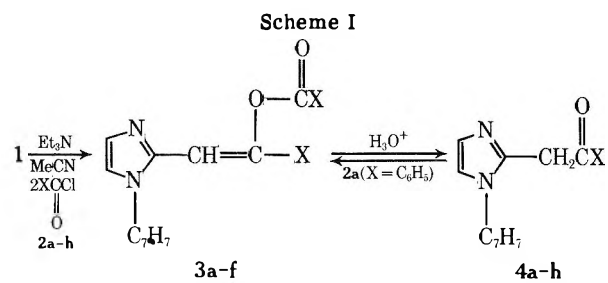
Imidazoles, in their behavior with acid chlorides, can be made to react in a number of ways. In the absence of N substituents, benzoylation[1] and acetylation[2] in inert solvents give rise to N-substituted derivatives. Imidazole with benzoyl chloride (BzCl) in aqueous alkali, instead, initially provides a 1,3-dibenzoyl cation which then suffers hydrolytic ring cleavage to give 1,2-dibenzoylaminoethylene.[3] N-Substituted imidazoles have also been shown to react with BzCl; on conducting the reaction in Et_3N-containing acetonitrile, 2-benzoyl derivatives are obtained.[4]

Interest in the electrophilic substitution pattern of 1,2-disubstituted imidazoles[5] prompted a study of the behavior of 1-benzyl-2-methylimidazole (**1**) with various benzoyl chlorides.[6] This showed that **1** with 2 equiv of various benzoyl chlorides in Et_3N-containing acetonitrile gave enol esters **3a–e** in essentially quantitative yield. Subsequent acid hydrolysis then provided 2-(2-imidazolyl)acetophenones **4a–e** (Scheme I). The present paper demonstrates the generality of the method.

Scheme I



3a–f **4a–h**

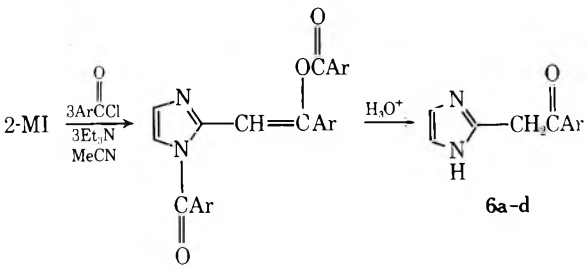
X: **a**, C_6H_5; **b**, *p*-$CH_3OC_6H_4$; **c**, *p*-$CH_3C_6H_4$; **d**, *p*-ClC_6H_4; **e**, *p*-$O_2NC_6H_4$; **f**, $(CH_3)_3C$; **g**, Cl_3C; **h**, C_2H_5O

Formation of **3a–e** is surprising since, to our knowledge, a nonactivated 2-methyl group on a 1,2-disubstituted imidazole is reluctant to partake in electrophilic processes. 1,2-Dimethylimidazole, for example, undergoes hydroxymethylation at C-5 exclusively;[5] lithiation, previously reported to proceed solely at C-5,[7] has recently been shown to occur at both C-5 and at the C-2 methyl.[8] In the case at hand, formation of **3a–e** is to be ascribed to an irreversible O-aroylation of anionic intermediates serving to displace all prior equilibria in favor of a final conjugated system. O-Aroylation stems, *i.e.*, from minimal anion solvation in the polar, aprotic acetonitrile, a view consistent with the observation that **4a** with BzCl under the reaction conditions provides **3a**.

In the present work, the reactions of **1** with some acyl chlorides were examined. Acetyl chloride, under the reaction conditions, formed intractable product mixtures.

When lacking α hydrogens, acyl chlorides such as pivaloyl- and trichloroacetyl chloride (**2f,g**) and also ethyl chloroformate (**2h**) behaved as their aromatic counterparts. Compound **4f** resulted from acid treatment of **3f;** however, **4g** and **4h** were obtained directly from **1a.** The fact that optimal yields of **4h** required the use of at least 2 equiv of chloroformate ester leads us to suspect the intermediacy of enol esters which, being highly reactive, would be destroyed during the aqueous work-up.

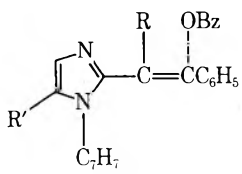
In a related study, treatment of 2-methylimidazole (2-MI) with 3 equiv each of aroyl chloride and Et_3N gave N-substituted enol esters **5a–d;** subsequent hydrolysis then gave the corresponding Imidazolylacetophenones **6a–d.**



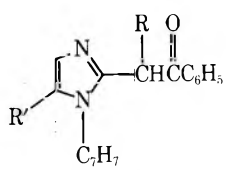
5a–d

(a. Ar = C_6H_5; b, Ar = p-$CH_3OC_6H_4$; c, Ar = p-$CH_3C_6H_4$; d, Ar = p-$O_2NC_6H_4$)

Methyl groups located at C-5 of an N-substituted imidazole do not respond to this benzoylation technique. For example, given two alternatives, BzCl reacted with the 2- rather than the 5-methyl substituent of 1-benzyl-2,5-dimethylimidazole[2] (**7b**) and gave enol ester **8a.** 1-Benzyl-5-methylimidazole[2] (**7a**), lacking a 2 substituent, underwent benzoylation at C-2 to yield 2-(1-benzyl-5-methylimidazolyl) phenyl ketone (**10**) in direct analogy with literature reports.[4] Higher homologs of **1a,** *i.e.,* 1-benzyl-2-ethylimidazole[5] (**7c**) and 1-benzyl-2-isopropylimidazole[5] (**7d**), were also examined. These experiments were suggested by our earlier results[5] which showed that the rate of hydroxymethylation at C-5 was enhanced by the presence of electron-donating groups at C-2. On going from 2-Me to 2-*i*-Pr, one would expect benzoylation to start occurring at C-5. This was not the case; BzCl with **7c** gave **8b** albeit in diminished yield, while **7d** failed to react altogether. Hydrolysis of **8a** and **8b** provided **9a** and **9b,** respectively.

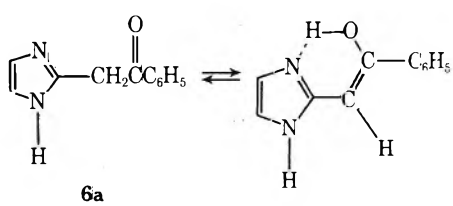


8a, 8b



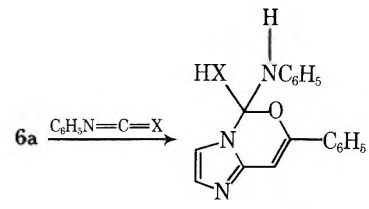
9a, R = H; R′ = CH_3
b, R = CH_3; R′ = H

The phenacylimidazoles as free bases exist as keto–enol mixtures. For the case of **4a** the enol content amounted to *ca.* 40% as arrived at by total integration of nmr signals at δ 4.42 ($CH_2C{=}O$) and 6.05 (HC=COH). Ir data for **6a** showed, in addition to a C=O band at 1680 cm^{-1}, also significant OH absorption. The possibility offered by intramolecular N···H···O bonding undoubtedly promotes enolization.



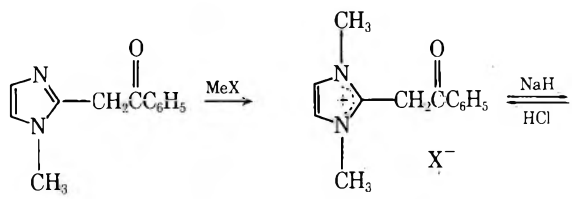
6a

The partial enolic character of **6a** is reflected in some of its reactions. On treatment with phenyl isocyanate and isothiocyanate, for example, 1:1 adducts were obtained; these, lacking C=O absorptions, were assigned structures **11a** and **11b.**

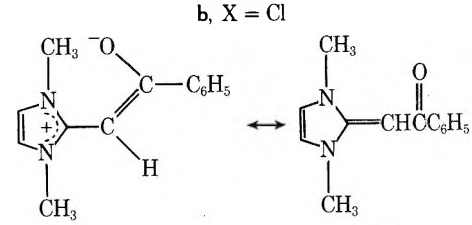


11a, X = O
b, X = S

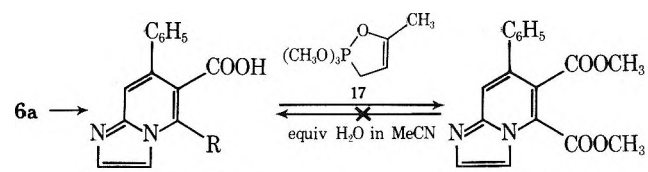
Zwitterions result on anionizing quaternary salts related to **4a.** Considerations of symmetry made us examine **13a,** which was prepared by treatment of **12**[6] with MeI. On addition of NaH to a THF solution of the cation, H_2 was evolved and a strongly basic, water-soluble, and relatively high-melting solid resulted. Ir inspection indicated no C=O absorption, while nmr considerations (equivalency of the imidazolyl protons and Me groups) showed the molecule to be symmetrical. These data all point to betaine **14** and minimize the contribution of ketene–aminal hybrid **15.** Protonation of **14** in alcoholic HCl regenerated quaternary salt **13b,** which was spectrally (ir and nmr) identical with **13a.**



12 **13a**, X = I
b, X = Cl

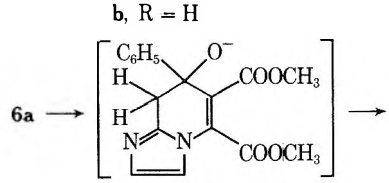


14 **15**

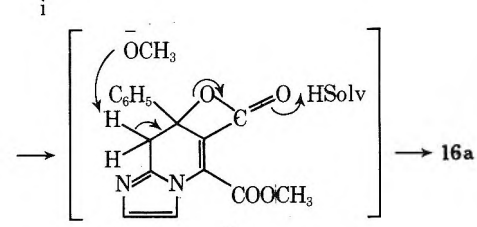


16a, R = $COOCH_3$
b, R = H

18



i



ii

Dimethyl acetylenedicarboxylate in MeOH or MeCN reacted with **6a** to give imidazo[1,2-*a*]pyridine **16a** (70 and 40%, respectively). The location of the COOH and $COOCH_3$ functions at C-5 and C-6, respectively, is based on the following. Esterification of **16a** with oxaphospholene **17**[9] gave diester **18**. The action thereon of 1 equiv of H_2O under the reaction conditions failed to regenerate **16a**, thus eliminating **18** from the reaction path leading to **16a**. Mechanistically, the key transition state in this transformation, namely i, resembles the one envisaged in Stobbe condensations,[10] in which monoesters of dicarboxylic acids are ultimately produced via γ-lactones. Whereas in the case at hand, γ-lactone formation is sterically unfavorable, a β-lactone such as ii is quite feasible. Subsequent CH_2O^--induced proton abstraction, facilitated by formation of an aromatic 10-π-electron system, then completes the process. A comparable rationale accounts for formation of **16b** from **6a** and ethyl propiolate.

Experimental Section

General. Melting points were determined on a Fisher-John block and are uncorrected. Nmr spectra (Varian A-60, TMS as internal standard) and ir data (Perkin-Elmer 337) were consistent with assigned structures. All enol esters and their hydrolysis products are listed in Tables I and II. The preparation of compounds serving as prototypes in these studies is given in detail.

Compound 3a. To a solution of 5.2 g (0.03 mol) of **1** in 30 ml of MeCN containing 6.7 g (0.066 mol) of Et_3N was added dropwise and below 10° 9.2 g (0.066 mol) of BzCl. After 2 hr at room temp, dilution with 100 ml of Et_2O and 300 ml of H_2O gave, on filtration, 11.2 g (98%) of **3a**: mp (C_6H_6) 144–146°; ir (KBr) 1730 cm^{-1} (C=O), 1660 cm^{-1} (C=C), 1240 cm^{-1} (C–O–C); nmr ($CDCl_3$) δ 8.40–8.15 (m, 2, arom H), 7.70–6.80 (m, 15, arom H), 6.67 (s, 1, CH=C), 5.17 (s, 2, $CH_2C_6H_5$).

2-{2-(1-Benzylimidazolyl)}acetophenone (4a). A solution of 2 g of **3a** in 20 ml of 3 *N* HCl was refluxed for 30 min. The solution was rendered basic, giving an oily product which was taken up in C_6H_6. Drying and evaporation of the organic phase gave crude **4a**; it was converted to the hydrochloride salt by treatment with *i*-PrOH/HCl. Yield: 1.1 g, which was recrystallized from *i*-PrOH–Et_2O to melt at 203–204°.

The free base, a yellow oil, had bp 190° (0.1 mm), which *slowly* solidified on standing to melt at *ca.* 70°.

Compound 5a. Gradual treatment of 36 g (0.45 mol) of 2-methylimidazole with 210 g (1.5 mol) of BzCl and 150 g (1.50 mol) of Et_3N in 500 ml of MeCN under conditions offered for **3a** gave 150 g (85%) of product: mp (C_6H_6) 172–173°; ir (KBr) 1710 cm^{-1} (ImC=O), 1740 cm^{-1} (C=C–O–C=O).

2-(2-Imidazolyl)acetophenone (6a). Compound **5a**, 60 g (0.152 mol), was held at reflux for 1 hr in 300 ml of a 2:1 mixture of HOAc:concentrated HCl. Solvent was then removed and was replaced by H_2O from which the BzOH was removed by scrubbing with C_6H_6. Introduction of $NaHCO_3$ to the aqueous phase admixed with *i*-Pr_2O gave, on prolonged stirring, slowly crystallizing tan **6a**: yield 77%; mp 112–114°; ir (KBr) 1680 cm^{-1} (C=O). The HCl salt, recrystallized from EtOH–Et_2O, had mp 252–253°.

2-(1-Benzyl-5-methylimidazolyl) Phenyl Ketone (10). The reaction of 5.2 g (0.03 mol) of 1-benzyl-5-methylimidazole[2] with 9.3 g (0.066 mol) of BzCl and 6.6 g (0.066 mol) of Et_3N in 30 ml of MeCN under conditions and work-up as offered for **3a** gave 6.7 g (81%) of **10**: mp (EtOH) 118–119°; ir (KBr) 1630 cm^{-1} (C=O); nmr ($CDCl_3$) δ 2.12 (d, 3, Im-5CH_3).

Anal. Calcd for $C_{18}H_{16}N_2O$: C, 78.24; H, 5.84; N, 10.14. Found: C, 78.36; H, 5.82; N, 10.13.

The Reactions of 6a with Phenyl Isocyanate and Isothiocyanate. Compounds 11a and 11b. A solution of 1.86 g (0.01 mol) of **6a** and 1.2 g (0.01 mol) of C_6H_5NCO in 15 ml of THF was refluxed for 2 hr during which time **11a** started separating out. On filtration and recrystallization from aqueous DMF, it melted at 182–183°: yield 2.9 g (90%); ir (KBr) 3300–2300 cm^{-1} (NH, OH, C_6H_5), no carbonyl absorptions.

Anal. Calcd for $C_{18}H_{15}N_3O_2$: C, 70.81; H, 4.95; N, 13.76. Found: C, 70.56; H, 5.10; N, 13.75.

In a related reaction, treatment of equimolar amounts of **6a** and C_6H_5NCS in refluxing MeCN for 2 hr gave 67% yield of **11b**: mp (*i*-PrOH) 161–163°; ir (KBr) 3300–2300 cm^{-1} (NH, SH, C_6H_5), no carbonyl absorptions.

Table I
Enol Esters 3f, 5a–d, and 8a,b[a]

Compd	Yield,[b] %	Mp, °C	Formula[c]
3f	58	124–126	$C_{21}H_{28}N_2O_2$
5a	85	172–173	$C_{25}H_{18}N_2O_3$
5b	80	177–178	$C_{28}H_{24}N_2O_6$
5c	68	197–198	$C_{28}H_{24}N_2O_3$
5d	95	223–224	$C_{25}H_{15}N_5O_9$
8a	61	151–152	$C_{26}H_{22}N_2O_2$
8b	67	125–126	$C_{26}H_{22}N_2O_2$

[a] For physical data of enol esters 3a–e see table in ref 6. [b] Yields based on product melting within a few degrees of analytical material. [c] Satisfactory analytical data (±0.4% for C, H, N) were reported for all compounds in this table.

Table II
Hydrolysis Products Derived from Esters (Table I)[a]

Compd	Yield, %	Mp, °C	Formula[b]
4f	74	54–55	$C_{16}H_{20}N_2O$
4g[c]	84	147 dec	$C_{13}H_{11}Cl_3N_2O$
4h[c]	47	176–177	$C_{14}H_{16}N_2O_2 \cdot HCl$
6a	83	252–253	$C_{11}H_{10}N_2O \cdot HCl$
6b	65	255–258	$C_{12}H_{12}N_2O_2 \cdot HCl$
6c	69	268–270	$C_{12}H_{12}N_2O \cdot HCl$
6d	76	233–237	$C_{11}H_9N_3O_3 \cdot HCl$
9a	70	207–209	$C_{19}H_{18}N_2O \cdot HCl$
9b	95	108–109	$C_{19}H_{18}N_2O$

[a] For physical data of compounds 4a–e see ref 6. [b] Satisfactory analytical data (±0.4% for C, H, N) were reported for all compounds in this table. [c] Obtained directly from **1** and **2g** and **2h**, respectively, under conditions identical with those given for **3a** (see Experimental Section).

Anal. Calcd for $C_{18}H_{15}N_3OS$: C, 67.27; H, 4.70; N, 13.07. Found: C, 67.04; H, 4.76; N, 12.93.

Compound 13a. A solution of 20 g (0.10 mol) of **12**[6] in 75 ml of MeCN was treated cautiously at 30° with 18 g (0.13 mol) of MeI. The insoluble quaternary salt, 28.3 g (80%), was isolated after 24 hr: mp (MeOH) 240–241°; ir (KBr) 1685 cm^{-1} (C=O); nmr ($CDCl_3$) δ 7.88 (s, 2, Im 4- and 5-H), 5.57 (s, 2, CH_2), 3.98 (s, 6, Im 1- and 3-CH_3).

Anal. Calcd for $C_{13}H_{15}N_2OI$: C, 45.63; H, 4.42; N, 8.19. Found: C, 45.97; H, 4.41; N, 8.22.

Betaine 14. To 100 ml of a THF solution containing 1.75 g (0.06 mol) of 80% NaH in oil was added portionwise and with stirring 20 g (0.059 mol) of **13a** over a period of 0.5 hr. Stirring was continued until H_2 evolution ceased whereupon solvent was removed and replaced with 400 ml of $CHCl_3$. On removal of the insolubles the filtrate was again taken to dryness. C_6H_6 was then added to give, on stirring, solid **14**. This was isolated by filtration, giving on trituration with Me_2CO 8.3 g (66%) of betaine: mp of analytical sample (MeCN) 180–181°; nmr ($CDCl_3$) δ 8.09–7.80 (m, 2, 2 aromatic o-H), 7.53–7.25 (m, 3, 3 aromatic H), 6.79 (s, 2, Im 4- and 5-H), 5.10 (s, 1, C=CH), 3.57 (s, 6, Im 1- and 3-CH_3); ir (KBr) no carbonyl absorption.

Anal. Calcd for $C_{13}H_{14}N_2O$: C, 72.87; H, 6.59; N, 13.07. Found: C, 73.02; H, 6.52; N, 13.02.

Compound 16a. A solution of 1.86 g (0.01 mol) of **6a** in 15 ml of MeOH was treated with 1.4 g (0.01 mol) of dimethyl acetylenedicarboxylate. The temperature rose to 47° as yellow product was deposited. The material was collected by filtration after 24 hr, giving 2.05 g (70%) of fluffy needles: mp (aqueous MeOH) 227–228°; ir (KBr) 1670 (COOH), 1740 cm^{-1} (COOMe); nmr ($CDCl_3$) δ 8.1–7.2 (m, 7, aromatic H), 6.4 (s, 1, C 8-H), 3.2 (s, 3, CH_3).

Anal. Calcd for $C_{16}H_{12}N_2O_4$: C, 64.86; H, 4.08; N, 9.46. Found: C, 65.01; H, 4.15; N, 9.68.

Esterification of 16a to 18. One gram (0.052 mol) of oxaphospholene **17**[9] was introduced dropwise and with cooling into a suspension of 1.5 g (0.05 mol) of **16a** in 20 ml of CH_2Cl_2; after 1 hr the clear solution was scrubbed with H_2O, 10% $NaHCO_3$, and H_2O, respectively, to leave, on drying and evaporation, 1.55 g (95%) of

diester 18: mp (C_6H_6–petroleum ether) 181–182°; ir (KBr) 1710 cm^{-1} (COOMe); nmr ($CDCl_3$) δ 4.55 (s, 3, CH_3), 4.40 (s, 3, CH_3).

Anal. Calcd for $C_{17}H_{14}N_2O_4$: C, 65.80; H, 4.55; N, 9.03. Found: C, 65.85; H, 4.76; N, 9.06.

Compound 16b. Under conditions corresponding to those offered for **16a**, equivalent amounts of **6a** and ethyl propiolate provided 0.6 g (25%) of acid **16b**: mp (aqueous EtOH) 233–234°; ir (KBr) 1660 cm^{-1} (COOH).

Anal. Calcd for $C_{14}H_{10}N_2O_2$: C, 70.38; H, 4.23; N, 11.76. Found: C, 70.59; H, 4.44; N, 11.84.

Acknowledgment. The authors extend their thanks to Messrs. P. van den Bosch and H. Eding for microanalytical results, to Dr. J. W. de Haan for most helpful interpretations of spectral data, and to Mr. H. J. J. Loozen for stimulating discussions during the course of this work. We gratefully acknowledge the BASF, Ludwigshafen, West Germany, for generous gifts of starting imidazoles used in this work.

Registry No.—**1**, 13750-62-4; **2a**, 98-88-4; **2g**, 76-02-8; **2h**, 541-41-3; **3a**, 52083-14-4; **3f**, 52855-65-9; **4a**, 52083-19-9; **4a** HCl, 52855-66-0; **4f**, 52855-67-1; **4g**, 52855-68-2; **4h** HCl, 52855-69-3; **5a**, 52855-70-6; **5b**, 52855-71-7; **5c**, 52855-72-8; **5d**, 52855-73-9; **6a**, 52855-74-0; **6a** HCl, 52855-75-1; **6b** HCl, 52855-76-2; **6c** HCl, 52855-77-3; **6d** HCl, 52855-78-4; **7a**, 52726-21-3; **7b**, 52726-27-9; **7c**, 39269-64-2; **8a**, 52855-81-9; **8b**, 52855-84-2; **9a HCl**, 52855-82-0; **9b**, 52855-85-3; **10**, 52855-83-1; **11a**, 52855-79-5; **11b**, 52855-80-8; **12**, 52083-24-6; **13a**, 52855-86-4; **14**, 52855-87-5; **16a**, 52855-88-6; **16b**, 52855-90-0; **17**, 26192-22-3; **18**, 52855-89-7; 2-methylimidazole, 693-98-1; phenyl isocyanate, 103-71-9; phenyl isothiocyanate, 103-72-0; dimethyl acetylenedicarboxylate, 762-42-5; ethyl propiolate, 623-47-2; *p*-methoxybenzoyl chloride, 100-07-2; *p*-methylbenzoyl chloride, 874-60-2; *p*-nitrobenzoyl chloride, 122-04-3.

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Allylic Rearrangement of 17α-Vinyl-17β-hydroxy Steroids

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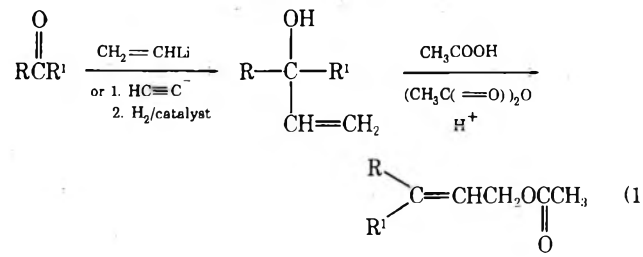
It is well known that generation of a cationic center at C-17 in steroids can promote the 1,2 shift of the C-18 methyl group (the Kägi–Miescher rearrangement).[1] For example, Morrow, Culbertson, and Hofer reported[2] 17-methyl-18-nor-17α-pregna-5,13,20-trien-3β-ol (**1a**) as a by-product of the acid-catalyzed isomerization of 17α-pregna-5,20-diene-3β,17-diol (**4a**). This same group also reported[2] that the direct acid-catalyzed conversion of the latter compound (**4a**) to pregna-5,17(20)-diene-3β,21-diol (**5a**) proceeded erratically (with generally 8–15% yield). They demonstrated, however, that allylic rearrangement of 17α-pregna-5,20-diene-3β,17-diol 3-acetate (**4b**) using thionyl chloride in an ether–pyridine mixture, followed by treatment of the rearranged chloride **6b** with potassium acetate (and subsequent saponification) was a good alternative to the direct one-step acid-catalyzed process.

In an effort to facilitate allylic rearrangements of the type cited above and avoid the unnecessary formation of an intermediate allylic halide (*e.g.*, **6** and **11**), we decided to examine the behavior of 17α-vinyl-17β-hydroxy steroids in a mixture of acetic acid–acetic anhydride containing a strong acid catalyst. Earlier we had reported[3] such reaction conditions as the key step in a method for the bishomologation of simple ketones to functionalized trisubstituted olefins (eq 1).



(1)

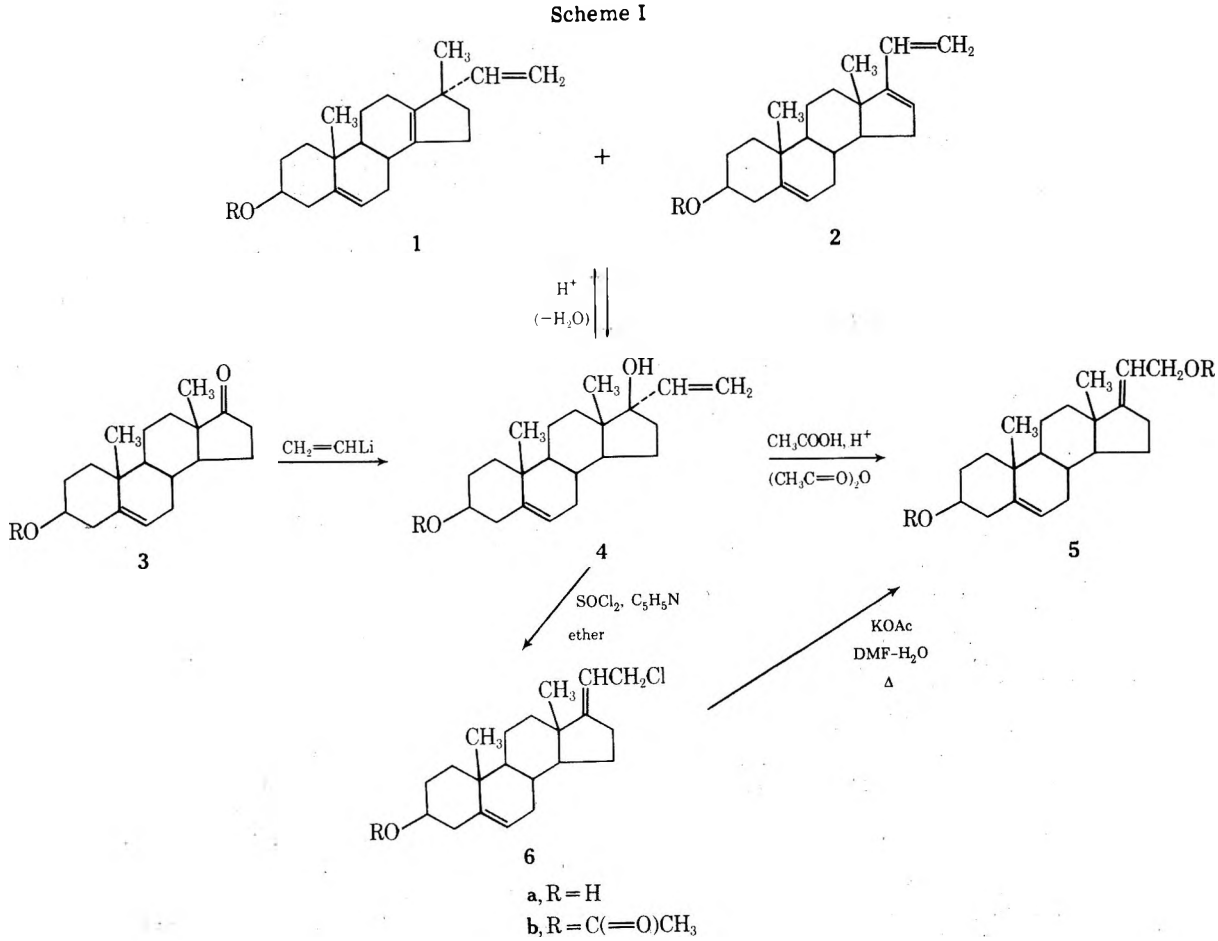
The first system we examined was 3-methoxy-19-nor-17α-pregna-1,3,5(10), 20-tetraen-17-ol (**8**), obtained in 97% yield by the addition of vinyllithium to estrone methyl ether (**7**). Subsequent acid-catalyzed rearrangement of alcohol **8** in a mixture of acetic acid and acetic anhydride proceeded smoothly, affording 3-methoxy-19-norpregna-1,3,5(10),17(20)-tetraen-21-ol acetate (**9**) in approximately 65% yield after purification *via* column chromatography. The identity of this rearranged allylic acetate (**9**) was confirmed by nmr analysis as well as comparison of its melting point and infrared spectrum with the corresponding physical properties previously reported[4] for this same compound, which had been synthesized from the corresponding bromide (**11**) as outlined in Scheme II. The only other component in our crude rearrangement product was a relatively nonpolar substance, subsequently shown by nmr analysis to be a mixture of aromatic ethers.

To further demonstrate the utility of our rearrangement conditions, we used as our next substrate 17α-pregna-5,20-diene-3β,17-diol (**4a**), prepared in approximately 80% yield by the addition of vinyllithium to dehydroisoandrosterone acetate (**3b**). As expected, the rearrangement afforded pregna-5,17(20)-diene-3β,21-diol diacetate (**5b**) in >60% yield after purification *via* column chromatography. As in the previous system examined, a mixture of at least two unsaturated compounds (determined by the vinyl patterns observed on its nmr spectrum) was formed during the reaction. Since the rearrangement we report proceeded in high yield to afford the desired allylic acetates (**5b** and **9**) and the elimination by-products failed to separate on silica gel tlc, we made no further effort to characterize them.

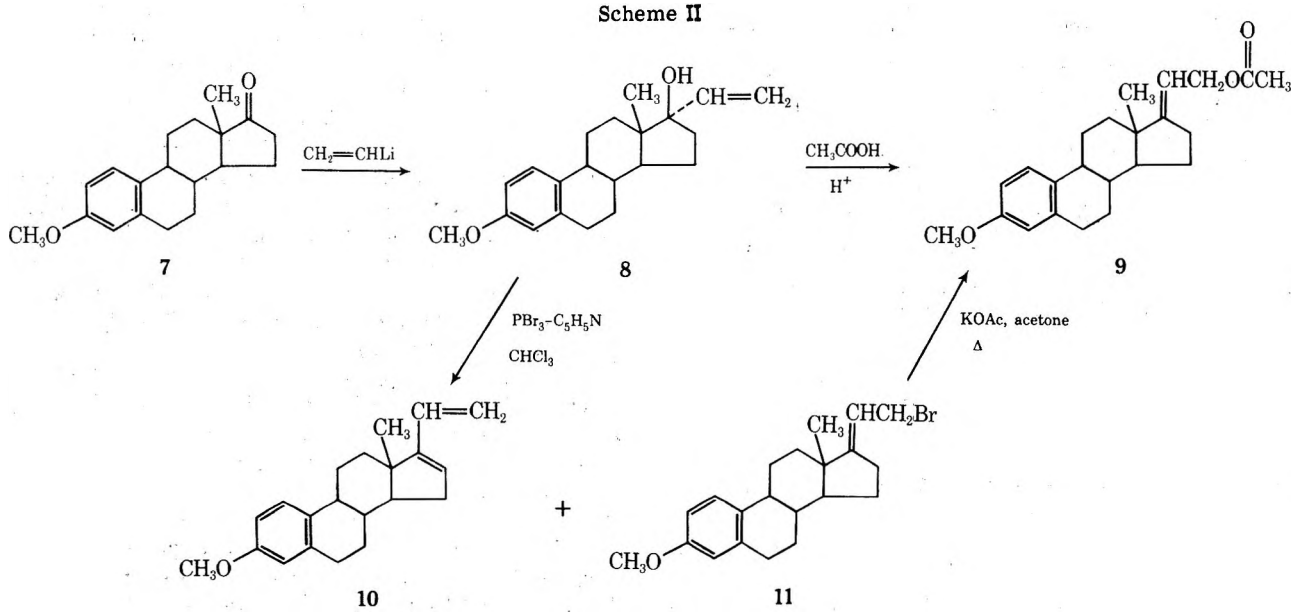
Experimental Section[5]

3-Methoxy-19-nor-17α-pregna-1,3,5(10),20-tetraen-17-ol (8). Treatment of a solution of 702 mg (2.47 mmol) of 3-methoxyestra-1,3,5(10)-trien-17-one (**7**) in 15 ml of anhydrous tetrahydrofuran with 3.0 ml of 2.5 *M* vinyllithium–tetrahydrofuran solution[6] at room temperature for 30 min, using experimental conditions similar to those described for the preparation of diol **4a**, afforded crude alcohol **8** contaminated by hydrocarbon impurities evidently present in the vinyllithium reagent. The product was purified *via* chromatography on 50 ml of Florisil (60–100 mesh). Elution with hexane–25% ether afforded 746 mg (97%) of crystalline alcohol **8**: mp 110–112° (lit.[4] mp 114–115°); λ_{max} (KBr) 3560, 3495, 1617, 1508, 1255, 1142, 1025, 930 and 910 cm^{-1}; δ_{TMS} ($CDCl_3$) 6.42–5.07

Scheme I



Scheme II



(complex pattern, three vinyl H's, peaks at 6.42, 6.26, 6.13, 5.97, 5.39, 5.37, 5.28, 5.26, 5.11, 5.07), 3.81 (OCH_3), 3.52 (OH), 0.95 ppm ($18\text{-}CH_3$).

3-Methoxy-19-norpregna-1,3,5(10),17(20)-tetraen-21-ol Acetate (9). To a solution of 190 mg (0.61 mmol) of tertiary vinylcarbinol 8 in 15.0 ml of glacial acetic acid and 3.0 ml of acetic anhydride was added 189 mg of *p*-toluenesulfonic acid monohydrate. After stirring this mixture at room temperature for 3 hr, the reaction was quenched by pouring it into 300 ml of saturated aqueous sodium bicarbonate solution and shaking this mixture vigorously until carbon dioxide evolution had ceased. Extraction with ether afforded 220 mg of crude product, which was subsequently chromatographed on 25 ml of silica gel. Elution with hexane–5% ether afforded 70 mg of an oil, homogeneous on silica gel tlc. The nmr spectrum indicated the presence of two aromatic methyl ethers in a ratio of 2.5:1, both of which exhibited a vinyl pattern: δ_{TMS} (CCl_4) 1.13 ($18\text{-}CH_3$, major component), 0.93 ppm ($18\text{-}CH_3$, minor component).

Elution with hexane–10% ether afforded 136 mg (63%) of allylic acetate 9 as a viscous oil, homogeneous on silica gel tlc and pure by nmr analysis: δ_{TMS} ($CDCl_3$) 4.51 (d, J = 7.0 Hz, $CH_2O\text{-}C(=O)CH_3$), 3.73 (OCH_3), 1.99 ($OCOCH_3$), 0.82 ppm ($18\text{-}CH_3$). Crystalline acetate 9 was obtained by dissolving the chromatographed material in warm methanol and chilling this mixture: mp 59–60° (lit.[4] mp 67–68°).

17α-Pregna-5,20-diene-3β,17-diol (4a). Vinyllithium–tetrahydrofuran solution[6] (6.0 ml, 2.5 *M*) was added dropwise rapidly to a solution of 912 mg (2.76 mmol) of 3β-acetoxyandrost-5-en-17-one

(**3b**) in 20 ml of 1:1 anhydrous tetrahydrofuran–ethyl ether cooled to 10° in a water bath. After stirring this mixture at room temperature for 4 hr, the reaction was quenched by slow dropwise addition of water. The mixture was subsequently diluted with 200 ml of water, and the product was isolated by extraction with ether. Recrystallization from benzene, which effected removal of hydrocarbon polymers evidently present in the vinyllithium reagent, afforded 690 mg (78%) of crystalline diol **4a**: mp 181–183° (lit.[7] mp 184.5–186°); λ_{max} (KBr) 3280, 1053, 1028, 917 cm^{-1}; δ_{TMS} (CD_3COOD) 6.36–5.03 (complex pattern, 4 vinyl H's, peaks at 6.36, 6.19, 6.06, 5.90, 5.43, 5.33, 5.23, 5.06, and 5.03), 1.04 (19-CH_3), 0.94 ppm (18-CH_3).

Pregna-5,17(20)-diene-3β,21-diol Diacetate (5b). Treatment of 329 mg (1.04 mmol) of tertiary vinylcarbinol **4a** under the same conditions as described above for the preparation of allylic acetate **9** afforded 376 mg of crude product, which was subsequently chromatographed on 50 ml of silica gel. Elution with hexane–5% ether afforded 84 mg of a viscous oil, homogeneous on silica gel tlc. Recrystallization of this fraction from methanol afforded 60 mg of white crystals: mp 72–78°. The nmr spectrum indicated the presence of at least two unsaturated compounds. In addition to more than one vinyl pattern, peaks were observed at δ_{TMS} ($CDCl_3$) 2.05 ($OCOCH_3$), 1.10, 1.07, 1.02, 0.94 ppm.

Elution with hexane–10% ether afforded 254 mg (61%) of crystalline diacetate **5b**: mp 132–133° (lit.[8] mp 134–135°); δ_{TMS} ($CDCl_3$) 4.60 (d, J = 7.0 Hz, $CH_2OC(=O)CH_3$), 2.06 (6 H's, $OC(=O)CH_3$), 1.06 (19-CH_3), 0.81 ppm (18-CH_3).

Acknowledgment. The authors wish to thank Dr. Kurt Rorig of Searle Laboratories, a division of G. D. Searle & Co., for a generous gift of both 3-methoxyestra-1,3,5(10)-trien-17-one and 3β-acetoxyandrost-5-en-17-one. We also wish to acknowledge Dr. Harvey W. Posvic of Loyola University of Chicago for his helpful suggestions during the course of this project.

Registry No.—**3b**, 853-23-6; **4a**, 10291-86-8; **5b**, 53210-12-1; **7**, 1624-62-0; **8**, 6885-48-9; **9**, 34965-79-2.

Reference and Notes

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(5) Reactions were carried out under a nitrogen atmosphere. The isolation of reaction products was accomplished by extracting the aqueous layer thoroughly with the specified solvent. Anhydrous magnesium sulfate was used to dry the combined extracts, and the solvent was removed on a rotary evaporator under reduced pressure. Melting points were determined on a Fisher-Johns block and are corrected. The nmr spectra were recorded with a Varian A-60 nmr spectrometer and infrared spectra were obtained using a Beckman Acculab 1 spectrophotometer.
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Ion Cyclotron Resonance Studies of Allene Mercurinium Ions

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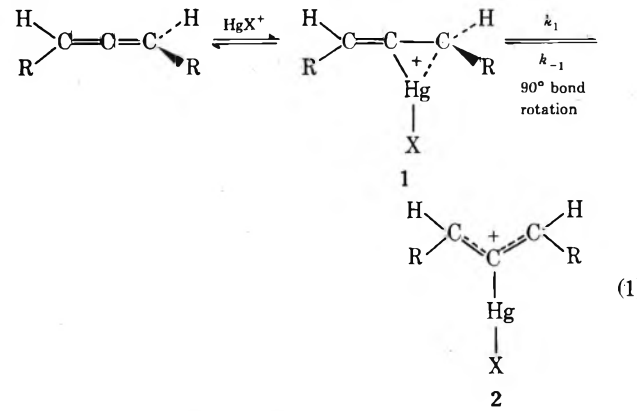
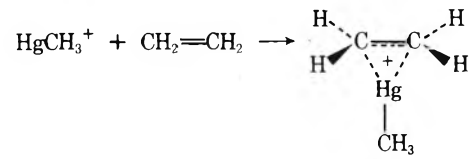
The generally accepted mechanism for the oxymercuration of alkenes in protic solvents involves a bridged or π-complexed mercurinium ion intermediate.[1] Several investigators have also suggested that mercurinium ions are involved in the alkoxymercuration of allenes.[2] The oxymercuration of optically active allenes[2] has provided convincing evidence for π bridging since a considerably driving force exists for **1** to form a planar resonance stabilized allylic carbonium ion **2** (eq 1). The formation of optically active products in these reactions[2] precluded exclusive product formation from the planar cation **2** providing evidence for either a mercurinium ion intermediate or a π-bridged transition state. Recently, additional experimental[3] and theoretical[4] evidence has been reported in support of this mechanism. Despite the extensive research on this reaction, unequivocal evidence for mercurinium ions under oxymercuration reaction conditions has not been reported. However, long-lived mercurinium ions derived from alkenes have been observed in solution by nmr spectroscopy.[5]



(1)

We have recently provided the first evidence for the existence of π-bridged cyclic mercurinium ions in the gas phase by using ion cyclotron resonance (icr) mass spectrometry.[6] In this previous study we established that the ion molecule reaction of $HgCH_3^+$ with ethylene resulted in the formation of a new ion that corresponded to the mass $C_2H_4HgCH_3^+$ as in eq 2. This was a significant finding since there are few known examples of ion cyclotron resonance (icr) studies on volatile organometallic compounds. Foster and Beauchamp[7] have reported that ion molecule reactions of $Fe(CO)_5$ afford ions containing two iron atoms.


(2)

We now report the observation of a mercurinium ion derived from the reaction of $HgCH_3^+$ and allene in the gas phase employing icr mass spectrometry and find that the rate of formation of this ion is the same order of magnitude as the theoretical collision rate constant. We have also examined the relative energies of the various ions formed with extended Hückel molecular orbital calculations to aid in identification of the most probable structures of the product ions.

Experimental Section

A Varian V-5900 ion cyclotron resonance mass spectrometer was used for the observations. A flat cell with the drift plates separated by 1.1 cm was used. Some cell modifications and our operating techniques were described previously.[8,9] Additional modifications are as follows. A Veeco Model RG-830 ionization gauge together with a Model 523H Barocel are now used in place of a cold cathode gauge to monitor cell pressure. The cell was modified for pulsed electron beam modulation by adding a control grid and appropriate pulsing electronics.[9] A new emission current control amplifier based on a Burr-Brown Model 3013/15 according to a design of J.

L. Beauchamp replaced the unit originally supplied by Varian; this unit allows regulation of emission currents down to 4×10^{-9} A. An oil diffusion pump was added so that the cell can be pumped either with it or with the original ion pump.

Allene was obtained from J. T. Baker Chemical Co. and dimethylmercury was synthesized by T. Weibel of this department. All gases were degassed by freeze–pump–thaw techniques at 77°K before use.

Standard bond angles and distances for allene were used in the extended Hückel calculations.[10] The carbon–mercury bond distances have been given elsewhere.[4] One-electron wave functions and energies were computed using the following valence orbital ionization potentials (VOIP's) for the diagonal elements of the Hamiltonian matrix (H_{ii}, in eV).

$H(H_{1s}) = -13.60$	$H(C_{2p}) = -10.77$
$H(C_{2s}) = -21.20$	$H(Cl_{3s}) = -25.77$
$H(Cl_{3p}) = -13.69$	$H(Hg_{6s}) = -10.44$
$H(Hg_{6p}) = -5.00$	$H(Hg_{5d}) = -15.66$

The resonance integrals, H_{ij}, were evaluated using the Wolfsberg–Helmholz expression[11] with $K = 1.75$ for both σ and π interactions: $H_{ij} = 1.75S_{ij}(H_{ii} + H_{jj})/2$. The overlap integrals, S_{ij}, were calculated using Clementi's[12] double ζ atomic self-consistent field wave functions. The Herman–Skillman[13] functions given for the 1^+ metal ion were used for mercury. Charges were iterated to self-consistency using a charge sensitivity factor of 2.00 eV/electron.

Results and Discussion

Dimethylmercury was introduced into the icr mass spectrometer at 2–3 $\times 10^{-6}$ Torr with 22 eV ionizing electrons. The mercury-containing ions are given by eq 3. Through a

$$CH_3—Hg—CH_3 \xrightarrow[\text{electrons}]{22\text{ eV}} Hg(CH_3)_2^+\ (28\%) + HgCH_3^+\ (41\%) + Hg^+\ (31\%) \quad (3)$$

second inlet 2–18 $\times 10^{-6}$ Torr of allene was introduced. Pulsed electron beam modulation in the icr cell at room temperature gave the spectrum shown in Figure 1. Upon adding allene a prominent new peak corresponding to the mass of $C_3H_4HgCH_3^+$ is observed. The mercury-containing ion peaks were broad and consistent with the unresolved mercury isotope distribution from 198 to 204 amu. When special efforts were made to obtain higher resolution the mercury isotopic peaks could be resolved for the primary ions produced from $(CH_3)_2Hg$. In addition to the $C_3H_4HgCH_3^+$ product ion, new absorption signals corresponding to $C_3H_4Hg^+$ and probably $C_3H_4Hg(CH_3)_2^+$ were observed at high sensitivity. The relative intensities of these three new ions are $C_3H_4HgCH_3^+$ (~97%), $C_3H_4Hg^+$ (~3%), and $C_3H_4Hg(CH_3)_2^+$ (<1%). These observed ion peaks are tentatively assigned to structures **3**, **4**, and **5** in eq 4.

$$Hg(CH_3)_2 \xrightarrow[22\text{ eV}e^-]{C_3H_4} \underset{\mathbf{3}}{\text{[}C_3H_4HgCH_3\text{]}^+} + \underset{\mathbf{4}}{\text{[}C_3H_4Hg\text{]}^+} + \underset{\mathbf{5}}{\text{[}C_3H_4Hg(CH_3)_2\text{]}^+} \quad (4)$$

The $C_3H_4Hg^+$ peak is overlapped by much stronger $(CH_3)_2Hg^+$ and $C_3H_4HgCH_3^+$ peaks on either side which precludes quantitative pressure studies on this ion. In preliminary investigations with olefins such as 2-butene the log of the [Hg–olefin]$^+$ intensity increases linearly with olefin pressure to support a bimolecular formation reaction.

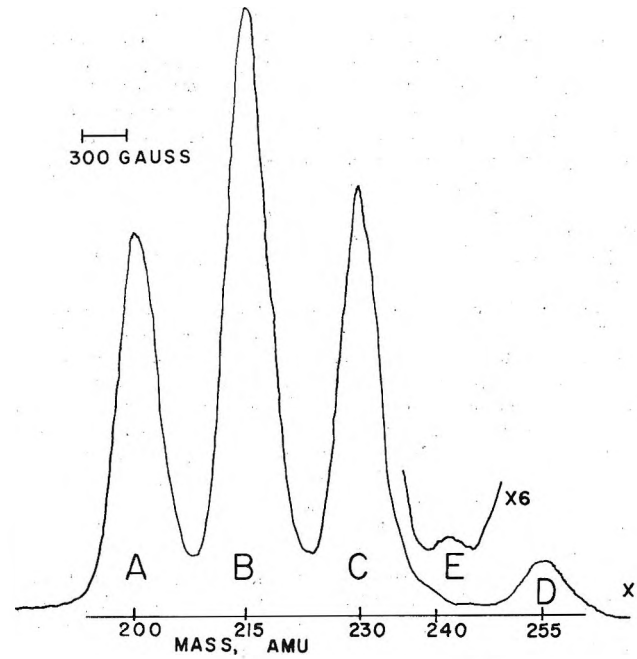


Figure 1. Icr spectrum of a mixture of ~6 $\times 10^{-6}$ Torr of allene and ~2 $\times 10^{-6}$ Torr of $Hg(CH_3)_2$ at 22 eV ionizing electron energy. Peaks A, B, C, D, and E are assigned to Hg^+, CH_3Hg^+, $(CH_3)_2Hg^+$, $CH_3HgC_3H_4^+$, and $HgC_3H_4^+$, respectively.

The $C_3H_4HgCH_3^+$ peak could be studied quantitatively with respect to allene pressure. The log of the $C_3H_4HgCH_3^+$ intensity increases linearly with allene pressure and the log of the CH_3Hg^+ intensity decreases linearly with allene pressure to support the bimolecular reaction (reaction 5). The rate constants from these measurements are discussed below.

As additional confirmation of reaction 5, ion ejection experiments, in which a reactant ion is ejected by a strong rf field, were performed on both $HgCH_3^+$ and $C_3H_4^+$. These

$$CH_3Hg^+ + C_3H_4 \longrightarrow \underset{\mathbf{3}}{CH_3HgC_3H_4^+} \quad (5)$$

experiments clearly indicate that the formation of **3** occurs by collision of $HgCH_3^+$ with neutral allene and precludes its formation by collision of $C_3H_4^+$ with dimethylmercury. It is possible that collision of $(CH_3)_2Hg^+$ with allene could also lead to ion **3**; this could not be excluded by ion ejection since some **3** is ejected along with $(CH_3)_2Hg^+$. We stress that reaction 5 definitely occurs but that this reaction is not necessarily the only pathway to the product **3**.

Ion ejection experiments also indicate that Hg^+ reacts with allene to form **4**. Again, the reaction of $HgCH_3^+$ with allene to produce ion **4** could not be definitely tested by ion ejection. However, ion **4** is also produced by ionization of elemental mercury at 40 eV and 8–9 $\times 10^{-6}$ Torr of allene. Thus reaction 6 definitely occurs.

$$Hg^+ + C_3H_4 \longrightarrow HgC_3H_4^+ \quad (6)$$

It was not possible to clearly test whether $Hg(CH_3)_2^+$ leads to **5** or not because of the low intensity of **5**. The intensity of ion **5** was always weak but it appears to be reproducibly formed. It seems probable that **5** is a loosely bound radical ion complex and its structural assignment is tentative.

The net loss of CH_3Hg^+ corresponds to a rate constant of $1.5 \pm 0.5 \times 10^{-10}$ cm^3 sec^{-1} mol^{-1} and the formation rate constant of $CH_3HgC_3H_4^+$ (see eq 5) is $1.4 \pm 0.5 \times 10^{-10}$ cm^3 sec^{-1} mol^{-1}. These rates appear comparable but $HgCH_3^+$ may also be produced by reaction 7. This reaction

$$C_3H_4^+ + Hg(CH_3)_2 \longrightarrow CH_3Hg^+ + C_3H_4 + CH_3 \quad (7)$$

was demonstrated by ion ejection of $C_3H_4^+$ which reduces the intensity of CH_3Hg^+. Thus, the net rate constant for loss of CH_3Hg^+ is a result of its loss and formation in reactions 5 and 7. The rate constant for loss of CH_3Hg^+ from reaction 5 is expected to be comparable to the theoretical collision rate constant calculated from $K = 2\pi e(\alpha_\parallel/\mu)^{1/2}$ where μ is the reduced mass of the ion–neutral system and $\alpha_\parallel$ is the parallel component of the polarizability of allene (29.6×10^{-25} cm^3) which is perpendicular to the nodal plane of the double bond and hence in the direction of probable attack by the positive ion.[14] We find K (theory) = 6.9×10^{-10} cm^3 sec^{-1} mol^{-1}. If the isotopic polarizability of allene (55.5×10^{-25} cm^3) is used the theoretical rate constant becomes 9.5×10^{-10} cm^3 sec^{-1} mol^{-1}. It is seen that the net rate constant for loss of CH_3Hg^+ is 5–6 times smaller than the theoretical maximum expected from reaction 5 alone. Thus, we may reasonably conclude that the rate constant for loss of CH_3Hg^+ from reaction 5 is somewhat larger than the measured net rate constant and that product **3** is formed with less than 20% efficiency.

The suggested product ions in reactions 5 and 6 are adducts in which the unknown reaction exothermicity must be distributed among internal vibrational and rotational modes such that dissociation is not complete. Although our mass resolution cannot exclude product ions with one less hydrogen atom, it seems that stabilization of some adduct ions will be facilitated by the heavy Hg and the large number of other atoms. The efficiency of vibrational to translational relaxation is unknown in such heavy atom systems. In these experiments the reactant ions have only thermal kinetic energies and the adduct ions are undoubtedly the primary products. The dissociation of these adduct ions could best be studied quantitatively by varying the kinetic energy of the reactant ions.

As noted above, reactions 5 and 6 do not involve $C_3H_4^+$. At least two pathways involving $C_3H_4^+$ are given in eq 7 and 8. The evidence for reaction 8 is an observed decrease

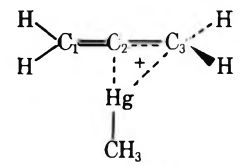
$$C_3H_4^+ + Hg(CH_3)_2 \longrightarrow Hg(CH_3)_2^+ + C_3H_4 \quad (8)$$

in $(CH_3)_2Hg^+$ upon ejection of $C_3H_4^+$. The mechanism for reaction 7 could either involve dissociative charge exchange or formation of **5** followed by dissociation. The relevant appearance potentials are $C_3H_4^+$ (10.2 ± 0.2 eV), $(CH_3)_2Hg^+$ (9.0 ± 0.2 eV), and CH_3Hg^+ (10.4 ± 0.2 eV)[15]; so dissociative exchange is just possible and neither mechanism can be clearly excluded. The appearance potentials are favorable for a charge exchange mechanism for eq 8.

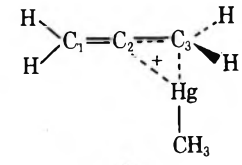
An ion residence time in the icr cell of about 3×10^{-3} sec establishes ions **3** and **4** as truly stable gas-phase species. The relative intensities of ions **3–5** did not change much with electron energy over a range of 20–70 eV. Thus, although these adduct ions are internally excited, they do not seem to be on the verge of dissociation.

We also wish to suggest the probable structure for ions **3** and **4** based upon extended Hückel (EH) molecular orbital calculations.[16] We first examined the geometry of **3** to establish whether any deviation of the 180° C_1–C_2–C_3 bond angle of the allene due to partial σ bonding occurs.[17] However, our calculations indicate that any deviation of the linear allene in the π complexes with Ag^+, Hg^+, Hg^{2+}, $HgCH_3^+$, and $HgCl^+$ results in an increase in the total energy of the ion. Previous calculations[4,6] have suggested that silver ion and mercury ion complexes with ethylene are also essentially planar ions that are more adequately described as π complexes rather than as σ-bonded cyclic intermediates with rehybridization at carbon.

We next examined the potential energy required to move the $HgCH_3^+$ moiety over at a fixed distance (2.347Å) from the C_2–C_3 double bond to afford ions **6** and **7**. The unsymmetrically bonded ions **6** and **7** are 13.0 and 19.0 kcal/mol higher in energy than ion **3** where the mercury atom is equidistant between the C_2–C_3 carbons. Our calculations also suggest that the highly reactive allene complex ion derived from interaction with Hg^{2+}, where considerably greater perturbation of the π bond results in a substantial charge on carbon, would also be more stable in the gas phase when symmetrically bonded to C_2–C_3.



6



7

A potential driving force exists for alkyl substituted ions such as **1** to form a planar resonance stabilized allylic carbonium ion **2** (eq 1). The possibility that the resonance stabilized cation may also be formed in the gas phase in the absence of solvent prompted us to calculate the total energy difference between the mercurinium ions of $HgCH_3^+$ and Hg^+ and their open cation structures **2** and **4**. The mercurinium ions **3** derived from allene and Hg^{2+}, $HgCH_3^+$, and $HgCl^+$ are all considerably lower in energy than their corresponding planar allylic cations **2**. Our calculations suggest that a 90° C_2–C_3 bond rotation for **3** with concomitant rehydridization at C_2 in the gas phase would be endothermic by 142 kcal/mol (see eq 1). In contrast, the open acyclic cation **4** is calculated to be 27 kcal/mol more stable than the allene π complex of Hg^+. However, it should be noted that conversion of the cyclic π complex to **4** would have a calculated activation energy of at least 53 kcal/mol. This estimate is based upon the increase in total energy observed upon a 90° C_2–C_3 bond rotation of the π complex of allene and Hg^+ without rehybridization at C_2. In contrast, the π complexes, **3**, of Hg^{2+}, $HgCH_3^+$, and $HgCl^+$ do not exhibit a higher total energy on 90° bond rotation than their corresponding rehybridized allylic planar cations **2**.[21] These data suggest that the exothermic conversions of the allylic planar cations **2** of Hg^{2+}, $HgCH_3^+$, and $HgCl^+$ to the cyclic π-complex cations **3** could occur without substantial activation energy. Thus, we wish to suggest that the ion derived from $HgCH_3^+$ and allene is a π-bridged cyclic mercurinium ion, (**3**) while the ion derived from Hg^+ (**4**) is an acyclic planar allylic cation *if* the cyclic π-complex **3** has sufficient internal energy to achieve bond rotation to form resonance stabilized planar ion **4**.

Acknowledgment is made to the National Institutes of Health (ES 00761-03) for support of this work. We thank J. Beauchamp for a schematic of his emission control circuit and T. Weibel for the synthetic work.

Registry No.—**3**, 53198-73-5; **4**, 53198-74-6; **5**, 53198-75-7; dimethylmercury, 593-74-8; allene, 463-49-0.

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(21) The calculated charge distributions on carbon and mercury are also consistent with the above results. With the ions derived from Hg^{2+}, $HgCH_3^+$, and $HgCl^+$, conversion from the π complex to the allylic cation resulted in a significant increase in charge at C_1 and C_2 and a concomitant decrease in charge on mercury. The opposite trend was noted with Hg^+ ions thus rendering the cation **2** more stable since mercury can more readily accommodate a positive charge than carbon.

Trimeric Structure and Mixed Cycloaddition from the Nickel-Catalyzed Reaction of Norbornadiene

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Received August 2, 1974

Since Cookson[2] reported on the cycloaddition of norbornadiene using $Fe(CO)_5$ as a promotor, several investigators have studied the reaction which yields a myriad of norbornyl dimers, ketones, and trimers.[3] Efforts to catalyze a mixed [2 + 2] cycloaddition of norbornadiene and other olefins have been few.[4] In fact, to the best of our knowledge, no one has been successful in coupling norbornadiene and norbornene. In this paper, we wish to present a structure proof for one of the trimeric compounds of norbornadiene and to present evidence that $(Ph_3P)_2Ni(CO)_2$ catalyzes the mixed cycloaddition of norbornadiene to the dimer which is a pseudo norbornene.

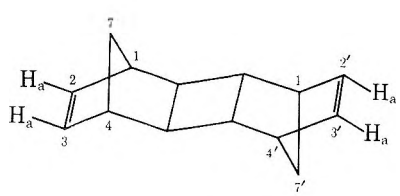
Table I

Position (see Figure 1)	Trimer, δ, ppm	exo, trans, exo Dimer	
2,2′,3,3′-Olefinic protons	5.93	6.01	
1,1′,4,4′-Bridgehead protons	2.61	2.61	
7,7′-Bridge methylenes	1.90 and 1.82 AX	1.88	1.79
	1.20 and 1.12 quartet	1.32	1.23

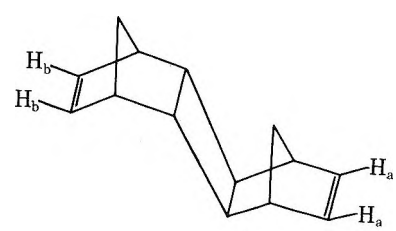
Chemical shift data garnered from the nmr spectrum of trimer IV are listed in Table I.

By comparing the nmr spectra of IV with well-characterized spectra of analogous dimers, several conclusions could be made. A single olefinic resonance at 5.77[3a,5] accounting for four protons indicated that compound IV had two carbon–carbon double bonds and the protons on them were in identical environments. Mass spectral analysis of IV confirmed the molecular weight as 276 and a *m/e* of 280 for the hydrogenated product of IV confirmed the presence of two carbon–carbon double bonds. Dimers which have an *exo*-cyclobutane ring across the norbornyl unit from the olefin moiety, as in I, have single olefin resonances between 5.65 and 5.97.[3a] In structures having both endo- and exo-bonded cyclobutane rings, as in II, two olefinic resonances are found. Finally, in compounds such as III where both rings have endo-bonded cyclobutanes, a single olefin resonance is observed around 6.15 to 6.25.[3] Thus, from the close agreement between dimer I and trimer IV nmr spectra (Table I),[9] it was reasonable to conclude that each outer norbornyl unit of IV had an exo-bonded cyclobutane ring across from the olefin.

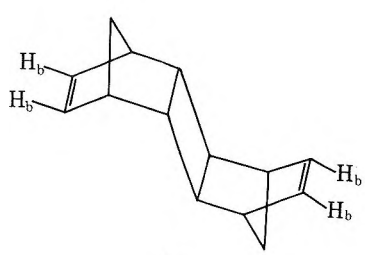
The bridge proton resonances provided additional proof for the identical character of the two exterior norbornyl units. Again, based on the nmr spectra of dimer structures, the two bridge protons (at 7 or 7′) will appear in the spectra as a 4-line AB or AX quartet. Their resonance positions are also a function of the position of the cyclobutane ring. In the spectrum of IV, there appears to be only one AX quartet which indicates again that the outer norbornyl units are identical.



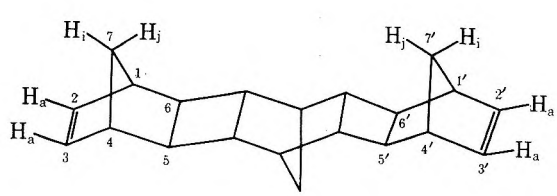
I
exo,trans,exo



II
endo,trans,exo



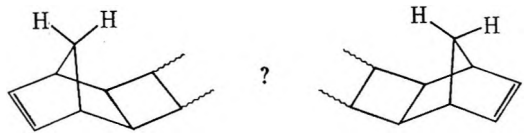
III
endo,trans,endo



IV
exo,trans,exo,trans,exo

Table II
Relative Concentrations of Products as Obtained from Gc

	Dimer	Trimer
Standard	87 ± 5	0.57 ± 0.04
Fortified expt	200 ± 10	2.50 ± 0.34



The final question as to how these two units are bonded to the central norbornyl fragment was solved by assuming that trimer originates from dimer plus monomer. Since this catalyst makes only exo,trans,exo dimer (I), it was logical to suspect that this dimer was the timer precursor. Thus if I leads to IV and the two olefin moieties are identical, then exo,trans,exo,trans,exo must describe the stereochemistry of the trimeric compound. In order to test this hypothesis, two parallel experiments were run. Two sets of reaction tubes were charged with identical amounts of catalyst and norbornadiene. Then, to each of the second set of reaction tubes, 0.50 g of exo,trans,exo dimer was added. All the tubes were treated identically in degassing, irradiation, and analysis. The results are shown in Table II. The results of these experiments show a fourfold increase of trimer in the fortified case confirming that dimer I was converted to IV and thereby proving the stereochemistry of the trimer.

These results also prove that nickel catalyzed a mixed coupling between norbornadiene and a norbornene-type molecule.[6] The obvious difference between norbornene and the pseudo norbornene (dimer I) is the cyclobutane ring which must be activating the transannular olefin. This effect is being investigated further.

Experimental Section

Glc analyses were performed on a Varian Model 1740 chromatograph using a 6 ft, 20% carbowax 20 M on 80–100 mesh Chromosorb W column. Nmr data were collected on Varian A-60 and HA-100[7] spectrometers.

Correlation of Trimer Preparation and Fortified Experiment. Standard. To three, 10 × 100 mm Pyrex test tubes containing 0.35 g (0.056 mmol) of bis(triphenylphosphine)dicarbonylnickel(0), 5.00 ml of freshly prepared norbornadiene was added using a vacuum line. These samples were degassed through three freeze–thaw cycles, sealed, and irradiated for 30 hr with Pyrex-filtered[8] light from a Hanovia 450-W mercury arc. The yields for Table II were garnered from glc data.

Fortified. To each of three test tubes prepared identically as above, 0.50 g (2.72 mmol) of exo,trans,exo dimer was added. These samples were analyzed and run simultaneously with the three standard samples.

Preparation of Trimer. In a typical experiment to prepare trimer IV a 450-W Hanovia mercury lamp equipped with a Pyrex filter, cooling jacket, and a "merry-go-round" sample holder was used to irradiate a sealed-degassed sample containing 6.5 ml of neat norbornadiene and 0.0465 g (7.28×10^{-2} mmol) of $(Ph_3P)_2Ni(CO)_2$. A total yield of 31% was obtained after 3 days of irradiation in which 93% was dimer I and 5% was trimer IV. There was a trace of another dimer which was not identified. Purification was effected through fractional sublimation giving white solid, mp 205–206°, *m/e* 276.

Anal. Calcd for $C_{21}H_{24}$: C, 91.25; H, 8.75. Found: C, 91.43; H, 8.84.

Acknowledgment. The authors are grateful to Cities Service Oil Company for partial support of this work.

Registry No.—I, 53166-41-9; IV, 53187-83-0; $(Ph_3P)_2Ni(CO)_2$, 13007-90-4; norbornadiene, 121-46-0.

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(8) Appropriate filters were used to ensure that only the metal complex absorbed the light.
(9) Spectra of dimers I, II, and III were obtained from compounds prepared in some of our previous studies.[3h]

Tetrachlorocyclopentadienoneiron Tricarbonyl

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Contribution No. 2186 from the Central Research Department, Experimental Station, E. I. du Pont de Nemours and Company, Wilmington, Delaware 19898

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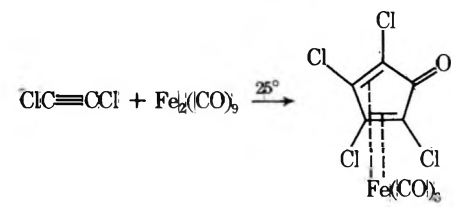
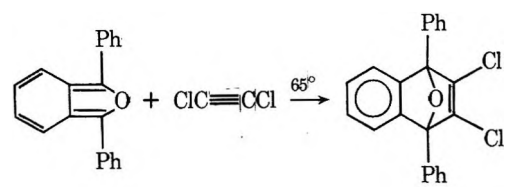
Few transition metal complexes of chlorocarbons are known and those with iron as the transition metal have been obtained indirectly by a series of metallation–halogenation reactions.[1] It has now been found that diiron nonacarbonyl reacts readily with dichloroacetylene to form tetrachlorocyclopentadienoneiron tricarbonyl (1) in moderate yield. The yellow-orange complex **1**, isolated by chromatography on alumina, is sufficiently stable at its melting point of 101–102° to be melted and remelted without change, and crystalline samples were unchanged on handling in air. The compound is, however, photodegraded in solution, slowly by incidental light and rapidly by irradiation with a low-pressure ultraviolet lamp.



1

Dichloroacetylene, prepared by the solution method of Siegel, *et al.*,[2] was used as an approximately 20% solution in ether. No explosions were encountered during several such preparations, but suitable precautions against the possibility of violent detonation and toxic vapors should nevertheless be taken. Preparations of dichloroacetylene in ether were routinely monitored by gas chromatography. Although dichloroacetylene is not a reactive dienophile, it could be derivatized easily at atmospheric pressure by Diels–Alder addition to diphenylisobenzofuran to form adduct **2**.



2

An attempt to generate tetrachlorocyclobutadiene from hexachlorocyclobutene and diiron nonacarbonyl gave no products readily elutable from alumina. Reaction of hexachlorocyclobutene with disodium iron tetracarbonyl resulted in a low yield of tetrachlorocyclobutadiene dimer, indicative of the intermediacy of tetrachlorocyclobutadiene, but no indication of a stable chlorocarbon complex with iron was found.

Experimental Section

Preparation of Dichloroacetylene. Solutions of dichloroacetylene in ether were prepared by a literature procedure.[2] As claimed by these authors, the liquid phase synthesis seems to greatly reduce the danger of explosion during preparation, so that C_2Cl_2–ether solutions were prepared and allowed to react without incident in the present work. In view of the explosion and toxicity hazards, however, dichloroacetylene should be confined to the hood and proper shielding and protective clothing should be used.

A typical synthesis was carried out with a solution of 1000 g of 85% KOH pellets in 700 ml of glycol heated at 140° and stirred with a paddle stirrer. The system was kept under an inert atmosphere by a slow stream of nitrogen (100 cm^3/min) while a mixture of 656 g (5.0 mol) of trichloroethylene and 370 g (5.0 mol) of ether was added at a rate of 3–5 ml/min over a period of 4–5 hr. Product was collected as formed in a receiver cooled at −80° and topped by a −15° condenser. When the addition was completed and the system purged with nitrogen, the liquid product was decanted from the ice, dried at 25°, and distilled through a Widmer column. The fraction with bp 33–35° was taken after a small foreshot containing volatile impurities was discarded. The C_2Cl_2–ether cut, 344 g, was assayed by gc with a column of 30% didecyl phthalate on 60–80 mesh Chromosorb W held at 50°. Ether has the shorter retention time on this column.

Using 0.67 as the gc weight factor for ether, three determinations gave 0.87, 0.73, and 0.80 for an average value of 0.80 as the weight factor for dichloroacetylene. With these weight factors, the concentration of C_2Cl_2 in the above preparation was found to be 19%. The conversion was 14% and the yield based on 276 g of unrecovered trichloroethylene was 33% (65.4 g) of C_2Cl_2.

Tetrachlorocyclopentadienoneiron Tricarbonyl (1). A mixture of 9.5 g (0.10 mol) of C_2Cl_2 in ~50 ml of ether and 9.1 g (0.025 mol) of diiron nonacarbonyl was stirred at 25° for 1 day, by which time the initial moderate gas evolution had ceased. Gc indicated the C_2Cl_2 to be more than half gone. Another 9.1 g (0.025 mol) of $Fe_2(CO)_9$ was added and the mixture was stirred another day. Only a trace of C_2Cl_2 remained. The dark mixture was filtered and the solid extracted several times with ether. Evaporation of the combined ether solutions to 50° (0.5 mm) gave a mixture of crystals and amorphous solid as residue. This residue was dissolved in dry benzene, filtered, and chromatographed on an 8.5 in. × 1.5 in. column of Woelm neutral alumina. Elution with 1:1 benzene–pentane rapidly removed 0.68 g (7%) of hexachlorobenzene, mp 223.5–225.5° after recrystallization from benzene, identified by comparison of its ir spectrum with that of a known sample.

Elution with tetrahydrofuran gave 1.5 g of yellow-orange crystals, mp 101–102°. Further elution with 3:1 tetrahydrofuran–methanol gave another 3.3 g of crystals, mp 100–102°, followed closely by a mixture of crystals and amorphous dark material. The combined crops of product, 4.8 g, are 27% tetrachlorocyclopentadienoneiron tricarbonyl. An analytical sample was recrystallized from pentane: mp 101–102°; ir (KBr) 4.73 and 4.85 (Fe–CO), 5.78 (sh) and 5.94 (conjugated C=O), 7.27, μ (coordinated CCl=CCl).

Anal. Calcd for $C_8Cl_4FeO_4$: C, 26.86; Cl, 39.64; Fe, 15.61; mol wt, 357.7. Found: C, 26.94; Cl, 39.39; Fe, 15.70; mol wt, 351 (vp osmometry, PhH at 37°).

Diels–Alder Addition to Dichloroacetylene. At 25–65°, C_2Cl_2 undergoes Diels–Alder addition to only the most reactive dienes. Thus, no reaction was detected with tetraphenylcyclone at 65°, and a very slow oxygen-initiated polymerization to C_2Cl_2–diene–O_2 terpolymer occurred with 2,3-dimethylbutadiene at 35°. However, 1,3-diphenylisobenzofuran reacted readily with C_2Cl_2 at 65°.

A solution of 1.35 g (0.005 mol) of 1,3-diphenylisobenzofuran and 1.9 g (0.02 mol) of C_2Cl_2 in ~15 ml of ether and 50 ml of dry benzene was refluxed (65°) for 3 days, during which time the color lightened after 3–4 hr, and then darkened. Solvents were removed, the residue was extracted with hexane, and the hexane solution was concentrated to give 0.45 g of nearly colorless crystals, mp 134–135°. A second crop, 0.71 g, mp 132–134°, raised the total of 1.16 g (64%) of 2,3-dichloro-1,4-diphenyl-1,4-epoxynaphthalene (**2**). A sample was recrystallized from hexane for analysis: mp 134.5–135°; ir (KBr) 3.26 (=CH), 6.22 and 6.67 (aromatic C=C), 9.0 and 9.9 (may be COC), 13 and 14 μ (mono- and disubstituted aromatic).

Anal. Calcd for $C_{22}H_{14}Cl_2O$: C, 72.34; H, 3.86; Cl, 19.41. Found: C, 72.69; H, 4.17; Cl, 19.43.

Cyclopentadiene did not react with C_2Cl_2 in 1 day at 25°, but Diels–Alder addition was observed at 100° for 15 hr. Distillation of the 100° reaction mixture gave, in addition to tars, a low yield of 2,3-dichlorobicycloheptadiene[3] codistilling at *ca.* 68° (22 mm) with dicyclopentadiene. The components of the mixture were identified by ir, nmr, and gc–mass spectrometry.

Tetrachlorocyclobutadiene Dimer.[4] A number of highly chlorinated olefins were exposed to diiron nonacarbonyl and to disodium iron tetracarbonyl. In some cases, little interaction occurred at 25–50°. In others, any iron–chlorocarbon complexes which may have been formed were readily decomposed.

Reaction of $Fe_2(CO)_9$ with hexachlorocyclopentadiene occurred readily at 25° to give 19% of decachlorodicyclopentadienyl as the only product isolated by chromatography. A related compound with no allylic chlorine, 5,5-dimethoxytetrachlorocyclopentadiene, did not react readily with $Fe_2(CO)_9$ at 50°. Similarly, the diene system in tetrachloro-α-pyrone did not appear to react with $Fe_2(CO)_9$ at 25–50°, and hexachlorocyclobutene reacted poorly.

A more nucleophilic reagent, disodium iron tetracarbonyl, reacted with hexachlorocyclopentadiene at 0–25° with formation of a black, amorphous insoluble solid. With hexachlorocyclobutene, disodium iron tetracarbonyl reacted exothermically to give (after chromatography and recrystallization) 5% of tetrachlorocyclobutadiene dimer, mp 160.5–161.5°, after recrystallization from methylene chloride–hexane.

Anal. Calcd for C_8Cl_8: C, 25.31; Cl, 74.69. Found: C, 25.72; Cl, 74.24.

The ir spectrum corresponded to that reported in the literature,[4] as did the melting point.

Registry No.—**1**, 53336-51-9; **2**, 53336-59-7; dichloroacetylene, 7572-29-4; diiron nonacarbonyl, 20982-74-5; 1,3-diphenylisobenzofuran, 5471-63-6; hexachlorocyclopentadiene, 77-47-4; disodium iron tetracarbonyl, 14878-31-0; tetrachlorobutadiene dimer, 53336-52-0.

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Synthesis of 1,4-Dihydro-1,4-dimethyl-1,4-epoxynaphthalene and Conversion to 1,4-Dimethyl-1,2,3,4-tetrahydronaphthalene and *o*-Diacetylbenzene[1]

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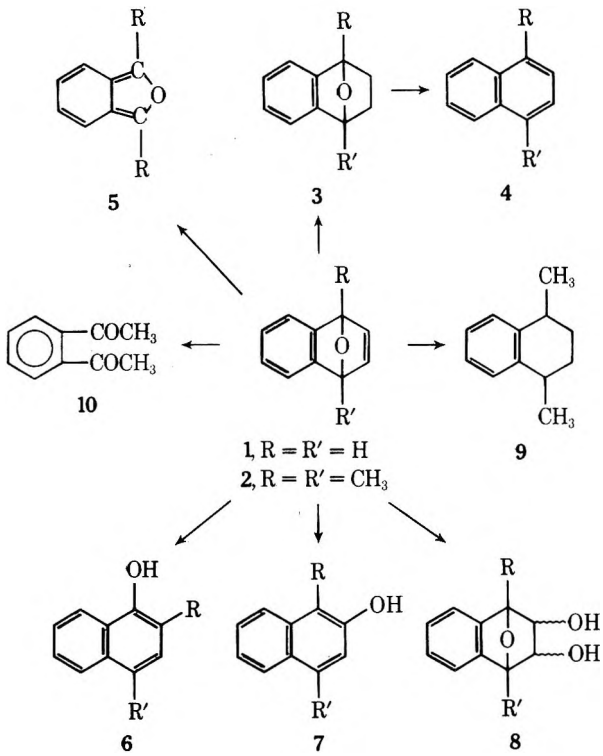
Compounds of the type 1,4-dihydro-1,4-epoxynaphthalene (**1**) are of synthetic interest because they can be synthesized from the reaction of a benzyne with a furan[4] and transformed into a variety of naphthalene derivatives in good yields by relatively simple experimental procedures. For example, the parent **1** (R = R′ = H) was reduced to the tetrahydro derivative **3** (R = R′ = H), which on treatment with methanolic acid yielded naphthalene **4** (R = R′ = H) in 90% yield.[5] Obviously, a variety of 1-monosubstituted and 1,4-disubstituted naphthalenes are accessible by this route. By more involved chemistry, the availability of the

Scheme I



unstable dialkylisobenzofurans (**5**), which may be trapped *in situ*, are accessible.[6] Acid-catalyzed rearrangements of **2** have been shown to yeld both 2,4-dimethyl-1-naphthol (**6**) and 1,4-dimethyl-2-naphthol (**7**) depending on reaction conditions,[7,8] whereas oxidation yields the glycols,[8] **8**. In the work herein described we report an improved synthesis of 1,4-dihydro-1,4-dimethyl-1,4-epoxynaphthalene (**2**) from *o*-bromofluorobenzene (*via* benzyne) and 2,5-dimethylfuran,[4] as well as the one-step conversions of **2** to 1,4-dimethyl-1,2,3,4-tetrahydronaphthalene (**9**) and *o*-diacetylbenzene (**10**). The versatility of **2** as an intermediate is increased by realizing that it, and analogous compounds, can also be made by the generation of benzyne from anthranilic acid derived precursors.[4] The transformations discussed above are outlined in Scheme I.

Many syntheses of **9**, which involved double alkylation of benzene with dichlorohexanes[9] or diallyl,[10] have been reported but all suffer from low yields and/or the lack of proof of structure and purity of the product obtained. Cyclization of 5-phenyl-2-hexanol[11] and 5-phenyl-2-hexanone[12] to **9** by acid has also been reported. Perhaps the best previous method is that involving the catalytic reduction of 1,2-dihydro-1,4-dimethylnaphthalene[13] prepared previously by a multistep synthesis from benzene and succinic anhydride.[14] We have found that catalytic reduction of **2** affords **9** rapidly in almost quantitative yield. This finding stands in contrast to the earlier report[5] that hydrogenation of **1** (R = R' = H) over Pd/C yielded **3** (R = R' = H) which did not further absorb hydrogen. However, no details as to catalyst or hydrogen pressure were given.[5] We assume that **9** is the cis isomer because catalytic reduction of benzylic alcohols and epoxides has been shown to proceed with inversion.[15]

o-Diacetylbenzene (**10**) has been prepared by many methods[16] but all suffer from low yields, rare starting materials, or both. We have found that oxidation of **2** using the Starks phase transfer method[17] yields **10** in 69% yield. Undoubtedly, this route could be used to synthesize other o-diacylbenzenes.

The synthesis of the key intermediate **2** *via* *o*-bromofluorobenzene and 2,5-dimethylfuran[4] and the synthesis of 2,5-dimethylfuran have been improved.

Experimental Section[18]

2,5-Dimethylfuran. A 50-ml Claisen flask containing 13.0 g of freshly fused zinc chloride was fitted with a dropping funnel containing 100 g of freshly distilled 2,5-hexanedione and a magnetic stirrer. About 10 ml of the dione was added and the flask was heated with a bath held in the 150–160° range. Distillation of a two-phase distillate soon took place. The reaction volume was kept about constant by addition of dione. The temperature of the distillate varied from 90 to 95°. All of the dione was added at such a rate that after 3 hr the entire product had been collected. The organic layer of the distillate was separated from the aqueous layer, dried over anhydrous $MgSO_4$, and distilled through a short column to yield 60 g (71%) of pure 2,5-dimethylfuran, bp 92.5–93.0°, which remained colorless at room temperature for several days.[19] After this procedure had been worked out we repeated the procedure which uses Amberlyst 15 (a cationic resin).[20] In our hands the yield was good but the product invariably colored on standing even after distillation. Perhaps our batch of catalyst was different from that used previously.

1,4-Dihydro-1,4-dimethyl-1,4-epoxynaphthalene (2). In a 100-ml three-necked thoroughly dried flask equipped with a reflux condenser, mechanical stirrer, and pressure-equalizing dropping funnel were placed 0.8 g (0.033 g-atom) of sublimed magnesium,[21] 2.8 g (0.03 mol) of 2,5-dimethylfuran, and 15 ml of tetrahydrofuran (THF). After flushing with dry nitrogen the mixture was heated to reflux and a solution of 5.26 g (0.03 mol) of freshly distilled *o*-bromofluorobenzene in 10 ml of THF was added dropwise during 15 min. After 2 hr at reflux the reaction mixture was cooled and treated with ammonium chloride solution. A conventional work-up afforded 4.66 g (90%) of **2**: bp 131–134° (about 45 mm) (house vacuum); nmr ($CDCl_3$) τ 8.66 (s, 6, CH_3), 3.43 (s, 2, vinyl H), and 3.13 (symmetrical m, 4, ArH). Ref 6b gives **2**, bp 120° (35 mm), and ref 7a gives mp 35°.

In earlier synthesis of **2** from 2,5-dimethylfuran and diazotized anthranilic acid, the furan was used in 100% excess.[22] In view of the present lack of availability of this reagent, our present synthesis may be the most efficient with regard to 2,5-dimethylfuran.

1,4-Dimethyl-1,2,3,4-tetrahydronaphthalene (9). A mixture of 10.0 g of **2** and 0.5 g of 10% Pd/C[23] in 75 ml of pure methanol was shaken at 40 psi of hydrogen in a Parr apparatus. Absorption of hydrogen ceased after 20 min. After a conventional work-up 9.0 g (97%) of **9** [bp 63–64° (0.4 mm); nmr ($CDCl_3$) τ 8.80 (d, 6, CH_3), 8.39 (m, 4, CH_2), 7.32 (m, 2, CH), 3.03 (s, 4, ArH); mass spectrum *m/e* 160; 98% pure by glpc][24] was obtained by distillation through a small column.

***o*-Diacetylbenzene (10).** A well-ground mixture of 63.2 g (0.4 mol) of $KMnO_4$ and 48 g (0.4 mol) of anhydrous $MgSO_4$ was added through a length of Gooch tubing to a well-stirred mixture of 17.2 g (0.1 mol) of **2**, 0.5 g of Aliquat 336,[25] 450 ml of benzene, and 450 ml of water in a 2-l. three-necked flask at such a rate that gentle reflux occurred (30–60 min). After a further reflux for 30 min and a conventional work-up which included thorough washing of the MnO_2 with acetone there was obtained 11.2 g (69%) of **10**, bp 95–98° (0.08 mm) (ref 16c reports a bp of 148–150° (14 mm)). The 2,4-DNPH derivative melted at 210° dec.[26]

Registry No.—**2**, 4705-93-5; **9**, 4175-54-6; **10**, 704-00-7; 2,5-dimethylfuran, 625-86-5; 2,5-hexanedione, 110-13-4; *o*-bromofluorobenzene, 1072-85-1.

References and Notes

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(18) All melting and boiling points are uncorrected. The nmr equipment used was purchased in part with funds granted to the Department of Chemistry by the National Science Foundation.
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(23) Obtained from Engelhardt.
(24) A column, 8 ft × 0.25 in., packed with 30% silicone gum rubber, SE-30, on fire brick in a Varian Aerograph A90-P3 apparatus, was used.
(25) Methyltricaprylammonium chloride obtained from the General Mills Co., Kankakee, Ill.
(26) S. Goldschmidt and A. Zoebelein, *Chem. Ber.*, **94**, 169 (1961), give a mp of 210°.

Selenium Dioxide Oxidation of *d*-Limonene. A Reinvestigation[1]

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In several studies[3-6] of the selenium dioxide oxidation of limonene (**1**), the tertiary alcohol **3** has been reported to be formed in yields varying from only a trace to almost 40%.[3] Although some authors[3,6,7] have worried about why the less electron-rich disubstituted double bond was preferentially attacked by selenium dioxide, it is not so surprising in view of the fact that oxymercuration[8] and especially the ene reaction with formaldehyde[9] both preferentially attack the disubstituted olefinic linkage in limonene (**1**).

The great enigma in connection with the *d*-limonene oxidation, however, was the reports[3,6] that the product alcohol **3** was optically active. In the body of their paper Trachtenberg and Carver[3] made no mention of the fact that **3** was optically active, but, in the Experimental Section they report for alcohol **3** $[\alpha]D$ +13.6° (neat, isolated by preparative glc). It should be noted that this formation of optically active alcohol **3** is inconsistent with their proposed mechanism.[7] Wilson and Shaw[6] reported $[\alpha]^{29}D$ −43.0° (c 1.24, isolated by preparative glc) for alcohol **3** and noted that the formation of this optically active product was inconsistent with all of the proposed mechanisms for the selenium dioxide oxidation of olefins.[10,11] Sakuda[4] reported $[\alpha]D$ +1.40° for **3** but said that this small rotation could be ascribed to impurities in the product. Thomas and Bucher[5] reported $[\alpha]D$ 0° for their distilled alcohol **3**.

The mechanism which we have proposed[11] for the selenium dioxide oxidation of olefins (Scheme I) would involve an initial ene reaction between selenious acid and *d*-limonene followed by dehydration to produce the allylseleninic acid **2**. A [2, 3] sigmatropic rearrangement followed by solvolysis would then give the product $\Delta^{1,8(9)}$-*p*-menthadien-4-ol (**3**). According to this mechanistic sequence, the reaction proceeds through the symmetric allylseleninic acid **2**; thus, the allylic alcohol **3** would be produced as the racemate. Therefore, Wilson's and Shaw's[6] claim of optically active alcohol **3** was incompatible with our proposed mechanism.[11]

Scheme I

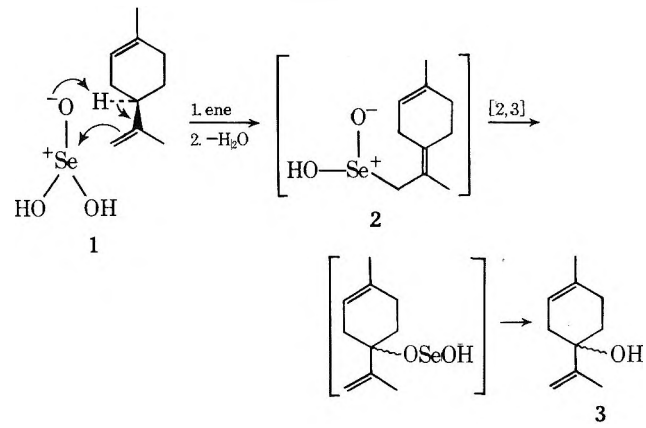

Table I
Experimental Conditions for the SeO_2-H_2O_2 Oxidation of *d*-Limonene

Expt	SeO_2, mmol	H_2O_2, mol	*d*-Limonene, mol	Reaction time
a	32	0.66	0.6	4 hr
b	32	0.66	0.3	4 hr
c	16	0.66	0.6	4 hr
d	32	0.66	0.6	20 min

We have repeated all of the four *d*-limonene oxidations reported by Wilson and Shaw.[6] The reaction conditions are summarized in Table I and are described more fully in ref 6. The procedure of Thomas and Bucher[5] was used to synthesize an authentic sample of alcohol **3**. Glc of the above four reaction product mixtures indicated that each reaction did yield some of the alcohol **3**, along with at least 27 other products. Experiment a was examined in order to determine the optical activity of the product alcohol **3**, formed in 0.2% yield (by glc). Isolation of alcohol **3** by distillation followed by preparative glc resulted in a material which showed optical activity; $[\alpha]^{29}D$ +11.9° (*c* 1.27). Although this material appeared to be homogeneous when examined by glc on OV-17, it showed several impurities on DEGS, which could possibly have been responsible for the observed rotation. The alcohol **3** was then isolated again, this time using a more elaborate purification sequence.

After a rapid distillation, the alcohol **3** was isolated by preparative tlc followed by preparative glc on an OV-17 column. This alcohol was then further purified by another preparative glc on a DEGS column. This very pure alcohol **3** was optically inactive; $[\alpha]^{29}D$ 0.000° (*c* 1.27). That alcohol **3** had survived this sequence follows from the observations that the ir of the purified material was identical with that of authentic alcohol **3** and the melting point of the purified material's phenylurethane was not depressed by admixture of the phenylurethane of authentic alcohol **3**.[12]

We submit, therefore, that the selenium dioxide oxidation of *d*-limonene (**1**) results in racemic $\Delta^{1,8(9)}$-*p*-menthadien-4-ol (**3**), as predicted by our mechanism[11] and as shown in Scheme I. The reports[3,6] which describe formation of optically active alcohol **3** are apparently in error. The optical activity which they observed in alcohol **3** was likely due to optically active impurities, for, if the alcohol **3** is rigorously purified, it is found to be optically inactive.

Experimental Section

Gas–liquid chromatography was performed on Hewlett-Packard Models 402 (flame ionization), 700 (flame ionization), and 700 (thermal conductivity) gas chromatographs with the following columns: column a, 0.25 in. × 48 ft stainless steel containing 10% OV-17 on Chromosorb W; column b, 0.125 in. × 6 ft glass containing 3% OV-17 on 100–120 mesh Chromosorb Q; column c, 0.25 in. × 6 ft stainless steel containing 5% DEGS on 100–120 mesh Chromosorb W; column d, 0.125 in. × 4 ft glass containing 3.8% UCW-98 on 100–120 mesh Chromosorb W; column e, 0.125 in. × 6 ft stainless steel containing 10% Carbowax 20M on 80–100 mesh Chromosorb W.

***d*-Limonene (1)** was obtained from Eastman Kodak and was purified by passing it through an alumina column followed by distillation: bp 91–92° (45 mm); $[\alpha]^{29}D$ +112.5° (c 1.24) [lit.[6] $[\alpha]^{29}D$ +116.5° (c 1.24)]. Glc showed the material to be >99% pure.

$\Delta^{1,8(9)}$-*p*-Menthadien-4-ol (3). The procedure of Thomas and Bucher[5] was used to prepare an authentic sample of alcohol **3**. After distillation, bp 40–41° (0.18 mm), preparative glc on column a afforded the alcohol **3**: $n^{20}D$ 1.4969; ir (neat) 3400 (OH), 3015 (>C=C(H)), 3095, 1640, 1440 and 895 cm^{-1} (>C=CH_2); nmr ($CDCl_3$) δ 5.36 ($w/2$ = 10 Hz, 1, vinyl H), 5.05 (m, $w/2$ = 4 Hz, 1, vinyl H), 4.86 (m, $w/2$ = 4 Hz, 1, vinyl H), 2.13 (m, 4, C=CCH_2), 2.01 (s, 1, OH, removed by D_2O wash), 1.85 (s, 3, C=CCH_3), 1.8–1.7 (2, CH_2), and 1.71 ppm (s, 3, C=CCH_3); mass spectrum (70 eV) *m/e* (rel intensity) 152 (16) (M^+), 137 (11), 134 (47), 124 (9), 123 (17), 119 (63), 109 (16), 105 (17), 97 (18), 94 (4), 93 (20), 92 (15), 91 (44), 84 (92), 83 (12), 79 (17), 77 (20), 69 (100), 68 (18), 67 (18), 65 (13), 55 (17), 53 (16), 51 (11), 43 (30), 41 (51), 39 (34); phenylurethane mp 124–125.5° [lit.[4–6,13] bp 50° (0.01 Torr); $n^{20}D$ 1.4967; ir 3370, 3100, 1640, and 900 cm^{-1}; nmr δ 5.3 (m, 1), 5.05 (s, 1), 4.85 (s, 1), 2.5–1.8 (m, 6), 1.9 (s, 3), and 1.7 ppm (s, 3); mass spectrum, *m/e* (rel intensity) 69 (100), 84 (86), 41 (55), 43 (30), 39 (25), fragments at *m/e* 53, 55, 67, 68, 77, 79, 83, 91, 93, 94, 97, 109, 119, 123, 124, 137 (10–20), and 152 (13) (M^+); phenylurethane mp 126–127°[3] or 130–121°[4]].

Selenium Dioxide Oxidation of *d*-Limonene (1). We have repeated all of the four oxidations reported by Wilson and Shaw;[6] see Table I and ref 6. A description of experimental procedure a follows. A solution of selenium dioxide (3.6 g, 32.4 mmol) in 75 g of 30% hydrogen peroxide solution (0.66 mol) was added to a solution of 81 g (0.6 mol) of purified *d*-limonene (**1**) in 100 ml of THF. The solution was briefly heated whereupon a vigorous exotherm commenced. During the exothermic reaction, the stirred flask was intermittently cooled with an ice bath as necessary to keep the solution from boiling out through the condenser. After the exotherm subsided, the solution was heated at reflux for 4 hr whereupon the mixture became red. The two-phase system was cooled, brine was added, and the lower phase was removed. Glc, column b, indicated that the upper layer contained the desired alcohol **3**. The upper layer was distilled at reduced pressure. A large forerun contained mostly pure limonene, bp 30–50° (0.65 mm). A fraction, bp 50–58° (0.65 mm), contained the desired alcohol **3** along with several other products. Glc, column b, indicated that the overall yield of the alcohol **3** was 0.2%. A glc purified sample, using column a, coinjected with the alcohol **3** prepared earlier and showed optical activity: $[\alpha]^{29}D$ +11.9° (c 1.23). Although this glc purified sample appeared to be homogeneous on column b, it was seen to be impure when examined on column c. Since these impurities could have been responsible for the observed rotation, the alcohol **3** was carried through a more extensive purification procedure.

The bp 50–58° (0.65 mm) fraction was subjected to preparative tlc on silica gel. The alcohol **3** was removed from the plate (R_f 0.4, 10% ethyl acetate in hexane). The resultant alcohol **3** was then subjected to preparative glc on column a, followed by another preparative glc on column c to give alcohol **3** which appeared to be homogeneous on glc columns b, c, d, and e. This very pure alcohol **3** was optically inactive; $[\alpha]^{29}D$ 0.000 (c 1.27).

Since there was a possibility that the extensive purification had somehow altered the alcohol **3**, an ir spectrum of this very pure material was taken and shown to be identical with the spectrum of the authentic alcohol **3** prepared earlier. The phenylurethane of this extensively purified alcohol **3** had mp 126–127°, which was not depressed upon mixing with the phenylurethane of the authentic alcohol **3** (mmp 125–127°).[12]

Acknowledgment. We are grateful to the National Science Foundation (GP-30485X) for financial support of this research.

Registry No.—**1**, 5989-27-5; **3**, 28342-82-7; SeO_2, 7446-08-4.

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(12) We consider it unlikely that alcohol **3** could have racemized during the purification procedure. Samples of alcohol **3** were usually injected into the glc columns as neat liquids. The glc peaks corresponding to impurities were gradually eliminated during the purification sequences and there were never any hints of decomposition of alcohol **3**. No compounds corresponding to dehydration of alcohol **3** were seen in the glc trace of purified product.
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Some Carbanionic Reactions of Halomethyl Aryl Sulfones[1]

Summary: Chloro- and bromomethyl aryl sulfones are easily converted into carbanions in the presence of concentrated aqueous sodium hydroxide and quaternary ammonium catalyst. These carbanions are readily alkylated and condense with carbonyl compounds giving oxiranes. The same conditions can be applied for alkylation of dihalomethyl aryl sulfones.

Sir: Halomethyl sulfones should form carbanions relatively easily, since both sulfonyl group and halogen atom act as carbanion-stabilizing substituents. There are, however, only a few papers describing reactions of these carbanions. Thus Truce, *et al.*,[2] reported alkylation of bromomethyl sulfone carbanions with trialkylboranes in the presence of potassium *tert*-butoxide in THF–*tert*-butyl alcohol solvents. Potassium *tert*-butoxide[3] and NaH[4] have also been applied in the synthesis of α-sulfonyloxiranes from chloro- and bromomethyl aryl sulfones and carbonyl compounds.

We have found that aqueous concentrated sodium hydroxide in the presence of a quaternary ammonium salt catalyst[5] (we use triethylbenzylammonium chloride–TEBA) can be used efficiently for the generation of α-halosulfonyl carbanions and for a variety of their reactions, some of which have not been described previously.

Thus chloromethyl[6] and bromomethyl *p*-tolyl sulfones[7] are readily alkylated under these conditions with mono- and dihaloalkanes giving α-haloalkyl or α-halocycloalkyl *p*-tolyl sulfones in high yields.

Although the starting sulfones contain an active methylene group only negligible dialkylation is observed. However, the alkylation is sometimes accompanied by dehydrohalogenation leading to α,β-unsaturated sulfones. This reaction occurs particularly easily in cases in which allyl or benzyl groups have been introduced. Thus, carrying out the alkylation under somewhat elevated temperature, it is possible to prepare directly the unsaturated sulfones.

Some dihaloalkanes are able to substitute both hydrogen atoms in halomethyl sulfones giving α-halocycloalkyl sulfones (Scheme I).

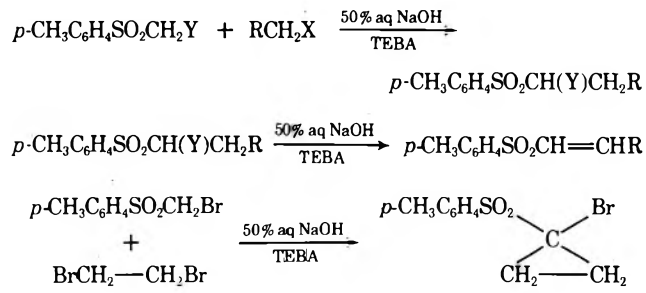
The α-halosulfonyl carbanions generated under the catalytic two-phase conditions react with aldehydes and ketones giving corresponding sulfonyl-substituted oxiranes (Scheme II). The yields of these oxiranes are high, often ~90%. In the case of aldehydes the trans epoxide isomers are the only products isolated. The sulfonyloxiranes are reported[8] to be of limited stability, rearranging easily into α-sulfonyl aldehydes.

However, the rather mild conditions in which the condensation takes place allow one in almost all cases, but that of acetophenone, to isolate pure oxirane.

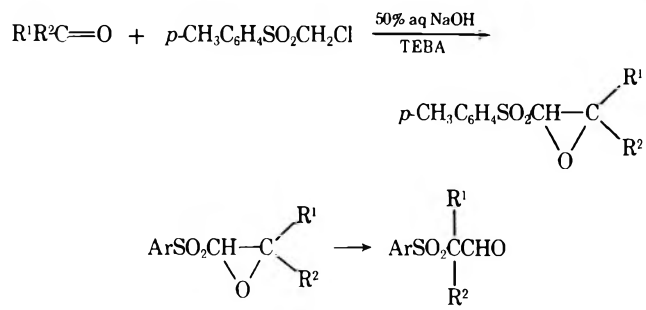
Aldehydes, being strong electrophiles, are able to react with halomethyl *p*-tolyl sulfones in the presence of concentrated aqueous sodium hydroxide without a catalyst. Owing to complete mutual insolubility of the phases, this reaction is believed to proceed directly at the phase boundary. Similar phenomena have been already observed.[9]

Dihalomethyl sulfones should be still stronger C–H acids as compared with monohalomethyl analogs. However, their carbanionic reactions are almost unknown. The case reported by Hine,[10] formation of difluorocarbene by base-induced decomposition of difluoromethyl phenyl sulfone, which appears to proceed *via* the corresponding carbanion, is to our knowledge the only example.

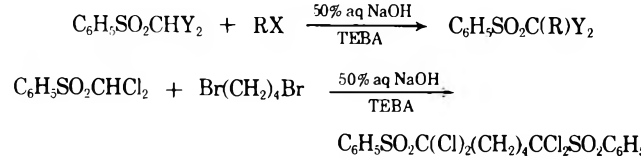
Scheme I



Scheme II



Scheme III



Readily accessible dihalomethyl aryl sulfones,[11] in the presence of aqueous sodium hydroxide and a quaternary ammonium salt catalyst, are easily converted into the corresponding dihalomethyl sulfonyl carbanions, being efficiently alkylated with various alkyl halides (Scheme III). The reaction with α,ω-dihaloalkanes leads to the corresponding α,ω-dihalo sulfonylalkanes.

Some examples of alkylated halomethyl sulfones and sulfonyloxiranes are presented in Tables I and II.

The procedures for both reactions are very simple. Examples follow.

1. **α-Bromopropyl *p*-Tolyl Sulfone.** Bromomethyl *p*-tolyl sulfone (2.0 g, 8 mmol), ethyl bromide (0.96 g, 8.8 mmol), 50% aqueous sodium hydroxide (15 ml), and TEBA (0.05 g) were vigorously stirred at 30–35° for 1 hr (mild exothermic effect). The mixture was diluted with water and the product was isolated and purified by recrystallization from ethanol (Table I, first entry).

2. ***trans*-Styryl *p*-Tolyl Sulfone.** The procedure is as described above; benzyl chloride was used instead of ethyl bromide. The reaction was carried out at 85–90° for 1 hr, yield 70%, mp 119–121° (lit.[14] mp 121–122°).

3. **2,2-Dimethyl-3-*p*-tolylsulfonyloxirane.** Chloromethyl *p*-

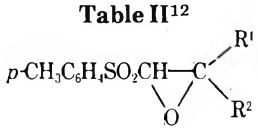
Table I[12]

$ArSO_2CH(Y)Z \xrightarrow{RX} ArSO_2C(R)YZ$

Ar	Y	Z	RX	Yield, %	Mp, °C
p-$CH_3C_6H_4$	H	Br	C_2H_5Br	67	98–100
p-$CH_3C_6H_4$	H	Br	C_4H_9Br	68	41–42[a]
p-$CH_3C_6H_4$	H	Cl	$C_6H_5CH_2Cl$	60	79–81[b]
C_6H_5	Cl	Cl	$C_6H_5CH_2Cl$	84	145–147
C_6H_5	Cl	Cl	C_2H_5Br	72	74–76
C_6H_5	Br	Br	$C_6H_5CH_2Cl$	75	168–170
1-p-Tolylsulfonyl-1-bromocyclopropane				73	138–140
1,6-Di-p-tolylsulfonyl-1,1,6,6-tetrachlorohexane[d]				87	214.5–216

[a] Bp 146–149° (0.1 mm). [b] Lit.[13] mp 79–82°. [c] Alkylation with ethylene dibromide. [d] Molar ratio of dichloro sulfone to dibromobutane 2:1.

Table II[12]



R^1	R^2	Yield, %	Mp, °C Obtained	Lit.[3]
C_6H_5	C_6H_5	90	105–107	106–107
CH_3	CH_3	91	94–95	93.5–94
C_6H_5	H	60	153–154	157–159 dec
$(CH_3)_2CH$	H	65	82–84	
$(CH_2)_5$		90	54–55	54–55

tolyl sulfone (3.06 g, 15 mmol), 50% aqueous sodium hydroxide (10 ml), acetonitrile (2 ml), TEBA (0.05 g), and acetone (1.04 g, 18 mmol) were stirred at 30–35° (mild exothermic effect) for 45 min. The product was isolated and purified by crystallization (carbon tetrachloride–hexane) (Table II, second entry).

4. α,α-Dichloropropyl Phenyl Sulfone. Dichloromethyl phenyl sulfone (2.25 g, 10 mmol), ethyl bromide (1.3 g, 12 mmol), 50% aqueous sodium hydroxide (10 ml), and TEBA (0.05 g) were vigorously stirred at 35–40° for 1 hr (exothermic effect). The mixture was diluted with water and the product was isolated and crystallized from methanol (Table I, fifth entry).

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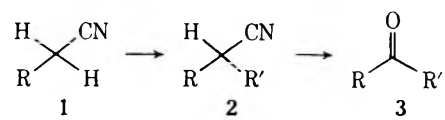
The Oxidative Decyanation of Secondary Nitriles *via* α-Hydroperoxynitriles

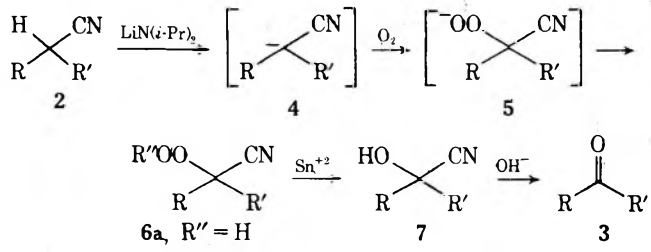
Summary: The oxidative decyanation of secondary nitriles to ketones was effected by trapping nitrile anions with molecular oxygen, reducing the resulting α-hydroperoxynitriles to cyanohydrins with stannous chloride, and converting the cyanohydrins to ketones with sodium hydroxide.

Sir: To demonstrate the functional equivalence of primary nitriles **1** as acyl carbanion equivalents[1] required methodology for effecting the monoalkylation[2] of **1** and the oxidative decyanation of secondary nitriles **2** to ketones **3**. Proce-



dures which accomplish the latter transformation (**2** → **3**) effect the oxidation of nitriles to cyanohydrins *via* intermediate α-chloro,[3] α-iodo,[4] and α-thiophenoxynitriles[5] and subsequent conversion of the cyanohydrins to ketones. Few procedures, however, allow for the direct introduction of an oxygen substituent α to a nitrile.[6] We now wish to report a general oxidative decyanation procedure which realizes this objective.

Secondary nitrile anions **4** generated using lithium diisopropylamide trapped molecular oxygen at −78° to afford lithium α-cyanohydroperoxides **5**. Quenching **5** with aqueous acid or acetyl chloride provided the isolable α-hydroperoxynitrile[7] **6a** or the acetate derivative **6b**, respectively. The reduction of **5** with an acidic stannous chloride solution[8] furnished the cyanohydrin **7**. Subsequent exposure of **7** to aqueous sodium hydroxide afforded the ketone **3** in good overall yield from the nitrile **2** (Table I).[9] For example, **2** (R = CH_2Ph; R′ = CH_3) was sequentially converted to **6a**, **7**, and **3** in isolated yields of 92, 89, and 98%, respectively. In contrast to reported oxidative decyanation procedures,[4,5] this methodology was applicable to the synthesis of dialkyl ketones as well as alkyl aryl and diaryl ketones from **2**. Primary nitriles **1** afforded only low yields of al-



6a, R″ = H
b, R″ = Ac

Table I
The Oxidative Decyanation of Secondary Nitriles 2 to Ketones 3

R	R'	Isolated yield of ketone 3, %
CH_3	$CH_2(CH_2)_3CH_3$	67
CH_3	c-C_6H_{11}	78
CH_3	CH_2Ph	82
CH_2Ph	CH_2Ph	90
CH_2Ph	$CH_2(CH_2)_2CH_3$	83
CH_2Ph	c-C_5H_9	70
	$-(CH_2)_5-$	64[a]
Ph	CH_3	86
Ph	CH_2CH_3	69
Ph	$CH(CH_3)_2$	81
Ph	c-C_6H_{11}	74
p-FPh	CH_3	92
p-ClPh	CH_3	79
α-Np	CH_3	80
p-PhPh	CH_3	82
Ph	Ph	92

[a] Isolated as the 2,4-dinitrophenylhydrazone derivative.

dehydes[10] **3** (R' = H). However, secondary carboxylic esters underwent α-hydroxylation in good yield.[11]

The following is a typical experimental procedure. To a solution of 1.1 mmol of lithium diisopropylamide in 3.0 ml of THF at −78° under a nitrogen atmosphere was added 145 mg (1.0 mmol) of **2** (R = CH_2Ph; R' = CH_3) in 1.0 ml of THF. Dry oxygen gas was bubbled (250 ml/min) into the lithionitrile solution for 30 min at −78°. The reaction was quenched with 2 ml of 1 *M* stannous chloride in 2 *M* hydrochloric acid and allowed to stir for 30 min at 0°. Following an ether–water work-up procedure which involved washing with 1 *M* sodium hydroxide, the product was chromatographed on Merck silica gel F254 to afford 110 mg (82%) of phenylpropanone which was identical with an authentic sample.[12]

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(11) For example, methyl cyclohexanecarboxylate afforded the α-hydroxy derivative in 69% yield. Similar α-hydroxylations of carboxylic esters have recently been reported: (a) E. Vedejs, *J. Amer. Chem. Soc.*, **96**, 5944 (1974); (b) P. E. Pfeffer and L. S. Silbert, U.S. Patent 3,652,612 (March 28, 1972) [*Chem. Abstr.*, **76**, 139938z (1972)].

(12) We would like to thank the Research Corporation for their financial support and the University of Colorado for a Summer Research Initiation Faculty Fellowship.

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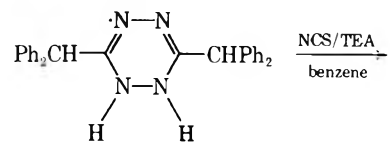
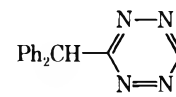
A Mild and Efficient Oxidizing Agent for Dihydroxybenzenes

Summary: A mild, efficient oxidizing reagent, *N*-chlorosuccinimide–triethylamine complex, is reported for the conversion of *o*-quinones from catechols and diphenyldiazomethane from benzophenone hydrazone and oxidative coupling of anthrone to bianthrone.

Sir: In the course of the preparation of the tetrazine I (*e.g.*, reaction 1), we discovered a marked activation effect of triethylamine (TEA) on the oxidation reactions of *N*-chlorosuccinimide (NCS).





(1)

I

Preliminary experiments indicate that the TEA–NCS reagent is a mild oxidizing agent for the conversion of catechols to o-quinones, hydroquinones to *p*-quinones, benzophenone hydrazone to diphenyldiazomethane, and *p*-toluenesulfonylhydrazide to *p*-toluenesulfonyl chloride and the coupling of anthrone to bianthrone. While the scope and limitations of this reagent are still under investigation, we report here on the oxidation of some dihydroxybenzenes.

There exists a number of methods for the oxidation of hydroquinones and catechols to quinones. Chromic and nitric acids,[1-3] ferric chloride,[4,5] silver oxide,[6] silver carbonate/Celite,[7] manganese dioxide,[8] sodium dichromate,[9] sodium chlorate/vanadium pentoxide,[10] thallium triacetate,[11] iodic acid,[12] cerric ammonium nitrate,[13] and o-chloranil[14] have been used for this transformation. Pfitzner–Moffatt[15] type oxidations have also been employed recently by Martin, *et al.*,[16] to convert hydroquinone to quinone.

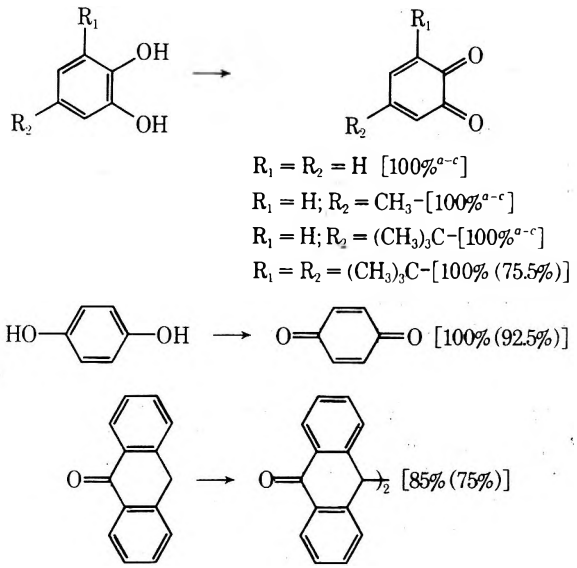
Scheme I is indicative of the efficacy of the TEA–NCS reagent.

The reaction is rapid (~10 min), quantitative (*via* nmr and ir), and takes place under mild conditions (−25 to 0°). In the case of catechol oxidations, only the red form of the *o*-quinone was observed.

The following control experiments are indicative of the specific effect of TEA: (1) the hydroxy benzenes did not react with NCS in the absence of TEA, and (2) contrary to recent reports on other aliphatic hydroxyl oxidations,[16,17] the hydroxy benzenes *did not* react with NCS in the *presence* of dimethyl sulfide (DMS) and the *absence* of TEA.

To our knowledge, TEA–NCS has not been used in the past as an oxidizing reagent. However, pyridine was used in the moderate yield NCS oxidation of alcohols to ketones.[18]

Scheme I



[a] Percentage obtained by nmr and ir analysis. [b] Isolated yields are in parenthesis, identical with authentic sample, one spot on tlc, no depression in mixture melting point. [c] Sterically unhindered *o*-quinones are unstable in concentrated solution, undergoing both polymerization and Diels–Alder dimerization. The degradation (at 35°) could be followed by nmr and a black polymer was rapidly formed in concentrated solution. However, dilute solutions of the beautiful red material could be kept for several days with no extensive degradation at 5–10°. It is best to use these unhindered *o*-quinones relatively soon after synthesis.

Corey and Kim[17] have noted that, in the NCS–DMS oxidations, TEA was the base of choice that gave the best yields.

A typical experimental procedure is given below.

To a stirred and cooled (−25°) solution of 400 mg (3 mmol) of *N*-chlorosuccinimide in 15 ml of methylene chloride was added 445 mg (2 mmol) of 3,5-di-*tert*-butylcatechol. After a 10-min interval, 0.3 ml of TEA was added dropwise. Stirring at −25° was continued for 10 min. The mixture was filtered and the filtrate evaporated. The dark red residue was dissolved in hot hexane, filtered, evaporated down to a few milliliters (until crystallization was apparent), and allowed to cool. The crystalline product (333 mg, 75.5%) thus obtained was identical in all respects with authentic o-quinone (Aldrich Chemical Co.).

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γ-Alkylation of 2-Butynoic Acid. A Route to Controlled Prenol Homologation

Summary: The novel γ-alkylation of 2-butynoic acid allows a facile synthesis of *Z* trisubstituted olefins, and of *Z* isoprenoid systems in particular.

Sir: The elaboration of polyisoprenoid compounds has recently been the focus of numerous studies owing to the crucial role of polyisoprenoids in many biological systems. Insect juvenile hormones[1] and insect sex attractants[2] are isoprenoid in nature. The long-chain polyprenols exemplified by bactiprenol and dolichol participate in polysaccharide and glycoprotein synthesis in both prokaryotic and eukaryotic systems.[3]

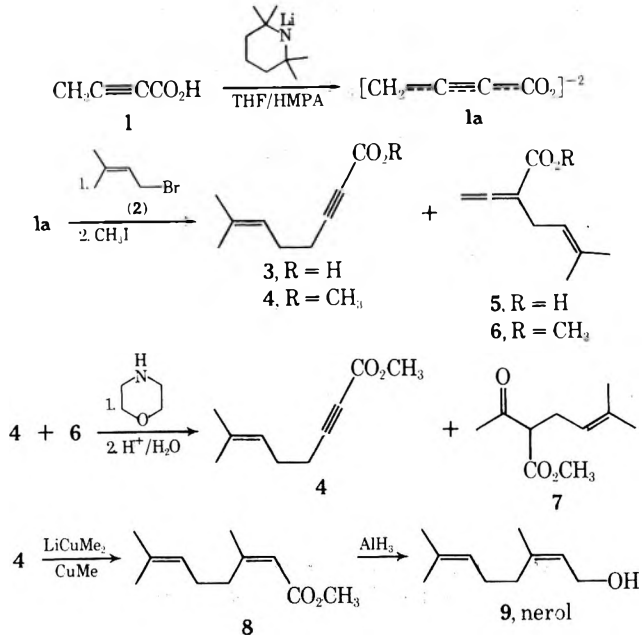
The synthesis of *E* polyisoprenoid systems has been well established, and new preparations are still being described.[4] There are, however, very few preparations of *Z* trisubstituted olefins.[2,5,6] Recently Casey and Marten[5] reported a technique for isoprenoid synthesis involving γ-alkylation of methyl acetoacetate[5a] and stereospecific olefin synthesis using enol acetates and lithium dimethyl cuprate.[5b] We wish to report an alternative route to (*Z*)-isoprenols permitting a greater degree of stereoselectivity in the olefin synthesis. The technique involves the novel γ-alkylation of 2-butynoic acid (**1**) with 1-bromo-3-methyl-2-butene (**2**), esterification of the resulting 7-methyloct-6-en-2-ynoic acid (**3**), and treatment of this methyl ester (**4**) with lithium dimethyl cuprate[7] to give the desired methyl (*Z*)-3,7-dimethylocta-2,6-dienoate (**8**). This ester is reduced to nerol [(*Z*)-3,7-dimethylocta-2,6-dien-1-ol, **9**] with AlH_3.[8]

Alkylation of α,β-unsaturated esters and aldehydes always leads exclusively or preponderantly to α substituanion of methyl 2-butynoate primarily in the α position, giving the allene, methyl 2,3-butadienoate, as the major product. Katzenellenbogen and Crumrine[10] were able to partially γ-alkylate the copper(I) dienolate of ethyl (*E*)-3-methyl-2-hexenoate with allyl bromide, but use of 3,3-disubstituted allyl bromides gave only α-alkylation.

The development of α-alkylation of carboxylic acids *via* their dianions[11] suggested to us that the negatively charged dianion of 2-butynoic acid might be delocalized in such a way that the alkylation process would favor γ-alkylation.

We found that treatment of 2-butynoic acid (**1**) with slightly more than a 2 molar ratio of lithium 2,2,6,6-tetramethylpiperidide[12] yields a dianion (**1a**) which, when alkylated with 1-bromo-3-methyl-2-butene (**2**), yields a mix-

Scheme I



ture of the salts of two acids, **3** and **5**. These acid salts are methylated with MeI in DMF to form esters **4** and **6**. The ratio of ene–yne ester (γ-alkylation, **4**) to ene–allene ester (α-alkylation, **6**) is 2.2:1.[13] The yield of the desired product(**4**) is 53–59% by gc. The dianion (**1a**) formation is carried out by rapidly adding a 10% solution of **1** in dry HMPA to a solution of lithium 2,2,6,6-tetramethylpiperidide (2.1 molar ratio to **1**) in dry THF (7 volumes of THF/volume of HMPA) which is at −100°. The addition should not be so rapid as to elevate the reaction temperature above −60°. The reaction mixture is then cooled to −90°, and the bromide (**2**) (equimolar with butynoic acid) is added rapidly. The cold bath is then allowed to warm to −70°, and the reaction is maintained at this temperature for 1.5 hr, at which time it is quenched with excess MeOH.

The variation of the HMPA:THF ratio in this reaction was limited by the relatively high freezing point of HMPA. Use of a 1:1 HMPA:THF ratio limited the lowest temperature to *ca.* −60°, owing to crystallization of HMPA from the solution. The yield of desired product (**4**) was small, and the ratio of **4**:**6** was essentially the same as for the run using 7:1 THF:HMPA. The use of much smaller amounts of HMPA caused a reduction in the ratio of **4**:**6**. At 50:1 THF:HMPA, the ratio of **4**:**6** was ~1:1.

Increasing the temperature in the dianion formation step (at 7:1 THF:HMPA) led to a lower yield of product, probably due to condensations between butynoic anions and unionized acid. Decreasing the dianion formation temperature below −100° caused problems of inhomogeneity due to crystallization of HMPA and/or dilithium butynoate from the reaction mixture.

After methylation, the resulting desired γ-alkylation product **4** may be separated from the α-alkylation product **6** by treatment with morpholine[14] in Et_2O at 20° for 1 hr, followed by acid work-up. Separation of **4** from **7** is then possible by means of silica gel column chromatography using EtOAc–Skelly B eluents. The ene–yne ester **4** is isolated in 36–40% yield, calculated from **1**.

Treatment of **4** (5 g, 30.4 mmol) with a mixture of $LiCuMe_2$ (8 molar ratio to **4**) and CuMe (2 molar ratio to **4**) at −70° in THF for 6 hr was followed by a typical work-up,[15] giving **8** (4.1 g, 22.4 mmol, 74% yield) as a mixture with a *Z*:*E* ratio of 54:1 (isomeric purity of 98.2%) by gc. This compares with a *Z*:*E* ratio of 7.1:1 previously reported for the same compound,[5b] achieved by a different route. The two isomers can be differentiated by their nmr spectra (60 MHz in $CDCl_3$, TMS as internal standard): *Z* isomer, δ 1.90, assigned to the 3-methyl group; *E* isomer, δ 2.18, also assigned to the 3-methyl group.

A mixture of $LiCuMe_2$ and CuMe was used to ensure that no MeLi was present in the reaction mixture, since Corey and Katzenellenbogen[7] have suggested that the presence of MeLi leads to increased amounts of *E* isomer. When only CuMe was used to effect the addition across the acetylenic bond, the reaction was very slow, leaving large amounts of starting material after 6 hr at −70° in THF.

In a separate attempt to synthesize the *E* isomer of **8**, **4** was treated with a mixture of $CuLiMe_2$ (3 molar ratio to **4**) and MeLi (0.5 molar ratio to **4**) in THF. The reaction was started at 0° and allowed to warm to 22° over 4 hr. The resulting product ratio (gc) was 1:1.6 *Z*:*E*, with no starting material remaining. This ratio of products was so disappointing that this reaction to synthesize the *E* isomer of **8** was not pursued any further.

Treatment of **8** with AlH_3[8] yields the desired product, nerol (**9**). Comparison of the nmr spectrum [as above, with 120 mg of Eu(FOD)$_3$ added] of synthetic nerol with the spectrum of the purified commercially available material shows the two to be identical. The synthetic material also has the same retention time (gc) as the natural material, and a mixture of the two are eluted as one peak.

The isomerization technique of Cardillo, *et al.*,[4] applied at the neroate stage (**8**) potentially allows homologation of isoprenoid units with complete stereochemical control at each double bond.

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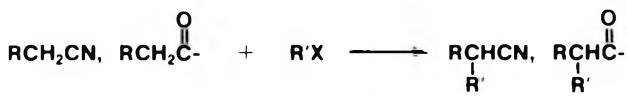
Phase-Transfer Catalysts

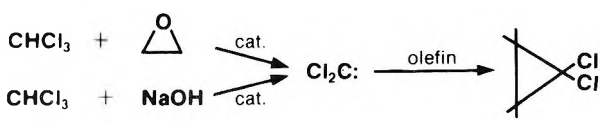
Phase-transfer catalysis has been applied to a great variety of organic reactions.[1,2] By this technique reactions are conducted in aqueous-organic two-phase systems in the presence of a phase-transfer catalyst, thus eliminating the necessity for anhydrous solvents. The most widely used phase-transfer catalysts are quaternary ammonium and phosphonium salts. The acceleration effects of these quaternary salts are so dramatic that they have become very important in preparative organic chemistry. Some successful applications of phase-transfer catalysts are:

C-Alkylation[1,2] (by *phase-transfer* or *ion-pair extraction*) of nitriles, ketones, malonates, β-diketones, β-cyanoacetates, β-ketoesters, β-ketosulfones, etc.

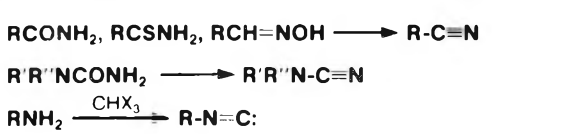


Alkylating reactivity: R′Cl > R′Br > R′I

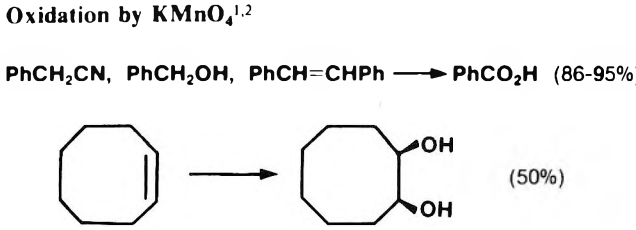
Generation of Dichlorocarbene[1,2] (in homogeneous or two-phase systems)



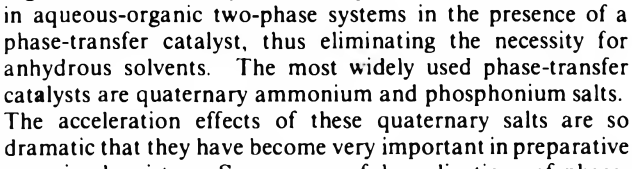
Synthesis of Nitriles and Isonitriles[2]



Oxidation by $KMnO_4$[1,2]



Nucleophilic Displacements[2-5]



Other Reactions:[1,2] **Hydrolysis of Esters and Sulfonyl Chlorides; Benzoin Condensation; Deuterium Exchange; $NaBH_4$ Reduction; Wittig Reaction.**

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Quaternary Ammonium and Phosphonium Salts Useful as Phase-transfer Catalysts

85,657-6	Adogen 464	100g $5.40; 500g $12.70
14,712-5	Benzyltriethylammonium bromide	25g $11.25; 100g $29.50
14,655-2	Benzyltriethylammonium chloride	25g $7.80; 100g $22.10
14,711-7	Benzyltrimethylammonium bromide	25g $10.90; 100g $28.75
B3260-2	Benzyltrimethylammonium hydroxide (Triton B), 40% in MeOH	100g* $5.00
B3280-7	Benzyltriphenylphosphonium chloride	25g $9.00; 38.9g† $15.00 100g $25.00
85,582-0	Cetyltrimethylammonium bromide	100g $5.00; 500g $15.00
14,111-9	Methyltributylammonium iodide	25g $8.40; 100g $22.00
17,242-1	Tetrabutylammonium chloride	25g $7.10; 100g $18.80
15,583-7	Tetrabutylammonium hydrogen sulfate	25g $11.15; 100g $29.40
17,878-0	Tetrabutylammonium hydroxide, 40% in water	50g* $8.00; 250g* $25.35
14,077-5	Tetrabutylammonium iodide	25g $4.50; 100g $11.00
14,002-3	Tetraethylammonium bromide	250g $7.50; 1kg $19.80
11,304-2	Tetraethylammonium chloride	25g $4.00; 100g $12.00
17,780-6	Tetraethylammonium hydroxide, 20% in water	100g* $6.05; 500g* $17.70

†Decimole unit
*Solution weights

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